A Case of Critical Lower-Limb Ischemia in a 29-Year-Old Man with Autoimmune Polyglandular Syndrome Type 1 (APS-1)

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Patient: Male, 29-year-old
Final Diagnosis: Autoimmune polyglandular syndrome type 1
Symptoms: Left foot redness and swelling
Medication: —
Clinical Procedure: Angioplasty
Specialty: Endocrinology and Metabolic • Surgery

Objective: Rare disease
Background: Autoimmune polyglandular syndrome type 1 (APS-1) is an extremely rare autoimmune disorder with an autosomal recessive inheritance pattern. Its manifestations present in chronological sequence of the components mucocutaneous candidiasis, Addison disease, and hypoparathyroidism. Vascular calcification is a very rare manifestation of the disease, and it may be severe, causing critical lower-limb ischemia and significant morbidity.

To the best of our knowledge, this is the first such case to be reported in Jordan and the Arab region.

Case Report: We present the case of a 29-year-old patient diagnosed with autoimmune polyglandular syndrome type 1 (APS-1). He has Addison disease, hypoparathyroidism, and mucocutaneous candidiasis. He presented with features of critical lower-limb ischemia and bacterial infection of the left foot. The patient underwent a successful angioplasty, and received management of his bacterial and fungal infections and the chronic endocrinopathies.

Conclusions: Autoimmune polyglandular syndrome type 1 (APS-1) is a very rare disorder. Recognizing its syndromic nature will facilitate an active search for the component diseases and the possible complications, which would allow early diagnosis and management. This applies to the rare vascular complications, which can lead to significant morbidity.

MeSH Keywords: Addison Disease • Angioplasty • Candidiasis, Chronic Mucocutaneous • Hypoparathyroidism • Peripheral Arterial Disease • Polyendocrinopathies, Autoimmune

Abbreviations: APS-1 – autoimmune polyglanular (or polyendocrine) syndrome type 1; APECED – autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; AIRE gene – autoimmune regulator gene

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Autoimmune polyglandular syndromes (APS) are rare syndromes diagnosed by the coexistence of at least 2 autoimmune endocrinopathies. In addition, nonendocrine autoimmune manifestations may be present [1]. Autoimmune polyglandular syndrome type 1 (APS-1) is defined by the coexistence of at least 2 of 3 major component diseases: chronic mucocutaneous candidiasis, autoimmune adrenal insufficiency, and primary hypoparathyroidism, or only 1 if a sibling has the disease [1–3]. The syndrome is a rare disorder with an autosomal recessive inheritance pattern [1,2,4,5]. Vascular calcification is a rare manifestation of the syndrome [6], and it can be severe, causing significant lesions and ischemia [7]. We present the case of a young patient with mucocutaneous candidiasis and multiple endocrinopathies who presented with features of critical lower-limb ischemia.

Case Report

A 29-year-old male patient presented with acute left-foot redness, swelling (Figure 1B), and chronic dystrophic nails of hands and feet with discoloration (Figures 1, 2). The distal pulses were diminished, with monophasic signals on Doppler examination, and he previously had amputation of left fourth toe due to gangrene. He was a known case of adrenal insufficiency and hypoparathyroidism, taking hydrocortisone, fludrocortisone, and calcium supplements and alphacalcidol. The patient had no intermittent claudication or resting pain, he was not diabetic, and he was a non-smoker. Treatment was started with an intravenous antibiotic (Piperacillin/Tazobactam) and antifungal medications (intravenous Fluconazole and Miconazole ointment). Bacterial and fungal cultures showed *Morganella morganii* and *Candida albicans* sensitive to the given medications. Lab investigations showed elevated WBC count 21.3/mm$^3$, elevated ESR and CRP, low parathyroid hormone 1.2 ng/l (N 13–54), hypocalcemia Ca 1.7 mmol/l (N 2.1–2.6), and hyperphosphatemia P 1.69 mmol/l (N 0.8–1.6). Otherwise, he had normal kidney, liver, and thyroid function tests, and normal adrenocorticotropic hormone levels.

**Figure 1.** The feet of the patient on admission: (A) The right foot showing signs of chronic candidiasis of the nails, including discoloration, dystrophy, and brittle nails. (B) The left foot showing signs of acute infection, chronic candidiasis, dystrophy of nails, and signs of critical ischemia, including the amputated 4th toe and gangrene of the tip of the 1st toe.
sporadic autosomal recessive pattern and caused by genetic dystrophy (APECED) [2]. It is a very rare disorder inherited in a and autoimmune polyendocrinopathy-candidiasis-ectodermal type 3 (the rarest). APS-1 is also known as Whitaker syndrome in the literature: type 1 (juvenile type), type 2 (adult type), and according to multiple endocrinopathies. Three types are described in Polyglandular autoimmune syndromes are a rare heterogeneous group of genetic diseases of the immune system leading to multiple endocrinopathies. Three types are described in the literature: type 1 (juvenile type), type 2 (adult type), and type 3 (the rarest). APS-1 is also known as Whitaker syndrome and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) [2]. It is a very rare disorder inherited in a sporadic autosomal recessive pattern and caused by genetic mutations affecting the autoimmune regulator (AIRE) gene on chromosome 21 [2,5,8]. Studies have demonstrated the presence of various circulating tissue-specific autoantibodies that cause dysfunction of the target endocrine glands [4,9]. Also, the mutations lead to defective T cells and neutralizing autoantibodies against IL-22, IL-17A, and/or IL-17F, leading to the immunodeficiency underlying candidiasis [4,9–11].

The syndrome clusters in certain ethnic populations, including Iranian Jews, Sardinians, and Finns [8]. The highest prevalence was reported in Iranian Jews with 1 case per 9000, Sardinians with 1 case per 14 400, and Finns with 1 case per 25 000 [8,12–14]. Low incidences (1: 90 000 to 1: 200 000) had been reported in Norway, Sweden, Poland, Slovenia, Slovakia, Russia, Great Britain, Ireland, and Italy [8,15,16,17,18,19]. To the best of our knowledge, the present case is the first to be reported in Jordan and the Arab region. It is suspected that this disorder is underdiagnosed because of a lack of knowledge of the condition, the long intervals between the development of manifestations, the variability of disease severity, and the wide spectrum of clinical presentation [5].

In APS-1, which is the focus of the present report, 2 out of 3 main components are sufficient for diagnosis, or only 1 if a sibling has the disease [2,3]. In our patient, all 3 components were present: chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency or Addison disease. Classically, these components occur in chronological order, with mucocutaneous candidiasis usually occurring earliest, followed by hypoparathyroidism, then adrenocortical failure [2]. Additional endocrine and nonendocrine manifestations may be present, including diabetes type 1, hypothyroidism, gonadal failure, alopecia, vitiligo, nephropathy, enamel hypoplasia, pure red cell aplasia, pernicious anemia, asplenia, malabsorption, and autoimmune hepatitis [3,5,8,20].

Vascular calcification is an extremely rare manifestation of the syndrome. Our patient presented with critical lower-limb ischemia due to significant stenosis of popliteal and tibial vessels and diffuse calcifications of the abdominal aorta and lower-limb vasculature. Vascular calcification in general is an active cellular process that occurs in response to metabolic insults causing disturbance in the balance between inhibiting and promoting factors of vascular calcification [21,22]. It is suggested that certain cells in the vessel wall can be triggered to differentiate into osteoblast-like cells, including vascular smooth muscle cells, stem cells, and pericytes [21,23]. Proposed triggers include oxidative stress, hyperphosphatemia, bone morphogenetic protein, vitamin D, and parathyroid hormone [21,23]. Proposed inhibitors include fetuin, osteotectrin, osteopontin, and pyrophosphate [21,23].

Vascular calcification is usually associated with aging, atherosclerosis, diabetes mellitus, and chronic kidney disease. Oxidative stress, hyperphosphatemia, bone morphogenetic protein, vitamin D, and parathyroid hormone are all factors that contribute to vascular calcification. In APS-1, these factors are exacerbated due to the chronic inflammation and immunodeficiency associated with the disorder. Additionally, patients with APS-1 often have underlying cardiovascular disease, which further contributes to vascular calcification. This case highlights the importance of recognizing and treating APS-1 in order to prevent complications associated with vascular calcification such as myocardial infarction and stroke.
Figure 3. CT angiography of the abdominal aorta and lower limbs on admission showing the heavy calcifications of the arteries, which appear as hyperdense white areas. (A) CT angiography MIP (maximum intensity projection). (B) Magnification and focus on the popliteal area of the MIP image. (C) CT angiography VIP (volume intensity projection). (D) Magnification and focus on the popliteal area of the VIP image. The arrows in (B, D) point to the site of severe stenosis in the popliteal artery.
disease [21,24–26]. One study found coronary artery calcification in 3 out of 30 cases of sporadic idiopathic hypoparathyroidism [27]. There are few reported cases in the literature of aortic and/or lower-limb arterial calcification associated with APS-1 [6,7,21,28], and only 2 of them had critical lower-limb ischemia [7,21]. Shikata et al. [6] proposed the progressive vascular calcification as a peculiar non-random part of APS-1. Also, Ohga et al. [7] proposed that progressive vascular calcification will eventually be recognized as a rare, unexplained, but grave component of APS-1.

The management of our patient included a revascularization procedure for limb salvage, and correction of serum calcium and phosphate disturbances. In APS-1, hypocalcemia is due to hypoparathyroidism and the gastrointestinal manifestations of the syndrome, including intestinal malabsorption, pancreatic exocrine failure, celiac disease, and intestinal lymphangiectasia. Calcium levels should be monitored on follow-up and maintained in the low-normal range [20,21].

Conclusions

Autoimmune polyglandular syndrome type 1 (APS-1) is a very rare disorder. Recognizing its syndromic nature will facilitate an active search for the component diseases and possible complications, which would allow early diagnosis and management. This applies to the rare vascular complications, which can lead to significant morbidity.

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Conflict of interest

None.

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