Mixed phenotypic presentation of autoimmune polyendocrine syndrome type II in adolescent female

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Abstract

Autoimmune polyendocrine syndrome (APS) is a constellation of multiple endocrine and various autoimmune diseases. The hallmark features of APS are gradual onset, circulating autoantibodies, and tissue or organ infiltration by lymphocytes. There are genetic basis and failure of the immune system to maintain self-tolerance to a variety of molecules, which manifest as autoimmunity over a period of time. Age of onset of the syndrome may range from early infancy to adulthood, new onset of autoimmunity of the given syndrome can manifest throughout life. We report a case of an adolescent female with endocrine and non-endocrine manifestation of APS, starting at a very young age of 7 years with nephritis and hypertension as an unusual association.

Keywords: Autoimmune disease, autoimmune polyendocrine syndrome, endocrine

Introduction

Clinical manifestation of APS is varied from latent form to clinically overt syndrome, however, latent or subtle forms are more frequent than overt manifestations.⁴ Autoimmunity in APS may be a result of genetic predisposing and/or failure of self-tolerance by the immune system.⁵ The hallmark features of APS are gradual onset, circulating autoantibodies, and tissue or organ infiltration by lymphocytes. APS categorized into a rare monogenic (APS type 1) form and common polygenic variety (APS type 2), however, Neufeld and Blizzard⁶ classified APS into four main types (type 1, type 2, type 3, type 4) shown in [Table 1]. It was reported that it takes more than 2 decades between the onset of two endocrinopathic manifestations.⁷ A person suffering from APS may have multiple endocrine manifestations as well as variable frequency of non-endocrine autoimmune diseases, however, limited data are available in the pediatric population.⁸-¹³ Endocrinopathies are primary adrenal insufficiency, autoimmune thyroiditis, type 1 diabetes mellitus, and hypoparathyroidism.⁹ Autoimmune conditions are associated with variable frequency, which include pernicious anemia, celiac disease, hypogonadism, vitiligo, immune gastritis, parathyroid disease, myasthenia gravis, Sjögren's syndrome, rheumatoid arthritis alopecia areata, and nephritis.⁸-¹³ We report a case of APS in an adolescent female with two endocrine and eight autoimmune manifestations of APS, clinically categorized as APS type 2 with overlapping features of type 1 and type 3.

Case Details

An adolescent female, presented with the complaints of vitiligo, starting from the face and involved the whole body for the last 7 years, progressive abdominal distension, breathlessness, and paleness of body for last 5 years, swelling of feet, New York Heart Association (NYHA) grade IV dyspnea, palpitation, and fever for 5 days. There was no history of tubercular contact, liver disease, or any skin problem in any of the family members. On physical examination, there was severe pallor, icterus,
grade 3 clubbing [Figure 1], raised jugular venous pressure (JVP), pedal edema, bilateral crept, massive hepatosplenomegaly (7 cm and 16 cm, respectively), vitiligo [Figure 2], loud P2, hypertension (BP = 140/90 in the right arm, 160/100 in right leg), stunting (Ht. 138 cm vs. 159.8 cm, <-3 SD), wasting (Wt. 22 kg vs. 31, <-3 SD), and sexual maturity rating (SMR) Tanner stage 1. On laboratory evaluation, there was bicytopenia, hypoalbuminemia, iron deficiency anemia, secondary hyperparathyroidism, vitamin D deficiency, proteinurea, hematuria, and low cortisol levels, antibodies against parietal cells and anti-thyroid peroxidase (TPO) antibody and increased levels of anti-tissue transglutaminase (TTG) antibody. Biochemical findings at admission and follow-up were shown in [Table 2]. Imaging studies reveal features of portal hypertension (dilated portal vein, altered liver echotexture, increased resistive index in the hepatic artery), and fibrotic changes of liver on fibro scan. Renal color doppler showed increased resistive index in bilateral intersegment arteries, and 2-D Echo showed left ventricular (LV) dilatation and pulmonary arterial hypertension (PAH). Duodenal biopsy showed moderate villous atrophy, lymphomononuclear infiltration of lamina propria, increased intraepithelial lymphocytes, confirming celiac disease [Figure 3]. Also, antibodies were present against parietal cells and TPO. Fasting and postprandial blood glucose and thyroid profile were normal. Antinuclear antibodies (ANA), anti dsDNA, and autoimmune liver profile were normal. Out of three endocrinopathies, features of subclinical adrenal insufficiency and autoimmune thyroiditis, were present in index case with celiac disease, vitiligo, antiparietal cell antibody, a diagnosis of autoimmune polyglandular syndrome type 2 was considered.

### Table 1: Biochemistry of Patient at admission and in follow up

| Parameters                    | Admission | Follow up at 3 months |
|-------------------------------|-----------|-----------------------|
| Hemoglobin (g/dl)             | 2.4       | 10                    |
| Leucovte Count (cell/mm³)     | 2210      | 4200                  |
| Sodium (mEq/l)                | 143       | 137                   |
| Potassium (mEq/l)             | 4.5       | 4                     |
| Urea (mg/dl)                  | 45        | 30                    |
| Creatinine (mg/dl)            | 0.5       | 0.6                   |
| Protein (g/dl)                | 4.5       | 6                     |
| Albumin (g/dl)                | 2         | 3.5                   |
| SGOT (iu/l)                   | 48        | 35                    |
| SGPT (iu/l)                   | 89        | 45                    |
| Iron (µg/dl)                  | 8         | 20                    |
| Ferritin (ng/ml)              | 118       | 100                   |
| Random Sugar (mg/dl)          | 80        | 100                   |
| Calcium (mg/dl)               | 6.6       | 8.94                  |
| Phosphate (mg/l)              | 3.4       | 6.2                   |
| Alkaline Phosphate (iu/l)     | 642       | 881                   |
| iPTH (pg/ml)                  | 140       | 80                    |
| 25 (OH) vitamin D (nmol/l)    | 16.5      | 77                    |
| Protinuria                    | 3+        | 3+                    |
| Hematuria (cell/hpf)          | 3-5       | 10-15                 |

The child was started on a gluten-free diet, calcium, iron, vitamin D supplements, hydrocortisone, and antihypertensive. In follow-up, hepatosplenomegaly regressed, anemia, and total counts improved but the child developed depression in the skull. Computed tomography (CT) scan of the head, however,
was normal. Also, CT scan abdomen showed no evidence of adrenal atrophy.

### Discussion

We report an adolescent girl diagnosed as autoimmune polyendocrine syndrome (APS)-type-2 presented with subclinical adrenal insufficiency, autoimmune thyroiditis, hyperparathyroidism secondary to vitamin D deficiency, celiac disease, myocardiitis, vitiligo, pernicious anemia, leucopenia, autoimmune hepatitis, alopecia, and unusual features of nephritis and hypertension. There are limited data available on APS in the pediatric population.[12-14] Kirmizibekmez et al.[15] report a case of adolescent boy presenting as APS-2 with features of Addison disease, Hashimoto thyroiditis, celiac disease, and autoimmunity for type-1 diabetes mellitus. Whereas Smith et al.[16] reported a case of APS-2 presented with persistent fatigue and skin color changes after viral prodrome. The present case has subclinical adrenal insufficiency, autoimmunity against thyroid gland, liver, gastric cells, established celiac disease. There are four types of presentation of APS, the present case resembles type 2 APS, but there are certain associations in index cases found in other types of APS. Clinical presentation of type-1 APS has shown in Table 1, however, it may be associated with vitiligo, pernicious anemia, and nephritis, our case was initially presented with vitiligo, anemia, cardiac failure, nephritis, hypertension, and laboratory evidence of subclinical adrenal insufficiency. This observation showed that APS clinically presents with features of non-endocrine autoimmune diseases and later endocrine features, which ultimately depend upon interaction between genetic and environmental factors. Therefore, there is overlapping features co-exist between different types of APS.[17] The present case has established features of celiac disease (histological proven), as we started gluten-free diet, adolescents showed a response and there is a regression of organomegaly, improvement in anemia and leucocyte count. A study by Valenzise et al.[18] showed that 28.9% of children with Hashimoto thyroiditis have associated with one autoimmune disease (AD) and 0.9% were associated with two AD, the common ADs were celiac disease and type 1 diabetes. Our case has two endocrinopathy and eight ADs. Currently, management of these diseases is restricted to the pharmacological replacement therapy, i.e. hormones, however before starting the therapy subclinical adrenal insufficiency should be ruled out as a treatment of an endocrine disease may also trigger the onset of another endocrine disease.[16] The highlight of the present case was that an adolescent presented with a mixed phenotypic presentation of APS at the time of diagnosis with overlapping features of type 1, 2, and type 3.

### Conclusion

We report a rare condition in childhood with a mixed phenotypic presentation of APS. In the case of monoglandular autoimmune endocrinopathy, latent manifestation of endocrine and non-endocrine autoimmune diseases can be rule out by organ-specific screening of autoantibodies.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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