Case Report

Chronic mucocutaneous candidiasis and rheumatoid arthritis in autoimmune polyendocrinopathy

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ABSTRACT

Chronic mucocutaneous candidiasis is a heterogeneous group of disorders characterized by early-onset chronic recurrent mucocutaneous infections with *Candida albicans*. It is associated with several endocrinopathies such as hypoparathyroidism, hypoadrenalism, and hypogonadism with or without other autoimmune diseases such as vitiligo, alopecia areata, pernicious anemia, and hepatitis. Here, we describe a case of chronic mucocutaneous candidiasis with polyendocrinopathy with unusual presentations and rheumatoid arthritis.

Key words: Cutaneous candidiasis, Polyendocrinopathy, Rheumatoid arthritis

Chronic mucocutaneous candidiasis is a heterogeneous group of disorders characterized by early-onset chronic progressive and recurrent mucocutaneous infections with *Candida albicans* [1]. The disease is usually resistant or poorly responded to treatments due to defect in T helper 17 with resultant defective response to candida spp. [2-4]. It can be present with or without autoimmune endocrinopathies such as hypoparathyroidism (90%), hypoadrenocorticism (80%), hypogonadism (30–50%), type 1 diabetes mellitus (20%), thyroid disease (20%), hypopituitarism (15%) with cutaneous autoimmune disorders such as alopecia areata (30%), vitiligo (20%), urticaria (up to 60%), and lupus-like panniculitis. Other autoimmune disorders such sa hepatitis (15–40%), Sjögren-like syndrome (20–40%), pernicious anemia (15%), and pneumonitis (15–40%) may also be present [5]. Three major entities of polyendocrinopathy are recognized, APS1, APS2, and APS3 as well as the extremely rare X-linked syndrome of immune dysregulation, polyendocrinopathy, and enteropathy. Type I polyglandular autoimmune syndrome (PGA-I) is a rare disorder with sporadic autosomal recessive inheritance. The three major components of PGA-I are as follows: Chronic mucocutaneous candidiasis, hypoparathyroidism, and autoimmune adrenal insufficiency [6]. The classic symptom triad consists of chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and autoimmune adrenal insufficiency [7-9]. Among these, at least two of the major components should be present or, alternatively, one component if a sibling is affected for the confirmation of the diagnosis.

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Arthritis is not described as a part of the syndrome in most of the large APECED cohorts [10]. Here, we describe a case of CMC with polyendocrinopathy with unusual, atypical presentations, and rheumatoid arthritis.

CASE REPORT

A 19-year-old Iraqi girl, who was the fifth baby of her first cousin's parents, presented to the dermatological outpatient unit of Basrah Teaching Hospital (Iraq) with complaints of chronic recurrent episodes of widespread erythematous scaly cutaneous skin lesions since early childhood which was poorly responding to treatment. She had negative family history regarding the same condition.

On examination, the patient was tired, pale, tachypneic, and looked younger than her real age. The patient's height was 149 cm, weight was 60 kg, and there was the loss of secondary sexual characteristics and amenorrhea. The skin had wide, generalized striae located mainly at the abdomen, arms, and thighs with widespread erythematous, scaly plaques with maceration and fringed borders and stellated papules beyond the border of the original lesions affecting mainly the body and limbs flexures. Some of the lesions especially within deep folds were wet with a bad odor with involvement of angles of mouth, tongue, and one fingernail (Fig. 1).

During the examination, the blood pressure was 95/50 mmHg, and the pulse rate was 110 bpm. The investigations revealed the following: Thyroid-stimulating hormone (TSH) 4.4 uIU/ml and anti-thyroid peroxidase (TPO) was negative. There was low follicle-stimulating hormone (FSH), luteinizing hormone (LH), and low dehydroepiandrosterone (DHEA). Low early morning serum

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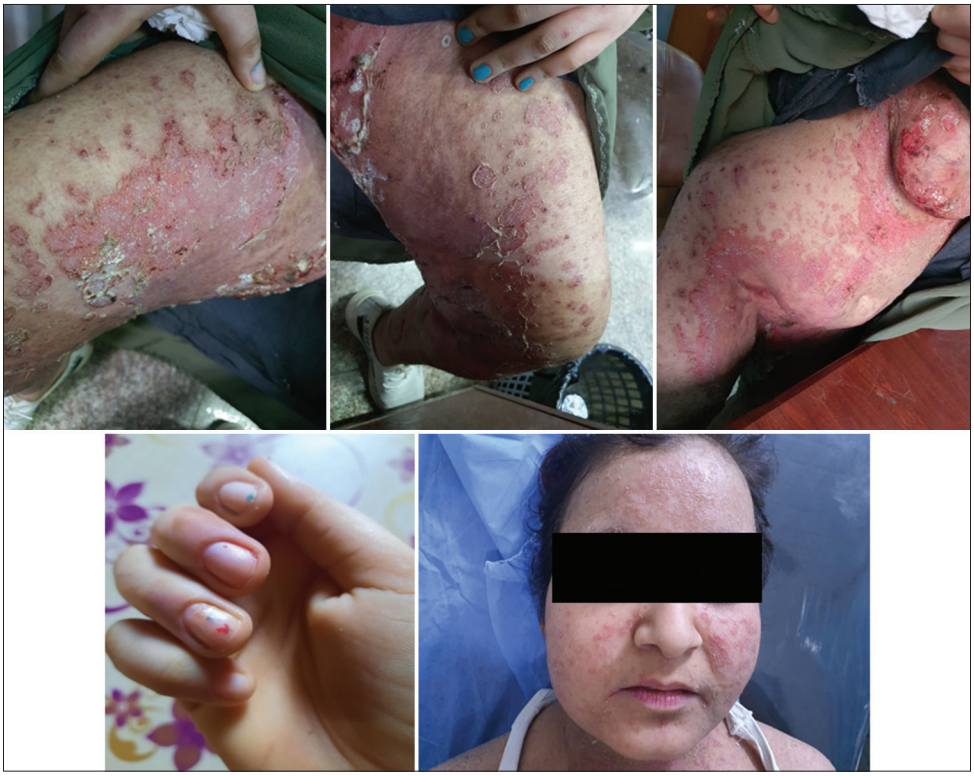

Figure 1: Clinical characteristics of the patient

cortisol with an appropriate, response following adrenocorticotropic hormone (ACTH) stimulation, HbA1c was 5.1, vitamin D 36 ng/ml, DXA scan Z score –3.5, and bone mineral density (BMD) was 0.540 for the spine. Parathyroid hormone was 27 pg/ml (10-65), serum calcium was 7.7 mg/dl, serum phosphate was 5.74 mg/dl (2.5–4.5), hemoglobin was 8.7 g, white blood cell (WBC) count was 7000/dl, and normal renal indices.

The scraping and light microscopic examination of the scales was positive for candida. The skin biopsy was done which was consistent with chronic candidal fungal infection. The diagnosis of mucocutaneous candidiasis with multiple endocrinopathies (in form of hypoparathyroidism, hypoadrenalism, and hypogonadism) was considered, and treatment with repeated successive courses of systemic fluconazole (300 mg weekly for 4 weeks duration), itraconazole (200 mg daily for the 1-month duration), terbinafine (250 mg daily for the 1-month duration), and topical antifungal drugs (clotrimazole cream, econazole cream, and ketoconazole cream) along with topical antibiotics and topical drying agent where and when required with poor response to treatment. Unfortunately, we did not use adjunctive therapy such as granulocyte colony-stimulating factor (G-CSF) that may increase IL-17 production [11], because it is costly and not available in our locality.

Meanwhile, the patient was referred to the endocrinologist for further evaluation because of her symptoms. The patient was treated medically with oral calcium, a physiological dose of corticosteroid, and gonadal hormone replacement with frequent monitoring. She was given some instructions which helped her to improve her life such as an increase in dietary calcium intake, doing moderate exercise, awareness regarding symptoms of hypoadrenalism, and using medical alert bracelets. She became better but after 10 months, she developed multiple symmetrical joint pain, early morning stiffness, and swelling that affected both wrists, knees, and ankles. At that time investigations show erythrocyte sedimentation rate (ESR) of 120 mm/h, C-reactive protein (CRP) of 34 mg, rheumatoid factor (RF) was negative, and anti-cyclic citrullinated peptide (CCP) was weakly positive. Magnetic resonance imaging (MRI) was done for the left ankle due to the presence of severe swelling which revealed talar bone marrow edema and tibiotalar effusion. Hence, the patient was finally diagnosed to have seropositive rheumatoid arthritis and treated with 10 mg weekly methotrexate tablets and a local corticosteroid injection to the left ankle. After 1 month, she was reevaluated and had only mild arthralgia. At that time, ESR was 28 mm/h, hemoglobin was 10 g/dl with normal liver function tests.

DISCUSSION

Type I polyglandular autoimmune syndrome is a rare disorder consisting of three main components namely CMC, hypoparathyroidism, and autoimmune adrenal insufficiency. In this report, we presented a female patient with chronic, recurrent mucocutaneous candidiasis with polyendocrinopathy. Although she did not have diabetes mellitus and thyroid diseases, this is not a problem since these two diseases are reported in only 20% of cases, that is, the absence of their association does not exclude this disorder. The main problem of our patient is the chronic, recurrent progressive mucocutaneous candidiasis since early childhood that was not or poorly responded to treatment with loss of normal well-being and normal growth regarding her age, which gave

a clue for the presence of underlying endocrine disorders. The genetic study was not done for her because it was not available in our locality, due to delay in the diagnosis, the financial condition of the patient, and she consulted a primary care center only. The generalized striae, without any previous history of systemic and topical steroids, that our patient had an unusual presentation and unlikely to be seen in adrenal insufficiency which is a part of polyendocrinopathy. Hence, an appropriate response following ACTH stimulation and negative history of steroid abuse let us consider this finding as a novel character of this syndrome which had not been reported by other studies.

Autoimmune polyendocrine syndromes, also called polyglandular autoimmune syndromes, are a heterogeneous group of rare diseases characterized by autoimmune activity against more than one endocrine organ, although non-endocrine organs can be affected. Autoimmune polyendocrine syndrome type 1, an autosomal recessive syndrome due to mutation of the AIRE gene resulting in hypoparathyroidism, adrenal insufficiency, hypogonadism, vitiligo, candidiasis, and others [12].

A diagnosis of hypoparathyroidism was made on the basis of low serum calcium and high serum phosphate. The parathyroid hormone level was in the lower range of normal. Other potential causes of hypocalcemia, such as renal disease, were excluded from the findings of normal renal function. In our patient, the hypocalcemia was asymptomatic; however, she received oral Ca and Vitamin D therapy. The primary complaint of the patient was only amenorrhea and hypopituitarism along with hypogonadism was diagnosed later on. Hence, she received sex hormone replacement therapy to protect the bone and for her wellbeing.

Rheumatoid arthritis (RA) is one of the most common autoimmune inflammatory arthritides, affecting from 0.5% to 1% of the general population worldwide [13]. The occurrence of arthritis in polyendocrinopathy is very rare and there are few reported cases [14]. Some of these cases showed the development of Juvenile idiopathic arthritis before the appearance of a symptom of polyendocrinopathy [15,16]. The occurrence of the adult type of rheumatoid arthritis was reported in two patients only [7,17]. To the best of our knowledge, this is the third case worldwide of rheumatoid arthritis with polyendocrinopathy type 1. Here, in our patient, the diagnosis of rheumatoid arthritis was made depending on the 2010 American College of Rheumatology/European League against Rheumatism Classification Criteria for Rheumatoid Arthritis [18]. The collection of all these disorders makes the patient at risk of severe morbidity which includes the complications of hypoparathyroidism, basal ganglia calcification, the complications of hypoadrenalism: Arrhythmia and the deformities of rheumatoid arthritis.

CONCLUSION

Chronic recurrent mucocutaneous candidiasis poorly responds to conventional antifungal treatment. This should raise the suspension of the managing physician to the presence of associated conditions. We described such a case to highlight this rare syndrome with its unusual presentations to increase awareness regarding this disorder.

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