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Case Report

Co-trimoxazole-induced erythema annulare centrifugum

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Abstract

Erythema annulare centrifugum (EAC) is an infrequent cutaneous disease characterized by figurate erythematous eruptions that enlarge centrifugally at a rate of 1-3 mm/ day with central clearing resulting in an annular or polycyclic appearance. The characteristic skin eruptions of EAC are associated with various underlying systemic disorders, including infections, autoimmune and endocrine diseases, malignancies, and the use of certain drugs like diuretics, non-steroidal anti-inflammatory agents, antimalarials, gold, amitriptyline, finasteride, penicillins, and salicylates, though the causal association has not been established. Lesions usually involve the thighs, legs, and buttocks and are characterized histopathologically by dermal perivascular lymphohistiocytic infiltrate. EAC is a benign self-limited disease.

A 64-year-old man with pulmonary nocardiosis, on treatment with co-trimoxazole, presented with peripherally spreading raised red-coloured eruptions over thighs, buttocks, and arms. He developed similar lesions in the past, which resolved spontaneously. Cutaneous examination revealed multiple discrete annular erythematous plaques over flexural areas, thighs and buttocks. Skin biopsy showed coat-sleeve peri-appendageal inflammatory infiltrate in the dermis. Pulmonary nocardiosis was confirmed by positive cultures from broncho-alveolar lavage and PCR. A diagnosis of erythema annulare centrifugum, deep type, possibly associated with nocardiosis and/or co-trimoxazole, was made. The lesions subsided after stopping co-trimoxazole.

Key words

Erythema annulare centrifugum, pulmonary nocardiosis, co-trimoxazole.

Introduction

Erythema annulare centrifugum (EAC), an uncommon inflammatory skin disorder, is characterized by figurate erythematous eruptions that enlarge centrifugally with central clearing, resulting in an annular or polycyclic appearance.[1] The exact cause of EAC is largely unknown, is considered a reactive process precipitated by infections (bacterial, mycobacterial, viral, fungal, filarial), autoimmune and endocrine diseases (hepatitis, Hashimoto's thyroiditis, Sjogren syndrome), malignancies (squamous cell carcinoma, lymphoma, myeloma, breast cancer) and drugs (penicillin, salicylates, hydroxychloroquine, co-trimoxazole, finasteride, hydrochlorothiazide).[2]

EAC is classified into superficial and deep types; the superficial type of EAC is clinically characterized by the presence of trailing scales at edges of the lesions and histopathologically by the presence of perivascular cellular infiltrate in the superficial dermis with pronounced epidermal changes, whereas the deep type of EAC is characterized clinically by having infiltrated borders and histopathologically by the

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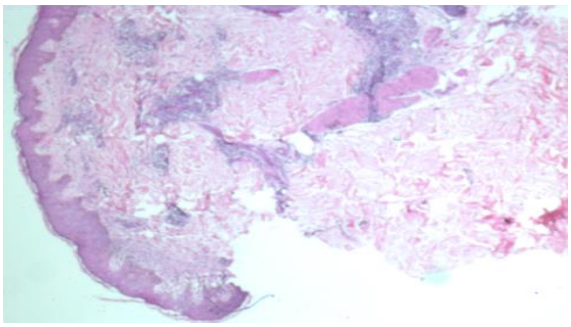
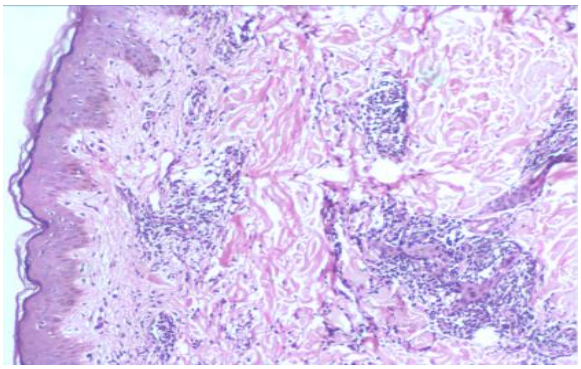
Figures1A & 1B characteristic annular erythematous plaques over the right buttock and left axilla.





Figures 2A & 2B Photomicrograph of histopathology inhaematoxylin-eosin stain showing hyperkeratosis, spongiosis, and coat-sleeve peri-appendageal mononuclear inflammatory infiltrate in the dermis in 4x(Fig 2A) and 40x(Fig 2B) resolutions.

presence of coat sleeve-like perivascular inflammatory infiltrate in the deep dermis with minimal epidermal changes.[3,4] EAC is more prevalent in the fifth decade of life with equal incidence in men and women.[1] EAC may involve any site on the skin, trunk, thighs, legs, and buttocks being more frequently affected.[3] The course of EAC is variable, lasting from days to decades, with a mean of 2.8 years.[1,2]

Case report

A 64-year-old man with pulmonary nocardiosis for six months, on treatment with co-trimoxazole (CTM-trimethoprim 80mg and sulphamethoxazole 400mg) twice a day, presented for dermatology consultation with recurrent history of peripherally spreading raised red-coloured eruptions over both arms associated with pruritus. He developed similar lesions two months ago, which resolved spontaneously within four days. Family history was unremarkable. Cutaneous examination revealed multiple discrete annular erythematous plaques, predominantly over all flexural areas, thighs **(Figures 1A&1B)**, and buttocks of sizes 1-3cm. Examination of hair, nails, oral and genital mucosa found no abnormalities. Skin biopsy from the margin of the annular plaque showed hyperkeratosis, spongiosis, and coat-sleeve peri-appendageal mononuclear inflammatory infiltrate in the dermis **(Figure 2A&2B)**. Skin scrapping for KOH and fungal culture were negative.

Pulmonary nocardiosis was confirmed by positive cultures from broncho-alveolar lavage **(Figure 3A&3B)** and PCR detection as Nocardia beijingensis. Haemogram with peripheral smear, electrolytes, renal, liver, and thyroid function tests were normal. Viral screening (for HIV, Hepatitis B, and C) was non-reactive. ANA, p-ANCA, and c-ANCA

Figure 3A showing colonies of chalky-white cotton candy appearance on the surface indicating Nocardia spp. growth in blood agar.

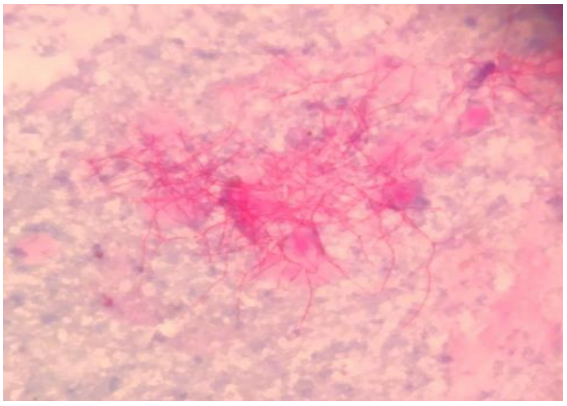


Figure 3B showing thin, fine branching clusters of weakly acid-fast organisms (Nocardia spp.) on acid-fast bacilli stain of culture material.

autoantibodies, CB-NAAT were negative. Radiography of the chest revealed bilateral opacities **(Figure 4)**. CT scan of the chest showed bronchiolitis and bronchiectasis in the right middle lobe and lingua. Abdominal ultrasonography and MRI brain were normal. Based on the above clinicopathological findings, the diagnosis of erythema annulare centrifugum, deep type, possibly associated with nocardiosis and/or co-trimoxazole, was made. The lesions subsided after stopping CTM **(Figure 5)**. He was later started on linezolid. The lesions reappeared upon rechallenge with co-trimoxazole followed by resolution of lesions on discontinuation of the drug.

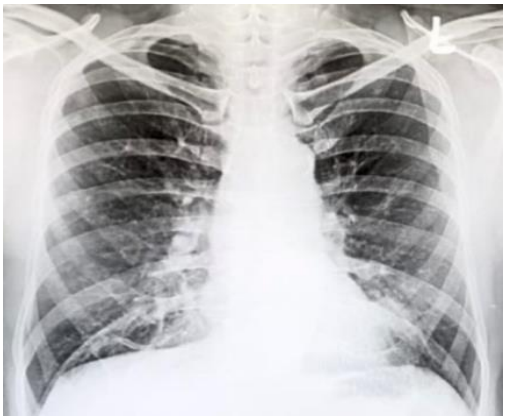


Figure 4 Radiograph chest showing bilateral opacities.

Figure 5 showing healed lesions after discontinuing CTM.

Discussion

EAC is a rare benign inflammatory cutaneous disorder characterized by polycyclic annular erythematous lesions that enlarge centrifugally with central clearing, first described by Darier in 1916 and classified in 1978 by Ackerman into a superficial and a deep type.[1,2,5] Histopathologically, a dense perivascular inflammatory infiltrate is present in the mid and lower dermis.[3] EAC is thought to represent a distinct cutaneous hypersensitivity reaction to different causes and underlying systemic diseases.[2]

The diagnosis in our patient was arrived at after ruling out Tinea corporis (no papules and/or

crusts in the margins, negative family history, and skin scrapings for KOH). Other diagnoses were ruled out based on clinical and biochemical profiles. Histopathological examination of skin biopsy from the margin of the annular plaque confirmed the diagnosis of Erythema Annulare Centrifugum, deep type.

Treatment of the underlying disease often resolves EAC, with the prognosis being excellent, except when associated with underlying malignancy or other systemic diseases.[6] Nevertheless, a complete physical examination and diagnostic workup are crucial to exclude an underlying disorder. However, no causative agent can be identified sometimes, and in these cases, EAC is considered idiopathic.[6] Topical medications like corticosteroids, tacrolimus and calcipotriol, oral metronidazole, subcutaneous etanercept, and subcutaneous interferon-α have been all used with some benefit in EAC.[3]

EAC is often under-diagnosed as there are numerous conditions mimicking EAC, including tinea corporis, subacute cutaneous lupus erythematosus, annular pityriasis rosea, erythema migrans, erythema marginatum, erythema gyratum repens, annular sarcoidosis, necrolytic migratory erythema, granuloma annulare, cutaneous T-cell lymphoma, granuloma faciale, erythema multiforme, secondary syphilis, and Wells syndrome.[1,2,6]

Traditionally reported drug associations with EAC are diuretics, non-steroidal anti-inflammatory agents, antimalarials, gold, amitriptyline, finasteride, penicillins, and salicylates.[2] The eruptions in our patient were thought to be due to pulmonary nocardiosis and/or CTM. But the etiology was later confirmed to be due to CTM administration based on the temporal association with drug use, resolution of the lesions after drug discontinuation, and reappearance of lesions upon rechallenge with the drug and resolution following withdrawal.

Our case is noteworthy as CTM was mentioned as the causative factor of EAC in quite a few cases historically. This case sheds light upon the fact that co-trimoxazole should be considered as a possible causative agent for EAC and highlights the need for a high index of suspicion to detect the causative agent or underlying disorder, as withdrawal of the drug or effective management of the underlying disorder often aids in the resolution of lesions.

Key message There is a need for diagnostic suspicion to detect the underlying disorder or causative agent of EAC, as withdrawal of the drug or effective management of the underlying disorder often aids in the resolution of lesions.

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