Endocrinology, Diabetes & Metabolism CASE REPORTS

J Lima Ferreira and others | Autoimmune polyglandular syndrome type 1

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Hypoparathyroidism as the single major component for decades of autoimmune polyglandular syndrome type 1

Joana Lima Ferreira, Francisco Simões de Carvalho, Ana Paula Marques and **Rosa Maria Príncipe**

Endocrinology Department, Hospital Pedro Hispano, Matosinhos Local Health Unit, Matosinhos, Portugal

Correspondence should be addressed to J Lima Ferreira
Email
joanalferreira@gmail.com

Summary

Autoimmune polyglandular syndrome type 1 (APS-1) is a very rare autoimmune entity, accounting for about 400 cases reported worldwide. It is characterized by the presence of at least two of three cardinal components: chronic mucocutaneous candidiasis (CMC), hypoparathyroidism and Addison's disease. It typically manifests in childhood with CMC and years later with hypoparathyroidism. A 50-year-old man was referred to the Endocrinology outpatient clinic due to irregular follow-up of primary hypoparathyroidism diagnosed at age 7. Previous analysis reported frequent fluctuations of calcium and phosphate levels and persistent hypercalciuria. He presented several comorbidities, including bilateral cataracts, other ocular disorders, transient alopecia and chronic gastritis. Due to weight loss, fatigue, gastrointestinal complaints and the findings at objective examination, Addison's disease and CMC were investigated and confirmed. Antifungal therapy and hormonal replacement were started with evident clinical improvement. Regarding hypoparathyroidism, calcium-phosphate product decreased and other extraskeletal calcifications were diagnosed, such as nephrolithiasis and in basal ganglia. Further evaluation by genetic analysis revealed homozygosity for a frameshift mutation considered to be a pathogenic variant. It was reported only in two Asian siblings in compound heterozygosity. This case highlights the broad phenotypic spectrum of APS-1 and the significative intra-familial phenotype variability. A complete clinical history taking and high index of suspicion allowed the diagnosis of this rare entity. This case clarifies the need for regular long-term follow-up. In the specific case of hypoparathyroidism and Addison's disease in combination, the management of APS-1 can be complex.

Learning points:

- Autoimmune polyglandular syndrome type 1 (APS-1) is a deeply heterogeneous genetic entity with a broad spectrum of clinical manifestations and a significant intra-family phenotypic variability.
- Early diagnosis of APS-1 is challenging but clinically relevant, as endocrine and non-endocrine manifestations may occur during its natural history.
- APS-1 should be considered in cases of acquired hypoparathyroidism, and even more so with manifestations with early onset, family history and consanguinity.
- APS-1 diagnosis needs a high index of suspicion. Key information such as all the comorbidities and family aspects would never be valued in the absence of a complete clinical history taking.
- Especially in hypoparathyroidism and Addison's disease in combination, the management of APS-1 can be complex and is not a matter of simply approaching individually each condition.
- Regular long-term monitoring of APS-1 is essential. Intercalary contact by phone calls benefits the control of the disease and the management of complications.

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Background

Autoimmune polyglandular syndrome type 1 (APS-1) is also known as autoimmune polyendocrinopathy-candidiasis -ectodermal dystrophy (APECED) or Whitaker syndrome (1, 2). It is an inherited monogenic disease, mainly in an autosomal recessive pattern (3, 4). A loss of function of the autoimmune regulator (*AIRE*) gene, which plays an important role in self-tolerance, may result in the escape to deletion of autoreactive cells and induce an autoimmune disease (3, 5). To date, more than 100 mutations have been identified (4, 5). Worldwide, a prevalence of 1/80 000 to 1/100 000 was estimated, which is higher in certain populations such as Finland (1/25 000), Sardinia (1/14 500) and Persian Jews in Israel (1/9000) (6, 7, 8, 9).

APS-1 is characterized by the presence of at least two of three major components: chronic mucocutaneous candidiasis (CMC), hypoparathyroidism and Addison's disease (primary adrenal insufficiency) (4). It manifests mostly in childhood with CMC (4).

We describe an atypical presentation of APS-1, whose first and only manifestation for decades was hypoparathyroidism. This case highlights the broad phenotypic spectrum of APS-1 and it expands the knowledge of a very rare mutation. It demonstrates well the gradually progressive course of APS-1 and the need for regular long-term follow-up, because it is difficult to manage and other autoimmune disorders may appear throughout lifetime, until at least the fifth decade (1).

Case presentation

A 50-year-old man was referred to the Endocrinology outpatient clinic due to irregular follow-up of primary hypoparathyroidism, diagnosed at age seven after several episodes of generalized tonic-clonic seizures. The patient was followed-up by several specialists, showing frequent fluctuations of calcium and phosphate levels and persistent increase in calcium in 24-h urine (Table 1).

His past medical history was notable in ophthalmological conditions: had bilateral cataracts at age 25, glaucoma at age 47 treated with selective laser trabeculoplasty and recurrent keratitis for a year. The patient also had beard loss at age 40 which progressed 2 years later to two hair loss patches, with no results after topical minoxidil, but with spontaneous growth years later. He underwent a hemithyroidectomy at age 45 due to a Bethesda IV thyroid nodule, without thyroid malignancy in pathology. Cervical ultrasound 1 year ago showed no abnormalities. Due to dyspepsia and abdominal discomfort, he was diagnosed with cholelithiasis at age 46. As the symptoms persisted after the cholecystectomy, he performed an upper endoscopy which revealed chronic gastritis. Abdominal radiography showed a 3 mm calcium density spot in the projection of the left kidney. He denied previous infections and teeth disorders.

The patient was medicated daily with 1500 mg of elemental calcium (calcium lactate gluconate and calcium carbonate), calcitriol 0.75 mcg, levothyroxine 88 mcg and esomeprazole 20 mg. Calcium and active vitamin D supplements were recurrently increased by the patient in case of paresthesia or fatigue.

His family history was significant for his parents' consanguineous marriage (second cousins) and his only brother, a 40-year-old man with primary hypoparathyroidism diagnosed at age 16. The patient

Table 1 Laboratory findings over time.

Parameters	Previous year	1st OP clinic[a]	1 month after	3 months after[b]	Reference range
PTH, pg/mL	0.2	0.2	–	–	15.0–68.3
Total calcium,[c] mg/dL	8.6–11.9	10.9	8.8	8.3	8.4–10.2
Phosphate, mg/dL	4.4–4.9	4.3	4.2	4.8	2.3–4.7
Ca x Pi product,[d] mg^2/dL^2	41.3–57.1	46.9	37.0	39.8	< 55.0
Magnesium, mg/dL	1.8–1.9	1.77	1.8	1.7	1.6–2.6
25-OH-vitamin D, ng/mL	14.0	13.7	–	21.0	30.0–100.0
eGFR, mL/min/1.73 m^2	90.2	70.6	99.2	85.7	>90.0
24-h urine calcium, mg	569.0	–	–	432.0	100.0–300.0
Alkaline phosphatase, U/L	–	61.0	–	55.0	40.0–150.0
Sodium, mEq/L	135.0	122.0	134.0	138.0	136.0–145.0
Potassium, mEq/L	4.9	5.1	4.2	4.3	3.4–5.1
Cortisol, µg/dL	–	2.5	–	1.3	3.7–19.4
ACTH, pg/mL	–	1529.0	–	84.5	7.2–63.3

[a]Blood sample collected at 03:00 pm; [b]Blood sample collected at 8:00 am; [c]Albumin-corrected calcium; [d]Calcium-phosphate product.
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denied knowing other relatives with endocrine or non-endocrine disease.

The patient described occasional paraesthesia in the extremities and a 6-month history of weakness, musculoskeletal pain, fatigue, nausea, anorexia and weight loss of 6 kg. Furthermore, he reported dyspepsia, dysphagia (even under esomeprazole), constipation and flatulence. On examination, he presented with a blood pressure of 119/62 mmHg, heart rate of 78 b.p.m., BMI of 24.7 kg/m^2, onychomycosis (in four fingers and two toes) for 1 year (Fig. 1) and mucocutaneous hyperpigmentation (Fig. 2). Chvostek and Trousseau signs were absent. No evident loss of hair, beard or axillary hair was detected. Remaining examinations, including oral, were unremarkable.

Investigation

Adrenal insufficiency was suspected and a blood sample was collected from the patient after the visit. The analysis revealed hyponatremia, hyperkalaemia, hypercalcemia, high-normal phosphorus and a slight increase in creatinine. Two days later, cortisol deficiency was confirmed, associated with an extremely high level of adrenocorticotropic hormone (ACTH). Three months later, mineralocorticoid deficiency was diagnosed considering an elevated plasma renin concentration (186.6 pg/mL, RR: <32.6) in association with a low serum aldosterone concentration (31 pg/mL, RR: 48–270). Further investigation revealed positivity for 21-hydroxylase antibodies (2.2 U/mL, RR: <1).

Regarding hypoparathyroidism for more than 40 years, more frequent monitoring was indicated until the patient was well controlled, considering his irregular follow-up, unstable levels of calcium and phosphate and the presence of hypercalciuria. One month after the visit, calcium and phosphate levels were normal. Three months later, a slightly lower than normal calcaemia and an adequate calcium-phosphate product were achieved. Hypercalciuria persisted, although lower than before. Calcium sensing receptor antibodies were not detected in the plasma. Abdominal ultrasound revealed bilateral renal microlithiasis, with no signs of obstruction. Bone mineral density (BMD), determined by dual-energy X-ray absorptiometry (DEXA), was appropriate for gender and age at the femur neck and lumbar region but low at the

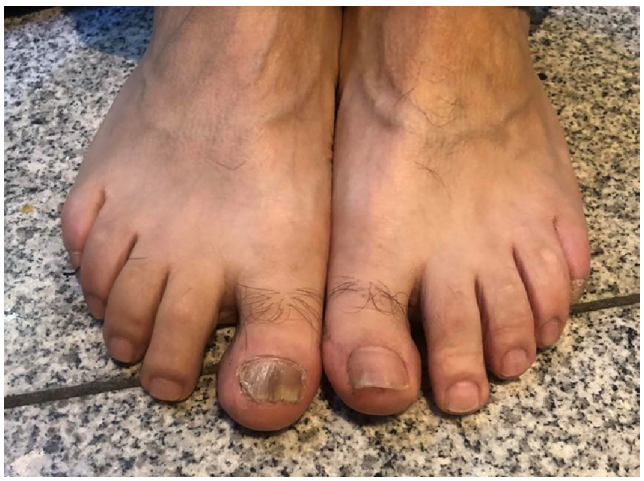

Figure 1
Onychomycoses in the right hallux and in the fifth left toe.

Figure 2
Mucocutaneous hyperpigmentation.

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forearm (T score: −3.6 s.d.; Z score: −3.2 s.d.). Cranial CT scan, performed in the context of headache investigation, did not reveal any abnormalities other than bilateral calcifications in the basal ganglia.

Due to gastrointestinal symptoms, the patient underwent endoscopic exams few weeks after the visit. Colonoscopy was unremarkable. Upper digestive endoscopy showed white exudates localized in the upper oesophagus, adherent to the mucosa, even with water irrigation (Fig. 3). Pathology of the biopsy tissue confirmed the diagnosis of oesophageal candidiasis. Further investigation revealed a high titre of anti-parietal cell antibodies (1:160), absence of anti-transglutaminase antibodies (0.8 UI/mL), absence of anti-intrinsic factor antibodies (<0.1 UI/mL) and normal vitamin B12 levels (825 pg/mL), which are in line with an autoimmune aetiology of the known chronic gastritis.

Other laboratory studies including blood count, fasting glucose, liver enzymes, pituitary hormones (except ACTH), free thyroxine and total testosterone levels were within the normal range. Anti-thyroglobulin antibodies were detected and anti-peroxidase antibodies were absent.

Childhood hypoparathyroidism is predominantly due to genetic disorders that cause congenital parathyroid agenesis/hypoplasia or disturbances in the calcium metabolism, unlike adulthood, when the most common cause is post-surgical (10, 11). Considering the coexistence of hypoparathyroidism, Addison's disease, onychomycosis and oesophageal candidiasis, genetic analysis of *AIRE* gene was performed. It revealed homozygosity for the pathogenic variant c.1103dup p. (Leu370Alafs*2), a frameshift mutation resulting in the introduction of a premature stop codon. Patient's brother declined a genetic counselling appointment. Blood tests from the two daughters revealed normal calcium levels.

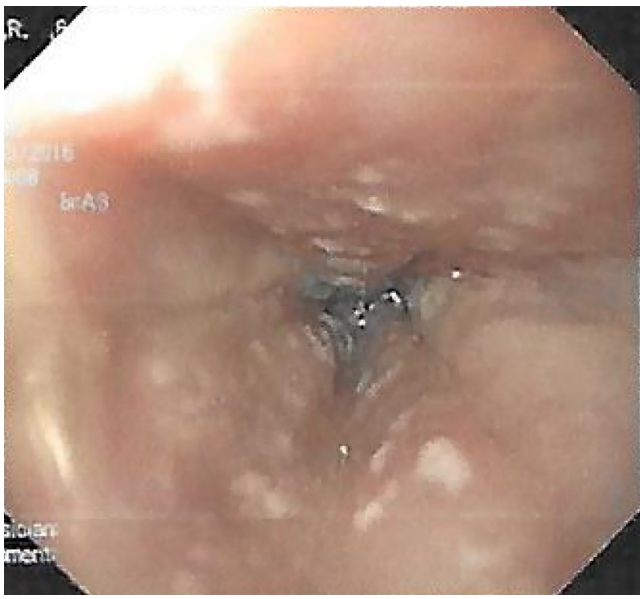

Figure 3
Oesophageal candidiasis at upper digestive endoscopy.

Treatment

In the first visit, the suspected adrenal insufficiency was explained to the patient and his wife and an informative leaflet was given. He was started on hydrocortisone 15 mg in two divided oral doses (10–0–5–0 mg) and advised to increase fluid intake. In the following days, the patient was contacted by phone and he emphasized an evident clinical improvement, with reducing weakness and increasing energy levels. Later, mineralocorticoid replacement was started with fludrocortisone 100 µg in the morning. Additionally, as he had a physically demanding occupation and had not regained much weight, daily hydrocortisone was increased to 20 mg in three divided oral doses (10–5–5–0 mg), with improved energy levels and no additional weight gain. The patient and his wife had a session about adrenal insufficiency and were given a steroid emergency card.

Regarding hypoparathyroidism, considering hypercalcemia (10.9 mg/dL) and the recurrent increasing in the dose of calcium or vitamin D supplementation in the previous months, the patient was asked to keep the defined daily dose as regular as possible and, in case of symptoms, contact the Endocrinology team. In fact, in the following months, the patient did not self-adjust the supplements.

For oesophageal candidiasis, oral fluconazole 200 mg once a day were taken for 14 days, with resolution of the symptoms. The patient was started on topical treatment with ciclopirox olamine twice daily for onychomycosis.

Outcome and follow-up

The patient showed weight regain and remained asymptomatic under replacement therapy with hydrocortisone and fludrocortisone. Six months after the diagnosis of adrenal insufficiency, he developed vomiting and diarrhoea since dawn and was taken to the hospital in the morning, where he arrived already unconscious. He went directly to the emergency room, where he was treated immediately with parenteral hydrocortisone and vigorous fluid resuscitation was performed. He was hospitalized for a week for the adrenal crisis in the context of septic shock due to acute gastroenteritis.

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A few months later, he repeated the upper endoscopy due to complaints of heartburn. It showed known chronic gastritis and no signs of oesophageal candidiasis. Giemsa stain revealed positivity for Helicobacter pylori, which was successfully eradicated after the fourth treatment.

Two years after the first visit, the patient is clinically stable. However, it has been difficult to maintain serum calcium in the target range without requiring higher doses of activated vitamin D analogue and calcium supplements, causing significative gastrointestinal intolerance and worsening hypercalciuria.

Discussion

This case illustrates an unusual presentation of APS-1, with late manifestation of CMC and Addison's disease (more than 40 years after the diagnosis of hypoparathyroidism). This case presents the three major components, reported in 40% of the patients (5). CMC, which affects oral cavity, oesophagus or skin, is generally the first manifestation (appearing before endocrine disorders and usually up to age 5) and the most common component, reported in almost all patients with APS-1 (3). In our case, CMC was the second characteristic to manifest with onychomycosis at age 49 and oesophageal candidiasis apparently later. Oesophageal candida hidden for some years cannot be excluded, but upper endoscopy did not show it at age 46 and dysphagia appeared after the onychomycosis. In both conditions, antifungal treatments were effective. Hypoparathyroidism occurs in up to 93% of cases and it is frequently the first endocrine manifestation, usually appearing after CMC and in the first decade of life (12). In our patient, it was the first manifestation of APS-1 and the only one for several decades. Addison's disease appears to have developed after CMC, but they were diagnosed at the same time. Adrenal insufficiency is diagnosed in more than 60% of cases, the great majority in the first three decades of life (4, 12).

The diagnosis of APS-1 must be considered in cases of isolated hypoparathyroidism. Autoantibodies to type 1 interferon (IFN) and to interleukin 17 family are early markers of T cell-mediated loss of immune tolerance. Their testing in suspected cases may be useful in the diagnosis of APS-1 since they are highly prevalent, especially IFN-ω and IFN-α (5, 13). The recognition of APS-1 is clinically relevant, as other manifestations may appear during the natural history. In addition to the major components, the patient had transient alopecia, ocular manifestations (recurrent keratitis and glaucoma) and chronic gastritis whose investigation revealed an autoimmune aetiology. Malabsorption syndrome was suspected due to gastrointestinal symptoms, intolerance to higher doses of calcium or vitamin D and a history of cholecystectomy. Analytic and endoscopic studies have revealed no additional disorders. Although hypothyroidism is secondary to hemithyroidectomy, the patient has thyroiditis with positive anti-thyroglobulin antibodies. These minor components are reported in literature (4, 12). To date, investigation has revealed no other endocrine conditions (type 1 diabetes mellitus, hypergonadotropic hypogonadism and panhypopituitarism), or non-endocrine diseases (vitiligo, hepatitis, splenic aplasia, nephritis, celiac disease, pernicious anaemia and pure red cell aplasia). Figure 4 shows the timeline of the patient's clinical manifestations. In some cases, immunomodulation for non-endocrine organ disease may be necessary (4). Even in the presence of gastrointestinal disease, symptoms should be regularly monitored due to the increased risk of oral and oesophageal squamous cell carcinoma (3).

APS-1 is often underrecognized probably due to its progressive course, leading to an unfortunate delay in diagnosis. However, in this case, it would be possible if the aetiology of hypoparathyroidism was previously investigated. Only several decades later, due to the simultaneous diagnosis of CMC and Addison's disease, APS-1 was suspected and confirmed. The detected mutation of the *AIRE* gene in our patient was previously described only in two Asian siblings in compound heterozygosity (14). Their presentation was with ungual candidiasis since age 1 and 7. The older sibling has also hypoparathyroidism. However, this article reports only

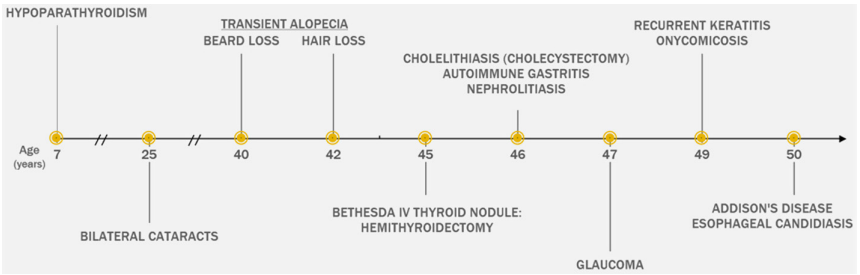

Figure 4
Timeline of patient's clinical manifestations.

the follow-up in their first decade of life (14). Both Asian siblings and our European brothers show a high intra-familial phenotypic variability, which is in line with the other reported cases (4).

Our patient has refractory hypoparathyroidism and a significant impairment of quality of life. He developed extraskeletal calcifications, such as premature cataracts, nephrolithiasis and calcifications of the basal ganglia. For these reasons, treatment with recombinant human parathyroid hormone (rhPTH) was considered (10). However, rhPTH is not sold in community pharmacies in Portugal and a national public report of May 24, 2019 concluded that there is no evidence of an additional benefit of rhPTH in adult patients with chronic hypoparathyroidism who are not adequately controlled with standard therapy alone. Thiazide diuretics may help to reduce hypercalciuria by decreasing urinary calcium loss, but they should not be used in APS-1 with Addison's disease due to the possible worsening of renal salt loss (15). Especially in hypoparathyroidism and Addison's disease in combination, management of APS-1 can be complex and it is not a matter of simply approaching individually each condition.

Patient's perspective

When I was a child, I was terrified of calcium levels in my blood and afraid of repeating convulsive episodes. My childhood and youth were very different from others. I got used to taking several pills daily. Although, this was not enough. If I forgot to take the medication, even once, I immediately felt paraesthesia or very fatigued. The doctors have never clarified the root cause of my hypoparathyroidism and I feel that my manifestations have never been valued enough. I tried for years and years to get the right dosage of calcium and vitamin D supplementation, in order to strike a balance between avoiding symptoms of hypocalcaemia and avoiding gastric disturbances. I took pills of several brands, but I continued to need frequent increases of the dosage. I was followed-up by several doctors. At a time when I felt more exhausted and misunderstood than ever, my General Practitioner referred me to an Endocrinology outpatient clinic with an interest in calcium metabolism. At that moment, I felt little energy to travel several kilometres, but my wife convinced me and helped me to go there. And it was really worth the effort! During the visit, I relived my past and I had the chance to explain my symptoms. The doctor focused on my fatigue, my weight loss and my skin tone. Actually, we ignored that my skin was much more tanned than before. What happened next was as simple as fast. A nurse collected some blood samples. Doctors explained the suspected cortisol deficiency and prescribed hydrocortisone pills. 'Cortisol is a vital hormone', they said. And they were right! I remember the times I was warned about the risk of decompensation in the future. But I did not realize that I would be in an urgent situation, because I strictly comply with the medication. But, 1 day, I woke up with vomits and diarrhoea. My body collapsed and everything was decompensated. My wife took me to the hospital. When I arrived, I was unconscious and I went directly to the emergency room. I had an adrenal crisis. Just due to an acute gastroenteritis and because I thought I would have time to take the pills again after the vomiting resolved. It was a really difficult and scary situation. But, in the end, everything was fine!

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent for publication of his clinical details and images was obtained from the patient.

Author contribution statement

Lima Ferreira J was the main writer of the manuscript. Lima Ferreira J and Príncipe R M provided assistance and follow-up to the patient. All the team members reviewed the manuscript.

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