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CLINICAL VIGNETTE

Acute Epstein-Barr Virus Mononucleosis – A Potential Role for Antibiotic Therapy

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Introduction

Acute mononucleosis due to Epstein-Barr Virus (EBV) commonly affects adolescents and young adults. It is generally self-limited and typically treated with supportive care. Uncommonly, patients with severe disease require admission for management of complications such as impending airway obstruction or inability to tolerate oral intake.[1] Patients may receive treatment with antibacterial agents prior to the diagnosis of acute EBV infection. However, antibiotics do not, in general, have an established role in the treatment of acute EBV itself. Some antibiotics may increase risk of adverse reactions such as rash.[2] Two unresolved questions include the potential role of anaerobic co-pathogens in the disease process and the potential benefit of anaerobic antibacterial therapy. This patient had severe acute mononucleosis due to EBV treated with metronidazole.

Case

A 21-year-old woman with no significant relevant past medical history was admitted with severe acute mononucleosis with concern for progressive airway obstruction. Her illness began six days prior to presentation, with nausea, malaise, and fatigue, and progressed to include sinus congestion and severe sore throat. She was initially evaluated in urgent care and prescribed azithromycin. Rapid Group A Streptococcus screening was negative and bacterial throat culture grew normal upper respiratory flora. Monospot screening returned positive, confirming acute EBV infection and she was contacted and advised to stop azithromycin after one dose. However, her symptoms worsened, such that she could hardly swallow or open her mouth due to neck pain and swelling, she was sent to the hospital for management. At presentation she was febrile to 38.2°C, hemodynamically stable, and had marked pharyngeal adenopathy with white tonsillar exudates and narrowing of her airway. CBC showed elevated neutrophil predominant WBC count of 17 k/mm^3 with atypical lymphocytes seen on peripheral smear. Liver enzymes were remarkable for an AST of 107 units/L and ALT 113 units/L. EBV screening included a positive monospot test, positive EBV VCA IgM, and negative EBV VCA IgG and EBNA IgG, consistent with acute EBV infection. Contrast CT of the neck showed marked pharyngeal, palatine, and cervical adenopathy without evidence of abscess. She received supportive care with IV fluids and, per ENT guidance, IV dexamethasone to treat airway swelling from day one through day three. The fever quickly resolved, and WBC count improved, but by hospital day four she showed no other improvement in symptoms or overall condition. The admission culture from a swab of the palatine tonsils then showed 4+ growth of *Prevotella melaninogenica*. She was then started on metronidazole 500mg IV every eight hours out of concern that anaerobic infection was augmenting her inflammatory response. She reported improvement 24 hours after starting metronidazole. After two days of therapy, she was able to tolerate adequate oral hydration and nutrition and was discharged to complete 7 days of metronidazole therapy. At primary care follow up, she reported continued improvement with no complications.

Discussion

This case highlights the potential benefit of implementing anaerobic antimicrobial therapy in patients with severe mononucleosis. This patient's symptoms did not show initial clinical response to supportive measures and steroids. She showed definite improvement 24 and 48 hours after initiating anaerobic antibacterial therapy and was well enough to be discharged. The apparent response to metronidazole suggests a potential role in treating severe mononucleosis with potential to improve the rate of symptom resolution and decrease length of hospital stay.

The mainstay of treatment for acute EBV mononucleosis is supportive care. It is generally accepted that antiviral therapy does not have a beneficial role in the treatment of acute EBV infection. Although acyclovir exhibits activity against EBV by decreasing viral shedding, randomized controlled trials have not shown clinically significant benefit when compared against placebo.[3] While steroids have a role in treating impending airway obstruction, the addition of steroids with antiviral treatment has not shown clinically significant symptomatic improvement relative to placebo.[4] However, multiple studies have shown the potential clinical benefit of administering anaerobic antibacterial therapy, as in this case.

Hedström *et al* compared 29 patients admitted with acute EBV infection who received standard of care to those who received anaerobic coverage, either metronidazole or clindamycin. The group treated with anaerobic coverage exhibited faster recovery than those who received standard of care, though two of the three patients treated with clindamycin developed rash.[5] A randomized controlled trial by Lennon *et al* involving 42 patients hospitalized for management of acute EBV compared treatment with metronidazole to standard of care and found a

statistically significance decrease in length of stay in the metronidazole treated group and no reported intolerance.[6] However, a double-blind controlled study of 40 patients by Spelman *et al* found no statistically significant improvement in the group treated with metronidazole.[7] The differing outcomes observed in these studies suggest certain subpopulations may benefit from the addition of anaerobic therapy.

The reason anaerobic therapy may provide clinical benefit in what is primarily a viral illness, may be due to the potential role of anaerobic co-pathogens. Stenfors and Räisänen found that acute EBV infection decreases immunoglobulin coating of bacteria on the tonsillar surface.[8] Marklund *et al* showed that relative to the control arm, patients with acute EBV showed decreased IgA concentrations in oral secretions.[9] Local immune dysfunction in the pharynx could potentially result in an increase in bacterial colonization of the tonsils, creating an environment where even typical oral anaerobic flora could exert pathogenic effects.

Studies are mixed regarding demonstration of anaerobic co-infection during acute EBV. Brook and de Leyva studied 22 patients with acute mononucleosis and showed elevated serum antibody levels to *Prevotella intermedia* and *Fusobacterium nucleatum* in the setting of acute EBV infection, suggesting potential roles in the disease process.[10] However, Danstrup and Klug screened 257 patients admitted with acute mononucleosis and reported a low rate of co-infection with *F. necrophorum* and other organisms that the authors considered potential pathogens.[11] However, their study did not consider the co-pathogenic potential of other oral anaerobes alone or in combination, including *Prevotella*, which were considered non-pathogenic mixed tonsillar flora.

Given inconclusive current literature, larger studies are needed that evaluate a broader range of potential anaerobic co-pathogens in acute EBV infection to assess for the potential benefit of anaerobic therapy. Current literature suggests the possibility that acute EBV infection may create an environment in the pharynx that facilitates oral anaerobes' role as co-pathogens in the local inflammatory process. Treatment with metronidazole may have potential to improve the rate of recovery and decrease hospital length of stay and is worth considering as adjunctive therapy in severe acute EBV infection.

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