

Case in Point

Epstein-Barr Virus–Induced Adrenal Insufficiency, Cardiac Tamponade, and Pleural Effusions

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Despite the typically mild, benign course of primary Epstein-Barr virus, clinicians must consider the possibility of more serious presentations, especially in the elderly and those patients who have complicated chronic illnesses.

The Epstein-Barr virus (EBV) is a common herpesvirus that infects humans worldwide and typically causes a syndrome known as infectious mononucleosis (IM). According to the CDC,¹ up to 95% of adults in the United States are infected with EBV by 35 to 40 years of age. Many healthy people become asymptomatic carriers and are the primary reservoirs for human-to-human transmission. Classic symptoms of IM are fever, pharyngitis, malaise, fatigue, and tender cervical lymphadenopathy (and in some cases, the spleen and liver become involved). Symptoms are usually self-limited and seldom fatal.

In this article, we report the rare case of a generally healthy patient with an acute EBV infection that caused adrenal insufficiency, cardiac tamponade, and nearly fatal pleural effusions requiring intensive manage-

ment. Despite the typically mild, benign course of primary EBV illness, clinicians must seriously consider the diagnosis in unexplained, severe clinical presentations with rare cardiopulmonary complications, such as pericardial and pleural effusions. Risk factors for such severe presentations include being elderly and having complicated chronic illnesses at time of disease onset. Diagnosis can often be made with monospot testing, but heterophil, antibody–negative IM is not unusual. In such a case, diagnosis can be confirmed by EBV titers or polymerase chain reaction (PCR) testing for EBV DNA sequences in pleural and pericardial fluid. Such a quick diagnosis can make other expensive tests and procedures unnecessary.

CASE PRESENTATION

Initial presentation and history

A 74-year-old white man presented with a 2-week history of pharyngitis, diffuse weakness, fatigue, malaise, and shortness of breath that initially developed with strenuous activity but was occurring at rest by the time of admission. For several weeks, he

had concomitant dry cough, pleuritic chest pain, and intermittent chills and fevers. The fevers spiked to 102°F 1 week before admission. The patient further noted severe tenderness of chronically enlarged cervical lymph nodes but no increase in size. He had no night sweats, hemoptysis, weight loss, palpitations, nausea, vomiting, or abdominal pain.

Medical history was significant for non–insulin-dependent type 2 diabetes mellitus, and chronic anterior cervical lymphadenopathies and buccal mucosal lesion. Subsequent biopsy revealed reactive lymph nodes and moderate squamous mucosa dysplasia, respectively. There was no history of cardiac or lung disease, tuberculosis exposure, solid tumors, or hematologic malignancies.

On physical examination, the healthy-appearing patient was in moderate respiratory distress (increased respiratory rate, use of intercostal accessory muscles) but afebrile, normotensive, and nonhypoxic. Oral mucosa was clear, with no pharyngeal hyperemia or tonsillar exudates. Four tender anterior cervical lymph nodes (the largest, 2×2 cm) were palpable.

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On lung auscultation, scattered expiratory wheezes and decreased breath sounds were noted at both lung bases, along with dullness to percussion at the bases. Cardiac examination was unremarkable for murmur, rub, gallop, or jugular venous distention. There was 3+ pitting pedal edema bilaterally. The rest of the physical examination was unremarkable and included no hepatosplenomegaly and no other lymphadenopathy.

tory deterioration. He was transferred to the medical intensive care unit (MICU) for artificial ventilation for respiratory failure and administration of vasopressors for hemodynamic support.

In the MICU, repeat chest CT showed larger bilateral pleural and pericardial effusions. The patient underwent thoracentesis, which revealed an exudative effusion with normal lactate dehydrogenase en-

radiograph and 2-D echocardiogram showed resolution of the pleural effusion and pericardial effusion, respectively.

Meanwhile, the EBV antibody titers obtained on admission came back with a high viral capsid antigen (VCA) immunoglobulin M (IgM) antibody titer of 1:2560; an early antibody titer of 1:40; and an EBV nuclear antigen (EBNA) antibody titer of under 1:5. All were diagnostic of current or recent infection. EBV serology repeated 2 weeks later showed lower VCA IgM antibody titer (1:1280); lower early antibody titer (1:20); and higher EBNA antibody titer (> 1.5). All indicated chronic infection.

Except for the confirmatory EBV titers, the extensive workup was negative. This included multiple laboratory serologies, full-body CT scans, lymph node pathology, and culture and cytopathology of pleural and pericardial effusions. The patient was successfully extubated a week later and subsequently discharged to a skilled nursing facility for aggressive rehabilitation.

DISCUSSION

EBV-induced IM most commonly appears in children and adolescents through a benign, self-limited presentation of fever, pharyngitis, and lymphadenopathy. Most adults older than 40 years have already been exposed to EBV and are immune to reinfection. However, older adults who contract IM can develop debilitating symptoms: high fevers, diffuse weakness, malaise, and fatigue with little or no pharyngitis, lymphadenopathy, or hepatosplenomegaly. Other associated severe conditions are rare. These include respiratory involvement, such as pneumonia and pleural effusions; neurologic involvement, such as Guillain-Barré syndrome; and liver involvement, such as acute hepatitis

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Hospital course

Laboratory results on admission revealed normocytic anemia and severe euvolemic hyponatremia (sodium, 114 mEq/L). Other extensive blood work demonstrated negative cardiac, rheumatologic, and infectious serologies, including monospot, liver function, and white blood cell count, except for 38% atypical lymphocytosis. The workup for euvolemic hyponatremia led to the diagnosis of syndrome of inappropriate antidiuretic hormone secretion. Given the high suspicion for malignancy, full-body computed tomography (CT) was performed. It was negative for discrete masses or lymphadenopathies, except for stable anterior cervical lymphadenopathies. Chest CT was negative for pulmonary embolism and infiltrates, but showed large bilateral pleural effusions and a small pericardial effusion. Two-dimensional echocardiogram (2-D echocardiogram) was normal, except for a small, hemodynamically insignificant pericardial effusion.

Within 24 hours of admission, however, the patient became obtunded and hypotensive with respira-

zyme. Cytopathology of pleural fluid showed reactive acute and chronic inflammatory cells with reactive mesothelial cells. Acid-fast bacteria, fungal, and bacterial cultures of the pleural effusion were negative. Repeat 2-D echocardiogram showed a very large pericardial effusion with pandiastolic moderate collapse of the right ventricle wall and atrial fibrillation with a rapid ventricular rate.

With impending cardiac tamponade, our cardiology consultant performed an emergent pericardiocentesis, which also revealed an exudative effusion with normal lactate dehydrogenase enzyme. Again, cytopathology of pericardial fluid showed reactive cells and negative acid-fast bacteria, fungal, and bacterial cultures.

Given the strong concern for malignancy, our general surgery consultant performed an excisional biopsy of the largest cervical lymphadenopathy which revealed benign pathology. Suspected adrenal insufficiency was confirmed by cosyntropin stimulation test. Administration of stress dose steroids resulted in normalization of blood pressure and serum sodium within 24 hours. Bedside chest

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and ascites.²⁻⁴ Diagnosis is typically based on clinical presentation and positive heterophil antibody, and confirmed with EBV titers. Active EBV infection is confirmed with IgM antibody to VCA and concurrent absence of antibody to EBNA.¹ This serology held true for our patient. In addition, 80% of patients with active EBV infection can produce antibody to early antigen. Over 4 weeks of illness, increasing or high IgG antibody to VCA and negative antibody to EBNA are also indicative of primary EBV infection.

Our older patient initially presented with the classic IM triad of fever, pharyngitis, and lymphadenopathy, but the diagnosis was clouded by atypical laboratory values and rare complications (adrenal insufficiency, cardiac tamponade, pleural effusions). As a result, multiple and extensive invasive diagnostic tests were performed.

Further obscuring the diagnosis was the lack of positive heterophil antibody, though subsequent EBV titers were confirmatory. Such a diagnostic dilemma was also reported by Horwitz and colleagues,⁴ who analyzed data on 27 adults, ages 40 to 72, with evidence of EBV primary infection, in addition to concurrent clinical findings of protracted fevers, jaundice, pleural effusion, or Guillain-Barré syndrome.

There were diagnostic difficulties with these patients because of their advanced age, extended febrile course, nonspecific symptoms, and atypical presentation, as also demonstrated in our patient. Fifteen patients underwent extensive inpatient diagnostic procedures, including bone marrow aspiration (8 patients), abdominal CT scan (4), liver biopsy (2), and lymph node biopsy (1). In general, the laboratory values for these older adults were similar to those for children and adolescents,

with the exception of more severe hepatic dysfunction and higher antibody responses to the restricted component of the early antigen complex. In 3 patients, what made the diagnosis particularly problematic was the lack of a heterophil antibody response. Yet, heterophil antibody-negative IM is not unusual. In up to 22% of patients with a clinical presentation of IM, the monospot test result can be negative; EBV and cytomegalovirus are the culprit organisms in most of these cases.^{5,6}

Although EBV seldom causes disease in immunocompetent individuals, it can potentially infect almost any organ and lead to rare multiorgan

Secondary immunologic responses are thought to play a significant role in these complicated cases.^{8,9}

Only 5% of cases are severe enough to require hospitalization, and only 100 deaths were registered in the United States between 1970 and 1980.¹⁰⁻¹² Most fatalities occur secondary to acute fulminant hepatitis, hemophagocytic syndrome, or splenic rupture.¹³⁻¹⁸

Cases of pulmonary involvement in IM fall into 1 of 3 general categories: chest radiographic abnormalities in patients without respiratory symptoms,¹⁹ lung histopathology on the autopsy of patients who died of nonrespiratory causes,²⁰ and primary

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complications, such as Guillain-Barré syndrome, myocarditis, liver failure, and Hodgkin lymphoma. Risk factors for such severe presentations include being elderly and having complicated chronic illnesses at the time of disease onset. According to our review of the literature, the type of IM complications most often observed and discussed (though still quite rare) are pulmonary complications, including pneumonias, pneumonitis, and pleural effusions. We did not find any case reports of EBV-induced pericardial effusions leading to cardiac tamponade, which our patient had. In addition, we found only 1 case in which EBV caused adrenal insufficiency.⁷

In this case, the 10-year-old male patient, unlike our immunocompetent patient, had Wiskott-Aldrich syndrome and developed adrenocortical insufficiency from acute IM, diagnosed clinically and serologically.

symptoms that were pulmonary in nature,^{5,19,21} as was the case with our patient. Mild respiratory symptoms can accompany IM, but severe symptomatic pulmonary manifestations of IM are uncommon in immunocompetent individuals, with only a few cases having been reported.^{5,19,21-24}

Haller and colleagues¹⁹ analyzed the literature reports of 12 immunocompetent patients (ages, < 1 month to 48 years) with acute EBV infection and concurrent symptomatic pulmonary involvement. Of the 5 patients who had severe hypoxemia, 2 required mechanical ventilation, 1 died of respiratory failure caused by acute respiratory distress syndrome, and 2 survived with supportive management. Chest radiographic findings in these 12 patients ranged from diffuse interstitial infiltrates to pleural effusions, either unilateral or bilateral.

The prevalence of EBV in pleural

effusions is unknown. EBV infection has been discovered in pleural effusions secondary to B-cell lymphoma, which has been linked to human herpesvirus.^{20,25} However, the role of EBV in the pathogenesis of nonmalignant pleural effusions has not been well studied. Thijsen and colleagues²⁶ conducted a prospective study with 60 patients to determine the prevalence and clinical relevance of EBV in pleu-

the serial decline in antiviral capsid antibodies with improvement in his clinical presentation, confirmed the diagnosis of primary EBV infection.

Furthermore, the initial absence of anti-EBV nuclear antigen titers and the subsequent conversion of this antibody from negative to positive further supported the diagnosis. The negative bacterial cultures, serologic tests, lymph node pathology, and cy-

adrenal insufficiency. These steroids were not intended as supportive therapy for his other rare secondary complications but may have provided some symptomatic benefit. There was no evidence that our patient had an underlying immunodeficiency that predisposed him to such a severe and protracted course of primary EBV infection with its rare complications.

This case provides 4 key teaching points. (1) Despite its typically benign and self-limited course, primary EBV infection has been implicated in severe and protracted clinical presentations with multiorgan complications, including pleural effusions and cardiac tamponade. (2) Clinicians must be cognizant of these rare complications, and of the diagnostic dilemma they can produce, especially in patients of advanced age, patients with atypical presentations, and patients with multiple chronic illnesses. (3) Monospot testing is usually instrumental in diagnosis, but acute monospot-negative EBV illnesses are possible. EBV titers or PCR testing of any exudative fluid for EBV DNA sequences should be strongly considered for early diagnosis in such cases. (4) Clinicians' increased awareness of atypical EBV manifestations can expedite diagnosis and thereby obviate the need for expensive tests and delay further morbidity and mortality. ●

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ral effusions. A relatively high percentage (40%) of pleural fluids tested positive for EBV DNA by real-time PCR testing of the pleural effusions, and this percentage increased to 59% in patients with unexplained pleural effusions. Furthermore, all patients with an extremely high EBV viral load in pleural fluid (> 10,000 gEq/mL) died within 6 months of illness onset.

These findings support using quantitative PCR testing of EBV DNA sequences in patients with explained and unexplained pleural effusions to determine the clinical relevance of EBV viral load in pleural fluid. Unfortunately, our patient's pleural effusions were never tested by PCR for EBV DNA sequences. We now wonder if, had this testing been done early in his hospitalization, it would have spared him further invasive and expensive diagnostic testing. We also cannot ignore the likelihood of a quicker diagnosis with the use of PCR testing for EBV DNA sequences in the pericardial fluid and the lymph node tissues. Nonetheless, the patient's initial high titers of IgM antibodies to EBV VCA, accompanied by

topathology of pleural and pericardial effusions made other infectious and noninfectious causes, such as malignancy, unlikely.

Other than supportive therapy for symptoms, there is no specific treatment for primary EBV infection. There are no antiviral medications or vaccines for this infection. Use of systemic corticosteroids remains controversial. Clinicians often provide a short course of steroids to control inflammation and swelling of the pharynx and tonsils. As anecdotally reported, use of systemic steroids has reduced the severity and duration of the illness, but there are no supporting published data. In controlled studies of benign, uncomplicated cases of IM, Collins and colleagues²⁷ found no significant clinical benefit. On the other hand, steroids are usually recommended for severe, complicated cases caused by secondary immunologic responses, such as hemolytic anemia, myocarditis, and encephalitis.¹⁹

Our patient responded well to high-dose systemic steroids for the specific management of subsequent

formation for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

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