Erythema annulare centrifugum: association with autoimmune polyglandular syndrome type 1

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INTRODUCTION

Autoimmune polyglandular syndrome (APS) is a syndrome characterized by multi-endocrine-organ defects due to enhanced autoimmune mechanisms and is caused by mutations in the autoimmune regulator (AIRE) gene 1,2,3. Its rarity and great variability in age of onset and manifestations make early diagnosis difficult.

Erythema annulare centrifugum (EAC) is a figurate erythema characterized by solitary or multiple annular erythematous lesions which may spread outwards or remain stationary 4. They often involve the trunk and proximal parts of the extremities. EAC pathogenesis is not yet completely recognized, but a hypersensitivity reaction to many internal and external stimuli have been highly suggested 4. We report an uncommon association of APS1 and EAC. To authors’ knowledge, only one other case has been reported so far 5.
**CASE REPORT**

An 18-year-old male was referred to our dermatology clinic with skin involvement in the form of multiple purplish annular erythematous plaques spread over his lower trunk and extremities. The lesions first appeared one year ago starting on his hands and arms. Later, new lesions developed over the axillary region, lower abdomen, thighs and legs. The eruptions began as small urticarial papules and plaques, which gradually spread. His lesions were asymptomatic except for mild pruritus. Physical examination revealed plaques with polycyclic progressive borders and fine scaling at the edge of some lesions (Figure 1). The lesions spread in a centrifugal pattern and central clearing was observed in comparison to the lesions’ borders. His mucous membranes, nails, teeth and hair were normal on examination. No fever, other general symptoms, lymphadenopathy, or hepatosplenomegaly were detected, but he complained of muscular weakness in the extremities. His past medical history was uneventful except for diabetes mellitus, first diagnosed three years ago.

On laboratory investigations, hypothyroidism, hypoparathyroidism, hypogonadism, and adrenal insufficiency were found, present from last year. Because of his endocrine disorders, he was receiving levothyroxine, prednisolone, and testosterone injections. Direct skin smear of lesions was negative for dermatophytosis. His family history was unremarkable. In the skin biopsy of the mentioned lesions, mild parakeratosis and spongiosis were observed. Moderate perivascular...
lymphohistiocytic infiltration with a coat-sleeve pattern was observed in the dermis with focal extravasation of erythrocytes in the papillary dermis (Figure 2a,b). According to the clinical signs and symptoms, laboratory findings, and also skin biopsy results, type 1 APS plus EAC was diagnosed for this patient.

**DISCUSSION**

An uncommon coexistence was observed in this patient, type 1 APS and EAC. Type 1 APS is a rare autosomal recessive disease which is diagnosed when two of the following triad of Addison’s disease, hypoparathyroidism, and chronic mucocutaneous candidiasis are present. Other less common involvements include type-I diabetes mellitus, autoimmune hepatitis, pernicious anemia, hypothyroidism, hypogonadism and malabsorption.

The gene responsible for this disease is AIRE (auto-immune regulator), in which 40 different forms of mutations have been reported so far. The homogenous phenotype of this syndrome which is seen in some Iranian patients is associated with a lower occurrence of candidiasis or keratopathy. Candidiasis was not observed in our patient, but because of the other two existing criteria, Addison’s disease and hypoparathyroidism, the diagnosis of type 1 APS was confirmed.

EAC is a reactive erythema characterized by annular or polycyclic lesions which may initially start as urticaria-like papules. The lesions have a slow migration (2-3 mm/d), reaching up to 10 centimeters in diameter and often followed by central clearing. With the regression of old lesions, during the next few days to weeks, new eruptions develop and the process can continue for several years. Two subtypes of EAC have been described, superficial and deep. The deep type has a firm indurated border with no scaling and is rarely pruritic. The superficial type has a scaly border and is pruritic in most patients.

Clinical and pathological findings in our patient were mostly consistent with the superficial type. Although most cases of EAC are idiopathic, various etiologies and associations have been suggested, including infective diseases, hormonal disorders, some foods, drugs and even occult solid and hematologic malignancies. APS has also been mentioned, but not reported as the etiology or a coexistent disease with EAC. Considering Candida infections as a probable cause of EAC lesions in APS 1 patients, evaluation and treatment of the current patient on this specific basis was considered. Neoplasia has been reported in a small percentage of cases. Therefore, it was of great importance to rule out neoplasia, tinea pedis, intestinal candidiasis, and other underlying infections in this patient.

In most cases, laboratory studies can be limited to CBC, urinalysis, and liver and kidney function tests. If the results are positive, other evaluations for cancer are then carried out. Based on different studies performed on the current patient, neoplasia was ruled out. The primary treatment of EAC is the diagnosis and treatment of the underlying disease; the diagnosis was type 1 APS in our patient and he received hormone replacement therapy according to the consultations of an endocrinologist.

The recommended symptomatic treatment which can be administered for the cutaneous lesions of such patients includes topical steroid for the superficial type and systemic steroid for the deep form, and anti-histamines for their pruritus. Although topical steroids and anti-histamines are not effective enough, topical calcipotriol and tacrolimus have recently shown satisfying results. Systemic prednisolone most often results in cutaneous clearing, but recurrence is common afterward. In recent studies, etanercept has proved convincing in the treatment of EAC. The role of Th1 and the rise in TNF-α and pre-inflamatory cytokine levels, which have been described in the pathogenesis of EAC, justify the positive response to anti TNF-α therapy (etanercept).

In our patient, in addition to controlling the underlying disease by appropriate hormone therapy, clearing the cutaneous lesions using agents such as calcipotriol and tacrolimus should be a priority. Although diagnosis and treatment of the underlying etiology in EAC is hardly possible and determining the exact relationship between type 1 APS and EAC and also its mechanism requires further research, type 1 APS should be considered as one of the etiologies of EAC or its associated conditions.

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