

# Infectious mononucleosis with leukemoid reaction, and systemic involvement

## Summary

**Introduction:** Epstein-Barr virus (EBV) infects more than 95% of the world's population and is associated with infectious mononucleosis as well as a number of cancers in various geographical locations. It can usually cause tonsillitis, fever and adenomegaly, however it can present in severe forms with hematological alterations, with alterations in the bone marrow or with systemic alterations involving several apparatuses and systems.

**Clinical case:** We present the case of a 2-year-old female patient who developed a febrile respiratory condition and torpidly progressed to respiratory distress, tonsil hypertrophy obstruction, adenomegaly, hepatosplenomegaly, carditis, hematological alterations with leukemoid reaction.

**Discussion/conclusion:** Mononucleosis whose classic presentation is characterized by the presence of fever, pharyngitis and generalized lymphadenopathy, it is produced by the Epstein Barr virus, it has been called the kissing disease affecting adolescents and adults however it can occur in children being a picture beyond tonsillitis, we observe serious cases such as the one we will describe, we must carefully observe all the data that are presented and be able to integrate the diagnosis early.

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## Introduction

The Epstein-Barr virus (EBV) was described in 1964 in cell cultures from samples of African Burkitt lymphoma.

Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a member of the herpes virus family. It is one of the most common human viruses. EBV is found all over the world.<sup>1</sup> 2 types of EBV have been identified, EBV-1 and EBV-2; in Europe and the United States, the EBV-1 type is 10 times more frequent, but they are evenly distributed in other settings such as Africa.<sup>2</sup>

EBV infects more than 95% of the world's population and is associated with infectious mononucleosis as well as a number of cancers in various geographical locations. It can usually cause tonsillitis, fever and adenomegaly, however it can present in severe forms.

Through saliva, it reaches the oropharyngeal epithelium and salivary glands where it infects epithelial cells, and virions infect B lymphocytes in tonsillar crypts. When it binds to the lymphoid cell, it initiates the binding of the viral glycoprotein gp 350/220 to the surface receptor of CD21 B lymphocytes, which is the receptor for the C3d component of complement, also called complement type 2 receptor (CR2). The entry of the virus occurs by endocytosis. When the virus enters the cytoplasm, a process of decapsulation and transport of DNA to the nucleus occurs. By the time this DNA molecule reaches the nucleus, it acquires a circular morphology and forms an episome. After infection, B lymphocytes begin the cell cycle and proliferate continuously, giving rise to immortalized lymphoblastoid cell lines, which can be propagated in vitro indefinitely. Infection of B lymphocytes by EBV is characterized by a state of viral dormancy, in which a series of molecules are produced in vitro due to the action of host cellular enzymes on the episome: latent infection membrane proteins (LMP1 and LMP2), nuclear antigens (EBNA), two small non-coding RNA fragments (EBER), as well as other RNA molecules that could encode proteins (BART). The proliferation and expansion of infected B lymphocytes along with reactive T cells result in the

growth of lymphoid tissue. The virus spreads through the blood. During the phase of acute EBV infection, more than 1 in 100 peripheral blood B lymphocytes are infected; however, after primary infection, EBV is only detected between 1-50 circulating lymphocytes/million, which thanks to the restricted expression of latency antigens are able to persist, despite immune surveillance. EBV infection elicits both a cellular and humoral response.<sup>3</sup>

Diagnosing EBV infection can be challenging because the symptoms are similar to other illnesses. EBV infection can be confirmed with a blood test that detects antibodies. About nine out of ten of adults have antibodies that show that they have a current or past EBV infection.

## Clinical case

A 2-year-old female began suffering 9 days before, with cough without treatment, 5 days before admission she began fever and persistent cough, treatment with ibuprofen, cefixime loratadine and dextromethorphan began, the next day eyelid edema was added, tobramycin eye drops were added, without improvement, A day later and two days before admission, eyelid edema increases, cough increases, fever persists, and a day before they notice an increase in neck volume and facial edema nasal congestion go to pediatrician indicates nebulized budesonide, loratadine, oxymetazoline does not improve on the contrary they observe deterioration. The next day they travel to their community 4 hours from their city of residence with their family doctor, who presents them to the service for probable drug poisoning.

Presents significant facial edema and increased abdominal volume, the patient is in poor general condition, low-grade fever with occlusion of the right eye and less of the left side, hyperemic pharynx grade IV tonsils with exudative hyperemia, with total obstruction, sterling breathing, right tonsil displaces the left, neck with increased volume at the expense of lymph nodes 5-7 cm in diameter, bilateral rales and respiratory distress, globose abdomen at the expense of hepatosplenomegaly, inguinal adenomegaly, a critically ill patient is admitted.

Paraclinical blood cytometry HB 12.6 HTO 37.8 plaquettes 198 000 leukocytes of **49 990** neutrophils 21% 10498 bands 3% LYMPHOCYTES 69% with 34 494 absolute with reactive lymphocytes, total bilirubin 2.21 1.8 direct TGO 519, TGP 313 FA 647 Proteins 5.9 DHL 2 598, PCR 2, X-ray bronchial pattern, and cardiomegaly (report mentions lung image of unpolished glass), liver ultrasound reports enlarged liver with regular borders, hyperechogenic hospital management. In 24 hours improvement is observed, the tonsils have decreased in size, their respiratory function improves, facial and neck edema decrease, the adenomegaly are smaller and less tense. After 48 hours, there was clear improvement in good general condition, control laboratory was hemoglobin 11.2, hematocrit 32 leukocytes **15 980**, neutrophils 41%, lymphocytes 56% 8 949 absolute and total bilirubin 1 TGO 309 TGP 236 FA 538 proteins 5.6 LDH 1428. The leukemoid reaction decreased markedly.

Normal chest X-ray.

#### Sample taken at admission:

Ac IgG Epstein barr 26.8 (positive greater than 20)

IgM greater than 160, positive greater than A 40

The evolution is favorable after graduating to the 5th grade. During his stay, he was managed with general measures, liquids as required, at the time of his admission dexamethazone. A week later, the patient went for re-evaluation, good general condition, occasional pain in the lower limbs and occasional abdominal pain, control ultrasound reported mild hepatosplenomegaly, hemoglobina 11.8, hematocrito 36.4, plaquetas 455 000, LEUCOS 16 950 79% lymphocytes.

Normal chest X-ray.

#### 15 days later: asymptomatic, asynological

One month later, HB 11.5 plaquettes 502 000 LYMPHOS 70% IgM CAPSIDE 78 IgG 11.8 (NORMAL). On this occasion, he presented with rhinorrhea without any other symptoms. Conservative treatment.

**3 months after hospitalization:** TGO 41, TGP 17, FA 171, GGT 9 leukocytes 6,480, hemoglobin 12.3, hematocrit 38, platelets 453,000 neutrophils, 45% lymphocytes, 45% monocytes, 6%.

IgM EBV 84 Igg 430. **(REACTIVATED)?**

6 months later, the patient was asymptomatic and assigned.

## Discussion

Infectious mononucleosis is a disease whose classic presentation is characterized by the presence of fever, pharyngitis and generalized lymphadenopathy, it is caused by the Epstein Barr virus, which belongs to the Herpesviridae family.

Its presentation differs depending on the age range in which it occurs. The most affected age group is between 10 and 20 years old with incidence rates of 6-8 cases per 1000 inhabitants/year. The incubation period varies between 4 and 6 weeks and is preceded by prodromes (asthenia, low-grade fever, myalgias) of 1-2 weeks. The typical picture then develops, with fever, odynophagia and exploratory data of pharyngeal inflammation and lymphadenopathy. The laterocervical lymph nodes are the most affected. This typical triad occurs in more than 50% of patients.<sup>4</sup>

In this case, the patient begins as a mild usual respiratory case that progresses rapidly from tonsillitis with fever, prior to admission they do not report adenomegaly, they initiate conventional management, however the evolution is torpid. When presented to the emergency

department, she presented with neck edema and deformity, facial edema including ocular occlusion, tonsils with obstruction and respiratory distress, tachycardia, respiratory problem, and a greatly enlarged abdomen at the expense of hepatosplenomegaly. We wonder why the evolution from a respiratory condition to a severe condition, the patient did not present risk factors, previously referred to healthy, weight and height within the normal, adequate diet and hygiene, physiopathology was already mentioned and is related to the state of immune response.

Most patients develop infectious mononucleosis (IM) after infection, while other types like EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH), chronic active EBV infection (CAEBV), EBV-associated lymphoproliferative disorder (EBV-LPD) are relatively rare. In more extreme circumstances, EBV infection can also lead to the development of malignancies such as lymphoma, nasopharyngeal carcinoma, and gastric cancer.<sup>5</sup>

The leukocyte count in patients with infectious mononucleosis is on average within the reference value, however, in Epstein Barr virus infection, there is intense proliferation of lymphocytes within the affected lymph nodes that can increase the leukocyte count, and leukocytosis may be found. Lymphocytes may be elevated and may have reactive lymphocytes and neutropenia occurs. Platelets within normal values or thrombocytopenia.

A leukemoid reaction consists of an increase in leukocytes above 50,000 mm<sup>3</sup> (some authors consider it to be more than 30,000 mm<sup>3</sup>), which can be confused with chronic myeloid leukemia. It occurs as a response to many diseases with massive release of immature leukocytes into the peripheral blood, there are 3 types, in this case lymphoid with a significant increase in lymphocytes and the presence of atypical or virocytes. Our patient presented a very high number, 49990, with a predominance of lymphocytes and the presence of atypical lymphocytes, which supports the viral process.

The use of corticosteroids in acute infectious mononucleosis is somewhat controversial. Most clinicians would prescribe a short course of corticosteroids for patients with any degree of airway obstruction, or autoimmune phenomena such as anemia and/or thrombocytopenia, in this case at the beginning due to the obstructive respiratory problem, we started management with dexamethasone and the response was favorable in the first hours and according to what was previously reported it was justified.

Several nucleoside analogs have in vitro activity against EBV [101] but a clinical benefit has not yet been proven for any of them. Valacyclovir is worth mentioning because it is generic and has very few side effects.<sup>6</sup> The rapid test for these antibodies (monospot) is used for the diagnosis of infectious IM. In the first week they are negative in 25% of cases and between 5-10% in the second. Once they are positive, they can stay for more than a year. In the presence of symptoms, positive heterophile antibodies have a sensitivity and specificity of approximately 85% and 94%, respectively. There are reports of elevation around 3 months and it is not a reactivation as initially thought.

Preventing or modifying primary EBV infection could reduce the incidence PTLD, and also certain lymphomas and nasopharyngeal carcinoma. EBV is a major environmental risk factor for multiple sclerosis (MS). Contracting EBV is essential to getting MS, and having a childhood case of infectious mononucleosis increases that risk. Vaccinating against EBV could be vaccinating against MS.<sup>7</sup> Ruyue et al describe in their paper regarding the chronic form of EBV and the use of, Sintilimab treatment for chronic active.<sup>8</sup>

Dasari et al in one review, evaluate the prophylactic and therapeutic vaccine approaches against EBV and various immunotherapeutic strategies against a number of EBV-associated malignancies. This review also describes the existing and future prospects of improved EBV-targeted therapeutic strategies. Expert opinion: It is anticipated that these emerging strategies will provide answers for the major challenges in EBV vaccine development and help improve the efficacy of novel therapeutic strategies.<sup>9</sup>

## Conclusion

EBV infection known in adolescents as kissing disease due to its transmission through saliva, other mechanisms such as blood and breast milk are currently known, the classic triad of tonsillitis, fever and adenomegaly can pass to severe forms and systemic involvement, such as this case with great respiratory compromise, obstruction, edema, lymphatic compromise, hepatosplenomegaly, etc. Therefore, we must consider the onset and evolution and consider these complications, and because of the leukemoid reaction we must follow up and that we know can cause depression at the level of the bone marrow with serious hematological alterations.

## Acknowledgments

None.

## Conflicts of interest

The author has no conflicts of interest to declare.

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