Case Report

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Domino effect in a patient with Epstein-Barr Virus infection and autoimmunity: A case report

The link between autoimmune diseases and viral infections has been characterized, but specific mechanisms behind this association remain a current area of investigation. Whether viral infections trigger or unmask autoimmunity, or if the pathologies occur concurrently, is not yet completely understood. Specifically, Epstein - Barr virus (EBV) is implicated in several autoimmune disorders, including Systemic Lupus Erythematosus (SLE). It is hypothesized that common immunologic pathways are activated in the two pathologic states. This case report is an example of this confusing presentation, and the importance of recognizing the association between autoimmunity and viral infections. This patient presented with symptoms concerning for SLE and hepatic autoimmunity with serology suggesting a recent infection with EBV. Given this complicated presentation, it is difficult to determine which disease state presented first in patients with evidence of both SLE and EBV infection and whether this information is clinically relevant for ongoing treatment and monitoring. Here, we provide an in-depth discussion of current genomic and immunological research that supports the associations amongst these disease pathologies.

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Introduction

Autoimmune diseases have increased in frequency in industrialized countries over recent years [1]. The etiology of autoimmune diseases, a self-reactive adaptive immune response, is an interesting topic of discussion as trends have emerged that associate infectious triggers with autoimmune disease onset [2]. For example, Epstein-Barr Virus (EBV) has been implicated in several autoimmune disorders [3]. However, a distinct subset of related human diseases, denoted auto inflammatory responses has arisen that are like autoimmune diseases in that they share the same inflammatory mediators but lack evidence of self-reactive lymphocytes. These 'responses' have clear genetic components and are activated by the innate immune system. Thus, to optimize treatment regimens, it is important to discern between response and disease states with patient presentations. Here we present a patient with autoimmune features and presence of an infectious trigger, with a presentation complicated by an intricate psychiatric history. Then we discuss the contribution of infection to autoimmune disease states and important distinctions between autoimmune diseases and autoinflammatory responses.

Case report

A 20-year-old woman with a remote history of untreated depression presented with abnormal liver enzymes and diffuses abdominal pain. She had recently initiated treatment for a UTI diagnosed at an urgent care and was transferred to our hospital for further workup of incidental findings of transaminitis. Upon further questioning, she also reported worsening fatigue and depressive symptoms for two weeks, and weight loss of 20 pounds over the past 3 months despite an intact appetite. The patient partially attributed the weight loss due to limited access to food given her current financial situation. Furthermore, she reported discomfort and migratory intermittent swelling of her PIP joints and bilateral knees for over a year. She also

described a feeling of blood draining from her fingertips that did not worsen with colder weather but did occur with changes in emotion. She denied a recent history of cough, sore throat, nausea, vomiting, diarrhea or other systemic symptoms such as fever or chills.

As far as past social history, she had multiple tattoos from the same vendor, sexual intercourse limited to her male partner of two years, and no history of IV drug use. She denied a history of autoimmune diseases in her family. She did report a remote history of sexual abuse in her youth which was not addressed through psychiatric or therapy-based services. Her only medications were over-the-counter multivitamins and naproxen, taken occasionally for diffuse body aches. She was not followed by a primary care provider and had no other medical diagnoses. She denied alcohol use and recent acetaminophen use.

Upon presentation to urgent care for possible urinary tract infection, AST and ALT were elevated to 311 and 721, respectively and she was transferred to our hospital for further workup. On admission, her labs were significant for pancytopenia (WBC 2.6, Hgb 11.2, Plt 8.6), AST and ALT were 242 and 509, respectively and bicarbonate of 20. Acute hepatitis panel was negative for: HBV surface antigen, HCV antibody, HBV core antigen IgM and HAV IgM. Urine drug screen was positive for trimethoprim and THC. Urine analysis was significant for specific gravity of 1.026 and ketones of 5 mg/dL. Erythrocyte sedimentation rate was elevated at 61 mm/hour and C-reactive protein levels were within normal limits.

On hospital day 2, ANA returned positive with antibodies positive for anti-dsDNA (1:640 titers) and anti-chromatin (>8 AI). Both complement C3 and C4 were low at 42 mg/dL and <8 mg/dL, respectively. Anti-phospholipid panel was within normal limits, but lupus anticoagulant panel was positive: APTT 44.6 (reference 24-37 seconds), dilute Russel viper venom screen 56.4 sec (reference 25.5-37.6 sec), silica clot time SCR 64.8 (26.2-45.2 seconds), silica clot time RAT 1.77 (0.84-1.16 sec). A peripheral blood smear showed rare atypical lymphocytes and decreased estimated platelets. EBV antibody to viral capsid antigen IgG was within normal limits (<10 U/mL), but EBV antibody to viral capsid antigen IgM was elevated to 356 U/mL (reference range 0.0-21.9 U/mL) and EBV antibody to early (D) antigen IgG was elevated to 29.2 U/mL (reference range 0.0-10.9 U/mL) suggesting recent EBV infection. Serum EBV by quantitative PCR was negative. Smooth muscle antibody IgG titers, mitochondrial M2 IgG antibody were within normal limits, but F-actin smooth muscle IgG antibody was elevated at 35 units (reference range 0-19 units). Rheumatology was consulted and she was started on hydroxychloroquine and prednisone. When she was clinically stable with improving symptoms on hospital day 3, she was discharged with a new diagnosis of lupus with close follow-up appointments with rheumatology scheduled.

The patient returned two days later to the ED with worsening abdominal pain that was now mostly localized to the left side with no radiation. A CT-abdomen obtained in the emergency department showed two separate locations of splenic infarcts not present on a CT-abdomen performed at the urgent care five days prior. Given the recent diagnosis of SLE and concern for a hypercoagulable state, she was started on heparin dosed per body weight, and hematology was consulted. Per hematology after discussion with the patient, she was switched from heparin to apixaban on hospital day 2.

This hospital course was complicated by migratory, intermittent headaches, photophobia, eye pain and vision changes. Reported vision changes included blurriness, diplopia in the left eye and crescent and spot-shaped images in the right eye. However, ophthalmology exam was grossly negative. The patient reported these symptoms were consistent with migraines, of which she had a remote history. On physical exam, neurological findings were normal and unremarkable, with intact cranial nerve function and vision. MRI-brain was performed which revealed chronic microvascular ischemic changes but no acute abnormalities or concerning features of lupus cerebritis. Rheumatology consultation recommended a lumbar puncture for further workup: CSF protein, glucose and cell counts were within normal limits. Within the CSF, anti-neuronal cell antibodies were elevated to 1.2 units (reference range 0.0-1.0 units), oligoclonal band profile was positive for elevated IgG at 1750 mg/dL (reference range 768-1632) and elevated CSF IgG/albumin ratio of 0.29 (reference 0.09-0.25), but CSF IgG, albumin and oligoclonal bands were within normal limits or negative. Anti-NMDA antibodies and EBV were not detected in the CSF.

By hospital day 4 of the second hospital admission, AST and ALT were decreased to 21 and 71, respectively, and pancytopenia improved from the first admission (WBC 7.7, Hgb 11.3, Plt 90). While the patient had persistent diffuse body aches and joint pains, her overall condition stabilized, and she was discharged on day 5 with primary care provider, rheumatology and psychiatry follow-up

appointments scheduled.

Discussion

Genetic predisposition, environmental factors and immune regulation contribute to pathogenesis of autoimmunity [4-6]. Molecular mimicry, epitope spreading, bystander activation, B and T cell activation, infections and autoinflammatory activation of innate immunity are potential mechanisms proposed to trigger autoimmune states [4,5,7]. The relationship between viral infections and autoimmune responses caused by elevated inflammatory physiologic states are a current area of investigation [8,9]. Infections have been demonstrated to be the initial trigger in the development of autoimmunity [9,10]. This is complicated by the fact that initial presentation of SLE often mimics infections and infections that involve similar organ systems can mimic SLE [9]. In this case report, we present an interesting patient who initially presented with isolated transaminitis, pancytopenia and symptoms of fatigue, diffuse body aches and recent worsening psychiatric history. Her laboratory findings were concerning for a recent EBV infection, SLE and autoimmune hepatitis. Antiphospholipid panel was negative, but the lupus anticoagulant panel was positive. It was not possible at the time of presentation to discern if the EBV infection occurred before the positive autoimmune labs, or vice versa. It is possible that EBV infection triggered an acute presentation or unmasked a chronic autoimmune illness.

EBV infections have known associations with autoimmune diseases and can even trigger disease onset [9-11]. This is partially due to transcription factors on multiple loci of genetic disorders. Notably, nearly half of the SLE risk loci are occupied by the EBV EBNA2 protein [12], implicating an association between EBV infections and SLE pathogenesis. One proposed mechanism is molecular mimicry. EBV DNA transcripts have been found to be cross reactive with common lupus autoantibodies. The proposed progression starts with individuals who are genetically pre-disposed to lupus, who are then infected with EBV, which causes the development of Anti-Ro or Anti-La autoantibodies. Epitopes then spread via B cells (immortalized by EBV) and generate pathologic lupus autoantibodies. Further evidence of the association between EBV and SLE is that in SLE, higher titers of antibodies against EBV antigen have been found when compared to healthy controls, with the elevation in titers predating first SLE symptoms [13]. IgA antibody titers against the EBV viral capsid antigen are associated with SLE flares [13]. Other studies confirmed these data, showing that SLE patients have higher levels of EBV in their B-cells [14]. Infectious mononucleosis in SLE results in T-cells that are not able to control production of immunoglobulins from EBV-infected B cells along with impaired EBV specific CD8+ T-cell response. This increase is independent of immunosuppressive therapy initiation and is associated with more frequent disease flares [14]. Together, these studies suggest EBV infection can occur before SLE onset, and EBV infection incites SLE flares. In a simple cohort study of 196 lupus patients tested for previous EBV infection via ELISA, all but one had evidence of previous EBV infection. In the matched controls, 22 of 392 did not have evidence of previous EBV infection. Gene-environment interactions are also evidenced with other autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, juvenile idiopathic arthritis and celiac disease [15]. This supports a hypothesis that EBV infections can trigger flares/presentations of these disorders in select patients who have genetic predisposition.

In addition to the association of infectious etiologies with SLE, evidence also supports a relationship between EBV infections and autoimmune liver diseases [3]. Autoimmune Liver Diseases (AiLDs), including Autoimmune Hepatitis (AIH), Primary Biliary Cirrhosis (PBC), and Primary Sclerosing Cholangitis (PSC), have a potential causative link with EBV [15], although there is limited data showing direct association with EBV and AiLD. Antinuclear Antibody (ANA) and Smooth Muscle Antibody (SMA) characterize type 1, while antibodies to liver kidney microsomal antigen type 1 (anti-LKM1) and anti-liver cytosol type 1 antibodies (anti-LC1) are characteristics of type 2. While case reports suggest EBV infections induce AIH type I in pediatric and adult populations, it remains unclear whether this is a true connection or solely partially due to the rarity of these cases [3,16]. Distinguishing SLE with non-specific liver enzyme elevations from SLE with true AIH is challenging due to clinical and diagnostic overlap. Concurrent SLE and AIH is considered a rare finding. A retrospective cohort study in Brazil found that only 0.8% of patients with SLE also met diagnostic criteria for AIH [17]. Of 847 patients with childhood-onset SLE, 43% had positive serology for anti-smooth muscle antibodies, indicating that not all patients with anti-smooth muscle antibodies met the criteria for concomitant AIH. Another case report demonstrated false-positive serologies for acute hepatitis A and autoimmune hepatitis in a patient with acute EBV infection, with negative ANA and SLA hepatitis serologies 4 months after initial presentation [18].

Rarely, patients may have SLE and concomitant AIH. A liver biopsy is necessary to distinguish AIH from SLE with non-specific liver findings. Biopsy findings in AIH include interface hepatitis, rosetting of hepatocytes, and fibrosis, while liver biopsy in patients with SLE usually demonstrates changes consistent with drug-toxicity or other non-specific findings [19]. Making this distinction successfully has important pharmaceutical implications as it may influence decisions regarding appropriate immunosuppressant therapies.

It has been proposed that liver injury in patients with autoimmune hepatitis is the result of an immunological attack directed against liver cells with EBV as a possible trigger [20]. This suggests that EBV could trigger genetic predisposition to autoimmune states, or provoke an autoimmune reaction in liver cells, similar to the potential pathogenesis of SLE triggered by EBV [15,21]. One proposed mechanism is that EBV triggers auto-reactive CD4+ T lymphocytes recognizing liver-specific auto antigens [22]. Apart from case reports, no comprehensive studies link EBV infection with the development of AIH. Additionally, the potential mechanisms that may be involved in pathogenic process of AIH following EBV infection, such as molecular mimicry, have not been explored extensively. At best, it can be stated that EBV induced AIH in individual cases, but overall, there is no evidence linking EBV with AIH.

In this patient with concomitant elevation of EBV IgG antibodies (including against the early antigen), lupus anticoagulant antibodies, and a vague clinical presentation of fatigue, diffuse body aches and joint pains, it is difficult to discern which pathology occurred first. Did the EBV infection cause a lupus flare in this patient who was already predisposed to SLE, or did EBV trigger a new-onset SLE diagnosis? Furthermore, her presentation is complicated by a history of abuse that likely contributed to the depressive symptoms. Although depression can be a reported symptom of SLE, this patient's history of abuse makes it difficult to ascertain if the depression was an early sign of SLE or associated with her predisposing history.

Infectious triggers have been explicitly described in relation to autoimmune diseases and auto inflammatory response states that mimic true autoimmune diseases in patients with genetic predisposition. This case report further supports these findings with help from the literature. Furthermore, our report demonstrates a need for further studies to elucidate which disease state presented first in patients with evidence of both SLE and EBV infection and whether this information is clinically relevant for ongoing treatment and monitoring.

Conclusion

Given this complicated presentation, it is difficult to determine which disease state presented first in patients with evidence of both SLE and EBV infection and whether this information is clinically relevant for ongoing treatment and monitoring. Here, we provide an in-depth discussion of current genomic and immunological research that supports the associations amongst these disease pathologies.

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