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Patient: A 60-year-old Thai woman from Kamphaeng Phet

Chief complaint: Bilateral blue-greyish patches on the temporal and periocular areas for 3 years

Present illness:
The 60-year-old woman presented with bilateral blue-greyish macules on the temporal and periocular areas for 5 years. The lesion progressed to bilateral blue-greyish patches and became darkened for 3 years. She denied any topical cream or drug use previously.

Past history: The patient has been diagnosed with chronic myeloid leukemia. She has been concurrently treated with imatinib mesylate 300 mg/day for 7 years.

Family history: No family members experienced the same condition.

Physical examination:
General appearance: A Thai woman, not pale, no jaundice
HEENT: not pale conjunctivae, anicteric sclerae, no lymphadenopathy
Heart & Lungs: Normal
Abdomen: No hepatosplenomegaly
Extremities: No pitting edema

Dermatological examination:
Skin: Bilateral symmetrical multiple ill-defined blue-greyish macules coalescing into patches localized on the both lateral sites of forehead, temporal and periocular areas
Mucosae: Bilateral blue-greyish macules on the upper conjunctivae, blue-greyish patches on the hard palate
Nails: Normal

Histopathology: Slide No.58-2068 (Right face)
A punch biopsy shows unremarkable epidermis with hyperkeratosis. The dermis shows a few dermal melanin-containing dendritic cells in the upper dermis. Inflammatory cells are minimal. Immunohistochemical study shows positive dermal dendritic cells with S100 and Melan-A.

Diagnosis: Imatinib mesylate induced acquired dermal melanocytosis

Treatment: Q-switched Nd:YAG 1064 nm, 3% Hydroquinone cream apply before bedtime.

Discussion:
Imatinib mesylate is a tyrosine kinase inhibitor. It has been approved for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST).1 In clinical trials with imatinib mesylate, common side effects of nausea, emesis, diarrhea, periorbital edema, fluid retention, and myelosuppression have been documented.2

Cutaneous adverse effects include superficial edema (48–65%), maculopapular rash (~67%), pigmentary changes with hypo/depigmentation (41%), hyperpigmentation (~4%), the other are lichenoid reaction, psoriasiform rash/psoriasis, pityriasis rosea-like eruption, acute generalized exanthematous pustulosis, Stevens–Johnson syndrome, urticaria, neutrophilic dermatosis, xerosis and chelitis has been reported.

Many reports have described pigmentary changes secondary to treatment with imatinib mesylate. They are generally characterized by localized, patchy, or diffuse hypopigmentation and depigmentation but rarely hyperpigmentation. The median time of onset of pigmentary changes is 4 weeks (range 2–14) after the initiation of therapy. The localized changes may diffusely spread over the next few weeks.3 The pigmentary change is usually reversible with a dose reduction or discontinuation of therapy.

There are only a few case reports of imatinib mesylate induced hyperpigmentation. Pigmentation associated with imatinib mesylate has been described not only in the skin, but also involving the palatal mucosa, nails, teeth, gums, and hair.4-6 The mechanism of this pigmentation remains exclusive. It has been attributed to the formation of a drug–melanin metabolites. Other proposed theories include drug-induced cytotoxic response to epidermal ‘neo antigen’ and the presence of a specific KIT mutation and its interaction with other receptors.7
### Report cases of hyperpigmentation caused by imatinib mesylate and histopathology

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age, years/ Sex</th>
<th>Disease</th>
<th>Dosage, mg/day</th>
<th>Time to onset</th>
<th>Skin eruption</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexandrescu et al. (2008)</td>
<td>50/M</td>
<td>GIST</td>
<td>600</td>
<td>8 weeks</td>
<td>Hyperpigmentation of the back</td>
<td>Increased basal melanin pigment and a mild perivascular lymphohistiocytic infiltrate with melanin incontinence and melanophages</td>
</tr>
<tr>
<td>Li et al. (2012)</td>
<td>3 cases</td>
<td>CML/pelvic fibromatosis</td>
<td>400</td>
<td>4, 10 years</td>
<td>Grey-blue pigmentation of the hard palate</td>
<td>Deposition of fine, dark-brown, spherical granules in the dermis due to deposition of drug metabolites.</td>
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<tr>
<td>Kim et al. (2012)</td>
<td>65/F</td>
<td>GIST</td>
<td>400</td>
<td>Few months</td>
<td>Brownish or slate-blush pigmented patches appeared on the face, supraclavicular and scapular area</td>
<td>Scattered, spindle-shaped cells and dendritic cells containing abundant brown pigment in the dermis</td>
</tr>
<tr>
<td>Kagimoto et al. (2014)</td>
<td>62/F</td>
<td>GIST</td>
<td>300</td>
<td>8 months</td>
<td>Violaceous-grey of face, back and buccal mucosa</td>
<td>Lichenoid drug eruption</td>
</tr>
<tr>
<td>Song et al. (2014)</td>
<td>58/M</td>
<td>CML</td>
<td>ND</td>
<td>-</td>
<td>Ill-defined slate grey patch on the nose and hard palate</td>
<td>Increased basal pigmentation and dermal melanophages</td>
</tr>
<tr>
<td>Balasubramanian et al. (2015)</td>
<td>60/F</td>
<td>CML</td>
<td>400</td>
<td>6 months</td>
<td>Hyperpigmentation on the face, chest, extensor aspect of forearm</td>
<td>Increased number and activity of melanocytes in the epidermis</td>
</tr>
<tr>
<td>Ghuwawat et al. (2016)</td>
<td>5 cases</td>
<td>GIST/CML</td>
<td>400</td>
<td>1-6 months</td>
<td>Increased basal layer pigmentation with elastic degeneration in the upper dermis</td>
<td></td>
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</table>

Our patient presented with blue-greyish macules coalescing into patches localized on the face 2 years after the onset of imatinib administration. The histopathology shows few dermal melanin-containing dendritic cells in the upper dermis and immunohistochemical studies show S100 and Melan-A positivity. This case is considerably compatible with imatinib mesylate induced acquired dermal melanocytosis similarly to a case report from Kim et al in 2012.

There is no standard treatment of imatinib induced hyperpigmentation. Regarding the reversible nature of the pigmentation after discontinuation of the drug. Ghuwawat et al. treated their patient with modified Kligman's regimen (0.5% tretinoin + 4% hydroquinone + 0.1% fluocinolone acetonide) along with broad spectrum sunscreen with improvement noted after 6 weeks of therapy. Unfortunately, many case reports have not shown satisfactory improvement of the treatment as the patients need to continue imatinib therapy. Our patient has been treated with Q-switched Nd:YAG 1064 nm and 3% hydroquinone cream to apply before bedtime.

**Reference:**