Primary Sjogren’s Syndrome and Autoimmune Cytopenias
A Relation Often Overlooked

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Abstract
Primary Sjogren’s syndrome is an autoimmune disease wherein there is lymphocytic infiltration of salivary and lacrimal glands. This inflammation is thought to be caused by B-lymphocytes. The most common clinical feature of Sjogren’s is dryness of the mouth and eyes, but rare complications can occur such as autoimmune cytopenias. Here we report two cases of immune mediated cytopenias that were diagnosed to be due to Sjogren’s syndrome. In both cases, immune suppressive treatment was required.

Case 1
A 59-year-old female was admitted for symptomatic anemia after presenting to the emergency room with progressively worsening shortness of breath that had developed in the preceding 4 weeks. Her history was significant for hypothyroidism, depression, and hypertension. On admission, her pulse rate was 116 beats per minute, blood pressure was 108/60 mmHg and temperature was 98.5° F. Her conjunctiva was pale on exam, but there was no evidence of hepatosplenomegaly or lymphadenopathy. Blood work revealed a hemoglobin level of 5.5 g/dL; platelet count was 44/µL, and white cell count was within normal limits. Peripheral smear revealed basophilic stippling, nucleated red blood cells, and absence of schistocytes. Blood work revealed low haptoglobin (< 8 mg/dL), LDH was 778 U/L, retic count was 29.3%, total bilirubin was 2.4 mg/dL, direct Coombs test was positive (warm, polyspecific IgG), and so was the indirect Coombs test. The patient was a Jehovah’s Witness and refused transfusion; she was started on solumedrol for a diagnosis of autoimmune hemolytic anemia and immune-mediated thrombocytopenia.

Despite 48 hours of steroids, her hemoglobin and platelet count did not improve, and she was given IVIG, 30 gms daily for a total of 4 days. An autoimmune workup revealed strongly positive Ro or SSA antibody (632 AU/mL, < 99 AU/mL is normal for our lab) and La or SSB antibody (549 AU/mL, < 99 AU/mL is normal for our lab). Rheumatology consult was called. The patient admitted to having a long-standing history of dry mouth and dry eyes. Further serological workup revealed a positive rheumatoid factor 80 IU/mL (< 20 IU/mL is normal), anti-dsDNA and anti-Smith antibodies were negative.

Finally on day 6, despite steroids and IVIG, her hemoglobin and platelet counts did not improve; therefore, a decision to give rituximab was made. She was started on rituximab at a dose of 375 mg/m², given weekly for 4 consecutive weeks. Her hemoglobin level improved after the second infusion, and after the fourth infusion, her hemoglobin level was back to her baseline level (12.3 gm/dL). Similar to hemoglobin improvement, her platelet counts began to rise, and her level was 262/µL upon discharge. The patient continues to be followed up in the outpatient setting, and there has been no recurrence of her anemia or thrombocytopenia.

Case 2
A previously healthy 26-year-old female was admitted after routine blood work at her primary medicine doctor’s office revealed a platelet count of 6/µL. She was diagnosed with hyperthyroidism during her pregnancy several years ago and had been treated with propylthiouracil. She had no significant past medical history except for the history of hyperthyroidism. On enquiring, the patient admitted to having heavy menstrual bleeding the preceding 6 months and easy bruising on her lower extremities for the past
4 weeks. She denied any shortness of breath or fatigue, and systemic review was negative except as stated above. Physical exam failed to reveal hepatosplenomegaly or lymphadenopathy.

Her hemoglobin level was 11.5 g/dL, and platelet count was 11/µL on admission. A peripheral smear revealed basophilic stippling and some tear drop cells. She was started on IVIG for a diagnosis of idiopathic thrombocytopenia (ITP) and concurrently given prednisone at a dose of 1 mg/kg body weight. Her platelet count responded, and within 72 hours, her platelet count was within normal range. Blood work revealed strongly positive ANA (1:1280 titer), both RoSSA and La/SSB antibodies were strongly positive (458 AU/mL and 663 AU/mL respectively, normal being < 99 AU/mL for our lab), and rheumatoid factor was positive at 1:1280 IU/mL. Anti-thyroglobulin antibody (138 IU/mL, normal < 40 IU/mL) and anti-thyroid peroxidase antibodies (341 IU/mL, normal being < 35 IU/mL) were also positive, but her free T4 level was normal. After a 5-day course of IVIG, she was discharged home with her platelet count back to baseline, on 60 mg of prednisone daily with outpatient follow-up. In the outpatient setting, her platelet counts remained stable and a prednisone taper was initiated.

Discussion

Sjogren’s syndrome is among the most common autoimmune disorders, affecting as many as 3 to 4% of the adult population. Primary Sjogren’s syndrome (pSS) is a common chronic inflammatory autoimmune disorder associated with B lymphocyte hyper-reactivity. The hallmark of this disease is salivary and lacrimal gland infiltration with lymphocytes and subsequent functional impairment. Most patients have exocrine glands involvement, but the clinical presentation is non-specific and diverse ranging from the common “exocrine disease” manifestation of dry eyes and mouth to the less common non-Hodgkin’s lymphoma and autoimmune thyroiditis. This varied symptom manifestation results in an average diagnostic delay of 3 to 8 years following the appearance of the first symptoms.

Hematological manifestations are seen in pSS, and leukopenia is the most frequent hematologic abnormality noted in as many as 15% patients with Sjogren’s syndrome. Coombs positivity is another common hematologic abnormality in Sjogren’s syndrome, noted in 22 to 47% of patients observed in a study by Ramakrishna. There have been a few case reports of pSS associated with AIHA and immune mediated thrombocytopenia. The cytopenias may develop before the diagnosis of Sjogren’s syndrome, and sicca symptoms may not be the predominant manifestation. Anemia is another hematological manifestation noted, and the most common type being a mild normocytic anemia of chronic inflammation. Pure red-cell aplasia (PRCA) has also been noted in association with Sjogren’s syndrome. Case reports have also associated pSS and agranulocytosis. This could be from either reduced bone marrow neutrophil production, or increased peripheral destruction.

Hematological manifestations are usually asymptomatic; however, serious cytopenias can develop in some cases, necessitating treatment. Treatment generally includes immunosuppressive therapy, and corticosteroids seem to be the mainstay of treatment. However, azathioprine, cyclophosphamide, and methotrexate have been used in cases of autoimmune hemolytic anemia, thrombocytopenia, and agranulocytosis associated with Sjogren’s syndrome.

Rituximab has been used to treat idiopathic thrombocytopenic purpura (ITP) and Evans syndrome, described in several case reports and in small trials, with positive results. In a cohort of 25 patients with chronic ITP that were resistant to conventional therapies, weekly rituximab infusion at a dose of 375 mg/m² for 4 weeks showed an overall response rate of 52% with response being sustained for at least 6 months. A systematic review of the safety and efficacy of rituximab in patients with ITP showed that rituximab therapy was associated with mean complete response (platelet count > 150 × 10⁹ cells/L) and overall response (platelet count > 50 × 10⁹ cells/L) rates of 44 and 63%, respectively.

Based on data available from rituximab’s efficacy in autoimmune cytopenias, we can extrapolate that it would
be useful in the treatment of cytopenias associated with Sjogren’s syndrome.

Conclusion
We describe two cases of primary Sjogren’s syndrome with immune mediated anemia and thrombocytopenia. In one of our cases, rituximab was used successfully to treat hemolytic anemia while the other case responded to steroids and IVIG.

The hematological manifestations of pSS are of no clinical significance, but sometimes autoimmune cytopenias can occur, which can be potentially life threatening. Thus, pSS should be considered in the differential diagnosis of all patients who have otherwise inexplicable cytopenias. The occurrence of either high titer RF, hyperglobulinemia or a small monoclonal peak support a possible diagnosis of primary Sjogren’s syndrome, which should be actively sought by history, ocular examination, and antibody screening. The physician should always be aware of this association and keep pSS in the differential.

Disclosure Statement
The authors have no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References