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Infectious Mononucleosis Causing Severe Neutropenia: A Case Report

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Introduction: Mild, transient neutropenia during the initial phase of acute infectious mononucleosis is a common hematologic manifestation; however, severe neutropenia or agranulocytosis is a rare complication that may occur up to six weeks after symptom onset. We present a case of a young man with infectious mononucleosis and severe neutropenia.

Case Report: A 22-year-old man presented to the emergency department and was diagnosed with infectious mononucleosis. This diagnosis was confirmed by a heterophile antibody test and Epstein-Barr virus positive titers. A complete blood count (CBC) demonstrated an absolute neutrophil count of 0.1 x 10^9/L (reference range, 1.8-7.8 x 10^9/L). The patient was admitted to the hospital, and exhaustive testing for alternative etiologies was unremarkable. The patient's CBC normalized 10 days after the diagnosis.

Conclusion: This case highlights a critical, rarely encountered complication of infectious mononucleosis that emergency physicians should consider during clinical evaluation. [Clin Pract Cases Emerg Med. 2026;X(X):XXX–XXX.]

Keywords: *Epstein-Barr virus; infectious mononucleosis; severe neutropenia; agranulocytosis; case report.*

INTRODUCTION

Infectious mononucleosis (IM) is a common lymphoproliferative disease caused by Epstein-Barr virus (EBV), predominantly affecting adolescents and young adults.[1] Epstein-Barr virus is spread via salivary secretions, but it can also spread via respiratory droplets, blood, or organ transplant.[2] The disease classically presents with fever, pharyngitis, lymphadenopathy, and fatigue in over 50% of cases, although its clinical manifestations can vary widely, with hepatomegaly, splenomegaly, and palatal petechiae occurring less frequently.[2]

Hematological manifestations of IM are common with lymphocytosis being the most typical finding. Less common hematologic complications include transient cytopenias such as thrombocytopenia, hemolytic anemia, and neutropenia. Rarely, severe complications such as aplastic anemia and disseminated intravascular coagulation may also occur.[3] Mild, transient neutropenia with a left shift is a common finding during the first three to four weeks of illness.[4] However, severe, potentially life-threatening neutropenia (absolute neutrophil count $< 0.5 \times 10^9$/L) and agranulocytosis ($< 0.2 \times 10^9$/L) are very rare complications with as few as 20 cases reported in the literature.[5]

This case report describes a patient with acute IM complicated by severe neutropenia.

CASE REPORT

A 22-year-old male college student without significant medical history presented to the emergency department (ED) with a two-day history of acute fever, chills, sore throat, fatigue, and neck stiffness. He also endorsed a transient episode of confusion and hallucinations, during which he believed he was in Russia and Ukraine. He was not prescribed medications, and his only substance use was chewing tobacco. He denied injection drug use. He also denied recent travel or sick contacts. On physical exam, the patient appeared ill but was alert and

fully oriented. Vital signs included the following: blood pressure, 146/84 mm Hg; temperature, 100.3 °C; heart rate, 76 beats/min; respiratory rate, 19 breaths/min; and SpO_2, 100% on room air. He had pharyngeal erythema, bilateral tonsillar enlargement with white exudates, and tender anterior cervical lymphadenopathy. No meningismus, splenomegaly, or rash was present. His neurological exam was unremarkable. Diagnostic evaluation included a monospot test and a respiratory panel for COVID-19, influenza, and respiratory syncytial virus (Table 1). A rapid streptococcal test was ordered but never performed. Electrocardiography and chest radiography were unremarkable.

In the ED, the patient was treated supportively with antipyretics and intravenous (IV) isotonic fluids. Intravenous dexamethasone (8 mg) was administered for symptomatic relief of pharyngitis. Despite initial stabilization measures, the patient remained intermittently tachycardic and diaphoretic. Due to new-onset severe neutropenia and a history of fever, blood cultures were ordered, and empiric broad-spectrum antimicrobial therapy was initiated (cefepime 1 g IV every 6 hours and vancomycin 1.25 g IV every 12 hours).

Given the patient's symptoms of neck stiffness (despite no meningismus), diaphoresis, and a transient episode of confusion, meningitis or encephalitis was considered. A lumbar puncture (LP) was performed, and magnetic resonance imaging (MRI) of the brain and neck soft tissues were obtained. Following the LP, acyclovir (800 mg IV) was administered. He was admitted for management of severe neutropenia and consultation with infectious diseases.

In the hospital, the patient underwent additional testing, and the cerebrospinal fluid analysis was unremarkable (Table 2). Brain MRI was normal. Neck soft-tissue MRI showed bilateral enlargement of the jugulodigastric lymph nodes, compatible with IM.

Based on recommendations from the infectious diseases service, IV acyclovir, cefepime, and vancomycin were discontinued on hospital day 2. The patient's fever, sore throat, and fatigue were managed conservatively. By day 3, the patient demonstrated both clinical and laboratory improvement, and he was discharged home with activity restrictions and close outpatient follow-up with his primary care physician (PCP).

The patient followed up with his PCP one week after hospital discharge, and a repeat complete blood count was ordered. The patient achieved complete clinical and hematologic recovery, and no secondary infections were identified (Table 3).

CPC-EM Capsule

What do we already know about this clinical entity?
Infectious mononucleosis (IM) is a common lymphoproliferative disease caused by Epstein-Barr virus.

What makes this presentation of disease reportable?
Severe neutropenia developed as a rare complication of acute infectious mononucleosis.

What is the major learning point?
Most cases occur during the third to fourth week of illness. Management of infection-related neutropenia is primarily supportive.

How might this improve emergency medicine practice?
Emergency physicians should recognize severe neutropenia as an IM complication, particularly when patients present with persistent fever or new symptoms.

DISCUSSION

The differential for neutropenia includes malignancy (leukemia), autoimmune disorders (systemic lupus erythematosus), medication adverse effects (clozapine), nutritional deficiencies (cobalamin deficiency), or severe infection (disseminated tuberculosis). The case illustrates severe neutropenia as a rare but important complication of IM. Mild transient neutropenia commonly occurs within the first three to four weeks of illness; however, progression to severe neutropenia and agranulocytosis is rare. Most cases of severe neutropenia occur during the third to fourth week of illness and last approximately one week.[4,5] Massoll et al reported a case of agranulocytosis occurring 26 days after IM diagnosis with rapid spontaneous resolution.[6] Stevens et al conducted a review identifying 18 reported cases of severe granulocytopenia as a complication of IM, noting that bone marrow examination most commonly reveals a paucity of mature neutrophil precursors, and most patients recover without any specific intervention or treatment.[5]

The pathogenesis of EBV-associated severe neutropenia involves multiple mechanisms. Larochelle et al demonstrated that EBV can directly infect human neutrophils and induce apoptosis via the Fas–Fas ligand pathway, with 77% of neutrophils undergoing apoptosis within 20 hours of in vitro exposure to EBV.[7] Apoptosis can be prevented by administration of granulocyte-macrophage colony-stimulating factor (GM-CSF).[7] The EBV genome has been detected in neutrophils of IM patients but not in those of healthy EBV-seropositive donors, supporting a direct viral effect.[7] Additionally, antibody-mediated mechanisms have been implicated. Stevens et al demonstrated opsonic antineutrophil activity in a patient with IM-associated severe neutropenia.[5] Savard and Gosselin reviewed the broader immunosuppressive effects of EBV on phagocyte-mediated innate immunity, noting that the neutropenia and monocytopenia during acute EBV infection may temporarily compromise immune defense.[8] Carter's early work suggested that excessive peripheral destruction, rather than impaired bone marrow production, is the primary mechanism, as maturation and release

Table 1. Diagnostic blood tests collected at the time of initial admission at the emergency department in a patient diagnosed with infectious mononucleosis.

Test	Value	Reference range
Complete blood count with differential count;		
Hemoglobin	14.3 g/dL	12.0-17.0 g/dL
Hematocrit	41.7%	36.5-49.3%
White blood cells	**3.1 x 10^9/L**	4.0-10.5 x 10^9/L
Platelet count	165 x 10^9/L	140-350 x 10^9/L
Absolute neutrophil count	**0.1 x 10^9/L**	1.8-7.8 x 10^9/L
Absolute lymphocytes	2.0 x 10^9/L	1.0-3.0 x 10^9/L
Absolute monocytes	0.9 x 10^9/L	0.3-1.0 x 10^9/L
Reactive lymphocytes	**3%**	0%
Erythrocyte sedimentation rate	**19 mm/hr**	0-15 mm/hr
C-reactive protein	95.9 mg/L	<10.0 mg/L
Comprehensive metabolic profile;		
Creatinine	1.27 mg/dL	0.53-1.30 mg/dL
Blood urea nitrogen	16 mg/dL	7-28 mg/dL
Sodium	**134 mmol/L**	135-145 mmol/L
Potassium	4.8 mmol/L	3.5-5.2 mmol/L
Chloride	**99 mmol/L**	100-109 mmol/L
Carbon dioxide	24 mmol/L	21-31 mmol/L
Anion gap	11	3-11
Heterophile antibody test/ monospot test with Epstein-Barr virus reflex	**Positive**	
Influenza A PCR nasal swab	Not detected	Influenza A PCR nasal swab
Influenza B PCR nasal swab	Not detected	Influenza B PCR nasal swab
Respiratory syncytial virus, nasal swab	Not detected	Respiratory syncytial virus, nasal swab

*Abnormal values are shown in bold.
dL, deciliter; *g*, gram; *hr*, hour; *L*, liter; *mg*, milligram; *mm*, millimeter; *mmol*, millimole; *PCR*, polymerase chain reaction.

Table 2: Additional laboratory testing during hospitalization in a patient diagnosed with infectious mononucleosis.

Test	Value	Reference range
Peripheral blood smear	No blasts, atypical lymphocytes, band cells or immature cells detected	
Blood culture	No growth detected	
HIV 1/2 Ag/Ab	Non-reactive	
Hepatitis C virus Ab EIA screen	Non-reactive	
Lumbar puncture		
CSF appearance	clear	
CSF total nucleated cells	2	0-5 cells/mm^3
CSF Neutrophils	0%	0-2%
CSF lymphocytes	70%	63-99%
CSF monocytes	30%	3-37%
CSF RBC	2	0-5 cells/mm^3
CSF glucose	68 mg/dL	40-70 mg/dL
CSF protein	28 mg/dL	15-45 mg/dL
CSF culture	No growth detected	

Ab, antibody; *Ag*, antigen; *CSF*, cerebrospinal fluid; *dL*, deciliter; *EIA*, enzyme immunoassay; *HIV*, human immunodeficiency virus; *mg*, milligram; *mm^3*, cubic millimeter; *RBC*, red blood cell.

of leukocytes from the bone marrow appeared normal.[4]

The differential diagnosis of severe neutropenia in the setting of IM should include medication-induced (particularly if ampicillin or amoxicillin was administered), hemophagocytic lymphohistiocytosis (HLH), aplastic anemia and hematologic malignancy.[3,9] Epstein-Barr virus is recognized as a trigger of HLH, characterized by prolonged fever, hepatosplenomegaly, cytopenia, and elevated ferritin.[3] A bone marrow biopsy is warranted to exclude these diagnoses, particularly if cytopenias are prolonged or progressive.[9]

Management of infection-related neutropenia is primarily supportive.[9] The use of GM-CSF in this setting remains controversial; it may be considered when the absolute neutrophil count is less than 0.1 × 10^9/L. However, the evidence supporting its use in viral-associated neutropenia is limited.[9] Empiric broad-spectrum antibiotic therapy should be initiated promptly if the criteria for febrile neutropenia are met.[9] The prognosis is generally favorable, with most patients experiencing spontaneous recovery of neutrophil counts within approximately one week.[5]

CONCLUSION

Emergency physicians should be aware that severe neutropenia can occur due to infectious mononucleosis.

Table 3. Changes in absolute neutrophil count from initial emergency department evaluation, hospital day 3, and 10 days post-emergency department visit in a patient diagnosed with infectious mononucleosis.

Time and Location	Absolute Neutrophil Count
Initial ED	0.1 x 10^9/L
Hospital day 3	0.5 x 10^9/L
10 days post-ED visit	5.1 x 10^9/L

ED, emergency department; *L*, liter.

Moreover, recurrence or persistence of fever, or the development of new symptoms after the initial IM diagnosis, may signal severe neutropenia and should be investigated and treated accordingly.[6]

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