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Information for Authors:

Purpose

The mission of the *University of Virginia Journal of Medicine* is to provide residents, fellows, and faculty members the opportunity to publish original materials generated from their experiences in patient care or patient care related research. Broadly, each edition will include 5-10 case reports, 3-4 clinical reviews and updates on recent advances, and 1-2 clinical commentaries. **The journal will give UVA housestaff the opportunity to work with the faculty in writing medical case reports, thus providing a forum for learning about the process of journal article submission and revision.** In addition, the journal offers referring physicians in the state of Virginia, alumni of the medicine training programs, and healthcare providers associated with the University the opportunity to learn from the breadth of clinically based educational experiences generated from patient care at the University of Virginia.

Article Submission

Only original, unpublished materials will be considered for publication. Inclusion of housestaff on all articles is strongly recommended. Submissions should be made electronically to Cathy Keefe-Jankowski (ck8h@virginia.edu). Any images or figures accompanying the article should be emailed as separate .jpg files. When submitting a manuscript, authors should provide full disclosure of any duplicate publication of any content of the paper in a cover letter to the Editor.

Manuscript Format

- Authors are encouraged to follow the AMA writing style as outlined in *Writing and Publishing in Medicine*, 3rd Edition, Edward J. Huth, MD. Accepted manuscripts are edited in accordance with the *American Medical Association Manual of Style: A Guide for Authors and Editors*, 9th edition. All measurements should be expressed in SI units. Abbreviations that are nonstandard should be avoided; other abbreviations must be defined on first use. Generic drug names are preferred. The manuscripts must be free of any identifying patient information in order to respect confidentiality.

Images

- Any supporting images for an article must be submitted as .jpg files of at least 360 dpi. Files should be sent as separate attachments, and not imbedded within the article text. A placeholder such as <<image 1>> should be used within the text. Please take into consideration that all images will be converted to black and white for printing.

References

- All information not considered statements of common knowledge must be supported by citation of published articles in the medical scientific literature.

- Literature sources must be cited according to AMA guidelines.

  Examples of Reference Style:
  Journal Article
  1. Spock MR, McCoy D. Extraterrestrial transfusion methods. *J Interplanetary Med.* 2800;13:53-65.

  Book
  1. West H. *Reanimation in Theory and Practice*. Arkham, MA: Miskatonic University Press; 1923.

Guidelines for Article Review Process

- Manuscripts will be blindly reviewed by two members of the review board. Decisions regarding acceptance for publication will be based on the strength of the paper compared with other papers in the literature, the need for the *University of Virginia Journal of Medicine* to represent a balanced picture of important advances in internal medicine, and the number of accepted papers in the paper's category and topic area. In addition, reviewers will score submissions based on the following criteria.
  i. Originality of case presentation
  ii. Clarity of teaching points
  iii. Balanced and evidence-based representation of recommendations
  iv. Quality of the writing

UVa Journal Article Categories:

Clinical Vignettes: *length - 800-1600 words*
- Clinical vignettes describe patients with classic presentations of rare diseases or common diseases with unusual or interesting aspects. Authors are encouraged to present a brief review of pertinent literature and discuss salient parts of the patient diagnosis. Clinical Vignettes are coauthored by the resident or fellow and the attending physician who supervised the care of the patient and focus on one or two teaching points related to diagnosis, management, or treatment.

UVa Images in Medicine: *length - maximum 250 words*
- Presentation of a radiographic image or digital photograph of an intriguing patient case accompanied by a brief case report. Authors should focus on the diagnosis and management of underlying pathophysiology related to the presented image and associated medical condition.

Medical Grand Rounds: *suggested length - 1600-3200 words*
- A review article written by an attending physician who recently presented during Medical Grand Rounds at the University of Virginia. Specifically, this article should provide readers a thorough overview of recent scientific and technologic advances, discussed during the Grand Rounds and developed at the University of Virginia, which have contributed to the overall understanding and management of specific conditions.

Clinical Review Article: *length - 1600-3200 words*
- A comprehensive review article written by an attending physician based on a thorough assessment of the literature with the goal of outlining the current understanding of the pathophysiology and up-to-date practice guidelines for specific clinical topics.

Clinical Commentary: *length - 1600-3200 words*
- The Clinical Commentary offers attending or resident physicians an opportunity to provide a unique clinical perspective on a component of patient care, education, or medical advancements. The scope of this submission is quite broad and may incorporate discussion of controversial issues in the practice of medicine, topics related to or examples of patient care that have affected the author's personal or professional outlook, and/or commentaries about health care policy or public health.

The Academic Hospitalist Corner: *length - 1600-3200 words*
- This section is dedicated to the emerging field of inpatient hospitalist medicine. Article submissions may be case reports, clinical reviews, perspective pieces, and/or commentaries on medical education and training as related to hospitalist medicine.

Chief Resident Clinical Medicine Conference: *length - 1600-3200 words*
- A report that describes a rare or unusual case, with an emphasis on processes of differential diagnosis, work-up, and management that are also applicable to commonly encountered medical conditions. The article should include a thorough discussion of several diagnostic dilemmas with the goal of addressing both the management of complex pathophysiology and the process of systematically arriving at difficult diagnoses.

Tutorials in Medicine: *length - 1600-3200 words*
- A classic presentation of a disease process with board-style questions about the case. This is followed by a discussion of one or more of the following: differential diagnosis, pathophysiology, management, or treatment. These should be authored by an attending physician with resident or fellow physician collaboration.

Clinical Research: *length - 1600-3200 words*
- Presentation of original data from clinical research conducted wholly or in part at the University of Virginia. Research accepted for publication must be current, well-executed, and applicable to patient care.

Rare Association of Senior-Loken Syndrome with Biliary Obstruction Secondary to Type I Choledochal Cyst

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Senior-Loken syndrome (SLS) is a rare autosomal recessive condition characterized by nephronophthisis (NPHP), a cystic kidney disease that causes progressive renal failure, and retinopathy. Gastrointestinal anomalies, with the exception of hepatic fibrosis, have not been documented in SLS. To our knowledge and according to a MEDLINE search, this is the first report of a case of choledochal cysts (CDC) associated with SLS.

CASE REPORT

A 24-year-old African-American man with a history of SLS associated with blindness and chronic kidney disease treated with peritoneal dialysis presented to an outside hospital with a 1-week history of abdominal pain, nausea, vomiting, and anorexia. The patient was afebrile, with a pulse of 121 beats/min, blood pressure of 121/69 mm Hg, respiratory rate of 24 breaths/min, and O_2 saturation of 98% on room air. Physical examination revealed scleral icterus and an abdomen that was tender to palpation in the right upper quadrant. There was no rebound or guarding present, and the patient had a negative Murphy's sign. Laboratory findings included albumin, 2.6 g/dL (normal range 3.5-5.7 g/dL); total bilirubin, 4.9 mg/dL (0.3-1.2 mg/dL); conjugated bilirubin 3.6 mg/dL (0.0-0.5 mg/dL); alkaline phosphatase, 437 U/L (40-150 U/L); alanine aminotransferase, 36 U/L (<55 U/L); aspartate aminotransferase, 108 U/L (<35 U/L), white cell count, 10.4 x 10^9 (4-11 x 10^9), hemoglobin, 10.8 g/dL (14-18 g/dL), platelet count, 352 k/µL (150-405 k/µL); prothrombin time, 21.7 seconds (12.5-15.2 seconds). A contrast computed-tomographic scan of the abdomen demonstrated a macronodular liver consistent with cirrhosis and central biliary and pancreatic ductal dilatation. An attempt at endoscopic retrograde cholangiopancreatography (ERCP) was unsuccessful because of a long complicated common bile duct stricture that could not be stented. The patient was then transferred to the University of Virginia Health System (UVA) for further management.

At UVA, a biliary sphincterotomy was performed during ERCP, and the common bile duct was cannulated; however, the wire could not be advanced beyond the common bile duct stricture. Pressure cholangiogram revealed multiple common bile duct strictures as well as massive dilatation of the intrahepatic ducts proximal to the level of the porta hepatis, consistent with a type I CDC (Figures 1 and 2). The patient completed a 10-day course of intravenous antibiotics and was discharged home with scheduled follow-up to discuss future surgical exision of the cyst. Unfortunately, he was lost to follow-up.

DISCUSSION

SLS is a rare autosomal recessive condition characterized by NPHP and retinopathy.[1] Senior et al[2] first described the syndrome in 1961, and Loken et al[3] described the condition in 2 siblings in the same year.

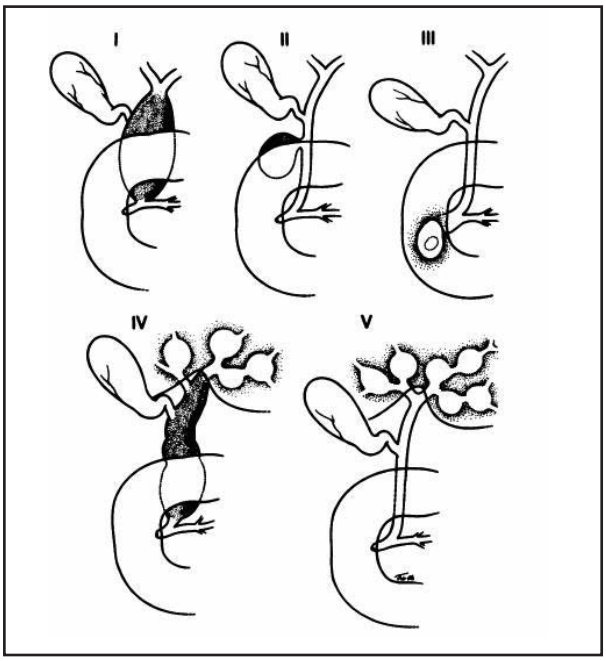

Figure 1. Alonso-Lej classification of choledochal cyst with the Todani modification [40,41]

NPHP comprises a group of autosomal-recessive cystic kidney diseases which are the most frequent genetic causes of end-stage renal disease in children and young adults.[4,5] Polyuria and polydipsia due to an impaired ability to concentrate urine are the earliest clinical signs and are followed by signs associated with advanced renal disease, such as anemia and growth retardation.[6-8] NPHP is usually insidious in nature and progressively leads to end-stage renal disease requiring renal replacement therapy, usually before patients reach the age of 20 years. Histologic examination of the kidneys shows fibrosis or dilated tubules with a thickened tubular basement membrane and cysts at the corticomedullary junction.[5-7,9] Several gene loci for NPHP have been identified, but the locus IQCB1 9 (also called NPHP5) has been identified as the most frequent cause of SLS.[10-12] IQCB1 codes for the protein nephrocystin-5, which is expressed in primary renal epithelial cells. Nephrocystin-5 also interacts with retinitis pigementosa GTPase regulator expressed by photoreceptor cilia. This interaction causes ciliary dysfunction, which is central to the pathogenesis of SLS,[13] and 10% of individuals with NPHP have ocular involvement, which characterizes SLS.[13] The eye disease may be congenital amaurosis of Leber type, pigmentary retinal degeneration, or retinitis punctata albescens.[7,14-17] The retinal lesions in SLS are variable and may be severe, leading to childhood blindness. Ophthalmic examination usually reveals pigmentary retinal changes. Electroretinogram is useful in the diagnosis of these varieties.[7] Other ocular findings, including cataracts, Coats disease, and keratoconus, have also been reported.[18]

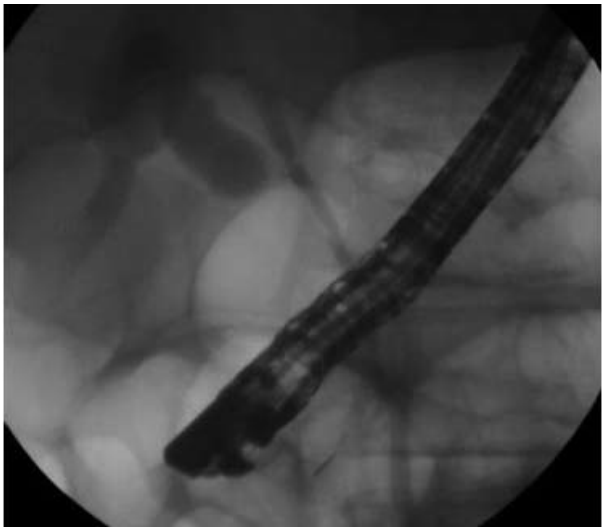

Figure 2. Type I choledochal cyst

SLS has also been associated with hepatic fibrosis, as first described in 1973 by Boichis et al,[19] adding to the spectrum of congenital diseases that affect the kidney and liver. This association has been reported in only a handful of patients.[20-23] Biopsy results have shown periportal bridging fibrosis and bile duct proliferation.[22] In the majority of patients with SLS and portal fibrosis, portal hypertension has not been observed.[24] A case of cholestatic liver disease and NPHP has been reported. Similar to our patient, this patient had mild transaminitis with marginally elevated alkaline phosphatase and bilirubin. Unlike our case, however, imaging studies in this individual did not reveal any cystic abnormalities or intra- or extrahepatic ductal dilation, and histologic examination revealed only bile duct proliferation.[25]

The diagnosis of CDC is usually made in childhood, with most cases being diagnosed in the first decade of life.[26,27] Presentation in adulthood occurs in 20% of patients, with symptoms related to biliary tract pathology, including right upper-quadrant pain, jaundice, cholangitis, and pancreatitis.[28,29] The cause of CDC is still uncertain. Most patients have an anomalous pancreaticobiliary junction, which has been thought to allow reflux of pancreatic enzymes into the bile duct, increasing ductal pressure and causing the duct to dilate.[30] Another possible cause is partial distal obstruction, attributable to a stricture, web, or sphincter-of-Oddi dysfunction.[31] In the past, CDC were treated by use of drainage procedures (cystoduodenostomy or cystojejunostomy),[32-34] but complications have been reported, including anastomotic stricture, biliary calculi associated with stasis, recurrent cholangitis, and malignant transformation of the retained cyst wall.[35,36] To prevent these long-term complications, cyst excision is recommended, and the treatment of choice is cyst excision with Roux-en-Y hepaticojejunostomy.[37-39]

CONCLUSION

SLS is a rare entity that presents with familial juvenile NPHP and retinal dystrophy. Hepatic fibrosis has also been documented, but to the best of our knowledge the association of choledochal cysts and SLS has not previously been reported. We suggest that this association may represent a different syndrome or an unrecognized feature of the previously described syndrome. Establishment of this relationship will require long-term follow-up and additional case investigation and reporting.

REFERENCES

1. Francois J. Leber's congenital tapetoretinal degeneration. *Int Ophthalmol Clin.* 1968;8:929-947.
2. Senior B, Friedmann AI, Braudo JL. Juvenile familial nephropathy with tapetoretinal degeneration. *Am J Ophthalmol.* 1961;52:625-633.
3. Loken AC, Hanssen O, Halvorsen S, Jolster NJ. Hereditary renal dysplasia and blindness. *Acta Paediatr.* 1961;50:177-184.
4. Betts PR, Forest-Hay I. Juvenile nephronophthisis. *Lancet.* 1973;2:475-478.
5. Georges B, Cosyns JP, Dahan K, et al. Late onset renal failure in Senior-Loken syndrome. *Am J Kidney Dis.* 2000;36;1271-1275.
6. Warady BA, Cibis G, Alon V, Blowey D, Hellerstein S. Senior-Loken syndrome: revisited. *Pediatrics.* 1994;94:111-112.
7. Fillastre JP, Guenel J, Riberi P, Marx P, Whitworth JA, Kunh JM. Senior-Loken syndrome (nephronophthisis and tapetoretinal degeneration): a study of 8 cases from 5 families. *Clin Nephrol.* 1976;5:14-19.
8. Sarangapani S, Chang L, Gregory-Evans K. Cataract surgery in Senior-Loken syndrome is beneficial despite severe retinopathy. *Eye.* 2002;16:782-785.
9. Waldherr R, Lennert T, Webber HP, Fodisch HJ, Scharer K. The nephronophthisis complex: a clinicopathologic study in children. *Virchows Arch A Pathol Anat Histol.* 1982;394:235-254.
10. Caridi G, Murer L, Bellantuono R, et al. Renal-retinal syndromes: association of retinal anomalies and recessive nephronophthisis in patients with homozygous deletion of the NPH 1 locus. *Am J Kidney Dis.* 1998;32:1059-1062.
11. Omran H, Sasmaz G, Haffner K, et al. Identification of a gene locus for Senior-Loken syndrome in the region of the nephronophthisis type 3 gene. *J Am Soc Nephrol.* 2002;13:75-79.
12. Otto EA, Loeys B, Khanna H, et al. Nephrocystin-5, a ciliary IQ domain protein, is mutated in Senior-Loken syndrome and interacts with RPGR and calmodulin. *Nat Genet.* 2005;37:282-288.
13. Giridhar S, Padmaraj R, Senguttuvan P, Twins with Senior-Loken syndrome. *Indian J Pediatr.* 2006;73:1041-1043.
14. Satran D, Pierpont ME, Dobyns WB. Cerebello-oculo-renal syndromes including Arima, Senior-Loken and COACH syndromes: more than just variants of Joubert syndrome. *Am J Med Genet.* 1999;86:459-469.
15. Dekaban A. Hereditary syndrome of congenital retinal blindness (Leber), polycystic kidneys, and maldevelopment of the brain. *Am J Ophthamol.* 1969;68:1029-1037.
16. Hussels IE. Congenital amaurosis and nephronophthisis: a new syndrome. *Birth Defects.* 1971;7:199-201.
17. Schimke RN. Hereditary renal-retinal dysplasia. *Ann Intern Med.* 1969;70:735-744.
18. Gleeson JG, Keeler LC, Parisi MA, et al. Molar tooth sign of the midbrain-hindbrain junction: occurrence in multiple distinct syndromes. *Am J Med Genet A.* 2004;125:125-134.
19. Boichis H, Passwell J, David R, et al. Congenital hepatic fibrosis and nephronophthisis: a family study. *Q J Med.* 1973;42:221-233.
20. Proesmans W, Van Damme B, Macken J. Nephronophthisis and tapetoretinal degeneration associated with liver fibrosis. *Clin Nephrol.* 1975;3:160-164.
21. Robins DG, French TA, Chakera TMH. Juvenile nephronophthisis associated with skeletal abnormalities and hepatic fibrosis. *Arch Dis Child.* 1976;51:799-801.
22. Witzleben CL, Sharp AR. "Nephronophthisis-congenital hepatic fibrosis": an additional hepatorenal disorder. *Hum Pathol.* 1982;13:728-733.
23. Delaney V, Millaney J, Bourke E. Juvenile nephronophthisis, congenital hepatic fibrosis and retinal hypoplasia in twins. *Q J Med.*1978;186:281-290.
24. Fernandez-Rodriguez R, Morales JM, Martinez R, et al. Senior-Loken syndrome (nephronophthisis and pigmentary retinopathy) associated to liver fibrosis: a family study. *Nephron.* 1990;55:74-77.
25. Popovic-Rolovic M, Kostic M, Sindjic M, Jovanovic O, Peco-Antic A, Kruscic D. Progressive tubulointerstitial nephritis and chronic cholestatic liver disease. *Pediatr Nephrol.* 1993;7:396-400.
26. Powell CS, Sawyers JL, Reynolds VH. Management of adult choledochal cysts. *Ann Surg.* 1981;193:666-676.
27. Sela-Herman S, Scharschmidt BF. Choledochal cyst, a disease for all ages. *Lancet*. 1996;347:779.
28. Ishida M, Tsuchida Y, Saito S, Hori T. Primary excision of choledochal cysts. *Surgery.* 1970;68:884-888.
29. Deziel DJ, Rossi RL, Munson JL, Braasch JW, Silverman ML. Management of bile duct cysts in adults. *Arch Surg.* 1986;121:410-415.
30. Iwai N, Yanagihara J, Tokiwa K, et al. Congenital choledochal dilatation with emphasis on pathophysiology of the biliary tract. *Ann Surg.* 1992;215:27-30.
31. Metcalfe MS, Wemyss-Holden SA, Maddern GJ. Management dilemmas with choledochal cysts. *Arch Surg.* 2003;138:333-339.
32. O'Neill JA Jr, Clatworthy HW Jr. Management of choledochal cysts: a fourteen-year follow-up. *Am Surg.* 1971;37:230-237.
33. Trout HH III, Longmire WP Jr. Long-term follow-up study of patients with congenital cystic dilatation of the common bile duct. *Am J. Surg.* 1971;121:68-86.
34. Fonkalsrud EW, Boles ET Jr. Choledochal cysts in infancy and childhood. *Surg Gynecol Obstet.* 1965;121:733-742.
35. Nagorney DM, McIlrath DC, Adson MA. Choledochal cysts in adults: clinical management. *Surgery.* 1984;96:656-663.
36. Powell CS, Sawyers JL, Reynolds VH. Management of adult choledochal cysts. *Ann Surg.* 1981;193:666-676.
37. Jordan PH, Goss JA, Rosenberg WR, Woods KL. Some considerations for management of choledochal cysts. *Am J Surg.* 2004:187;434-439.
38. Stain SC, Guthrie CR, Yellin AE, Donovan AJ. Choledochal cyst in the adult. *Ann Surg.* 1995;222:128-133.
39. Chi-Leung L, Sheung TF, Chung ML, Chi ML, Ronnie TP, Wong J. Choledochal cysts in adults. *Arch Surg.* 2002;137:465-468.
40. Alonso-Lej F, Revor WB, Pessago DJ. Congenital choledochal cyst with a report of 2, and an analysis of 94 cases. *Surg Gynecol Obstet.* 1959;108:1-30.
41. Todani T, Yasuhiro W, Narasue M, et al. Congenital bile duct cysts: classification, operative procedures, and review of 37 cases including cancer arising from choledochal cyst. *Am J Surg.* 1977;134:263-269.

New-Onset Diabetes with Ketoacidosis in a Patient with Graves Hyperthyroidism: Case Report and Review of the Literature

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The simultaneous presentation of thyrotoxicosis and new-onset diabetes with DKA is rare. Failing to recognize the presence of both conditions can lead to difficulties in management as well as adverse clinical outcomes. We report a case of new-onset diabetes mellitus and diabetic ketoacidosis (DKA) presenting simultaneously with Graves hyperthyroidism, and present a review of relevant literature. We suggest that in patients with DKA, physical findings suggestive of Graves disease, persistent tachycardia, and the lack of an obvious precipitant for DKA should prompt evaluation for hyperthyroidism.

CASE REPORT

A 44 year old woman presented to the emergency department of the University of Virginia Health System. She reported new-onset dyspnea along with progressive palpitations and tachycardia occurring for a period of several months. An examination by her primary physician 2 months earlier revealed low thyroid-stimulating hormone (TSH) (0.01 μIU/mL), but additional evaluation and treatment had not been initiated. The patient reported that she had lost approximately 70 pounds during a 6-month period despite a good appetite. She also reported polyuria and polydipsia occurring for at least 3 weeks and new-onset abdominal pain with nausea. She denied fever, cough, chest pain, dysuria, and skin rash. Her medical history included hypertension, obesity, and a remote history of preeclampsia complicated by HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Medications on admission were valsartan, bumetanide, loratadine, potassium chloride, and a multivitamin.

Physical examination revealed a temperature of 36.4° C, respiratory rate 26/min, pulse rate 165 beats/min (regular), blood pressure 192/113 mm Hg, and oxygen saturation 95% with ambient air. She exhibited centripetal obesity (body mass index 34.5). Eye exam revealed mild proptosis and periorbital edema consistent with Graves ophthalmopathy. The patient's thyroid was diffusely enlarged—approximately 2 times normal size—without palpable nodules. Her cardiac exam disclosed a regular tachycardia with a 1/6 systolic murmur. Her neurologic, lung, and abdominal exams were unremarkable, but she had trace ankle edema.

Electrocardiography showed sinus tachycardia at a rate of 160 to 170 bpm, which slowed to approximately 130 bpm with intravenous metoprolol. Laboratory tests revealed TSH of <0.01 μIU/mL, free thyroxine (T4) 2.6 ng/dL (reference interval 0.7-1.5 ng/dL), free triiodothyronine (T3) 10.0 pg/mL (reference interval 2.3-4.2 ng/dL), blood glucose 320 mg/dL, and serum bicarbonate of 7 mmol/L (anion gap 25). Arterial blood gas analysis findings were a pH of 7.17, pCO_2 of 27, and PaO_2 of 97, and urinalysis demonstrated large ketones but no evidence of urinary tract infection. Additional laboratory results included a potassium of 4.7 mmol/L (reference interval 3.4-4.4 mmol/L), blood urea nitrogen 11 mg/dL, creatinine 0.8 mg/dL, calcium 10.2 mg/dL (reference interval 8.4-10.2 mg/dL), magnesium 1.9 mg/dL (reference interval 1.6-2.6 mg/dL), white blood cell count 11,000/μL, hemoglobin 15.1 g/dL (mean corpuscular volume 83 fL), platelets 314,000/μL, human chorionic gonadotrophin negative, lipase 26 U/L (reference interval 8-78 U/L), and an undetectable troponin I. Chest x-ray exhibited no evidence of infection or heart failure.

The patient was admitted to the general medicine service with the diagnoses of diabetic ketoacidosis (DKA) and hyperthyroidism, and the endocrinology service was consulted. Further laboratory testing revealed a hemoglobin A1c of 11.1%, random cortisol 29 μg/dL, triglycerides 173 mg/dL, high-density lipoprotein cholesterol 39 mg/dL, and low-density lipoprotein cholesterol 97 mg/dL. The patient was treated with standard intravenous fluid

and insulin therapy, and her DKA resolved within 24 hours. Technetium-99m scintigraphy revealed diffusely increased uptake (estimated 24-hour iodine uptake of 62%) consistent with Graves disease. Treatment for thyrotoxicosis was initiated with propranolol and methimazole. Anti–glutamic acid decarboxylase 65 (GAD65) antibodies were later found to be elevated at 1.72 nmol/L (reference interval ≤0.02 nmol/L). Outpatient care following discharge included intensive subcutaneous insulin therapy, radioiodine ablation with 10 mCi of I-131, and subsequent thyroid hormone replacement.

DISCUSSION

DKA is a complication of severe insulin deficiency. Inadequate insulin administration is a common cause of DKA in patients with severe beta-cell failure (e.g., in type 1 diabetes), and DKA may also be precipitated in these patients by a variety of stresses including infection (e.g., pulmonary or urinary tract), cardiovascular or cerebrovascular ischemic events, and pancreatitis. In our patient, in whom no other contributory factors were identified, we believe that DKA was precipitated by progressive thyrotoxicosis in the setting of previously undiagnosed beta-cell failure.

Several case reports have described thyrotoxicosis as a precipitant of DKA, generally in the setting of previously diagnosed diabetes.[1-3] However, it is rare for a patient to be simultaneously diagnosed with Graves hyperthyroidism and new-onset diabetes with DKA. When these disorders occur concomitantly, it is imperative that both are promptly recognized, because they may significantly impact each other and lead to severe morbidity and even death. For example, thyroid storm has been reported to conceal and delay the diagnosis of DKA, contributing to cardiac arrest.[4] Conversely, DKA may precipitate thyroid storm in hyperthyroid patients, and DKA may mask the signs of severe thyrotoxicosis.[2,5] In patents with DKA, the persistence of significant tachycardia after fluid resuscitation or the absence of other DKA precipitants should raise suspicion for thyrotoxicosis.[1] Such patients may also display findings more specifically associated with hyperthyroidism, such as goiter or ophthalmopathy.

Thyroid hormones have multiple effects on carbohydrate, lipid, and protein metabolism.[6] It is well established that thyrotoxicosis can worsen glycemic control in patients with preexisting diabetes.[7] Available data regarding the effects of excess thyroid hormone in individuals without diabetes is less uniform, possibly reflecting variability of experimental design and different populations studied. A majority of studies suggest that basal and postprandial glucose concentrations are elevated in nondiabetic patients with thyrotoxicosis,[8,9] although normal glucose concentrations are observed in some studies.[10,11] Basal insulin concentrations and insulin responses to glucose challenge have been reported to be increased[9,10,12-14] or normal[11] in thyrotoxicosis. Some studies suggest that the relative amount of insulin present for the degree of glycemia may be reduced in thyrotoxicosis,[14,15] a finding that may reflect an increased metabolic clearance rate of insulin,[10,11] beta-cell impairment,[14,15] or both. One study of thyrotoxic patients reported impaired insulin secretion with oral, but not intravenous, glucose challenge, suggesting abnormal gut-mediated glucose-insulin signaling.[16] Studies in which the hyperinsulinemic euglycemic clamp procedure was used suggest that thyrotoxicosis can be associated with reduced[10,13] or normal[11] peripheral insulin sensitivity. Thyrotoxicosis may promote hepatic insulin resistance, with increased basal hepatic gluconeogenesis that is relatively resistant to suppression by insulin.[17] Abnormalities of glucose metabolism usually resolve promptly when euthyroidism is restored.[8,9,17]

Thyrotoxicosis is also associated with increased adipocyte lipolysis, increased circulating free fatty-acid concentrations, and increased hepatic lipid oxidation, thus promoting ketogenesis.[11,14,18,19] In fact, one reported case of ketoacidosis unrelated to diabetes was attributed to severe thyrotoxicosis.[18] Prevailing insulin and counterregulatory hormone (e.g., glucagon, catecholamine) action will further influence overall rates of lipid oxidation and ketogenesis. For example, the increase of plasma beta-hydroxybutyrate and glycerol observed with insulin suppression (via somatostatin infusion) is amplified by experimental thyrotoxicosis.[19] Thus, thyrotoxicosis in the setting of relative insulin deficiency is characterized by a unique predilection toward ketoacidosis.

The etiology of our patient's insulin deficiency was unclear. Our patient's age and body habitus suggested the possibility of type 2 diabetes; diabetic ketoacidosis may occur in patients with type 2 diabetes, and hyperthyroidism has been associated

with DKA in type 2 diabetes.[1] Another consideration was that of ketosis-prone type 2 diabetes mellitus (also called atypical diabetes, Flatbush diabetes,[21] and diabetes type 1B), which can present as DKA in the setting of transient beta-cell dysfunction. Unlike our patient, however, such patients are commonly African-American and experience significant amelioration (or remission) of their diabetes. The presence of anti-GAD65 antibodies in our patient suggested autoimmune, or type 1, diabetes. Indeed, our patient's increasing insulin requirements over the year following her diagnosis, her persistently low C-peptide 1 month after improved glycemic control—in addition to the elevation of anti-GAD65 antibodies—are all suggestive of autoimmune-related beta-cell destruction. The prevalence of autoimmune thyroid disease (including Graves disease) is increased in patients with autoimmune diabetes mellitus,[7] and patients with newly diagnosed Graves disease have an increased frequency of anti-GAD antibodies as well as other islet-cell antibodies.[20]

Thyroid test abnormalities related to nonthyroidal illness are common in hospitalized patients and must be considered when thyroid tests are performed in the setting of DKA. Nonthyroidal illness may be accompanied by mildly to moderately low TSH values, although rarely less than 0.05 μIU/mL. T3 values generally decrease with illness of any type, and both T3 and T4 may be decreased with more severe illness. Nonetheless, laboratory tests confirmed thyrotoxicosis in our patient, and physical exam findings along with thyroid scintigraphy confirmed Graves disease.

CONCLUSION

In summary, thyrotoxicosis can precipitate DKA in patients with known and previously undiagnosed diabetes. The presenting symptoms and signs of both conditions may overlap (e.g., weight loss, nausea, tachycardia), and untoward consequences may follow delayed diagnosis of either entity. We recommend biochemical thyroid evaluation in patients with DKA who have symptoms or signs suggesting thyroid disease (e.g., goiter), those who demonstrate persistent tachycardia despite appropriate fluid resuscitation, and those with no obvious precipitating factors for DKA. However, when thyroid testing is performed in this setting, care must be taken to differentiate biochemical thyrotoxicosis from thyroid test abnormalities related to nonthyroidal illness.

REFERENCES

1. Sola E, Morillas C, Garzon S, Gomez-Balaguer M, Hernandez-Mijares A. Association between diabetic ketoacidosis and thyrotoxicosis. *Acta Diabetol.* 2002;39:235-237.
2. Bridgman JF, Pett S. Simultaneous presentation of thyrotoxic crisis and diabetic ketoacidosis. *Postgrad Med J.* 1980;56:354-355.
3. Lee HL, Yu E, Guo HR. Simultaneous presentation of thyroid storm and diabetic ketoacidosis. *Am J Emerg Med.* 2001;19:603-604.
4. Lin CH, Chen SC, Lee CC, Ko PC, Chen WJ. Thyroid storm concealing diabetic ketoacidosis leading to cardiac arrest. *Resuscitation.* 2004;63:345-347.
5. Kunishige M, Sekimoto E, Komatsu M, Bando Y, Uehara H, Izumi K. Thyrotoxicosis masked by diabetic ketoacidosis: a fatal complication. *Diabetes Care.* 2001;24:171.
6. Utiger RD. The thyroid: physiology, thyrotoxicosis, hypothyroidism, and the painful thyroid. In: Felig P, Frohman LA, eds. *Endocrinology and Metabolism*. 4th ed. New York: McGraw-Hill; 2001;261-347.
7. Cooppan R, Kozak GP. Hyperthyroidism and diabetes mellitus: an analysis of 70 patients. *Arch Intern Med* 1980;140:370-373.
8. Andersen OO, Friis T, Ottesen B. Glucose tolerance and insulin secretion in hyperthyroidism. *Acta Endocrinol (Copenh).* 1977; 84:576-587.
9. Al-Shoumer KA, Vasanthy BA, Al-Zaid MM. Effects of treatment of hyperthyroidism on glucose homeostasis, insulin secretion, and markers of bone turnover. *Endocr Pract.* 2006;12:121-130.
10. Ohguni S, Notsu K, Kato Y. Correlation of plasma free thyroxine levels with insulin sensitivity and metabolic clearance rate of insulin in patients with hyperthyroid Graves' disease. *Intern Med.* 1995;34:339-341.
11. Randin JP, Tappy L, Scazziga B, Jequier E, Felber JP. Insulin sensitivity and exogenous insulin clearance in Graves' disease: measurement by the glucose clamp technique and continuous indirect calorimetry. *Diabetes.* 1986; 35:178-181.
12. Rovira A, Valdivielso L, Ortega R, Valverde I, Herrera Pombo JL. Plasma glucose, insulin, proinsulin, C-peptide and glucagon before and after a carbohydrate-rich meal in hyperthyroid patients. *Diabete Metab.* 1987;13:431-435.
13. Jap TS, Ho LT, Won JG. Insulin secretion and sensitivity in hyperthyroidism. *Horm Metab Res.* 1989;21:261-266.
14. Bech K, Damsbo P, Eldrup E, et al. Beta-cell function and glucose and lipid oxidation in Graves' disease. *Clin Endocrinol (Oxf).* 1996;44:59-66.
15. Lam KS, Yeung RT, Ho PW, Lam SK. Glucose intolerance in thyrotoxicosis roles of insulin, glucagon and somatostatin. *Acta Endocrinol (Copenh).* 1987;114:228-234.
16. Ikeda T, Fujiyama K, Hoshino T, Takeuchi T, Mashiba H, Tominaga M. Oral and intravenous glucose-induced insulin secretion in hyperthyroid patients. *Metabolism.* 1990;39:633-637.
17. Cavallo-Perin P, Bruno A, Boine L, Cassader M, Lenti G, Pagano G. Insulin resistance in Graves' disease: a quantitative in-vivo evaluation. *Eur J Clin Invest.* 1988;18:607-613.
18. Wood ET, Kinlaw WB. Nondiabetic ketoacidosis caused by severe hyperthyroidism. *Thyroid.* 2004;14:628-630.
19. Muller MJ, Acheson KJ, Jequier E, Burger AG. Thyroid hormone action on lipid metabolism in humans: a role for endogenous insulin. *Metabolism.* 1990;39:480-485.
20. Maugendre D, Verite F, Guilhem I, Genetet B, Allannic H, Delamaire M. Anti-pancreatic autoimmunity and Graves' disease: study of a cohort of 600 Caucasian patients. *Eur J Endocrinol.* 1997;137:503-510.
21. Banerji MA, Chaiken RL, Huey H, et al. GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4. *Diabetes.* 1994:43:741-745.

Pancytopenia and Troponin Elevation Secondary to Ehrlichiosis Infection: A Case Report and Review of the Literature

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We present a case of *Ehlirchia chaffeensis* infection complicated by pancytopenia, exacerbation of heart failure (HF) symptoms, and elevation of cardiac enzymes. These symptoms may be consistent with the rarely reported myocardial involvement of ehrlichiosis, because the patient's laboratory abnormalities and HF exacerbation resolved with doxycycline therapy. We discuss the constellation of clinical and laboratory findings that may indicate the presence of ehrlichiosis-induced myocarditis.

CASE REPORT

A 74-year-old man with a medical history significant for coronary artery disease, congestive heart failure, and chronic obstructive pulmonary disease presented with a 1-week history of fever; chills; anorexia; nausea; nonbloody, nonbilious emesis; and a cough productive of white sputum. The patient denied chest pain but reported new onset dyspnea on exertion, which had left him unable to walk without severe shortness of breath. On admission the patient denied exposure to ticks or sick contacts. The patient's medical history was significant for coronary artery disease for which he had undergone 5-vessel coronary artery bypass surgery, and he had received a biventricular implantable cardioverter-defibrillator for complete heart block. He also had ischemic left ventricular dysfunction, with an estimated ejection fraction of 20%-25% on recent transthoracic echo-cardiogram, moderate aortic stenosis, chronic kidney disease, Type II diabetes mellitus, and a recently noted increase in prostate-specific antigen to 31.2.

The patient resided in Charlottesville, VA, and worked as a mechanic. He reported smoking 2-3 packs a day for 40 years and quitting 20 years ago. He also reported an extensive alcohol history, but only occasional use recently. He denied any illicit drug use. His family history was notable for coronary artery disease, hypertension, and diabetes mellitus. His medications included lisinopril, digoxin, simvastatin, ezetimibe, aspirin, sustained-release metoprolol, furosemide, inhaled fluticasone propionate and salmeterol, tiotropium bromide, and insulin. He had no known drug allergies. Review of systems other than those previously mentioned was notable for weight gain and increasing orthopnea.

On admission, the patient was febrile, with a temperature of 38.7°C. His blood pressure was 140/68 mm Hg, pulse rate 104 beats/min, respiratory rate 24 breaths/min, and oxygen saturation was 97% on 2 L of oxygen via nasal cannuli. On physical exam the patient appeared to be in no acute distress. No appreciable jugular venous distension was observed, and no cervical, axillary, or inguinal lymphadenopathy was detected. The patient was tachycardic with a normal S1 and S2; he had an S3 and a 2/6 systolic murmur best heard at the right upper sternal border but audible throughout. His lungs were clear to auscultation bilaterally, and his abdomen was soft, nontender, and without appreciable organomegaly. Extremities showed no clubbing or cyanosis, and only trace edema. His neurologic exam was grossly intact. No rashes were noted.

Laboratory evaluation revealed the following: sodium was 129 mmol/L, potassium 4 mmol/L, chloride 95 mmol/L, bicarbonate 23 mmol/L, blood urea nitrogen 30 mg/dL, creatinine 1.5 mg/dL, and glucose 302 mg/dL. Total protein was 7.3 mg/dL, albumin 4.4 g/dL, total bilirubin 1 mg/dL, alkaline phosphatase 62 U/L, alanine aminotransferase 33 U/L, and aspartate aminotransferase 45 U/L. The patient was pancytopenic, with a white blood cell count of 2,990 uL (75% neutrophils, 15% lymphocytes, 8% monocytes, 0% eosinophils, and 1% basophils).

Hemoglobin and hematocrit were both reduced at 11.5 g/dL and 34.9%, respectively (mean corpuscular volume 90.6 FL). Platelets were also low at 120 k/μL. Prothrombin time, international normalized ratio, and partial thromboplastin time were within normal limits. Arterial blood gas analysis revealed a pH of 7.47, PCO_2 of 33.3 mm Hg, and PO_2 of 107.1 mm Hg. The patient's B-type natriuretic peptide was 831 pg/mL. His initial troponin was 0.13 ng/mL, and he had a free digoxin level less than 0.15 ng/mL. An electrocardiogram showed a normal paced rhythm. His chest x-ray revealed mild pulmonary vascular congestion but no acute cardiopulmonary disease. Urinalysis demonstrated 2+ protein, trace glucose, small blood, no leukocyte esterase, and no nitrites. A urine culture demonstrated greater than 100,000 colony-forming units of *Escherichia coli* that were resistant to ciprofloxacin. Blood cultures were negative.

In the emergency department the patient was started on ceftriaxone 1 g intravenously and azithromycin 500 mg orally for presumed community-acquired pneumonia. The patient was admitted to the general medicine service, where he received continued treatment with ceftriaxone and azithromycin. He remained febrile and tachycardic. His troponins continued to rise peaking at 0.43 ng/mL 2 days after admission. This finding was thought to be secondary to the patient's tachycardia and possible demand ischemia. At this time, a transthoracic echocardiogram demonstrated global left ventricular hypokinesis but no focal wall segment abnormalities, and the estimated ejection fraction was 25%. A repeat chest x-ray showed mild pulmonary vascular congestion but no pleural effusions or focal consolidations. A repeat electrocardiogram continued to show a normal paced rhythm. The patient was not started on heparin for suspected acute coronary syndrome because his pancytopenia continued to worsen as his white blood cell count, hemoglobin, and hematocrit all dropped slightly, and his platelets reached a nadir of 66,000 uL 2 days into admission. At this time, the patient's clinical picture and mental status worsened dramatically. There was concern that he was suffering microangiopathic hemolytic anemia, and appropriate laboratory tests were performed. Prothrombin time was 16.0 seconds, international normalized ratio 1.2, and partial thromboplastin time 39.7 seconds. D-dimer and uric acid were both elevated at 928 ng/mL and 11 mg/dL, respectively. Lactate dehydrogenase was normal at 345 U/L, and haptoglobin and fibrinogen levels were elevated at 274 mg/dL and 464 mg/dL, respectively. A peripheral blood smear showed reactive lymphocytes and neutrophils but no signs of schistocytes, malignancy, or an infiltrative process. On further questioning, the patient admitted that his dogs were infested with ticks and frequently slept with him in his bed. On the basis of this new information, doxycycline was added to the patient's antibiotics, and *E. chaffeensis* titers were sent for analysis. The patient experienced a rapid resolution of his fever, shortness of breath, mental status changes, and laboratory abnormalities 2 days after the doxycycline was started, and the patient was discharged in stable condition. His *E. chaffeensis* titers returned positive at 1:128.

DISCUSSION

Ehrlichae are obligate intracellular bacteria that most often infect human hosts during the summer months. The 2 most prevalent ehrlichial infections are human granulocytic anaplasmosis (HGA), caused by *Anaplasma phagocytophilum*, and human monocytic ehrlichiosis (HME), caused by *E. chaffeensis.* These 2 diseases have similar clinical manifestations, laboratory abnormalities, and expansively affected geographic locales. However, HGA, with a reported annual incidence of 1.6 cases per million, is slightly more prevalent in the eastern north-central United States, whereas HME, with a reported annual incidence of 0.7 cases per million, is most common in the south-central US. HGA is carried by *Ixodes scapularis* or *Ixodes pacificus* ticks, with the white-footed mouse being the suspected animal reservoir. HME is carried by the *Ambylomma americanum* tick, and is suspected to be carried by the white-tailed deer.

The incubation period for HGA is typically less than 7 days but can be as long as 14 days. HGA manifests as an acute infection.[2] Nonspecific symptoms such as fever, malaise, myalgia, headache, and chills, occur in two-thirds or more of cases.[3,4] Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain occur in 50% of HME patients; cough or other evidence of respiratory involvement occurs in 25%;

and central nervous system involvement, often manifesting as changes in mental status, occurs in 20%.[5] Skin findings were absent in our patient, but this is not unexpected. Only 36% of patients with HME infection exhibit a rash,[5] and rash was present in only 1 of 41 documented HGA infections.[6] Because of the low reported incidence of rash, suspicion for coinfection with *Borrelia burgdorferi, Rickettsia rickettsii,* or *Neisseria meningitides* should be suspected when a rash is present.[7]

Along with the multitude of clinical abnormalities, many laboratory changes can be found in ehrlichial infections. Leukopenia, often accompanied by a left shift, and thrombocytopenia are the most frequent manifestations, occurring in 50%-90% of patients. Anemia, elevation of transaminases, hyponatremia, and elevated plasma creatinine concentration are other common findings.[6] Leukopenia, usually both lymphopenia and neutropenia, occurs early in the infection and usually resolves after the first week, with or without treatment.[5] This stage is often followed by a lymphocytosis with atypical lymphocytes.[2] Some authors suggest the initial neutrophil count is inversely related to the duration of symptoms before treatment.[2] The frequency of cytopenias is not explained by bacterial lysis of infected cells, because only a minority of leukocytes are infected, and platelets and erythrocytes are not infected at all.[3,4] The cytopenias are also not explained by marrow involvement, because most HME cases reveal normal or hypercellular bone marrow. Instead, the cytopenias and the elevated transaminases are thought to be explained by the detection of intrahepatic macrophage-rich inflammatory infiltrates, often accompanied by hematophagocytic cells.[8,9] The associated hyponatremia may be explained by cytokine-mediated increases in endothelial permeability.[10]

Myocardial involvement is rarely documented in ehrlichial infections.[4,11-13] Prior cases of ehrlihicial myocarditis have shown elevation of creatine kinase MB and troponin. Chest x-rays have shown cardiomegaly, interstitial edema, and bilateral pleural effusions. Electrocardiograms typically show decreased QRS amplitude in the limb leads. Echocardiograms have revealed left ventricular dilation and diffuse hypokinesis, resulting in decreased ejection fraction. Histopathologically, *E. chaffeensis* has been shown to produce myocardial inflammatory cell infiltrates with edema, while not infecting endothelial cells in vivo.[9] Some authors suggest that macrophages activated by *E. chaffeensis* infiltrate the myocardium and induce production of proinflammatory cells and cytokines,[14,15] similar to the mechanism responsible for the hepatits and hepatic necrosis induced by *E. chaffeensis.*[15,16] These mechanisms may explain the etology of the HF exacerbation in our patient, who had severe left ventricular dysfunction at baseline. Interestingly, cardiac involvement is much more frequent with Lyme disease, occurring in 1.5%-10% of cases in North America.[17] *B. burgdorferi* infection can result in cardiac conduction abnormalities and even cause complete heart block.[18] Lyme disease causes similar inflammatory cell infiltrates that lead to the cardiac manifestations of conduction system abnormalities, myocarditis, cardiomyopathy, and rarely, degenerative valvular disease.[19,20]

All of the previously mentioned clinical and laboratory changes may be caused by a variety of diseases, complicating the proper diagnosis of ehrlichiosis. There are 5 methods available for the diagnosis of HME and HGA, but indirect fluorescent antibody is widely preferred. This test uses an enzyme-linked immunosorbent assay and tests for the presence of antibodies specific to HME and HGA. Other diagnostic methods include examination of the peripheral blood smear for characteristic intraleukocytic morullae, polymerase chain reaction of HME and HGA, immunochemical staining for ehrlichial antigens in tissue, and clinical diagnosis. Though the indirect fluorescent antibody is favored, the majority of patients are seronegative during the acute phase,[3,5] and therapeutic decisions must often be based on clinical suspicion and laboratory findings.

No controlled trials have examined antimicrobial efficacy for either HME or HGA, but doxycycline is the treatment of choice on the basis of in vitro studies and retrospective analysis.[5,21,22] Tetracycline and chloramphenicol also appear to be effective. Retrospective analysis shows that patients treated with doxycycline typically defervesce in 2 to 3 days, with resolution of leukopenia and thromobocytopenia typically occurring on day 3 of treatment.[23] Doxycycline can be administered orally or intravenously at 100 mg twice daily for 10 days or for 3 to 5 days after defervescence.[24]

CONCLUSION

In conclusion, we present a case of *E. chaffeensis* infection complicated by troponin elevation and HF exacerbation. Although cardiac involvement secondary to tick-borne illnesses such as ehrlichiosis and Lyme disease is extremely rare, it should be considered in patients who present with fever, pancytopenia, troponin elevation, and symptoms of HF exacerbation. Our patient's ehrlichial titers and rapid resolution of laboratory and clinical abnormalities soon after starting doxycycline treatment are consistent with possible ehrlichial-induced HF, though there are no other objective data to support this claim.

REFERENCES

1. Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States: a practical guide for physicians and other health-care and public health professionals. *MMWR Recomm Rep.* 2006;55:1-27.
2. Aguero-Rosenfeld ME, Horowitz HW, Wormser GP, et al. Human granulocytic ehrlichiosis: a case series from a medical center in New York State. *Ann Intern Med.* 1996;125:904-908.
3. Olano JP, Walker DH. Human ehrlichioses. *Med Clin North Am.* 2002;86:375-392.
4. Paddock CD, Childs JE. Ehrlichia chaffeensis: a prototypical emerging pathogen. *Clin Microbiol Rev.* 2003;16:37-64.
5. Fishbein DB, Dawson JE, Robinson LE. Human ehrlichiosis in the United States, 1985 to 1990. *Ann Intern Med.* 1994;120:736-743.
6. Bakken JS, Krueth J, Wilson-Nordskog C, Tilden RL, Asanovich K, Dumler JS. Clinical and laboratory characteristics of human granulocytic ehrlichiosis. *JAMA.* 1996;275:199-205.
7. Bakken JS, Dumler JS. Human granulocytic ehrlichiosis. *Clin Infect Dis.* 2000;31:554-560.
8. Dumler JS, Dawson JE, Walker DH. Human ehrlichiosis: hematopathology and immunohistologic detection of Ehrlichia chaffeensis. *Hum Pathol.* 1993;24:391-396.
9. Walker DH, Dumler JS. Human monocytic and granulocytic ehrlichioses: discovery and diagnosis of emerging tick-borne infections and the critical role of the pathologist. *Arch Pathol Lab Med.* 1997;121:785-791.
10. Stone JH, Dierberg K, Aram G, Dumler JS. Human monocytic ehrlichiosis. *JAMA.* 2004;292:2263-2270.
11. Williams JD, Snow RM, Arciniegas JG. Myocardial involvement in a patient with human ehrlichiosis. *Am J Med.* 1995;98:414-415.
12. Vanek NN, Kazi S, Cepero NM, Tang S, Rex JH. Human ehrlichiosis causing left ventricular dilatation and dysfunction. *Clin Infect Dis.* 1996;22:386-387.
13. Malik A, Jameel MN, Ali SS, Mir S. Human granulocytic anaplasmosis affecting the myocardium. *J Gen Intern Med.* 2005;20:C8-C10.
14. Lee EH, Rikihisa Y. Anti-Ehrlichia chaffeensis antibody complexed with E. chaffeensis induces potent proinflammatory cytokine mRNA expression in human monocytes through sustained reduction of IkappaB-alpha and activation of NF-kappaB. *Infect Immun.* 1997;65:2890-2897.
15. Ismail N, Soong L, McBride JW, et al. Overproduction of TNF-alpha by CD8+ type 1 cells and down-regulation of IFN-gamma production by CD4+ Th1 cells contribute to toxic shock-like syndrome in an animal model of fatal monocytotropic ehrlichiosis. *J Immunol.* 2004;172:1786-1800.
16. Sehdev AE, Dumler JS. Hepatic pathology in human monocytic ehrlichiosis: Ehrlichia chaffeensis infection. *Am J Clin Pathol.* 2003;119:859-865.
17. Wang G, van Dam AP, Schwartz I, Dankert J. Molecular typing of Borrelia burgdorferi sensu lato: taxonomic, epidemiological, and clinical implications. *Clin Microbiol Rev.* 1999;12:633-653.
18. McAlister HF, Klementowicz PT, Andrews C, Fisher JD, Feld M, Furman S. Lyme carditis: an important cause of reversible heart block. *Ann Intern Med.* 1989;110:339-345.
19. Sigal LH. Early disseminated Lyme disease: cardiac manifestations. *Am J Med.* 1995;98:25S-28S; discussion 28S-29S.
20. Lelovas P, Dontas I, Bassiakou E, Xanthos T. Cardiac implications of Lyme disease, diagnosis and therapeutic approach. *Int J Cardiol.* 2008;129:15-21.
21. Dumler JS, Bakken JS. Ehrlichial diseases of humans: emerging tick-borne infections. *Clin Infect Dis.* 1995;20:1102-1110.
22. Brouqui P, Raoult D. In vitro antibiotic susceptibility of the newly recognized agent of ehrlichiosis in humans, Ehrlichia chaffeensis. *Antimicrob Agents Chemother.* 1992;36:2799-2803.
23. Everett ED, Evans KA, Henry RB, McDonald G. Human ehrlichiosis in adults after tick exposure. Diagnosis using polymerase chain reaction. *Ann Intern Med.* 1994;120:730-735.
24. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2006;43:1089-1134.

Novel Precipitants of Apical Ballooning Syndrome (Takotsubo Cardiomyopathy)

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Apical ballooning syndrome (ABS) is an emerging clinical condition characterized by transient left ventricular (LV) wall motion abnormalities, mild increases in biomarkers of cardiac damage, and electrocardiographic evidence of ischemia. Symptoms are usually preceded by a stressful emotional or clinical event such as exacerbation of chronic obstructive pulmonary disease or altercations with family members. We report 3 cases of ABS precipitated by situations not previously described in the medical literature.

First described in 1991, transient LV ABS, or Takotsubo cardiomyopathy, occurs primarily in female patients who report sudden onset of symptoms similar to those of acute coronary syndrome.[1] Imaging of the LV shows wall-motion abnormalities that do not fit a single coronary artery distribution. Patients usually have mild increases in cardiac troponin and electrocardiographic evidence of ischemia.

Frequently, patients are able to recall a stressful event prior to the onset of symptoms. These stressful events may be emotional, such as having a family member arrested or having a heated argument, or physiological, such as acute worsening of a clinical disease such as asthma or chronic obstructive pulmonary disease. Onset related to precipitating events such as these is not included in the proposed diagnostic criteria for ABS[2] but is an interesting feature of the illness.

We report the summaries of 3 patients cared for at the University of Virginia Health System who suffered ABS and had precipitating stressors that are described here but have not been previously reported in the literature.

CASE REPORTS

Patient 1: Kyphoplasty

A 76-year-old woman was undergoing kyphoplasty for a vertebral fracture. Shortly after waking from her procedural sedation, the patient complained of chest pain. Transthoracic echocardiogram (TTE) was performed and showed global LV dysfunction. Electrocardiography showed diffuse ST-segment elevation. The patient had a TTE done just 2 weeks

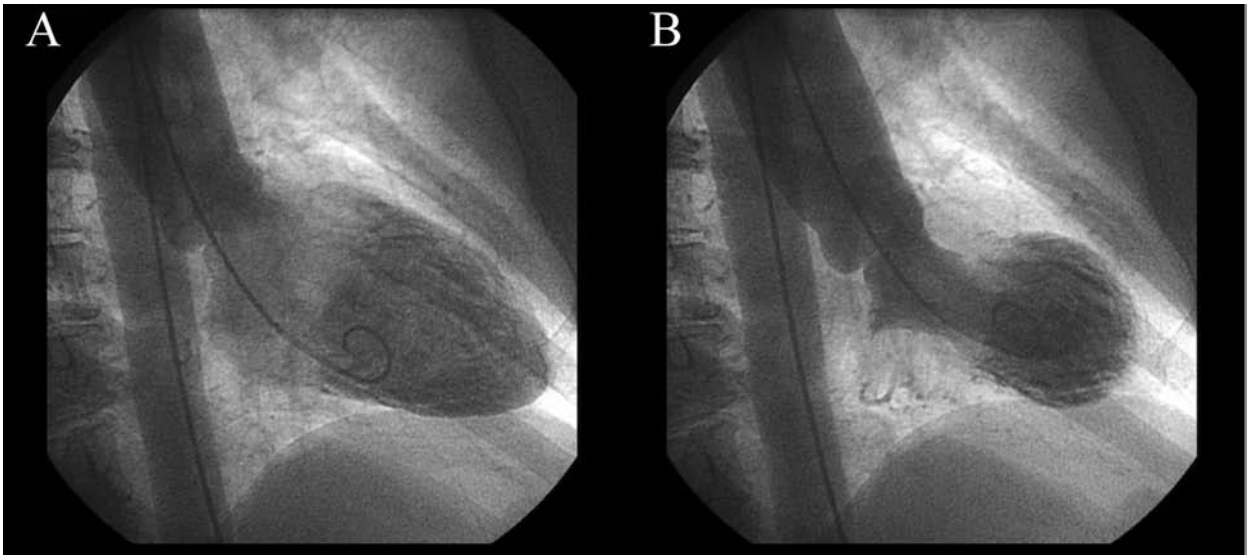

Figure 1. A. Still-frame image from the left ventriculogram with the heart in diastole for patient 3, as described in the text. B. Apical ballooning and basal contraction during systole, classically described in apical ballooning syndrome.

prior to this event, which showed normal LV function. Cardiac catheterization showed 3+ mitral regurgitation and ejection fraction of 25%. Four days later, repeat TTE showed an ejection fraction of 55% and resolution of the mitral regurgitation.

Patient 2: Electroconvulsive Therapy

A 53-year-old woman suffered from severe depression and elected to undergo electroconvulsive therapy for treatment. Immediately on awakening, the patient reported crushing substernal chest pain. Electrocardiogram showed T-wave inversions in leads 1, aVL, v5, and v6. TTE showed global LV dysfunction. Coronary catheterization revealed no evidence of atherosclerosis. Six months after discharge, the patient was seen for outpatient follow-up and had normal LV function.

Patient 3: Colonoscopy Preparation

A 66-year-old woman was prescribed bowel preparation with polyethylene glycol for screening colonoscopy. The patient had a long history of atypical chest pain, and recent nuclear stress test results were interpreted as indicating low risk for coronary disease. The patient developed chest pain while taking the polyethylene glycol and was reassured by her cardiologist. When the symptoms did not abate, the patient was evaluated in the emergency department and was noted to have an elevated troponin level. Coronary catheterization revealed no coronary stenoses and global LV dysfunction (Figure 1). Echocardiography performed 3 weeks later showed normal LV function.

DISCUSSION

These patients are a subset of cases from a larger retrospective case series we investigated at the University of Virginia Health System. Each patient described in this report experienced a stressor, either emotional or physiologic, that has not been previously described in association with ABS. Among the 31 cases in our series, there was a nearly even breakdown in the number of patients with a physiologically stressful precipitant (11 patients, 35%), an emotionally stressful precipitant (10 patients, 32%), and no identified precipitant (10 patients, 32%) (Table 1). This breakdown is similar to other large case series that have been reported.[3,4]

Multiple pathophysiologic explanations for ABS have been proposed, but none is universally accepted at this time. One early leading theory was that transient multivessel vasospasm was the culprit. Transient occlusion of a large wraparound

Table 1. Precipitating Events for Apical Ballooning Syndrome in Patients Treated at the University of Virginia Health System

Case No.	Clinical History	Stressor
1	Recent death of a friend	Emotional
2	Lung abscess	Clinical
3	Chronic abdominal pain exacerbation	Clinical
4	Received bad news	Emotional
5	Chronic obstructive pulmonary disease exacerbation	Clinical
6	Doing chores at home	Neither
7	Sudden onset angina	Neither
8	Watching television	Neither
9	Son arrested for drug possession	Emotional
10	Electroconvulsive therapy	Emotional
11	Lawnmower caught fire	Emotional
12	Severe migraine	Clinical
13	Very high anxiety about health	Emotional
14	Chronic obstructive pulmonary disease exacerbation	Clinical
15	Coiling of cerebral aneurysm	Clinical
16	Anniversary of death of significant other	Emotional
17	Sudden onset angina	Neither
18	Sudden onset angina	Neither
19	Sudden onset angina	Neither
20	Chronic obstructive pulmonary disease exacerbation	Clinical
21	Sudden onset angina	Neither
22	Chronic obstructive pulmonary disease exacerbation	Clinical
23	Diverticulitis	Clinical
24	Sudden onset angina	Neither
25	Recent motor vehicle crash and trauma	Clinical
26	Sudden onset angina	Neither
27	Stressful death of husband	Emotional
28	Son arrested	Emotional
29	Disagreement with daughter	Emotional
30	While hiking	Neither
31	Colonscopy preparation	Clinical

left anterior descending artery has been suggested as a mechanism for ABS. Subsequent researchers have reported large series documenting that neither vasospasm nor wraparound anatomy are consistently found in ABS patients. It is well known that acute intracranial events, such as hemorrhage and hematoma, can induce LV dysfunction similar to ABS through an unknown neurocardiogenic mechanism. Many researchers now believe that patients with microvascular dysfunction may be predisposed to catecholamine-induced myocardial stunning that manifests as ABS.

The typical clinical course of most patients includes full recovery from symptoms within days and return of normal LV function within weeks, although there are documented cases of ejection fraction normalization occurring in less than 2 days. Some patients do require critical care support, vasopressors, and endotracheal intubation. In our series, 6 patients (19%) required these interventions, and all survived to discharge. Recommended treatments are based on expert opinion and are largely drawn from clinical experience treating patients with acute decompensated heart failure. There are no specific therapies and treatment is supportive.

CONCLUSIONS

Awareness of ABS is important for clinicians because ABS is more common than suspected, with studies suggesting up to a 2% incidence among patients with suspected acute coronary syndrome. We document 3 cases of ABS with unique stressors, highlighting the importance of a thorough history in identifying stressors beyond those that are classically described. Greater awareness of this condition will also help physicians to counsel patients on the expected course, which is different from both acute coronary syndrome and acute decompensated heart failure.[5]

REFERENCES

1. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. *J Cardiol.* 1991;21(2):203-214.
2. Bybee KA, Kara T, Prasad A, Lerman A, et al. Transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med.* 2004;141:858-865.
3. Desmet WJR Adriaenssens BFM, Dens JAY. Apical ballooning of the left ventricle: first series in white patients. *Heart.* 2003;89:1027-1031.
4. Kurisu S, Sati H, Kawagoe T, et al. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J.* 2002;143:448-455.
5. Pilgrim TM, Wyss TR. Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome: a systematic review. *Int J Cardiol.* 2008;124:283-292.

Capecitabine-Associated Cardiotoxicity: Case Report and Review

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Cardiotoxicity associated with the chemotherapeutic drug capecitabine has been reported since 2001. To further characterize this complication, we analyzed data collected from all available case reports of capecitabine-associated carditoxicity and from one of our own patients and also compared the toxicity of capecitabine with that of 5-fluorouracil (5-FU), a related chemotherapeutic drug that has been associated with cardiotoxicity. The clinical presentation of cardiotoxicity associated with capecitabine was similar to that of 5-FU, often manifesting as the acute coronary syndrome. Time from first dose to onset of symptoms was longer (mean 4.1 days) for capecitabine than for 5-FU alone. This difference likely reflects a cumulative dose effect, which was found to occur at a mean drug load of 8.4 grams/m^2. Coronary vasospasm and direct toxic effects are possible mechanisms of injury, but definitive evidence is lacking. Neither coronary artery disease nor its risk factors are clear predictors of cardiotoxicity. Treatment includes temporary discontinuation of therapy and initiation of acute coronary syndrome protocol. Resolution of symptoms can be expected within 24-48 hours. Administering capecitabine at a reduced dose of 50%-70% with concurrent calcium channel blocker and nitrate therapy may be a reasonable alternative to permanent discontinuation of therapy.

INTRODUCTION

Capecitabine is an orally administered carbamate member of the fluoropyrimidine class of chemotherapeutics approved for the treatment of colorectal and metastatic breast cancer. Although cardiotoxicity is a well-described side effect of 5-fluorouracil (5-FU), a low incidence of serious cardiac events was observed in phase III trials for capecitabine.[1] Case report data suggest that capecitabine may be associated with cardiotoxicity similar to that which occurs with 5-FU, including the acute coronary syndrome, but data are limited regarding the clinical presentation, mechanism, risk factors, and treatment of this complication. To further define this adverse effect of chemotherapy, we collected and analyzed data from all reported cases since adverse cardiac events were first described in 2001 and from a previously unreported case patient treated at the University of Virginia Health System.

CASE REPORT

A 59-year-old female patient with grade 2-3 basaloid squamous cell carcinoma of the anal canal underwent transanal excision at the University of Virginia Health System. She had mild hyperlipidemia and no history of cardiac disease. Treatment with curative intent was initiated with a regimen that included mitomycin-C infusion on day 1, plus combined chemoradiotherapy. Oral capecitabine was administered at 1580 mg/m^2 daily in chronomodulated divided doses with concurrent intensity-modulated radiation therapy to an intended treatment-goal dose of 54 Gy in 30 fractions. On the fourth day of irradiation, approximately 5 hours after receiving her morning dose of capecitabine and after walking her dog, the patient experienced chest pressure and dull jaw and left arm pain accompanied by nausea and dyspnea. The pain lasted about 1 hour and resolved with rest. She subsequently experienced 2 more episodes that day, each occurring after minimal activity and with similar symptoms. She was awakened by identical pain the following morning, and presented to the emergency department after developing severe shortness of breath and palpitations, which resolved spontaneously. Electrocardiography (ECG) showed sinus tachycardia and diffuse, nonspecific ST-T wave changes. Troponin I was mildly elevated on admission. A transthoracic echocardiogram revealed a normal ejection fraction and no segmental wall-motion abnormalities. The patient underwent cardiac catheterization, which showed no evidence of coronary stenosis.

The patient's radiation therapy with adjunct capecitabine treatment was resumed the following

day and resulted in a recurrence of her anginal pain, which was successfully treated with nitrates. The next day, she again experienced exertional chest pain, which lasted 3 hours and was relieved by sublingual nitroglycerin. The patient was readmitted to the hospital, and ECG at that time displayed sinus tachycardia in the setting of negative troponins. Because the treatment of her anal carcinoma was of curative intent, the decision was made to continue capecitabine therapy at a reduced dose with concurrent oral isosorbide mononitrate administration. A total daily capecitabine dose of 765 mg/m^2 in 2 divided doses was administered for the next 6 days, with no recurrence of symptoms. Capecitabine therapy was then increased to a total daily dose of 1315 mg/m^2, and the patient was able to complete the 30-day course of intensity-modulated radiation therapy without further incidents. Throughout the course of chemoradiotherapy the patient did not experience any clinically significant signs of mucosal toxicity or cytopenias.

MATERIALS AND METHODS

We performed a Medline search using the keywords *capecitabine* plus either *cardiotoxicity* or *coronary spasm*, and identified 13 reports, 12 in English and 1 in French, which described a total of 20 patients. To case data from these reports we added data from the case described above, thus collecting data for a total of 21 reported cases of acute angina occurring after capecitabine monotherapy.[2-14] Case reports were reviewed for patient demographic data, type of cancer, adjunct therapies, and cardiac risk factors. Presenting symptoms, time to onset of symptoms from first dose, and capecitabine dose were recorded. A total drug load was calculated by summing the doses given during the interval prior to the onset of symptoms. In cases in which the time of symptom onset fell between divided doses and was not specified, the time to onset and total drug load were calculated using the interval extending until just after the administration of the last known dose prior to symptoms. Cardiac evaluation data were also recorded, including cardiac enzymes, ECG, echocardiogram, stress test, and coronary angiogram results.

RESULTS

Among the 20 cases identified in our literature review and the patient we describe (Table 1), all reported symptoms were consistent with first-episode anginal chest pain (Table 2). Reported cardiac evaluation varied; of 12 cases for which ECG results were reported, 8 (66.7%) showed changes consistent with ischemia. Two of 7 cases (28.6%) with reported echocardiogram results also had wall-motion abnormalities, 3 of 4 cases (75.0%) had reported stress test results that were positive for inducible ischemia, and 3 of 9 cases (33.3%) with reported cardiac enzyme measurements described increases in cardiac enzymes. For 8 cases cardiac catheterization results were reported, and in all of these cases cardiac catheterization revealed no significant coronary disease.

Cancers requiring chemotherapy included colorectal cancer in 12 patients, gastric cancer in 4 patients, breast cancer in 4 patients, and ovarian cancer in 1 patient. Cases included equal numbers of male and female patients. The mean age of all patients was 58 years (range 34-81 years). Of 19 cases for which risk factors for coronary artery disease were reported, 9 patients (50%) had no risk factors, 5 (27.8%) had 1 risk factor, and 5 (27.8%) had preexisting coronary artery disease. Two of these 19 case patients had reported cardiotoxicity on prior 5-FU exposure.

In all cases capecitabine was administered in divided doses, with a mean daily dose of 1762.5 mg/m^2 (range 1500-2700 mg/m^2 per day). The mean time from first dose to onset of symptoms was 4.1 days (median 2 days, range 3 hours to 17 days). The calculated mean total drug load was 8.4 grams/m^2 (median 5.3 grams/m^2, range 1.25-35 grams/m^2).

DISCUSSION

Capecitabine undergoes a multistep enzymatic conversion that culminates in the production of its active metabolite, 5-FU, preferentially within tumor tissue.[2] Cardiotoxicity is a well-known side effect of 5-FU, first described in 1969 as part of a multidrug chemotherapeutic regimen,[15] and later widely reported with 5-FU monotherapy.[16] Although the cardiotoxicity of 5-FU has been extensively studied, far fewer studies have been reported concerning capecitabine-induced cardiotoxicity.

INCIDENCE

The reported incidence of 5-FU–associated cardiac events varies widely, from 0.55% to 18%.[13,15,17,18] Because of the limited number of reported cases of

Table 1. Cases of Capecitabine-Induced Cardiotoxicity*

Case No.	Source (Ref #)	Symptoms	Diagnostic results	Capecitabine Dose, mg/m^2	Other Treatment	Time to Symptom Onset, h	Total Drug Load, g	Sex	Age, y	Cardiovascular Risk Factors	Type of Cancer
1	(2)	• Chest pain • Nausea • Dyspnea at rest & on exertion	• ECG WNL • Stress echo ST elevation, changes in precordial & inferior leads • CCath WNL	825 BID	• Oxaliplatin • Radiotherapy	408	28.05	M	71	• None	Rectal adenocarcinoma
2	(3)	•Angina on exertion	• ECG WNL • Echo WNL • Stress test 2-mm ST elevation in anterior-lateral leads	2000 QD	• Prior cyclophosphamide, methotrexate, and 5-FU	48	4	F	44	• None	Infiltrating ductal breast carcinoma
3	(4)	• Chest pain • Nausea & vomiting	• ECG new multidistribution TWI • Repeat ECG ST elevation multidistribution • CCath WNL • CK & troponin WNL	2500 QD	• Concurrent irinotecan+oxaliplatin+raltitrexed • Prior 5-FU	36	7.5	M	60	• Prior 5-FU ST elevation • Angina	Rectal adenocarinoma
4	(5)	• Chest pain	• ECG nonspecific ST changes • Troponin WNL • Stress test 4-mm elevation in inferiolateral leads • CCath WNL	2000 BID	• None	48	8	F	54	• None	Colon adenocarcinoma
5	(6)	• Angina	• ECG WNL • CCath WNL • Troponin WNL	1000 BID	• Concurrent irinotecan • Prior FA+5-FU	48	3	M	57	• Prior 5-FU ST elevation • Angina • Prior troponin elevation • Smoking	Colon adenocarcinoma
6	(7)	• Angina at rest	• ECG ST elevation • Echo WNL • Troponin WNL • CCath WNL	1500 QD	• Vinorelbine • Radiotherapy	48	3	F	63	• HTN	Breast carcinoma with liver metastasis
7	(8)	• Angina	• NR	2000 QD	• NR	NR	NR	NR	39	• NR	Gastric carcinoma
8	(9)	• Chest pain at rest.	• ECG ischemic changes in inferior leads, TWI inferior & anteriolateral •Troponin WNL •Echo LVH	2500 QD	• Raltitrexed	3	1.25	F	81	• HTN	Sigmoid adenocarcinoma
9	(10)	• Angina	• NR	1500 BID	• NR	48	6	F	44	• None	Ovarian carcinoma
10	(10)	• Angina • Nausea	• ECG ST changes	1000 BID	• Irinotecan	48	4	M	60	• None	Metastatic colon carcinoma

11	(10)	• Chest pain • Nausea • Tachycardia • Hypotension • Death	• ECG myocardial infarction • Echo hypokinesia • CK & Troponin elevated	1000 BID	• NR	48	4	M	68	• None	Colon carcinoma
12	(11)	• Chest pain	• ECG anterior-lead ischemia	NR	• NR	NR	NR	F	41	• NR	Metastatic breast carcinoma
13	(12)	• Chest pain • Dyspnea	• ECG ischemic changes in inferolateral leads • Troponin mildly elevated • Echo hypokinetic anterior septum • CCath WNL	1875 QD	• Cyclophosphamide, doxorubicin, 5-FU, tamoxifen, paclitaxel, docetaxel, and letrozole	72	5.625	F	52	• Smoking	NR
14	(13)	• Angina	• NR	1250 BID	• NR	120	10	F	67	• Smoking • Angina	Colorectal adenocarcinoma
15	(13)	• Angina	• NR	1250 BID	• NR	48	2.5	M	73	• Angina	Colorectal adenocarcinoma
16	(13)	• Angina	• NR	1250 BID	• NR	360	35	M	77	• Smoking • HTN • Angina • Cardiac insufficiency	Colorectal adenocarcinoma
17	(13)	• Angina, • Dyspnea	• NR	1000 BID	• Carboplatin and docetaxel	96	6	M	57	• Smoking	Gastric carcinoma
18	(13)	• Angina	• NR	1000 BID	• Carboplatin and docetaxel	72	4	F	34	• None	Gastric carcinoma
19	(13)	• Angina • Arrythmia	• NR	1000 BID	• Carboplatin and docetaxel	168	12	M	70	• None	Gastric carcinoma
20	(14)	• Chest pain	• ECG WNL • Troponin WNL • Echo WNL • Stress test WNL • CCath WNL	1350 BID	• Concurrent capecitabine and oxaliplatin • Prior 5-FU, leucovorin, and irinotecan	72	8.1	M	54	• Smoking	Rectal adenocarcinoma with metastasis to liver and diaphragm
21	Our case	• Chest Pain • Jaw tightness	• ECG WNL • Troponin elevated • CCath WNL	3000 QD	• Mitomycin-C • Radiotherapy	96	10	F	59	• Hyperlipidemia	Squamous cell rectal carcinoma

*ECG indicates electrocardiograph; WNL, within normal limits; CCath, cardiac catheterization; BID, twice a day; Echo, echocardiogram; QD, once a day; 5-FU, 5-fluorouracil; TWI, T-wave infarct; CK, creatine kinase; HTN, hypertension; NR, not reported; LVH, left-ventricular hypertrophy.

capecitabine-associated cardiotoxicity, accurate estimation of the incidence of cardiac effects with this agent is difficult. One retrospective analysis of phase III data from nearly 1200 patients with metastatic colorectal cancer randomized to capecitabine monotherapy or 5-FU infusion found similarly low incidences of cardiovascular complications in both treatment groups, reporting a 3% incidence of all adverse cardiac events, with 0.7% of the 5-FU treatment group experiencing serious adverse effects compared to 0.8% of the capecitabine group.[19] A recent prospective study including 153 patients receiving capecitabine and oxaliplatin therapy for colorectal cancer revealed a significantly higher (6.5%) overall incidence of cardiotoxicity, including a 4.6% incidence of angina-like pain,[17] results suggesting that variation in the incidence of cardiotoxicity with capecitabine is similar to that with 5-FU.

CLINICAL PRESENTATION

Although multiple presentations of cardiotoxicity attributed to 5-FU have been reported, including dysrhythmia, heart failure, cardiogenic shock, myocardial infarction, and sudden death, angina-type chest pain remains the most common clinical presentation, reported in 62%-89% of cases of cardiotoxicity.[15,20,21] Ischemic changes on ECG have been reported in as many as 88% of cases,[18,20] and

Table 2. Demographic Data, Risk Factors, and Cardiac Evaluation

Demographic Data and Risk Factors	**No. of Cases Reported (% of Total Cases)**	**Results**
Age, y	21 (100%)	
Mean		58
Range		(34-81)
Sex	20 (95%)	
Male		10 (50%)
Female		10 (50%)
Type of cancer	21 (100%)	
Colorectal		12 (57.2%)
Gastric		4 (19%)
Breast		4 (19%)
Ovarian		1 (4.8%)
Daily capcitabine dose, mg/m^2	21 (100%)	
Mean		2201.2
Range		(1650-4000)
Time to onset of symptoms, days	19 (90%)	
Mean		4.1
Median		2
Range		(3 hours-17 days)
Total capcitabine drug load , mg/m^2	19 (90%)	
Mean		8.53
Median		6
Range		(1.25-35)
Cardiac Risk Factors	19 (90%)	
Preexisting coronary artery disease		5 (26.3%)
1 Risk factor		5 (26.3%)
0 Risk Ffactor		9 (47.4%)
Prior 5- fluorouracil cardiotoxicity	19 (90%)	2 (10.5%)
Reported Cardiac Evaluation	**Cases Reported (% Total Cases)**	**No. Tests Positive for Signs of Cardiotoxicity (% Reported)**
Electrocardiogram	12 (57%)	8 (66.7%)
Echocardiogram	7 (33.3%)	2 (28.6%)
Cardiac enzymes	9 (42.9%)	3 (33.3%)
Cardiac catheterization	8 (38%)	0 (0%)
Stress test	4 (15%)	3 (75%)

echocardiography revealing temporary regional or global left-ventricular dysfunction occurred in 24%-56% of cases in which cardiotoxicity was reported.[13,15,18] Serum levels of cardiac enzymes often remain within normal limits, and coronary angiography in the absence of prior cardiac history is rarely positive for significant stenosis.[15,18]

In comparison, our data from cases of capecitabine-induced cardiotoxicity revealed several similarities in presentation. As with 5-FU, angina was the predominant presenting symptom, occurring in all of the cases. Electrocardiogaphic changes consistent with ischemia in one or multiple vascular distributions were present in a similar fraction of the cases (66.7%), as was hypokinesis on echocardiography (28.6%). Although a significant number of the cases in our series did report elevations in cardiac enzymes (33.3%) or inducible ischemia on stress testing (75.0%), in cases in which it was performed coronary angiography was negative .

Despite the similarity of the presenting symptoms and diagnostic results, our series revealed important differences in the timing and onset of symptoms in capecitabine-induced angina compared to similar events reported with 5-FU. The onset of 5-FU cardiotoxicity in the majority of cases occured within hours after the start of the initial infusion to 18 hours following its completion.[7,15,22] This time of onset suggests that 5-FU cardiotoxicity is a result of a peak-dose effect, because infusional 5-FU requires little time to reach a peak dose. In contrast, in our series the onset of cardiotoxicity in patients treated with capecitabine occurred at a mean of 4.1 days after administration of the first oral dose, with a median of 2 days and a range of 3 hours to 17 days.

This substantially longer time to onset of symptoms supports the suggestion by Frickhofen et al[4] that myocardial effects associated with capecitabine are likely the result of a cumulative dose effect rather than a peak effect. Plasma concentrations of 5-FU after intravenous infusion have been reported to be many-fold higher than those of capecitabine, whereas capecitabine produces large serum concentrations of a 5-FU precursor, 5'-DFUR (doxifluridine), thus providing a long-lasting source potentially responsible for the cumulative drug effect.[23] This theory is further supported by our total drug-load data calculated from case reports. We found the mean cumulative total drug load at which cardiotoxicity was reported to be 8.4 grams/m^2, with a median of 5.3 grams/m^2. Clinically, this distinction between the onset of 5-FU and capecitabine cardiotoxicity suggests that delayed cardiotoxicity with capecitabine can be expected beyond the time frame attributable to absorption alone, and provides a window of reference during which increased vigilance for possible cardiotoxicity should be maintained.

MECHANISM

Although ischemia secondary to coronary vasospasm is generally accepted as the cause of angina-type pain associated with 5-FU treatment, the exact mechanism of cardiotoxicity remains unknown. Spasm of epicardial coronary arteries or microvasculature has been suspected clinically on the basis of inducible ST-elevations during stress test or segmental wall-motion abnormalities on echocardiography in the setting of normal coronary angiography findings.[2] This theory is supported by a report of coronary vasospasm observed during angiography in a patient experiencing chest pain during 5-FU treatment.[24] This vasospastic phenomenon may be accounted for in part by studies implicating 5-FU in endothelin-1 release and endothelial activation.[3]

In addition, evidence for direct toxicity to endothelial cells and cardiomyocytes has been identified in rabbit models, and the 5-FU metabolites fluoroacetate and fluorocitrate have been shown to interfere with myocardial cell metabolism via depletion of high-energy phosphates or inhibition of the tricarboxylic acid cycle, also potentially leading to myocardial hypoxia and ischemic changes.[15,18,25] Other suggested mechanisms of myocardial injury include thrombogenic effects and autoimmune reaction.[17]

Capecitabine-induced cardiotoxicity may be mediated through 5-FU rather than through upstream metabolites, and therefore capecitabine and 5-FU likely share a common mechanism of inducing myocardial injury.[4] Another mechanism may involve thymidine phosphorylase (TP), an enzyme required for the activation of the pyrimidine nucleoside phosphorylase that converts 5'-DFUR to 5-FU in tumor tissue. TP is an angiogenic peptide identical to platelet-derived endothelial cell growth factor[2] and has been shown to be concentrated in tumor tissue, where it is thought to be produced by

infiltrating nonneoplastic cells responding to hypoxia.[26]

The increased concentration of TP in tumor tissue is thought to play a role in the selective metabolism of capecitabine to 5-FU in neoplastic tissue, as well as conveying a superior side-effect profile. TP may also be present in increased concentrations in areas of myocardial ischemia, where it may contribute to collateral angiogenesis in response to hypoxic conditions in these areas. This effect suggests that subclinical myocardial ischemia may predispose patients to capecitabine cardiotoxicity via the same mechanism that gives the agent its antineoplastic properties.[4]

RISK FACTORS

Despite several attempts to identify risk factors for fluoropyrimidine-associated cardiotoxicity, data remain equivocal for both 5-FU and capecitabine. Whereas prospective studies by La Bianca et al[27] and Meyer et al[22] found an increased risk of 5-FU cardiotoxicity in patients with preexisting coronary artery disease (CAD), a metaanalysis by Robben et al[20] detected no association with cardiotoxicity and CAD for age- and sex-matched patients. Jensen et al[13] also failed to implicate CAD as a risk factor for cardiotoxicity but did report a correlation of preexisting CAD to higher-grade cardiotoxicity.

In a prospective trial of colorectal cancer patients treated with capecitabine and oxaliplatin, Ng et al[17] observed that CAD appeared to be associated with an increased risk for cardiotoxicity, but this finding did not reach statistical significance owing to low numbers of study patients. Risk factors for CAD did not demonstrate any correlation with cardiac events in this trial, however, because the vast majority (84%) of patients with cardiotoxicity had only 0 or 1 risk factor. These results are consistent with the dichotomous results identified in our data. We found that of 18 cases reporting risk factors for CAD, 5 patients (27.8%) had known ischemic heart disease, whereas 13 patients (72.2%) had either 0 or 1 risk factor. These data suggest that although CAD may predispose patients to capecitabine-induced cardiac injury, patients with little or no risk for atherosclerotic CAD appear to be at least equally vulnerable to cardiotoxicity.

Other risk factors associated with 5-FU cardiotoxicity include previously undetected myocardial ischemia,[28] dihydropyrimidine dehydro-genase deficiency marked by excessive mucosal toxicity,[29] prior cardiac radiotherapy, and prior or concomitant anthracycline-based chemotherapy,[22] none of which were reported in any of the cases included in our analysis.

TREATMENT

Because fluoropyrimidine agents are included in first-line treatment protocols for many malignancies and have been shown to improve survival when used in combined chemo-radiotherapy,[30] the presentation of cardiotoxicity after chemotherapy with 5-FU or capecitabine can be a serious treatment obstacle. The reports in this series included inconsistent data regarding approaches to this problem and generally described the use of nitroglycerin or calcium-channel blockers targeted toward acute symptom relief. Although nitroglycerin is known to be effective in the acute setting, the benefit of prophylactic nitrates or calcium channel blockers as a means to continue fluoropyrmidine therapy is unclear.[13,15] Discontinuation of the agent is considered the only definitive intervention, with full resolution of symptoms reported within 31 hours with 5-FU and 45 hours for capecitabine.[13] For 5-FU, the rate of recurrent cardiotoxicity when treatment is resumed is known to be high, and only one of the cases in this series describes an attempt to resume treatment with capecitabine.[20]

In a recent study by Jensen et al,[13] however, a 50%-70% reduction of original treatment dose, administered alone or in combination with antianginal therapy, allowed successful continuation of chemotherapy with no further cardiotoxicity in the majority of study patients. These results suggest that discontinuation of fluoropyrimidine therapy after cardiac side effects may not be necessary in all cases. This study corroborates our anecdotal experience, in which our patient was successfully maintained on capecitabine therapy after an initial 50% dose reduction and subsequent titration up to a dose of 83.3% of the original while receiving concomitant long-acting nitrate therapy.

CONCLUSION

This review of cases corroborates reports of serious cardiotoxicity associated with capecitabine, often presenting as myocardial ischemia during the first 2 to 4 days of treatment. Although the mechanism of

injury has yet to be fully elucidated, toxicity appears to be attributable to a cumulative dose effect mediated by preferential conversion to 5-FU by thymidine phosphorylase. Larger studies will be necessary to accurately determine the incidence and identify any risk factors that may predispose patients to this complication.

Treatment recommendations include a full cardiac evaluation, including ECG and measurement of cardiac enzymes. Although coronary angiography in the majority of cases is negative, this modality remains the gold standard to rule out thrombotic coronary vascular occlusion, especially in patients with multiple risk factors for CAD. Treatment of the acute coronary syndrome is appropriate pending angiography results. Capecitabine should be stopped immediately, and complete resolution of symptoms can be expected within 48 hours after the last dose. Because of the potential for improved tumor local control or overall survival with capecitabine treatment,[30] continuation of therapy at 50%-70% of the original dose should be considered after the resolution of cardiotoxicity. Concurrent administration of prophylactic calcium channel blockers and nitrates may serve to prevent further symptoms.

REFERENCES

1. Cassidy J, Twelves C, Van Cutsem E, et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with 5-fluorouracil/leucovorin. *Ann Oncol.* 2002;13:566-575.
2. Arbea L, Coma-Canella I, Martinez-Monge R, et al. A case of capecitabine-induced coronary microspasm in a patient with rectal cancer. *World J Gastroenterol.* 2007;13:2135-2137.
3. Sestito A, Sgueglia GA, Pozzo C, et al. Coronary artery spasm induced by capecitabine. *J Cardiovasc Med.* 2006;7:136-138.
4. Frickhofen N, Beck F-J, Jung B, et al. Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. *Ann Oncol.* 2002;13:797-801.
5. Wijesinghe N, Thompson PI, McAlister H. Acute coronary syndrome induced by capecitabine therapy. *Heart Lung Circ.* 2006;15:337-339.
6. Aksoy S, Karac B, Dincer M, et al. Common etiology of capecitabine and fluorouracil-induced coronary vasospasm in a colon cancer patient. *Ann Pharm.* 2005; 39:573-574.
7. Schnetzler B, Popova N, Collao Lamb C, et al. Coronary spasm induced by capecitabine. *Ann Oncol.* 2001;12:723-725.
8. Bertolini A, Flumano M, Fusco O, et al. Acute cardiotoxicity during capecitabine treatment: a case report. *Tumori.* 2001;87:200-206.
9. Desrame J, Bronstein J-A, Triolet C, et al. Coronary insufficiency after an oral intake of capecitabine. *Gastro Clin Biol.* 2001;25:829-830.
10. Labadie J, Kuppens IELM, Boot H, et al. Capecitabine induces severe angina-like chest pain. Ann Int Med. 2004;140:494-495.
11. Cardinale D, Colombo A, Colombo N. Acute coronary syndrome induced by oral capecitabine. *Can J Cardiol.* 2006; 22:251-253.
12. Singer M. Cardiotoxicity and capecitabine: a case report. *Clin J Oncol Nurs.* 2003; 7:71-75.
13. Jensen SA, Sorensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. *Cancer Chemother Pharmacol.* 2006;58:487-493.
14. Saif MW, Quinn MG, Thomas RR, et al. Cardiac toxicity associated with capecitabine therapy. Acta Oncol. 2003;42:342-344.
15. Becker K, Erckenbrecht JF, Häussinge D, et al. Cardiotoxicity of the antiproliferative compound fluorouracil. *Drugs.* 1999; 57:475-484.
16. Dent RG, McColl I. 5-Fluorouracil and angina. *Lancet.* 1975; I:347-348.
17. Ng M, Cunningham D, Norman AR. The frequency and pattern of cardiotoxicity observed with capecitabine used in conjunction with oxaliplatin in patients treated for advanced colorectal cancer (CRC). *Euro J Cancer* 2005;41:1542-1546.
18. de Forni M, Malet-Martino MC, Jaillais P, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. *J Clin Oncol.* 1992;10:1795-1801.
19. Van Cutsem E, Hoff PM, Blum JL, et al. Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. *Ann Oncol.* 2002;13:484-485.
20. Robben NC, Pippas AW, Moore JO. The syndrome of 5-fluorouracil cardiotoxicity: an elusive cardiopathy. *Cancer.* 1993;71:493-509.
21. Akhtar SS. Salim KP. Bano ZA. Symptomatic cardiotoxicity with high-dose 5-fluorouracil infusion: a prospective study. *Oncol.* 1993;50:441-444.
22. Meyer CC, Calis KA, Burke LB, et al. Symptomatic cardiotoxicity associated with 5-fluorouracil. *Pharmacotherapy.* 1997;17:729-736.
23. Budman DR, Meropol NJ, Reigner B, et al. Preliminary studies of a novel oral fluoropyrimidine carbamate: capecitabine. *J Clin Oncol.*1998;16:1795-1802.
24. Shoemaker LK, Arora U, Rocha Lima CM. 5-fluorouracil-induced coronary vasospasm. *Cancer Control.* 2004;11:46-469.
25. Alter P, Merzum M, Soufi M, et al. Cardiotoxicity of 5-fluorouracil. *Cardiovasc Hematol Agents Med Chem.* 2006;4:1-5.
26. Takahashi Y, Bucana CD, Liu W, et al. Platelet-derived endothelial cell growth factor in human colon cancer angiogenesis: role of infiltrating cells. *J Natl Cancer Inst.* 1996;88:1146-1151.
27. Labianca R, Beretta G, Clerici M, et al. Cardiac toxicity of 5-fluorouracil: a study on 1083 patients. *Tumori.* 1982;68:505-510.
28. Rezkalla S, Kloner RA, Ensley J, et al. Continuous ambulatory ECG monitoring during fluorouracil therapy: a prospective study. *J Clin Oncol.* 1989;7:509-514.
29. Tuchman M, Stoeckeler JS, Kiang DT, et al. Familial pyrimidinemia and pyrimidinuria associated with severe fluorouracil toxicity. *N Engl J Med* 1985;313:245-249.
30. Rich TA, Shepard RC, and Mosley ST. Four decades of continuing innovation with fluorouracil: current and future approaches to fluorouracil chemoradiation therapy. *J Clin Oncol.* 2004;22:2214-2232.

The Diagnosis and Management of Heparin-Induced Thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is a well-recognized adverse effect of heparin therapy that may cause significant morbidity and mortality. HIT is an immune-mediated thrombocytopenia and is characterized by the formation of antibodies directed against heparin platelet factor 4 (PF4) complexes. HIT usually occurs within 5 to 10 days after initiation of heparin treatment[1,2] and is associated with venous and arterial thromboses,[3,4] which develop in 20% to 50% of patients.[5,6] Reported estimates of the frequency of HIT vary widely. A critical assessment of true HIT suggests a frequency of 0.2% to 3% in patients exposed to heparin for more than 4 days, but this may vary by clinical setting.[4,7-10] Patients may develop thrombosis in association with HIT, a condition referred to as heparin-induced thrombocytopenia with thrombosis syndrome (HITTS).

PATHOPHYSIOLOGY

The clinical manifestations of HIT are initiated by antibodies directed against the complex of heparin bound to PF4, a heparin-neutralizing protein contained in the alpha granules of platelets. The Fc portion of the immune complex binds to the Fc gamma RIIA receptors on the platelet surface.[11] If activated receptors are present at high enough density on the platelet surface, platelet activation is induced, which in turn promotes platelet aggregation and thrombin generation. This pathway leads to further release of PF4, creating a positive feedback loop.[12] Several mechanisms for this transient hypercoagulable state have been proposed. The release of procoagulants from activated platelets and generation of platelet microparticles have been postulated as the primary event.[13] In addition, because heparin-dependent antibodies can also nonspecifically bind to heparan sulfate on the surface of endothelial cells,[14] thrombosis can result from endothelial cell activation and/or increased tissue factor and thrombin generation due to endothelial cell injury.[15,16] HIT is associated with increased in vivo thrombin generation, as evidenced by the presence of elevated levels of thrombin-antithrombin complexes. Sustained platelet activation contributes to platelet clearance and thrombin generation that can lead to thrombocytopenia and thrombosis.[16]

CLINICAL MANIFESTATIONS

Recognizing the syndrome is the first step in establishing a diagnosis of HIT. The presence of unexpected thrombocytopenia, a platelet count that has fallen 50% or more from a prior value, necrotic skin lesions at heparin injection sites, and thrombosis associated with new onset of thrombocytopenia are indicators of the possibility of HIT in a patient who has been treated with a heparin product.[1]

In HIT, the timing of onset of thrombocytopenia after the initiation of heparin therapy varies according to the history of heparin exposure.[17] Because heparin-dependent antibodies usually develop between days 5 to 8 after exposure to heparin, HIT typically occurs 5 to 10 days after the initiation of heparin therapy[1,2] and rarely later. A precipitous decline in platelet count (within 24 hours) may occur on reexposure to heparin in patients who were treated with heparin in the past 100 days and have detectable levels of heparin-dependent antibodies.[17] In a minority of patients, the onset of thrombocytopenia and development of thromboses begin several days after heparin is discontinued, a pattern that may be due to high-titer heparin-dependent antibodies that can activate platelets even in the absence of heparin.[18]

The thrombocytopenia in HIT is rarely severe. The platelet counts are typically above 20,000/μL, with a median platelet count nadir of 60,000/μL.[19] As a result, spontaneous bleeding is unusual. With discontinuation of heparin exposure and institution of an alternative anticoagulant, the platelet count recovers rapidly (median 4 days) in most patients.[20]

The major manifestations of venous thrombosis are lower-extremity deep-venous thrombosis (DVT) and pulmonary embolism. Studies suggest that patients who have lesser degrees of platelet count decline are

often identified because of thrombotic complications. In a small study, compression ultrasonography or venography of the lower limbs revealed DVT in up to 50% of patients with HIT who had no clinical evidence of thrombosis.[21] In a retrospective study of patients with isolated HIT in whom heparin was discontinued and followed by no other treatment, the 30-day cumulative risk for thrombosis was 52.8%.[22] Other manifestations of venous thrombosis include venous limb gangrene secondary to distal ischemic necrosis following DVT and cerebral venous thrombosis. Arterial thrombosis is less common, but can present with a variety of clinical manifestations including stroke, myocardial infarction, limb ischemia, or organ infarction.[1]

Why thromboses develop in some patients with HIT and not in others is unknown, as both groups of patients have heparin-dependent antibodies. The risk of HIT is higher following the use of unfractionated heparin (UFH) than with low molecular weight heparin (LMWH) (relative risk 5.3; 95% confidence interval 2.8-9.9)[7] and is higher in surgical than in medical patients (RR 3.2; 95% CI 2.0-5.4).[8] Heparin-dependent antibodies are more likely to form in patients undergoing cardiac surgery, likely because these patients are more often repeatedly exposed to UFH because of its common usage in cardiac procedures. Orthopedic patients who receive LMWH for DVT prophylaxis are less likely to develop HIT than cardiac patients. Interestingly, orthopedic patients who receive UFH have a higher incidence of developing heparin-dependent antibodies than patients who received LMWH.[9,10] Among patients in whom antibodies do form, orthopedic patients are much more likely to develop thrombosis. The amount of heparin required to cause HIT can be small. Patients have developed this disorder after exposure to a heparin flush or after the use of heparin-coated catheters.[23,24]

LABORATORY DIAGNOSIS

HIT is a clinical diagnosis supported by serologic and/or functional assays for heparin-dependent antibodies. The enzyme immunoassay (EIA) is a serologic assay that is rapid and easy to perform. The assay has become the most frequently ordered diagnostic test. Patients with higher antibody titers (OD 1.0 to 1.2) have a greater likelihood of having clinically symptomatic HIT.[25] The test has a sensitivity greater than 97% but a specificity of only 74%-86% for detecting heparin-dependent antibodies associated with HIT. The positive predictive value of EIA can be low (10% to 93%), but the negative predictive value is high (greater than 95%).[26] Thus, a negative test strongly suggests the absence of HIT, whereas the clinical utility of a positive test remains to be determined. Functional tests such as the ^{14}C-serotonin release assay (SRA), and the heparin-induced platelet aggregation assay (HIPA) detect the platelet-activating effect and not just the presence of antibodies to heparin-PF4 complexes.[26] The SRA is currently considered the gold standard diagnostic test for HIT. A test is positive if platelets exposed to a therapeutic (0.1 U/mL) concentration of heparin release 14C-serotonin substrate but do not release it when exposed to high (100 U/mL) concentrations of heparin. The SRA has a sensitivity and specificity >95%. However, this functional test is expensive, difficult to standardize, entails the use of radioactive materials, and does not provide rapidly available results.[26] The HIPA is a functional assay that detects platelet aggregation as a measurement of antibody activation of platelets. Aggregation is measured at low (0.1 to 0.3 U/mL) and high (10 to 100 U/mL) heparin concentrations. A positive test shows no aggregation without added heparin, aggregation with the addition of a low concentration of heparin, and loss of aggregation with high heparin concentrations. The HIPA is >90% specific but suffers from lack of sensitivity.[26] Like the SRA, the HIPA study is difficult to standardize, labor-intensive, and is available only at institutions offering platelet aggregometry.

The diagnostic interpretation of these laboratory tests must be made in the context of the clinical estimation of the pretest probability of HIT. A pretest clinical scoring system has been developed that accounts for the degree of thrombocytopenia, timing of plateletcount fall, presence of thrombosis or other sequelae of HIT, and the likelihood of other alternative diagnoses to explain the thrombocytopenia (Figure 1).[27] Thus, if the pretest clinical score is intermediate to high, a positive EIA is considered supportive of the diagnosis of HIT; otherwise, a functional assay should be performed to make the diagnosis.

MANAGEMENT

The goal for management of HIT is to reduce the thrombotic risk by reducing platelet activation and thrombin generation. Immediate cessation of the heparin product is the first intervention in a patient

with intermediate or high clinical suspicion of HIT.[1] All potential sources of heparin exposure, including heparin-coated catheters and heparin flushes, must be discontinued.[23,24] LMWH should not be substituted for UFH, because antibodies cross-react between heparin products.[7] Cessation of heparin exposure alone is not sufficient, because patients with HIT have sustained thrombin generation that places them at risk for thrombosis, limb amputation, and death for days to weeks following heparin exposure.[1] If HIT is strongly suspected or confirmed, routine ultrasonography of the lower limbs is recommended because clinically inapparent thrombosis is common, and the presence of thrombosis influences the duration of anticoagulation.[1,21] Alternative anticoagulation must be initiated whether or not a clot is found to turn off further thrombin generation. Prophylactic platelet transfusion for the prevention of bleeding is relatively contraindicated in acute HIT. Bleeding is an uncommon clinical feature, and platelet transfusions have been linked to thrombotic events. In situations in which overt bleeding occurs, however, platelet transfusions may be appropriate.[1] A low platelet count does not prevent the use of appropriate alternative anticoagulation.

Recognition of the role of in vivo thrombin generation in the development of HIT provides the rationale for current therapies that emphasize reduction of thrombin generation either via direct inhibition of thrombin or by inhibiting factor Xa. Management of patients with HIT requires the use of a rapid-acting, alternative anticoagulant followed by warfarin therapy for longer-term treatment.[1] Three parenteral direct thrombin inhibitors are currently available for treatment of patients with HIT—lepirudin, argatroban, and bivalirudin.[28-33] Only one parenteral anti-Xa drug, fondaparinux, is available in the US.[34,35] Only 2 therapies (lepirudin and argatroban) are approved by the US Food and Drug Administration (FDA) for treatment of HIT.[1]

Lepirudin is a recombinant hirudin, given preferably by intravenous infusion without a bolus (or for severe thrombosis with a 0.2 mg/kg bolus) at 0.10 mg/kg per hour.[1] The drug is monitored by measurement of the activated partial thromboplastin time (aPTT), with the dose adjusted to achieve a ratio of the patient's aPTT to the laboratory reference value of 1.5 to 2.5. The drug has a half-life of 80 minutes and is primarily cleared by the kidneys. Disadvantages of lepirudin include rapid accumulation of the drug, anticoagulant effect in patients with renal insufficiency, and the tendency for patients receiving the drug to develop

Figure 1- Clinical Scoring System for HIT *

Thrombocytopenia

2 - Platelet count fall >50% and platelet nadir ≥20,000/μL
1 - Platelet count fall 30–50% or platelet nadir 10,000–19,000/μL
0 - Platelet count fall <30% or platelet nadir <10,000/μL

SCORE (Clinical Probability)
0-3 – Low
4-5 – Intermediate
6-8 – High

Timing of Platelet Count Fall

2 - Clear onset between days 5–10 of heparin therapy
Platelet count fall ≤1 day in a patient with prior heparin exposure within last 30 days
1 - Consistent with days 5–10 fall with heparin exposure, but not clear (e.g. missing platelet counts)
Onset of fall after day 10, or fall ≤1 day in a patient with prior heparin exposure within last 30–100 days
0 - Platelet count fall <4 days without recent heparin exposure

Thrombosis or Other Sequelae

2 - Confirmed presence of new thrombosis, skin necrosis, or acute systemic reaction after intravenous unfractionated heparin
1 - Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis
0 - None

Other Causes for Thrombocytopenia

2 - None apparent
1 - Possible
0 - Definite

*Adapted from Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost* 2006 Apr;4(4):759-65.

antihirudin antibodies that may paradoxically enhance its anticoagulant activity.[29] Thus, daily monitoring of aPTT should be performed throughout the course of lepirudin administration to assess the need for dose reduction.[28,29] Antibodies to lepirudin develop in approximately 30% of patients after initial exposure and in about 70% of patients after repeated exposure.[30] The incidence of anaphylaxis in patients with HIT treated with lepirudin has been estimated to be 0.015% on first exposure and 0.16% in reexposed patients.[36,37] Because fatal anaphylaxis has been reported after sensitization to lepirudin, patients should not be treated with this agent more than once.[1]

Argatroban is a small synthetic molecule that is a direct thrombin inhibitor.[31] The effect of argatroban is monitored by the aPTT, but dose-dependent increases also occur in the prothrombin time (PT).[38] The drug has a half-life of 40 minutes in individuals with normal hepatic function. The suggested starting dose is 2 µg/kg per minute by continuous intravenous infusion. The dose is adjusted to maintain the aPTT at 1.5 to 3 times the baseline but not to exceed 100 seconds.[1] Because argatroban is mostly metabolized by the liver and excreted in bile, a conservative lower starting dose of 0.5 µg/kg per minute is suggested in patients with hepatic dysfunction as well as in those with combined hepatic and renal dysfunction.[31] No antibody formation has been recognized, and reexposure to the drug is not contraindicated.

Bivalirudin is a genetically altered recombinant hirudin that is FDA approved for anticoagulation during percutaneous coronary interventions (PCI) in patients with HIT.[33] Off-label, bivalirudin has been successfully used to treat HIT patients not undergoing PCI.[32,33] Because of its short half-life of 25 minutes, bivalirudin is an attractive alternative to heparin for patients with HIT. The drug is cleared by the kidneys, but its clinical effect is also terminated by a self-destruct mechanism engineered into the molecule so that the half-life is still relatively short, 3-4 hours, in patients with kidney disease. The use of bivalirudin in the treatment of HIT has not been investigated in clinical trials.

Fondaparinux is a synthetic pentasaccharide that requires antithrombin to inactivate factor Xa.[35] Fondaparinux is monitored by anti-Xa assay, but routine monitoring is not recommended. Sincethe drug is highly cleared by the kidneys, the 17-hour half-life markedly increases in patients with renal insufficiency. Recent studies suggest possible cross-reactivity in vitro with heparin-dependent antibodies; however, there is only one report suggesting the development of clinical HIT in a patient receiving fondaparinux.[34] Notably the author reporting the fondaparinux cross-reaction continues to use the drug in patients with HIT.[35] Although not yet approved for treatment of HIT, increasing numbers of anecdotal reports describe patients with HIT being successfully managed with fondaparinux in lieu of a direct thrombin inhibitor,[1] particularly as a subcutaneous home therapy to complete bridging to warfarin therapy.[35]

Danaparoid is a heparinoid that is approved by the US FDA for prophylaxis in patients undergoing hip-replacement surgery, but is not FDA-approved for HIT[39-41] and was recently withdrawn from the US market by the manufacturer. The drug is approved for treatment and prevention of HIT in other countries. It is cleared by the kidneys and can be monitored by its antifactor Xa activity.

In the absence of prospective clinical trials comparing one antithrombotic agent with another for management of HIT, selection of an alternative anticoagulant is based on patient-specific factors such as hepatic or renal dysfunction, drug pharmacokinetics, institutional drug availability, and physician experience in the use of the agent (Figure 2). All of these agents require careful dosing because none has an antidote to provide immediate reversal of anticoagulation. Their short half-lives are the best form of reversal. The use of recombinant factor VIIa for hemostasis in severe bleeding has been reported,[41] but its use increases the underlying hypercoagulable risk of HIT. The decision to use recombinant FVIIa must take into account the risk of bleeding versus thrombotic consequences. At our institution, patients with HIT and renal insufficiency are usually treated with argatroban, whereas those with hepatic impairment are usually treated with lepirudin because of the modes of excretion and inactivation.

Appropriate duration of alternate anticoagulant therapy for HIT is not well defined. Several observational studies suggest that the risk for symptomatic thrombosis is substantial, ranging from 23% to 52%. Furthermore, prospective studies suggest that the risk for thrombosis in a patient with isolated HIT can persist for up to 6

weeks; therefore, some experts recommend alternative anticoagulation for up to 2 to 3 months.[1] In patients with evident thrombosis, at least 3-6 months of anticoagulation is required, depending on the location and severity of the thrombotic event. HIT is a transient hypercoagulable state, however, and thus HIT by itself is not an indication for long-term anticoagulation once therapy for the underlying thrombotic event has been completed.

SPECIAL CONSIDERATIONS ON WARFARIN

For patients who have HIT/HITTS, therapy with a direct thrombin inhibitor or fondaparinux is typically followed by a transition to warfarin for more convenient, less costly, outpatient therapy. Bridging to warfarin is started only when the platelet count has recovered to at least 100,000/μL, preferably above 150,000/μL, indicating cessation of the antibody-induced platelet activation.[1] The increased thrombin generation in active HIT can be neutralized by direct thrombin inhibitors or anti-Xa drugs, but warfarin cannot neutralize thrombin. Therefore, warfarin by itself is a poor drug to use early in the treatment course of HIT when thrombin levels are high. Warfarin should be initiated at low maintenance doses of 5 mg daily and overlapped with the alternative anticoagulant. The overlap must be for a minimum of 5 days and be continued until the international normalized ratio is therapeutic for at least 2 days. These recommendations are based on reports of warfarin-induced skin necrosis and venous gangrene of the limbs occurring in patients receiving warfarin without appropriate overlap with a direct-acting anticoagulant drug.[1]

When HIT is recognized in a patient already on warfarin, the drug must be stopped and reversed by using either vitamin K or fresh-frozen plasma.[1] The rationale is to try to avert warfarin-induced skin necrosis that may occur early in the course of HIT. In addition, warfarin may prolong the aPTT and lead to underdosing of alternative anticoagulant, which also increases the risk of warfarin-induced skin necrosis.[1]

Figure 2- Drugs Available for Treatment of HIT

	Half-life	Elimination	Other Features
ARGATROBAN	40-50 minutes	Hepatic	• Increases INR more than lepirudin and bivalirudin • Requires INR ~ 4.0 during overlapping DTI / warfarin before stopping DTI
LEPIRUDIN	80 minutes	Renal	• Development of antihirudin antibody greatly increases DTI half-life • Risk of anaphylaxis on re-exposure
BIVALIRUDIN	25-36 minutes	Renal	• Not FDA approved for HIT • Data obtained from PCI
FONDAPARINUX	17-21 hours	Renal	• Not FDA approved for HIT but case reports and studies support its use

HEPARIN RECHALLENGE AFTER AN EPISODE OF HIT

There is limited information on whether the overall risk of clinical HIT is different for patients with a history of HIT on heparin reexposure compared to patients without a history of HIT. As a result, perioperative heparin reexposure should be restricted to the surgical procedure itself, and alternative anticoagulant should be used for preoperative or postoperative anticoagulation. The limited experience with alternative anticoagulants for cardiac surgery and the inability to readily reverse their anticoagulant effects are important considerations. Ideally, heparin reexposure should not be planned until heparin-dependent antibodies are no longer detectable.[1]

Patients with a history of HIT more than 100 days previous to planned cardiopulmonary bypass and without persistent antibodies have undergone successful anticoagulation with UFH during the intraoperative period.[42] Theoretically, a secondary immune response to heparin should not occur for at least 3 days after reexposure to heparin. Therefore, a brief exposure to heparin during the surgery should not immediately elicit antibodies.[1] An alternative anticoagulant should be used after surgery to prevent late-onset heparin-induced thrombosis. Patients with recent HIT who still have detectable heparin-dependent antibodies are at risk for rapid-onset HIT on heparin reexposure. To allow the reuse of heparin during the intraoperative period, delaying surgery until the heparin-dependent antibodies become undetectable is recommended, if possible. Alternatively, the successful use of bivalirudin[43,44] and lepirudin[45,46] has been reported for cardiopulmonary bypass. For patients undergoing coronary angioplasty and stent placement who have acute or recent HIT, the successful use of argatroban,[47] bivalirudin,[48] and lepirudin[49] has likewise been reported.

CONCLUSIONS

Establishing a diagnosis of HIT in patients with complicated medical conditions can be challenging. Other causes of thrombocytopenia such as sepsis, platelet consumption, drugs (particularly antibiotics), and underlying hematologic disease should be excluded. In HIT, platelet counts typically recover after discontinuation of heparin and administration of alternative anticoagulation. This temporal pattern gives a clinical clue to the accuracy of the diagnosis. Although laboratory tests are available to detect antibodies involved in HIT, the diagnosis is still made largely on a clinical basis.

Strategies to prevent HIT and its complications must be implemented in every medical center. Documentation of HIT should be included in the patient's medical records, and future exposure to heparin should generally be avoided, particularly for the 3-6 months following the diagnosis. Furthermore, patient education is important for HIT patients, who should be informed that because they have developed HIT they are at risk for thrombosis or worsening thrombosis if heparin is readministered in the next 100 days. Many questions about HIT remain unanswered; however, with early recognition of HIT and initiation of appropriate alternate anticoagulant therapy, the morbidity and mortality associated with this disorder can be reduced.

REFERENCES

1. Warkentin TE, Greinacher A, Koster A, and Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest*. 2008:340S-380S.
2. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med*. 2001;344:1286.
3. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular weight heparin or unfractionated heparin. *N Engl J Med*. 1995;332:1330-1335.
4. Girolami B, Prandoni P, Stefani PM, et al. The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. *Blood*. 2003;101:2955-2959.
5. Greinacher A, Farner B, Kroll H, et al. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis: a retrospective analysis of 408 patients. *Thromb Haemost*. 2005;94:132-135.
6. Steen L, Pifarre R, Moran JF. Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. *Am J Med*. 1999;106:629-635.
7. Prandoni P, Siragusa S, Girolami B, Fabris F. The incidence of heparin-induced thrombocytopenia in medical patients treated with low-molecular-weight heparin: a prospective cohort study. *Blood*. 2005;106:3049.
8. Warkentin TE, Sheppard JA, Sigouin CS, et al. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. *Blood*. 2006;108:2937.
9. Warkentin TE, Sheppard JA, Horsewood P, et al. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood*. 2000;96:1703.
10. Greinacher A, Eichler P, Lietz T, Warkentin TE. Replacement of unfractionated heparin by low-molecular-weight heparin for postorthopedic surgery

antithrombotic prophylaxis lowers the overall risk of symptomatic thrombosis because of a lower frequency of heparin-induced thrombocytopenia. *Blood.* 2005;106:2921.
11. Rauova L, Zhai L, Kowalska MA, et al. Role of platelet surface PF4 antigenic complexes in heparin-induced thrombocytopenia pathogenesis: diagnostic and therapeutic implications. *Blood.* 2006;107:2346.
12. Newman PM, Chong BH. Heparin-induced thrombocytopenia: New evidence for the dynamic binding of purified anti-PF4-heparin antibodies to platelets and the resultant platelet activation. *Blood.* 2000;96:182.
13. Hughes M, Hayward CP, Warkentin TE, et al. Morphological analysis of microparticle generation in heparin-induced thrombocytopenia. *Blood.* 2000;96:188.
14. Visentin GP, Ford SE, Scott JP, et al. Antibodies from patients with heparin-induced thrombocytopenia/thrombosis are specific for platelet factor 4 complexed with heparin or bound to endothelial cells. *J Clin Invest.* 1994;93:81.
15. Blank M, Shoenfeld Y, Tavor S, et al. Anti-platelet factor 4/heparin antibodies from patients with heparin-induced thrombocytopenia provoke direct activation of microvascular endothelial cells. *Int Immunol.* 2002;14:121.
16. Warkentin TE, Hayward CP, Boshkov LH, et al. Sera from platelets with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: An explanation for the thrombotic complications of heparin-induced thrombocytopenia. *Blood.* 1994;84:3691.
17. Lubenow N, Kempf R, Eichner A, et al. Heparin-induced thrombocytopenia: temporal pattern of thrombocytopenia in relation to initial use or reexposure to heparin. *Chest*. 2002;122:37-42.
18. Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. *Ann Intern Med.* 2001;135:502-506.
19. Warkentin TE. Clinical presentation of heparin-induced thrombocytopenia. *Semin Hematol.* 1998;35:9.
20. Warkentin TE. Clinical picture of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-Induced Thrombocytopenia.* 3rd ed. New York: Marcel Dekker; 2003:53-106.
21. Tardy B, Tardy-Poncet B, Fournel P, et al. Lowerlimb veins should be systematically explored in patients with isolated heparin-induced thrombocytopenia. *Thromb Haemost.* 1999;82:1199-1200.
22. Warkentin T, Kelton JG. A 14-year study of heparin- induced thrombocytopenia. *Am J Med.* 1996;101:502-507.
23. Heeger PS, Backstrom JT. Heparin flushes and thrombocytopenia. *Ann Intern Med.* 1986;105:143.
24. Laster J, Silver D. Heparin-coated catheters and heparin-induced thrombocytopenia. *J Vasc Surg.* 1988;7:667.
25. Zwicker JI, Uhl L, Huang W-Y, Shaz BH, Bauer KA. Thrombosis and ELISA optical density values in hospitalized patients with heparin-induced thrombocytopenia. *J Thromb Haemost.* 2004;2:2133-2137
26. Pouplard C, Amiral J, Borg JY, et al. Decision analysis for use of platelet aggregation test, carbon 14-serotonin release assay, and heparin-platelet factor 4 enzyme-linked immunosorbent assay for diagnosis of heparin-induced thrombocytopenia. *Am J Clin Pathol.* 1999;111:700-706.
27. Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost.* 2006;4:759-765.
28. Huhle G, Hoffmann U, Song X, et al. Immunologic response to recombinant hirudin in HIT type II patients during long-term treatment. *Br J Haematol.* 1999;106:195-201.
29. Eichler P, Friesen HJ, Lubenow N, et al. Antihirudin antibodies in patients with heparin-induced thrombocytopenia treated with lepirudin: incidence, effects on aPTT, and clinical relevance. *Blood.* 2000;96:2373-2378.
30. Lubenow N, Eichler P, Lietz T, Greinacher A. Lepirudin in patients with heparin- induced thrombocytopenia—results of the third prospective study (HAT-3) and a combined analysis of HAT-1, HAT-2, and HAT-3. *J Thromb Haemost.* 2005;3:2428-2436.
31. Levine RL, Hursting MJ, McCollum D. Argatroban therapy in heparin-induced thrombocytopenia with hepatic dysfunction. *Chest.* 2006;129:1167.
32. Bartholomew JR. Bivalirudin for the treatment of heparin induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-Induced Thrombocytopenia.* 3rd ed. New York, NY: Marcel Dekker; 2003;475-507.
33. Francis JL, Drexler A, Gwyn G, et al. Bivalirudin, a directthrombin inhibitor, is a safe and effective treatment for heparin-induced thrombocytopenia [Abstract]. *Blood.* 2003;102(suppl 1):164a.
34. Warkentin TE, Maurer BT, Aster RH. Heparin-induced thrombocytopenia associated with fondaparinux. *N Engl J Med.* 2007;356:2653-2655.
35. Warkentin TE. Fondaparinux versus direct thrombin inhibitor therapy for the management of heparin-induced thrombocytopenia (HIT): bridging the river coumarin. *Thromb Haemost.* 2008;99(1):2-3.
36. Greinacher A, Lubenow N, Eichler P. Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. *Circulation.* 2003;108:2062.
37. Cardenas GA, Deitcher SR. Risk of anaphylaxis after reexposure to intravenous lepirudin in patients with current or past heparin-induced thrombocytopenia. *Mayo Clin Proc.* 2005;80:491.
38. Sheth SB, DiCicco RA, Hursting MJ, et al. Interpreting the International Normalized Ratio (INR) in individuals receiving argatroban and warfarin. *Thromb Haemost.* 2001;85:435.
39. Wilhelm MJ, Schmid C, Kececioglu D, et al. Cardiopulmonary bypass in patients with heparin-induced thrombocytopenia using Org 10172. *Ann Thorac Surg.* 1996;61:920.
40. Gillis S, Merin G, Zahger D, et al. Danaparoid for cardiopulmonary bypass in patients with previous heparin-induced thrombocytopenia. *Br J Haematol.* 1997;98:657.
41. Alving BM. How I treat heparin-induced thrombocytopenia and thrombosis. *Blood.* 2003;101:31-37.
42. Potzsch B, Klovekorn WP, Madlener K. Use of heparin during cardiopulmonary bypass in patients with a history of heparin-induced thrombocytopenia [Letter]. *N Engl J Med.* 2000;343:515.
43. Vasquez JC, Vichiendilokkul A, Mahmood S, et al. Anticoagulation with bivalirudin during cardiopulmonary bypass in cardiac surgery. *Ann Thorac Surg.* 2002;74:2177–2179.
44. Davis Z, Anderson R, Short D, et al. Favorable outcome with bivalirudin anticoagulation during cardiopulmonary bypass. *Ann Thorac Surg.* 2003;75:264–265.
45. Koster A, Kuppe H, Hetzer R, et al. Emergent cardiopulmonary bypass in five patients with heparin-induced thrombocytopenia type II employing recombinant hirudin. *Anesthesiology.* 1998;89:777–780.
46. Koster A, Hansen R, Kuppe H, et al. Recombinant hirudin as an alternative for anticoagulation during cardiopulmonary bypass in patients with heparin-induced thrombocytopenia type II: a 1-year experience in 57 patients. *J Cardiothorac Vasc Anesth.* 2000;14:243–248.
47. Lewis BE, Matthai WH Jr, Cohen M, et al, for the ARG-216/310/311 Study Investigators. Argatroban anticoagulation during percutaneous coronary intervention in patients with heparin-induced thrombocytopenia. *Cathet Cardiovasc Interv.* 2002;57:177–184.
48. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA.* 2003;289:853–863.
49. Manfredi JA, Wall RP, Sane DC, et al. Lepirudin as a safe alternative for effective anticoagulation in patients with known heparin-induced thrombocytopenia undergoing percutaneous coronary intervention: case reports. *Cathet Cardiovasc Interv.* 2001;52:468–472.

Clinical Significance of Mobile Carotid Echoes

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Background: Mobile plaques in the aorta are associated with complex aortic atherosclerosis and increased risk of embolic events. The significance of mobile structures seen on ultrasonography of the carotid arteries is unclear. We investigated whether the presence of such mobile carotid echoes was predictive for major adverse cardiovascular events in intermediate-risk patients age 16 years and older.

Methods: Since 1995, 727 patients had carotid intimal-medial thickness measured at the cardiology practice of the University of Virginia Health System. We detected mobile carotid echoes of varying sizes and dimensions in a total of 11 patients, age 48 to 69 years (mean age 60 years). We then performed a retrospective analysis of 705 patients to determine the incidence of major adverse cardiovascular events (new myocardial infarction, revascularization, stroke, or transient ischemic attack). Twenty-two patients were lost to follow-up.

Results: During a mean follow-up period of 4.8 years (range, 2.0 to 9.3 years), 20 patients had major adverse cardiovascular events, 7 had myocardial infarctions, 7 required revascularization, and 6 had a stroke or transient ischemic attack. None of the events, however, occurred in the 11 patients with mobile echoes (*P* =.73). With one exception, the mobile echoes were confined to the carotid bulb.

Conclusions: The presence of mobile carotid echoes did not predict major adverse cardiovascular events in these intermediate-risk patients. These data suggest that the location of mobile echoes is important for determining cardiovascular risk.

Multiple trials have shown a direct association between increased carotid intimal-medial thickness (IMT) and risk of myocardial infarction (MI) and stroke.[1-8] Prediction of myocardial events by measurement of atherosclerosis at a different site (the carotid artery) is a manifestation of the diffuse nature of atherosclerosis.[9] In these trials, carotid IMT data were used for predicting cardiovascular events, but it is also possible that different morphologies of the atherosclerotic plaques observed via carotid ultrasonography may also be important in risk prediction.

During the past decade at the University of Virginia Health System (UVA), among the cohort of patients whose carotid IMT we measured with carotid ultrasonography, we found 11 patients with mobile structures emanating from carotid plaques. Mobile thrombi in the aorta have been recognized to be associated with complex aortic atherosclerosis and an increased risk of embolic events, particularly cerebral embolism.[10-13] It is not known whether mobile structures seen on ultrasonography of the carotid arteries carry a similar risk in asymptomatic patients. We therefore investigated whether the presence of such mobile structures in the carotid arteries or their anatomic location within the artery predicted major adverse cardiovascular events (MACE).

METHODS

Since 1995, high-resolution, noninvasive ultrasonographic measurements of the common carotid artery, carotid bulb, and internal carotid artery IMT have been available for clinical use at UVA. Many of the IMT studies were performed on individuals who were considered to be at intermediate risk for MACE and were referred by their preventive cardiologist, and some studies were ordered by primary care physicians. As of July 2003, 727 patients 16 years old and older had been studied.

Carotid IMT studies were performed with an 11-MHz vascular ultrasound probe and a Toshiba

Powervision 6000 SSA370A machine (Otawara-Shi, Tochigi, Japan). Near- and far-wall common (5 mm proximal to the carotid bulb), near- and far-wall bulb (center of the bulb), and far-wall internal (5 mm distal to the bulb) bilateral carotid measurements were made at end-diastole, as determined by an electrocardiographic tracing.[8,14] A single experienced ultrasound technician performed imaging and measurements. Plaques were included in measurements if any were present, and any mobile or oscillating intraluminal structures were noted and identified as "mobile echoes." The anatomic locations within the common carotid, bulb, or internal carotid, as well as the structural appearance and dimensions of these mobile structures, were also recorded.

At the time of the carotid IMT study, information was also collected on age, sex, height, weight, systolic blood pressure (BP), diastolic BP, and patient-reported smoking, hypertension, diabetes, or prior MI/stroke/transient ischemic attack. Patients reporting prior MI/stroke/transient ischemic attack were not included in this analysis. Measurements of serum lipids were not collected at the time of the carotid IMT study; therefore, risk quantitation by Framingham or other score was not possible in this population. Measurements were entered into a clinical database, and age-specific quartiles of thickness were developed, as previously described.[14]

A retrospective analysis of 705 patients was then performed to determine the incidence of MACE, which was defined as new MI, arterial revascularization (coronary artery bypass grafting or percutaneous coronary intervention), or stroke/transient ischemic attack. One death, a cardiac arrest with documented ventricular fibrillation, was classified as an MI. Twenty-two patients were lost to follow-up. Patients were contacted by telephone to conduct follow-up questionnaires regarding the occurrence of MACE, comorbidities, current medications, current diet, and smoking history. Events reported by patients were confirmed through paper and electronic medical records. MI was confirmed by laboratory records of elevated cardiac enzymes and/or by electrocardiographs consistent with the diagnostic criteria for MI as defined by the American Heart Association/American College of Cardiology guidelines.[15,16]

The UVA institutional review board approved this analysis. To analyze differences in baseline patient characteristics for any 2 of the 3 groups of patients with mobile echoes and no events, patients with events and no mobile echoes, and patients without events and no mobile echoes, we used χ^2/Fishers exact tests to compare categorical variables and a Wilcoxon rank-sum test to compare continuous variables. In patients with and without mobile echoes, we used a Fishers exact test for analysis of the final composite endpoint of MACE as a dichotomous variable. Statistical analyses were performed with SAS version 9.1 (Cary, NC) and R (www.r-project.org).

Given that 1.6% of the entire cohort had mobile echoes on carotid ultrasonography, this study had more than 80% power to detect at least 1 event if the event rate in the mobile echoes subgroup was 14% or greater. All continuous variables are expressed as means ± SEM, unless otherwise specified. All reported *P* values are 2-sided.

RESULTS

Characteristics of the study patients with mobile echoes, as well as those with and without cardiovascular events, are shown in Table 1. Patients ranged in age from 16 to 85 years (mean 57.5 years) at the time of imaging. During a mean follow-up period of 4.8 years (range, 2.0 to 9.3 years), 20 patients had MACE, 7 patients had MIs, 7 required arterial revascularization, and 6 had a stroke or transient ischemic attack. As reported previously, patients with events had higher carotid bulb and internal carotid IMT measurements than those who did not experience events ($P = .001$ for carotid bulb IMT; $P = .01$ for internal carotid IMT).[8] Patients with MACE had a higher incidence of hypertension and smoking than patients without MACE. Of the patients with MACE, 75% had a history of hypertension, compared with 43% of those without MACE ($P = .04$). The mean systolic BP in patients with MACE was 150 mm Hg, whereas it was 139 mm Hg in those who experienced no events ($P = .08$). Patients with events had a significantly wider pulse pressure than did those without events (67 ± 21 vs. 55 ± 15, respectively; $P = .015$). Only 7% of those without events were smokers, whereas 25% of those with events reported smoking ($P = .05$). There was no difference in other clinical characteristics, including

low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, age, and sex.

A total of 11 patients, age 48 to 69 years (mean 60 years) were found to have carotid mobile echoes of varying sizes and dimensions, such as that shown in Figure 1. None of the patients with mobile echoes were smokers. Of patients with mobile echoes, 18% had a history of hypertension, compared with 75% of those with events ($P = .01$). Additionally, patients with mobile echoes had a lower BMI than did those without mobile echoes and without events ($P = .009$). Patients with mobile echoes were also more likely to be female (73%) than were those without mobile echoes ($P = .07$).

The mobile echoes were confined to the carotid bulb in all but one of the patients. In that patient, the mobile echoes involved the proximal internal carotid as well as the carotid bulb. All of the mobile echoes were found to occur unilaterally rather than bilaterally. One patient with mobile echoes underwent a repeat screening study within 2 months, and the mobile echoes were found to be unchanged, emanating from the lumen of the posterior right carotid bulb. Another patient underwent a repeat study 1 year later, which revealed an unchanged mobile echo emanating from the posterior right carotid bulb. Neither patient had had any intervening neurologic or adverse cardiac events.

Table 1. Characteristics of Study Patients (N = 705) with Mobile Echoes (Group I), without MACE (Group II), and with MACE (Group III) during the Follow-Up Period.*

	Group I (+) Mobile Echo (–) Event n = 11	Group II (–) Mobile Echo (–) Event n = 674	Group III (–) Mobile Echo (+) Event n = 20	n
Carotid bulb IMT, mm	1.28 ± 0.43 †	1.39 ± 0.53‡	1.83 ± 0.59	705
Carotid bulb quartile, 1-4	2.09 ± 0.94†	2.45 ± 1.04‡	3.20 ± 1.05	705
Internal carotid IMT, mm	1.02 ± 0.68	0.96 ± 0.58‡	1.61 ± 0.91	416
Common carotid IMT, mm	0.87 ± 0.11	0.82 ± 0.18	0.88 ± 0.21	705
Systolic BP, mmHg	133 ± 24	139 ± 19	150 ± 24	689
Diastolic BP, mmHg	81 ± 11	84 ± 11	83 ± 12	688
Pulse pressure	53 ± 15	55 ± 15	67 ± 21	688
Age, years	60 ± 8	57 ± 12	61 ± 12	705
Sex, % male	27	54	55	705
BMI, kg/m^2	24 ± 5§	27 ± 5	25 ± 3	698
Smoking, % yes	0	7‡	25	678
H/O Hypertension, %	18†	43‡	75	678
NIDDM, % yes	0	4	8	678
LDL, mg/dL	167 ± 33	149 ± 41	136 ± 59	434
HDL, mg/dL	57 ± 16	46 ± 15	50 ± 21	446

*BP indicates blood pressure; BMI, body mass index; H/O, history of; IMT, intimal medial thickness; NIDDM, non–insulin-dependent diabetes mellitus; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

†Group I significant compared to group III.

‡Group II significant compared to group III.

§Group I significant compared to group II.

None of the patients with mobile echoes experienced MACE ($P = 0.73$) (Table 2). The relationship of mobile echoes and MACE within age-normalized quartiles of carotid bulb IMT is shown in Figure 2. Unlike patients who experienced MACE, patients with mobile echoes did not exhibit high carotid bulb IMT. Patients with mobile echoes had significantly less common and carotid bulb IMT than patients with MACE (Table 1). These data suggest that there was no significant association between the presence of mobile echoes and the occurrence of MACE.

DISCUSSION

The presence of mobile carotid echoes did not predict MACE in

this cohort of patients; no significant correlation was found between the presence of mobile echoes and an increased risk of MACE. This result suggests that mobile echoes in the carotid do not appear to confer a high risk such as that predicted by the presence of mobile echoes in the aorta, which have been associated with complex aortic atherosclerosis and an increased risk of embolic events, particularly cerebral embolism.[10-13]

In a prior study, we demonstrated that carotid IMT, specifically age-normalized carotid bulb and internal carotid IMT, predicted MACE in patients deemed to be intermediate risk by their physicians.[8] The same predictive value does not appear to apply to mobile carotid echoes. Perhaps the low number of cardiovascular events in this study may obscure a small increase in risk associated with mobile carotid echoes. Additionally, baseline clinical characteristics of the patients with mobile echoes may contribute to the explanation; none of the patients with mobile echoes had a history of smoking, and a significantly smaller percentage of those with mobile echoes had hypertension than did those without mobile echoes. Patients with mobile echoes were also more likely to be female, with a trend toward statistical significance. Alternatively, it is possible that large-vessel (aortic) mobile echoes may differ physiologically from moderate-vessel (carotid) mobile echoes. Importantly, our study involved asymptomatic moderate-risk patients who differed from those in the studies on aortic mobile echoes

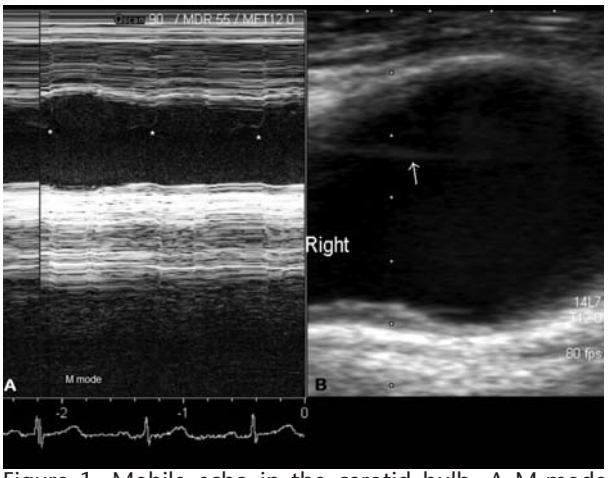

Figure 1. Mobile echo in the carotid bulb. A M-mode imaging of the thin, mobile, intraluminal echogenic structure that is seen emanating from the right carotid bulb in the 2-dimensional ultrasound shown (B) (arrow). Asterisks mark this mobile echo in (A), where it is shown on M-mode imaging to oscillate in and out of the carotid lumen with each cardiac cycle.

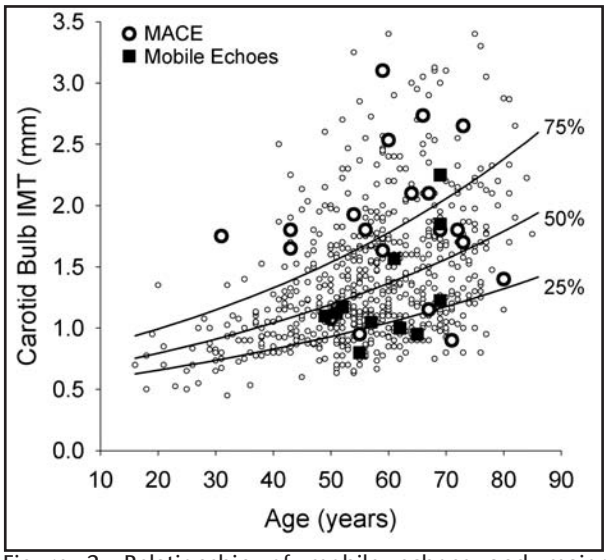

Figure 2. Relationship of mobile echoes and major adverse cardiovascular events (MACE) with age-normalized carotid bulb intimal-medial thickness (IMT). The large filled squares represent the patients with mobile echoes, the large bolded circles the patients with MACE, the small circles the patients without mobile echoes or MACE. The lines are exponential regression of all patients, defining quartiles of risk.

Table 2. Association of Mobile Echoes and Incidence of MACE*

	Event		
	Yes	No	Total
Mobile echoes			
Yes	0	11	11
No	20	674	694
Total	20	685	705

*$\chi^2 = 0.12$ with $P = .73$, suggesting no relationship.

performed in patients with more substantial atherosclerosis (e.g., after stroke).

The biologic origin of these mobile echoes in the carotids is unknown. One possibility is that they represent mobile extensions of the carotid plaques from which they emanate, and therefore would prove to be similar in composition to carotid plaques. Alternatively, these carotid mobile echoes could represent ultrasound reflections from boundaries between regions with differing blood-flow velocity, such as an eddy behind a plaque. A number of studies have shown that bilateral asymptomatic carotid plaques are associated more frequently with coronary artery disease and cerebrovascular disease than are unilateral plaques.[17-19] Furthermore, Touzé et al surmised that the etiology of unilateral carotid disease can be explained on the basis of local hemodynamic and anatomic factors, whereas bilateral disease, with its higher associated rates of symptomatic disease in other arterial beds, is indicative of systemic atherosclerosis.[19] This explanation may account for the absence of MACE in our patients with mobile echoes, all of whom were found to have unilateral mobile structures.

Kimura et al described 11 patients with recent acute cardioembolic stroke who were then found to have oscillating mobile structures in the extracranial internal carotid artery.[20] Hill and Brozyna recently reported a case of extensive mobile thrombus, characterized as a "floating" thrombus, in the internal carotid artery in a patient presenting with acute stroke; this patient was eventually treated surgically after a period of conservative medical therapy.[13] Mobile carotid plaques have also been reported in neurologically asymptomatic patients who did not experience adverse events in spite of nonsurgical treatment, suggesting a benign course in the absence of neurologic signs and symptoms.[21,22] In our study, none of the patients with mobile carotid structures experienced neurological deficits, nor did they have any known potential cardiac sources of emboli. The structures seen in our patients may therefore represent a benign process, rendered even less harmful by the lower risk profile of this patient population, or may be indicative of a process with a low enough risk so as to be undetectable in our population. Additionally, the location of these structures, primarily in the carotid bulb rather than the internal carotid, may explain a difference in event rate. The possibility exists that mobile structures in the carotid bulb are of different significance than those found in the internal carotid, and thus the carotid bulb may represent a more protected location. Notably, even the 1 patient in this study who had involvement of the proximal internal carotid artery also had involvement of the carotid bulb and did not suffer any major adverse events. Our results therefore do not support a surgical approach in asymptomatic patients, especially those with low-to-intermediate risk.

An intriguing correlation between the incidence of carotid plaques and the presence of aortic arch atherosclerosis has been described by Guo et al.[23] Given this correlation, further follow-up of our patients by performing transesophageal echocardiography to evaluate the aortic arch in those with mobile echoes may prove to be enlightening.

REFERENCES

1. Burke GL, Evans GW, Riley WA, et al. Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke.* 1995;26:386-391.
2. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *Am J Epidemiol.* 1997;146:483-494.
3. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation.* 1997;96:1432-1437.
4. Bots ML, Hofman A, Grobbee DE. Increased common carotid intima-media thickness: adaptive response or a reflection of atherosclerosis? Findings from the Rotterdam Study. *Stroke.* 1997;28:2442-2447.
5. Ebrahim S, Papacosta O, Whincup P, et al. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. *Stroke.* 1999;30:841-850.
6. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med.* 1999;340:14-22.
7. Belcaro G, Nicolaides AN, Ramaswami G, et al. Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: a 10-year follow-up study (the CAFES-CAVE study). *Atherosclerosis.* 2001;156:379-387.
8. Ali YS, Rembold KE, Weaver B, et al. Prediction of major adverse cardiovascular events by age-normalized carotid intimal medial thickness. *Atherosclerosis.* 2006;187:186-190.

9. Triposkiadis F, Sitafidis G, Kostoulas J, Skoularigis J, Zintzaras E, Fezoulidis I. Carotid plaque composition in stable and unstable coronary artery disease. *Am Heart Journal* 2005;150:782-789.
10. Tunick PA, Perez JL, Kronzon I. Protruding atheromas in the thoracic aorta and systemic embolization. *Ann Internal Med.* 1991;115:423-427.
11. Karalis DG, Chandrasekaran K, Victor MF, Ross JJ, Mintz GS. Recognition and embolic potential of intraaortic atherosclerotic debris. *J Am Coll Cardiol.* 1991;17:73-78.
12. Mitusch R, Stierle U, Tepe C, Kummerkloess D, Kessler C, Sheikhzadeh A. Systemic embolism in aortic-arch atheromatosis. *Eur Heart J.* 1994;15:1373-1380.
13. Hill SL, Brozyna W. Extensive mobile thrombus of the internal carotid artery: a case report, treatment options, and a review of the literature. *Am Surgeon.* 2005;71:853-855.
14. Rembold KE, Ayers CR, Wills MB, Rembold CM. Usefulness of carotid initmal medial thickness and flow mediated dilation in a preventive cardiology practice. *Am J Cardiol.* 2003;91:1475-1477.
15. Ryan TJ, Antman EM, Brooks NH, et al. 1999 Update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol.* 1999;34:890-909.
16. Ryan TJ, Antman EM, Brooks NP, et al. 1999 Update: ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation.* 1999;100:1016-1030.
17. Nowak J, Nilsson T, Sylven C, Jogestrand T. Potential of carotid ultrasonography in the diagnosis of coronary artery disease: a comparison with exercise test and variance ECG. *Stroke.* 1998;29:439-446.
18. Lernfelt B, Forsberg M, Blomstrand C, Mellstrom D, Volkmann R. Cerebral atherosclerosis as predictor of stroke and mortality in representative elderly population. *Stroke.* 2002;33:224-229.
19. Touze E, Warlow CP, Rothwell PM. Risk of coronary and other nonstroke vascular death in relation to the presence and extent of atherosclerotic disease at the carotid bifurcation. *Stroke.* 2006;37:2904-2909.
20. Kimura K, Yasaka M, Minematsu K, et al. Oscillating thromboemboli within the extracranial internal carotid artery demonstrated by ultrasonography in patients with acute cardioembolic stroke. *Ultrasound Med Biol.* 1998;24:1121-1124.
21. Escribano JM, Juan J, Rodriguez M, Bellmunt S, Matas M. Mobile carotid plaque [in Spanish]. *Revista de Neurologia.* 2001;33:836-839.
22. Szendro G, Sabetai MM, Tegos TJ, Dhanjil S, Lennox AF, Nicolaides AN. Mobile carotid plaques: the natural history of two asymptomatic and nonoperated cases. *J Vasc Surg.* 1999;30:357-362.
23. Guo Y, Jiang X, Chen S, Zhang S, Zhao H, Wu Y. Aortic arch and intra-/extracranial cerebral arterial atherosclerosis in patients suffering acute ischemic strokes. *Chin Med J (Engl).* 2003;116:1840-1844.

Necrotizing Pancreatitis: Management and the Role of Antimicrobials

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The possible presence of necrotizing pancreatitis should be considered in patients with severe acute pancreatitis (AP). Although mortality can be very high if infection occurs, antibiotics must be used cautiously. This review provides information on diagnosis and management of this complex disorder.

ASSESSMENT AND MANAGEMENT OF AP

Antibiotics are not indicated in the management of acute interstitial pancreatitis. Aggressive hydration, pancreatic rest through restriction of oral intake, and narcotic analgesia for pain management remain the mainstays of therapy.[1] In patients with severe AP, as evidenced by hemoconcentration (hematocrit ≥44% or failure of the hematocrit to decrease in the first 24 hours of treatment) or end-organ injury (renal or pulmonary impairment), necrotizing pancreatitis should be considered.[2-4] The degree of serum amylase or lipase elevation does not correlate with the severity of AP.[5]

Pancreatic necrosis can only be assessed on contrasted axial imaging studies (such as abdominal computed tomography with intravenous contrast dye).[6] Axial imaging studies are also useful because they may reveal cholelithiasis, choledocholithiasis (gallstone pancreatitis), or a pancreatic neoplasm. In patients with severe AP from biliary macro- or microlithiasis (particularly patients with cholangitis or extrahepatic biliary dilation), early endoscopic retrograde cholangiopancreatography with biliary sphincterotomy is indicated within the first 72 hours.[7] Radiological imaging is also useful to assess for hemorrhagic pancreatitis and to identify pseudoaneurysms, which should be treated (often by interventional radiology).

INFECTION IN AP

Approximately 30% of patients with severe AP develop infection, and mortality from AP may be as high as 30%-40% if sterile necrosis becomes infected.[8] Typically, gut-derived aerobic organisms such as *Escherichia coli* and *Pseudomonas, Klebsiella,* and *Enterococcus spp.* are the culprits. In 75% of cases, infections are monomicrobial. Fungal and gram-positive infections usually occur only after prophylactic antibiotic use for necrotizing pancreatitis.

Enteral (jejunal) feeding may reduce bacterial translocation and reduce infections associated with total parenteral nutrition in patients with severe AP.[9] Older experimental and clinical studies indicated a window of opportunity of 1-2 weeks when superinfection might be prevented by administering systemic antibiotics for severe necrotizing pancreatitis.[10-12] However, other prospective studies and more recent metaanalyses have not found prophylactic antibiotics efficacious in preventing infected pancreatic necrosis or in improving disease-related survival.[8,13-15]

Therefore, prophylactic antibiotics should not be administered even in patients with severe necrotizing pancreatitis who are relatively asymptomatic or do not manifest signs or symptoms of infection. However, if a patient with severe pancreatic necrosis develops fever, meets systemic inflammatory response syndrome criteria, has evidence of sepsis, or has imaging study results indicating emphysematous pancreatitis, then antibiotic coverage is reasonable—particularly in light of the significant mortality rate.

Given the increasing prevalence of extended-spectrum beta lactamase-producing organisms (eg, *Klebsiella and Enterobacter spp.*)[16,17] and the lack of definitive data demonstrating that antibiotics are efficacious in reducing pancreatic infection or mortality, it would be prudent to initiate antimicrobial therapy with a quinolone with or without anaerobic coverage (eg, ciprofloxacin and metronidazole) or with a more modest broad-

spectrum penicillin (eg, ampicillin-sulbactam). If the patient's fever, leukocytosis, or clinical status does not improve, then changing to a broader-spectrum penicillin (eg, piperacillin-tazobactam), a third- or fourth-generation cephalosporin (eg, ceftriaxone or cefepime), or a carbapenem (eg, meropenem or imipenem) may be considered. Lastly, in patients who have been on prolonged broad-spectrum antibiotic coverage, fungemia (and less likely, methicillin-resistant *Staphylococcus aureus*) must always be suspected.[1]

The role for sampling necrotic pancreatic tissue in the setting of suspected infection is debated.[1,18] Although the consensus is that tailoring antibiotic coverage is beneficial, the risk of seeding sterile necrosis must be balanced against the theoretical yield of needle-aspiration for gram stain/culture. If infection is suspected and repeat imaging studies show a pseudocyst or fairly well-organized (possibly liquefied) pancreatic necrosis, consideration should be given to endoscopic cystgastrostomy (at which time a sample can be obtained for gram stain and culture and a drain can be left to drain the abscess).[1]

SURGERY IN AP

If infected pancreatic necrosis is suspected, surgical consultation is always warranted. At select institutions, such as the University of Virginia Health System, endoscopic necrosectomy may be considered as an alternative or a bridge to surgical necrosectomy in selected patients with emphysematous or infected pancreatic necrosis.[19-21] Surgical necrosectomy remains the standard of care for severely ill patients with extensive pancreatic necrosis; however, surgical necrosectomy is better performed after pancreatic necrosis has been allowed to organize, which typically requires several weeks.[18,22] In cases in which surgical necrosectomy may require splenectomy, prophylactic vaccination against encapsulated organisms is indicated.

REFERENCES

1. Forsmark CE, Baillie J. AGA Institute technical review on acute pancreatitis. *Gastroenterology.* 2007;132:2022-2044.
2. Brown A, Orav J, Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. *Pancreas.* 2000;20:367-372.
3. Lankisch PG, Mahlke R, Blum T, Bruns A, Bruns D, Maisonneuve P, Lowenfels AB. Hemoconcentration: an early marker of severe and/or necrotizing pancreatitis? A critical appraisal. *Am J Gastroenterol.* 2001;96:2081-2085.
4. Lankisch PG, Blum T, Maisonneuve P, Lowenfels AB. Severe acute pancreatitis: when to be concerned? *Pancreatology.* 2003;3:102-110.
5. Agarwal N, Pitchumoni CS, Sivaprasad AV. Evaluating tests for acute pancreatitis. *Am J Gastroenterol.* 1990;85:356-366.
6. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. *Radiology.* 1990;174:331-336.
7. Cohen S, Bacon BR, Berlin JA, et al. National Institutes of Health State-of-the-Science Conference Statement: ERCP for diagnosis and therapy, January 14-16, 2002. *Gastrointest Endosc.* 2002;56:803-809.
8. Beger HG, Rau B, Isenmann R, Schwarz M, Gansauge F, Poch B. Antibiotic prophylaxis in severe acute pancreatitis. *Pancreatology.* 2005;5:10-19.
9. Abou-Assi S, O'Keefe SJ. Nutrition in acute pancreatitis. *J Clin Gastroenterol.* 2001;32:203-209.
10. Gloor B, Muller CA, Worni M, Stahel PF, Redaelli C, Uhl W, Buchler MW. Pancreatic infection in severe pancreatitis: the role of fungus and multiresistant organisms. *Arch Surg.* 2001;136:592-596.
11. Bassi C, Larvin M, Villatoro E. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev.* 2003:CD002941.
12. Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev.* 2006:CD002941.
13. Isenmann R, Runzi M, Kron M, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. *Gastroenterology.* 2004;126:997-1004.
14. Dellinger EP, Tellado JM, Soto NE, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. *Ann Surg.* 2007;245:674-683.
15. Bai Y, Gao J, Zou DW, Li ZS. Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in acute necrotizing pancreatitis: evidence from a meta-analysis of randomized controlled trials. *Am J Gastroenterol.* 2008;103:104-110.
16. Pitout JD, Nordmann P, Laupland KB, Poirel L. Emergence of enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) in the community. *J Antimicrob Chemother.* 2005;56:52-59.
17. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing enterobacteriaceae: an emerging public-health concern. *Lancet Infect Dis.* 2008;8:159-66.
18. Rodriguez JR, Razo AO, Targarona J, et al. Debridement and closed packing for sterile or infected necrotizing pancreatitis: insights into indications and outcomes in 167 patients. *Ann Surg.* 2008;247:294-299.
19. Voermans RP, Eisendrath P, Bruno MJ, Le Moine O, Deviere J, Fockens P. Initial evaluation of a novel prototype forward-viewing US endoscope in transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc.* 2007;66:1013-1017.
20. Voermans RP, Veldkamp MC, Rauws EA, Bruno MJ, Fockens P. Endoscopic transmural debridement of symptomatic organized pancreatic necrosis (with videos). *Gastrointest Endosc.* 2007;66:909-16.
21. Wang AY, Condron SL, Galysh R, Yeaton P. Fully-covered self-expandable metallic stents facilitate effective endoscopic pancreatic necrosectomy. *Gastrointest Endosc.* 2008;67:AB332.
22. Werner J, Hartwig W, Hackert T, Buchler MW. Surgery in the treatment of acute pancreatitis: open pancreatic necrosectomy. *Scand J Surg.* 2005;94:130-134.

Tutorials in Medicine

A Middle-Aged Man with Chest Pain and ST-Segment Elevation

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A 43-year-old man with chest pain and without significant medical history presented to the emergency department (ED) of the University of Virginia Health System (UVA). The patient reported the onset of pain after physical training at a local gymnasium on the day prior to presentation. The discomfort was increased with ambulation and upper extremity movement, and partially worsened on inspiration. Occasional nausea was noted; he denied other complaints, including dyspnea. Physical examination was normal, including normal vital signs and pulse oximetry; no chest wall tenderness was found. A 12-lead electrocardiogram (ECG) (Figure 1) was performed and revealed normal sinus rhythm with ST-segment elevation and prominent T waves.

Question 1. *Which diagnostic and management strategies are most appropriate in this patient at this time in the evaluation?*

A. Percutaneous coronary intervention (PCI) followed by admission to the coronary care unit.
B. Admission to an observation unit for rule-out of myocardial infarction (MI) and treatment with nitrates, aspirin, and intravenous heparin.
C. Repeat ECG/comparison to prior ECG and treatment with aspirin and nitroglycerin
D. Fibrinolysis

The correct answer is C. The patient received an aspirin and sublingual nitroglycerin. A repeat ECG was performed, which did not reveal significant change in the ST-segment and T-wave abnormalities during a period of approximately 15 minutes. A past 12-lead ECG from approximately 7 months prior (Figure 2) was obtained and did not demonstrate significant differences. He was admitted to an observation unit to rule out MI by use of serial assessment of ECGs and biomarkers.

A is incorrect because the clinical presentation, including results of the 12-lead ECG, are not strongly suggestive of ST-elevation MI (STEMI); thus PCI is not indicated at this time.

B is incorrect. Although the clinical presentation is not strongly suggestive of STEMI, concern nonetheless remains in this chest pain patient with ST-segment elevation; thus the need remains to rule out STEMI.

D is incorrect because at this point, the clinical suspicion for STEMI is low, and thus emergent fibrinolytic reperfuson therapy is not indicated.

Question 2. *Which clinical syndromes/ECG findings are typically NOT associated with significant ST-segment elevation?* (More than 1 answer may be correct.)

A. Sodium channel blocker cardiotoxicity.
B. Acute myopericarditis.
C. Pulmonary embolism.
D. Left bundle-branch block.
E. Benign early repolarization (BER).

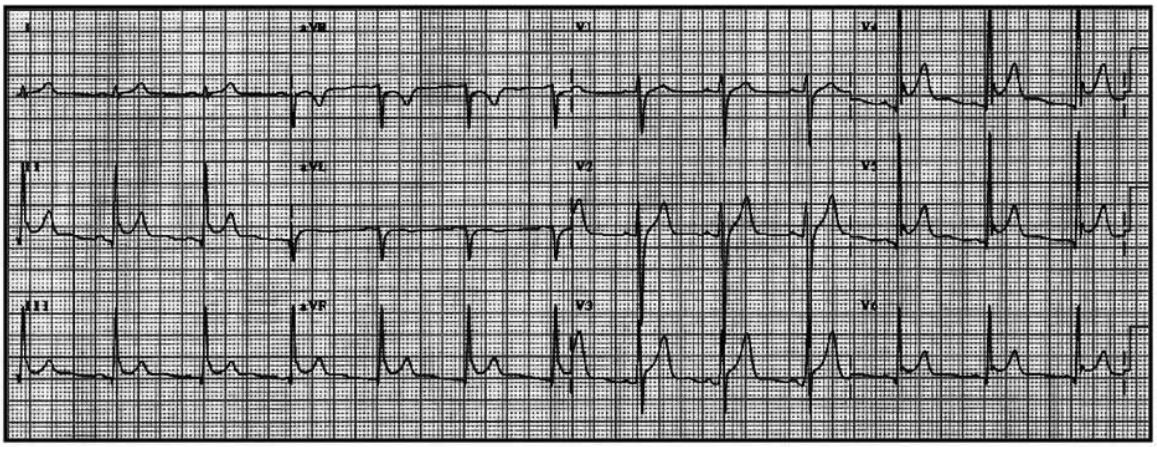

Figure 1. Patient's 12-lead electrocardiograph on presentation. Note the widespread ST-segment elevation.

F. Non-ST-elevation MI (NSTEMI).
G. Hypomagnesemia.
H. STEMI.

The correct answers are A, C, F, and G. None of these entities typically present with ST-segment elevation.

Incorrect answers are B, D, E, and H. Acute myopericarditis, left bundle-branch block, BER, and STEMI can all demonstrate ST-segment elevation.

Question 3. *What is the most likely etiology of the ST-segment and T-wave abnormalities observed on the ECG studies in this particular patient?*
A. STEMI.
B. Acute myopericarditis.
C. BER.
D. Left bundle-branch block.

The correct answer is C. The ECG findings (Figure 1) were felt to indicate BER. The chest radiograph was normal and routine basic laboratory studies were unrevealing.

A is incorrect. STEMI is unlikely owing to the widespread nature of the elevation coupled with the overall non-ill appearance of the patient.

B is incorrect. Although distinguishing acute myopericarditis from BER is difficult, the presence of similar ECG findings 7 months previously suggests the absence of pericardial inflammation.

D is incorrect because the QRS complex was normal in appearance; thus left bundle-branch block was not possible.

On the basis of the anaylsis of the preliminary findings in this patient and after results of the first biomarker studies were negative, cardiology consultation was sought. The cardiologist performed an imaging study.

Question 4. *What are the most appropriate additional diagnostic studies that, if employed in a timely fashion, can be used to rapidly evaluate for acute coronary syndrome (ACS)?* (More than 1 answer may be correct.)
A. Serial ECGs.
B. Chest radiography.
C. Serial serum marker analysis.
D. Comparison to prior ECGs.
E. Exercise stress testing.
F. Echocardiogram.

The correct answers are A, C, D, and F. All of these answers are potentially correct. Although cardiac catheterization likely would provide the most expeditious answer to this clinical question, this procedure is not indicated in this patient because of the low clinical suspicion.

B is incorrect because chest radiograph offers limited information regarding ACS.

E is incorrect because although exercise stress testing is an appropriate screening modality for significant coronary artery disease, it offers no useful data when exploring active ACS.

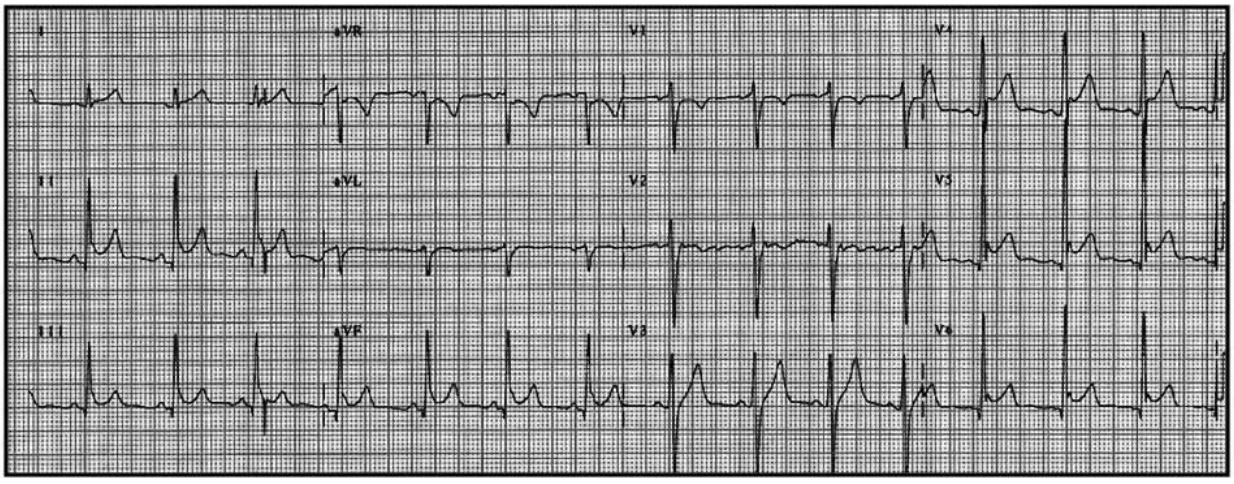

Figure 2. Prior 12-lead electrocardiograph (ECG). This ECG, as well as the ECG from Figure 1, demonstrate benign early repolarization with widespread ST-segment elevation, concave morphology of the elevated segment, notching of the J point, and prominent T waves.

DISCUSSION

BER is a normal electrocardiographic variant with no definitive association with underlying cardiac abnormality.[1] In fact, the clinical significance of BER largely rests on its distinction from other, more ominous cardiac syndromes that present with ST-segment elevation—namely STEMI and acute myopericarditis. The electrocardiographic syndrome of BER is characterized by a pattern of ST-segment elevation with prominent T waves. BER is not an uncommon ECG finding. For instance, this pattern was found in 29% of patients undergoing a screening health examination in the Kaiser system. In this study, those patients with early repolarization were more likely to be male, younger (less than age 40 years), and more athletically active than individuals lacking this finding. The long-term health of this subset of patients was similar to the control population who did not demonstrate BER; there was no increased rate of hospitalization, development of medical events, or higher mortality rate in this Kaiser system patient group.[2]

This pattern is observed in adolescent and adult patients with an age range of 16 to 80 years. As seen in the Kaiser system study, however, BER is usually seen in younger patients with an average age at observation of 39 years; it is uncommonly seen in individuals older than 50 years and rarely encountered in patients older than 70 years.[3,4] For unknown reasons, the BER pattern is seen more commonly in males; it is reportedly observed in African-American males more frequently as well, although this racial difference is somewhat controversial.

Very recent reports challenge the "benign" nature of BER with suggested associations with sudden cardiac death. Shu et al[5] noted the ECG similarities and differences between BER and Brugada syndrome. These 2 ECG diagnoses are associated with significantly different clinical outcomes—BER having a benign natural history and Brugada syndrome being associated with a very high rate of sudden cardiac death. On ECG, BER is characterized by a distinct J wave with associated ST segment elevation in the mid- to left precordial leads V3 through V6; Brugada syndrome, on the other hand, typically demonstrates right bundle-branch block (complete or incomplete) morphology and J wave with ST-segment elevation in the inferior and right precordial leads (V1 and V2). Furthermore, Di Grande and colleagues noted that although clinical findings seem to differentiate the 2 syndromes, similarities between BER and Brugada syndrome (response to heart rate, pharmacologic agents, and neuromodulation) could suggest an association in their underlying pathophysiology. The impact of this pathophysiologic association, however, is as yet unclear.[6]

Considering this potential deadly relationship, Haïssaguerre and colleagues[7] reported an association of BER findings with idiopathic ventricular fibrillation. They noted an increased rate of occurrence of BER in 206 sudden cardiac death patients compared to age-, sex-, and activity-matched control subjects; interestingly, their ECG definition of BER included only ST-segment elevation of at least 0.1 mV (1 mm) in the inferior and/or lateral leads. The reader should recall that BER ST-segment elevation "isolated" to the inferior leads is an uncommon event and should prompt consideration of other, less benign conditions and related outcomes. Thus, at this point, a significant association does not appear to exist between classic BER ECG findings and adverse outcome. The major issue appears to be ECG distinction of true BER from other repolarization syndrome variants such as Brugada syndrome, again highlighting the importance of ECG interpretation skills and patient care. In the Kaiser BER study, the long-term health of these early repolarization patients was similar to that of the non-BER population, with no increased rate of hospitalization, medical events, or mortality.[2]

The ECG features (Figure 3) of benign early repolarization include not only ST-segment elevation but also several other primary ECG characteristics, such as (*a*) concavity of the initial, upsloping portion of the ST segment, (*b*) notching or slurring of the J point, (*c*) slightly asymmetric, prominent T waves, (*d*) widespread distribution of the electrocardiographic abnormalities, and (*e*) relative permanence over time.[1,3,4] ST-segment elevation is the most prominent feature of BER (Figure 3A). Recall that the ST segment begins at the J or "juncture" point of the QRS complex, with the ST segment, extending to the T wave; in the normal state, the ST segment is neither elevated nor depressed. The ST segment is elevated in the BER pattern. The morphology of the elevated ST segment is a key feature of BER—the ST segment appears to have been evenly lifted off the baseline, starting at the J point and extending into the T

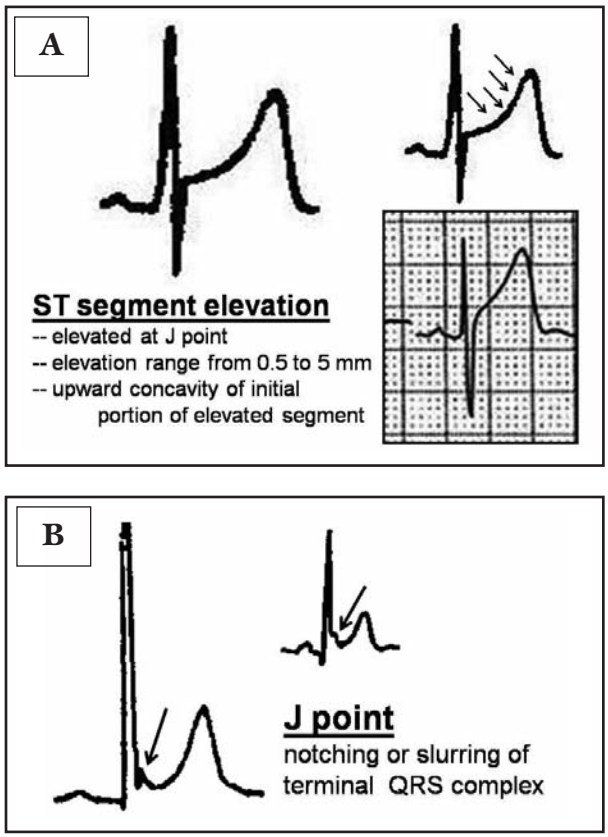

Figure 3. A, ST-segment elevation in benign early repolarization (BER). B, Notching of the J point, a characteristic feature of BER. C, Prominent T waves. D, 12-lead electrocardiograph (ECG) at presentation compared with the prior 12-lead ECG. Note the widespread distribution of the ST-segment–T-wave abnormalities as well as the temporal stability over a period of approximately 7 months.

wave, with preservation of the normal concavity. The magnitude of the elevation ranges from 0.5 to 5 mm, with more prominent ST-segment deviations occurring in the right to mid-precordial leads compared to the limb leads. The vast majority of patients (85%) demonstrate ST-segment elevation less than 2 mm in the precordial leads and less than 0.5 mm in the limb leads. Fewer than 5% of patients, however, will exhibit very prominent ST-segment elevation approaching 5 mm in magnitude. A highly characteristic feature of the elevated ST segment is irregularity of the J point, which is frequently notched, with an irregular contour (Figure 3B). Unfortunately, this finding is not consistently present on all BER ECGs.[1,3,4,7]

Prominent T waves are also encountered (Figure 3C). These T waves are often of large amplitude and concordant with asymmetric morphology. The height of the T waves is usually proportional to the amplitude of the QRS complex; larger QRS complexes are frequently associated with more prominent T waves. The amplitude of the T wave ranges from approximately 4 mm in the limb leads to 6 mm in the precordial leads. Most often, the T wave is concordant with the QRS complex. The contour of the T wave is minimally asymmetric, with the initial, upsloping portion more gradual in its rise to the apex compared to the terminal, downsloping segment with its more abrupt return to the baseline.[4,7]

The regional distribution (Figure 3D) of the ST-segment and T-wave abnormalities is greatest in the precordial leads, particularly the mid- to left precordial leads (leads V2 to V5). The BER pattern frequently demonstrates ST-segment elevation in

the precordial leads, followed by a combination of the precordial and limb leads. Importantly, the limb leads demonstrate ST-segment elevation much less often. In fact, fewer than 10% of patients have ST-segment elevation noted only in the limb leads. This "isolated" ST-segment elevation in the limb leads without similar findings in the precordial leads is uncommon and should prompt consideration of another explanation for the observed ST-segment abnormality, such as inferior STEMI or other more ominous repolarization abnormalities. This is particularly true in light of the somewhat different definition of early repolarization in the Haïssaguerre et al. study and its reported association with sudden death.[7]

The temporal stability, or relative permanence over time, of the pattern is another important feature (Figure 3D). Certainly, during very brief periods of observation in a single patient-care event, the ST-segment and T-wave abnormalities will not change—a useful feature in the differentiation from STEMI. During longer periods of observation, however, the magnitude of the changes can vary. In a very general sense, the longer the period of observation, the less static, or more dynamic the ST segment and T wave. Thus, comparisons over months to several years can demonstrate minimal change; conversely, many years to decades of ECG comparison can reveal significant alterations.[4,8]

The ECG differential diagnosis (Figure 4) of ST-segment elevation includes a number of interpretations, ranging from the malignant (STEMI) to the benign (BER). All patients with chest pain and ST-segment elevation are not experiencing STEMI, however. Four investigations of chest pain patients prior to hospitalization and in ED and coronary care unit settings illustrate this diagnostic dilemma very well.[9-12] Otto and Aufderheide, in a prehospital study of adult patients with chest pain reported that STEMI was not diagnosed in the majority of individuals manifesting ST-segment elevation meeting ECG criteria for fibrinolysis. Instead, left ventricular hypertrophy (LVH) and left bundle-branch block were diagnosed in the majority of the cases.[9] In 2 reviews of adult ED chest pain patients with ST-segment elevation on ECG who were treated at the UVA ED, investigators demonstrated that the ST-segment abnormality resulted from STEMI in only 15% to 31% of these populations; again, LVH and left bundle-branch block were seen

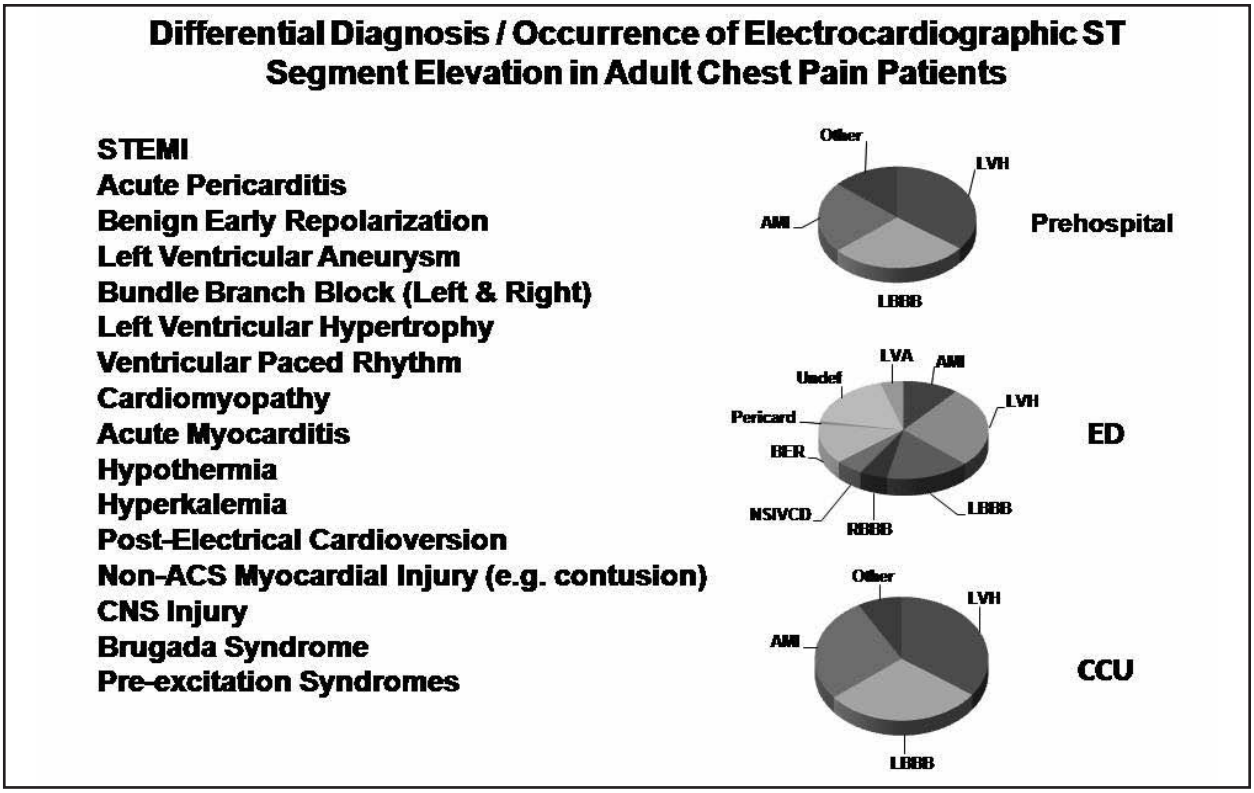

Figure 4. Differential diagnosis and occurrence patterns of electrocardiographic ST-segment elevation in 3 different clinical settings (prehospital, emergency department, and coronary care unit).

more often. In both of these settings, other findings associated with the ST-segment elevation included BER, acute myopericarditis, bundle-branch block, ventricular paced rhythm, and ventricular aneurysm.[10,11] In a more highly selected population in the coronary care unit, Miller et al[12] demonstrated that ST-segment elevation was noted frequently but was due to STEMI in only 50% of such patients.

With this rather broad spectrum of clinical entities causing ST-segment elevation, the clinician's ability to interpret the ECG in this setting directly impacts early therapy decisions and potentially affects the ultimate outcome. For example, a report by Sharkey et al noted that 11% of patients receiving fibrinolytic therapy for presumed STEMI were not experiencing acute MI; the ECG syndromes producing this pseudo-infarct ST-segment elevation included BER (30%), LVH (30%), and various intraventricular conduction abnormalities (30%).[13] Considering only BER and its occurrence in the various populations, this pattern is a not infrequent cause of ST-segment elevation in the acute care setting. For instance, BER has been reported to occur at variable frequency, depending on the specific population studied; 1% (general population), 2% (military recruits), 15% to 20% (ED chest pain patients), 23% to 48% (ED cocaine patients with chest pain), 29%,(routine physical examination patients). and 30% (coronary care unit patients admitted for rule–out of MI).[2,3,10,11,13-15]

Certainly, the adult chest pain patient who demonstrates ST-segment elevation must be rapidly evaluated; this rapid evaluation primarily focuses on the question of whether the patient is experiencing a STEMI. A number of ECG syndromes can be excluded quickly if the QRS complex is normal in both amplitude and duration. Bundle-branch block, ventricular paced patterns, and other intraventricular conduction abnormalities are excluded by noting a normal QRS complex width; LVH is removed from consideration by noting the absence of significant forces (ie, large amplitude of Q and R waves in leads V1 and V6, respectively). The ECG differential diagnosis can be further narrowed by deleting left ventricular aneurysm from the list if the patient does not have a past history of MI. Once these differential considerations have been made, the list of likely possibilities is narrowed, at this stage including STEMI, BER, and acute pericarditis.

Acute pericarditis and BER are often difficult to distinguish on the ECG. The ST-segment elevation encountered in the 2 syndromes is similar, both demonstrating a concavity of the initial, upsloping portion of the ST-segment–T-wave complex; thus, waveform analysis will likely be unrevealing in this particular application. The ST-segment elevation seen in acute pericarditis tends to be more widely distributed across the ECG. In pericarditis patients, the PR segment is frequently depressed, particularly in leads II, III, aVf, and V6; the PR segment is also elevated in lead aVr in such instances. The PR segment is usually normal in BER.[4,16,17] The T wave is frequently prominent in both acute pericarditis and BER and therefore of limited differential power. A comparison of the T wave to the ST segment, however, can be more helpful; a ration greater than 0.25 in lead V6 strongly suggests pericarditis.

The distinction of BER from STEMI, a more significant differentiation from pericarditis, is made by using several ECG tools, including an analysis of the ST segment, the presence of reciprocal change, and evolutionary changes. The initial, upsloping portion of the ST segment is concave in BER compared to the flattened, obliquely straight, or convex pattern observed in the STEMI patient.[10] By no means should this analysis tool be used to rule out STEMI in a patient with an otherwise consistent presentation. This morphologic analysis is not perfect; patients with STEMI may demonstrate concavity of this portion of the waveform, especially in patients with inferior ST-segment elevation MI or in patients presenting early in symptom onset during the hyperacute phase of injury. Smith has demonstrated that STEMI early in its course not infrequently presents with a concave form of the elevated ST segment.[18] Conversely, patients suffering nonacute MI may also manifest a nonconcave ST-segment presentation.

Reciprocal change, defined as ST-segment depression in leads distant from the area of acute infarction, is a very useful ECG finding for identification of STEMI; it is important to note that bundle-branch block, ventricular paced patterns, and LVH are excluded in this definition of reciprocal change. This exclusion is important in that these entities all demonstrate some form of ST-segment depression that is not considered reciprocal change.[9,19] Reciprocal change is not encountered in patients with BER; the ECG finding of ST-segment

depression greater than 1 mm in a patient with ST-segment elevation should suggest the possibility of acute infarction. In fact, the combination of ST-segment elevation greater than 1 mm in 2 anatomically contiguous leads and reciprocal ST-segment depression increases the diagnostic accuracy to more than 90% and indicate that the ST-segment elevation is the result of STEMI in the prehospital chest pain patient.[9] Similar test characteristics are noted in the ED patient population with respect to the reciprocal change and STEMI diagnosis.[19] Lastly, the performance of serial ECGs may demonstrate the dynamic ECG changes usually encountered in ACS patients—thus assisting in making the correct diagnosis. Conversely, waveform abnormalities associated with BER are relatively stable and unlikely to change over the short term compared to the dynamic ECG findings associated with ACS.

CASE CONCLUSION

In our patient the subsequent 12-lead ECGs did not reveal serial change during a 12-hour period; 2 additional biomarkers also remained negative. An echocardiogram was performed which revealed normal wall motion during periods of chest discomfort without evidence of pericardial fluid. The patient was discharged from the ED with a diagnosis of chest pain of uncertain cause; he underwent an outpatient exercise stress test with sestamibi. The results of this test were normal.

REFERENCES

1. Wasserburger RM, Alt WJ, Lloyd C. The normal RS-T segment elevation variant. *Am J Cardiol.* 1961;8:184-192.
2. Klatsky AL, Oehm R, Cooper RA, Udaltsova N, Armstrong MA. The early repolarization normal variant electrocardiogram: correlates and consequences. *Am J Med.* 2003;115:171-177.
3. Mehta MC, Jain AC. Early repolarization on scalar electrocardiogram. *Am J Med Sci.* 1995;309:305-311.
4. Aufderheide TP, Brady WJ. Electrocardiography in the patient with myocardial ischemia or infarction. In: Gibler WB, Aufderheide TP, eds. *Emergency Cardiac Care.* 1st ed. St. Louis: Mosby; 1994:169-216.
5. Shu J, Zhu T, Yang L, Cui C, Yan GX. ST-segment elevation in the early repolarization syndrome, idiopathic ventricular fibrillation, and the Brugada syndrome: cellular and clinical linkage. *J Electrocardiol.* 2005;38:26-32.
6. Di Grande A, Tabita V, Lizzio MM, et al. Early repolarization syndrome and Brugada syndrome: is there any linkage? *Eur J Intern Med.* 2008;19:236-240.
7. Haïssaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med.* 2008;358:2063-2065.
8. Kabara H, Phillips J. Long-term evaluation of early repolarization syndrome (normal variant RS-T segment elevation). *Am J Cardiol.* 1976;38:157-161.
9. Otto LA, Aufderheide TP. Evaluation of ST segment elevation criteria for the prehospital electrocardiographic diagnosis of acute myocardial infarction. *Ann Emerg Med.* 1994;23:17-24.
10. Brady WJ, Syverud SA, Beagle C, et al. Electrocardiographic ST segment elevation: the diagnosis of AMI by morphologic analysis of the ST segment. *Acad Emerg Med.* 2001;8:961-967.
11. Brady WJ, Perron AD, Martin ML, Beagle C, Aufderheide TP. Electrocardiographic ST segment elevation in emergency department chest pain center patients: etiology responsible for the ST segment abnormality. *Am J Emerg Med.* 2001;19:25-28.
12. Miller DH, Kligfield P, Schreiber TL, Borer JS. Relationship of prior myocardial infarction to false-positive electrocardiographic diagnosis of acute injury in patents with chest pain. *Arch Int Med.* 1987;147:257-261.
13. Sharkey SW, Berger CR, Brunette DD, Henry TD. Impact of the elctrocardiogram on the delivery of thrombolytic therapy for acute myocardial infarction. *Am J Cardiol.* 1994;73:550-553.
14. Parisi A, Beckmann C, Lancaster M. The spectrum of ST segment elevation in the electrocardiograms of healthy adult men. *J Electrocardiol.* 1971;4:136-44.
15. Hollander JE, Lozano M, Fairweather P, et al. "Abnormal" electrocardiograms in patients with cocaine-associated chest pain are due to "normal" variants. *J Emerg Med.* 1994;12:199-205.
16. Spodick DH. Differential diagnosis of the electrocardiogram in early repolarization and acute pericarditis. *N Engl J Med.* 1976;295:523-526.
17. Glinzton LE, Laks MM. The differential diagnosis of acute pericarditis from the normal variant: new electrocardiographic criteria. *Circulation.* 1982;65:1004-1009.
18. Smith SW. Upwardly concave ST segment morphology is common in acute left anterior descending coronary occlusion. *J Emerg Med.* 2006;31:69-77.
19. Brady WJ, Perron AD, Syverud SA, et al. Reciprocal ST segment depression: impact on the electrocardiographic diagnosis of ST segment elevation acute myocardial infarction. *Am J Emerg Med.* 2002;20:35-38.

A Career Development Curriculum for Internal Medicine Residents: Practical Application of Suggested Educational Reforms

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In the large academic internal medicine graduate training program at the University of Virginia Health System (UVA), a significant portion of housestaff expressed frustration with resources provided for career development. Because of the lack of a structured program for providing such resources, a significant portion of career training information was being shared informally and unreliably. We assessed the career development needs of our housestaff based on information about careers pursued by former trainees and the desires of current housestaff regarding their career plans. We then developed a longitudinal curriculum to summarize the most important information required for the pursuit of these career paths and transmit this information in a more structured format to internal medicine residents. Subjective indicators suggest that the curriculum has been successful at making housestaff more aware of career options, including novel career opportunities, and how to successfully pursue them.

INTRODUCTION

Many changes in graduate medical education have occurred during the past few years. Greater attention is now paid to outcomes-based research in all disciplines of medicine, including medical education. The Accreditation Council on Graduate Medical Education has played an integral role in transforming training curricula through programs such as the development of the 6 core competencies and ongoing Outcomes Project in 1999[1] and comprehensive work-hours reform in 2003.[2]

Missing from some core competencies are descriptions of the best practices and suggestions on how to accomplish them. Although innumerable texts address the teaching of medical knowledge, communication, and patient care, available literature that describes strategies for instruction on competencies such as professionalism and systems-based practice is less robust. Clearly, professional development and selection of a career track in the health care system involve elements of these latter competencies.

Approximately 30 physicians per year graduate from the internal medicine training program at UVA, and 74% of residents have gone on to fellowships since 2000. Despite this apparent success, in a 2007 year-end survey that asked residents how well they thought the program provided career development and support, the median response on a 9-point scale was 6.

We report on the progress of creating a resident-driven, longitudinal program that addresses many elements of career development, ranging from fellowships, to hospitalist positions, to ambulatory primary care. Consideration has also been given to training in skills that can be applied in multiple areas, such as how to prepare and discuss research and how to be successful in job interviews.

METHODS

Based on internal survey data that indicated housestaff concerns about the quality of career development training, we created a comprehensive curriculum addressing these concerns. Prior to the development of this curriculum, the vast majority of information about careers, fellowships, research, and licensure was exchanged informally between senior and junior residents as a form of "shadow" curriculum. In response, one resident generated an interest group to make this process somewhat more formal. This interest group became the model for our curriculum.

We generated a list of career-development topics we thought would be important to residents. Because the historic trend is for residents to pursue fellowship after completion of our training program, we did focus on fellowships but also included topics such as private practice, locum tenens jobs, and hospitalist positions. Consideration was made to the time of year best suited for some sessions, particularly those addressing fellowship applications. For example, the first *Nuts and Bolts* session was in July, when fellowship applicants are beginning the application process, and the second *Nuts and Bolts* session was in January, just prior to when fellowship programs begin offering interviews.

The basic format was a hybrid of didactic and small-group sessions. Pertinent material was first presented to the entire group, and then small groups were formed based on subspecialty interest (eg, cardiology, gastroenterology). This format gave residents the opportunity to ask questions that were specific to their field of interest. Small groups were led by third-year residents who had recently obtained fellowships, allowing these individuals an opportunity to mentor their more junior colleagues. Having just navigated the fellowship application process the previous year, third-year residents provided invaluable real-world experience. Discussions centered on the previous shadow information, such as which faculty members were the best writers of letters of recommendation, which were good research mentors, and what expectations programs had of applicants aside from their published materials.

Some topics were well suited to the distribution of printed materials to support the goal of career development. In preparing for the session on writing personal statements and completing Electronic Residency Application Service applications, curriculum vitae and personal statements from residents who had successfully obtained fellowships were collected and distributed. We drafted and distributed timelines with suggested milestones for the fellowship application process. Similarly, we collected sample posters and templates for residents to use in preparing to present their research at scientific meetings.

DISCUSSION

Subjective response to this curriculum has been overwhelmingly positive. The geriatrics fellowship program at the University of Rochester has had a similar response to their formal career development curriculum.[3] Attendance at all sessions is consistently high, dramatically higher than it is for many other conferences in the department. We have received a great deal of individual positive feedback about the program and suggestions for the future. Specifically, residents appreciated the dedication of time and resources to career development. Residents have also noted that the information provided was applicable, timely, and presented in a format that can be easily assimilated.

Prior to the availability of this curriculum, residents in our program exhibited a high level of success with the fellowship match process, with approximately 1 in 50 residents failing to match (the average for a 3-year period) in their chosen subspecialty. It therefore would be very challenging to assess the objective impact this program has on the success of our residents in obtaining a fellowship position.

The program will be continued, repeating the cycle annually with regular updates to the printed and presentation materials. We have created a leadership group with representatives from multiple postgraduate-year training levels and departmental staff. We hope this group will ensure that a broad range of interests are addressed and there is sufficient institutional memory to sustain the program.

This curriculum was presented in a workshop at the Association of Program Directors of Internal Medicine 2008 meeting. Feedback indicated that this program could potentially be easily recreated at any academic institution, whereas some community-based institutions were concerned that lack of access to subspecialty training would limit their ability to generate such a program.

Despite these shortcomings, our curriculum seems to have accomplished our goals of identifying the needs of our housestaff and providing them with resources to begin the process of securing a successful career after residency. We believe that

the success of the program is primarily attributable to the fact that the curriculum was conceived and directed by residents who have both an intimate knowledge of the material and a vested interest in helping one another embark on their careers of choice. This type of resident-driven program is in accord with other initiatives to reform graduate medical education.[4-6]

With the appropriate resources dedicated from a residency program and with housestaff initiative to gauge the interest and gather information to support one another in career planning, we believe similar programs can be successful in a wide variety of settings, from large academic institutional graduate medical education curricula to small community-based single residencies.

REFERENCES

1. ACGME Outcome Project. http://www.acgme.org/outcome/ comp/compFull.asp. Accessed 8/15/08.
2. Steinbrook R. The debate over residents' work hours. *N Engl J Med.* 2002;347:1296-1302.
3. Medina-Walpole A, Fonzi J, Katz P. Academic career development in geriatric fellowship training. *J Am Geriatr Soc.* 2007;55:2061-2067.
4. Meyers FJ, Weinberger SE, Fitzgibbons JP, Glassroth J, Duffy D, Clayton CP. Redesigning residency training in internal medicine: the consensus report of the Alliance for Academic Internal Medicine Education Redesign Task Force. *Acad Med.* 2007;82:1211-1219.
5. Weinberger SE, Smith LG, Collier VU. Redesigning training for internal medicine. *Ann Intern Med.* 2006;144:927-932.
6. Fitzgibbons JP, Bordley DR, Berkowitz LR, Miller BW, Henderson MC. Redesigning residency education in internal medicine: a position paper from the Association of Program Directors in Internal Medicine. *Ann Intern Med.* 2006;144:920-926.

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