CLINICAL VIGNETTE

What is the Utility of HLA-B51 Positivity in Behcet's Disease?

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Case Summary

A 69-year-old female presented with progressive vision loss for about one year. She was evaluated and followed by an outside ophthalmologist who noted bilateral, multifocal retinal artery occlusions. She has a complex past medical history of hypertension, hyperlipidemia, chronic migraines, breast cancer status post bilateral lumpectomy, osteoarthritis and degenerative disc disease of the spine. Her medications included daily lisinopril 10 mg, atorvastatin 40 mg, aspirin 81 mg, gabapentin 100 mg and ibuprofen 200 mg as needed for joint pain. She did not smoke, drink alcohol or have a history of illicit drug use. She had no family history of autoimmune disease.

Labs obtained at initial ophthalmology visits included normal inflammatory markers and no systemic symptoms, so the etiology was thought to be embolic. She underwent extensive embolic evaluation. MRA brain and neck was not revealing for any stenosis. Transthoracic echocardiogram was normal. Holter monitor showed intermittent SVT but no other underlying arrhythmias. Months after her initial evaluation, the patient noted onset of systemic symptoms including arthralgias, headaches which were different then her typical migraines, ringing in the ears, and jaw pain.

With the patient's new symptoms, she was referred to UCLA ophthalmology for further evaluation. Patient was found to have vasculitis on fluorescein angiogram of the left eye. Labs included normal ESR 10 mm/hr (normal $\leq$25mm/hr), a CRP 0.8mg/dL (normal <0.8mg/dL) CBC. Patient was urgently referred to Rheumatology for concern of possible vasculitis given angiogram results even though inflammatory markers were normal. Specifically, there was concern for possible Giant Cell Arteritis.

By the time of rheumatology consultation, her arthralgias had improved. She was still having mild pain in the neck, in the bilateral shoulders with radiation to the scapula, and in the left hip. She denied any swelling or stiffness of the joints. Her headaches localized to the posterior aspect of the head with radiation to the middle and frontal regions bilaterally. She denied any scalp tenderness. Her jaw pain improved with a recent root canal. Review of systems was negative for fevers, but positive for increasing fatigue, intermittent mouth ulcers and recurrent acne like rash on the lower extremities. She reported a single episode of chest pain a couple months prior, with negative evaluation. On physical exam, she was well appearing and in no acute distress. Vital Signs were unremarkable and she had no scalp tenderness and easily palpable radial, pedal, and bilateral temporal artery pulses. Her cardiovascular and lung exams were normal. No rashes were seen and there was no synovitis.

Based on the patient's history, further laboratory testing was done. Kidney function was normal with Creatinine 0.82 mg/dL, GFR 73 mL/min/1.73m2 and urinalysis did not show any blood or protein. HLA-B27, Toxocara antibody, CMV IgG, RPR, Treponema Pallidum antibody, Quantiferon-Gold, ANCA, ACE, and ANA were all negative. VZV IgG antibody was positive 1,182 (normal is <135.0). Protein C and S activity were normal. A monoclonal pattern was detected on serum protein electrophoresis and immunofixation was significant for monoclonal gammopathy consistent with IgG Lambda. HSV-1 IgG was positive 54.7 (normal is< 0.9) and HLA-B51 was positive.

Patient was referred to Hematology/Oncology for further evaluation of her monoclonal gammopathy. Given positive HSV-1 antibody, there was consideration that her recurrent aphthous ulcers could be due to HSV-1 but this did not explain her other symptoms. Furthermore, HLA-B51 positivity raised concern for possible Behcet's disease. Using the 1990 International Study Group (ISG) diagnostic criteria for Behcet's disease, the patient satisfied the clinical criteria based on recurrent oral ulcers, eye involvement, and skin lesions. The 1990 ISG criteria emphasizes recurrent oral ulcers plus any two of the following clinical criteria: recurrent genital ulcers, eye lesions, skin lesions, or positive pathergy test (which is a skin hyperreactivity to minimal trauma) to establish a diagnosis of Behcet's disease.[1] After review of literature, it was also found that HSV-1 is possibly associated with the pathogenesis of Behcet's disease and studies have reported the presence of IgG anti-HSV-1 antibodies in patients with Behcet's.[2,3] Therefore, after excluding all other possible causes, the patient was given a diagnosis of presumptive Behcet's disease. She was started on prednisone and after evaluation by Hematology/Oncology for monoclonal gammopathy, the plan is to start a steroid sparing agent like azathioprine.

Discussion

Behcet's disease is an inflammatory disorder that occurs more frequently along the "Silk Road," an ancient trading route from eastern Asia to the Mediterranean region.[3] Symptoms include recurrent oral and genital ulcers, ocular involvement and other

systemic manifestations including cutaneous, gastrointestinal, neurologic, and musculoskeletal.[3,4] Behcet's can cause inflammation in vessels of all sizes and can affect both arteries and veins.[3] The exact cause of Behcet's disease is unknown but it is thought to have a genetic component due to its association with the allele of the major histocompatibility complex (MHC). Specifically, the HLA-B51 allele located on the MHC locus of chromosome 6p has been found to have the strongest association with Behcet's disease.[3-5]

Although there is a strong association between HLA-B51 and Behcet's disease, it is not included as part of the diagnostic criteria.[1] Multiple studies have examined the link between HLA-B51 positivity and the development of Behcet's disease but no direct genetic link has been established thus far.[5] Therefore, getting a positive HLA-B51 test can be helpful for diagnosis but is not pathognomonic. Diagnosis of Behcet's is still based on clinical criteria.[1]

So, what does HLA-B51 positivity mean?

Studies have demonstrated that the presence of HLA-B51 was associated with moderately higher prevalence of genital ulcers, ocular and skin manifestations. A study by Maldini et al. revealed that HLA-B51 is related to eye involvement with relative risk of 1.13 (95% confidence interval 1.06–1.21 with $p < .0005$), but other clinical manifestations did not show any association.[6] A meta-analysis by Horie et al. found that HLA-B51 is a strong risk factor of ocular lesions with an odds ratio of 1.76 and $p = .000057$.[7] Furthermore, Horie et al. concluded that HLA-B51 carriers have an increased risk to develop ocular symptoms of Behcet's disease and the association becomes stronger towards the east along the ancient Silk Road.[7]

Ocular symptoms of Behcet's disease occur in 30-70% of cases.[8] The most common type is chronic, relapsing bilateral uveitis including the anterior segment, posterior segment, or both anterior and posterior segments (panuveitis).[8] The most serious ocular lesion is retinal disease as was seen in our patient.[4] There have been observational studies which demonstrated that HLA-B51 positivity suggests more refractory symptoms and poor ocular outcomes.[4] About 25% of patients with ocular disease become blind without treatment, therefore it is essential to diagnose these patients and start immunosuppressive treatment as early as possible.[4]

Conclusion

This case demonstrates how the analysis of HLA-B51 can significantly aid in diagnosing a difficult to diagnose disease that can cause significant morbidity if left undiagnosed and untreated. Behcet's disease can present with heterogenous clinical features. Since there is not a specific laboratory test or histologic pathology, it can be difficult to diagnose. Although there is not a direct link between the development of Behcet's disease and HLA-B51 positivity, it may serve as an additional criteria or consideration for diagnosis in symptomatic patients.

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