CLINICAL VIGNETTE

A Case of Extraglandular Sjögren's Syndrome

Rahul Vasavada, MD

Case Presentation

A 31-year-old male with no significant past medical history presented to the emergency department with twelve days of unremitting fevers. He reported associated sore throat, non-productive cough, and headache that coincided with the onset of his fever and chills. One month prior, he developed intermittent arthralgias in his knees, elbows, and ankle, but denied any joint swelling, rash, or persistence of symptoms. He initially presented to urgent care where he was prescribed amoxicillin/clavulanate. His fevers persisted and he presented to the ED. He was febrile to 38.9°C but hemodynamically stable. Physical exam revealed basilar crackles but was otherwise within normal limits. Initial laboratory tests included normal white blood cell count of 6.7 x 10^3/µL, C-reactive protein elevated to 13.1 mg/dL, erythrocyte sedimentation rate elevated to 102 mm/hr, with the remainder of his blood counts and metabolic panel within the normal range. Chest x-ray revealed ground glass attenuation in both lung bases, right greater than left. He was initially started on broad spectrum intravenous antibiotics, with infectious and rheumatologic consultations. Additional labs were negative for bacterial, viral or fungal infection including negative blood, fungal and urine cultures, HIV, EBV, CMV, HSV, hepatitis panel, respiratory viral panel, PCP DFA, quantiferon gold, and coccidioides IgG/IgM. His rheumatologic testing yielded markedly positive antinuclear antibody (ANA >1:1280), and strongly positive antibodies to SSA and SSB (156 and 147 respectively with normal range <20 u for each), but was otherwise negative (including negative RF, CCP, dsDNA, ANCA, and C3/C4 among others). CT's of the chest, abdomen, and pelvis did not reveal significant lymphadenopathy or lesions suspicious for malignancy. Lactate dehydrogenase was within normal limits and serum protein electrophoresis did not show monoclonal spike. His hospital course was complicated by non-pleuritic chest pain as well as severe headache in the setting of continued fevers despite antibiotic treatment, prompting further evaluation. Repeat CT chest confirmed presence of ground glass opacities without evidence of embolus, lymphadenopathy or significant effusion; bronchoscopy yielded negative results for infection or malignancy. Echocardiogram was also within normal limits and did not show evidence of vegetation. With worsening headache in setting of fevers, he underwent lumbar puncture. Cerebrospinal fluid (CSF) studies demonstrated a lymphocytic pleocytosis, concerning for aseptic viral meningitis versus NSAID induced lymphocytic pleocytosis. He was started empirically on intravenous acyclovir, but PCR for viral meningitis etiologies were negative and antiviral and antibiotic treatments were discontinued. Finally brain imaging performed was negative for cerebral vasculitis. Over the course of his hospitalization, his fever trended downward with slow improvement of headache, sore throat, and chest pain with symptomatic treatment. Given high titer ANA, highly positive SSA/SSB antibodies, and markedly elevated inflammatory markers in the setting of extensive negative workup, the patient's presentation is likely consistent with extraglandular Sjogren's syndrome. He was discharged with outpatient rheumatology follow-up and was started on hydroxychloroquine with reported gradual improvement and stabilization of his symptoms.

Discussion

The patient presented with fever of unknown origin (FUO), ultimately likely due to extraglandular Sjögren's syndrome. FUO refers to a protracted febrile illness whose underlying cause is unknown despite extensive diagnostic workup. FUO is defined as having fever greater than 38.3ºC on multiple readings, fever duration of at least three weeks, and uncertain diagnosis after one week of study in the hospital.[1] In a majority of cases, FUO is due to one of the following: infection, malignancy, or connective tissue disease. Yet the differential remains broad and can include other etiologies such as drugs, venous thrombus, hyperthyroidism, hematoma, alcoholic hepatitis, factitious fever, and others.[2]

After thorough history and physical that includes pertinent travel, drug/medication history and occupational exposure, an initial recommended laboratory and imaging workup generally includes the following: HIV testing, tuberculosis screening, multiple sets of blood cultures, heterophile antibody testing, echocardiography (infectious); C-reactive protein, erythrocyte sedimentation rate, Rheumatoid factor, antinuclear antibodies, creatine phosphokinase (rheumatologic/connective tissue disease); lactate dehydrogenase, serum protein electrophoresis, and computed tomography (CT) scan of chest, abdomen, and pelvis (malignancy). [1-3] Additional history or examination findings may also prompt further testing such as lumbar puncture, as was in this case. A substantial percentage of patients remain undiagnosed despite extensive hospital workup for FUO, with studies citing proportions as high as 30 - 51%.[4,5] Yet even for those in whom a definitive diagnosis was not established, they were found to have a favorable prognosis, with

very low associated mortality and with a majority ultimately experiencing resolution of their fevers.[6,7]

Our patient's presentation is likely a manifestation of extraglandular Sjögren's syndrome (SS). SS is an autoimmune condition associated with impaired exocrine gland function typically resulting in sicca symptoms (dry eyes, dry mouth), but can also present with extraglandular disease. Extraglandular SS can affect a variety of organs ranging from the kidneys, hematologic system, lungs, heart, gastrointestinal tract, skin and joints, and both the peripheral and central nervous system. It is believed that the extraglandular manifestations of SS arise from autoimmune-induced inflammation of ductal epithelial structures, immune-complex deposition, and lymphoproliferation.[8]

The patient did not present with characteristic symptoms of SS, but his recurring fever, headache, arthralgia, and interstitial lung disease (pulmonary ground glass opacities) could be explained by extraglandular manifestations. Arthralgias characterized by symmetric, intermittent joint involvement is seen in many patients, while inflammatory myopathy has also been reported.[8] Many SS patients also present with associated lung disease due to desiccation of the respiratory mucosa from lymphocytic infiltration of the submucosal glands, affecting the upper airway and respiratory tract. Interstitial lung disease such as pneumonitis or cryptogenic organizing pneumonia is also a well-known association with SS.[9]

SS is associated with an array of both peripheral and central nervous system manifestations including multiple polyneuropathies, myelopathy due to spinal cord involvement, meningitis, cognitive disorders, and optic neuritis.[10] Interestingly the patient's severe headache with CSF studies consistent with a viral aseptic meningitis and lymphocytic pleocytosis has been described in literature as being a known complication of extraglandular SS.[10,11] While fever is not commonly seen in SS, it appears likely to have been associated with the patient's aseptic meningitis. Additionally fever can occur in patients with pulmonary manifestations of extraglandular SS.

Although not seen in our patient, SS can affect the kidneys resulting in interstitial nephritis, renal tubular dysfunction, and glomerulonephritis.[12] Patients can also experience an array of associated skin conditions including Raynaud phenomenon, erythema nodosum and even cutaneous vasculitis due to immune complex deposition. Because SS can overlap with other autoimmune diseases, its presence can also be associated with autoimmune thyroid disorders as well as Celiac disease. Finally, SS poses an increased risk of developing lymphoproliferative disorders, including up to six times increased relative risk of non-Hodgkin lymphoma.[13]

The overlap of SS with other autoimmune conditions, known as secondary SS, makes the diagnosis more challenging. Notably SS often overlaps with rheumatoid arthritis, systemic lupus erythematosus, and systemic scleroderma. Ultimately the presence or absence of disease-specific antibodies aids in making a final diagnosis. The patient's strongly positive SSA/SSB antibodies and ANA with otherwise negative infectious, rheumatologic and oncologic workup points to a likely diagnosis of extraglandular SS in this case.

Conclusion

Fever of unknown origin poses a diagnostic challenge that requires thorough evaluation. A majority of cases can be ascribed to either infection, malignancy or connective tissue disease. In this case an atypical diagnosis of extraglandular Sjögren's syndrome is likely. While providers are often familiar with the sicca symptoms of primary SS, it is important to recognize the vast and varied extraglandular manifestations of SS when considering alternative diagnoses.

REFERENCES

1. **Mourad O, Palda V, Detsky AS**. A comprehensive evidence-based approach to fever of unknown origin. *Arch Intern Med*. 2003 Mar 10;163(5):545-51. Review. PubMed PMID: 12622601.
2. **Horowitz HW**. Fever of unknown origin or fever of too many origins? *N Engl J Med*. 2013 Jan 17;368(3):197-9. doi: 10.1056/NEJMp1212725. PubMed PMID: 23323894.
3. **Cunha BA, Lortholary O, Cunha CB**. Fever of unknown origin: a clinical approach. *Am J Med*. 2015 Oct;128(10): 1138.e1-1138.e15. doi: 10.1016/j.amjmed.2015.06.001. Epub 2015 Jun 18. Review. PubMed PMID: 26093175.
4. **de Kleijn EM, Vandenbroucke JP, van der Meer JW**. Fever of unknown origin (FUO). I A. prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. *Medicine (Baltimore)*. 1997 Nov;76(6):392-400. PubMed PMID: 9413425.
5. **Bleeker-Rovers CP, Vos FJ, de Kleijn EM, Mudde AH, Dofferhoff TS, Richter C, Smilde TJ, Krabbe PF, Oyen WJ, van der Meer JW**. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. *Medicine (Baltimore)*. 2007 Jan;86(1):26-38. PubMed PMID: 17220753.
6. **Knockaert DC, Dujardin KS, Bobbaers HJ**. Long-term follow-up of patients with undiagnosed fever of unknown origin. *Arch Intern Med*. 1996 Mar 25;156(6):618-20. Pub Med PMID: 8629872.
7. **Vanderschueren S, Knockaert D, Adriaenssens T, Demey W, Durnez A, Blockmans D, Bobbaers H**. From prolonged febrile illness to fever of unknown origin: the challenge continues. *Arch Intern Med*. 2003 May 12; 163(9):1033-41. PubMed PMID: 12742800.
8. **Oxholm P, Asmussen K**. Primary Sjögren's syndrome: the challenge for classification of disease manifestations. *J Intern Med*. 1996 Jun;239(6):467-74. Review. PubMed PMID: 8656139.
9. **Hatron PY, Tillie-Leblond I, Launay D, Hachulla E, Fauchais AL, Wallaert B**. Pulmonary manifestations of Sjögren's syndrome. *Presse Med*. 2011 Jan;40(1 Pt 2):e49-64. doi: 10.1016/j.lpm.2010.11.002. Epub 2010 Dec 30. Review. PubMed PMID: 21194883.

10. **Perzyńska-Mazan J, Maślińska M, Gasik R**. Neurological manifestations of primary Sjögren's syndrome. *Reumatologia*. 2018;56(2):99-105. doi: 10.5114/reum.2018.75521. Epub 2018 May 9. Review. PubMed PMID: 29853725; PubMed Central PMCID: PMC5974632.
11. **Rossi R, Valeria Saddi M**. Subacute aseptic meningitis as neurological manifestation of primary Sjögren's syndrome. *Clin Neurol Neurosurg*. 2006 Oct;108(7):688-91. Epub 2005 Jul 28. PubMed PMID: 16054750.
12. **Maripuri S, Grande JP, Osborn TG, Fervenza FC, Matteson EL, Donadio JV, Hogan MC**. Renal involvement in primary Sjögren's syndrome: a clinicopathologic study. *Clin J Am Soc Nephrol*. 2009 Sep;4(9):1423-31. doi: 10.2215/CJN.00980209. Epub 2009 Aug 13. PubMed PMID: 19679669; PubMed Central PMCID: PMC2736689.
13. **Ekström Smedby K, Vajdic CM, Falster M, Engels EA, Martínez-Maza O, Turner J, Hjalgrim H, Vineis P, Seniori Costantini A, Bracci PM, Holly EA, Willett E, Spinelli JJ, La Vecchia C, Zheng T, Becker N, De Sanjosé S, Chiu BC, Dal Maso L, Cocco P, Maynadié M, Foretova L, Staines A, Brennan P, Davis S, Severson R, Cerhan JR, Breen EC, Birmann B, Grulich AE, Cozen W**. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood*. 2008 Apr 15;111(8):4029-38. doi: 10.1182/blood-2007-10-119974. Epub 2008 Feb 8. PubMed PMID: 18263783; PubMed Central PMCID: PMC2288717.

Submitted November 2, 2018