Heterophile antibody positive, acute cytomegaloviral infection in an immunocompetent pre-teen: An atypical presentation of an atypical infection

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Received 21 May 2014; received in revised form 25 July 2014; accepted 24 August 2014

KEYWORDS
Acute CMV; Mononucleosis-like infection; Monospot test; Transaminitis of unknown etiology; Leukopenia of unknown etiology; Atypical viral infection in an immunocompetent individual

Summary
Mononucleosis and mononucleosis-like illnesses comprise a significant proportion of pediatric and adolescent infectious illnesses. By far, the most common cause of these illnesses is Epstein–Barr virus, which causes mononucleosis, and a distant second is cytomegalovirus, which is the most common cause of mononucleosis-like illnesses. This case provides an interesting juxtaposition of laboratory findings of an adolescent who was heterophile antibody positive but acute Epstein–Barr virus antigen–antibody negative. A subsequent immunologic assay resulted in a final diagnosis of an acute cytomegaloviral infection. This is, to our knowledge, the first such report in the literature.

Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) are fairly common infectious agents as illustrated by the high seropositivity of immunocompetent adults against both viruses [1,2]. The transmission of both viruses is usually through an exchange of oral or other bodily fluids, either by direct contact or through a fomite [1,2]. For most individuals, a sub-clinical acute course is expected; however, there is a significant proportion of individuals who suffer from more clinically apparent acute viral infections. Both infections, if symptomatic, may present similarly [1,3,4].

In general greater than 90% of patients suspected of having infectious mononucleosis (IM) or mononucleosis-like illness (MLI) have an acute EBV infection [3]. Most of these cases are supported by
confirmatory serology, and CMV is only suspected in the setting of a negative heterophile antibody test [3,4].

The case presented here is unusual with regard to the demographics of the patient, the relative absence of the most common symptoms of CMV MLI, and the conflicting laboratory results. To our knowledge, this is the first report of an Epstein–Barr virus naive, heterophile antibody positive, acute cytomegaloviral infection.

A 12-year-old Hispanic-American male was brought by his father to his pediatrician’s office with complaints of fatigue, night sweats, fever, and headache. The patient’s symptoms began approximately four days previously and were worse at night. The fever was quantified at home with a $T_{\text{max}}$ of 38.6°C, and the patients were treated with ibuprofen. The patient denied any changes in appetite, weight loss, coughing, nausea, vomiting, shortness of breath, or abdominal pain. No significant past medical history was noted. Aside from ibuprofen, no current medication use was noted. The patient had not traveled in the past six months.

The patient’s vital signs were within normal limits, and on physical exam, no abnormalities were noted. The physical exam included a visual inspection of the oropharynx, a fundoscopic examination to exclude increased intracranial pressure, tactile examination for lymphadenopathy, cardiopulmonary auscultation, abdominal palpation, and inspection for rashes.

A rapid Influenza A and B and a purified protein derivative test were ordered and performed in the clinic and found to be negative after 30 min and 72 h, respectively. In addition, a chest X-ray was performed that did not illustrate any acute cardiopulmonary abnormalities, opacifications, or granulomatous foci. Laboratory investigations (Quest Diagnostics, Miramar, FL) included a complete blood count, a comprehensive metabolic panel, a lipid profile panel, and a urinalysis. Significant abnormalities noted included a low white blood cell count of $2.9 \times 10^3 \mu$L with neutropenia (absolute neutrophil count of 777), relative lymphocytosis suggested by a differential of 51.5% lymphocytes and 26.8% neutrophils, and mild transaminitis with an alanine aminotransferase of 43 U/L and an aspartate aminotransferase of 43 U/L.

At this stage, our clinical experience with children with constitutional symptoms, leukopenia, relative lymphocytosis, and mild transaminitis led us to suspect the patient was infected with mononucleosis. Consequently, a heterophile antibody test and a confirmatory EBV antibodies test were ordered (Quest Diagnostics, Miramar, FL). The monospot test was found to be positive after repeat analysis; however, the EBV viral capsid antigen (VCA) Immunoglobulin M and Immunoglobulin G (IgG) as well as the EBNA IgG tests were all negative. This indicated either a false positive monospot or a false negative EBV antibodies test, which are both highly unusual.

Given the high specificity of the EBV antibodies test and the pursuant higher negative predictive value of the VCA and EBNA tests compared with the lower positive predictive value of the monospot test for the prediction of acute EBV, we chose to investigate the possibility that a virus had cross-reacted causing a false positive monospot in the setting of an MLI. Consequently, as the most common etiology of MLI is CMV, we performed anti-CMV serology testing. The IgG level of CMV was undetectable; however, the anti-CMV IgM was found to be 2.5 times the upper limit of normal at 2.7 U.

At this stage, the patient’s parents were contacted and counseled regarding the finding of an acute CMV infection causing a MLI. They were informed of the necessity of adequate hydration, administering non-steroidal anti-inflammatory medications for fever and body aches, and avoiding strenuous activities. They were also informed of the possible, but rare, complications of MLI. The patient subsequently improved and his symptoms resolved without further intervention.

Discussion

Infectious mononucleosis is a common viral syndrome that results from an acute EBV infection. In contrast, mononucleosis-like illnesses have etiologies ranging from viral, which is the most common, to bacterial and parasitic [3]. The classic presentation of patients with IM is malaise, headache, fever, non-purulent pharyngitis, and tonsillitis (though thick white exudate may be present) accompanied by cervical lymphadenopathy, most typically in the posterior chain. More rarely, other signs may also be noted, including rash, splenomegaly, and hepatomegaly [1,3,4]. Patients with MLI will typically have similar but milder symptomatology [1,3].

When IM or MLI is suspected, additional investigations include a CBC, which frequently shows lymphocytosis and/or atypical lymphocytes, liver function tests to diagnosis transaminitis, and the heterophile antibody (or monospot) test [1,3,4]. The monospot test is predicated on the fact that IgM antibodies in the serum are generated against glycoproteins on EBV infected cells (i.e., the Paul–Bunnell antigen) as well as (rarely) CMV.
infected cells and can cross-react with animal erythrocytes to cause agglutination [3,5]. The monospot test is 87% sensitive with a confidence interval (CI) of 79–95% and is 91% specific (CI 82–99%) for IM [4].

Confirmation of an EBV infection is generally obtained by the detection of antibodies to the VCA of EBV and by a positive EBV nuclear antigen (EBNA) test. These assays are even more sensitive (97%, CI 95–99%) and specific (94%, CI 89–99%) for IM than the monospot test [3,4]. During the course of IM, VCA IgM and IgG are produced before the heterophile antibody, which reaches its peak level two to five weeks after the initial infection. Thus, tests for the heterophile antibody are falsely negative in one-fourth of IM patients in the first week, making tests for VCA and EBNA more definitive for the diagnosis of acute EBV infection [3].

MLI is frequently considered when a clinical presentation is similar to IM with a negative heterophile antibody (or monospot) test and/or negative anti-EBV serology [4]. Moreover, 92% of MLI cases (versus just over 50% of acute EBV cases) are found to have transaminitis [1,3]. The demographic that most commonly presents with CMV MLI is women in their twenties [2].

In the setting of a CMV infection, it is possible to note anemia and thrombocytopenia on a CBC as well as cold agglutinins [1]. Anti-CMV serology, spin amplified urine culture for pp65 antigen detection, and/or CMV polymerase chain reaction (PCR) can be used to definitively detect the presence of an acute CMV infection [1,3,4].

In our case, a strongly positive anti-CMV IgM test result following a negative EBNA and VCA test result, even in the setting of a positive monospot test, was adequate to confirm our diagnosis of acute MLI and its CMV etiology. The negative EBNA and VCA results following a positive monospot test definitively excluded EBV as the etiological cause of the illness given EBNA and VCA would rise before a true positive monospot. This precluded the idea of IgM false positivity for CMV. However, this new serological profile raises questions for future research regarding possible cross-reactivity of anti-CMV IgM with the Paul–Bunnell antigenic glycoproteins.

Funding
No funding sources.

Competing interests
None declared.

Ethical approval
Not required.

References