ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
www.scielo.cl

Andes pediatr. 2022;93(4):579-584
DOI: 10.32641/andespediatr.v93i4.3890

CLINICAL CASE

Conjunctival mass as the first manifestation of Epstein Barr virus infection

Masa conjuntival como primera manifestación de infección por virus del Epstein Barr

Laura Bettin Torres[a,b], María Alejandra Cerquera Jaramillo[a,b], Luis Alberto Ruiz Robles[a,b]

[a]Facultad de Medicina. Universidad Militar Nueva Granada. Bogotá D. C., Colombia.
[b]Servicio de Oftalmología. Hospital Militar Central. Bogotá D. C., Colombia.

Received: January 24, 2022; Approved: July 29, 2021

What do we know about the subject matter of this study?

The existence of Epstein-Barr virus, its epidemiology, transmission mechanisms, and most frequent clinical manifestations in adults and children are fully known.Treatment is known to be symptomatic, as well as its association with lymphoproliferative syndrome and other neoplasms.

What does this study contribute to what is already known?

It describes a rare case of the onset of the disease with ophthalmologic signs and symptoms, which highlights the importance of considering it as a differential diagnosis when faced with similar clinical pictures.

Abstract

The Epstein Barr virus is an infectious disease with a high worldwide prevalence, which can present multiple systemic manifestations. The ophthalmological findings are the least frequent and nonspecific and, therefore, its diagnosis is complicated and delayed; however, it should always be considered as a diagnostic possibility in the presence of atypical ocular and periocular inflammatory clinical pictures. **Objective:** To describe the clinical case of a patient with the presence of a conjunctival mass as the first finding in Epstein Barr virus infection. **Clinical Case:** A 4-year-old boy with a 4-day history of left upper eyelid edema and ptosis associated with a large, fast-growing, elevated, painful, and salmon-colored upper bulbar conjunctival mass with extension to the upper fornix associated with bilateral cervical and inguinal lymphadenopathy. Initially, a lymphoproliferative disorder was suspected, with blood count with lymphocytosis and atypical lymphocytes, elevated lactate dehydrogenase, peripheral blood smear with an increase in white blood cells and some atypical lymphocytes, bone marrow aspirate with a predominance of granulocytes and predominantly CD8-positive T lymphocytes and an increase in Gamma-Delta T lymphocytes. The orbit CT scan showed thickening of the left upper eyelid with peripheral enhancement and the abdominal CT scan showed splenomegaly. Biopsy confirmed chronic Epstein Barr virus infection with positive IgM and indeterminate IgG antibodies. Symptomatic management was indicated with satisfactory evolution and complete resolution of the conjunctival lesion and lymphadenopathy. **Conclusion:** Epstein Barr virus infection should be considered as a possible diagnosis in atypical ocular and periocular inflammatory manifestations in the pediatric population.

Keywords:
Conjunctival Neoplasms;
Lymphoproliferative Disorders;
Epstein-Barr Virus Infections;
Blepharoptosis;
Atypical Ocular Inflammation

Correspondence:
Laura Bettin Torres
laurabettinmd@gmail.com

Edited by:
Luisa Schonhaut Berman

How to cite this article: Andes pediatr. 2022;93(4):579-584. DOI: 10.32641/andespediatr.v93i4.3890

Introduction

Epstein Barr virus (EBV) infection is considered a highly prevalent infectious disease present in 85%-96.7% population worldwide[1,2]. EBV is a type 4 double-stranded DNA virus enclosed in a nucleocapsid and surrounded by a viral envelope,that belongs to the herpesvirus family[3]. It is transmitted by oral secretions or direct contact, causing the primary infection through the involvement of epithelial cells of the oropharynx and nasopharynx, which subsequently hosts in B lymphocytes, mainly in mucosa-associated lymphoid tissues[4,5]. This generates a humoral and cellular immune response, associated with a reactivation capacity due to latency in memory B lymphocytes, Natural Killer lymphocytes, or T lymphocytes, thus generating the so-called latent infection[3,6].

The disease can manifest itself at any age but commonly presents in childhood asymptomatically or with mild symptoms such as fatigue, fever, malaise, sweating, lymphadenopathy, hepatosplenomegaly, and pharyngitis[5,7]. When primary infection develops in adolescence or young adults, it causes infectious mononucleosis in 30-70% of cases[8,9]. Early complications such as thrombocytopenia, aplastic anemia, agranulocytosis, pneumonia, airway obstruction, myocarditis, hepatitis, renal or hepatic failure, genital ulcers, acalculous cholecystitis, splenomegaly, encephalitis, and hypersensitivity have been described[7]. In more severe cases, EBV is responsible for multiple neoplasms such as gastric carcinoma and nasopharyngeal carcinoma and has been associated with lymphoproliferative syndromes such as Hodgkin's or Burkitt's lymphoma, mainly in immunosuppressed patients[7,8].

Regarding ophthalmologic manifestations, studies and case reports are scarce, but patients have been described with conjunctivitis, dry eye, keratitis, scleritis, uveitis, ocular hypertension, necrotizing retinitis, choroiditis, papillitis, dacryocystitis, and ophthalmoplegia[4,6,10]. In the pediatric population, palpebral and periorbital edema is the most common sign in 11-29% of cases[10,11,12]. Only a few cases of conjunctival masses or tumors have been described as the first manifestation or before systemic symptoms of infectious mononucleosis[13,14].

The objective of this report is to describe the case of a patient with a conjunctival mass as the first finding of EBV infection, postulating it as a possible clinical presentation in atypical ocular inflammatory processes in the pediatric population.

Clinical Case

A 4-year-old male patient, with complete vaccination schedule for his age, eutrophic, and with no previous pathologic history, was admitted with a 4-day history of clinical symptoms consisting of rapidly progressive edema and ptosis of the left upper eyelid, associated in the last 2 days with the appearance of a painful mass in the upper bulbar conjunctiva, with no other associated symptomatology. On admission, 3 mm left ptosis was observed with involvement of the upper orbito-palpebral sulcus (figure 1), a 10 mm diameter mass located on the upper bulbar conjunctiva, elevated, and salmon-colored (figure 2), extending to the upper conjunctival fornix, associated with multiple bilateral cervical and inguinal lymphadenopathies. The ophthalmologic evaluation showed normal visual acuity, ocular movements and pupillary reflexes, and slit lamp exam and fundoscopy without anomalies.

Together with pediatrics, a possible lymphoproliferative disease was suggested, so further extension studies were performed finding in the orbital CT scan a thickening of the left upper eyelid with peripheral enhancement, with 12 mm diameter and 0.9 mm thickness (figure 3); facial CT scan showed multiple cervical adenopathies, between 4-8 mm, with tendency to form conglomerates in the cervical lymph node levels Va, Vb, and IV; chest CT scan showed a single 2.8 mm nodule in the lateral segment of the middle lobe; abdominal CT scan showed liver size at the upper limit of normality (112 mm) and splenomegaly, and splenic index 177 mm (mean 124 mm) (figure 4).

Laboratory tests showed relative lymphocytosis of 50% with normal leukocyte count for age (14,100) and atypical lymphocytes of 17% without anemia or thrombocytopenia; renal function and electrolytes were within normal range; elevated lactate dehydrogenase (LDH) 453 U/L [150-300 U/L]; peripheral blood smear showed increased white blood cells and some atypical lymphocytes; bone marrow aspirate showed granulocytic predominance with mainly CD8-positive T cells and increase levels of Gamma-Delta T cells, without significant increase of CD34 precursors. In the immunoproliferative study of conjunctival cells by flow cytometry, CD8 positive T cells were predominant with the usual phenotype. Indirect human immunodeficiency virus (HIV) study was negative.

Given the findings and results, the pediatric hematology-oncology unit suggested a possible viral process (Epstein Barr or cytomegalovirus), immune disorder, or less probably, lymphoproliferative neoplasm. Excisional biopsy of the conjunctival lesion showed a diffuse pattern of large cells with Reed-Stemberg-like popcorn morphology with reactivity for CD45, CD20, MUM1, BCL-2, CD30, PAX-5 with weak nuclear expression, Oct-2 positive, and BOB-1 negative, and associated abundant T lymphocytes population of usual morphology expressing CD2, CD3, CD5, CD7, CD43,

and Granzyme with predominance of CD8 positive cytotoxic T lymphocytes and fewer CD4 positive T helper cells. In addition, fewer B lymphocytes reactive for CD79a, abundant histiocytes reactive for CD68, and lysozyme and EBV RNA positivity in immunoblastic B cells were observed. The final report was morphologic and immunophenotypic findings compatible with chronic EBV infection. Antibodies for Epstein Barr IgM positive 15.13 IU/ml (positive > 11 IU/ml) and IgG 10.85 IU/ml (indeterminate 9 - 10.9 IU/ml) were obtained, ruling out cytomegalovirus infection.

In the evaluation by pediatric infectiology, symptomatic management and follow-up were recommended. During the check-up visits, complete resolution of the conjunctival lesion was observed with adequate healing after excisional biopsy (figure 5), complete resolution of ptosis, and, at the serological level, decrease of antibodies for Epstein Barr IgM (4.54 UI/ml), and increase of IgG (12.66 UI/ml), and cellular immunity studies with CD3, CD4, and CD8 lymphocytes within the normal range for age. At 15 months of follow-up, the patient remains asymptomatic.

Discussion

EBV is a well-known infectious entity in the pediatric population that can present with multiple systemic manifestations. Ocular presentations can present a challenge to the pediatrician and ophthalmologist as they are infrequent and present a wide variety of differential diagnoses. In our case, the first manifestation of EBV infection was a rapidly growing unilateral upper conjunctival mass associated with cervical and inguinal adenopathy and splenomegaly with no other ocular or

Figure 1. Ptosis of 3mm with left upper eyelid edema, and filling of the superior orbito-palpebral sulcus.

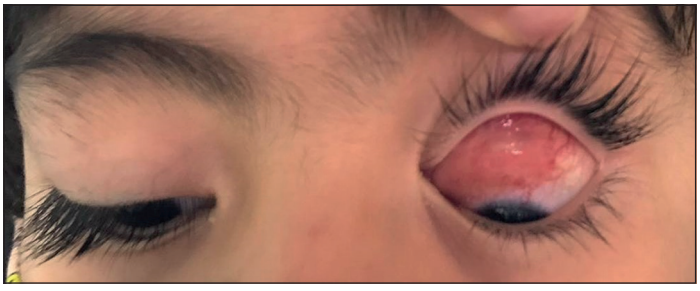

Figure 2. Mass of 10mm of diameter depending of the bulbar superior conjunctiva and extending to superior fornix.

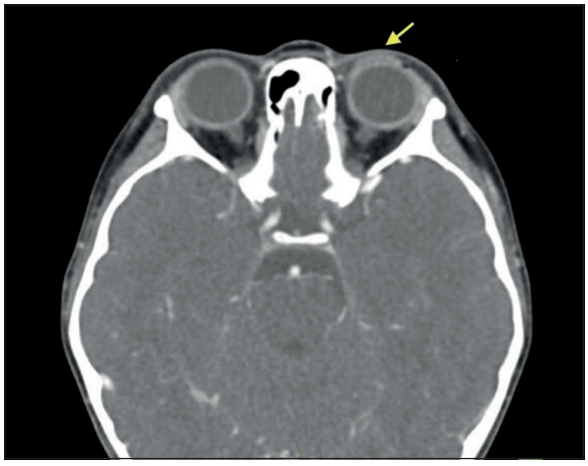

Figure 3. Axial orbital CT scan. Thickening of the left upper eyelid of 12 mm diameter and 0.9 mm thickness associated with peripheral enhancement.

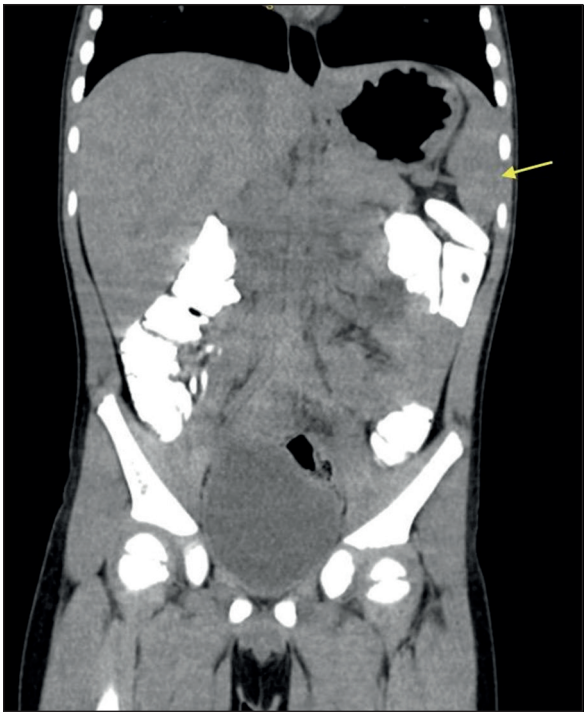

Figure 4. Abdominal CT scan. Liver size at the upper limit of normality (112 mm) and splenomegaly, with a splenic index 177 mm (mean 124 mm).

systemic symptoms at the same time. In the few case reports described, these masses have the characteristics of being salmon-colored or red, painless, and tend to be in the upper or medial conjunctiva with varying sizes ranging from 0.5 to 2.5 cm, as described in our patient[14,15].

Clinically, there are several differential diagnoses in the pediatric population regarding conjunctival masses such as lymphoproliferative processes, which was the first diagnostic impression in our patient. Lymphoproliferative processes represent 25-33% of acquired conjunctival lesions in adults and are much rarer in children[14,16]. The greatest proportion in adults are lymphomas and in children, it is lymphocytic proliferations that raise concern about the development of Burkitt or Hodgkin's lymphoma, so a complete diagnostic examination should be performed[14]. Other exceptional causes of conjunctival masses include Parinaud oculoglandular syndrome and local rickettsia vaccination[17,18].

Histologically, conjunctival masses in initial stages consist of dense B-cell lymphocytic infiltrates with follicular hyperplasia and histiocytes[13,19], subsequently acquiring a "Reed-Sternberg-like" cell morphology with T-cell and plasma cell infiltration[19]. In our case, there was evidence of lymphocytic and histiocytic proliferation associated with the appearance of "Reed-Sternberg-like" cells characteristic of EBV infection.

The diagnosis of acute or chronic infection is made with the identification of symptoms, associated with serological studies such as IgM - IgG antibodies against the viral capsid antigen, EBV nuclear antigen, or EBV polymerase chain reaction (PCR)[20,21]. The study of heterophile antibodies has been described for the detection in the first month or atypical presentations, but it is not very sensitive in children under 12 years of age, between 25-50%[20,21].

Ophthalmologically, aqueous and vitreous humor studies have been performed for PCR detection of the virus in cases of severe ocular inflammation, finding antibodies in 10% of active cases[22,23]. In our patient, the diagnosis was a challenge, given the absence of the usual symptoms of EBV infection and the isolated presence of adenopathy, lymphocytosis with atypical lymphocytes, and splenomegaly, the biopsy of the conjunctival mass allowed establishing a definitive diagnosis. Therefore, EBV infection should be suspected in any patient with an atypical ocular or orbital inflammatory process as a differential diagnosis.

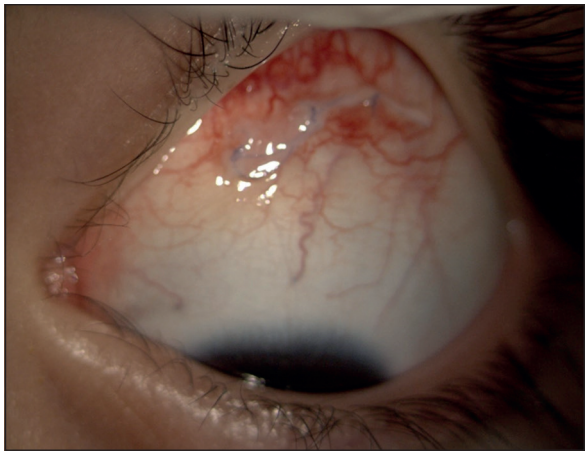

Figure 5. Bulbar conjunctiva on the 5th day after excisional biopsy, partial resolution of the conjunctival mass.

Treatment is controversial since generally the disease is self-limited and there is no consensus about it[21,24]. Basic support with hydration, fever and pain management with antipyretics and anti-inflammatory drugs is indicated[21]. Contact sports should be avoided to prevent complications such as spleen rupture for at least 3 weeks after resolution of symptoms[21]. The efficacy of antiviral drugs is debated; the use of acyclovir and valacyclovir has been described to reduce the proliferation of the virus and therefore decrease symptoms, mainly in immunosuppressed patients; however, their use is not recommended[4,5,21,24]. Regarding corticoids, there is not enough evidence for their recommendation; they can be used in patients with severe complications due to EBV such as upper airway obstruction, hemolytic anemia, thrombocytopenia, severe cardiac compromise, or neurological complications[5,21]. The use of rituximab has been described for the treatment of EBV-associated post-transplant lymphoproliferative disorder in the context of allogeneic stem cell transplantation with remission rates above 80%[25].

Regarding ophthalmologic manifestations, each clinical presentation should be individualized for targeted treatment[6,10].

Conclusions

EBV can be categorized as one of the infectious diseases with major systemic manifestations, although nonspecific, mainly in the pediatric population. We present an atypical case of EBV infection in a child, whose first manifestation was ophthalmologic as a conjunctival mass, which is unusual. Although ocular manifestations are infrequent, due to the possibility of involvement of periocular and all eye segments, EBV infection should be suspected in atypical ocular and periocular inflammatory presentations.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed ac-

cording to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

References

1. Kuri A, Jacobs BM, Vickaryous N, et al. Epidemiology of Epstein-Barr virus infection and infectious mononucleosis in the United Kingdom. BMC Public Health. 2020;12;20(1):912.
2. Balfour HH Jr, Sifakis F, Sliman JA, et al. Age-specific prevalence of Epstein-Barr virus infection among individuals aged 6-19 years in the United States and factors affecting its acquisition. J Infect Dis. 2013;208(8):1286-93.
3. Weinberg J. Virus de Epstein Barr. En: Nelson Tratado de Pediatría Ed 21ª. Editorial Elsevier 2020;1715-8.
4. Bolis V, Karadedos C, Chiotis I, et al. Atypical manifestations of Epstein-Barr virus in children: a diagnostic challenge. J Pediatr (Rio J). 2016;92(2):113-21.
5. Dunmire SK, Verghese PS, Balfour HH Jr. Primary Epstein-Barr virus infection. J Clin Virol. 2018;102:84-92
6. Cunningham E, Zierhut M. Epstein-Barr Virus and the Eye. Ocul Immunol Inflamm. 2020; 28(4):533-7
7. Lu G, Xie ZD, Zhao SY, et al. Clinical analysis and follow-up study of chronic active Epstein-Barr virus infection in 53 pediatric cases. Chin Med J (Engl). 2009;122(3):262-6.
8. Johannsen, E. Kaye K. Epstein-Barr virus (infectious mononucleosis). InR. Dolin (ed.) Principles and practice of infectious diseases, 6th ed., vol. 2. Churchill Livingstone, Philadelphia, 2005;1801-21.
9. Draborg AH, Duus K, Houen G. Epstein-Barr virus in systemic autoimmune diseases. Clin Dev Immunol. 2013;2013:535-738.
10. Alba-Linero C, Rocha-de-Lossada C, Rachwani-Anil R, et al. Anterior segment involvement in Epstein-Barr virus: a review. Acta Ophthalmol. 2021. doi: 10.1111/aos.15061.
11. Chan CW, Chiang AK, Chan KH, et al. Epstein-Barr virus-associated infectious mononucleosis in Chinese children. Pediatr Infect Dis J. 2003;22(11):974-8.
12. Gao LW, Xie ZD, Liu YY, et al. Epidemiologic and clinical characteristics of infectious mononucleosis associated with Epstein-Barr virus infection in children in Beijing, China. World J Pediatr. 2011;(1):45-9.
13. Vaivanijkul J, Boonsiri K. Conjunctival tumor caused by Epstein-Barr virus-related infectious mononucleosis: Case report and review of literature. Orbit 2017,36(2):91-4.
14. Feinberg A, Spraul C, Holden J, et al. Conjuntival Lymphocytic Infiltrates Associated with Epstein-Barr Virus. Ophthalmology 2000;107(1):159-63.
15. Chervenkoff JV, Rajak SN, Brittain PG, et al. Case report: a diagnostically challenging conjunctival mass caused by the Epstein-Barr virus. BMC Ophthalmol. 2015;15:129. doi: 10.1186/s12886-015-0111-2.
16. Spraul CW, Grossniklaus HE. Analysis of 24,444 surgical specimens accessioned over 55 years in an ophthalmic pathology laboratory. Int Ophthalmol. 1997-1998;21(5):283-304. doi: 10.1023/a:1006047803924. PMID: 9756437.
17. Meisler DM, Bosworth DE, Krachmer JH. Ocular infectious mononucleosis manifested as Parinaud's oculoglandular syndrome. Am J Ophthalmol. 1981;92:722-6.
18. Ormerod LD, Dailey JP. Ocular manifestations of cat-scratch disease. Curr Opin Ophthalmol. 1999;10(3):209-16.
19. Kim HJ, Ko YH, Kim JE, et al. Epstein-Barr Virus-Associated Lymphoproliferative Disorders: Review and Update on 2016 WHO Classification. J Pathol Transl Med. 2017;51(4):352-8. doi: 10.4132/jptm.2017.03.15.
20. Gardner BP, Margolis TP, Mondino BJ. Conjunctival lymphocytic nodule associated with the Epstein-Barr virus. Am J Ophthalmol. 1991;112(5):567-71.
21. Valachis A, Kofteridis D. Mononucleosis and Epstein - Barr virus infection: Treatment and medication. Virus Adapt Treat. 2012;4:23-8.
22. Yamamoto S, Sugita S, Sugamoto Y, et al. Quantitative PCR for the detection of genomic DNA of Epstein-Barr virus in ocular fluids of patients with uveitis. Jpn J Ophthalmol. 2008;52(6):463-7.
23. Chodosh J, Gan Y, Sixbey J. Detection of Epstein Barr virus Genome In ocular Tissues. Ophthalmology 1996;103:4,687-90.
24. Andrei G, Trompet E, Snoeck R. Novel Therapeutics for Epstein-Barr Virus. Molecules. 2019;12;24(5):997.
25. Styczynski J, Gil L, Tridello G, et al. Response to rituximab-based therapy and risk factor analysis in Epstein Barr Virus-related lymphoproliferative disorder after hematopoietic stem cell transplant in children and adults: a study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Clin Infect Dis. 2013:57(6):794-802.