Autoimmune Polyglandular Syndrome Type 1 : A Case Report

S M Assad[1], Dipti Chand[2], Archana Deshpande[2], Ashish Nimsarkar[3]

ABSTRACT

Autoimmune polyendocrine syndromes comprise a group of entities characterised by gradual functional impairment of multiple endocrine glands due to loss of immune tolerance, presence of circulating autoantibodies and lymphocytic infiltration of the affected tissues or organs, eventually leading to organ failure. These syndromes are now categorised as the rare monogenic form, autoimmune polyendocrine syndrome type 1 (APS-1), and the more common polygenic variety, autoimmune polyendocrine syndrome type 2 (APS-2).

Here we report a clinically diagnosed case of APS-1.

Introduction :

APS-1, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), MEDAC (multiple endocrine deficiency autoimmune candidiasis syndrome), juvenile autoimmune polyendocrinopathy, or Whitaker's syndrome (OMIM 240300), is a rare autosomal recessive disease caused by mutations in the autoimmune regulator gene (AIRE) located on chromosome 21q22.3, and is clinically defined by the association of at least two of three major component diseases: chronic mucocutaneous candidiasis, primary hypoparathyroidism, and autoimmune adrenal insufficiency.[1-3] The syndrome usually presents in infancy with a slight female preponderance and approximately 500 patients have been reported worldwide.[3]

Case Report :

A 21-year-old girl, born out of a non-consanguineous marriage, presented to the emergency medical services with recurrent generalised tonic clonic seizures. The patient was 17 years of age when she started getting seizures and was on multiple anti epileptics. She also had history of recurrent oral ulcerations and white lesions on the tongue and the palate since the past 5 years and deformed nails of the fingers and toes since the past 8 years. She had a delayed menarche, at the age of 18 years and had irregular menstrual cycles, being amenorrhoeic since the last 3 months at presentation. Her family history was unremarkable.

On examination she was found to be well built with normal higher mental functions and no neuropsychiatric symptoms. Onychodystrophy and subungual hyperkeratosis of the little finger of the left hand ***(Fig. 1A)*** and toenails were present ***(Fig. 1B).*** Oral cavity revealed pearly white plaques on the hard palate and tongue, which when scraped revealed an erythematous base ***(Fig. 2).*** She was Tanner Stage IV for breast development and Tanner Stage III for pubic hair, with absent axillary hair. She also had a hypopigmented patch on the left eyelid which was suggestive of vitiligo.

For evaluation of seizure, a computerized tomography scan of the head was performed which showed diffuse calcification of both the basal ganglia ***(Fig. 3).*** ECG had a prolonged ST segment and a QTc of 588 msec. Blood glucose level, complete blood count, liver and renal function tests were normal. Metabolic panel was done which revealed, serum calcium = low value (N=8.5-10.2 mg/dl), ionic calcium = 0.56 (1.05-1.3 mEq/L) and serum inorganic phosphate = 7.6 (N=3.4-4.5 mg/dl). Serum parathyroid hormone was < 2.50 (N=14-72 pg/ml) which made a diagnosis of primary hypoparathyroidism. The laboratory markers for other endocrine insufficiencies were unremarkable, 25-OH Vitamin D = 29.7 (N=30-100 ng/ml), serum

[1]Post Graduate Student, [2]Associate Professor, [3]Assistant Professor, Department of Medicine, Government Medical College and Hospital, Nagpur, India

Address for Correspondence -
Dr. S. M. Assad
E-mail : smassad27@outlook.com

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FSH = 5.70 mIU/ml, serum LH =1.94 mIU/ml, FT3 = 3.02 (N=2.60-4.80 pg/ml), FT4 = 0.96 (N=0.61-1.12 ng/dL), serum TSH = 2.471 (N=0.27-4.20 µIU/ml), serum cortisol = 10.3 (N=6.2-19.4 µg/dl), plasma ACTH = 7.33 (<46 pg/ml). Other laboratory tests ruled out celiac disease (anti-endomysial antibody - negative), diabetes mellitus (HbA1c 5.1), and B12 deficiency (serum B12 400 pg/ml). Oral swab sent for culture identified Candida albicans. Ophthalmologic examination did not reveal any evidence of dry eyes and keratopathy. Imaging studies of the abdomen-pelvis and the thorax were normal.

The presence of primary hypoparathyroidism along with mucocutaneous candidiasis and nail dystrophy, led to the clinical diagnosis of APS-1 in this patient. Interestingly, this patient was being treated as a case of seizure disorder with multiple anti epileptics. The patient is currently under treatment with supplemental calcium, activated vitamin D, anticonvulsants and antifungal medications and is being followed up at regular intervals.

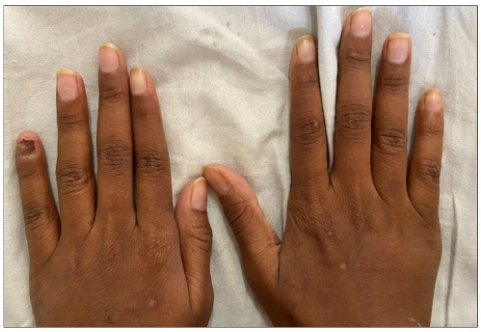

Figure 1A : **Onychodystrophy of left little finger**

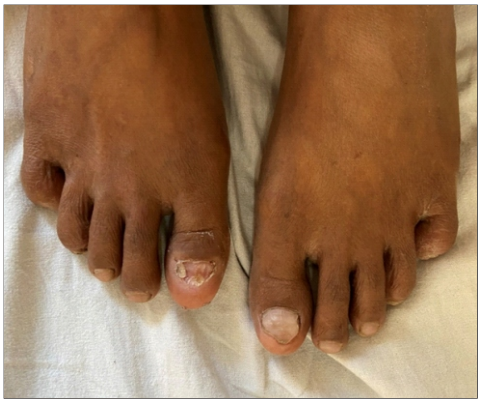

Figure 1B : **Onychodystrophy of toes**

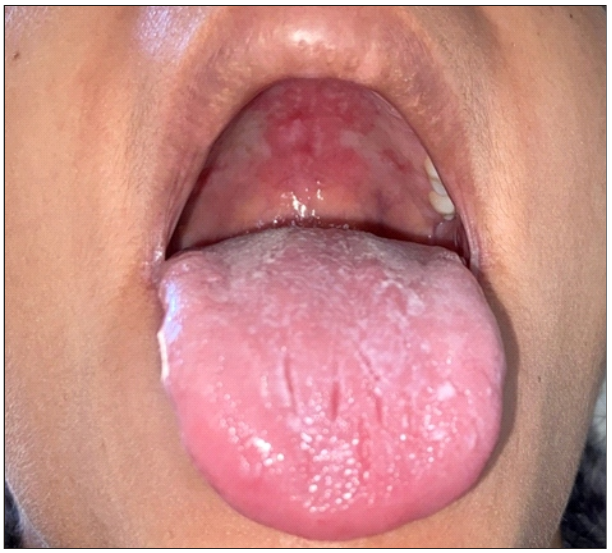

Figure 2 : **Chronic Oral Candidiasis**

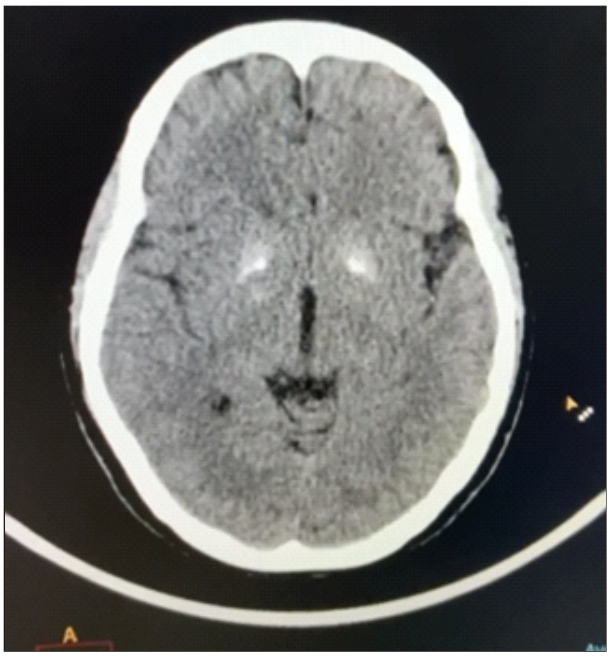

Figure 3 : **CT Brain Transverse view showing bilateral basal ganglia calcification**

Discussion :

Clinical Manifestations

APS-1 usually manifests in infancy or childhood 2-5, and the three major components of the disease develop in chronological order : candidiasis first, appearing before the age of 5; hypoparathyroidism before the age of 10; and finally, adrenal insufficiency, before 15 years of age.[3,4,6]

Chronic superficial infection with Candida albicans is the most common manifestation in APS-1, being nearly always present and is not very responsive to treatment.[3,5,7,8] The etiology is associated with anti-cytokine autoantibodies (anti-IL-17A, IL-17F, and IL-22) related to T helper (TH) 17 T cells and depressed production of these cytokines by peripheral blood mononuclear cells.

Hypoparathyroidism is seen in 70%-93% of the cases.[1-5] It has a gender variation, affecting 98% of female patients, but only 71% of male patients[9] and presents with symptoms of hypocalcemia; paraesthesias, cramps or seizures.

Primary adrenal insufficiency (AI) or Addison's disease has a prevalence of 60%-100%, with peak incidence at 12 years of age.[1-4,10] It can be life-threatening and should be rapidly recognized and treated. Symptoms include fatigue, weight loss, salt craving, hypotension, abdominal pain and increased pigmentation of the skin.

Hypergonadotropic hypogonadism appears in 12%-60% of the patients,[1-4,10] with a three times higher prevalence amongst females,[1,3] due to the blood testis barrier that protects Leydig cells from an autoimmune attack. Most of the affected female patients have primary amenorrhea with absence or early interruption of spontaneous pubertal development, and others develop premature menopause.[5]

Hypothyroidism is relatively uncommon, affecting 30% of the APS-1 patients. It develops more often following puberty and by middle age, usually before the age of 30.[3,5-7] Hyperthyroidism is rare.[5]

Type 1 diabetes mellitus has been described in up to 18% of the APS-1 subjects.[1-3] Nonendocrine manifestations include hypoplasia of the dental enamel (77%), alopecia (40%), vitiligo (26%), intestinal malabsorption (18%), pernicious anaemia (31%), chronic active hepatitis (17%), and nail dystrophy.[1-4] A debilitating manifestation is the development of refractory diarrhea / obstipation. Pure red cell aplasia and asplenism are also known associations.[4,5] Patients with APS-1 have an increased rate of death due to cancer,[11] adrenal and hypocalcemic crises, and certain conditions induced by aberrant autoimmune responses, particularly hepatitis, nephritis, and pneumonitis.

In our patient, candidiasis appeared at 13 years of age, involving the nails at first followed by oral candidiasis 3 years later. Symptoms of hypocalcemia appeared at the age of 17, although we believe hypoparathyroidism was already present months or even years before that. Our patient did not have adrenal insufficiency. Nevertheless, as we did not check anti-adrenal autoantibodies, the adrenal autoimmunity was not excluded. Although the hormonal studies were normal at present, the patient had signs of hypogonadism which is likely to progress to premature ovarian failure mandating a close follow up.

Genetics and Disease Mechanisms :

The underlying genetic abnormality in APS-1 is a mutation in the AIRE gene mapped to chromosome 21q22.3.[12] AIRE gene promotes the negative selection of autoreactive thymocytes and induces self- tolerance. To date, more than 115 mutations[13] including small insertions, deletions, and single nucleotide substitutions[14] have been reported with the predominant gene mutation varying across different ethnic groups.[15,16] Autoantibodies to type 1 interferons, namely interferon- and interferon- , are the most prevalent type of autoantibody in APS-1 and are present in almost all patients.[6,17] Autoantibodies to the interleukin-17 family of cytokines, especially interleukin-22,35,36 reach a prevalence exceeding 90%.[18] Disease associated organ-specific autoantibodies also appear, targeting the intracellular proteins that have key functions in affected organs ***(Table 1).***

Diagnosis :

The diagnosis of APS-1 is usually made clinically when two of the three major component disorders are found in an individual patient.[4,19] Genetic analysis of the AIRE gene should be undertaken to identify mutations. Detection of antiinterferon á and antiinterferon omega antibodies can identify most of the cases with APS-1 with sensitivity, specificity, and predictive values exceeding 98%.[6,20] Our case

Table 1 **- Self Antigens in APS-1, and the corresponding associations**

APS-1 components	Antigens
Adrenal insufficiency	21-OH, 17α-OH, scc
Hypogonadism	scc, 17α-OH, TSGA10
Hypoparathyroidism	NALP5, CaSR
Hypothyroidism	TPO, Tg
Type 1 diabetes	GAD65, IA-2, insulin
Gastrointestinal dysfunction	TPH, HDC, GAD65
Immune hepatitis	CYP1A2, CYP2AC, AADC, TPH, HDC
Immune gastritis	H^+/K^+ ATPase intrinsic factor
Lung disease	KCNRG
Vitiligo	Melanocyte, SOX9, SOX10, AADC
Alopecia	TH, hair follicles
Candidiasis	IL -17A, IL-17F, IL-22

21-OH: 21-hydroxylase, 17α-OH: 17α-hydroxylase, scc: side-chain cleavage enzyme, NALP5 NACHT leucine-rich-repeat protein 5, CaSR: calcium-sensing receptor, TPO: thyroid peroxidase Tg: thyroglobulin, GAD65: glutamic acid decarboxylase 65, IA-2: protein tyrosine phosphatase TPH: tryptophan hydroxylase, HDC: histidine decarboxylase, CYP1A2 and CYP2AC: cytochrome P450 1A2 and 2A6, AADC: aromatic l-amino acid decarboxylase, TH: tyrosine hydroxylase.

met the clinical criteria for the diagnosis of APS-1. Other family members were also screened but did not demonstrate any symptoms or signs of the disease. Genetic studies and antibodies could not be done due to non-availability of resources at our centre and financial constraints.

Diagnosis of each underlying disorder should be done based on their typical clinical presentations. Mucocutaneous candidiasis may be detected in the oral mucosa or from stool samples. Physical examination findings of hyperpigmentation, vitiligo, alopecia, tetany, and signs of hyper - or hypothyroidism should be looked for. Screening for organ specific autoantibodies is useful in assessing the risk of the development of endocrine insufficiencies in the future. Laboratory tests, including a complete metabolic panel, phosphorous and magnesium, thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH; morning), haemoglobin A1c, plasma vitamin B12 level, and complete blood count with peripheral smear looking for Howell-Jolly bodies (asplenism).

Treatment :

The mainstay of the treatment is to meticulously supply the various deficiencies and hormone replacement and management of complications. Patients should have a minimum of two follow-up visits per year, and asymptomatic carriers should be followed at least annually.

Chronic mucocutaneous candidiasis is treated with antifungals, azoles are effective but better avoided because of drug resistance and interference with steroidogenesis.[21] Hypoparathyroidism requires vitamin D supplements along with calcium and magnesium. Glucocorticoid replacement must be initiated immediately for adrenal insufficiency and doses should be increased during periods of acute stress. L-thyroxine supplementation is administered in cases of hypothyroidism, always after ruling out or treating adrenal insufficiency. Estrogen or androgen replacement should be started at pubertal age in hypogonadal children. Other symptoms, such as keratitis, pneumonitis, hepatitis, or enteritis, may require immunosuppressive treatment. Vaccination is recommended against pneumococcus, meningococcus, Haemophilus influenzae type b, and influenza.[22]

Conclusion :

APS-1 is a complex syndrome characterized by multiple endocrine and non-endocrine manifestations. Although rare, it must be diagnosed in early stages, given its high morbidity and mortality. Regular follow-up is essential to identify new disease manifestations, which may develop throughout the lifetime. The special diagnostic approaches, and the management of patients with APS-1 and their relatives, are best performed in centres with special expertise in autoimmune endocrine diseases.

References :

1. Neufeld MB, Blizzard RM. Polyglandular autoimmune diseases. In: Pinchera A, Doniach D, Fenzi GF, Baschieri L, eds. Symposium on autoimmune aspects of endocrine disorders. New York: Academic Press; 1980. p. 357-65.
2. Neufeld M, Maclaren NK, Blizzard RM. Two types of autoimmune Addison's disease associated with different polyglandular autoimmune (PGA) syndromes. Medicine. 1981;60(5):355-62.
3. Ahonen P, Myllarniemi S, Sipila I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. New Engl J Med. 1990;322(26):1829-36.
4. Betterle C, Greggio NA, Volpato M. Clinical review 93: autoimmune polyglandular syndrome type 1. J Clin Endocrinol Metab. 1998;83(4):1049-55.

5. Perheentupa J. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. J Clin Endocrinol Metab. 2006;91(8):2843-50.
6. Meager A, Visvalingam K, Peterson P, Moll K, Murumagi A, Krohn K, et al. Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. PLoS Med. 2006;3(7):e289.
7. Zlotogora J, Shapiro MS. Polyglandular autoimmune syndrome type I among Iranian Jews. J Med Genet. 1992;29(11):824-6.
8. Vogel A, Strassburg CP, Obermayer-Straub P, Brabant G, Manns MP. The genetic background of autoimmune polyendocrinopathy--candidiasis-ectodermal dystrophy and its autoimmune disease components. J Mol Med (Berl). 2002;80(4):201-11.
9. Gylling M, Kaariainen E, Vaisanen R, Kerosuo L, Solin ML, Halme L, et al. The hypoparathyroidism of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy protective effect of male sex. J Clin Endocrinol Metab. 2003;88(10):4602-8.
10. Soderbergh A, Myhre AG, Ekwall O, Gebre-Medhin G, Hedstrand H, Landgren E, et al. Prevalence and clinical associations of 10 defined autoantibodies in autoimmune polyendocrine syndrome type I. J Clin Endocrinol Metab. 2004;89(2):557-62.
11. Bensing S, Brandt L, Tabaroj F, et al. Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. Clin Endocrinol (Oxf) 2008;69:697-704.
12. Buzi F, Badolato R, Mazza C, Giliani S, Notarangelo LD, Radetti G, et al. Autoimmune Polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome: time to review diagnostic criteria? J Clin Endocrinol Metab. 2003; 88:3146-8.
13. Bruserud Ø, Oftedal BE, Wolff AB, Husebye ES. AIRE-mutations and autoimmune disease. Curr Opin Immunol. 2016;43:8-15.
14. Cetani F, Barbesino G, Borsari S, Pardi E, Cianferotti L, Pinchera A, et al. A novel mutation of the autoimmune regulator gene in an Italian kindred with autoimmune Polyendocrinopathy-candidiasis-ectodermal dystrophy, acting in a dominant fashion and strongly Cosegregating with hypothyroid autoimmune thyroiditis. J Clin Endocrinol Metab. 2001;86:4747-52.
15. Seifi-Alan M, Shamsi R, Setoodeh A, Sayarifard F, Aghasi P, Kompani F, et al. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy: report of three cases from Iran. J Pediatr Endocrinol Metab. 2016;29:979-83.
16. Weiler FG, Dias-da-Silva MR, Lazaretti-Castro M. Autoimmune polyendocrine syndrome type 1: case report and review of literature. Arq Bras Endocrinol Metabol. 2012;56:54-66.
17. Dalin F, Nordling Eriksson G, Dahlqvist P, et al. Clinical and immunological characteristics of autoimmune Addison's disease: a nationwide Swedish multicenter study. J Clin Endocrinol Metab 2017;102: 379-89.
18. Kisand K, Bøe Wolff AS, Podkrajsek KT, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17- associated cytokines. J Exp Med 2010;207: 299-308.
19. Capalbo D, De Martino L, Giardino G, Di Mase R, Di Donato I, Parenti G, et al. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy: insights into genotype-phenotype correlation. Int J Endocrinol. 2012;2012: 353250.
20. Meloni A, Furcas M, Cetani F, Marcocci C, Falorni A, Perniola R, et al. Autoantibodies against type I interferons as an additional diagnostic criterion for autoimmune polyendocrine syndrome type I. J Clin Endocrinol Metab. 2008;93(11):4389-97. Epub 2008 Aug 26.
21. Husebye ES, Perheentupa J, Rautemaa R, Kämpe O. Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type I. J Intern Med 2009;265:514-29.
22. Perheentupa J. APS-I/APECED: the clinical disease and therapy. Endocrinol Metab Clin North Am. 2002;31(2):295-320, vi.