Hoagland Sign as an Aid for Antimicrobial Stewardship—A Case Report

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Abstract
Hoagland sign is an early and transient bilateral painless upper eyelid edema observed in patients with Epstein-Barr virus (EBV)-related infectious mononucleosis. This sign can predate the appearance of exudative pharyngitis and cervical lymphadenopathy. Usually, this sign disappears by first week of infection. Here, we describe the occurrence of late onset Hoagland sign in a 14-year old boy who presented to us on 10th day of fever. Hoagland sign appeared after 10 days from symptom onset in our patient. Despite persistence of fever, the presence of Hoagland sign which appeared prior to confirmation of EBV infection was a helpful indicator for stopping antibiotics. In view of tonsillar hypertrophy with potential airway compromise and biochemical parameters suggestive of possible secondary hemophagocytic lymphohistiocytosis, he was initiated on steroids with which defervescence and prompt resolution of symptoms occurred. EBV can present as acute undifferentiated febrile syndrome which might result in inappropriate use of antibiotics. This case highlights the importance of using clinical clues like Hoagland sign to optimize antimicrobial stewardship.

Keywords
Hoagland sign, ebstein barr virus, infectious mononucleosis

Introduction
Infectious mononucleosis is a clinical syndrome most frequently seen in children and adolescents. The most common etiologies include Epstein-Barr virus (EBV), followed by cytomegalovirus (CMV), human immunodeficiency virus (HIV), and, very rarely, by other agents, including Toxoplasma gondii, hepatitis A, B, and C virus, and human herpes virus type 6. In adolescence transmission dynamics of EBV is related to kissing, unprotected sexual intercourse, blood transfusion, hematopoietic stem cell transplantation, and solid organ transplantation. Periodic secretion of EBV into salivary secretions in household members and caregivers has also been proposed as a mechanism of transmission in preadolescent age group.3

Despite EBV infection being common in adolescent and young adults, majority of pediatric population often remains asymptomatic.3 Prodromal symptoms observed like fever, lethargy, and odynophagia are relatively nonspecific. Differential diagnosis include streptococcal pharyngitis, CMV infection, toxoplasmosis, and acute HIV.4 Diagnosis of infectious mononucleosis can be made by heterophile antibody test (Monospot test), serology, or EBV polymerase chain reaction (PCR). Monospot test is specific but not particularly sensitive with a false negative rate of as high as 25% in the first week, 5% to 10% in the second, and 5% in the third. Serologic tests which detect immunoglobulin M (IgM) against viral capsid antigen (VCA) and early antigen (EA) are more sensitive to detect early EBV infections than Monospot test. As both Monospot and serology are not very sensitive to detect EBV-related infectious mononucleosis (IMN) within first 2 weeks, in most of the cases empirical antibiotics are initiated. It is in this context that Hoagland sign which is fairly specific to EBV-related IMN will help in antimicrobial stewardship.

Case Report
A 14-year-old boy studying in 9th grade with no comorbidities presented with complaints of high-grade fever, sore throat, cough, myalgia, and fatiguability for 10 days. Fever was high grade, continuous, associated with chills, and rigor, without any diurnal variation and partially relieved on taking oral antipyretics. Other than sore throat, there were no other localizing symptoms. Cough was predominantly nonproductive. He had no history of skin rash, eschar, ecchymosis, joint pain,
limitation of movements, headache, photophobia, sinus pain, ear discharge, dysuria, loin pain, increased frequency of micturition, urethral discharge, diarrhea, constipation, blood, or pus in stools. He had no history of loss of weight, loss of appetite, or night sweats. He had no history of recent travel, consumption of unpasteurized milk, or pets at home. He was taken to nearby hospital on day 5 of fever from where he was started empirically on ceftriaxone and doxycycline. In view of persistent fever despite 5 days of antibiotics, he was referred to our tertiary care center.

On examination on 10th day of fever, he was febrile with axillary temperature recorded as 102°F. His blood pressure was 110/70 mm Hg, heart rate was 100 beats/min, respiratory rate 20/min, and oxygen saturation 99% in room air. Bilateral follicular tonsillitis was observed. Posterior cervical lymph nodes were palpable. His liver was palpable 3 cm below right costal margin and spleen tip was palpable 3 cm below left costal margin. There was no evidence of polyserositis or any signs of meningeal irritation. Respiratory, cardiovascular, and central nervous system were normal on examination. Bilateral painless upper eye lid edema without conjunctival congestion (Hoagland sign) was observed by day 14 of illness. Eyelid edema bilateral painless upper eyelid edema without conjunctival congestion (Hoagland sign) was observed by day 14 of fever and it disappeared within 2 days.

Initial laboratory investigations showed normal total white blood cells count with lymphocyte predominance, thrombocytopenia, elevated lactate dehydrogenase, SGOT, and SGPT. Prothrombin time and activated partial thromboplastin time were within normal range. Laboratory values during the hospital stay are given in Table 1. Peripheral smear showed marked lymphocytic leukocytosis with many atypical lymphocytes (>20%). In view of age of the patient, follicular tonsillitis, hepatosplenomegaly, posterior cervical lymph node enlargement, and peripheral smear finding, provisional diagnosis of infectious mononucleosis was made. Monospot test performed in first and second week of illness was negative. Since the patient was having persistent fever for 14 days despite antibiotics, he was also investigated to rule out other tropical fever syndromes, tuberculosis, brucellosis, infective endocarditis, and heterophile negative infectious mononucleosis. Electrocardiogram and chest X-ray showed no abnormalities. Serum lactate dehydrogenase was 400 U/L (140-280).

Serology for HIV, HCV, and HBV was negative. IgM and IgG antibodies against CMV, HSV, and toxoplasma were negative. Mantoux test was negative. Urine routine was insignificant with no proteinuria. Sputum TRUNAT for Mycobacterium tuberculosis, sputum cultures, serial blood cultures, urine cultures, and serial throat swab cultures were all negative. USG abdomen showed hepatosplenomegaly. Antistreptolysin O titer was within normal limits. Screening ECHO showed no evidence of infective endocarditis. IgM viral capsid antibody (VCA) and early antigen (EA) performed on day 20 turned out to be positive, thereby confirming EBV-related IMN. EBV qualitative PCR also turned out to be positive. In view of

![Figure 1. EBV ELISA by Immunofluorescence.](image-url)

**Table 1. Baseline Investigations During Hospital Stay.**

|                          | First Day | Third Day | Fifth Day | Seventh Day | Tenth Day |
|--------------------------|-----------|-----------|-----------|-------------|-----------|
| Hemoglobin (g/dL)        | 13.5      | 13.0      | 13.2      | 12.8        | 13.0      |
| Total leucocyte count (/mm³) | 5,400     | 6,000     | 6,200     | 5,440       | 5,020     |
| Differential count (/mm³) | P30L70    | P34L60    | P32L60    | P38L62      | P34L66    |
| Platelet count (/mm³)    | 1,30,000  | 1,10,000  | 1,00,000  | 1,10,000    | 1,00,000  |
| Serum creatinine (mg/dL) | 1         | 1         | 0.9       | 0.8         | 1.1       |
| Direct and conjugated bilirubin (mg/dL) | 0.8/0.2 | 0.6/0.2 | 0.4/0.2 | 0.8/0.2 | 0.6/0.2 |
| SGOT/SGPT (U/L)         | 150/250   | 136/242   | 164/270   | 160/250     | 147/264   |
| Sodium/Potassium (mEq/L) | 136/3.6   | 134/3.8   | 136/4     | 138/4       | 134/3.8   |
| Alkaline phosphatase (IU/L) | 40        | 36        | 40        | 28          | 32        |
| Total protein/Albumin (g/dL) | 6.6/3.6   | 6.4/3.4   | 6.6/3.8   | 6.6/3.4     | 6.8/3.4   |
persisting fever even after 2 weeks, a workup for hemophagocytic lymphohistiocytosis (HLH) was also performed. His serum ferritin level was >1,000 ng/mL (7-140), serum fibrinogen <140 mg/dL (250-350), and serum triglycerides was 260 mg/dL (<220 mg/dL). These values were suggestive of EBV-related probable secondary HLH.

Hemophagocytosis could not be confirmed as patient was not willing for bone marrow biopsy. Fine needle aspiration cytology and biopsy from posterior cervical lymph nodes showed only reactive changes. By day 20, patient developed tachypnoea, tachycardia, and grade 4 bilateral tonsillar enlargement. In view of persisting fever due to EBV-related probable secondary HLH and possible upper airway obstruction due to tonsillar enlargement, he was started on prednisolone 1 mg/kg with which he became afebrile and clinically better. Steroids were tapered off and stopped over next 3 weeks.

**Discussion**

In majority of cases, infectious mononucleosis is a self-limiting illness. However, in certain cases, it can lead to complications like hemolytic anemia, myocarditis, hepatitis, meningoencephalitis, demyelination, splenic rupture, upper airway obstruction, and so on. Acute phase of infectious mononucleosis can last for 18 days on average, as was also observed in our patient. Usually, IMN presents with fever, sore throat, significant fatigueability, tonsillar enlargement, and posterior cervical lymphadenopathy. Clinical findings like hepatomegaly, splenomegaly, nausea, vomiting, rash, palatal petechiae, periorbital, and eyelid edema are found in less than 20% of cases.

Colonel Robert J Hoagland first characterized upper eyelid edema as a symptom of viral mononucleosis in 1952 classically described as “Hoagland sign.” In a series of young military recruits with infectious mononucleosis, he noticed supraocular or upper eyelid edema. Eyelid edema was not accompanied by conjunctivitis, inflammation, or tenderness of eyelids. This symptom was observed in 19 of the 56 participants in this study. Hoagland sign is seen in around 10% of patients with IMN and is seen only for a few days at the time of presentation. This sign is observed very early in disease course before occurrence of exudative pharyngitis and cervical lymphadenopathy, and usually manifests before more than 20% atypical lymphocytes get observed in peripheral smear. In most cases, this sign disappears by first week. Though rare, this sign helps in distinguishing EBV-related infectious mononucleosis from other viral or streptococcal pharyngitis. Hoagland sign is supposed to be due to EBV replication in nasopharyngeal lymphoid tissues leading to lymphoproliferation and obliteration of lymphatic channels. But the exact pathophysiology is yet to be understood. In our case, this sign which appeared before confirmation of EBV serological positivity helped in stopping antibiotics.

Hemophagocytic syndrome, also known as HLH, can be triggered by EBV. EBV-associated secondary HLH is an infrequent complication and can manifest as persisting high grade fever as in our patient. The clinical and biochemical features in our patient as well as prompt defervescence on initiation of steroids, is suggestive of probable secondary HLH due to EBV. Hypoalbuminemia and D-dimer levels were identified as potentially valuable predictors for HLH in pediatric EBV-associated IMN. Steroids and intravenous immunoglobulins are the mainstay in treatment of EBV-associated HLH. As secondary HLH can manifest as persisting fever, there is a tendency to prescribe antimicrobials judiciously which might result in collateral damage and antimicrobial resistance. So diagnosing IMN and secondary HLH will help in antimicrobial stewardship.

Even though treatment of IMN is supportive, steroids are indicated in the setting of secondary HLH, autoimmune hemolytic anemia, impending upper airway obstruction due to tonsillar hypertrophy, and in case of thrombocytopenia.

**Conclusion**

Rare clinical signs like Hoagland sign help to diagnose EBV-related IMN at the earliest prior to a positive serology or Monospot test, and thereby serve as a very useful tool in the practice of antimicrobial stewardship. Hoagland sign is classically described as a very early manifestation in IMN. This case demonstrates the fact that Hoagland sign can also manifest in second week of illness. Persistence of high grade fever for 3 weeks in patients with EBV-related infectious mononucleosis should prompt physicians to consider EBV-associated secondary HLH.

**Author contribution**

Wrote the first draft: LJN. Contributed to the writing of the manuscript: LJN, AR, AG, KVS, KP. Jointly developed the structure and arguments for the paper: LJN, AR, AG, KVS, KP. Made critical revisions and approved final version: LJN, AR, AG, KVS, KP. All authors reviewed and approved the final manuscript.

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References

1. Dumoulin A, Eyer M. Common causes of infectious mononucleosis. Rev Med Suisse. 2018;14(622):1799-1802.
2. Dunmire SK, Verghese PS Balfour HH. Primary Epstein-Barr virus infection. J Clin Virol. 2018;102:84-92.
3. Stumpfig ND, Seroy J. Monospot test. In: StatPearls [Internet]. StatPearls Publishing; 2021.
4. Ebell MH. Epstein-Barr virus infectious mononucleosis. Am Fam Physician. 2004;70(7):1279-1287.
5. Cozad J. Infectious mononucleosis. Nurse Pract. 1996;21(3):14-16, 23, 27-28.
6. Luzuriaga K, Sullivan JL. Infectious mononucleosis. N Engl J Med. 2010;362(21):1993-2000.
7. Kakani S. Airway compromise in infectious mononucleosis: a case report. Cases J. 2009;2:6736.
8. Hoagland RJ. Infectious mononucleosis. Prim Care. 1975;2:295-307.
9. Louppides S, Kakoullis L, Parpas G, Panos G. Upper eyelid oedema in a patient with pharyngitis/exudative tonsillitis and malaise: Hoagland sign in infectious mononucleosis. BMJ Case Rep CP. 2019;12(12):e233719.
10. Burger J, Thurau S, Haritoglou C. Bilateral lid swelling during infectious mononucleosis (Hoagland-sign). Klin Monatsbl Augenheilkd. 2005;222(12):1014-1016.
11. Imashuku S. Clinical features and treatment strategies of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Crit Rev Oncol Hematol. 2002;44(3):259-272.
12. Huang J-S, Chen C-N, Cheng Y-J, Yang Hypoalbuminemia is an independent predictor for hemophagocytic lymphohistiocytosis in childhood Epstein-Barr virus-associated infectious mononucleosis. Eur J Haematol. 2012;89(5):417-422.
13. Shi J, Chu C, Yu M, et al., et al. Clinical warning of hemophagocytic syndrome caused by Epstein-Barr virus. Ital J Pediatr. 2021;47(1):3.