DOI: 10.7860/JCDR/2015/10755.5748

Case Report

Internal Medicine Section

A Case of Autoimmune Polyglandular Syndrome (APS) Type II with Hypothyroidism, Hypoadrenalism, and Celiac Disease - A Rare Combination

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ABSTRACT

Autoimmune Polyglandular syndrome (APS) are rare condition characterised by presence of immune dysfunction of two or more endocrine glands and other non-endocrine organs. APS is divided into 2 major subtypes based on age of presentation, pattern of disease combinations and mode of inheritance. APS 1(juvenile) usually manifest in early adolescence or in infancy. It is characterised by multiple endocrinal deficiency with mucocutaneous candidiasis and ectodermal dystrophy. Of the endocrine diseases, hypoparathyroidism form an important component followed by Addison's disease, type 1A diabetes, hypogonadism and thyroid disease. On the other hand APS II usually manifest in 3rd or 4th decade of life with female preponderance. Endocrine diseases commonly include autoimmune thyroid disease (graves or autoimmune thyroiditis), type 1A diabetes, and Addison's disease. Hypoparathyroidism is of rare occurrence and there is no mucocutaneous candidiasis. We report here a case of APS type II in a 29-year-old male who initially presented with hypothyroidism, which was soon followed by Addison's disease. The involvement of thyroid gland preceding the involvement of adrenal is of rare occurrence. The patient also had celiac disease which makes the combination further uncommon.

Keywords: Adrenal insufficiency, Autoimmune thyroiditis, Poly-endocrinopathies

CASE REPORT

A 29-year-old male came with history of progressive weight loss, pigmentation of skin, recurrent pain abdomen and vomiting since six months. The patient said he had lost 30 kg of weight in last one year. His appetite had decreased and he had undue craving for salt. The patient gave history of primary hypothyroidism since one year and was maintaining euthyroid state on 100 µg of eltroxin. On examination there was pallor of conjunctiva, BP was 90/70 mm of Hg, pulse 100 beats per min, feeble and respiratory rate 18 breaths per minute. There was darkening of skin and pigmentation of palm and buccal cavity. Axillary and pubic hairs were normal and testis was of normal size. Cardiovascular system examination and respiratory system examination was normal. There was no organomegaly. He denied any history of papules, rashes, vesicles and hypo pigmented skin patch. There was no history of haemoptysis, hematemesis, melena, and hematuria. Laboratory investigations are mentioned in [Table/Fig-1].

Peripheral blood film showed microcytic hypochromic red blood cells with aniso-poikilocytosis and pencil cells. Gastroscopy showed atrophic duodenal villi. Duodenal biopsy showed classical changes of celiac disease includes- 1) atrophic villi with crypt hyperplasia and infiltration of mononuclear cells in lamina properia [Table/Fig-2]. Increase in the number of intraepithelial lymphocytes [Table/Fig-3].

Chest X-ray PA view, Electrocardiogram, and 2-dimentional echocardiography did not show any abnormality. A diagnosis of APS type II was made comprising of autoimmune hypothyroidism, autoimmune adrenal insufficiency, celiac disease and associated iron deficiency anaemia. The patient was started on intravenous saline, additional salt and hydrocortisone. Total body iron replacement was done using iron sucrose. Once the condition was stabilised he was put on thyroxine, fludrocortisone, prednisolone and gluten free diet. On six month of follow up patient was symptom free, had gained 20 kg of weight, and has haemoglobin was 14 g/dL.

DISCUSSION

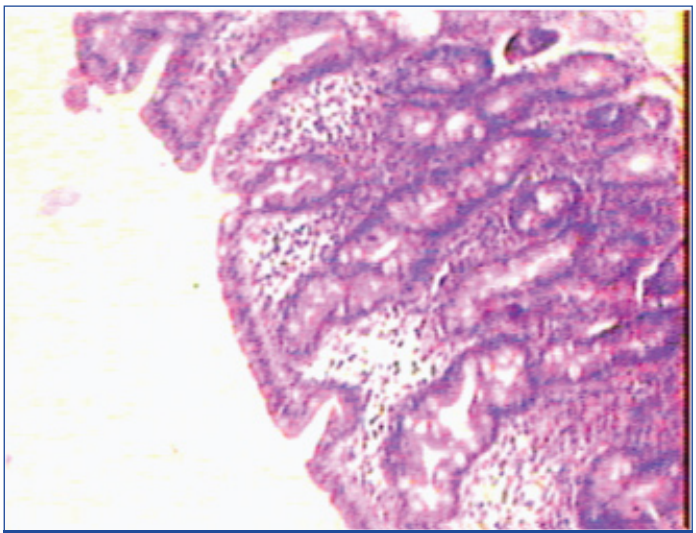
APS are rare polyendocrinopathies characterized by the failure of several endocrine as well as nonendocrine organs caused by immune-mediated destruction of endocrine tissues. APS type II is a rare endocrine disorder with a frequency of 1.4–2.0/100 000 and female preponderance [1]. Characteristics of the two types of APS are summarised in [Table/Fig-4]. Type 1A diabetes, autoimmune thyroid disease, Addison's disease are the common endocrine diseases. It may also lead to hypogonadism and diabetes insipidus in rare situation. Of the non-endocrine involvement pernicious anaemia, vitiligo, alopecia, and rarely myasthenia gravis and celiac disease may be seen [2].

APS type I is a monogenic disorder with classic pattern of inheritance and appearance during childhood or early adolescent and hence is known as juvenile APS. It is characterised by persistent chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal failure [3]. Type II is a more complex genetic disorder with variable presentation and female preponderance. It is commonly seen in 3rd or 4th decades. The variability in presentation has led one group of clinicians to split it as type II, type III and type IV. APS type II consist of Addison disease plus thyroid autoimmunity or type 1A diabetes; APS type III refers to thyroid autoimmunity plus one another autoimmunity (but not Addison's disease or type 1A diabetes); APS type IV refers to two or more organ specific autoimmune diseases. On the other hand, another group considers all the above combinations as APS II [3].

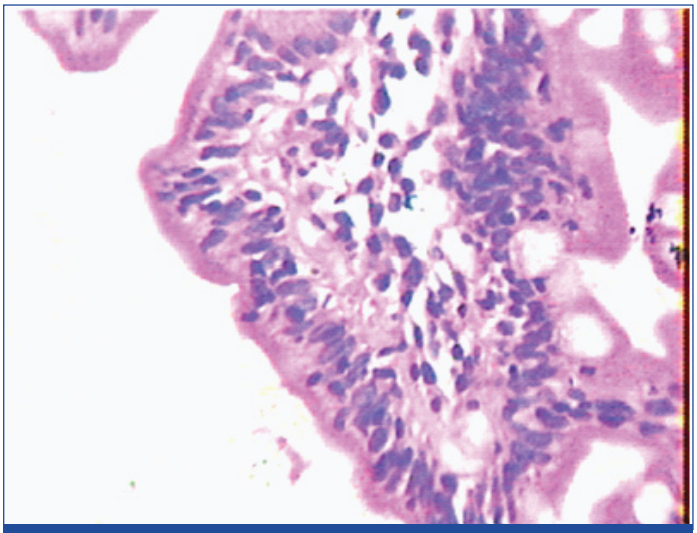
When all the combinations of type II, III and IV are considered as APS type II, the commonest first component is type 1A diabetes, followed by Graves' disease, Hassimato thyroiditis, Addison's disease and vitiligo in descending order of association. Of the various combinations of components, type 1A diabetes and thyroid are seen more frequently followed by thyroid and adrenal. The time between onset of first and second manifestation is longest between type 1A

Parameters	Values	Reference value
Hb	7.9 g/dL	13.3-16.2 g/dL
TLC	5.42×103/mm^3	3.54-9.06×103/mm^3
DLC	N- 64%, L- 33%, E- 3%	N-40-70%, L20-50%, E-0-6%
Platelets	165×103/mm^3	165-415×103/mm^3
MCV	54 fL	79-93.3 fL
MCH	20 pg/cell.	26.7-31.9 pg/cell
Blood sugar	70 mg/dL	65-95 mg/dL
Blood urea	23 mg/dL	7-20 mg/dL
Serum creatinine	1.07 mg/dL	06-1.2 mg/dL
S. Bilirubin-Total	1.02 mg/dL	0.3-1.3 mg/dL
Direct	0.34 mg/dL	0.1-0.4 mg/dL
AST	55 IU/L	12-38 IU/L
ALT	50 IU/L	7-41 IU/L
Total protein	6.73 g/dL	6.7-8.6 g/dL
S. Albumin	3.92 g/dL	3.5-5.5 g/dL
S. LDH	430 IU/L	115-221 IU/L
S. Iron	56 µg/dL	70-140 µg/dL
TIBC	350 µg/dL	250-406 µg/dL
% Saturation	16.0%,	16-35%
S. Ferritin	08 ng/mL	29-248 ng/mL
S. Sodium	105 meq/L	136-146 meq/L
S. Potassium	5.0 meq/L	3.5-5 meq/L
S. Phosphorus	4.6 mg/dL	2.5-5.5 mg/dL
S. Calcium	8.9 mg/dL	8.5-10.5 mg/dL
S.ACTH	107 pg/mL	6-76 pg/mL
S. Cortisol (8.00 am)	0.93 µg/dL	5-25 µg/dL
S. Cortisol (4.00 pm)	0.83 µg/dL	5-15 µg/dL
S. FT4	1.40 ng/mL	0.7-1.24 ng/mL
S. TSH	2.0 µIU/mL	0.35-4.5 µIU/mL
S. Paratharmone (intact)	30.13 pg/mL	10-55 pg/mL
S. TTG	61 U/mL	6-10 U/mL
Anti TPO antibodies (by RIA)	> 100 IU/mL	<35 IU/mL
Anti GAD antibodies	Not detected	0-5 IU/mL

[Table/Fig-1]: Laboratory Investigations
Abbreviations; Hb- Hemoglobin, TLC-Total Leukocytes count, DLC- Differential Leukocytes count, N-Neutrophils, L- Lymphocytes, E- Eosinophils, MCV- Mean Corpuscular Volume, MCH- Mean Corpuscular Hemoglobin, AST-Aspartate aminotransferase, ALT- Alanine aminotransferase, LDH-Lectate Dehydrogenase, TIBC- Total Iron Binding Capacity, ACTH- Adreno Cortico Tropic Hormone, S. FT4- Serum free thyroxin, S. TSH- Serum Thyroid Stimulating Hormone, TTG IgA - Tissue Trans-glutaminase antibody, TPO – Thyroid Per-oxidise, GAD- Glutamic Acid Decarboxylase



[Table/Fig-2]: Duodenal biopsy showing atrophic villi with crypt hyperplasia and infiltration of mononuclear cells in lamina properia



[Table/Fig-3]: Duodenal biopsy showing increase in the number of intraepithelial lymphocytes

	APS type I	APS type II
Prevalence	Very rare	Relatively common
Incidence	<1:100,000/yr	1–2:100,000/yr
Male to Female ratio	3:4	1:3
Onset	Childhood	Adulthood, 3rd or 4th decade
Inheritance	Monogenic Autosomal recessive	Polygenic dominant inheritance
Concomitant disease	Mutations in APECED gene on Ch. 21	HLA-DR3, HLA-DR4 associated
Autoimmune endocrine diseases	Mucocutaneous candidiasis (70–80%)	No candidiasis
	Hypoparathyroidism (80–85%)	Thyroid disease (70–75%)
	Addison's disease (60–70%)	Type 1 diabetes (50–60%)
	Type 1 diabetes (<20%)	Addison's disease (40%)
	Hypogonadism (12%)	Hypoparathyroidism (3%)
	Thyroid disease (10%)	Hypopituitarism (0–2%)
	Alopecia areata	Hypogonadism
	Dental enamel hypoplasia	Myasthenia gravis
Non-endocrine diseases	Immune gastritis,	Vitiligo
	Pernicious anemia,	Alopecia
	Celiac disease,	Pernicious anemia,
	Vitiligo	Celiac disease,
	Sjogren's syndrome	
	Immune hepatitis,	

[Table/Fig-4]: Characteristics of the autoimmune polyglandular syndromes (APS) [2,3]
Abbreviations; APECED, autoimmune poly endocrinopathy-candidiasis-ectodermal dystrophy

diabetes and thyroid disease. When thyroid disease appears as first component, the second immunopathy appears relatively early [4].

The genetic inheritance of APS II is polygenic. The disease is inherited as autosomal dominant trait with incomplete penetrance. Genetic susceptibility of APS II is related to human leukocyte antigens (HLA). However, HLA loci alone are not responsible for the genetic inheritance. There is an interaction between non-HLA loci, HLA loci and environmental factors. Genotype DR3/4, DQ2/DQ8 with DRB1*404 are associated with autoimmune Addison's disease in 30% of the patients [5].

Our patient was a male in 3rd decade of life at the time of onset of disease which was thyroiditis. Very soon it was followed by Addison's disease and celiac disease. Both the following components were diagnosed simultaneously. The recommended course of action for diagnosing APS II in a patient with monoglandular autoimmune endocrinopathy is functional screening for second endocrine gland every 3 y till the patient is of 75 y. This is because circulatory antibodies may be present well before the development of clinical manifestation and the presence of auto-antibodies provide a clue to early diagnosis of auto-immune endocrine disorders. When second endocrine gland involvement is detected, organ specific antibodies should be sought for [4].

CONCLUSION

To conclude a varieties of combination may occur in APS II. Commonly it is the involvement of adrenal gland preceding the involvement of

thyroid gland with a long latent period. Rarely thyroid gland may precede the involvement of adrenal gland and then the latent period is shorter. Whenever there is a monoglandular involvement of endocrine gland there is all possibilities of involvement of second gland at later date.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Aug 04, 2014**
Date of Peer Review: **Jan 26, 2015**
Date of Acceptance: **Jan 26, 2015**
Date of Publishing: **Apr 01, 2015**