Posaconazole Induced Diffuse Lentigines: A Case Report

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ABSTRACT

Objective: To report a case of posaconazole induced diffuse lentigines.

Case presentation: A 57-year-old Thai male with acute promyelocytic leukemia who received chemotherapy and antifungal drug prophylaxis then appeared abruptly generalized multiple discrete well-defined brownish macules on face, lips, trunk, back, both arms, forearms, both thighs, legs, both palms and soles about eight days after received posaconazole.

Conclusion: Multiple lentigines could be found in patients who received immunosuppression or immunomodulation, and antifungal drugs such as voriconazole.

Keywords: Drugs induces multiple lentigines; eruptive lentiginosis (Siriraj Med J 2018;70: 182-183)

INTRODUCTION

Lentigo is a skin lesion which is a well circumscribed, light to dark-brown macule. The pathogenesis is included melanocytic hyperplasias which comprise of intraepidermal melanocytic hyperplasia and increased melanin formation. Lentigo simplex is associated with multiple clinical manifestations such as LEOPARD syndrome (lentigines, electrocardiographic (ECG) conduction defects, ocular hypertelorism, pulmonary stenosis, abnormalities of genitals, growth retardation, and sensorineural deafness), and LAMB syndrome (lentigines, atrial myxomas, mucocutaneous myxomas, and blue naevi), and Peutz–Jeghers syndrome.[1,2] LEOPARD syndrome is determined by an autosomal dominant with a mutation in PTPN11 which results in excessive signaling through the RAS/MAP kinase pathway, which can lead to the development of junctional naevi.[2] In the syndromic lentiginosis, the lentigines are usually present at birth or early life and increase in number by age.

Shortly, development of multiple lentigines should raise more concern about medication induced lentigines. The immunosuppressive or immunomodulatory drugs can cause eruptive naevi or eruptive lentiginosis.[2] Furthermore antifungal drugs have been shown to cause generalized lentiginosis.[3,4,5]

CASE PRESENTATION

A 57-year-old Thai male presented with dizziness and dyspnea and was diagnosed with acute myeloid leukemia from bone marrow biopsy in July 2016. Initially, he was admitted for chemotherapy as 3+7 regimen which included cytarabine and idarubicin for 3 days. After flow cytometry result shown as acute promyelocytic leukemia, chemotherapy regimen was changed to all-trans retinoic acid (ATRA) and posaconazole was prescribed for prophylaxis of fungal infection.

After 8 days of posaconazole and ATRA treatment, he abruptly developed generalized multiple discrete well-defined brownish macules on the face, upper lip (Fig 1), trunk, back, both arms, forearms, both thighs, legs, both palms, and soles. The skin lesions were diagnosed as lentigines by dermatologists. He was discharged with posaconazole treatment for prophylaxis of fungal infection was prescribed, because the number of lentigines was continually increasing. Photoprotection and observation for skin cancer were advised.

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Received 28 February 2017 Revised 27 April 2017 Accepted 4 May 2017
doi:10.14456/smj.2018.30

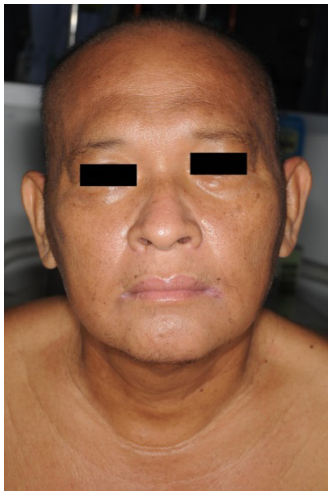

Fig 1. Multiple discrete well-defined brownish macules on face and upper lip representing multiple lentigines in the reported patient.

At follow-up period, posaconazole was withdrawn due to the improvement of leukemic disease. Lentigines faded to light brown macules and no new lesion was detected after 2 months of posaconazole discontinuity.

He had underlying diseases which included hypertension, dyslipidemia, impaired fasting glucose. His current medications were quinapril, atenolol, manidipine, simvastatin, and gemfibrozil which he had received for many years before this current illness.

DISCUSSION

Multiple lentigines could be induced from immunosuppression or immunomodulation, which have been reported in cyclophosphamide, doxorubicin, vincristine, oral prednisolone,[2] etanercept[6] and antifungal drugs such as voriconazole. Voriconazole was frequently reported as a drug which caused diffuse lentigines and photosensitivity.[3,4,5]

Voriconazole is a broad-spectrum triazole antifungal agent which is associated with acute photosensitivity and carcinogenesis of skin. The mechanism of the photosensitivity is unknown, while an indirect retinol effect secondary to the antifungal's impact on CYP450 enzymes has been proposed to contribute to the underlying mechanism. Voriconazole inhibits P450 enzymes, including CYP3A4 and CYP2CP which metabolize tretinoin, which leads to increased retinol levels which might exacerbate the acute photosensitivity.[3] Affected patients may present with photo distributed erythema, cheilitis or erosions (usually of the lower lip which is a sun-exposed area), accelerated photoaging, or pseudoporphyria cutanea tarda.

Chronic phototoxic effects and lentigo formation from voriconazole frequently affects a patient with Fitzpatrick type VI skin. The development of lentiginous pigmentation can be found in both children and adults who received voriconazole.[4] After discontinuation of voriconazole, the skin lesions of sun-exposed areas may leave solar elastotic changes, multiple lentigines, and ephelides.[5]

Posaconazole is the second-generation triazole antifungal agent like voriconazole and is currently approved only for use against invasive fungal infections as prophylaxis in immunocompromised patients.[7] From our literature review, there was no recently reported posaconazole induced photosensitivity. However, in this case, the patient received chemotherapy which included cytarabine, idarubicin, and all-trans retinoic acid (ATRA) which had no reports about inducing lentigines and photosensitivity. Regarding timeline of his medication, the start of posaconazole was associated with the development of skin lesions and improvement of lentigines was demonstrated after stopping posaconazole. Although there was no report that it induced multiple lentigines, this may be due to its recent wide usage. On the other hand, there were many studies which revealed voriconazole-induced multiple lentigines. Posaconazole was the same generation triazole antifungal agent as voricosanazole, therefore posaconazole might induce diffuse lentigines. The more extensive study would be required to determine association and risk factors of posaconazole and multiple lentigines or photosensitivity.

Concerning treatment, most reports of voriconazole-associated squamous cell carcinoma have occurred in immunocompromised patients with elevated risk of skin cancer. Hence, the treatment recommended was photoprotection and surveillance for skin cancer.[4]

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