Cytomegalovirus Primary Infection in an Immunocompetent Female with Mononucleosis Features: A Review of Mononucleosis-Like Syndromes

Shohinee Sarma, MD MPH, Derek Little, MD, Tooba Ali, MBBS, Emily Jones, MD, Shariq Haider, MD FRCPC
DOI: 10.22374/cjgim.v13i3.258

Abstract
The clinical triad of fever, pharyngitis, and lymphadenopathy was first described in 1889 as "glandular fever" and later defined as infectious mononucleosis. We present a case report and review of mononucleosis-like syndromes in an immunocompetent patient. The review of common etiologies includes Epstein-Barr virus, acute human immunodeficiency virus, human herpesvirus 6, cytomegalovirus, and Toxoplasmosis gondii.

RESUME
La triade clinique de la fièvre, de la pharyngite et de la lymphadénopathie a été décrite pour la première fois en 1889 sous le nom de « fièvre glandulaire » et plus tard définie comme une mononucléose infectieuse. Nous présentons un rapport de cas et un examen des syndromes de type mononucléose chez un patient immunocompétent. L’examen des étiologies communes comprend le virus d’Epstein-Barr, le virus de l’immunodéficience humaine aiguë, l’herpès virus humain 6, le cytomegalovirus et la toxoplasmose gondii.

A 37-year-old, immunocompetent female was referred to the emergency department by her family physician with a three-week history of fever, pharyngitis, fatigue, night sweats, and abdominal pain. She was treated with a one-week course of clarithromycin without improvement by her family physician as an outpatient. The patient was otherwise healthy. Past medical history was significant for endometriosis and infertility. She was pursuing clomiphene citrate inductions.

She was afebrile in the emergency department. Vital signs demonstrated sinus tachycardia at 100 bpm, respiratory rate 18, oxygen saturation 98% on room air, blood pressure of 154/99 mmHg. Physical examination revealed hepatosplenomegaly, but no lymphadenopathy, rashes, or tender joints. The posterior pharynx was clear, and the remainder of her examination was unremarkable.

The patient was otherwise healthy. Past medical history was significant for endometriosis and infertility. She was pursuing clomiphene citrate inductions.

Previous laboratory investigations by her family physician noted lymphocytosis with smudge cells. However, investigations in hospital showed lymphocytosis (WBC 11.6×10^9/L and lymphocytes of 8.6×10^9/L) and a normal peripheral smear. An inpatient hematology consult excluded hematological malignancy. Computed tomography of the abdomen confirmed hepatosplenomegaly with no lymphadenopathy. Her CD4/CD8 ratio was 0.2 in keeping with a viral infection. Bacterial cultures were negative. Serology for hepatitis B and C were negative. Human immunodeficiency
ultrasonography showed resolving hepatosplenomegaly. Repeat quantitative CMV PCR samples were negative.

The clinical triad of fever, pharyngitis, and lymphadenopathy was first described in 1889 as “glandular fever” and later defined as infectious mononucleosis.1 A typical mononucleosis syndrome presents with acute febrile illness with more than 50% lymphocytes or monocytes, with at least 10% atypical lymphocytes.1 In an immunocompetent patient with mononucleosis-like symptoms, the differential diagnosis includes EBV, acute HIV, human herpesvirus 6 (HHV-6), cytomegalovirus CMV, Toxoplasmosis gondii and Group A beta-hemolytic streptococcus (GAS) (Table 1). We present a review of these etiologies and their clinical presentations.

Epstein-Barr Virus
EBV is a herpesvirus with a worldwide prevalence of 95% in adults.3 Primary infection often occurs in children ages one to five and manifests as a non-specific viral illness.3 It commonly develops in adolescents and young adults with a peak in the second and third decades of life.2,3 Patients present with fever, pharyngitis, posterior cervical lymphadenopathy (bilateral, tender, and non-fixed), and malaise. Other findings include hepatosplenomegaly, jaundice, and palatal petechiae.2,3

Investigations demonstrate a lymphocytosis with atypical lymphocytes and mildly elevated liver enzymes in 50% of cases.2 Diagnoses can be confirmed with a monospot heterophile antibody test or EBV-specific antibody testing. A positive monospot test is highly specific but can be falsely negative in 25% of patients within the first week of symptom onset, 5–10% in the second week, and 5% in the third week. Repeat testing or EBV-specific antibody testing is useful.2 IgG and IgM antibodies against viral capsid antigens and nuclear antigens are more specific.3

Treatment is supportive with adequate fluid intake, rest, and analgesia (non-steroidal anti-inflammatory drugs or acetaminophen). There is insufficient evidence to support the use of corticosteroids for symptom control. However, they may be considered for upper airway obstruction due to hypertrophy of lymphoid tissue, occurring in 1% of cases.3 There is no benefit to treatment with acyclovir or ranitidine.2 Other complications, although rare, include acute interstitial nephritis, autoimmune hemolytic anemia, myocarditis, cranial nerve palsies, encephalitis, meningitis, mononeuropathies, and thrombocytopenia.2 The risk of splenic rupture is 0.1% and contact sports should be avoided for a minimum of three to four weeks for those with associated splenomegaly.2

Cytomegalovirus
CMV is a member of the Herpesviridae family with a worldwide prevalence of 40–100% in adults. It is acquired early in life virus (HIV) testing was not done in the absence of risk factors and a normal percent CD4 count. Epstein-Barr virus (EBV) monospot test was negative. Quantitative polymerase virus (PCR) for cytomegalovirus (CMV) in blood samples was positive with a value of 965.25 units per mL using real-time PCR assay.

The patient was diagnosed with CMV viremia and treated with a two-week course of valganciclovir with resolution of symptoms. The decision to treat this patient was based on the persistence of symptoms over three weeks. Two-month follow-up revealed a healthy patient with a normal complete blood count. Hematology follow-up was arranged and outpatient abdominal

Table 1. Differential Diagnosis for Mononucleosis-like Illnesses

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Viral</th>
<th>Bacterial</th>
<th>Protozoal</th>
<th>Malignancy</th>
<th>Inflammatory</th>
<th>Medication reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>Human herpes virus-6</td>
<td>Group A Beta-hemolytic streptococcus pyogenes</td>
<td>Toxoplasmosis gondii</td>
<td>Non-Hodgkin lymphoma</td>
<td>Systemic lupus erythematosis</td>
<td>Carbamezepine</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>Adenovirus</td>
<td>Bartonella henselae</td>
<td>Malignancy</td>
<td>Hodgkin lymphoma</td>
<td>Sarcomiosis</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>Corynebacterium diphtheriae</td>
<td>Francisella tularensis</td>
<td>Inflammatory</td>
<td></td>
<td></td>
<td>Serum sickness hypersensitivity reaction</td>
</tr>
</tbody>
</table>
through congenital transmission. Primary CMV mononucleosis is uncommon in adults without close contact with children. Risk of transmission occurs with sexual contact or shedding in saliva, urine, or breast milk. CMV is associated with severe primary illness and reactivation in immunocompromized hosts including transplant recipients and HIV-positive patients. Common clinical presentations in the immunocompromized host include pneumonitis, hepatitis, uveitis, retinitis, colitis, encephalitis, and graft rejection. Primary CMV infection in immunocompetent hosts is relatively scant in the medical literature and is usually asymptomatic.

In 10% of immunocompetent cases, primary CMV infection presents as a mononucleosis syndrome. Symptoms common to both EBV and CMV include fever, malaise, sore throat, headache, and fatigue. However, CMV is less associated with tonsillitis, pharyngitis, and lymphadenopathy compared to EBV. Splenomegaly and lymphadenopathy occur less frequently in immunocompetent hosts. A 2008 systematic review of severe CMV disease in 290 immunocompetent patients revealed the gastrointestinal tract and central nervous system as the primary sites of infection. The prevalence of CMV pneumonia is as high as 50% in immunocompetent critically ill patients with ventilator-associated pneumonia or acute respiratory distress syndrome.

Diagnostic testing includes CMV IgM and IgG serology for acute infections and reactivation. Quantitative or qualitative PCR is the gold standard for diagnosis. Presence of owl’s eye viral inclusion bodies in histopathological specimens is highly specific. Treatment of immunocompetent patients has limited evidence. Antiviral drugs including ganciclovir, valganciclovir, and foscarnet (HHV-6A and HHV-6B) and ganciclovir (HHV-6B) can be used in children, immunocompromized patients or those with severe disease.

**Human Immunodeficiency Virus Type 1**

Acute infection with HIV virus type 1 (HIV-1) presents with a self-limiting mononucleosis-like syndrome lasting two to four weeks. Symptoms include fever, pharyngitis, myalgia, headache, rash, lymphadenopathy, oral and genital ulcerations, and gastrointestinal disorders. HIV is often a diagnosis that is missed in the acute phase. Approximately, 50% of HIV patients worldwide are diagnosed in later stages of disease with CD4+ T-cell counts less than 350 cells/mm³ or an AIDS-defining illness. Late detection decreases life expectancy, increases HIV transmission, and creates complexity in treatment and drug adherence.

A British retrospective study of 1045 patients with glandular fever reported that 72.7% of cases were missed at the initial outpatient consultation. Retrospective testing from 563 patients with negative EBV heterophile tests showed that 1.2% of patients actually had primary HIV-1 infection. Another recent cohort study demonstrated that missed opportunities for HIV diagnosis often occurred despite healthcare access. The majority of missed diagnoses occurred in primary care centres (60%) and in hospitalized settings including internal medicine, surgical, oncology, psychiatry, and dermatology departments. Qualitative data noted the primary reason for not testing was the perception that the patient did not have high risk factors. Late presentations included hematologic disorders, herpes zoster rash, severe unexplained dermatologic presentations, newly diagnosed Hepatitis B and C infection, unexplained weight loss, and infectious mononucleosis.

Nucleic acid testing for HIV RNA provides the earliest detectable evidence. In the early symptomatic stage, enzyme-linked immunosorbent assay (ELISA) testing can be negative, but HIV-1 RNA and plasma p24 antigen testing are used. Healthcare providers should perform ongoing risk factor assessments to allow for early diagnosis and antiretroviral treatment.

**Toxoplasmosis Gondii**

Toxoplasmosis gondii is an obligate intracellular protozoan parasite that infects birds and mammals. Acute infection occurs after transmission of the parasite by the fecal-oral route from contaminated cat feces, consumption of undercooked or raw meat containing tissue cysts, or transplacentally. Reactivation of latent infection occurs primarily in immunocompromized patients.
Acute infection in immunocompetent adults is largely asymptomatic with only 10% developing a self-limited and non-specific illness. Symptoms include malaise, fever, and cervical or occipital lymphadenopathy (tender or non-tender, discrete, and firm). Illness may also manifest with fever, pharyngitis, myalgia, and atypical lymphocytosis. Rare complications include chorioretinitis, myocarditis, polyserositis, hepatitis, pneumonitis and encephalitis. Reactivation in immunocompromized patients can be life-threatening and most commonly manifests as toxoplasmic encephalitis with altered level of consciousness, focal neurological deficits, seizures, and other neurological symptoms.

Diagnostic tests include serologic identification of anti-toxoplasmosis IgM and IgG antibodies. IgG levels appear after 1–2 weeks, peak at 6–8 weeks, and then decline to a baseline detectable level for life. IgM levels rise after acute infection and remain elevated for up to 18 months. Acute infection in immunocompetent adults rarely requires treatment. Severe symptoms can be treated with a combination of pyrimethamine, sulfadiazine, and folinic acid for 4–6 weeks.

**Group A Beta-Hemolytic Streptococcus**

GAS accounts for approximately 5–15% of infectious acute pharyngitis, predominantly in those under 15 years old. Recognition of this pathogen is of importance due to the risk of developing rheumatic fever if left untreated. However, rates of rheumatic fever after GAS pharyngitis are rare. According to the Infection Disease Society of America, GAS is the only cause of acute pharyngitis which should be treated with antibiotics.

Clinical presentation usually includes fever, sore throat, and odynophagia. Tonsillar exudates and tender cervical lymphadenopathy may occur. Unlike EBV, which involves the reticuloendothelial system, GAS typically lacks a systemic lymphocytosis or hepatosplenomegaly. There are multiple clinical prediction tools to diagnose GAS pharyngitis and guide appropriate antibiotic treatment. Unfortunately, they all lack specificity.

Current guidelines recommend all suspected cases have throat swabs performed for rapid antigen testing, unless they have clear viral symptoms of coryza or rhinorrhea. Positive rapid antigen testing does not require confirmation with bacterial culture, nor should negative rapid antigen tests be confirmed with bacterial culture. Treatment of confirmed cases is with penicillin or a cephalosporin for a 10-day course.

Non-group A streptococci can also cause acute pharyngitis with a clinical presentation similar to GAS. However there is little evidence to support treating these infections.

**Discussion**

In this case, the patient’s hepatosplenomegaly and previous laboratory investigations showing smudge cells raised the suspicion for a hematologic malignancy. However, a hematology consult in hospital did not show any evidence of smudge cells with repeat blood work and outpatient follow-up demonstrated resolving hepatosplenomegaly with valgancyclovir treatment.

In immunocompetent patients presenting with symptoms of mononucleosis, the differential diagnosis should include other possibilities that fit a mononucleosis-like syndrome. CMV commonly affects young patients and is less associated with tonsillitis, pharyngitis, and lymphadenopathy. HHV-6 can present with headaches, encephalitis, and abdominal pain. Consideration of acute HIV mononucleosis should prompt early serologic testing. Toxoplasmosis is often associated with undercooked food or cat excrement, requiring anti-IgM antibody testing to distinguish from EBV. Although EBV infectious mononucleosis may be suspected, the general practitioner should consider a complete review of other infectious etiologies.

**Competing Interests**

All authors declare that they have no competing interests.

**Funding**

There was no funding source for this case report.

**Contributors**

All authors contributed to the case presentation, literature review, and final draft. All authors were involved in the editing process and approve the version submitted for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Informed Consent**

Written informed consent was obtained from the patient described in the case report. A copy of the informed consent is available in the patient’s chart if requested. The patient was advised that their name and initials are not included in the manuscript and we will endeavour to conceal their identity.

**References**