

Case report



## SARS-COV-2 AND EBV COINFECTION IN CHILDREN: CASE REPORTS AND DISCUSSION

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### ABSTRACT:

Coronavirus infection also affects the population aged between birth and 18 years, although in most cases, SARS-CoV-2 infection (COVID-19) in children follows a milder clinical course than in adults. Concurrent viral infections in paediatric patients with COVID-19 are not uncommon. Epstein–Barr virus (EBV), a B-lymphotropic human herpesvirus, typically establishes primary infection early in life. While initial infection is frequently asymptomatic, viral persistence may later manifest clinically as infectious mononucleosis. To date, data describing the clinical features and outcomes of SARS-CoV-2 and EBV coinfection in children remain limited.

**Purpose:** This report describes two pediatric cases of SARS-CoV-2 and EBV coinfection managed at the Department of Pediatrics, “Trakia” Hospital, Stara Zagora, during the COVID-19 pandemic (2020–2021). The first case involved a 5-year-old child presenting with fever and radiographic evidence of atypical pneumonia. The second case concerned a 15-year-old adolescent who initially experienced a mild course of COVID-19 but subsequently, during the convalescent phase, developed clinical signs consistent with infectious mononucleosis, accompanied by hepatitis and pericardial effusion.

**Material/Methods:** Laboratory evaluation in both cases revealed elevated inflammatory markers, including C-reactive protein, D-dimer, and ferritin.

**Results:** Serological testing confirmed dual infection with SARS-CoV-2 and EBV. Both patients received antibiotic therapy, immunomodulatory agents, and supportive symptomatic treatment, resulting in full clinical recovery and normalization of laboratory parameters. Although the clinical course of COVID-19 in children is generally favorable, including in cases of EBV coinfection, EBV may contribute to the development of more severe complications and organ dysfunction, such as multisystem inflammatory syndrome in children (MIS-C).

**Conclusions:** Therefore, in pediatric patients with COVID-19, comprehensive diagnostic evaluation should include serological screening for potential concomitant viral infections, particularly EBV.

**Keywords:** SARS-CoV-2, EBV, children, pneumonia, mononucleosis,

### INTRODUCTION

Coronavirus infection represents a global public health challenge. Although COVID-19 predominantly affects adults, SARS-CoV-2 infection can also pose a clinically relevant risk to children of all ages. Pediatric cases account for approximately 1–5 % of all confirmed COVID-19 infections, and the disease in children is generally milder or asymptomatic compared to adults, with a more favorable prognosis and low mortality rates [1, 2, 3, 4, 5]. A substantial proportion of children exhibit minimal or no symptoms, which contributes to silent viral transmission [4, 6]. Typical clinical manifestations include fever, cough, fatigue, and sore throat, whereas gastrointestinal symptoms such as vomiting and diarrhea occur less frequently [4, 5, 6, 7]. Nevertheless, severe disease, hospitalization, and even fatal outcomes may occur, particularly in children with underlying comorbidities. Severe presentations may involve pneumonia, respiratory distress, and multisystem involvement. Multisystem Inflammatory Syndrome in Children (MIS-C), although rare, represents a potentially life-threatening post-infectious complication characterized by systemic inflammation and may resemble toxic shock syndrome or Kawasaki disease, often requiring intensive care [3, 7]. Coinfection with additional viral pathogens is not uncommon among children with SARS-CoV-2 infection. Epstein–Barr virus (EBV), a ubiquitous B-lymphotropic human herpesvirus (HHV-4), infects more than 90 % of the global population by adulthood. Primary EBV infection during childhood is usually subclinical; however, complications such as upper airway obstruction, hepatitis, and neurological involvement may occur. Chronic active EBV infection, characterized by persistent viraemia for more than six months, is associated with progressive immunosuppression and organ infiltration by EBV-positive lymphocytes, potentially resulting in pancytopenia, haemophagocytosis, multiorgan dysfunction, or EBV-driven lymphoproliferative disease if untreated. Coinfection with SARS-CoV-2 and EBV is biologically plausible and has been increasingly recognized. However, data describing the clinical presentation, course, and outcomes of such coinfection in

pediatric populations remain scarce. Moreover, EBV reactivation has been reported in association with MIS-C, indicating a possible role in immune dysregulation [7].

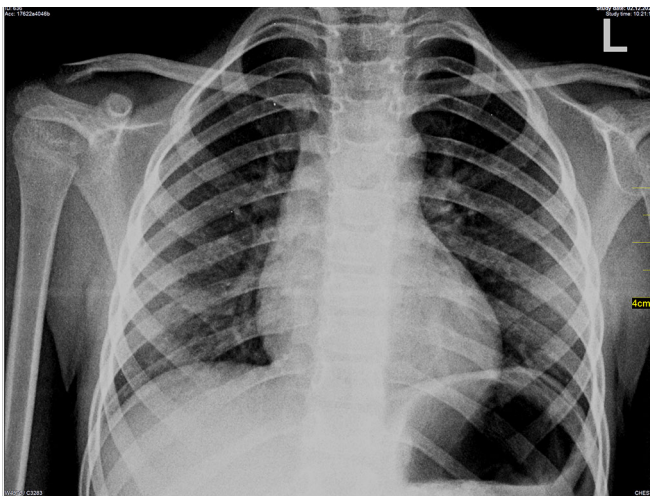
In this report, we present two clinical cases of SARS-CoV-2 and EBV coinfection diagnosed and managed at the Department of Pediatrics, “Trakia” Hospital, Stara Zagora, during the COVID-19 pandemic in 2020–2021.

#### MATERIALS AND METHODS:

##### Case 1:

A 5-year-old female patient presented with a 3–4-day history of high-grade fever (up to 39.6°C), rhinorrhea, cough, and fatigue. Initial outpatient management proved ineffective, and due to radiographic evidence of pneumonia, the child was referred for hospital admission. It was noted that the patient had been in close contact with parents experiencing an acute respiratory infection approximately 20 days prior to symptom onset. Clinically, a marked febrile-intoxication syndrome was observed, disproportionate to the pulmonary findings. No lymphadenopathy was detected; however, mild hepatomegaly was present. Chest radiography on admission demonstrated bilateral interstitial pneumonia (Fig. 1).

**Fig. 1.** Initial chest X-ray of a 5-year-old girl with pneumonia (etiologically related to COVID-19 and EBV viruses).



##### Case 2:

A 15-year-old male patient presented with a sore throat, low-grade fever, and general malaise. After an initial two-week period of clinical improvement, the patient developed a high-grade fever up to 39°C. On examination, cervical lymphadenopathy, hepatosplenomegaly, and features of lacunar tonsillitis were noted. Laboratory investigations revealed markedly elevated inflammatory markers, moderate leukocytosis with lymphocytosis, the presence of activated lymphocytes, and increased levels of LDH, ferritin, D-dimer, and aminotransferases. Serological testing confirmed concurrent SARS-CoV-2 and EBV infection, whereas rapid antigen testing for SARS-CoV-2 and blood

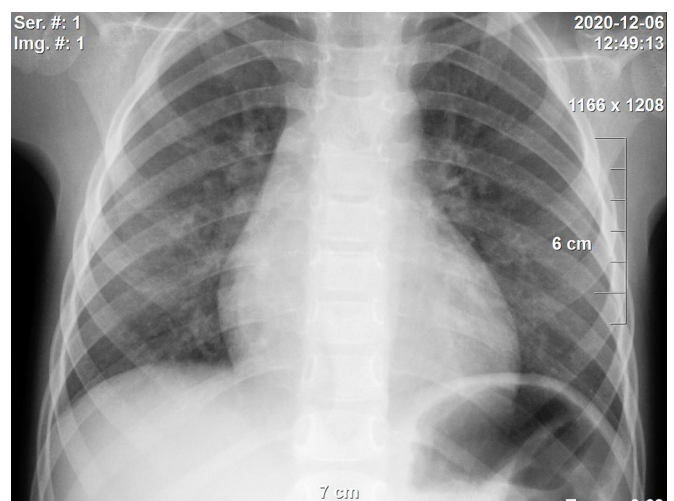
cultures were negative (Table 1). Chest radiography was unremarkable. Abdominal ultrasonography confirmed hepatosplenomegaly, and echocardiography detected a small reactive pericardial effusion with preserved ventricular function.

#### RESULTS:

Laboratory evaluation revealed elevated inflammatory markers and a fivefold increase in D-dimer above the reference range. Serological testing confirmed dual infection with SARS-CoV-2 and EBV, while rapid antigen testing for SARS-CoV-2 and blood cultures for bacterial agent were negative (Table 1). Abdominal ultrasonography showed no pathological changes.

Therapeutic management included cefoperazone/sulbactam, ciprofloxacin, methylprednisolone, isoprinosine, and supportive symptomatic treatment. Defervescence occurred on day six of hospitalization. Follow-up chest radiography revealed improvement of the infiltrative changes, with residual interstitial involvement paracardially, more pronounced in the right interlobar region (Fig. 2). The patient was discharged after 13 days with normalized inflammatory parameters and favorable D-dimer trends, demonstrating a good clinical recovery.

**Fig. 2.** Follow-up chest X-ray of the same 5-year-old female child after treatment



Therapeutic management included clarithromycin, methylprednisolone, ibuprofen, and hepatoprotective therapy with Silimarine. Fever persisted for 13 days, followed by gradual normalization of aminotransferases, inflammatory markers, and D-dimer. For both patients, treatment comprised antibiotic therapy, short-term immunomodulation with methylprednisolone, and supportive symptomatic care, leading to favorable clinical outcomes. At the three-month follow-up, both children were asymptomatic, with laboratory parameters within normal ranges.

**Table 1.** Laboratory evaluation

Laboratory tests	Case 1: 5-year-old female	Case 2: 15-year-old male	Cut-off value
Hemoglobin, Hb (g/L)	108 g/L	140 g/L	110-135 g/L
Leucocytes, Leuc (G/L)	9,0 G/L	18,2 G/L	3.5-10.5 G/L
Platelet Count, PLT	231 G/L	160 G/L	140-440 G/L
St %	7 %	7 %	0-6%
Sg %	65 %	20 %	48-60%
Lymphocytes, Ly (%)	27 %	66 % - some of the Ly are activated	20-40%
Monocytes, Mo (%)	1%	7%	9-13%
CRP (mg/dL)	89,4 mg/dL	30,1 mg/dL	0-6 mg/dL
ALAT (U/L)	20 U/L	603 U/L	1-48 U/L
ASAT (U/L)	26 U/L	311 U/L	1-45 U/L
GGTP (U/L)	NA*	484 U/L	1-55 U/L
LDH (U/L)	225 U/L	538 U/L	1- 248 U/L
Creatin kinase CK (U/L)	NA	52 U/L	1-240 U/L
KK – MB	NA	17 U/L	<24 U/L
Troponin (ng/mL)	NA	< 0.20	0.20 (ng/mL)
D-dimer (mg/l)	2,66 mg/L	< 0,5 mg/L	< 0,55 mg/L
Feritin (ng/ml)	202 ng/mL	< 70 ng/mL	13-150 ng/mL
Anti SARS Cov-2 IgM	positive	positive	Immunochromato- graphic method
Anti SARS Cov-2 IgG	6.92 U/L ECLIA**	7.03 U/L ECLIA**	0,8 BAU/ml
EBV VCA Ig M	0,63 U/L	0.12 U/L	<0,12 U/L
EBV VCA Ig G	0,22 U/L	4.21 U/L	<0,21 U/L

\*NA - Not Available, \*\*ECLIA - Electrochemiluminescence immunoassay

#### DISCUSSION:

Children constitute approximately 1–5 % of confirmed COVID-19 cases, with no clear age or sex predilection. The mean reported age of infection in the pediatric population is 6.7 years [8]. Most childhood cases are characterized by a mild clinical course, requiring only symptomatic and supportive care; hospitalization is infrequent, and mortality remains exceptionally low (< 0.1%) [4, 9]. Several hypotheses have been proposed to explain the generally milder disease in children, including age-related differences in innate and adaptive immune responses, lower expression of angiotensin-converting enzyme 2 (ACE2) receptors in the lower respiratory tract, and the immunomodulatory influence of concurrent viral colonization of the nasopharynx [7, 10]. Children typically exhibit higher levels of broadly reactive IgM and increased anti-inflammatory cytokine (IL-10) secretion by B-lymphocytes. In contrast, adults may demonstrate reduced T-cell competency associated with chronic antigenic ex-

posure and thymic involution. Additionally, children rarely have comorbidities and possess greater pulmonary regenerative capacity [11].

The most frequent clinical manifestations of COVID-19 in children include fever (50 %) and mild cough (38 %), followed by sore throat, rhinorrhoea, myalgia, and fatigue. Gastrointestinal symptoms, such as diarrhoea and vomiting, may appear early in the disease course, likely due to ACE2 expression in intestinal epithelial cells [3, 7, 11, 12]. A considerable proportion of pediatric patients present with concomitant respiratory infections. In a retrospective cohort of 101 hospitalized children with COVID-19 in Wuhan, 81 exhibited coinfection, most often with *Mycoplasma pneumoniae* and Influenza A/B, and less commonly with RSV, adenovirus, parainfluenza virus, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* [13].

Epstein–Barr virus (EBV) infection is highly prevalent, with seropositivity approaching 90% in adults. While primary infection in immunocompetent individuals is fre-

quently asymptomatic, EBV may reactivate under immunological stress and can be clinically significant in immunocompromised patients. Because EBV infection shares multiple clinical features with COVID-19, including fever, fatigue, myalgia, anorexia, and pharyngitis, coinfection may complicate diagnosis. In a study from Wuhan, 55.2 % of adult COVID-19 patients tested positive for EBV VCA IgM, and these individuals exhibited significantly higher body temperature, CRP, and transaminase levels [14, 15, 16].

In the patients analyzed here, SARS-CoV-2 and EBV coinfection was confirmed serologically. In the first case, radiographic evidence of pneumonia, household viral exposure, and an atypical febrile profile supported dual testing, with positive SARS-CoV-2 Ig M and IgG and EBV VCA IgM. In the second case, clinical improvement after initial SARS-CoV-2 infection was followed by the onset of infectious mononucleosis with hepatitis during convalescence, with high titres of SARS-CoV-2 IgG and EBV VCA IgG. Laboratory abnormalities included elevated CRP, D-dimer, and ferritin, findings consistent with published reports [17, 18].

The second patient was evaluated for possible multisystem inflammatory syndrome in children (MIS-C), given hepatic involvement and pericardial effusion. However, the patient did not fulfill CDC diagnostic criteria for MIS-C, and the clinical picture was instead attributed to EBV infection. This aligns with multicentre data in which EBV reactivation is detected in only a minority of MIS-C cases [19].

Recent studies indicate that active EBV markers are detected significantly more frequently in hospitalized

COVID-19 patients than in controls, and EBV may potentiate interstitial lung involvement and systemic inflammation. Coincident infectious mononucleosis has been increasingly reported in adolescents and adults with SARS-CoV-2 infection, and SARS-CoV-2 itself may act as a trigger for EBV reactivation [19, 20].

Although paediatric COVID-19 generally maintains a favourable prognosis, EBV coinfection may contribute to greater inflammatory burden, hepatic dysfunction, and, in rare cases, multisystem involvement [14, 15, 16]. Therefore, extended serological evaluation for concomitant infections, including EBV, should be considered in children presenting with atypical, prolonged, or severe manifestations of COVID-19.

#### CONCLUSION:

Coinfection with SARS-CoV-2 and EBV, while rare, may complicate the clinical course in children and contribute to systemic inflammation. Comprehensive diagnostic assessment and timely intervention are essential to ensure favorable outcomes. Awareness of such coinfection is crucial for pediatricians managing COVID-19 during the pandemic and beyond.

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