Case 5

A 70-year-old Thai man from Petchburi

Chief complaint: Multiple blue-black macules and patches on both lower legs for 5 years

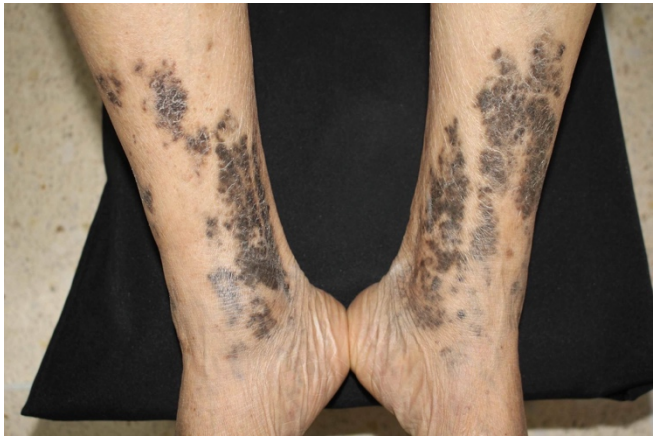

Fig 5.1

Present illness:

A slowly progressive blue-black macules and patches developed on both lower legs for 5 years. The patient was unaware of onset and reported gradual progression. There was no previous trauma or inflammation. No oral, conjunctival mucosa or teeth pigmentary changes.

Past history

- Adult-onset immune deficiency with anti-IFN-γ autoantibody
- Disseminated *M. abscessus* infection with history of Sweet syndrome (currently on clarithromycin 1g/day and doxycycline 200 mg/day for 6 years)
- Hypertension, dyslipidemia (currently on Enalapril, Simvastatin, Aspirin)

Physical examination

- HEENT: No pale conjunctivae, anicteric sclerae
- Lymph node: Not palpable
- Heart: Regular, normal S_1,S_2, no murmur
- Lungs: Normal breath sound, no adventitious sound
- Abdomen: No hepatosplenomegaly
- Extremities: Present of varicose veins, no swelling

Dermatologic examination (Fig 5.1)

- Multiple blue-black macules coalescing into patches on both lower legs
- Solitary erythematous edematous plaque on left lacrimal sac area
- Ill-defined erosive erythematous patch overlying atrophic scar on right mandibular area

Histopathology (S18-17682, Left leg)

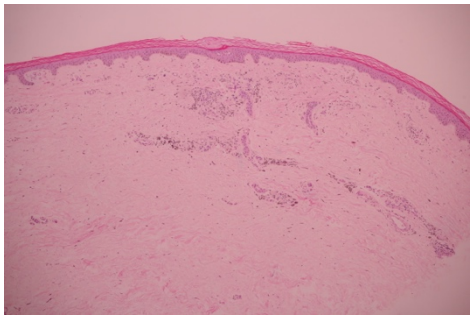

Fig 5.2

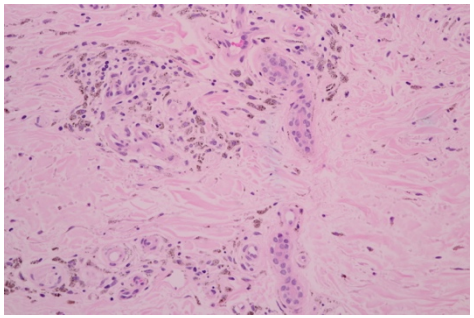

Fig 5.3

- Perivascular inflammatory cells infiltrate of lymphocytes and macrophages filled with brown pigment in the upper to mid dermis
- Dark brown coarse granule pigment within macrophage located in the upper to deep dermis

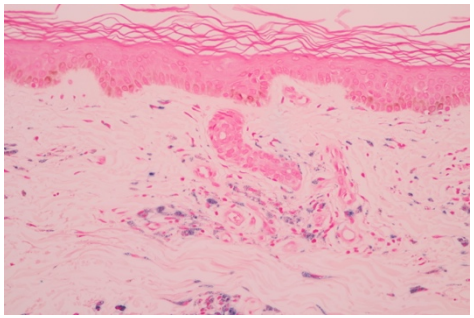

Fig 5.4

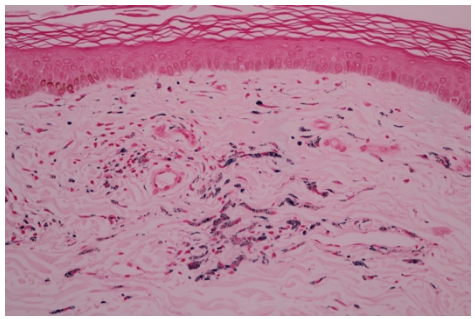

Fig 5.5

Perls stain (Fig 5.4): Positive
Masson Fontan (Fig 5.5): Positive

Diagnosis: Doxycycline-induced hyperpigmentation

Treatment: Q-switched Alexandrite laser (755 nm)

Presenter: Pintusorn Kungvalpivat, MD

Consultant: Somsak Tanrattanakorn, MD

Discussion:
Neutralizing anti-interferon-γ autoantibody associated with adult-onset immunodeficiency was first described in 2012 by Browne et al.[1] and now is an emerging medical issue worldwide. Most of the patients were from East Asia. The mean age of onset was 52±13.7 years[2] without significant difference in sex distribution. IFN-γ and IFN-γ-IL-12 pathway play an important role in the host immune system against mycobacterial pathogens and other opportunistic infections, such as *Salmonella* species and Varicella zoster virus.[1]

Nontuberculous mycobacteria is a common cause of skin, soft tissue, and bone infection.[3] From literature review between 2004 and 2016 by Isano et al.[2] rapidly growing mycobacteria (RGM) were more frequently isolated of all species than slow-growing mycobacteria (SGM) with *M. abscessus* was the most frequently isolated from Thai patients.[2] The most common organs involved were the lymph nodes. Other major involved organs were bones and joints, lungs, blood, skin, bone marrow, soft tissue, liver, pleura, muscle, bronchus and spleen. Lymphadenitis presented most commonly in the cervical region.[2] This indicates *M. abscessus* and most RGM prefer lower temperatures for culture of 30-37°c.

Treatment for *M. abscessus* should be combination therapy with clarithromycin or azithromycin-containing regimen, combined with amikacin plus imipenem or cefoxitin. However, there still is differences in susceptibility pattern among strains and host status, and the antimicrobial minimum inhibitory concentrations (MIC) of these anti-mycobacterial drugs do not always represent in-vivo activity.[4]

Doxycycline is a commonly used antibiotic in the treatment of infections. The biological activity of doxycycline expands beyond their antibiotic mechanisms including anti-inflammatory and anti-degenerative properties, making it beneficial in non-infectious diseases, including dermatological conditions.[5] Well-known side effects of doxycycline are photosensitivity, teeth discoloration, nausea, vomiting and diarrhea.[6] Cutaneous hyperpigmentation is a common side effect of minocycline and, to a lesser extent, of doxycycline which has rarely been described. The higher incidence of pigmentary changes among patients taking minocycline may be the result of prolonged prescription period and higher lipophilic properties which can penetrate tissue more easily.[7],[8]

To date, there were few reports of doxycycline-induced cutaneous hyperpigmentation, with both suprapharmacological and therapeutic doses. The cutaneous hyperpigmentation may be localized in areas of previous inflammation or scars[9] or on the normal skin, especially, of the anterior shin.[5],[6],[10] Previously, biopsies of doxycycline-induced hyperpigmentation revealed increased basal melanization, suggesting activation of melanocytes either by the tetracycline derivatives or by other co-stimulus. Also, the presence of melanin or melanin-like pigment in the histiocytes of the upper dermis was found, in contrast, histiocytes of the lower dermis and subcutaneous fat store pigment with increased amounts of iron and calcium, and no melanosomes were detected suggesting a different nature of the pigment.[6] Furthermore, histochemical and biophysical data suggest the presence of doxycycline, possibly chelated with iron and/or calcium, within the pigment lesions.[8]

The clinical differential diagnosis of hyperpigmentation disorders includes systemic diseases such as Addison's disease and hemochromatosis, medications such as minocycline and amiodarone, and primary skin diseases such as pigmented purpuric dermatosis. A thorough physical examination to document all affected areas may limit the differential based on the distribution of pigmentation. Histologic examination can be helpful to identify the location of pigment, patterns of staining, and features that would be suggestive of a particular condition.

For the treatment of doxycycline-induced cutaneous hyperpigmentation, partial to complete resolution of hyperpigmentation has been described after cessation of prolonged doxycycline therapy in 8 to 12 months.[6],[10] However, recovery may take up to several years.[11] Over the past decade, different Q-switched lasers has been reported for treatment of minocycline-induced cutaneous hyperpigmentation, the excellent results were achieved by Q-switched Alexandrite (755nm) due to the greater depth of penetration.[12],[13],[14],[15] This might considered as therapeutic option for doxycycline-induced cutaneous hyperpigmentation also.

The long-term use of doxycycline for chronic diseases, both infectious and dermatological conditions, is common. Physicians should be aware of irreversible adverse reactions. And patients should be made aware of the possibility of skin and nail changes.

References

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