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General Medicine

CASE REPORT OF TYPE 3 MULTIPLE AUTOIMMUNITY SYNDROME - A MYRIAD OF AUTOIMMUNITY!

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ABSTRACT The co-occurrence of at least three autoimmune diseases in the same patient is defined as multiple autoimmune syndrome (MAS) [1]. They make up a heterogeneous group of disorders where multiple alterations in the immune system result in a spectrum of syndromes. Abnormalities of both humoral and cell-mediated immunity have been described. The pathogenesis of multiple autoimmune disorders is not fully known, perhaps environmental triggers and genetic susceptibility are involved. We describe a case of 38 years old female patient with type 3 MAS, who initially was diagnosed to have hypothyroidism, and later went on to develop systemic lupus erythematosus (SLE), autoimmune hemolytic anemia (AIHA) and primary ovarian failure (POF). Such a combination of disorders is hitherto not described in literature.

KEYWORDS : autoimmunity, coexistence, heterogenous, syndrome, susceptible

INTRODUCTION

Multiple autoimmune syndrome (MAS) is a group of autoimmune disorders characterized by the co-occurrence of three or more autoimmune diseases in a single patient. It is classified into three subgroups – type 1, type 2 and type 3. We report a case of 38 years old female patient who was diagnosed to have type 3 MAS with autoimmune thyroid disorder (AITD), systemic lupus erythematosus (SLE), autoimmune hemolytic anemia (AIHA) and primary ovarian failure (POF) hitherto not described in literature.

Case Report

A 38-years-old lady, was admitted with history of multiple joint pains (affecting small joints of fingers, elbows, wrists, knees and ankles) associated with morning stiffness and intermittent swelling for past 1 year. She also noticed pigmentation of the skin over the cheeks, chin and nose. There was no itching. There was history of hair loss and generalized weakness. Her menstrual cycles had stopped 5 months prior to hospital admission. There was no history of increased facial hair, acne, nipple discharge or fetal loss. She was diagnosed to be hypothyroid and was on oral levothyroxine 75mcg one year prior to hospital admission.

On admission, she was coherent, lean, had pallor, pigmentation of skin over the nose, cheeks and chin sparing the nasolabial folds. There was no icterus, clubbing and cyanosis. She was afebrile, with pulse rate of 102/minute, blood pressure 100/70 mm Hg, and respiratory rate of 18/minute. Systemic examination was normal except for mild splenomegaly. Locomotor examination did not show signs of inflammation, restriction of movement, or deformity. None of her family members had similar complaints.

She underwent investigations which are as summarized in **table 1 and 2**. Additionally, her stool for occult blood was negative. Chest radiograph was normal while ultrasound of abdomen revealed mild splenomegaly.

Table 1: Lab investigations (hematological and biochemical tests)

Investigations	Values
Hemoglobin (Hb)	7.1gm/dl
Total leucocyte count	2,200 cu mm
Differential count	78 % neutrophils, 12% lymphocytes
MCV	82.6fl
Hematocrit	21.3
Peripheral smear	Polychromasia, normocytic and few macrocytic, normochromic RBCs, few spherocytes
Reticulocyte count	2.1%
Serum B_{12}	815 pg/ml (N:180-914pg/ml)
Serum folic acid	13.17ng/ml (N: 3- 20 ng/ml)
Serum iron	46.5mcg/dl (N:26-170 mcg/dl)
Serum ferritin	648.8ng/ml (N:20-150 ng/ml)
Serum lactate dehydrogenase (LDH)	846.7IU/L (N:140-280IU/L)
Direct Coomb's test (DCT)	Strongly positive (3+)
Indirect Coomb's test	Negative
Hb electrophoresis (capillary electrophoresis)	Normal adult AA pattern
Total serum proteins	7.0g/dl
Serum albumin	3.53 g/dl
Serum globulin	3.47 g/dl
PT (INR)	1.1
Serum creatinine	0.9 mg/dl
Total bilirubin	2.9 mg/dl
Indirect	1.9 mg/dl
Alanine transaminase (ALT)	39 U/L
Aspartate transaminase (AST)	76 U/L
Urine – Routine analysis	Normal
Urine pregnancy test (UPT)	Negative

Table 2: Lab investigations (hormonal and antibody assay)

Investigations	Values	Normal range
Antibodies to antinuclear antigen (ANA)	Positive (1 :640)	
Antibodies to double stranded DNA(dsDNA) - ELISA	Positive	
Lupus anticoagulant (LA)	Not found	
Rheumatoid factor (RA)	Negative	
Anti-citrullinated antibodies (anti CCP)	Negative	
Anti-thyroid peroxidase (TPO) antibodies	543.7IU/L	< 9 IU/L
Anti-thyroglobulin antibodies	214 IU/L	< 116 IU/L
Serum TSH (CLA)	1.64µIU/L	0.3-4.5µIU/L
Serum cortisol level 8AM	16.75 mcg/dl	6-25mcg/dl
Follicular stimulating hormone (FSH)	64.14 mIU/ml	Premenopausal females (4.7 to 21.5 mIU/mL)
Serum prolactin	15 ng/ml	Nonpregnant females: 2 - 29 ng/mL
Hbsag	Negative	
Anti HCV antibodies	Non-reactive	
Antibodies to HIV 1 and 11	Non-reactive	

As she was fulfilling the American College of Rheumatology (ACR) criteria of SLE (5/11), she was diagnosed to have systemic lupus erythematosus (SLE) with autoimmune thyroid disease (AITD), primary ovarian failure (POF) and autoimmune hemolytic anemia

(AIHA). Pelvic examination and ultrasound of pelvis done by gynecologist were normal. She was started on oral prednisolone 40 mg/day (1mg/kg) with hydroxychloroquine 400 mg once a day. She was transfused two units of packed red blood cells. One week after initiation of treatment, her WBC and platelet counts improved to 2,800/cu mm and 98,000/cu mm respectively. She was then asked to follow-up in the out-patient clinic.

DISCUSSION

Autoimmune diseases are chronic conditions initiated by the loss of immunological tolerance to self-antigens. They are characterized by inflammation and production of a variety of autoantibodies directed against target specific multiple organs. Their etiology is poorly understood, but immunological, hormonal and environmental factors in a genetically susceptible individual are the major triggering factors [2]. A patient suffering from one autoimmune disease has 25% chances of acquiring another autoimmune disease [3]. Our patient was diagnosed to be hypothyroidism one year back, however, the cause was not evaluated. One year later, she presented to us with polyarthritis, facial pigmentation, fatigability and hair loss. On evaluation, she was found to have SLE. This led to the suspicion of presence of other autoimmune disorders. As she had autoantibodies both to thyroglobulin and thyroid peroxidase, the cause of her hypothyroidism was AITD. Further, she had amenorrhoea for 4 months with increase in FSH in menopausal range giving rise to the possibility of primary ovarian failure (POF). A widely used definition of POF is premature menopause with amenorrhoea $\geq$ 4 months and two FSH levels $\geq$ 30IU/ml at an interval of at least 1 month [4,5]. Though the etiology is largely variable, in presence of other autoimmune disorders, possibility of autoimmune oophoritis was high. Definitive diagnosis can be established by ovarian biopsy.

The occurrence of a combination of at least three autoimmune diseases in the same individual is defined as multiple autoimmune syndrome (MAS) [1,3]. The definition of multiple autoimmune syndrome is based on 91 reported cases of such associations in the literature. It is classified into three groups according to the prevalence of their associations with one another. Type 1 MAS comprises myasthenia gravis, thymoma, polymyositis and giant cell myocarditis. Type 2 includes Sjögren's syndrome, rheumatoid arthritis (RA), primary biliary cirrhosis, scleroderma and autoimmune thyroid disease. Type 3 includes AITD, myasthenia gravis and/or thymoma, Sjögren's syndrome, pernicious anemia, idiopathic thrombocytopenic purpura (ITP), Addison's disease, insulin-dependent diabetes mellitus, vitiligo, AIHA, SLE and dermatitis herpetiformis [3,5]. Other conditions which may be found are acquired primary hypogonadism, hypophysitis, RA and ulcerative colitis. This classification helps to detect a new condition liable to appear in a patient who has had two previous autoimmune disorders. Our patient had AITD, SLE, AIHA and primary ovarian dysfunction, thus satisfying the criteria of MAS Type 3. HLA-B8, DR3 and DR5 are the important genetic factors implicated in the etiopathogenesis of type 3 MAS [6]. Genetic studies could not be done in our patient due to the lack of availability.

Mohan et al reported a case of MAS with vitiligo, alopecia areata and ulcerative colitis [6]. Yet another case reported by Adib Sereshki et al, MAS was associated with AIHA, hypothyroidism and Addison's disease in a 30-year-old woman [7]. Masood et al described a 42-year-old female patient with MAS with AIHA, systemic lupus erythematosus, psoriasis and type 1 diabetes mellitus [8]. A case of MAS resulting in vitiligo, RA, hypothyroidism and coeliac disease was described by Harpreet et al [9]. Agarwal et al documented a case of MAS with hypothyroidism, coeliac disease and undifferentiated connective tissue disorder [10].

Thus, our patient had clustering of four autoimmune disorders as discussed above. The presence of one autoimmune disease should alert physician to watch for the development of another one in an individual. To our knowledge, such a constellation of autoimmune disorders (AITD, SLE, AIHA and POF) has not been described earlier in the literature.

CONCLUSION

Development of one autoimmune phenomenon indicates the need for continued surveillance for the occurrence of new autoimmune disease in predisposed patients. MAS may initially present as a single disorder and may evolve over years into a complex syndrome.

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