Case Study

Primary Sjögren's syndrome presenting as autoimmune bicytopenia- A rare event

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Primary Sjogren's (pSS) is a chronic multisystem autoimmune disease predominantly affecting the exocrine glands. Extra glandular involvement might involve the musculoskeletal, renal, pulmonary, haematological and the central nervous system. Hematological abnormalities are common in Sjögren's syndrome, including anemia, leukopenia, thrombocytopenia, and lymphoproliferative disorders. Cytopenias in pSS are usually mild. Clinically significant immune-mediated cytopenia may be a rare initial manifestation of an pSS especially in children. The present case reports a fourteen-year-old girl with a rare atypical manifestation of bicytopenia as an initial presenting feature of pSS. Unexplained cytopenias in any patient should alert a physician to investigate for pSS.

Keywords: Bicytopenia, Sjögren's syndrome, Schirmer's test

INTRODUCTION

Primary Sjogren's syndrome (pSS) is a chronic multisystemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands (specifically the salivary and lacrimal glands) leading to sicca symptoms. Extra glandular manifestations are frequently underdiagnosed and include vasculitis, neuropathy, glomerulonephritis, arthritis, hematological abnormalities and interstitial lung disease[1]. Clinically important cytopenias may be the presenting feature of an pSS and is rarely reported in children (Table 1). The pathophysiology and prevalence of cytopenia in SS is still an area of ongoing research. Sometimes a patient can present with severe anemia, leukopenia or thrombocytopenia prior to the development of sicca symptoms. This case reports an unusual presentation of pSS and hence should be included in the differential diagnosis in patients with unexplained cytopenias.

CASE REPORT

A 14-year-old female child presented with complaints of weakness, pallor and mucosal bleeding since last two months of duration. There was no history of fever, oral ulcers, weight loss, rash, icterus, joint swelling, or history of drug intake. General examination revealed severe pallor, petechial rashes on both arms, dry eyes with no evidence of lymphadenopathy, organomegaly, parotid gland enlargement and dental caries. Laboratory investigations revealed anemia and thrombocytopenia (hemoglobin - 6.8 g/dL, white blood cell count -7100/mm^3 and platelet count- 24,300/mm^3) with elevated acute phase reactant (ESR-43 mm/hr). Peripheral blood smear was suggestive of normocytic normochromic red blood cells. Direct Coombs test was negative. Infectious profile (HIV, hepatitis B and C, Ebstein Barr virus, Cytomegalovirus) was negative. Renal function, liver function, urine routine, CT chest and abdomen, and Vitamin B12 levels were within normal limits. LDH levels were elevated [860 U/L (313-618 U/L)]. Bone marrow examination was suggestive of normal marrow morphology with mild erythroid hyperplasia with normal megakaryopoesis. Autoimmune workup revealed positive Antinuclear antibodies (1/640 -speckled fluorescence pattern), negative anti-dsDNA, normal

complement (C3, C4) levels, strongly positive anti-Ro/SSA (96.3U) and anti-La/SSB (82.3U), positive rheumatoid factor and negative Antiphospholipid (APLA) antibodies. Schirmer's test was significantly positive (2 mm in right eye and 3 mm in left eye). Parents did not consent for salivary gland biopsy. Our patient fulfilled the 2017 ACR EULAR (American College of Rheumatology-European League Against Rheumatism) Classification diagnostic criteria for pSS. A final diagnosis of pSS with autoimmune bicytopenia was considered and he was initiated on oral prednisolone (1 mg/kg/day) and azathioprine (2 mg/kg/day) with gradual improvement in bicytopenia and ESR levels. At 2 months of follow-up period, corticosteroid was tapered successfully with remission in his bicytopenia and normalization of ESR (hemoglobin -11.2 g/dL, WBC -8900/mm^3 and platelets count -1.6 lakh/mm^3, ESR -5 mm/hr).

Table 1. Characteristics of reported immune cytopenias in Sjogren's syndrome reported in all patients

Author	Age /Gender	Hematological manifestations	ANA	Treatment
Schattner et al. (2000)	a) 32 yrs/Female	Autoimmune hemolytic anemia	Weakly Positive	Corticosteroid/azathioprine
	b) 77 yrs/Female	Neutropenia	Weakly Positive	Corticosteroid
	c) 58 yrs/Female	Thrombocytopenia	Positive	Corticosteroid/cyclophosphamide
Klepfish et al. (2001)	40 yrs/ female	Neutropenia, thrombocytopenia	Positive	Asymptomatic, didn't receive immunosuppressant
Kamath et al. (2011)	32 yrs/Female	Anemia and thrombocytopenia	Positive	Corticosteroid
Khattri and Barland (2012)	a) 59 yrs/Female	Autoimmune hemolytic anemia, Thrombocytopenia	Not reported	Corticosteroid/IVIG/Rituximab
	b) 26 yrs/Female	Thrombocytopenia	Positive	Corticosteroid/IVIG
Komaru et al. (2013)	36 yrs/Female	Autoimmune hemolytic anemia	Positive	Corticosteroid
Yu W et al. (2017)	59 yr, female	Pancytopenia	Positive	Corticosteroid/IVIG
Martínez et al. (2018)	50 yrs/Female	Anemia and thrombocytopenia	Positive	Corticosteroid/Azathioprine

DISCUSSION

Sicca symptoms are characteristic for diagnosis of pSS. However, extraglandular involvement is common and protean which may precede or exist with the sicca manifestations (as in our case). Haematological manifestations of pSS are not uncommon, but they are mostly recognized as mild laboratory abnormalities of no clinical significance in patients whose pSS is already diagnosed [2,3] . In an Australian cohort of 27 pSS patients, hematological manifestations was detected in 40% of patients [2]. In contrast, Sandhya P et al reported 25 patients (7.5%) having hematological manifestations in a cohort of 332 pSS patients in South India [3] . Break down of hematological manifestations in the study were as follows: thrombocytopenia (n=14), leucopenia (n=2), monoclonal gammopathy of undetermined significance (n=4), pseudolymphoma (n=2), Kikuchi's disease (n=1) and unexplained hepatosplenomegaly(n= 2). Unlike our case, pSS is usually characterized by a mild normocytic normochromic anaemia, mild thrombocytopenia and leucopenia which are not

clinically significant enough to require treatment [2]. Immune-mediated anemia, red cell aplasia, and thrombocytopenia have been reported in pSS [4]. Similar to our case, bicytopenia or pancytopenias can be the sole presenting feature in pSS [4, 5]. Presence of autoantibodies against various cell lineage could be one of the triggering factor for cytopenias [5]. Based on literature, Antineutrophil and anti-RBC antibodies were observed in 45% and 22% of patients with pSS respectively [6,7] . Patients with pSS with positive anti-Ro antibodies (similar to our patient) had a higher frequency of hematological involvement such as anemia and thrombocytopenia [8] . The treatment of pSS involves management of the sicca symptoms and immunosuppression for extraglandular manifestations (corticosteroids, azathioprine, cyclophosphamide, methotrexate, cyclosporin, danazol, rituximab, plasmapheresis or immunoglobulin in refractory cases) [15].

CONCLUSION

We highlight this case to increase awareness amongst physicians regarding children presenting with unexplained cytopenias should be specifically screened for Sjogren's syndrome. Conversely, periodic hematological review of patients with Sjogren's syndrome is critical to pick up clinically significant cytopenias.

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