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Case Report

Suspected new syndrome: idiopathic chronic systemic inflammatory dryness – a case report

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ABSTRACT

The current article discusses a peculiar and identifies an atypical autoimmune disease termed as the idiopathic chronic systemic inflammatory dryness. In the reported case, the clinical signs are to some extent identical to Sjogren's syndrome with dry eyes, dry mouth and dry vagina but the biomarkers are negative for it. On the other hand, the biomarker for systemic sclerosis is positive but no clinical signs or symptoms of it were present. The present case also has a probable association with history of toxoplasmosis. The article is of utmost importance in the discourse of development and research of concurrent immunology and understanding of autoimmune diseases.

Keywords: Autoimmune disease, Dry eyes, Toxoplasmosis, Anti-PM/Scl antibody, Inflammation, Sjogren's syndrome, Systemic sclerosis

INTRODUCTION

The article reports a newly identified syndrome of chronic systemic inflammation with systemic dryness of idiopathic etiologic origin. Over the time the understandings of systemic inflammatory diseases have undergone a radical change and perceptions of autoimmune disturbances have been developed. In the discussed clinical case, the patient had a spectrum of symptoms suggestive of Sjogren's syndrome but anti-nuclear antibodies immunoblot results were specific for systemic sclerosis, with positive anti-PM/Scl antibodies, although no symptoms of it were noticed in the patient.[1] The condition couldn't have been diagnosed as Sjogren's syndrome as well as the anti-Sjogren's-syndrome-related antigen A or anti-Ro/SS-A and anti-Sjogren's-syndrome-related antigen B anti-La/SS-B antibodies were negative in ANA immunoblotting result[2]. All other symptoms of connective tissue disorders or autoimmune diseases were absent. Thus, the article presents a unique case of overlapping syndrome with specific symptoms but of unknown domain in medical science. The case might open up new frontier in the understanding of autoimmune pathologies.

CASE REPORT

The case is of a patient 27 years old, Slavic ethnicity, primiparous female from the city Nizhny Novgorod, Russia. The patient consulted in day-care unit with complaints of chronic inflammation and dryness for past 6 months. As per anamnesis given by the patient, the patient was admitted in hospital in her city for bacterial vaginosis and urethritis in April 2023. The onset was sudden and complex anti-fungal and anti-bacterial therapy was given through oral and intravenous route with drugs including fosfomycin, fluconazole, sertaconazole, cifran, amoxicillin-clavulanate, furazolidone and levofloxacin. On treatment there was complete resolution of the infection but chronic inflammation of urethra and vagina persisted along with dry eye with opportunistic infection occurring from time to time with pus accumulation under eyelids without history of hypopyon. The patient complained of itchy eyes, skin and vagina with dry eyes and vagina, continuous hair-fall, dysuria, intense pain in vagina, in eyes and itchy skin and reported intense dyspareunia resulting into loss of sex life. The patient was emotionally distressed and in a panicking condition. On

general and observation under colposcope, inflammation and hyperemia of vagina with five pus filled cavities on the cervix as seen in Figure 1 and two flat topped papules on the inner wall of vulva were noticed as seen in Figure 2. Result of hysteroscopy confirmed additional endometriosis. Skin was pale and dry. Heart sounds were normal on auscultation; no changes of heart borders were noticed on percussion. The blood pressure on both hands was 130/70 mm Hg, pulse was 75 beats per minute. Lung field was clear with normal vesicular breathing, SpO_2 98%. The patient had severe dry eyes with 3 mm wetting of paper after 5 minutes on Schimmer's test, visibly pulsating long ciliary artery and lacrimal artery as seen in Figure 3 with slightly hard eyeballs on digital palpation, indicating an increased intra-orbital pressure (IOP).[3] The oral cavity showed mild dryness on observation. Urinary bladder was palpable. No changes were noticed on the big bone joints in the upper and lower arms, muscle tone and skin turgor were intact. Mild Veraguth's fold was observed on the forehead as seen in Figure 4, indicating development of chronic depression.[4] Patient reported allergic reaction to tetracycline group of drugs. The patient was given clindamycin 150 mg per os (PO) 2 times a day for 7 days for antibacterial management, ciprofloxacin 0.3% eye drop as antibacterial management of eye infection, hypromellose 3 mg/ml eye drop 3 times a day as a tear substitute, since cevimeline was not available in the market locally, pilocarpine 2% eye drop 2 times a day as a strategy to release excess IOP, aceclofenac 100 mg 2 times a day for 14 days with rabeprazole 20 mg 2 times a day as a gastro-protector for 14 days, both to be taken 30 minutes before meal and lorazepam 2 mg on feeling of intense emotional distress. Most of the symptoms were indicating towards Sjogren's syndrome but because of persisting infection immediate specific or generalized cytostatic management could not be started. Although at this point it is to be noted that the did not have parotid gland enlargement, purpura, leucopenia or lymphadenopathy which are generally found in Sjorgen's syndrome as malignant associations. The patient was followed up in the out-patient department (OPD) as no indication of hospitalization was observed. Complex therapeutic regimen and clinical analysis were started.

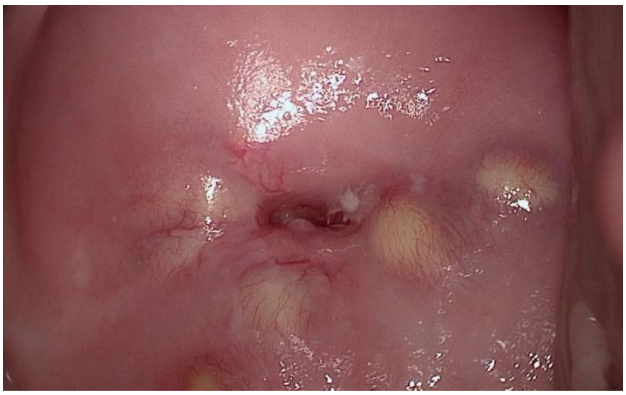

Figure 1: Colposcopic view of cervix with five pus filled cavity.

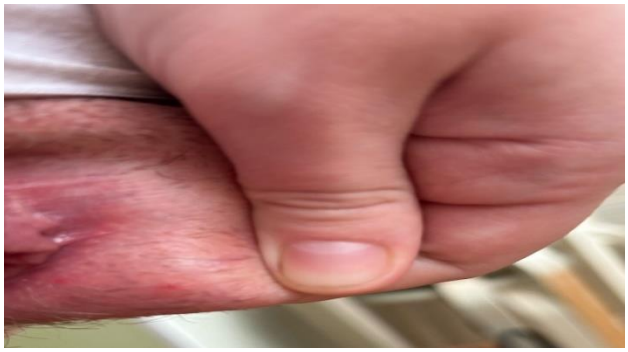

Figure 2: Papule on the inner wall of vulva.

Figure 3: Dry eyes with pulsating long ciliary artery and lacrimal artery.

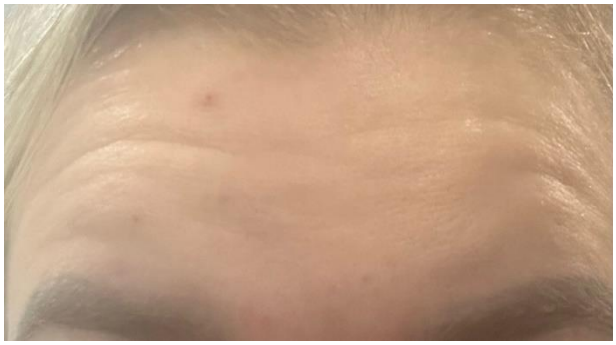

Figure 4: Forehead showing mild Veraguth's fold.

The result of complete blood count showed all blood cells and cell parameters to be normal, including erythrocyte sedimentation rate (ESR) at 4 mm/hour. The biochemical analysis of blood with liver function test showed alanine transaminase (ALT), aspartate transaminase (AST), bilirubin within normal physiological range; creatinine, fasting glucose, gylcated hemoglobin (HbA1C), serum protein, uric acid was also within normal range; and C-reactive protein (CRP) was slightly elevated at 5.5 mg/l. Rheumatoid factor was negative. The lipid profile showed cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL) and triacylglycerol (TAG) within normal range. Triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH) were within normal range. Ultrasonography of urinary bladder confirmed increased diameter of ureter, increased echogenicity and

vascularization of ureter without any signs of varicosis. Ultrasonography of abdomen showed mild hepatomegaly. Electrocardiography (ECG) report showed mild sinus bradycardia with heart rate at 58 beats per minute on an average without any deviation of axis. Echocardiogram result showed all heart valves to be normal with no signs of pulmonary hypertension, no changes were noticed in aorta and left ventricular ejection fraction (LVEF) was preserved at 65%. Magnetic resonance imagining (MRI) of the brain showed slightly increased width of the perineural space of the ophthalmic nerves on both sides of the ophthalmic tract. Contrast enhanced computer tomography (CE-CT) of chest showed no pathological changes or signs of interstitial lung diseases.[5] ANA immunoblotting results were as shown below in Table 1, with only autoantibody immunoglobulin G (IgG) to antigen PM-Scl being positive.

Table 1: ANA immunoblotting result.

Name of test	Result
Autoantibody IgG to antigen nRNP/Sm	Negative
Autoantibody IgG to antigen Sm	Negative
Autoantibody IgG to antigen RNP-70, -A-C	Negative
Autoantibody IgG to antigen Ro-52	Negative
Autoantibody IgG to antigen PM-Scl	Positive
Autoantibody IgG to antigen Jo-1	Negative
Autoantibody IgG to antigen CENP B	Negative
Autoantibody IgG to antigen PCNA	Negative
Autoantibody IgG to antigen dsDNA	Negative
Autoantibody IgG to antigen neocleosome	Negative
Autoantibody IgG to antigen ribosomal protein P	Negative
Autoantibody IgG to antigen histone	Negative
Autoantibody IgG to antigen SS-A	Negative
Autoantibody IgG to antigen SS-B	Negative
Autoantibody IgG to antigen Scl-70	Negative
Antimitochondrial M2 antibody IgG	Negative

RNP: Ribonucleoprotein, PM: polymyositis, CENP: centromere proteins, PCNA: proliferating cell nuclear antigen, ds DNA: double stranded deoxyribonucleic acid, SS-A: Sjogren's-syndrome-related antigen A, SS-B: Sjogren's-syndrome-related antigen B

Test for anti-Ro and anti-La antibodies was repeated to rule out false negative but the result was negative again. Inhibitor C1-esterease was measured to check if the patient had hereditary angioedema but it was found to be in normal range along with C3 and C4 complements in normal range too. As per observation made by ophthalmologist, the patient had chorioretinal dystrophy of the right eye and mild peripheral degeneration of the cornea in the left eye. A random screening test was done to rule out any persistent bacterial or viral infections; hepatitis B, hepatitis C, human immunodeficiency virus (HIV), herpes simplex virus (HSV) 1, HSV2, IgG-Lamblia sp., IgG-*Echinococcus* sp., IgG-*Chlamydia* sp., *Taenia solium*, IgM and IgG-*Rubella* sp. were negative. Only IgG - *Toxoplasma gondii* was positive with a high avidity of 96% and IgM - *Toxoplasma gondii* was negative. Hence, it was found that the patient in far past had toxoplasmosis. MRI brain could not detect any cyst formation or formation of any similar structure, hence chronic toxoplasmosis was ruled out. After 7 days of antibacterial and anti-fungal therapy, agitation of the patient reduced, pus filled cavities of the cervix and papules on the inner-wall of vulva disappeared. Irritation of the eyes were reduced to some extent due to continuous application of sol. Pilocarpine 2% and, hypromellose 3 mg/ml eye drops. In OPD follow up the patient was next prescribed methotrexate 2.5 mg every alternate day along with hypromellose 3 mg/ml eye drop 3 times a day, pilocarpine 2% eye drop 2 times a day, aceclofenac 100 mg 2 times a day with rabeprazole 20 mg 2 times a day as a gastro-protector and lorazepam 2 mg on feeling of intense emotional distress for 15 days. Methotreaxate was prescribed on alternate days to prevent the risk of re-infection. In the third OPD visit, the patient condition improved, pain sensation was reduced, psycho-emotional agitation was reduced and inflammation and hyperemia of vagina and urinary bladder, eye irritation and itchiness were reduced too. Unfortunately, after third OPD visit, the patient turned out to be non-compliant and did not follow up with the treatment and clinical check-ups.

Diagnosis and assessment

Considering the through clinical check-up and clinical analysis done, the patient was diagnosed with autoimmune disease of unknown etiology. The patient as per clinical and immunological blood tests conducted, the patient was only positive for anti-PM/Scl antibody which is positive generally in a wide spectrum of auto-immune diseases and the patient had high IgG and avidity against *Toxoplasma gondii*.[6]

DISCUSSION

This is a unique case of autoimmune disease of unknown etiology. The patient showed classical symptoms of Sjogren's syndrome with dry eyes, dry mouth and dry vagina; the dryness was to such an extent that there was recurrent opportunistic infection because of lack of protection provided by mucous, saliva and tear.[7] But all gold standard immunological markers for diagnosis of Sjogren's syndrome i.e. anti-Ro antibody and anti-La antibody were absent on repeated analysis of the two, ruling out the chance of false-negative.[8] On the other hand, the patient tested positive for anti-PM/Scl antibody which is found to be positive primarily in systemic sclerosis and in a wide spectrum of autoimmune diseases like polymyositis, and dermatomyositis.[9] But the patient showed no symptoms of systemic sclerosis and biomarker for dermatomyositis and polymyositis, anti-Jo antibody were negative with clear lungs and no clinical signs of these diseases.[10] Patient discussed is primiparous and the pregnancy was without any complication, hence chance of

anti-phospholipid syndrome is directly ruled out. It is to be noted here that the discussed had high IgG and avidity against *Toxoplasma gondii. T. gondii* has been reportedly associated with stimulation and onset of multiple rheumatic diseases like rheumatoid arthritis, systemic lupus erythematosus.[11,12] While considering this clinical case, the study is incomplete without considering the fact that *T. gondii* infection in humans stimulates an impressively intense expression and increment of cell-automated immune response generated primarily by autophagy related genes. In the mechanism of innate immune response, by the action of xenophagy, light chain 3B (LC3B)-coated autophagosomes play a vital role, fusing with lysosome in order to digest the pathogen.[13] In some *in-vivo* studies the role of LC3 group of protein subtypes in aberrant and prolonged T-cell activation. Thus, LC3 may be considered as a marker of such T-cell activation in organism.[14] Thus in the current scenario, role of *T. gondii* past infection might be considered as a provocative factor, though it should be stressed that the case fails to establish a direct relation or association. Considering the clinical scenario, the current case is being thus reported as idiopathic chronic systemic inflammatory dryness. The mainstay of the management to this patient was symptomatic. Although it should be stressed here that due to lack of compliance of the patient on mild reduction of symptoms, efficacy of methotrexate is yet to be confirmed.

CONCLUSION

The clinical scenario discussed in the article is important for the medical community from the point of view of retrospection in immunology and the study and research of autoimmune diseases. It put forwards a new type of autoimmune disease of unknown etiology which has only positive anti-PM/Scl antibody biomarker with symptoms resembling to Sjogren's syndrome but immunologically overlapping with systemic sclerosis without any known clinical signs of the same. The suspected association of the case with high IgG and avidity against *T. gondii* cannot be ignored as well. Hence, the article put forwards a new syndrome, the idiopathic chronic systemic inflammatory dryness for discourse and discussion in the medical community.

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