CASE 16

A 12-year-old girl presents to clinic with a sore throat and fever. She says she feels very tired. Physical examination reveals notable cervical lymphadenopathy, but the spleen is not palpable. A heterophile agglutinin test is negative. On histology, the image shown in Figure 3-13 is seen.

What is the most likely diagnosis?
Infectious mononucleosis syndrome resulting from cytomegalovirus (CMV) infection. CMV is a double-stranded linear virus in the family Herpesviridae. Infected cells have intranuclear inclusions, and on histology have an “owl’s-eye” appearance, as seen in the center of Figure 3-13.

What is the presentation of this condition?
In the majority of people, CMV infection is asymptomatic. In those with symptoms, it usually presents with a mononucleosis-like syndrome, which includes pharyngitis, cervical lymphadenopathy, fever, lethargy, and, less often, splenomegaly. Unlike the mononucleosis syndrome seen with Epstein-Barr virus, the heterophile agglutinin test (monospot test) is negative. CMV can be transmitted by direct contact, blood transfusions, organ transplantation, breast milk, sexual contact, and vertically (ie, mother to fetus). It is one of the TORCHes infections (Toxoplasmosis, other infections, Rubella, Cytomegalovirus, Herpes simplex virus, Syphilis).

What populations are at risk for complications of this condition?
The populations most at risk are those with decreased cellular immunity, such as patients with AIDS and organ transplants (especially bone marrow and lung transplants). The main complication in the transplantation population is CMV pneumonia. The main complication in the AIDS population is CMV retinitis, which usually presents when the CD4+ cell count is < 50 cells/mm³. In both populations, prophylactic ganciclovir can be given.

How does this condition present in patients infected congenitally?
In patients congenitally infected with CMV, the complications include petechiae, jaundice, microcephaly, microsomnia, retinitis, neurologic abnormalities, and deafness. At-risk fetuses are those whose mothers have a primary infection, which is seen with high IgM levels (the IgG levels could be low or high). Mothers with low IgM levels and high IgG levels likely have a secondary infection and are more likely to be able to prevent transmission from mother to fetus.

What is the appropriate treatment for this condition?
Although most patients do not need treatment, the treatment is ganciclovir, a nucleoside analog. This drug requires activation by viral kinase, which phosphorylates the drug and allows it to inhibit CMV DNA polymerase. Acyclovir is not effective against CMV.

What are the most common side effects of the treatment for this condition?
Ganciclovir is more toxic than acyclovir. Side effects include leukopenia, neutropenia, thrombocytopenia, and renal toxicity.
**CASE 17**

A woman who has recently returned from a city in Southeast Asia presents to her physician with sudden-onset fever, severe muscle pain in her back and extremities, and recent joint pain in her knees. Examination reveals an erythematous rash that covers her face and body and generalized lymphadenopathy.

**What is the most likely diagnosis?**
This woman is likely experiencing **dengue fever**, also known as “breakbone fever” because of the severe joint and muscle pain associated with it.

**What is the vector for this condition?**
The vector is the *Aedes aegypti* mosquito. These mosquitoes are diurnal and live near cities. They are most commonly found in pools of stagnant water. This distinguishes them from malaria-carrying *Anopheles* mosquitoes, which are nocturnal and are less populous near urban areas. Once a rare disease in the United States, dengue fever began to reappear in the 1970s, when bans on pesticides such as DDT allowed these mosquitoes to thrive. The same vector can also carry yellow fever and chikungunya.

**Which microorganism causes this condition?**
Dengue fever is a disease caused by a positive, single-stranded RNA virus of the *Flaviviridae* family. This family also includes St. Louis encephalitis virus, Japanese encephalitis virus, hepatitis C virus, and West Nile virus.

**How does this condition differ from yellow fever?**
Yellow fever virus is also a member of the *Flaviviridae* family and has a similar endemic region and transmission as dengue fever virus. However, yellow fever presents with high fever, black vomit, and jaundice and is not associated with severe joint and muscle pain.

**After recovering from this condition, will the patient be immune to it in the future?**
The dengue fever virus has four serotypes. The patient will develop lasting immunity to the serotype of the virus with which she was infected but not to the remaining three serotypes. This means that she could contract dengue fever four times in all.

**Infection with a different serotype of this virus poses what potential complications?**
The most serious complications of dengue fever are dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), both of which can be fatal. These conditions are characterized by bleeding (often from the gastrointestinal tract or from mucosa); petechiae, ecchymoses, or purpura; thrombocytopenia; fluid leakage (manifested as pleural effusions, ascites, or hemoconcentration); and shock. Such complications most frequently occur in patients who have already been infected with another serotype of the virus. One theory underlying this phenomenon, termed **antibody-dependent enhancement**, proposes that antibodies from previous infections actually allow for increased viral replication upon reinfecion with a different serotype. This has also hindered the development of a vaccine, since the vaccine must provide adequate protection against all four serotypes or it could put the patient at risk for DHF/DSS.
CASE 22

A 22-year-old woman presents to the emergency department in labor. This is her first pregnancy, and she has received no prenatal care. In the emergency department she has a normal spontaneous vaginal delivery of a boy. The baby appears normal at birth, but 12 hours later he begins to show signs of lethargy. He becomes tachypneic, his blood pressure drops, and his hands and feet begin to feel cold.

What infectious agents are most frequently responsible for neonatal sepsis?
Group B streptococci (GBS), Escherichia coli, and Listeria monocytogenes are common causes of sepsis, pneumonia, and meningitis in newborns. GBS often colonizes the vaginal flora of women and can be transmitted vertically during vaginal delivery. This patient's lack of prenatal care, primiparous vaginal delivery, and onset soon after birth make GBS sepsis a likely diagnosis.

What is the next step in identifying the causative agent?
In Gram staining of a blood sample, GBS appear as gram-positive cocci, L monocytogenes appears as motile gram-positive rods, and E coli appears as gram-negative rods.

How did the infant become infected?
These bacteria can spread through the placenta or be acquired from the birth canal during delivery. The mother may be infected or colonized but asymptomatic. However, pregnant and postpartum women are also at risk for GBS urinary tract infection or chorioamnionitis.

What prenatal testing is routinely performed to reduce the infant's risk of this infection in the birth canal?
If the patient receives good prenatal care, cultures of the mother's vagina and rectum are performed between 35 and 37 weeks of gestation to determine whether she is colonized with GBS.

What treatment is initiated if prenatal testing is positive?
Treatment of GBS in infected mothers or newborns involves the use of antepartum antibiotics such as penicillin. In mothers who are colonized vaginally or rectally, but who are not actively infected, intrapartum penicillin is recommended.

If the baby develops meningitis from this organism, what cerebrospinal fluid findings are expected?
In bacterial meningitis, the cerebrospinal fluid may show bacteria on Gram stain. In addition, the WBC count is elevated, primarily with neutrophils; the protein level is elevated; and the glucose level is reduced.
CASE 23

A 3-year-old boy is brought to the pediatrician by his mother. The mother states that 2 days ago the child started refusing solid foods, preferring his bottle and applesauce. Today, the mother noticed a rash on her son's extremities and tongue (Figure 3-18), and found that he was also running a low-grade fever, which prompted her to bring him to the doctor.

![Figure 3-18.](Reproduced, with permission, from Shah BR, Lucchesi M. Atlas of Pediatric Emergency Medicine. New York: McGraw-Hill, 2006: Figure 3-65.)

What is the most likely diagnosis?
This is a case of hand-foot-mouth disease, caused by coxsackie A virus. This syndrome presents with a tender rash on the palms, soles, and often the buttocks and painful vesicles on the oral mucosa. This patient’s avoidance of solid food strongly suggests involvement of the oral mucosa.

What other microorganisms are included in this family that caused this condition?
The Picornaviridae are a family of single-stranded positive-sense RNA viruses. The members of this family cause a wide array of illness, possibly because of the high virulence of positive-sense single-stranded RNA, which can be directly translated into protein products by host ribosomes. Members of the Picornaviridae family include:
- Poliovirus
- Echovirus
- Hepatitis A virus
- Coxsackie viruses
- Rhinovirus

What other conditions can this microorganism cause?
Herpangina, which presents with sore throat, red vesicles on the back of the throat, pain with swallowing, and fever. Herpangina is a mild, self-limited disease that presents in children and usually results in complete recovery. Less commonly, coxsackie A virus can cause petechial and purpuric rashes, which may also have a hemorrhagic component.

What illnesses may be caused by the group B coxsackie viruses?
The coxsackie B virus may cause aseptic meningitis, myocarditis, pericarditis, dilated cardiomyopathy, orchitis, and epidemic pleurodynia (fever, headache, spasms of the chest wall muscles, and pleuritic pain). Nephritic syndrome may also occur after a coxsackie B virus infection.

What other infections commonly presents with a rash of the palms and soles?
Other than Coxsackie A virus, Rocky mountain spotted fever caused by Rickettsia rickettsii and secondary Syphilis commonly present with a rash on the palms and soles (mnemonic: CARS).
CASE 25

A 9-year-old girl is brought to a public clinic by her mother. The family immigrated to the United States from Guatemala 3 years previously. Her mother reports the girl seems very small for her age and has been continually lethargic for quite some time. Physical examination reveals a small girl with a thin, scaphoid abdomen. Relevant laboratory findings are as follows:

Hematocrit: 36%
Mean corpuscular volume: 73 fL
WBC count: 11,000/mm³
Differential: 35% segmented cells, 1% bands, 33% lymphocytes, 21% eosinophils

What is the most likely diagnosis?
Hookworm, or nematode, infection. The findings of eosinophilia and microcytic anemia with recent immigration from an endemic area are highly suggestive of this condition.

What is the next step in confirming the diagnosis?
Stool ova and parasite tests can confirm the presence of characteristic small, round eggs and occasional worms approximately 1 cm in size. Stool ova and parasite tests can also be used to delineate the species of helminth.

What are the species of hookworms?
Ancylostoma duodenale, Necator americanus, and Ancylostoma braziliense are the most common hookworms. Of the three, A duodenale and N americanus cause the classic gastrointestinal symptoms and microcytic anemia seen in this patient. A braziliense, however, can manifest as a condition known as cutaneous larva migrans, in which the larva migrate to the subcutaneous tissue and create pruritic, serpiginous tracts underneath the skin.

What other helminth is known to cause anemia?
Diphyllobothrium latum, a tapeworm, causes vitamin B₁₂ deficiency leading to a macrocytic anemia.

How does this infection cause disease in humans?
Percutaneous infection occurs generally through the soles of the feet and is acquired commonly from sandboxes. The larvae pass into the lungs, and 8–21 days later they cross the pulmonary vasculature and enter the airways. They ascend to the pharynx and are swallowed. By the time they reach the small intestine, the larvae have become adult worms. The adults “hook” onto the mucosa and feed on the host’s blood with the help of an orally secreted factor X inhibitor. This results in the microcytic anemia. The females produce eggs that are passed through the stool and deposited in the soil.

What are the appropriate treatments for this condition?
Since hookworm is a helminthic infection, mebendazole and albendazole are the first-line agents. These agents disrupt helminthic microtubule synthesis, leading to structural weakening and death of helminthic cells. Pyrantel pamoate can be used as a second-line agent.
An 18-year-old woman presents to clinic with a fever and headache. She also complains of vaginal itching and dysuria. When asked, she says that she recently became sexually active. Physical examination reveals tender inguinal lymphadenopathy and red, pustular, painful vesicles on her labia majora (Figure 3-19).

**What is the most likely diagnosis?**
Herpes simplex virus type 2 (HSV-2). The pathognomonic findings for herpes infections are painful vesicles. Both HSV-1 and HSV-2 can cause genital herpes, but more than 80% of genital lesions are due to HSV-2.

**What are the characteristics of this pathogen?**
HSV-2 is a member of the Herpesviridae family, which are double-stranded DNA viruses and include: HSV-1, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus, human herpesvirus-6, and human herpesvirus-8. They can be recognized by multinucleated giant cells on Tzanck smear and by eosinophilic intranuclear inclusions.

**What is the differential diagnosis of painful genital lesions?**
Chancroid caused by *Haemophilus ducreyi* infection. Lymphogranuloma venereum caused by *Chlamydia trachomatis* and granuloma inguinale caused by *Klebsiella granulomatis* also cause painful genital lesion.

**What is the typical course of this infection?**
HSV-2 is transmitted by direct contact of the virus with mucosal surfaces or open skin surfaces. It can also be transmitted from mother to newborn during delivery. Approximately 80% of infected patients are asymptomatic. The primary infection often presents with constitutional symptoms such as fever, headache, malaise, and myalgia. Later, genital vesicles may appear that can rupture and leave behind painful ulcers. Other genital symptoms include itching and tender inguinal lymphadenopathy. Like other viruses in the family, HSV-2 becomes latent and can be reactivated. Triggers for reactivation include fever, trauma, emotional stress, sunlight, and menstruation. Upon reactivation, there is often a viral prodrome that involves tenderness, pain, and burning at the future site of vesicle eruption. The lesions last 4–15 days before crusting over and reepithelializing.

**Where do herpesvirus species remain latent?**
In the peripheral nervous system ganglia. HSV-1 tends to remain latent in the trigeminal ganglion, reactivating and causing oral herpes or "cold sores." HSV-2 and VZV tend to remain latent in the dorsal root ganglia of the sensory afferents. This gives rise to the pathognomonic dermatomal distribution of reactivated zoster infections.

**What is the treatment for this condition?**
The treatment for HSV-2 is acyclovir, a nucleoside analog that acts by inhibiting viral DNA polymerase when it is phosphorylated by viral thymidine kinase. However, because efficacy requires viral thymidine kinase activity, any herpesvirus lacking a functional thymidine kinase will be resistant.