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Case Report Open Access

Autoimmune polyendocrine syndrome type IIIC and ankylosing spondylitis: a case report

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Autoimmune polyendocrine syndrome (APS) is an autoimmune disorder defined by multiple endocrinopathies and the presence of other systemic or organ-specific autoimmunities. This case study, reports on a 46-year-old woman with confirmed idiopathic hyperparathyroidism, who was referred for inflammatory back pain. HLA-B27 positivity, recurrent anterior uveitis and radiologic findings led to ankylosing spondylitis (AS) diagnosis. By further investigations, a subclinical atrophic autoimmune thyroid disease (AITD) was also diagnosed for her in addition to a history of premature ovarian failure. According to the absence of adrenal insufficiency in addition to an AITD and systemic autoimmune disorder, APS type IIIC was the most probable diagnosis. To the best of our knowledge, this is the first case report of APS type III associated with AS.

Keywords: ankylosing, autoimmune, Hashimoto disease, hypoparathyroidism, polyendocrinopathies, primary ovarian insufficiency, spondylitis.

Introduction

Hypoparathyroidism (HP) is an endocrinopathy, which can be sporadic or associated with other glandular dysfunctions. It causes hyperphosphatemia and hypocalcemia, which can induce muscular and neurologic abnormalities. Hypoparathyroidism can be associated with other endocrinopathies, known as autoimmune polyendocrine syndromes (APS). Autoimmune polyendocrine syndromes have four types; a type I and II are more prevalent and mainly identified by adrenal gland insufficiency and type III is defined by an autoimmune thyroid disorder (AITD) without adrenal gland dysfunction [1]. If the polyendocrinopathy cannot fulfill the types I-III criteria, it is identified as APS type IV [1].

Clinically, patients that suffer from HP have radiologic and clinical manifestations similar to spondyloarthropathies [2]. Several case reports reinforce the claim that HP patients have been misdiagnosed by ankylosing spondylitis (AS) [3]. In this article, we report on a referred patient with confirmed HP, inflammatory back pain and recurrent anterior uveitis, which led to diagnosis of AS by radiologic features and human leukocyte antigene-B27 (HLA-B27) positivity. During our further work up, a premature ovarian failure (POF) and a subclinical AITD were also diagnosed, which led to suspicion of APS type IIIC.

Case presentation

A 46-year-old woman was referred to our rheumatology outpatient clinic with the chief complaint of an inflammatory back pain with progressive morning stiffness since two years ago. She had a 16-year history of HP with the onset history of peripheral tetany, hypocalcemia; PTH deficiency and basal ganglia calcification in brain computed tomography (CT), which was diagnosed during breast feeding of her first normal gravidity at 30 years old. She also mentioned a two-year history of recurrent acute anterior uveitis in addition to a POF, which occurred at age 38, after which she had not received hormone replacement. She had no history of abortion or any medical problems during her uniparous gravidity. She had a history of rheumatoid arthritis, POF and laryngeal carcinoma from her mother, sister and father, respectively. She was not a current or former smoker. She did not mention any other remarkable family or past medical histories. She was not from Jewish ethnicity.

Upon her examination, per minute pulse and respiratory rates were 80 and 20, respectively, with blood pressure of 120/80 mmHg. Her musculoskeletal

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examinations revealed limitation in lumbar flexion with Schober's test of 4 cm, Sacroiliac Joints (SI) tenderness, chest expansion of 6 cm, lateral flexion measurement of 19 cm, neck rotation of 80 degrees and symmetric tragus to wall of 7 cm with Bath Ankylosing Spondylitis Metrologic Index (BASMI): 2.8. Severe crepitation and positive patellar grind test were detected in both knee joints without any effusion. Muscle forces were normal; Trousseau's and Chvostek signs were negative. Bath ankylosing spondylitis functional index (BASFI) was 3.5, bath ankylosing spondylitis disease activity index (BASDAI) was 4.3 and visual analogue scale (VAS) was 4. There was no remarkable abnormality in the remaining systemic physical examination.

Laboratory data showed a hypocalcemia (calcium 7.8 mg/dL (8.5-10.5 mg/dL)), hyperphosphatemia (Phosphorus 6 mg/dL (2.5-4.5 mg/dL)), PTH deficiency (20 pg/mL (10-65 pg/mL)) and vitamin D deficiency (20 ng/mL) with normal serum albumin. Acute phase reactant concentration were elevated with erythrocyte sedimentation rate (ESR) level of 53 mm/hour and C-reactive protein (CRP) level of 20 mg/dL with upper normal limit of 6. Complete blood count (CBC), repeated fasting blood sugar (FBS), postprandial blood sugar, hemoglobin A1C, lipid profile, serum creatinine, electrolytes concentration, liver function tests and urine analysis were normal. Anti-thyroglobulin antibody (ATGA) was positive with titer of 232.6 IU/mL (1-115), negative anti-tissue transglutaminase antibody (Immunoglobulin A) and anti-thyroid peroxidase antibody (TPO Ab). Luteinizing hormone, follicular stimulating hormone and estradiol were in the range of menopausal phase. The thyroid function test showed an elevated Thyroid Stimulating Hormone (TSH) level of 8.42 μIU/L; free T3 and free T4 were in the normal range. Thought, she had been on glucocorticoid prescription for two years, basal cortisol concentration at 8 am was 6.1 μg/dL (6.2-20) and adrenocorticotropic hormone was 23.2 pg/mL (7.2-64). HLA-B27 was positive.

Axial CT sections of the brain showed bilateral symmetric basal ganglia and dentate nuclei calcification in favor of HP (Fig. 1). In the Magnetic Resonance Imaging (MRI) of sacroiliac joints; active inflammation was observed on both sides (Fig. 2). Axial abdominal CT scan showed a stone in the right kidney, other organs were unremarkable (Fig. 3). Chest CT scan revealed an ascending aortic calcification (Fig. 4). The initial dual energy x-ray absorptiometry bone density (DXA) showed total T-score of 1.0 and 0.3 for spine and femur, respectively. Ultrasonography was performed on thyroid glands, which showed an atrophic pattern; the right and left lobe had a diameter of 14×14.2 mm and 14×15 mm, respectively. There was no nodule or cyst with a normal cervical lymph nodes.

She had taken daily medications of 1000 mg calcium carbonate, 400 mg sevelamer and 1 μg calcitriol for HP treatment. Prednisolone 5 mg/day and betamethasone drop were prescribed for her recurrent anterior uveitis

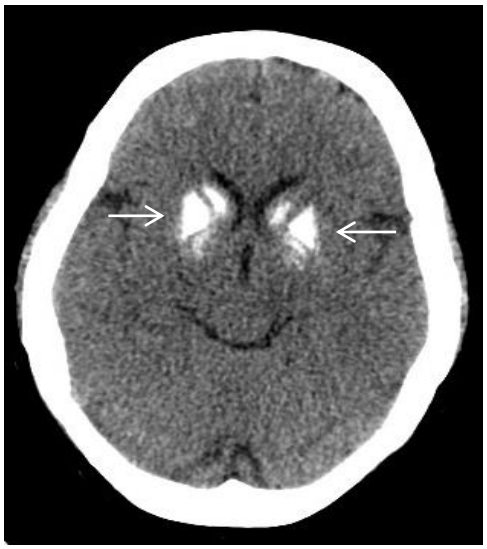
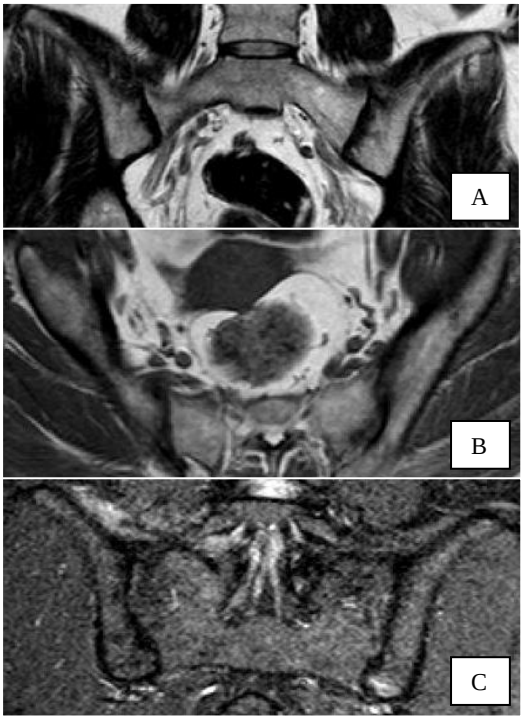


Fig. 1. Bilateral and symmetric calcification of the basal ganglia and dentate nuclei marked in the brain computed tomography scan by white arrows



A, T2; B, T1; C, STIR views

Fig. 2. Sacroiliac joints inflammation present with bone marrow edema in the magnetic resonance imaging

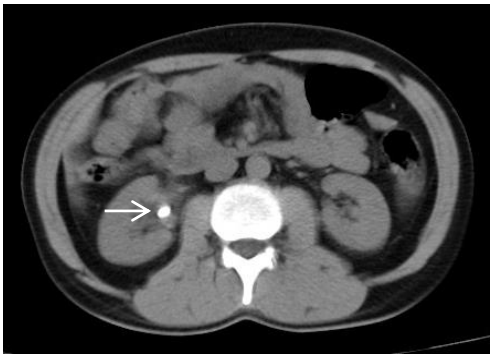


Fig. 3. Axial section of abdominal computerized tomography scan; a calcific stone highlighted in the major calyx of right kidney by a white arrow

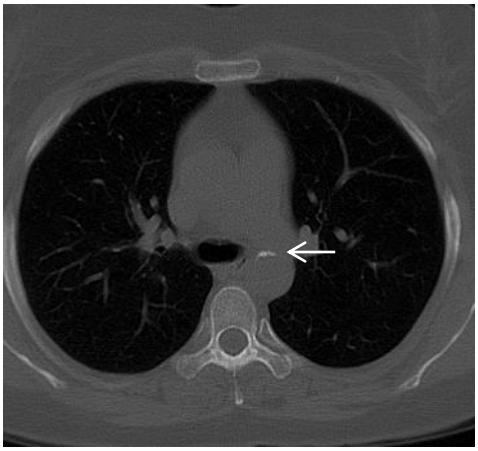


Fig. 4. Chest computed tomography; ascending aorta has evident calcification (white arrow) secondary to possible ankylosing spondylitis-related aortitis.

since two years ago. In addition, daily indomethacin 150 mg and sulfasalazine 1500 mg were started for her inflammatory back pain with good response to treatment according to VAS, BASDAI and BASFI after six months.

Discussion

In this article, we report on a case of APS type III associated with AS whereas its association with other systemic autoimmune diseases were reported previously [4,5]. Autoimmune polyendocrine syndrome is a disorder characterized by multiple endocrine gland dysfunctions in addition to other systemic or organ autoimmunity. It has four different types, which are differentiated according to the combination of pathologic organs [1]. Type I is mainly defined by the triad of Addison's disease, candidiasis and HP. It is an autosomal recessive disorder, which is caused by mutation in the autoimmune regulator (AIRE) on chromosome 21 with a noticeable prevalence among Iranian Jews [6]. Type II is characterized by adrenal gland insufficiency and AITD or diabetes mellitus. It is the most prevalent of APSs with a female dominant pattern [1]. Type III is differentiated from previous types by the absence of Addison's disease and obligatory presence of an AITD, with three different subtypes. Types IIIA and IIIB are associated with immune-mediated diabetes and pernicious anemia, respectively. Type IIIC is identified by the presence of an AITD with another organ or systemic autoimmune disorder and if the disorder cannot complete the preceding criteria it will be categorized as APS type IV [7].

The AITD is a key feature of APS type III, which differentiates it from previous types. It is mainly characterized by immune mediated destruction of thyroid gland with the presence of antibodies against thyroglobulin and thyroid peroxidase [8]. According to a study performed at John Hopkins immunology laboratory on 4977 blood samples, 31 percent (1553 samples) had positive autoantibody profile. Among them, 642 were positive for both and 206 samples were positive only for ATGA [9]. Emmungil et al. [10] designed a case-control study to elucidate the prevalence of AITD in AS patients. Among 80 patients, eight individuals had positive autoantibody profile in addition to an abnormal ultrasonography pattern of thyroid gland. Half of them had positive ATGA with negative TPO Ab and the rest of them were vice versa. Seven patients had normal free T3, free T4 and TSH concentration. In this case, AITD was in the form of subclinical hypothyroidism and the atrophic pattern of thyroid gland, which is compatible with chronic thyroiditis [11].

Premature ovarian failure is a disorder with diverse etiologies. Regarding the autoimmune nature, POF is recorded in all APS types by the presence of autoimmunity against steroidogenic enzymes and ovarian steroid cells. Multiple genetic polymorphisms and loci were also discovered in addition to Turner's syndrome and fragile X syndrome as rare causes. We can't discuss on positive family history of our patient for POF because the karyotypes and genetic analyses of her and her sister were not available.

Lack of adrenal insufficiency is a key point in distinguishing the APS type III from types I and II. It is remarkable to mention that the corticosteroid prescription made the adrenal biochemical tests invaluable but basal morning cortisol level of higher than 5 μg/dL, despite chronic glucocorticoid usage and normal serum Na-K, lowered the probability of Addison's disease [12]. On the other hand, lack of the mucocutaneous evidences of candidiasis and normal FBS reinforced APS type III diagnosis. It is important to note that adrenal stimulation test with cosyntropin was not done earlier.

Kim et al. [13] report a woman with APS type IIIA who was also diagnosed with primary HP according to the laboratory findings and basal ganglia calcification. Hypoparathyroidism is caused by heredity, acquired or idiopathic etiologies, which its late onset and denied neck surgery or environmental injuries; heredity and acquired origins were ruled out in the present case. Calcification of the basal ganglia is a common radiologic finding in patients with idiopathic HP. An Indian investigation was performed on 145 patients with idiopathic HP, 73.8% showed basal ganglia calcification. This result can approve the idiopathic origin of HP in our case. In addition, a renal stone was incidentally found. This is not an HP-related complication and calcification thus it seemed unrelated.

According to Goswami et al. [2], HP can produce structural abnormalities resembling spondyloarthropathies. In their study, forty patients with HP were examined for spine, SI joint and hip structural abnormalities and were compared with healthy individuals. Three patients showed complete AS skeletal deformities and fourteen showed syndesmophytes, SI joint inflammation and new bone formation in hip joint. The HLA-B27 statuses of both groups were comparable. Kajitani et al. [3] reported on a forty year-old man with prolonged inflammatory back pain and reduced muscle forces. On examination, typical AS posture was reported with abnormal range of motion of hip joints. Severe hypocalcemia, negative HLA-B27 and the absence of nonskeletal AS manifestation led to the diagnosis of HP, which mimicked AS. There was also another case report, which showed HP camouflage by spondyloarthropathies manifestations [14]. In addition to these AS mimicry by HP, there were also a few case reports with AS and HP co-existence [15].

Aortic calcification (AC) is a phenomenon associated with multiple conditions, mostly important is arteriosclerosis, aortitis and hypothyroidism. There are a few articles that have reported ascending aorta inflammation in AS patients as its rare non-skeletal involvement. On the other hand, several studies showed the protective role of T3 hormone on vessel calcification. Interestingly, AC was also reported in three children with APS type I. Confusingly, AC is also prevalent among menopausal women due to multifactorial etiologies like smoking and hyperlipidemia. We couldn't find any definite etiology for AC in the present case but the subclinical nature of AITD (normal free T3 level) in the absence of menopausal risk factors of AC, in addition to elevated concentration of ESR and CRP suggest the possibility of secondary calcification due to AS-related aortitis.

In conclusion, inflammatory back pain with progressive morning stiffness, radiologic sacroiliitis and positive HLA-B27 propose AS as a probable diagnosis. In addition, acute anterior uveitis and AC are compatible with nonaxial manifestation of this diagnosis. Consequently, the presence of a confirmed HP, POF and subclinical atrophic thyroiditis in association with a systemic autoimmune disorder may confirm the APS type IIIC despite the lack of evidence of vitiligo and alopecia. To the best of our knowledge, this was the first case report of APS type III associated with AS.

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