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Flu B or not Flu B: An atypical case of minimal change disease triggered by Influenza B presenting with multi-organ dysfunction

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Abstract

Minimal change disease (MCD) accounts for 10-15% of idiopathic nephrotic syndrome in adults. Patients typically present with nephrotic range proteinuria, hypertension, microscopic hematuria and can even progress to acute renal failure. MCD can be primary (idiopathic) or secondary from etiologies such as cancer, medications, autoimmune conditions and infections. The link between infectious etiologies for MCD is important to recognize, since MCD tends to show a good response to treatment of the underlying cause. Influenza A has been reported as a secondary cause of MCD and rarely, influenza A, not B, can also present with liver failure. We present an atypical case of a 60-year-old female with no past medical history who presented with liver failure along with acute kidney injury and nephrotic range proteinuria. She was diagnosed with liver failure and secondary MCD from influenza B, the first reported case, and made a full recovery with treatment of Influenza B.

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Introduction:

Minimal change disease (MCD) is the most common cause of nephrotic syndrome in children but accounts for nephrotic syndrome in only 10-15% in adults.[1,2] MCD is characterized by absent or minimal changes on light microscopy, negative or low-level staining on immunofluorescence, and foot process effacement on electron microscopy.[3] Patients typically present with nephrotic range proteinuria, hypertension, edema, thrombosis and occasionally severe infections due to immunoglobulin depletion and altered T cell function.[1-3] In a review of 95 adult patients with MCD, Waldman et al found that 29% had microscopic hematuria, 18% had acute renal failure on presentation, and 43% had hypertension.[1] MCD is characterized either as primary (idiopathic) or secondary, related to neoplasms, drug reactions, infections, autoimmune or other miscellaneous etiologies.[4] Infectious etiologies have been described only rarely, and a causal relationship between MCD and infections are controversial, since MCD represents a state of enhanced susceptibility to infections.[4] Resolution of MCD with treatment of the underlying infection suggests a causal relationship between the infection and MCD.[4] There have been case reports of MCD occurring following infections with Syphilis[5], Ehrlichiosis[6], HIV[7], Tuberculosis[8], Mycoplasma[9], Echinococcosis[10], Influenza A (H1N1)[11], Borreliosis[12], and even following vaccinations for TDAP[13] and Influenza A.[14] MCD has never been reported with a concurrent infection with Influenza B.

We describe a case of Influenza B presenting in a patient with nephrotic syndrome with the findings of MCD on electron microscopy.

Case Report:

A 60-year-old Caucasian female with no significant past medical history presented to the hospital with complaints of vomiting, sore throat, cough, fatigue, runny nose, and myalgia. She was a current smoker with a 30-pack-year smoking history. On presentation to the emergency room vitals were as follow: temperature of 100 °C, blood pressure of 126/63 mmHg and oxygenation was 97% on 4 liters nasal cannula. Physical exam was remarkable for dry oral mucosa, and mild wheezing bilaterally without crackles. No abdominal tenderness or hepatomegaly was present on examination. Complete blood count was unremarkable. Peripheral smear was negative for schistocytes. Basic metabolic panel was remarkable for an elevated creatinine (3.9 mg/dL) and blood urea nitrogen of (25 mg/dL). Liver function test was significant for elevated aspartate aminotransferase 9536 U/L, alanine aminotransferase 6452 U/L and an alkaline phosphatase of 128 U/L. Albumin was 4.1 mg/dL on admission, then decreased to 3.1 mg/dL the next day. Urinalysis was positive for proteinuria (300 mg/dL), trace leukocyte esterase, leukocyte count 11-20/hpf and red blood cell count greater than 100/hpf. Triglyceride level was 156 mg/dL. Hepatitis B and hepatitis C serologies were negative. Chest x-ray on admission was unremarkable. Patient was admitted for evaluation of renal insuffiency and elevated liver function studies. Three days later patient went into respiratory failure requiring intubation. Chest x-ray at that time revealed bilateral fluffy infiltrates, left side worse than right. Echocardiogram showed an ejection fraction of 55% and right ventricular peak pressure was 40-45 mmHg. During the hospital course there were no episodes of hypotension, only worsening hypertension. The patient was started on intravenous adequately dosed Vancomycin and piperacillin-tazobactam at 3.375g twice daily. Bronchoscopy was performed and washings came back positive for Influenza B, with the remainder of the viral panel negative for Influenza A, RSV, Parainfluenza, Rhinovirus, Metapneumovirus and Adenovirus. Ehrlichiosis serology was negative. Patient was started on oral Oseltamivir 30mg daily for 5 days. During the hospital course the patient's creatinine

continued to rise to a peak of 7.9 mg/dL and she became oliguric. Spot urine protein to creatinine ratio was 8.8g. Serum complement C3 and C4 were low at 45 mg/dL and 6 mg/dL respectably. ANCA, Anti GBM antibody, anti-nuclear antibody serologies were all negative. At this point the patient was started on oral prednisone 60mg daily for a presumed autoimmune disorder and renal biopsy was performed. Renal biopsy revealed two glomeruli out of 50 that were sclerotic on light microscopy, with the rest being histologically unremarkable. Immunofluorescent microscopy revealed no significant staining for immunoglobulins or complement. Electron microscopy revealed extensive effacement of podocyte foot processes affecting around 90% of the basement membrane surface area, consistent with a diagnosis of MCD. Steroids were discontinued once the diagnosis of MCD secondary to influenza B was made. Hemodialysis was initiated and continued three times a week for 3 months. Liver function began to improve. The patient made a full recovery with a creatinine of 1.3 mg/dL and return of liver enzymes to within normal limits.

Discussion:

The pathophysiology of MCD disorder is poorly understood, but is thought to involve immune dysregulation, reactive oxygen species generation, and alterations of podocytic proteins, CD80 (also called B7.1) and angiopoietin-like protein 4 (Angptl4).[3,15] A recent theory by Shimada et al suggests a "two-hit" hypothesis, with the first hit being induction of CD80 on podocytes by activation from cytokines or toll-like receptor activation by viruses or allergens resulting in a transient proteinuria following infections.[15] The second hit consists of altered immune functioning, with decreased inhibitory functioning, possible decreased regulatory T cell functioning, or decreased levels of CTLA-4, IL-10 or TGF-β, resulting in continued expression of CD80 and persistent proteinuria.[15] Other contributors possibly include increased IL-13 production from T cells, podocyte derived CD80 or angiopoietin-like-4 protein up regulation, or circulatory factors such as vascular permeability factor, and hemopexin.[16] B cells also likely play a role, with Rituximab found as being non-inferior to steroid treatment for steroid-dependent nephrotic syndrome in children.[17]

Influenza A, as well as other viruses including cytomegalovirus (CMV), Epstein Barr virus (EBV), human immunodeficiency virus (HIV), parvovirus, dengue virus, and others can present with hepatic injury.[18,19,20] The mechanism is clearly distinct from viruses which target the liver, including Hepatitis A through E, since most influenza strains are only capable of infecting respiratory epithelium.[21] Leading theories involve the "collateral damage" theory caused by activated CD8 T cells being recruited to the liver through activated integrins, and subsequently inducing apoptosis in hepatocytes that are sensitive to the Fas-mediated pathway of apoptosis, and the oxidative stress theory caused by the production of excessive cytokines during an infection.[19,21,22] The majority of these cases of liver failure resolve with supportive care and treatment of the underlying systemic condition, although some may require intensive liver specific treatment.[20] Influenza A, in children and in adult patients with underlying cirrhosis, and the H1N1 Influenza A pandemic in 2009 have been found to cause hepatic failure.[18,19,23]

Liver injury has been established as a cause of low complement levels, likely due to decreased production of the complement components made in the liver, which can increase susceptibility to infections such as Influenza.[24,25] The timing of the resolution of the elevated transaminases was concurrent with resolution of Influenza B infection. The lack of other causes for the liver dysfunction suggested that Influenza B infection caused both abnormalities of liver injury and MCD. This case of multi organ failure brings to attention how the diagnosis of secondary MCD due to Influenza B

could have been missed due to an atypical presentation.

This case further demonstrates the importance of a renal biopsy in the face of new onset proteinuria with multi organ failure to avoid a delay in therapy.

Conclusion:

Influenza B with multi-organ failure and proteinuria should be added to the differential diagnosis of secondary MCD. Renal biopsy is vital to guide appropriate medical therapy.

Declaration of Conflicting Interest:

The authors declare that there is no conflict of interest.

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EVMS does not require ethical approval for reporting individual cases or case series.

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Contributorship:

MB, JC and AM wrote the first draft of the manuscript. JC did the revisions. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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