Case Report

Acute Epstein-Barr Virus and SARS-CoV-2 Coinfection: A Case Report

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ABSTRACT: Introduction. The present case describes one of the few reported occurrences of coinfection by EBV and SARS-CoV-2, initially treated as streptococcal pharyngitis. Case Description. An 18-year-old female was admitted with whitish plaques in the throat associated with pain, cough, hoarseness, asthenia, tonsillar exudate, hypertrophy, hyperemia, and adenomegaly on the cervical region. Based on suspicion of bacterial tonsillitis, the patient was already taking amoxicillin with clavulanate. A rapid test was negative for group A streptococci. Laboratory exams revealed elevated counts of Anti-VCA IgM and Anti-VCA IgG for EBV. The cytomegalovirus (IgM and IgG) result was negative, and the blood count was within normal limits. However, a COVID-19 infection was confirmed by qPCR. The management was supportive treatment for symptom relief and isolation for 14 days. The patient remained afebrile and clinically stable during this period, with saturation ranging from 98% to 100%. However, the patient evolved with anosmia and ageusia. Then, olfaction training therapy was initiated, as well as continuing asthenia. Five days later, she presented petechiae on the chest and upper limbs, associated with mild pruritus. Conclusion. Epstein-Barr mononucleosis and COVID-19 are similar in some aspects, and their viruses may be associated with a coinfection, which could make the diagnoses difficult and aggravate the clinical condition. In addition, it is essential to emphasize the importance of laboratory tests to avoid erroneous treatments that may worsen the patient's condition and change his prognosis.

KEYWORDS: *Epstein-Barr, COVID-19, mononucleosis, SARS-CoV-2*

Introduction

Member of the herpes virus family, the Epstein-Barr virus (EBV) is responsible for infectious mononucleosis, mostly in individuals between 15 and 25 years old [1].

The disease progresses benignly, in general, but it is characterized by an extensive clinical polymorphism, and it may evolve severely.

Its classic symptoms are pharyngitis, cervical adenopathy, and fever, which tend to be self-limited.

However, occasionally hepatosplenomegaly can be observed, which might complicate liver failure and even splenic rupture.

The diagnosis is clinical in association with serological confirmation.

Lymphocytosis with atypical lymphocytes may be observed in the laboratory evaluation.

Commonly, palliative treatments are indicated for patients without complications, including rest and medications for symptom relief, such as antipyretics and analgesics [2].

Recently, with the installation of the SARS-CoV-2 pandemic, this infection was added to the vast list of differential diagnoses of EBV, given the symptomatological similarity [3,4].

Cough, fever, skin rash, and hoarseness are examples of symptoms that draw attention to both pathologies [5].

In this scenario, one of the challenges is the scarcity of studies that address the effect of a coinfection.

A study observed that a concomitant infection with both viruses brought a patient to a critical state, especially given the liver damage.

It was suggested that underlying EBV infection contributed to transaminitis [6].

The present clinical case describes one of the few reported occurrences of coinfection by EBV and SARS-CoV-2, initially treated as streptococcal pharyngitis.

Laboratory tests were determinant for the correct diagnosis and management.

Case Report

A previously healthy 18-year-old female, who provided a written informed consent for publication of these data, was admitted to the otolaryngology clinic with the complaint of

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whitish plaques in the throat associated with pain, cough, and hoarseness eight days ago.

In addition, she reported considerable asthenia.

The patient was already taking amoxicillin with clavulanate (Clavulin®), prescribed in a teleconsultation based on suspicion of bacterial tonsillitis.

In addition, the patient had noticed the appearance of adenomegaly on the right side of the anterior cervical region, which on physical examination, had a fibroblastic consistency, mobile and painful on palpation.

Examination of the oral cavity showed tonsillar hypertrophy and hyperemia, in addition to exudative tonsillitis, with whitish plaques adhering bilaterally.

A rapid strep test (Streptatest®, Biosinex, Illkirch-Graffenstaden, France) was performed to investigate possible bacterial pharyngitis caused by group A streptococci, but the result was negative.

Laboratory blood tests were requested (Table 1).

Figure 1. Clinical aspects. (A) Exudative tonsillitis. (B) Maculopapular rash in the middle of the thorax. (C) Maculopapular rash in the right upper limb.

Table 1. Laboratory results and reference values.

Laboratory Parameters	Case Patient	Reference value
Red blood cells	4.58 10^6/µL	4-5.2 10^6/µL
Hemoglobin	13.7 g/dL	12-16 g/dL
Hematocrit	40,1%	36-44%
VCM	87.5 fL	80-100 fL
HCM	29.9 pg	26-34 pg
CHCM	34.2 g/dL	31-37 g/dL
RDW	13,5%	11,5-14,5%
Leukocytes	100% 5930/µL	100% 4500-11000/µL
Neutrophils	31.2% 1850/µL	45.5-73.5% 1600-7700/µL
Eosinophils	2.2% 130/µL	0-4.4% 0-300/µL
Basophils	1,3% 77/µL	0-1% 0-200/µL
Lymphocytes	55.1% 3267/µL	20.3-47% 1000-3900/µL
Monocytes	10.2% 605/µL	2-10% 100-1000/µL
Platelets	293000/µL	150000-450000/µL
Hemosedimentation (ESR)	2mm	less than 20mm
Epstein Barr Virus IgM	greater than 160 U/mL	greater than 40 U/mL
Epstein Barr Virus IgG	37 U/ml	greater than 20 U/mL
Cytomegalovirus IgM	unresponsive	—----------
Cytomegalovirus IgG	less than 0.25 U/mL	greater than 1 U/ml

10.12865/CHSJ.50.03.14

On return to the consultation, the laboratory review identified elevated counts of Anti-VCA IgM and Anti-VCA IgG (Viral Capsid Antigens) for EBV. The result for cytomegalovirus (IgM and IgG) was negative, and the blood count was within normal limits, including the erythrocyte sedimentation rate (ESR) (Table 1).

After these results, the treatment with Clavulin® was discontinued, and supportive treatment for symptom relief was recommended.

Then, a COVID-19 test was requested following the World Health Organization pandemic protocol considering the symptoms described by the patient.

Two days after the appointment, the infection of COVID-19 was confirmed by performing a quantitative real-time polymerase chain reaction assay.

The sample was collected by nasopharyngeal swab through the following steps:

1. the entire soft end of the swab was introduced approximately 1.5cm into the nostril;
2. the swab was slowly rotated and gently pressed against the inside of the nostril 4 times, for a total of 15 seconds;
3. the swab was removed, and the procedures were repeated in the other nostril, using the same swab;
4. the swab was inserted in the sterile tube containing the viral transport medium and snapped off the end of the swab;
5. the tube was carefully closed.

Similarly, another swab was used to collect a sample from the oropharynx by scrubbing it in the tonsils.

This swab was inserted into the same tube as the other.

In this context, the management was supportive treatment for symptom relief and isolation for 14 days.

During this period, the patient remained afebrile and clinically stable.

The values of oxygen saturation ranged from 98-100%.

However, the patient evolved with anosmia and ageusia, so olfaction training therapy was indicated, besides continuing asthenia.

Five days later, she presented petechiae on the chest and upper limbs, associated with mild pruritus.

Discussion

As the COVID-19 infection episodes continue to appear, it is essential to consider the possibility of coinfection with other viruses, such as Epstein-Barr virus (EBV), as described in the present study.

Furthermore, having more than one viral infection at the same time can make it more challenging to manage a disease, emphasizing the need for accurate diagnosis and appropriate treatment.

Although the occurrence of COVID-19 and EBV coinfection seems uncommon, it is crucial to maintain a high index of suspicion for coinfection and perform appropriate diagnostic tests when patients present with overlapping symptoms of both infections.

Regarding the cutaneous rash, there is still a duality in its etiology, which comes from a phenomenon associated with EBV itself, given viral replication, or from sensitization to the drug.

This is because, as it happened to this patient, there are many cases in which infectious mononucleosis is mistakenly treated as bacterial pharyngitis, usually treated with amoxicillin.

One study showed that out of a sample of 184 patients, 34 had a rash during the disease.

Furthermore, 19 had a rash using amoxicillin during active EBV infection, representing 10.3%, while 108 had no rash [7].

Furthermore, a higher prevalence of the appearance of dermatological lesions in children is noted.

Another option for the etiology of the cutaneous rash would be SARS-CoV-2 itself, which is also associated with the development of this manifestation.

It is pointed out that 9-47% of patients present maculopapular rash while infected, with the highest prevalence in adults [8,9].

As described, the young woman in the case had no laboratory alteration concerning blood count.

In a SARS-CoV-2 infection, a common laboratory finding is lymphopenia (35-75%) since this virus significantly impacts the hematopoietic system, and it can be useful data to evaluate prognosis and hospitalization.

This condition can be observed during the incubation period, but it becomes more evident during the so-called "cytokine storm" when there is an increase in clinical manifestations [10].

On the other hand, in EBV infection, a lymphocytosis condition is observed, with the presence of atypical lymphocytes in the peripheral blood.

It was evidenced that, of the patients with atypical lymphocytes, the associated clinical condition in 55% of cases was infectious mononucleosis, with 33% with positive IgM for EBV [11].

Infectious mononucleosis can be caused by different etiologic agents, which justifies the request for Cytomegalovirus serology in the above case.

Although Epstein Barr is the most frequent, approximately 10% of the cases are caused by Cytomegalovirus, and the differential diagnosis is made through laboratory tests since the clinic is similar [12].

The ESR is a sensitive but not very specific test since it can identify inflammation, infection, or even a neoplastic process, but not its type or location.

Therefore, clinical evaluation and additional tests are required to confirm the pathology diagnosis.

One clinical condition that elevates the ESR is increased immunoglobulins, given an infectious and/or inflammatory process [10].

In the present case, the ESR was curiously within the normal range.

Still, infectious mononucleosis can course with hepatosplenomegaly, a condition that could be considered in the presence of an ESR above the reference value, as well as the C-reactive protein and transaminases.

In one reported case, a worsening of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels was observed during hospitalization for COVID-19, with subsequent positive serology for EBV.

In this case, the patient had a history of hypertension, hyperlipidemia, coronary heart disease, and arthritis, factors that justify the severity of the condition [6].

A possible acute complication is a splenic rupture, which despite being considered rare, as it occurs in only 0.1-0.5% of cases, is one of the most common causes of death from infection by this herpes virus, accounting for 9% [13].

This fact justifies rest recommendations for infected patients who present laboratory alterations.

Either the EBV reactivation or its acute infection has been proposed as a potential contributor to long COVID, which is characterized by symptoms such as fatigue and neurocognitive dysfunction, with a mean of 4 months of duration, as described in a previous investigation [14].

Through a cohort study design with 280 adults with prior SARS-CoV-2, the authors identified a strong association between the recent EBV reactivation and long COVID.

Given the above, the infectious-contagious diseases mentioned most often course with nonspecific symptoms, besides presenting at the same time similarities and clinical and laboratory differences, which can make diagnosis difficult and delay the start of treatment.

Thus, given the vast list of differential diagnoses, serology is a fundamental ally for adequately monitoring the patient associated with a good anamnesis.

Conclusion

Despite appearing at different times in human history, Epstein-Barr mononucleosis and COVID-19 are similar in many aspects, and their viruses may be associated in a coinfection, which could make the diagnoses difficult and aggravate the clinical condition.

With the advance of vaccination against SARS-CoV-2, cases of coinfection are expected to become even rarer.

In addition, it is important to emphasize the importance of laboratory analysis associated with clinical analysis to avoid erroneous treatments that may worsen the patient's condition and change his prognosis.

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Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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