Imatinib mesylate induced acquired dermal melanocytosis: A Rare Case Report.

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ABSTRACT:

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Imatinib mesylate induced acquired dermal melanocytosis is a very rare condition. Many reports have linked secondary pigmentary changes to treatment with imatinib mesylate. These changes are generally characterized by hypopigmentation and depigmentation but rarely hyperpigmentation. Among hyperpigmentation case reports, only one case of imatinib mesylate induced acquired dermal melanocytosis has been reported until now. We report case of a patient who presented with bilateral blue-greyish macules and patches on the temporal, periocular areas, upper conjunctivae and the hard palate. The patient has been diagnosed with chronic myeloid leukemia and concurrently treated with imatinib mesylate 300 mg/day. The skin biopsy was performed to confirm the diagnosis. Histopathology of the skin lesion showed few dermal melanin-containing dendritic cells in the upper dermis. Immunohistochemistry revealed positive dermal dendritic cells with S100 and Melan-A. Accordingly, the patient was diagnosed with acquired dermal melanocytosis, mostly from imatinib mesylate induced. The patient was treated with Q-switched Nd:YAG 1064 nm and 3% hydroquinone cream. Consequently, there has been a slight improvement of the patient's lesions. However, the patient could not discontinue taking imatinib mesylate due to the treatment for leukemia.

Key word: acquired dermal melanocytosis, imatinib mesylate, Q-switched Nd:YAG 1064 nm

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บทคัดย่อ:

ภูริชญ์ ภูรีศรีศักดิ์ ทนงเกียรติ เทียนถาวร รายงานผู้ป่วยที่เกิดปานดำชนิด DERMAL MELANOCYTOSIS จากยาอิมมาตินิบมีไซเลต (IMATINIB MESYLATE) วารสารโรคผิวหนัง 2560; 33: 297-305.

สถาบันโรคผิวหนัง กรมการแพทย์ กระทรวงสาธารณสุข

ยาอิมมาตินิบมีไซเลต (imatinib mesylate) ทำให้เกิดปานดำชนิด dermal melanocytosis เป็นภาวะที่พบได้น้อย มีหลายรายงานก่อนหน้าแสดงถึงการเปลี่ยนแปลงของสีผิวหลังจากได้รับยา อิมมาตินิบมีไซเลตโดยส่วนมากกล่าวถึงผิวสีขาวขึ้น แต่สีผิวคล้ำหลังได้รับยาพบได้น้อยกว่า ก่อนหน้านี้มีเพียงหนึ่งรายงานที่ทำให้เกิดปานดำชนิด dermal melanocytosis รายงานฉบับนี้เป็นการนำเสนอผู้ป่วยที่มีปื้นดำบริเวณขมับ รอบตา ตาขาว และเพดานปาก ก่อนหน้านี้ผู้ป่วยได้รับการวินิจฉัยเป็นมะเร็งเม็ดเลือดขาวเรื้อรังชนิดมัยอีลอยด์และได้รับการรักษา โดยรับประทานยาอิมมาตินิบมีไซเลต 300 มก.ต่อวัน ลักษณะทางพยาธิวิทยาและย้อมพิเศษเพิ่มเติม ของปื้นดำบริเวณหน้าเข้าได้กับปานดำชนิด dermal melanocytosis ผู้ป่วยได้รับการรักษาด้วย เลเซอร์และยาทาหลังจากติดตามผลการรักษาพบว่าปื้นดำจางลง อย่างไรก็ตามผู้ป่วยจำเป็นต้องรับประทานยาอิมมาตินิบมีไซเลตต่อเพื่อรักษาโรคมะเร็งเม็ดเลือดขาวเรื้อรังชนิดมัยอีลอยด์

คำสำคัญ: ยาอิมมาตินิบมีไซเลต, ปานดำชนิด dermal melanocytosis

Introduction:

Imatinib mesylate is one of the first tyrosine kinase inhibitors[1]. The drug inhibits tyrosine kinases, including *bcr-abl*, c-Kit, and platelet-derived growth factor receptors (PDGFR), which are central to the pathogenesis of human cancer. It has been approved for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST). The drug has also shown efficacy in the treatment of metastatic dermatofibrosarcoma protuberans, hypereosinophilic syndrome, other chronic myeloproliferative diseases, systemic mastocytosis, and AIDS- related Kaposi's sarcoma. Recently, the efficacy for systemic sclerosis and nephrogenic systemic fibrosis has also been reported[2].

In most clinical trials with imatinib mesylate, common side effects of the drug include nausea, emesis, diarrhea, periorbital edema, fluid retention, and myelosuppression[3]. Approximately 7% to 88.9% of patients in different series experienced cutaneous reactions in which the occurrence and severity were associated with the drug dosage. The reported cutaneous reactions include superficial edema (48–65%), maculopapular rash (~67%), pigmentary changes with hypo/depigmentation (41%), and hyperpigmentation (~4%)[2]. In addition, the other drug reactions consist of lichenoid reaction, psoriasiform rash/psoriasis, pityriasis rosea-like eruption, acute generalized exanthematous pustulosis, urticarial, neutrophilic dermatosis, xerosis and chelitis[2]. Severe reactions

such as exfoliative dermatitis, toxic epidermal necrolysis and Stevens Johnson syndrome could also occur[4].

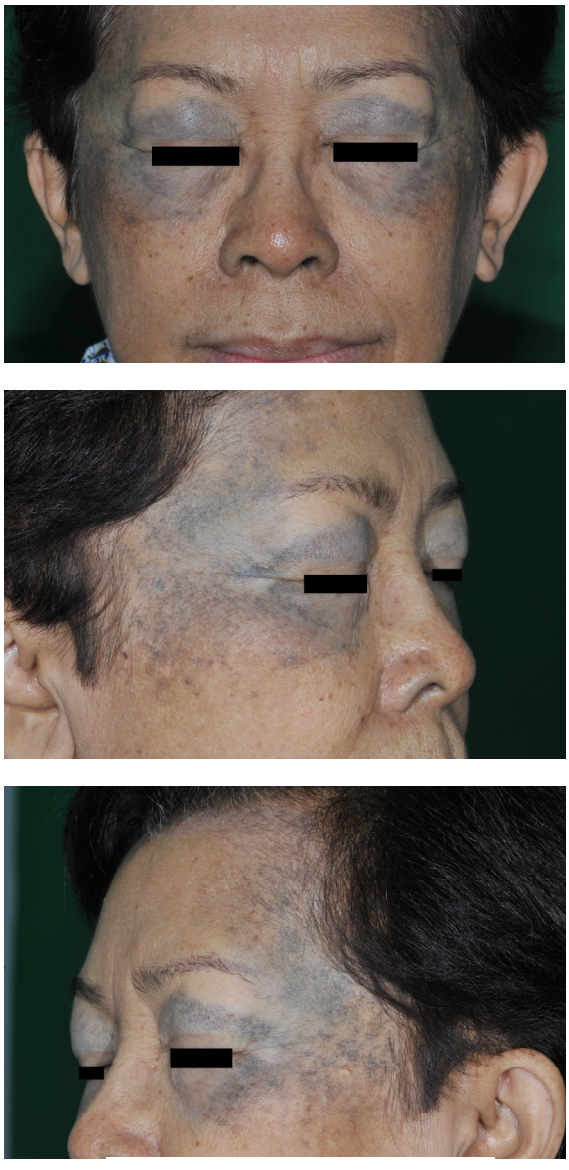

Figure 1 bilateral blue-greyish macules and patches on the temporal, periocular areas

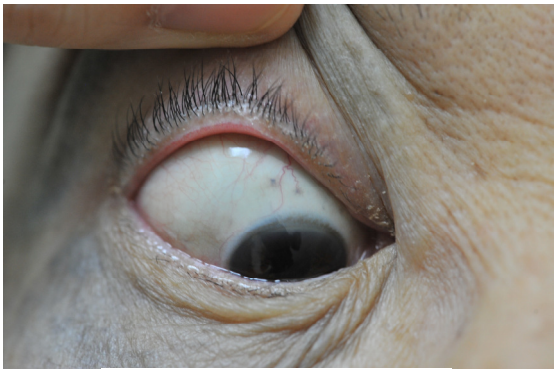

Figure 2 blue-greyish on the right upper conjunctiva

Figure 3 blue-greyish on the left upper conjunctiva

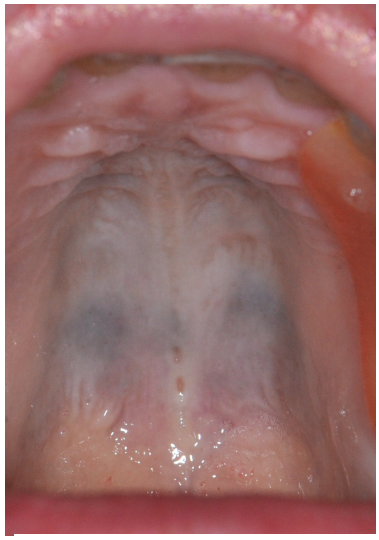

Figure 4 blue-greyish patches on the hard palate

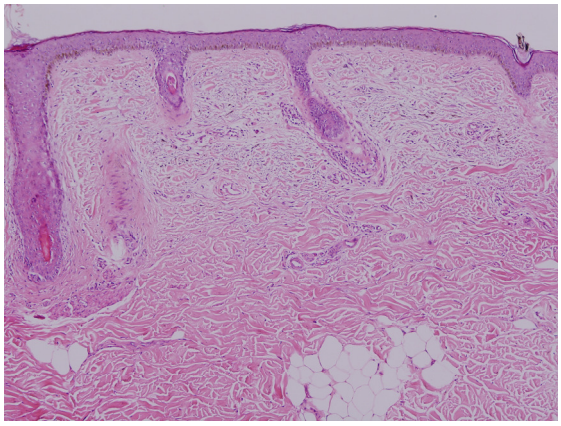

Figure 5 H&E 10x

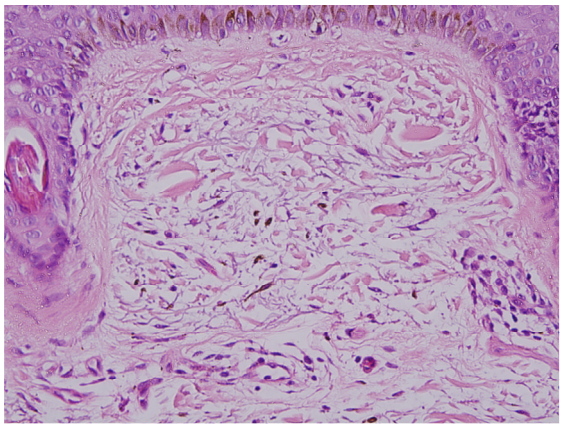

Figure 6 H&E 40x

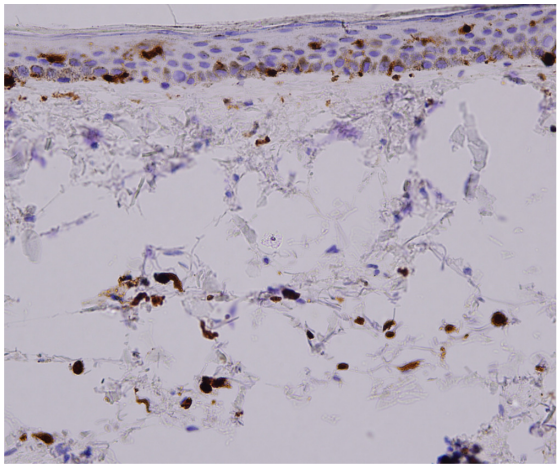

Figure 7 Melan-A 40x

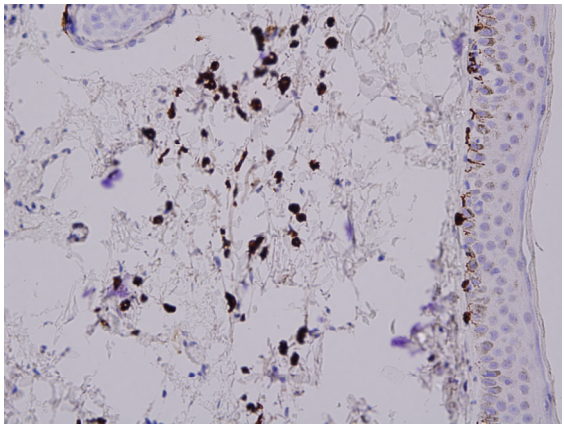

Figure 8 S100 40x

Many reports have described the secondary pigmentary changes to the treatment with imatinib mesylate. Pigmentary changes are generally characterized by localized, patchy, or diffuse hypopigmentation and depigmentation but rarely hyperpigmentation[2]. On average, the onset of pigmentary changes is 4 weeks (range 2–14) after the initiation of the therapy. The localized changes may diffusely spread over the next few weeks[5]. The pigmentary changes are usually reversible with a dose reduction or discontinuation of the therapy[2]. To date, among the rare hyperpigmentation reported cases, only one case of imatinib mesylate induced acquired dermal melanocytosis has been reported. We report here the same diagnosis; however, the patient in our case presented with hyperpigmentation on the skin, and the conjunctiva and palatal mucosa. The patient also responded to laser and topical treatment.

Table 1 Report case of hyperpigmentation caused by imatinib mesylate and histopathology

Authors	Age, years/Sex	Disease	Dosage, mg/day	Time to onset	Skin eruption	Histopathology
Alexandrescu et al.[3] (2008)	50/M	GIST	600	8 weeks	Hyperpigmentation of the back	Increased basal melanin pigment and a mild perivascular lymphohistiocytic infiltrate with melanin incontinence and melanophages
Li et al.[22] (2012)	3 cases	CML/pelvic fibromatosis	400	4, 10 years	Grey-blue pigmentation of the hard palate	Deposition of fine, dark-brown, spherical granules in the dermis due to deposition of drug metabolites.
Kim et al.[12] (2012)	65/F	GIST	400	Few months	Brownish or slate-bluish pigmented patches appeared on the face, supraclavicular and scapular area	Scattered, spindle-shaped cells and dendritic cells containing abundant brown pigment in the dermis
Kagimoto et al. (2014)	62/F	GIST	300	8 months	Violaceous-grey of face, back and buccal mucosa	Lichenoid drug eruption
Song et al.[16] (2014)	58/M	CML	ND	-	Ill-defined slate grey patch on the nose and hard palate	Increased basal pigmentation and dermal melanophages
Balasubramanian et al. (2015)	60/F	CML	400	6 months	Hyperpigmentation on the face, chest, extensor aspect of forearm	Increased number and activity of melanocytes in the epidermis

Authors	Age, years/Sex	Disease	Dosage, mg/day	Time to onset	Skin eruption	Histopathology
Ghunawat et al.[21] (2016)	5 cases	GIST/CML	400	1-6 months	Melasma-like pigmentation on the forehead and cheek	Increased basal layer pigmentation with elastotic degeneration in the upper dermis
Our case	60/F	CML	300	2 years	blue-greyish macules and patches on the temporal, periocular areas, upper conjunctivae and hard palate	few dermal melanin-containing dendritic cells in the upper dermis

M, male; F, female; ND, Not Determined; GIST, Gastrointestinal stromal tumor; CML, Chronic myeloid leukemia

Case report

A 60-year-old Thai woman from Kamphaeng Phet presented with bilateral blue-greyish macules on the temporal and periocular areas lasting for 5 years. The lesions progressed to bilateral blue-greyish patches and darkened for 3 years. The patient denied any uses of topical cream or drug previously. Furthermore, the patient has been diagnosed with chronic myeloid leukemia and concurrently treated with imatinib mesylate 300 mg/day for 7 years. Physical examination showed bilateral symmetrical multiple ill-defined blue-greyish macules coalescing into patches localized on both lateral sites of the forehead, temporal and periocular areas. Patient's mucosae showed bilateral blue-greyish macules on the upper conjunctivae and blue-greyish patches on the hard palate. Her nails were normal. Neither hepatosplenomegaly nor lymphadenopathy was present. Initially, the differential diagnoses were dermal melanocytosis, melasma, exogenous ochronosis and riehl's melanosis. However, histopathology of the skin lesion showed normal epidermis and there were few dermal melanin-containing dendritic cells in the upper dermis. Inflammatory cells were minimal. An immunohistochemical examination showed positive dermal dendritic cells with S100 and Melan-A. Therefore, the final diagnosis is acquired dermal melanocytosis, mostly from imatinib mesylate induced. The patient was treated with two times of Q-switched Nd:YAG 1064 nm combined with 3% hydroquinone cream. During the follow-up appointments, the lesions became lighter; however, the patient still

needs to continue taking imatinib mesylate for the treatment of leukemia.

Discussion:

From the clinical and histopathological perspective, the patient is provisionally diagnosed as dermal melanocytosis which includes a wide variety of acquired and congenital in terms of pathogenesis. In congenital dermal melanocytosis, for example bilateral nevus of Ota, is present with bilateral bluish to slate grey patches over the first (ophthalmic) and second (maxillary) branches of the trigeminal nerve[6]. The conjunctivae and the palatine mucosa are commonly involved[7]. Although the patient in our case has developed the lesions at the age of 55, congenital dermal melanocytosis mostly appears at birth or in childhood, and the latest manifestation was reported at the age of 30[8, 9]. In acquired dermal melanocytosis, the first type is acquired bilateral nevus of Ota-like macules with the presence of bilateral bluish-grey to grey and brown macules over zygomatic regions. It commonly occurs between the ages of 15 to 50[10]. Unlike our case, there is no involvement of the conjunctiva and the palatal mucosa[11]. The second type of acquired dermal melanocytosis that is most applicable to our case is imatinib mesylate induced acquired dermal melanocytosis. There is one reported case in which a patient took imatinib mesylate and developed brownish to slate-bluish pigmented patches on the face, supraclavicular and scapular area[12]. The skin biopsy showed dermal melanocytosis[12]. However, in the reported case, no involvement of the conjunctiva and the palatal mucosa was observed.

Imatinib mesylate is used widely as the first-line treatment for chronic myeloid leukemia (CML)[13]. The doses range from 300 to 800 mg per day, with the lowest and highest doses being administered for CML[14]. There is a marked increase for skin reaction at the doses of 400 mg or more per day[1]. The high doses could contribute to many side effects related to reported cutaneous pigmentary changes such as reported as localized, patchy, or diffuse hypopigmentation and depigmentation, but, rarely, reported as hyperpigmentation[15]. Pigmentation associated with imatinib mesylate does not only appear on the skin, but also the nails, teeth and hair[16-18]. For oral mucosa, hyperpigmentation is most frequently seen on the hard palate followed by soft palate, gum and buccal mucosa respectively[19, 20]. Although the mechanism of imatinib-induced hypopigmentation is well established through the inhibition of c-kit linked to melanocyte development, hyperpigmentation is attributed to the formation of drug–melanin metabolites. Other proposed theories include drug-induced cytotoxic reaction to epidermal 'neo antigen' and

the presence of a specific KIT mutation and its interaction with other receptors[21].

There are other case reports of imatinib mesylate induced hyperpigmentation shown in Table 1, but only one case of imatinib mesylate induced acquired dermal melanocytosis was reported by Kim et al. While the patient in our case has received imatinib mesylate 300 mg/day for two years before the lesions occurred, among the hyperpigmentation cases, the durations of treatment prior to hyperpigmented findings were from 3 months to 10 years over the course of imatinib mesylate therapy[22, 23].

There is no standard treatment of imatinib induced hyperpigmentation[22]. Regarding the reversible nature of the pigmentation after discontinuation of the drug, Ghunawat et al. treated their patients with modified Kligman's regimen (0.5% tretinoin + 4% hydroquinone + 0.1% fluocinolone acetonide) along with broad spectrum sunscreen with the improvement noted after 6 weeks of therapy. Unfortunately, many case reports have not shown satisfactory improvement of the treatment as the patients still need to continue imatinib therapy.

Conclusion:

Most pigmentary changes associated with the side effects of imatinib mesylate are hypopigmentation and depigmentation, but rarely, hyperpigmentation could occur. We report a rare case of the patient with imatinib mesylate treatment causing hyperpigmentation that is acquired dermal melanocytosis. In our case, the patient presented with blue-greyish macules coalescing into patches localized on the face for 2 years after the onset of imatinib administration. The histopathology showed few dermal melanin-containing dendritic cells in the upper dermis and immunohistochemical examination showed S100 and Melan-A positivity. The treatment consists of two times of Q-switched Nd:YAG 1064 nm and 3% hydroquinone. The patient's lesions have slightly improved after the treatments.

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