



Premature Ovarian Failure in Autoimmune Polyglandular Syndrome

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Abstract

Autoimmune polyglandular syndromes are a rare group of disorders of which Type II is the commonest. Premature ovarian failure is a minor feature of the disorder. The identification of the syndrome may take several years and different medical specialties need to be involved in the diagnosis and management of the case. The present case report describes the difficulties encountered in the diagnosis and successful management of a patient with the syndrome and its follow up. Some of the complications may be life threatening. Their work up and management becomes an expensive affair.

Key Words: Polyglandular syndrome, diabetes mellitus, autoimmune disorder, premature ovarian syndrome, addison disease

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Introduction

Autoimmune Polyglandular Syndrome (APS) are a group of disorders characterized by autoimmunity against two or more endocrine organs [1]. Premature Ovarian Failure (POF) due to autoimmunity may be a part of this syndrome which may severely compromise fertility. Three types of APS are described. Type I is rare and presents in childhood. It consists of mucocutaneous candidiasis, hypoparathyroidism and primary adrenal insufficiency presenting in that order. It is inherited in an autosomal recessive manner, has no HLA association and has an equal sex distribution. APS type III is ill defined and is the co-occurrence of autoimmune thyroid disease with two other autoimmune thyroid diseases with two other autoimmune disorders including diabetes mellitus Type I, pernicious anemia or a nonendocrine autoimmune disease in the absence of Addison's disease. APS type II occurs more frequently when compared to the other 2 varieties. Addison's disease is generally identified later and diabetes is the usual first condition to be diagnosed early because of its complications, as evidenced in the present case report. This paper reports a case of secondary amenorrhea which was ultimately found to have APS Type II which is a rare triad of Addison's disease, Hypothyroidism and Diabetes Mellitus with POF.

Case Report

Mrs A aged 34 years, married for 8 years presented with complaints of secondary amenorrhea since 6 years and mild dyspareunia and attacks of hot flushes. She attained menarche at the age of 11 years and since then her cycles had been regular with normal flow. She conceived spontaneously after one and a half years of marriage and after an uneventful antenatal period, delivered a healthy female baby by caesarean section. No history of postpartum hemorrhage and her puerperium was uneventful. Lactation was established immediately after delivery and she continued successful lactation for one year. In spite of discontinuation of breastfeeding menstruation did not resume. After two years of childbirth, she was evaluated for secondary amenorrhoea. Her serum levels of thyroid hormones were T3 -1.63 ng/ml (0.60-1.81 ng/ ml), T4 -8.5 µg/dl (5.5 – 11.0 µg/ dl), TSH- 38.9 mIU/ml (0.5 – 5.0 µIU/ ml), FSH – 100 IU/ml. She was diagnosed as a case of hypothyroidism and was started on thyroid supplementation therapy with 50 mcg of levothyroxine daily before breakfast.

After one and a half months, she developed petechial skin rash on the arms and thighs and bleeding from gums. Her serological tests showed Platelet Count- 15,000/ cu mm with a few

giant platelets, Hemoglobin-12.5 gm%, Prothrombin time- 16 seconds with a control of 14 seconds and INR of 1.0, and bleeding time - 4 minutes. A bone marrow trephine biopsy showed a normocellular marrow and was confirmatory of the diagnosis of immune mediated thrombocytopenic purpura.

She was diagnosed as a case of immune thrombocytopenic purpura and was started on steroids i.e. Tab Prednisolone 50 mg once daily in the morning. She continued steroids for 4 months at the same dose. After 4 months, patient developed bronchopneumonia with acute respiratory distress syndrome, hypotension and left ventricular dysfunction. There was also persistent hypokalemia and left vocal cord palsy which required hospitalization and ventilatory support for 3 weeks. Her workup at that time revealed Fasting Blood Sugar of 176 mg/dl, Postprandial Blood Sugar- 305 mg/dl, Serum electrolytes - Sodium-140 mEq/l, Potassium- 2.4 mEq/l, Chlorides- 102 mEq/l. Thyroid profile revealed TSH of 0.01 mIu/ml.

2D-Echocardiogram revealed an Ejection Fraction of 25% and severe left ventricular dysfunction. It was diagnosed as APS Type II (Addison 's disease, diabetes mellitus de novo with diabetic ketoacidosis and hypothyroidism) with Secondary Amenorrhea. She was started on Insulin therapy, adrenal corticosteroid replacement therapy and thyroid replacement therapy and was discharged after 3 weeks in hemodynamically stable condition. The hypokalemia was a part of diabetes ketoacidosis which reverted to normal with correction of the diabetic status.

At present, the patient attended Gynec O.P.D with us for evaluation of secondary amenorrhea 4 years after the onset. On examination, her height was 158 cms; weight was 51 Kgs. Secondary sexual characters were well developed. Her vitals were normal. Bimanual examination revealed a normal vaginal depth with vaginal dryness. Uterus was less than the normal in size, anteverted and mobile. Cervix was normal and healthy. In view of the insulin dependent diabetes, hypothyroidism and ovarian failure, APS II was suspected and her morning serum cortisol was estimated which was low normal and did not rise with ACTH challenge. As the patient was already on steroid treatment for thrombocytopenic purpura, florid symptoms of Addison's disease like anorexia, postural hypotension could not be observed. Other investigations were as follows, normal data of the laboratory given in parenthesis-

Hemoglobin	:	12.9 g/dl
Platelet count	:	340x10 ³ mm ³
Serum TSH	:	0.15 µIU/ml
Serum antimicrosomal antithyroid antibodies were elevated		
Serum cortisol (morning)	:	5 µg/ dl (5-23 µg/dl)
Serum FSH	:	49.7 IU/ml (less than 35 IU/L)
Serum LH	:	37.5 IU/ml (less than 40 IU/ L)
Serum Prolactin	:	6.1 ng/ml (2.8-20.3 ng/ml)
ECG	:	Normal

Ultrasonography of Pelvis- Uterus- Anteverted measuring 5.5×3.3×1.7 cm Endometrium thickness of 2 mm. Both ovaries were of normal size but there was no evidence of follicles. Chromosomal analysis showed normal XX karyotype with no structural anomalies.

Bone mineral density test revealed a Z- score of -3.8 suggestive of osteoporosis.

As the FSH and LH were in the menopausal range a diagnosis of premature ovarian failure (POF) was made. She was advised to take 0.625mg of conjugated estrogen for 21 days and 2.5 mg of medroxyprogesterone for the last 10 days of the menstrual cycle. She had withdrawal bleeding. She had general wellbeing apart from cyclical bleeding with hormone replacement. She is followed at monthly intervals for the past 2 years. At present, the patient is on hormone replacement therapy with calcium and vitamin D supplementation, levothyroxine 100µgm once daily, Insulin therapy and corticosteroid replacement therapy. She is having regular menstrual cycles and her premature menopausal symptoms have subsided.

Discussion

Our case appears to be a Type II variant of APS on the basis of the new proposed classification of Neufeld and Blizzard [1]. This Syndrome was originally described by Schmidt, as a syndrome with coexistent Thyroid and Adrenal Failure. Autoimmune Polyglandular Syndrome (APS) Type II or Schmidt's syndrome is characterized by Addison's disease associated with autoimmune thyroid disease and/or type 1 diabetes [2]. Though adrenal failure is an integral part of the syndrome, patient may identify diabetes mellitus

several years before adrenal insufficiency appears because diabetes is more frequently diagnosed [3].

APS Type II is a rather rare disease with an incidence of 1.4-4.5 cases in every 1,00,000 inhabitants. It affects mainly adult women, The mean age at presentation is 35 years [4,5]. The female to male ratio is 3-4:1. It is associated with HLA-DR3 and/or HLA-DR4 haplotypes, and the pattern of inheritance is autosomal dominant with variable expressivity [6]. Other disorders associated with APS Type II include the following hypogonadism (usually autoimmune oophoritis) and hypopituitarism, idiopathic thrombocytopenic purpura, myasthenia gravis, Parkinson disease, vitiligo, alopecia and seronegative arthritis [7]. Unlike with APS Types I and III, autoimmune POF is more commonly encountered with APS type II. An autoimmune response to steroidogenic enzymes and ovarian steroid cells appears to mediate the destruction of ovarian function [8]. A transvaginal sonography is more sensitive in identifying any remaining ovarian follicles. An ovarian biopsy may reveal lymphocytic infiltration of the ovary.

In the present case, the patient first manifested secondary amenorrhea and hypothyroidism. Later she developed Idiopathic thrombocytopenic purpura, which is considered a minor component of APS Type II [9]. Later she had full expression of APS Type II when she was diagnosed as Addisons disease and Insulin dependent diabetes mellitus. There may be a discrepancy in the clinical expression of APS TypeII. Incomplete forms of APS Type II are also described [10]. Hence biochemical and immunological screening tests may be helpful in predicting the functional failure of endocrine organs in patients with APS type II. Also their first degree relatives should be screened for the component disease. Children of women with any one of the autoimmune disorder should be screened for other disorders [11].

The pathogenesis of APS Type II is poorly understood. The postulated steps are as follows [9]:

1. Some degree of genetic susceptibility must exist.
2. The individual is exposed to an environmental trigger.
3. Next, a subclinical phase of active production of organ-specific antibodies occurs.
4. There is autoimmune activity and progressive glandular destruction. Still the individual is asymptomatic.
5. Overt clinical disease develops when extensive organ damage has occurred.

This syndrome is replete with autoantibodies reacting to target tissue-specific antigens.

POF is common and is seen in approximately 1% of women before the age of 40 years. The etiology is unknown in most cases. Specific sex chromosome anomalies can be identified in some patients. Autoimmune processes leading to POF are seen mumps oophoritis, or a physical insult such as irradiation or chemotherapy.

To conclude, POF though a minor component may be present in 4-9% of the patients [8]. By combined hormonal therapy with estrogen and progesterone, patient may resume menstrual function but regaining fertility is limited to the number of functioning follicles at the time of treatment initiation. Hormonal therapy is helpful in resuming menstrual function, relieving premature menopausal symptoms, promoting general well-being and also in preventing osteoporosis. Although immunotherapy with corticosteroids with or without in vitro fertilization (IVF) may be successful in the cases where some follicles are remaining, oocyte donation with IVF may be the best option for patients seeking fertility. Pregnancy rates are reduced when sibling's donated oocytes are used. Treatment of POF alone (without other components such as Addison's disease) with pharmacological doses of corticosteroids is not warranted because responsiveness to gonadotrophin administration is not achieved [12].

Declaration

No identifiable marks of the subject are included in the manuscript.

Written consent is taken from her to publish the case report.

There is no financial conflict.

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