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A young woman with fever, headache, and lymphadenopathy

A 33-YEAR-OLD Hispanic woman was admitted from the emergency department with a 5-day history of headache, fever, rash, and neck pain. Her symptoms started when she woke up with severe retro-orbital headache, photophobia, and a fever (temperature 40˚C, 104˚F). She was seen in an emergency department the following day, where a lumbar puncture and a computed tomography (CT) scan of the head were performed and were reportedly normal. The next day she noticed a generalized maculopapular rash and pain on the right side of her neck. On the 5th day, she was admitted through the emergency department because her symptoms persisted.

Her past medical history was significant for migraine headache, depression, and an abnormal Papanicolaou smear. She had undergone a cone biopsy of the cervix a few months earlier. She denied any history of sexually transmitted diseases and had had no sexual contact in the preceding 8 months. She had not traveled recently and had no history of intravenous drug use. She was a student who recently began a part-time job as a nurse assistant in a nursing home.

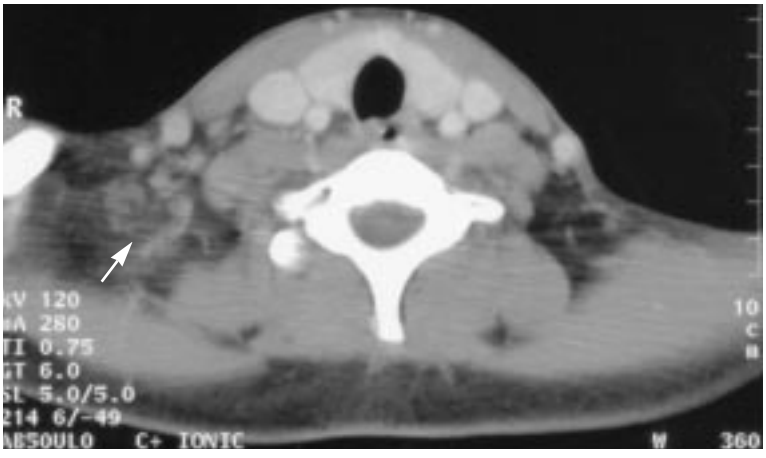

FIGURE 1. CT scan of the neck showing an increased number of lymph nodes with central necrosis in the right posterior triangle (arrow).

Physical examination

On admission, physical examination revealed an ill-appearing woman in mild acute distress. Her temperature was 37.2˚C (98.9˚F), blood pressure 113/66 mm Hg, heart rate 111 beats per minute, and respirations 20 per minute. A generalized maculopapular rash was present, and right-sided anterior and posterior cervical lymph nodes were large and tender on palpation. Smaller, tender left anterior cervical lymph nodes were also noted. There was no meningismus. The remainder of the physical examination was normal.

Additional testing

Additional test results were as follows:

- White blood cell count 2.02×10^9/L (normal range 4.0–11.0) with 70% granulocytes, 15% lymphocytes, 10% monocytes, 4% eosinophils, and occasional reactive lymphocytes
- Hemoglobin concentration 11.6 g/dL (normal range 12.0–16.0)
- Platelet count 105×10^9/L (normal range 150–400)
- Bone marrow biopsy revealed hypocellularity and no neoplastic cells
- Alkaline phosphatase 93 U/L (normal range 20–120)
- Aspartate aminotransferase 183 U/L (normal range 7–40)
- Total bilirubin 0.6 mg/dL (normal range 0–1.5).

TABLE 1

Differential diagnosis of infectious mononucleosis-like syndrome

Infectious causes

Viral
- Epstein-Barr virus
- Human immunodeficiency virus
- Cytomegalovirus
- Human herpesvirus 6

Bacterial
- Meningococcemia
- *Salmonella* bacteremia
- Streptococcal tonsillopharyngitis
- Bartonellosis (cat-scratch disease)
- Brucellosis
- Yersiniosis
- Tuberculosis
- Tularemia

Spirochetal
- Syphilis
- Leptospirosis
- Lyme disease

Parasitic
- Toxoplasmosis
- Malaria
- Trichinosis

Noninfectious causes

Rheumatic diseases
- Systemic lupus erythematosus
- Kawasaki syndrome
- Kikuchi disease
- Juvenile rheumatoid arthritis

Neoplastic and paraneoplastic diseases
- Lymphoma
- Angioimmunoblastic lymphadenopathy
- Castleman lymphadenopathy

Drugs
- Phenytoin
- Sulfonamides
- Dapsone

Other
- Sarcoidosis

Exudative tonsillitis with posterior cervical adenopathy suggests EB virus

Because of significant cervical adenopathy on admission, a CT scan of her neck was done and showed multiple small reactive and necrotic lymph nodes on the right side of the neck (FIGURE 1).

THE DIFFERENTIAL DIAGNOSIS

1 Which condition or conditions should be included in the differential diagnosis of this patient's illness?

- ❑ Infectious mononucleosis
- ❑ Toxoplasmosis
- ❑ Cytomegalovirus infection
- ❑ Acute retroviral syndrome
- ❑ All of the above

This case illustrates many of the important features of the infectious mononucleosis-like syndrome (IMLS) in an adult, which can be caused by all of the above. The constellation of symptoms includes fever, rash, headache, and lymphadenopathy. Rash and pharyngitis are frequent. Severe cases may be associated with meningitis, hepatitis, or transverse myelitis. IMLS is typically caused by acute Epstein-Barr virus infection, but other herpesviruses and a variety of other infectious and noninfectious processes may present with the same symptoms (TABLE 1).

Acute Epstein-Barr virus syndrome (infectious mononucleosis) most commonly affects young adults from 15 to 35 years of age. The diagnosis is established by accurate assessment of clinical, hematologic, and serologic manifestations of the illness. The presence of exudative tonsillitis with posterior cervical adenopathy suggests Epstein-Barr virus infection.

2 The most valuable test to diagnose infectious mononucleosis at presentation is:

- ❑ Immunoglobulin G (IgG) antibody against Epstein-Barr viral capsid antigen
- ❑ Antibodies against Epstein-Barr virus early antigen
- ❑ Antibodies against Epstein-Barr virus nuclear antigen
- ❑ Heterophile antibodies

Heterophile antibodies may be demonstrable at the onset of illness or may appear later in the course of the illness, and therefore are the most valuable test to diagnose infectious mononucleosis. Commercial spot tests are generally sensitive and specific for the

demonstration of heterophile antibodies. False-positive infectious mononucleosis slide tests have been reported in patients with lymphoma or hepatitis. A determination of Epstein-Barr virus-specific antibodies is rarely necessary for the diagnosis, because 90% of the cases are heterophile-positive. For the heterophile-negative cases and for the diagnosis in atypical cases, a determination of Epstein-Barr virus antibodies may help to establish a cause. The most valuable serologic finding is the presence of IgM antibody to Epstein-Barr viral capsid antigen, which is found during acute primary Epstein-Barr virus infection. Serum antibodies to Epstein-Barr virus early antigen and nuclear antigen peak 3 to 4 weeks after onset of infection. This syndrome is considered a self-limited illness, but it may result in serious complications, such as splenic rupture.

Cytomegalovirus infection is the most common identifiable cause of heterophile-negative IMLS. One distinguishing feature of cytomegalovirus infection is the absence of tonsillopharyngeal exudate, which is commonly seen in patients with Epstein-Barr virus-related pharyngitis. The diagnosis of cytomegalovirus mononucleosis-like syndrome is established by identification of an IgM-specific antibody or demonstration of a fourfold increase in cytomegalovirus-IgG antibody.

Up to 90% of patients with primary human immunodeficiency virus (HIV) infection may experience IMLS as they seroconvert. The prognosis may be worse if the symptoms persist longer or are more severe or if the HIV viral load is higher at the time of seroconversion. The diagnosis of HIV should be considered in any patient who experiences an acute infectious illness that cannot be explained by common infectious causes, regardless of the patient's HIV risk factors.

CONDITIONS THAT MIMIC IMLS

Infections

Toxoplasmosis. Infection by certain parasites can mimic IMLS. Only 15% of patients with primary infection with *Toxoplasma gondii* have symptoms, often with cervical lymphadenopathy and other features, including atypical lymphocytes. Chorioretinitis is a distinguishing feature of toxoplasmosis, since it does not occur in IMLS.

Malaria. Clinical manifestations of malaria include many symptoms that also occur in IMLS, such as fever, shaking chills, headache, myalgia, and arthralgia. The lack of lymphadenopathy, pharyngitis, and atypical lymphocytes on a peripheral blood smear in patients with malaria distinguishes it from IMLS.

Bacterial infections. A number of bacterial infections can present with symptoms resembling IMLS. Streptococcal tonsillopharyngitis, mainly with group A streptococcus, can mimic IMLS in its clinical features. However, splenomegaly and generalized adenopathy are absent in streptococcal tonsillopharyngitis. A direct throat antigen test that is specific for group A streptococcus has proven to be useful in diagnosing this infection.

Enteric fever (most often caused by *Salmonella typhi*) is worth mentioning, because some of its common features were seen in our patient—ie, pancytopenia, maculopapular rash on the trunk, and cervical adenopathy. The diagnosis usually is made by blood culture, stool culture, or both. Furthermore, pancytopenia is sometimes seen with any overwhelming bacterial infection but is also seen with viral infection.

Cat-scratch disease (bartonellosis) usually causes regional adenopathy without pharyngitis, but the oculoglandular form (Parinaud oculoglandular syndrome) may resemble IMLS.

Other bacterial infections (ie, brucellosis, meningococcemia, chlamydial and spirochetal infection) can mimic IMLS and the diagnosis is usually established by serology or cultures.

Several bacterial infections have symptoms resembling infectious mononucleosis-like syndrome

Noninfectious conditions that mimic IMLS

Noninfectious disorders such as autoimmune disorders and lymphoreticular neoplasms can also cause signs and symptoms mimicking IMLS. However, systemic lupus erythematosus, lymphoma, and other vasculitides have a longer duration of symptoms and a subacute onset, which help distinguish them from infection.

TABLE 2

The patient's serologic tests on admission

SEROLOGIC TEST	RESULTS	INTERPRETATION
Human immunodeficiency virus (HIV)	Negative ELISA*	Negative screening test for HIV
Cytomegalovirus titers	IgG positive, IgM negative	Previous exposure
Infectious mononucleosis slide test	Negative	No heterophile antibodies detected
Epstein-Barr virus titers (viral capsid antigen, nuclear antigen)	IgG positive, IgM negative	Previous exposure
Parvovirus titers	IgG positive, IgM negative	Previous exposure
Toxoplasma titers	IgG negative, IgM negative	No acute or prior infection
Human herpesvirus 6 titers† (total IgG/ IgM antibodies)	1:80	Positive titers
Hepatitis B, C (remote and acute panel)	Negative‡	No acute infection
Bartonella henselae titers	IgG positive, IgM negative	Previous exposure
Rapid plasma reagin	Nonreactive	Negative screening test for syphilis

*Enzyme-linked immunosorbent assay
†To document an acute viral infection, a fourfold increase in titers should be observed; convalescent titers of HHV-6 were 1:320
‡Hepatitis B surface antibody was positive, consistent with immunity to hepatitis B

The mode of HHV-6 transmission is not yet known

Kawasaki syndrome can also mimic IMLS. It presents with prolonged fever and a polymorphic exanthem. Although Kawasaki syndrome has been reported in a few adults, it is overwhelmingly a disease of children, particularly children of Asian ancestry.

Finally, drugs such as phenytoin, sulfonamides, and dapsone can produce a syndrome that mimics IMLS.

Multiple serologic tests were obtained and the results are shown in TABLE 2. The results indicated prior exposure to a number of viruses and current infection with human herpesvirus 6 (HHV-6).

HUMAN HERPES VIRUS 6 INFECTION IN ADULTS

Our patient illustrates the course of primary HHV-6 infection in an adult. HHV-6 was first isolated in 1986 by Salahuddin et al.[1] HHV-6 infection is often asymptomatic or minimally symptomatic, but it accounts for approximately 20% of visits to emergency departments for febrile illness in children between 6 and 12 months of age, and it is the commonest cause of fever-induced seizures in children under 2 years of age.[2] HHV-6 has been identified as the etiologic agent of exanthem subitum (6th disease, roseola infantum) in infants.

The clinical syndrome is fever followed by a maculopapular rash after the temperature normalizes. In addition to nonspecific febrile illness and otitis, the most frequent clinical symptoms are upper respiratory tract or gastrointestinal involvement.[3]

Modes of transmission

The exact mode of transmission has not yet been determined. Because HHV-6 is shed in saliva and urine, some postulate that these are the likely sources of transmission.[4] HHV-6 actively replicates in the salivary glands, stays latent in at least lymphocytes and monocytes, and persists in various tissues.[5] Complications of primary HHV-6 infection in children are uncommon.

Rare in adults

Primary HHV-6 infection is rare in adults because more than 90% of people seroconvert during childhood. In immunocompetent adults who are seronegative, HHV-6 infection may present as a mononucleosis-like illness with negative tests for Epstein-Barr virus and cytomegalovirus. These patients present with fever, lymphadenopathy, and hepatitis or encephalitis. Furthermore, HHV-6 has been implicated as a cause of other diseases such as Kikuchi lymphadenitis, a type of necrotizing lymphadenitis,[6] or associated with other diseases such as multiple sclerosis.

The findings on CT scan of the neck in our patient were described as "small reactive lymph nodes with necrotic center," which led to concern about possible suppurative lymphadenitis on admission. Sumiyoshi et al[7] found HHV-6 DNA in the lymphocytes of a young woman with acute HHV-6 infection.

Immunocompromised patients at risk

In contrast, HHV-6 infection or reactivation has been recognized as a cause of severe illness in immunocompromised adults, namely bone marrow or solid organ transplant recipients and HIV-infected patients. In these patients, HHV-6 infection or reactivation may result in bone marrow suppression, pneumonitis, encephalitis, hepatitis, fever, skin rash, and possible reactivation of other herpesviruses, especially cytomegalovirus. It may also complicate engraftment of the transplanted organ and lead to rejection and death.[5] In HIV-infected patients, HHV-6 infection or reactivation has indirect effects on HIV replication. It has been speculated that HHV-6 acts as a cofactor in the progression of AIDS.

Diagnosis of HHV-6 infection is based on viral culture, serology, and polymerase chain reaction testing

TESTING FOR HHV-6

The diagnosis of HHV-6 infection is based on viral culture, serology, and polymerase chain reaction.

Viral culture is the gold standard method for detecting HHV-6 in peripheral blood mononuclear cells. Inoculated cell cultures are examined 5 to 7 days after infection, looking for specific cytopathic effects, and immunologic confirmation is carried out by immunofluorescence or anticomplement immunofluorescence testing. This technique has a reported sensitivity and specificity of 86% and 100%, respectively, for specimens from solid organ transplant recipients, but it is not routinely performed in clinical laboratories.

Serologic testing is helpful in diagnosing HHV-6 infection if a seroconversion can be demonstrated for IgG from negative to positive. Clinicians should be aware that a single high IgG antibody titer represents previous exposure and that at least 90% of adults are seropositive. A fourfold increase in IgG antibody detected by immunofluorescence suggests infection, but the distinction between primary infection and reactivation may be difficult.

Qualitative polymerase chain reaction testing for HHV-6 is probably the most sensitive and specific means of documenting primary infection. Ideally, to distinguish primary infection from reactivation, a quantitative technique (viral load) should be used, but these techniques are still investigational.

3 Which of the following would be the appropriate therapy for HHV-6 in this patient?

- ❑ Start oral acyclovir
- ❑ Start oral ganciclovir
- ❑ Start intravenous acyclovir
- ❑ Start intravenous ganciclovir
- ❑ None of the above

The in vitro susceptibility data for HHV-6 show that acyclovir is inactive against the virus and that the response to ganciclovir is variable. The effectiveness of these antivirals in treating selected patients with severe HHV-6 infection (eg, those with encephalitis or post-transplant pneumonia) has not been established.

There is no specific treatment for HHV-6 itself. Symptomatic therapies for fever, headache, and other symptoms are appropriate.

CLINICAL COURSE AND FOLLOW-UP

For 2 days, the patient received broad-spectrum antibiotics for possible suppurative lymphadenitis. Her fever persisted during the

antibiotic therapy but slowly subsided on the 5th day after admission. The rash disappeared and the cervical lymph nodes became smaller and less tender. The headache and photophobia persisted for a week; she was discharged after these symptoms resolved.

At the time of her follow-up appointment in the outpatient department 3 weeks later, the patient's symptoms and signs had completely resolved. Viral titers were repeated, revealing a fourfold increase in the serum HHV-6 IgG titer, from 1:80 to 1:320. The presence of HHV-6 was confirmed by polymerase chain reaction on a serum specimen taken from the patient on admission.

LESSONS LEARNED

HHV-6, a herpesvirus first described 14 years ago, is a rare but important cause of IMLS in non-immunocompromised adults.

IMLS in adults is a frequent cause of visits to physician's offices and emergency departments; patients with severe manifestations of disease may be hospitalized for evaluation and therapy.

The differential diagnosis of IMLS is broad, encompassing a variety of infections, neoplasms, and immunologic disorders.

REFERENCES

1. **Salahuddin SZ, Albashi DV, Markham PD, et al.** Isolation of a new virus, HBLV, in patients with lymphoproliferative disorders. Science 1986; 234:596–601.
2. **Hall CB, Long CE, Schnabel KC, et al.** Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. N Engl J Med 1994; 331:432–438.
3. **Dockrell DH, Smith TF, Paya CV, et al.** Human herpesvirus 6. Mayo Clin Proc 1999; 74:163–170.
4. **Levy JA, Ferro F, Greenspan D, et al.** Frequent isolation of HHV-6 from saliva and high seroprevalence of the virus in the population. Lancet 1990; 335:1047–1050.
5. **Campadelli-Fiume G, Mirandola P, Menotti L.** Human herpesvirus 6: an emerging pathogen. Emerging Infect Dis 1999; 5:353–366.
6. **Bhat NA, Hock YL, Turner NO, et al.** Kikuchi's disease of the neck (histiocytic necrotizing lymphadenitis). J Laryngol Otol 1998; 112:898–900.
7. **Sumiyoshi Y, Kikuchi M, Ohshima K, et al.** A case of human herpesvirus-6 lymphadenitis with infectious mononucleosis-like syndrome. Pathol Int 1995; 45:947–951.

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