Facial hyperpigmentation:

Melasma and its mimickers

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Disclosures

- ET Browne and Company
- Novartis Therapeutics
- L’Oreal USA
Acquired disorders of facial hyperpigmentation

- Acquired disorders of facial hyperpigmentation
- Clinical features
- Differential Diagnosis
- Treatment

Skin Color
The most notable aspect of Human Diversity
Acquired disorders of facial hyperpigmentation

- Post inflammatory hyperpigmentation
- Pigmentary demarcation lines
- Riehls hypermelanosis (pigmented contact dermatitis)
- Melasma
- Drug induced hyperpigmentation
- Maturational hyperpigmentation
- Bilateral nevus of Ota-like macules
- Lichen planus pigmentosus

Melasma
Melasma – Epidemiology

- Few population based studies
- Estimated to affect more than 5 million people in the US
- Prevalence varies
  - 8% Latinas
  - 40% Southeast Asian women
- Women > men
Risk factors for melasma

• 5-50% of women with onset after pregnancy
• 8-34% women with melasma on oral contraceptives
• ~50% report a positive family history
• Chronic sun exposure
  • Occupational and recreational
• Anti-depressant/anxiolytic use

Clinical features of melasma

Mean age of onset 38 yrs
Women>men
• Skin phototypes: III-V
• Clinical patterns
  • Location
    • Centro facial (most common)
    • Malar
    • Mandibular
    • Rarely affects forearms
  • Epidermal vs dermal
    • Woods lamp examination less precise in dark skin types
      • Dermal deposition underestimated
• Associated with thyroid disease
• **Chronic course- only 8% will spontaneously remit**
Melasma

Increased number of melanocytes and epidermal melanin

Normal skin

Dermal melanin, melanophages
Solar elastosis, fragmentation of elastic fibers
EM: increase of large single melanosomes

Melasma, a photoaging disorder

Factors from the dermal microenvironment
- Vascularity on dermatoscopy
- Expression of VEGF, bFGF, IL-8
  • Release of mediators-arachidonic acid derivatives & plasminogen
  • Expression of stem cell factor

Endogenous and exogenous factors

Genetic factors
- 50%-64% patients with +FH
- Predisposition in Fitzpatrick Skin Types III – V

Hormonal factors
- Onset and/or worsening during pregnancy, OCPs
- Higher expression of estrogen receptors in lesional skin
- Melanocytes cultured with estradiol proliferate
- BUT no difference in circulating hormone levels of patients v. controls
- Incubation of skin explants with P+E irradiated with UVB → switch towards single melanosome morphology

Solar irradiation
- Photo distribution of skin lesions
- Melanocyte proliferation
- Melanin synthesis
  • Keratinocytes
  • Fibroblasts
- Visible light induces hyperpigmentation in dark skin

Etiology of melasma is unknown
Depigmenting agents and their mechanisms of action

Tyrosinase inhibitors:
- Hydroquinone
- Azelaic acid
- Kojic acid
- Arbutin
- Cysteamine

Increase epidermal turnover:
- Tretinoin
- Lactic acid
- Salicylic acid
- Glycolic acid

Inhibit melanosome transfer:
- Linoleic acid
- Soybean
- Niacinamide

Anti-inflammatory actions:
- Topical steroids
- Liquiritin

Increase epidermal turnover:
- Tretinoin
- Lactic acid
- Salicylic acid
- Glycolic acid

Inhibition of ROS:
- Ascorbic acid
- Polypodium leucotomos

Newer topical agents on the block

Cysteamine 5% cream-
Double blinded randomized study including 50 subjects
Daily application for 4 months.
Statistically significant improvements in Mexameter, MASI, IGA and patient assessment scores at 2 and 4 months

Methimazole 5% cream
Peroxidase inhibitor that blocks melanin synthesis. Minimally absorbed.
Randomized control trial of 50 subjects showed inferiority to 4% hydroquinone

Mechanism of action of tranexamic acid in melanogenesis

[Diagram showing the mechanism of action of tranexamic acid (TXA) in melanogenesis]

TXA Prevents activation of plasmin

Possible route for Tranexamic acid to inhibit melanogenesis

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Oral tranexamic acid (TA) in the treatment of melasma: A retrospective analysis

Hwee Chyen Lee, MRCP; Tien Guan Steven Thng, MRCP; FRCP; and Chee Leok Goh, MD, MRCP
Singapore

Background: Melasma is a common pigmented disorder among Asians and treatment is challenging. Oral tranexamic acid (TA) has emerged as a potential treatment for refractory melasma. Large-scale studies on its use, outcomes, and safety are limited.

Objective: We sought to evaluate treatment outcomes and adverse effects of oral TA in melasma in an Asian population.

Methods: We conducted a retrospective analysis of patients who received oral TA for melasma in a tertiary dermatologic center from January 2010 to June 2014.

Results: In all, 561 patients (91.4% female, 8.6% male) were enrolled. Median duration of treatment was 4 months. The majority (505 [89.7%]) improved, 56 (10.0%) had no improvement, and 2 (0.4%) worsened. Patients without family history of melasma had better response rates than those with family history (90.6% vs 60.0%, P = .03). Of the 503 who improved, response was seen within 2 months of TA initiation, with a relapse rate of 27.2%. Adverse events occurred in 40 (7.1%). Most were transient, but 1 developed deep vein thrombosis requiring prompt discontinuation. She was later given the diagnosis of familial protein S deficiency.

Randomized, placebo-controlled, double-blind study of oral tranexamic acid in the treatment of moderate to severe melasma.

Del Rosario E1, Fierrez-Polack E1, Zayas L J1, Hernandez A1, Tovar-Garza A1, Rodriguez M2, Hyman L8, Pandya AG1

44 Latino women with moderate to severe melasma. Randomized to 2 arms: 250 mg po bid x3 months + sunscreen vs placebo + sunscreen alone.

Results: Both groups improved. TA 49% REDUCTION in MASI vs 18% reduction in the placebo arm.

Melasma recurred when patients were off study meds.

Side effects and contraindications of oral tranexamic acid

• Side effects
  • Headaches
  • Menstrual irregularities
  • Nausea/abdominal bloating (take after a meal)
  • Back pain
  • Disturbances in color vision
  • Low risk of thromboembolic event

• Contraindications
  • History of thromboembolic events/coagulation disorders
  • Use of other prothrombotic drugs (OCPs)
  • Current treatment with blood thinners
# Approach to managing melasma

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<thead>
<tr>
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<th>Alternative agents</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>First line</strong></td>
<td>Triple combination therapy (hydroquinone 4-12%, 0.025% tretinoin, fluocinolone 0.01%) QD- for up to 6 months</td>
<td>Azelaic acid bid (maintenance)</td>
<td>Erythema \n Desquamation \n Pruritus \n Acne \n Confetti-like hypopigmentation \n Exogenous ochronosis</td>
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<td><strong>Second line</strong> (adjunctive therapy for refractory cases)</td>
<td>Glycolic acid chemical peels (30-50%) q 3 weeks x 6 months</td>
<td>Kojic acid \n Monotherapy with salicylic acid –minimal benefit \n Topical tranexamic acid 5% in liposomal base</td>
<td>PIH \n Scarring</td>
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<td>Oral tranexamic acid 325 mg (650 mg tablets)bid x 3 months Microneedling</td>
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<td><strong>Third line</strong> (adjunctive therapy for refractory cases)</td>
<td>Q-switched ruby laser and Q-switched Nd:YAG Picosecond laser Pretreat with HQ for 6 weeks</td>
<td>Intense pulse light provides modest benefit</td>
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UV-VL sunscreen enhanced the lightening affect of HQ UV- VL group showed:
- 15% improvement in MASI score
- 28% improvement in colorimetric values
- 4% improvement in melanin assessments
Post-Inflammatory Hyperpigmentation

**Exceedingly common**
- 58% of Asian acne subjects
- Occurs after inflammation or injury

Increased severity in darker skin

- **Intensity**
- **Duration**
  - 60% of Asian acne patients has PIH lasting more than one year
  - 22% of patients with PIH for more than 5 years
- Excoriation may be a modifiable risk factor
- Patients more concerned with PIH than underlying condition

*Journal of Dermatology 2016; 43:826-828*
At DAY 28 trichloroacetic acid had similar clinical, histologic, and spectroscopic features as acne induced PIH

Reproducible model for studying the mechanism of PIH

PIH can be prevented when the suction blister area remains completely protected from ambient solar exposure.

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- Melasma

- Drug induced hyperpigmentation

- Bilateral nevus of Ota-like macules

- Maturational hyperpigmentation

- Lichen planus pigmentosus
**Acquired Bilateral Nevus of Ota-like Macules (Hori’s Nevus)**

Discrete speckled brown (early) and grey (late) macule – ill-defined borders.

Bilateral malar cheeks

Risk factors – ultraviolet exposure and contraceptive use.

Chinese population based-study; prevalence of 2.5%

90% of cases observed in women

Prevalence rate peaks in the late forties

Histopathology
- Bipolar melanocytes in the papillary/mid dermis
- Perivascular distribution

Pathogenesis
- “Two hit theory” – faulty migration of inactive melanocytes in early life- reactivation by triggering factor
Picosecond laser achieved:
1. Significantly better clearance (p<.001)
2. Lower incidence of PIH (27.7% vs 54%) compared to nanosecond laser.
3. Duration of hyperpigmentation was significantly shorter on picosecond treated side.

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Maturational Hyperpigmentation

- Understudied entity
- Facial acanthosis nigricans?
- Brown to black patches – ill defined borders
- Associated with obesity
- Path: epidermal hyperplasia, prominent basal melanin
- Small study: 50% of patients had hyperglycemia and 36% had increased insulin levels
- Treatment: hydroquinone, value of weight loss is unknown.

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Pigmentary Demarcation Lines

- Futcher of Voight lines
- Abrupt transition between areas of darker and lighter pigmentation
- Represents the distribution of peripheral nerves in the skin
- 4000 patients attending a dermatology clinic in India
  - 243 (6%) found to have facial pigmentary demarcation lines
  - Women > men
  - Possible genetic predisposition
- Recalcitrant to treatment

Kathuria S. Indian J Dermatol Venereol Leprol 2012.
Singh N. Pigment Int. 2014.
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Pigmented Contact Dermatitis (Riehl's Hypermelanosis)
**Pigmented Contact Dermatitis (Riehl’s Hypermelanosis)**

- Asymptomatic
- Reticulate slate brown or grey hyperpigmentation
- More prominent on temples and forehead
- Patch test: standard series, hair series, cosmetic series and personal products
- Cetrimonium, gallate mix, thimerosal, and skin lightening creams most common allergens in PCD Indian study.

References:

- J Eur Acad Dermatol Venereol, 28: 1199–1206
- Dermatitis, 2018;5: 264-269

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Lichen Planus Pigmentosus

- Commonly described in India, Latin America and the Middle East.
- Brown to grey macules: forehead/temple and neck
- Asymptomatic
- Etiology unknown: UV, alma oil and mustard oil - possible associations.
- Treatment: tacrolimus 0.1% acitretin, topical corticosteroids.

Associated with frontal fibrosing alopecia
Acquired disorders of facial hyperpigmentation

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Drug Induced Hyperpigmentation

- Accounts for ~20% of cases of acquired pigmentation
- Possible mechanisms:
  - Accumulation of melanin
  - Accumulation of drug
  - Synthesis of new pigment (lipofuscin)
  - Deposition of iron
- Worsens over the course of months to years
- Distribution varies depending on offending agent
Medications associated with facial dyschromia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Clinical dyspigmentation and anatomic distribution</th>
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<tbody>
<tr>
<td>Duanorubicin</td>
<td>Photosensitive distribution</td>
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<tr>
<td>Gefitinib</td>
<td>Diffuse hyperpigmentation of face, trunk and legs</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Blue/grey hyperpigmentation forehead, nose, ears and mucous membranes</td>
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<tr>
<td>Eltrombopag</td>
<td>Photodistributed -Grey hyperpigmentation of the</td>
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<tr>
<td>Phenytoin</td>
<td>Melasma- like hyperpigmentation</td>
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<tr>
<td>Chloroquine and hydroxychloroquine</td>
<td>Photodistributed Fad, oral mucosa, nails</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Violaceous to lilac- face, neck, dorsal hands</td>
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<tr>
<td>Minocycline</td>
<td>Dark, blue macules in areas of acne scarring</td>
</tr>
<tr>
<td>*Bimatoprost, latanoprost</td>
<td>Periocular hyperpigmentation</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Violet/gray, photodistributed</td>
</tr>
<tr>
<td>Chlopromazine</td>
<td>Photodistributed</td>
</tr>
<tr>
<td>Desipramine, imipramine</td>
<td>Blue to slate gray, sun exposed areas</td>
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Facial hyperpigmentation Mimickers of Melasma

Know the differential diagnosis  
Clinical features  
Diagnosis  
Treatment