Kawasaki syndrome (KS) is a serious disorder affecting children aged 1 to 8 years. It mimics a range of other diseases of childhood. Diagnosis is based on physical examination findings coupled with the exclusion of other causes. To provide optimal care for patients, it is important to be aware of the differential diagnoses of KS, which include bacterial and viral infections; rheumatological diseases, which may be secondary to infectious diseases; and other causes, such as antimicrobial drug reactions. [Infect Med. 2008;25:311-316]

Key words: Kawasaki syndrome ■ Vasculitis ■ Hypersensitivity syndrome ■ Febrile rash

Differential Diagnosis

Since there is no specific diagnostic test for KS, the diagnosis hinges on meeting 4 of the 5 criteria as well as the presence of fever for 5 days. Because the diagnostic features often have different presentations, the diagnosis of KS may be difficult even for the experienced clinician. Thus, it is always important to consider the differential diagnosis when confronted with a child in whom KS is suspected. KS should be considered in any child with fever for more than 5 days, especially if the child has a rash and nonpurulent conjunctivitis. The differential diagnosis of KS is extensive and includes bacterial and viral infections and rheumatological diseases, among other causes.

Bacterial infections
Bacterial infections that play into the differential diagnosis include scarlet fever; staphylococcal scalded skin syndrome (SSSS); toxic shock syndrome (TSS); Rocky Mountain spotted fever (RMSF) and other forms of rickettsial infection, such as typhus; leptospirosis; rat-bite fever; and Yersinia pseudotuberculosis infection.1-10

Scarlet fever is a syndrome that results from erythrogenic exotoxin A production by group A Streptococcus. It is similar to KS in that it causes desquamation with time, including periungual desquamation. Infection also can cause cervical adenopathy, exudative tonsillitis, and strawberry tongue.

A few distinguishing features help differentiate scarlet fever from KS. Although a desquamating rash is a characteristic of both diseases, the rash associated with scarlet fever may become blanched. It is diffusely erythematous, resembling a sunburn, and is rough with a sandpaper
Kawasaki Syndrome or Infection? continued

The rash is most intense on the axillae and on the groin, abdomen, and trunk. It generally appears about 24 hours after the onset of fever. It is first seen on flexor surfaces of the extremities and becomes generalized in 24 to 48 hours. Pastia sign (Figure 1), nonblanching skin folds, and circumoral pallor also may be noted. Cephalic to caudal desquamation occurs about a week after the onset of rash. Finally, if physical findings are not sufficient to determine a diagnosis, checking antistreptolysin O titers can be helpful because levels may be elevated in patients with scarlet fever.

SSSS is another toxin-mediated disorder. It shares with KS the characteristics of a desquamating truncal rash and an erythematous, peeling, fissured “sunburst” rash around the mouth. Unlike KS, SSSS is preceded by an initial infection of the upper respiratory tract. Another distinguishing characteristic is that the rash of SSSS usually spares the palms, soles, and mucous membranes. The peeling is confined to areas around body orifices.

One to 2 days after the rash manifests, bullae may appear and exfoliate in sheets, which is referred to as a positive Nikolsky sign. Isolation of staphylococci from a site other than the blisters (eg, conjunctivae or nasopharynx) or from the blood will aid in the diagnosis.

TSS is generally caused by Staphylococcus aureus. Similarities between TSS and KS include edema of the face, palms, and soles. In addition, desquamation of the skin 1 to 2 weeks after illness onset, strawberry tongue, and bulbar conjunctival hyperemia are present in both illnesses. Distinguishing characteristics of TSS include shock, a widespread blanching erythroderma eruption that is most prominent on the trunk and extremities, and possible subconjunctival hemorrhage (Figure 2). Approximately 85% of TSS patients have *S aureus* isolated from their mucosa or wound sites, but isolation of the organism is not required to make the diagnosis.

RMSF, a rickettsial infection, is caused by the spirochete *Rickettsia rickettsii*. It is transmitted through the bite of a tick and is most prevalent in the southeastern and central Mississippi valley regions of the United States, with North Carolina and Oklahoma having the highest incidence. Similarities to KS include fever, maculopapular rash with involvement of palms and soles, and conjunctival hyperemia. In contrast to KS, RMSF causes a peripherally distributed eruption beginning on the ankles, wrists, and forehead, in which the initial lesions may blanch and appear as small red macules that rapidly progress to maculopapules and finally to petechiae. The onset of rash is preceded by a 3- to 7-day prodrome of chills, fever, and severe frontal headache, malaise, and anorexia. Thrombocytopenia, hypohyponatremia, elevated aminotransferase levels, hyperbilirubinemia, leukopenia, and coagulopathies might emerge. Serum antibodies reactive to *R rickettsii* may be detected by indirect immunofluorescence assay, but diagnostic levels might be undetectable until the second week after syndrome onset.

Febrile rickettsial infection includes epidemic and murine typhus, and it is transmitted by fleas or lice harboring *Rickettsia* species. Similarities to KS include high fever, a maculopapular petechial eruption, and cervical adenopathy. Some distinguishing characteristics include a 4- to 6-day prodrome with high fever,
chills, headache, and generalized aches and pains. In addition, the maculopapular rash is often centrally distributed, and neuroretinitis may be found. The indirect fluorescent antibody test is often used to confirm the diagnosis.

Leptospirosis is caused by the spirochete *Leptospira interrogans*, which is transmitted by dogs, swine, rodents, and contaminated water. Similarities to KS include a maculopapular rash with peripheral desquamation, conjunctivitis, cervical lymphadenopathy, and pharyngitis. One of the distinguishing characteristics is conjunctivitis with episcleral injection and uveitis that may be unilateral or bilateral and usually involves the entire uveal tract. The rash is maculopapular to generalized and may be petechial or purpuric. Erythema nodosa also may be noted.

The anicteric form of leptospirosis is the most common form and is associated with biphasic fever, myalgias, and chills. Acalculous cholecystitis or intense jaundice is occasionally seen in children. Laboratory studies that may aid in the diagnosis include those that evaluate for leukocytosis, hematuria, proteinuria, azotemia, and hyperbilirubinemia.

Rat-bite fever is a very rare syndrome caused by either *Spirillum minus* or *Streptobacillus moniliformis*. Similarities to KS include intermittent fever, rash on the palms and soles, and lymphadenopathy. It has many distinguishing characteristics, including a waxing and waning pattern of fever of 3 to 4 days’ duration alternating with afebrile periods lasting 3 to 9 days; this cycle may persist for weeks. The rash often develops 1 to 8 days after fever onset. Laboratory tests may indicate leukocytosis and may yield false-positive results for venereal diseases.

*Y. pseudotuberculosis* is transmitted by the ingestion of incompletely cooked pork, unpasteurized milk, or contaminated well water or by indirect contact with infected animals. This bacterium causes a fever, rash, lymphadenitis, and conjunctivitis similar to those seen with KS. Some distinguishing characteristics of *Y. pseudotuberculosis* infection include varying degrees of fever, a scarlatiniform rash, and mesenteric adenitis (which may mimic acute appendicitis). It is also associated with Parinaud oculoglandular syndrome, which includes unilateral conjunctivitis with conjunctival granulomas, ptosis, preauricular adenopathy, photophobia, and external signs of inflammation. Of interest, 75% of patients with clinically apparent *Y. pseudotuberculosis* infection are children younger than 15 years.

**Viral infections**

Viral infections that are symptomatically similar to KS include adenovirus infections as well as measles, German measles, roseola infantum, erythema infectiosum, and mononucleosis. Adenovirus infections, like KS, are characterized by a persistent high fever, pharyngitis (Figure 3), conjunctivitis, cervical lymphadenopathy, and rash.

Distinguishing characteristics of adenovirus infections include sore throat, rhinitis, and unilateral conjunctivitis that can include serous discharge, subconjunctival hemorrhages, and the formation of a grayish pink friable membrane on the palpebral conjunctiva. The conjunctivitis also is associated with an itching, burning, foreign-body sensation that is not seen in KS.

The discrete generalized erythematous maculopapular rash of adenovirus infections often appears while the child is febrile. Adenoviruses also can cause right iliac fossa abdominal pain. Direct antigen testing or viral culture can be used to detect adenoviruses.

Measles, caused by the rubeola virus, shares similarities with KS in that it is characterized by swelling of the hands and feet, a maculopapular rash with desquamation, conjunctivitis, and a maculopapular rash similar to KS. Of interest, 75% of patients with clinically apparent *Y. pseudotuberculosis* infection are children younger than 15 years.
tivitis, and fever that persists for 5 to 7 days. Some unique characteristics of measles include a 3- to 4-day prodrome of fever, conjunctivitis, coryza, and severe cough. In contrast to KS, the conjunctivitis of measles is exudative. The brick-red rash of rubella starts on the face, the neck, and behind the ears; it then extends down the trunk and onto the extremities. The rash is initially maculopapular and becomes more confluent before it begins to fade after 3 days, leaving behind a distinctive brownish hue. This is often followed by a branny desquamation that does not involve the hands and feet. In addition, Koplik spots on the buccal mucosa and a central, white coating of the tongue with an erythematous tip and margins may be seen.

Similarities between KS and German measles, which is caused by the rubella virus, include a maculopapular rash, adenopathy, and fever. German measles is distinguished from KS by a nonspecific prodrome of fever, coryza, sore throat, arthralgias, and adenopathy that occurs 1 to 5 days before exanthem onset; but this is more common in adolescents and adults than in infants and young children.

The rash is characterized by a non–desquamating, pale pink, morbilliform maculopapular eruption that begins on the face and neck and progresses down the trunk to the extremities. The rash is generalized in 24 to 48 hours, lasts 1 day in each area, and fades rapidly. In addition to cervical adenopathy, postauricular and occipital lymphadenopathy and arthralgias also may be noted.

Roseola infantum is caused by human herpesvirus 6 and usually occurs in children aged 6 to 36 months. It is characterized by persistent fever of 3 to 5 days’ duration, followed by rash and lymphadenopathy. Distinguishing features of roseola infantum include an erythematous and morbilliform rash that consists of rose-colored macules appearing on the neck, trunk, and buttocks and less frequently on the face and extremities that begins as the fever abates. The mucous membranes are often spared, and the rash resolves in 1 to 2 days. Patients with roseola infantum also are at increased risk for febrile convulsions. Laboratory studies often show leukopenia.

Erythema infectiosum (also called fifth disease) is caused by Parvovirus B19. Like KS, it is characterized by fever, adenopathy, and rash. Unlike KS, a prodrome of malaise, pharyngitis, coryza, and fever precedes the illness. The characteristic “slapped cheek” rash generally follows about 10 days later. In the second phase of the illness, the rash spreads to extremities and becomes symmetrical, morbilliform, and lacelike or annular with central clearing and is often mildly pruritic. It spares the mucous membranes, palms, and soles. In its final phase, the rash may remit and recur for weeks with stress, exercise, or bathing. Complications of erythema infectiosum include arthritis, hemolytic anemia, aplastic crisis, and nonimmune hydrops in the fetus and newborn.

Mononucleosis is caused by the Epstein-Barr virus (EBV). Similarities to KS include fever, rash, and cervical lymphadenopathy. Mononucleosis is typically characterized by a triad of membranous tonsilitis with or without exudates, cervical lymphadenopathy, and splenomegaly. The rash of mononucleosis is rare (5% to 10% of patients with EBV infection) and may appear as 2 different exanthems. The first type of exanthem is erythematous, maculopapular, and rubella-form and is more prominent on the trunk and proximal upper extremities (occasionally it is seen on the face, forearms, and legs). This is the classic, non–antibiotic-related EBV rash. The second type is an erythematous or copper-colored ampicillin-associated rash that begins on the trunk and spreads to the face and extremities. EBV infection can be diagnosed in the clinic with the monospot test or with specific EBV antibody tests.

Rheumatological diseases
A few rheumatological diseases cause symptoms similar to those of KS, including Gianotti-Crosti syndrome, Henoch-Schönlein purpura (HSP), and juvenile rheumatoid arthritis (JRA). Gianotti-Crosti syndrome, an infantile, papular acrodermatitis originally associated with hepatitis B surface antigen that may occur after viral infection, is caused by pathogens such as EBV, cytomegalovirus, enteroviruses, and respiratory syncytial virus. Like KS, this syndrome includes a desquamative rash and lymphadenopathy. The rash is characterized by a sudden eruption of symmetric, flat-topped, discrete, nonpuritic, skin-colored to erythematous papules on the malar face, extremities, and buttocks (Figure 4) that spares the trunk, mucous membranes, and antecubital and popliteal fossae. The lesions then fade and desquamate spontaneously within 2 to 3 weeks but may remain for up to 8 weeks. The lymphadenopathy is generalized and inguinal, and maxillary nodes can be enlarged for 2 to 3 months after onset.

HSP is a systemic vasculitis with deposition of IgA-containing immune complexes throughout the body. Like KS, HSP is characterized by fever; rapidly fading rash; swollen hands, feet, and periorbital areas; arthritis; and abdominal pain. Unlike KS, HSP is classically described as intermittent purpura, arthralgias, abdominal pain, and renal disease. HSP also may be preceded by an upper respiratory tract infection, mild fever, and headache.
Kawasaki Syndrome or Infection?

The initial lesions are symmetrical, blotchy, erythematous macules that become urticarial and then purpuric within a day. The palpable purpuric lesions are seen on the buttocks, extensor surfaces of extremities, back, scrotum and, occasionally, the face.

In a child younger than 2 years, edema of the scalp, hands, feet, and periorbital tissues may develop before the appearance of purpuric lesions. Cutaneous hemorrhage may be the sole manifestation of any attack, with arthralgia and arthritis noted as a migratory, periarticular swelling of the knees and ankles. Patients also may have colicky abdominal pain associated with vomiting and melena, and mild renal involvement with transient proteinuria, hematuria, and focal glomerular involvement. Abnormal findings on laboratory tests include leukocytosis, thrombocytosis, and elevated erythrocyte sedimentation rate (ESR). Skin biopsy specimens show IgA, C3, and fibrin deposits.

JRA has characteristics similar to those of KS, including lymphadenopathy, rash, and high, spiking fevers. These fevers are dramatic, with sweats and chills, and temperatures often spike to 40°C (104°F) before plunging to several degrees below normal (picket fence temperature). The rash is a transient, evanescent, salmon-colored, nonpruritic rash that is primarily noticeable on the chest and abdomen. It often appears and disappears with the fever spikes. Many patients may initially complain of mild sore throat and joint symptoms that become a progressively destructive arthritis primarily affecting the wrists. Hepatosplenomegaly during the rash, anemia, and leukocytosis also may be present.

Other differential diagnoses

Other syndromes with characteristics similar to those of KS include Stevens-Johnson syndrome (SJS), acrodynia, and convulsant hypersensitivity syndrome (CHS). SJS is a condition caused by a severe allergic reaction to drugs such as sulfonamides, NSAIDs, and phenytoin and by infections such as those caused by *Mycoplasma pneumoniae* and herpes simplex virus. Like KS, SJS is characterized by pharyngitis, fever, conjunctivitis, a maculopapular rash involving the hands and feet, and hemorrhagic lips. The rash tends to be vesicular with crusting of edematous, erythematous eruptions involving the face, hands, and feet. Bullous erythema multiforme, with lesions that may slough off as large pieces of skin, also may be noted. Stomatitis is an early and conspicuous symptom, beginning with vesicles on the tongue, lips, and buccal mucosa (Figure 5). This later becomes more severe and includes pseudomembranous exudation, excessive salivation, and ulcerations. Rhinitis with epistaxis and crusting of the nares also may be seen. The conjunctivitis of SJS is bilateral and often exudative. Laboratory testing may indicate an increased ESR, although the ESR is not as high as that seen in KS.

Acrodynia, also known as erythredema polyneuropathy or pink disease, is caused by mercury poisoning.
Similiar to KS, it is characterized by painful swelling of the hands and feet, a maculopapular rash, and irritability. Unlike KS, the erythema is blotchy and diffuse. Hands and feet also may be cold, clammy, pink or dusky red, and pruritic. In addition, hemorrhagic puncta may be seen. Laboratory studies may demonstrate albuminuria, hematuria, and the presence of mercury in urine.

CHS is a systemic reaction to anticonvulsant therapy. Like KS, it is characterized by fever, maculopapular rash, and lymphadenopathy. It includes involvement of visceral organs, and fulminant hepatitis may develop. The lymphadenopathy is generalized. The rash usually begins 2 to 8 weeks after the drug is begun and usually resolves when the drug is stopped. CHS may be followed by an eosinophilic colitis. Helpful findings from laboratory tests include leukocytosis with eosinophilia and a normal ESR.

TREATMENT

High-dose intravenous gamma globulin (IVIG) (2 g/kg) as a single dose along with high-dose aspirin (100 mg/kg/d) for 10 to 14 days followed by low-dose aspirin (5 mg/kg/d) until acute inflammatory mediators return to normal is the standard of care for KS. This therapy has been shown to reduce the incidence of coronary artery disease. The most serious complication associated with KS is a coronary artery aneurysm. Aneurysms may lead to sudden death, often within the first 30 days after the onset of KS. Usually IVIG is followed by a prompt end to most symptoms the child is having. On occasion, a second dose of IVIG is required. Any child whose status does not improve after a second dose of IVIG should be reevaluated.

REFERENCES

Fever and Rash: Infection or Kawasaki Syndrome?

Michael E. Ryan, DO, Terrah Keck, DO, Mary Frances Musso, DO, and Kimberly C. Capp, DO

Kawasaki syndrome (KS) is a common and serious disorder that most often affects children aged 1 to 8 years but mimics a range of other diseases of childhood. Diagnosis of KS is based on physical examination findings coupled with the exclusion of other causes. To provide optimal care for patients, it is important to be aware of the differential diagnosis of KS. We report a case of a 4-year-old boy who presented with persistent fever and cervical lymphadenitis; later, mucous membrane changes, rash, and conjunctival injection characteristic of KS developed. [Infect Med. 2008;25:320-322]

Key words: Kawasaki syndrome ■ Vasculitis ■ Hypersensitivity syndrome ■ Febrile rash

Kawasaki syndrome (KS) is a common vasculitis seen in the pediatric population. It also is known as mucocutaneous lymph node syndrome, and the cause is unknown. Epidemiologically, it is similar to an infectious disease; it has a seasonal occurrence and has been implicated in epidemics. Clinically, it is a vasculitis unresponsive to antibiotics. KS develops in healthy children and is the most common cause of acquired cardiac disease in the developed world. Chronic cardiac complications develop in 20% to 25% of children with untreated KS, and the most common and dangerous cardiac complication is coronary artery dilatation. It may result in rupture of the arteries and exsanguination. KS also may cause children to experience a prolonged course of arthritis, arthralgias, and crampy abdominal pain. Therefore, it is very important that KS is diagnosed accurately and treated appropriately and that clinicians are diligent about follow-up.

Case report
A 4-year-old boy with a past medical history of recurrent otitis media initially presented with a complaint of right ear pain and fever. Otitis media of the right ear was diagnosed, and amoxicillin therapy was begun. Four days later, the patient presented to his primary care physician because of persistent fever and enlargement of a left anterior cervical node. The ear pain had resolved, however. The patient was not taking in an adequate amount of fluids and thus was mildly dehydrated.

The patient’s temperature was 38.7°C (101.6°F). His right tympanic membrane was slightly red, with fluid behind it. His tonsils were more than 3 mm in diameter and were erythematous. He had an enlarged (2 cm in diameter) left anterior cervical node. His skin turgor was decreased and no rash was noted.

The patient was admitted with suspected retropharyngeal abscess and for receipt of intravenous fluids and further evaluation and therapy. Intravenous clindamycin was administered immediately. His initial laboratory studies revealed a white blood cell count of 18,480/µL, with 53% polymorphonuclear cells, 30% lymphocytes, 11% monocytes, and 6% eosinophils. His hemoglobin level was 10.8 g/dL, and the platelet count was 370,000/µL. The C-reactive protein level was 27 mg/L.

A CT scan of the neck showed no retropharyngeal abscess, but pansinusitis, bilateral middle ear opacification, and bilateral cervical adenopathy were evident. Further laboratory studies revealed an antistreptolysin O titer of less than 20 IU/mL, alanine aminotransferase level of 8 U/L, and aspartate amino-
Fever and Rash

The patient’s condition rapidly improved. He became afebrile, his rash resolved, and his eyes and lips improved. He began to eat and drink normally, and the cervical adenopathy resolved. He was discharged home on the fifth hospital day with instructions to continue taking aspirin and to follow up with the pediatric infectious disease clinic in 1 week. At the follow-up visit, peeling of the hands and feet was observed. The patient continued to do well with no evidence of coronary abnormalities.

Discussion

The diagnosis of KS is defined by the presence of fever of at least 5 days’ duration and 4 of the 5 following characteristics: conjunctival hyperemia, mucous membrane changes, distal extremity changes, polymorphous exanthema, and cervical adenopathy. The fever characteristic of KS is high and spiking. It is not affected by antibiotics or antipyretics and resolves within 24 to 48 hours of IVIG therapy. The onset of fever is considered the first day of the illness, from which all other events are measured.1

The conjunctival hyperemia seen in KS is characteristically nonexudative and is most apparent in the bulbar conjunctiva, with sparing of the limbic region around the iris. Hyperemia is noticeable a few days after the onset of fever and may persist for 1 to 2 weeks if left untreated.

Effects of KS on mucous membranes are extensive and include diffuse erythema of the oral and pharyngeal mucosa without discrete ulcerative lesions. The lips also may be injected, dried, or fissured, and the patient may have a strawberry tongue (Figure 1).

The distal extremity changes of KS are progressive and include erythema of the palms and soles along with indurative edema of the hands and feet. Periungual desquamation (Figure 2) of the fingers and toes follows the swelling and is noticed on days 10 to 25. Beau lines (transverse grooves across the fingernails) may appear 2 to 3 months after disease onset.

The polymorphous exanthema of KS is characterized by macules and papules without any vesicle or bullae formation. It is prominent on the trunk and extremities. In two-thirds of cases, there is periungual desquamation (Figure 2) of the fingers and toes, as seen here on a child’s fingertips.

Figure 1 – These images illustrate the characteristic white (top) and red (bottom) strawberry tongue seen in Kawasaki syndrome.

Figure 2 – Periungual desquamation follows swelling in Kawasaki syndrome, as seen here on a child’s fingertips.
Of cases, it is accentuated in the perineal area (Figure 3). Fever and sore throat manifest 2 to 5 days before the rash appears, and the rash fades without residua within 10 days.

The least prominent sign of KS is cervical adenopathy, which is present in about 50% of children with KS (other signs and symptoms discussed are present in about 90% of patients). This cervical adenopathy is characterized by an erythematous, indurated, nonsuppurative anterior cervical node of at least 1.5 cm in diameter (Figure 4).

Additional characteristics of KS include constitutional symptoms (irritability, fatigue, and anorexia), GI symptoms (abdominal pain with or without vomiting and diarrhea, hepatic dysfunction with possible hydrodrops of the gallbladder, and pancreatitis), skeletal symptoms (arthritis or tympanitis with possible hearing loss), and lymphoid symptoms (exudative tonsillitis).

Laboratory abnormalities may include an elevated ESR or increases in other acute phase reactants, elevated transaminase levels, thrombocytosis, and hypoalbuminemia.

Therapeutic agents mentioned in this article

Amoxicillin
Clindamycin
Intravenous immunoglobulin

Figure 3 – Perineal accentuation of exanthema occurs in two-thirds of cases of Kawasaki syndrome.

Figure 4 – Cervical adenopathy, characterized by an erythematous, indurated, nonsuppurative anterior cervical node of at least 1.5 cm in diameter, is less prominent than other signs or symptoms of Kawasaki syndrome. Nevertheless, it occurs in up to 50% of affected children.
IDAlert

What You Need to Know About the ACIP’s Recommendations on Herpes Zoster Vaccination

[Infect Med. 2008;25:323-325]

The CDC’s Advisory Committee on Immunization Practices (ACIP) recommends that all persons older than 60 years be immunized against the varicella-zoster virus that causes herpes zoster with a single dose of the live, attenuated virus vaccine Zostavax (Merck & Co, Inc, Whitehouse Station, NJ). Furthermore, it urges clinicians to offer the vaccine on the first available clinical encounter.

The recommendations, which will appear in Morbidity and Mortality Weekly Report (MMWR), can be accessed online.1 These recommendations are the first made by the ACIP advocating use of a live, attenuated virus vaccine for prevention of herpes zoster. The hope—promised by results of several clinical trials cited in the MMWR article—is that routine immunization of older adults will significantly ameliorate the incidence of and morbidity associated with herpes zoster.

About 1 million cases of herpes zoster are diagnosed annually in the United States. Many of them will be associated with postherpetic neuralgia (PHN), stated the ACIP, which summarized various other complications in its recommendations statement. Included are ocular symptoms and sequelae (ie, herpes zoster ophthalmicus); varicella-zoster virus viremia; and serious, potentially fatal neurological conditions and viral dissemination to viscera that can occur in persons who are immunocompromised. Older persons (beginning at about age 50) are particularly at risk for development of herpes zoster, with 2 studies calculating that 50% of persons who live to age 85 years will have experienced this condition and subsequent PHN.2,3

The Vaccine and Vaccination
Each 0.65-mL dose of the zoster vaccine (when reconstituted and stored at room temperature for up to 30 minutes) contains a minimum of 19,400 plaque-forming units of the Oka/Merck strain of varicella-zoster virus. This vaccine is appreciably more potent than the varicella vaccine routinely used in children to prevent chickenpox (ie, Varivax, also manufactured by Merck & Co, Inc). It is administered subcutaneously to the deltoid area. A single dose is all that is required (booster doses are not licensed for use).

Zoster vaccine should be stored in a freezer that maintains an average temperature of −15°C (5°F) or colder. Once reconstituted, the vaccine should be used immediately: within 30 minutes. After this time, the potency degrades. If unused, the reconstituted vaccine should be discarded.

The zoster vaccine is licensed for use only in persons 60 years and older. It is safe for use in persons receiving blood products. Persons who already have received immunization against varicella-zoster virus should not be re-immunized; however, the ACIP stated that concern regarding unintentional re-immunization in persons 40 years and older was slight because varicella vaccination did not begin in the United States until 1995. The ACIP also noted that clinicians need not question older patients about a history of chickenpox or conduct serological testing for varicella immunity before administering the vaccine. Persons who have had an episode of herpes zoster in the past can receive the vaccine, but it should not be used to treat acute herpes zoster or PHN or be used as prophylaxis against PHN. Precluding contraindications and precautions related to health status, persons with chronic renal failure, diabetes mellitus, rheumatoid arthritis, chronic pulmonary disease, or other chronic conditions can receive the vaccine.

Vaccine Coadministration
Although the zoster vaccine can be administered along with the trivalent inactivated influenza vaccine without compromising the effectiveness of either one, no data are available on the effects of administering the zoster vaccine with other vaccines that are routinely recommended for persons 60 years and older. Because simultaneous administration of most commonly used live, attenuated and inactivated vaccines, in general, has yet to be associated with impaired immune response and has not been associated with an increased rate of adverse events, the zoster vaccine can be administered in the setting of other indicated (inactivated) vaccines during the same office visit.

The ACIP reminded clinicians that when multiple vaccines are to
be administered during a single office visit, they should be administered to different anatomic sites using separate syringes. Although the zoster vaccine can be administered at any time along with an inactivated virus vaccine, it should be administered at least 4 weeks before or after administration of another live, attenuated virus vaccine. to some experts\(^5\) before immunosuppressive therapy is initiated. Otherwise, immunization is contraindicated in immunocompromised persons, including those receiving immunosuppressive drugs. However, exceptions and caveats to these guidelines exist (Table).

Although a history of neomycin-associated contact dermatitis is not a contraindication to receiving the zoster vaccine, persons who have a history of anaphylactic reaction to any component of the vaccine, including neomycin, should not receive it.\(^4\) Pregnant women—who are not in the target age group for herpes zoster immunization anyway—also should not receive the vaccine. 

Clinicians should be aware that the CDC and the vaccine’s manufacturer have established a registry to monitor maternal-fetal outcomes of pregnant women who inadvertently have been administered live, attenuated varicella-zoster virus–type vaccines within a month of becoming pregnant. The telephone number of the registry is 800-986-8999.

Persons who are receiving an antiviral medication, such as acyclovir, famciclovir, or valacyclovir, should not be vaccinated in the setting of active therapy. Rather, therapy should be discontinued for at least 24 hours before the zoster vaccine is administered and at least 14 days should elapse postvaccination before antiviral therapy is resumed.\(^4\) Because antiviral agents are active against herpesviruses, they could interfere with vaccine effectiveness.

**Table – Who should not receive the zoster vaccine because of immunocompromise**

<table>
<thead>
<tr>
<th>Persons who should not receive the vaccine</th>
<th>Exceptions</th>
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<tbody>
<tr>
<td>Persons with HIV/AIDS</td>
<td>Persons in whom leukemia is in remission and who have not received chemotherapy or radiation for at least 3 months(^4)</td>
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<tr>
<td>Persons with leukemia, lymphomas, or other malignant bone marrow or lymphatic neoplasms</td>
<td>At least a month should elapse between discontinuation of the immunosuppressive therapy and zoster vaccination(^4,a)</td>
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<tr>
<td>Persons receiving immunosuppressive therapy, including high-dose corticosteroids (&gt; 20 mg/d of prednisone or equivalent) for 2 weeks or more</td>
<td>Persons with impaired humoral immunity, such as hypogammaglobulinemia or dysgammaglobulinemia</td>
</tr>
<tr>
<td>Persons with evidence of any unspecified cellular immunodeficiency</td>
<td>Clinical discretion may be applied, but if a decision to vaccinate is made, the vaccine should be administered at least 24 months after the transplant procedure</td>
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<tr>
<td>Persons undergoing hematopoietic stem cell transplant</td>
<td>Vaccination should either occur weeks before therapy is initiated or at least 1 month after therapy is discontinued</td>
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<tr>
<td>Persons receiving recombinant human immune mediators and immune modulators (adalimumab, infliximab, and etanercept)</td>
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\(a\) Patients receiving short-term (< 14 days) or low to moderate doses of corticosteroids (< 20 mg/d of prednisone or equivalent) or topical, intra-articular, bursal, or tendon injections or long-term alternate-day low to moderate doses of short-acting systemic corticosteroids can receive the zoster vaccine. In addition, low-dose methotrexate (< 0.4 mg/kg/wk), azathioprine (< 3 mg/kg/d), or 6-mercaptopurine (< 1.5 mg/kg/d) therapy is not a contraindication for administration of zoster vaccine.
Additional Notes and Caveats

Clinicians are asked to document all immunizations in the patient’s medical record, per the ACIP’s General Recommendations on Immunization, published in 2006. The type of vaccine, the vaccine’s manufacturer, anatomic site and route of delivery, the date of vaccine administration, lot number of the vaccine, and name of the administering facility should be recorded. In addition, to help avoid inadvertent re-immunization, patients should be given a copy of the document containing a record of the vaccination.

If the zoster vaccine was inadvertently administered to a child, the ACIP recommends that the dose be counted as a single valid dose of varicella vaccine. If the erroneously administered dose of zoster vaccine was given instead of the first dose of varicella vaccine, a second dose of varicella vaccine is required. The ACIP has requested that such errors be reported to the Vaccine Adverse Event Reporting System (VAERS) whether or not an adverse event occurs.

Conversely, if a clinician mistakenly administers varicella vaccine to a person for whom the zoster vaccine was indicated, no specific safety concerns apply; however, the dose should be considered invalid, and the patient should immediately be given a dose of zoster vaccine. If a delay in recognition of the error occurs, the zoster vaccine should be promptly administered 28 days after the varicella vaccine was given.

As with other vaccines, clinically significant adverse events should be reported to VAERS even if a causal relation to vaccination is questionable. Clinicians are encouraged to enter reports electronically at https://secure.vaers.org/VaersDataEntryintro.htm. The Web site of the VAERS is www.vaers.hhs.gov and the telephone number is 800-822-7967.

REFERENCES

A 45-year-old Hispanic man who acquired HIV infection in April 2003 presented with a 24-hour history of worsening right lower quadrant pain accompanied by fever, decreased appetite, nausea, and vomiting. The pain was described as sharp, constant, and nonradiating. He denied any accompanying diarrhea, constipation, urinary frequency, dysuria, dyspepsia, reflux symptoms, or previous episodes of abdominal pain. There was no history of recent travel. His current CD4+ cell count was 239/µL. In May 2003, he had a CD4+ cell count nadir of 133/µL. His HIV RNA level has remained undetectable at less than 50 copies/mL since starting first-line antiretroviral therapy in June 2003. Therapy consists of coformulated zidovudine/lamivudine/abacavir and efavirenz. He has never had opportunistic infections or other major medical illnesses.

Physical examination revealed a temperature of 38.2°C (101°F); pulse rate, 106 beats per minute; 10 out of 10 tenderness over the right lower quadrant with muscle guarding; and positive Rovsing, obturator, and psoas signs. Rectal examination showed tenderness over the right rectal vault.

Laboratory analysis demonstrated a white blood cell count of 13 × 10^6/L (76% neutrophils). Findings from urinalysis were normal. Findings on a CT scan of the abdomen with contrast were normal with no evidence of appendicitis. Because of persistent abdominal pain with normal findings on the CT scan of the abdomen, colonoscopy was performed. Figures 1, 2, and 3 are images taken at the level of the terminal ileum. Figure 1 shows an impacted pill in the appendiceal orifice. Figure 2 shows the removal of the pill using forceps. Figure 3 shows mild residual inflammation of the appendiceal orifice after removal of the impacted pill.

Discussion
Abdominal pain is a frequent presenting symptom among HIV-positive patients seeking care at emergency departments. The incidence is estimated to be 12% to 45%. In one retrospective study conducted in 1997 at San Francisco General Hospital, abdominal pain was the sole complaint in 18% of the patients. The majority, however, reported other accompanying symptoms. The most common were nausea/vomiting (58%), diarrhea (32%), and fever (21%).

Evaluation of the cause of abdominal pain rests on thorough history taking and physical examination. The differential diagnosis of right lower quadrant pain in
a non-immunocompromised, HIV-negative patient includes appendicitis; diverticular disease and its complications; intra-abdominal abscesses; kidney stones; sexually transmitted diseases; enterocolitis; and intestinal obstruction from mechanical causes, such as strictures, masses, volvulus, and intussusception.

The differential diagnosis of right lower quadrant pain among HIV-positive patients also includes malignancies, such as lymphoma and Kaposi sarcoma, and opportunistic infections, such as those caused by mycobacteria (ie, *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare*) and cytomegalovirus. Immune reconstitution syndrome associated with recent introduction of antiretroviral therapy also may produce atypical presentations of disease. The list of differential diagnoses becomes more lengthy and complex as the CD4+ cell count declines.

Workup of abdominal pain in a patient with HIV infection is the same as that for the noninfected patient. However, because of the vast differential diagnoses, the probability of coexisting conditions caused by multiple pathogens, and atypical presentations of common disorders, radiological imaging such as CT and abdominal sonography should be used early in the assessment of abdominal pain in HIV-positive patients. Normal findings on a CT scan of the abdomen may lead the clinician to consider endoscopic procedures (ie, esophagogastroduodenoscopy or colonoscopy). Colonoscopy, in this case, served both diagnostic and therapeutic purposes.

Pill impaction that causes inflammation in the intestinal mucosa is an unusual cause of abdominal pain. The impacted pill was removed endoscopically. The patient was given metoclopramide, a prokinetic agent, for a week. Pill impaction has not recurred. To our knowledge, this is the first reported case of pill impaction presenting clinically as an appendicitis mimic in a patient who is HIV-positive.

It is unknown what causes pill impaction among HIV-positive patients. Varying degrees of enteropathy develop in HIV-infected patients, especially those who have advanced disease. AIDS patients have been shown to have delayed gastric emptying with impairment of both intestinal absorption and permeability, factors that may promote pill impaction with resulting local mucosal inflammation. None of the medications that are used to treat HIV infection have been shown to significantly affect intestinal function (absorption, permeability, and inflammation) or alter intestinal transit times.

Recurrent pill impaction should warrant manometric studies with or without gastric or small-intestine biopsies to determine the cause and appropriate treatment. Prokinetic agents, such as metoclopramide and erythromycin, and also octreotide provide short-term, symptomatic relief.

The case and images were submitted by Mauro Torno, MD, and Michael Shallman, MD, of Long Beach Health Department and St Mary Medical Center in Long Beach, Calif.

REFERENCES

YOUR CONTRIBUTIONS ARE INVITED!
Send slides or prints with a short description of what is shown. An honorarium will be awarded for each published photograph or set of photographs. Send to: Images, Infections in Medicine, 330 Boston Post Road, PO Box 4027, Darien, CT 06820-4027.

July 2008 INFECTIONS in MEDICINE 329
Streptococcus pneumoniae 19A: An Emerging Threat

Benjamin Estrada, MD
University of South Alabama, Mobile

Key words: Heptavalent pneumococcal conjugate vaccine (PCV7) Streptococcus pneumoniae 19A Multidrug resistance

Since the licensure of the heptavalent pneumococcal conjugate vaccine (PCV7) in 2000, the prevalence of invasive pneumococcal disease (IPD) among children in the United States has decreased significantly. The incidence of IPD caused by pneumococcal serotypes associated with PCV7 among children younger than 5 years decreased from 80 cases per 100,000 population in 1998 to 1999 to 4.6 cases per 100,000 population in 2003. Various studies have demonstrated that nasopharyngeal colonization with pneumococcal serotypes covered by the vaccine also has decreased. However, several studies suggest that in some settings, these bacterial populations have been replaced with \textit{Streptococcus pneumoniae} serotypes not covered by the vaccine.

Among the various pneumococcal serotypes (19A, 6A, 3, and 15) that have been recognized as emerging threats during recent years, \textit{S pneumoniae} 19A is, by far, the most prominent. This serotype has been associated not only with the development of IPD but also with a high level of resistance to multiple antibiotic classes.

IPD surveillance in Massachusetts during 2001 to 2006 identified a significant increase in cases caused by serotypes not covered by the PCV7. The percentage of infections caused by serotype 19A increased from 10\% during 2001 to 2003 to 41\% during 2005 to 2006. In Alaska, serotype 19A was the cause of 28.3\% of cases of IPD among children younger than 2 years between 2004 and 2006.

In addition to IPD, multiresistant serotype 19A also has been linked to the development of otitis media. As evidenced by Pichichero and Casey and by Jacobs and colleagues in 2 separate studies, a significant challenge related to this clinical situation is the high level of resistance that many of these isolates have to antibiotics (such as amoxicillin, trimethoprim, macrolides, clindamycin, oral cephalosporins, and ceftriaxone) most commonly used to treat otitis media in children.

The direct effect of PCV7 in serotype selection or replacement is not yet fully understood. Although serotype selection induced by lack of effectiveness of PCV7 against serotype 19A is believed to be 1 of the main factors associated with serotype 19A proliferation, it is not the only factor. Moore and colleagues have suggested that antibiotic resistance, clonal expansion, and capsular switching also have contributed to the emergence of this serotype as the predominant cause of IPD in the United States. In addition, it is important to emphasize that according to a recent study by Hwa Choi and colleagues, multidrug-resistant 19A serotypes began to increase in South Korea before the introduction of PCV7.

The introduction and widespread administration of PCV7 to children in the United States has led to a significant decrease in the incidence of IPD. However, it is important for clinicians to recognize that because of multiple factors, multidrug-resistant serotype 19A has emerged as a significant cause of pneumococcal disease. Clinicians need to consider the presence of this serotype in situations in which IPD is observed. In addition, infection with \textit{S pneumoniae} 19A should be considered in children with otitis media who fail to respond to antibiotic therapy.

REFERENCES


continued on page 334
A Differential Diagnosis of Drug-Induced Aseptic Meningitis

Clair Cascella, MD, Sara Nausheen, MD, and Burke A. Cunha, MD

Drug-induced aseptic meningitis should be included in the differential diagnosis of viral/aseptic meningitis. Clinicians should use historical clues in patients presenting with signs and symptoms of viral meningitis to aid in the differentiation of drug-induced aseptic meningitis from other causes of aseptic meningitis. Viruses are the most common cause of aseptic meningitis, with enteroviruses being the most common among viruses in cases presenting as aseptic meningitis. Ibuprofen is currently the most common cause of drug-induced aseptic meningitis. Drug-induced aseptic meningitis is a benign condition without long-term sequelae. The diagnosis of drug-induced aseptic meningitis is made by establishing a causal relationship between the use of the drug and the onset of signs and symptoms, supported by negative tests for infectious causes of symptoms and rapidity of resolution after the drug is discontinued. [Infect Med. 2008;25:331-334]

Key words: Drug-induced aseptic meningitis ■ Enteroviral meningitis

A septic meningitis refers to a nonbacterial inflammation of the leptomeninges.1 Viruses are the most common cause of aseptic meningitis, and the most common viruses that cause aseptic meningitis are enteroviruses. Drug-induced aseptic meningitis is rare but probably more common than the literature would suggest; therefore, it should be included in the differential diagnosis of aseptic meningitis, particularly if aseptic meningitis develops in association with the use of NSAIDs or other offending drugs (Table 1) and if clinical recovery is rapid following cessation of the drug or if results of viral studies are negative.

The pathogenetic mechanisms of drug-induced aseptic meningitis are not fully understood, but 2 major mechanisms have been proposed. One proposed mechanism is that the meninges are directly irritated by the intrathecal administration of drugs. The other is that the meninges are expressing an immunological hypersensitivity—most often a type 3 or type 4 hypersensitivity reaction—to the offending drug.2

An association between hypersensitivity reactions and underlying collagen-vascular disease or rheumatological disease has been reported.1-10 Typically, the cerebrospinal fluid (CSF) profile in drug-induced aseptic meningitis is that of a neutrophilic pleocytosis accompanied by a normal CSF lactic acid level and a variably elevated CSF protein level.1,3 Patients who have drug-induced meningitis may have eosinophils present in the CSF (fewer than 5%).

THE CLINICAL PICTURE

Patients who have drug-induced aseptic meningitis typically present with fever, headache, and nuchal rigidity. Signs and symptoms usually appear within 24 to 48 hours after drug ingestion, but symptoms may not occur until 2 years post-therapy.2,6 Drug-induced aseptic meningitis may develop in a patient who initially was able to tolerate the causative drug.1,6

In patients who have drug-induced aseptic meningitis, the typical CSF profile reveals a neutrophilic pleocytosis, with several hundred to several thousand white blood cells

Dr Cascella is a first-year medical resident in the department of medicine at Winthrop-University Hospital in Mineola, NY. Dr Nausheen is a second-year fellow in the infectious disease division at Winthrop-University Hospital. Dr Cunha is chief of the infectious disease division at Winthrop-University Hospital and professor of medicine at State University of New York School of Medicine in Stony Brook.

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per microliter; normal glucose levels; and variably elevated protein levels.\(^1\)\(^\_\)\(^2\)\(^\_\)\(^3\)\(^\_\) Results of CSF Gram stain and cultures are negative, and lymphocytic or eosinophilic pleocytosis may occur. Drug-induced aseptic meningitis is reversible, with most signs and symptoms resolving within 24 to 48 hours after the drug is discontinued.\(^2\)\(^4\)\(^7\)

<table>
<thead>
<tr>
<th>Table 1 – Medications known to cause aseptic meningitis</th>
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<td><strong>Medications</strong></td>
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<td>NSAIDs</td>
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\(^a\)With serum levels ≈ 70 mg/dL.


DIFFERENTIAL DIAGNOSIS

The differential diagnosis of aseptic meningitis is extensive and includes infectious and noninfectious causes (Table 2).\(^1\)\(^-\)\(^10\) Drug-induced aseptic meningitis is a common cause as well. Other causes include infections such as mumps, rubella, hepatitis B, and others, as well as noninfectious conditions like post-vaccination, post-injection, or post-surgery.
### Table 2 – Causes of acute aseptic meningitis

<table>
<thead>
<tr>
<th>Infectious causes</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
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<tbody>
<tr>
<td><strong>Bacterial</strong></td>
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<tr>
<td>Lyme disease</td>
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<td>T. pallidum</td>
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<tr>
<td>Leptospirosis</td>
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<td>T. pallidum infection</td>
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<td>Mycobacterium tuberculosis infection</td>
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<td>M. pneumoniae</td>
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<tr>
<td>Subacute bacterial endocarditis</td>
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<td>Rocky Mountain spotted fever</td>
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<tr>
<td>Parameningeal infection (epidural subdural abscess, sinus or ear infection)</td>
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<td>B. recurrentis infection</td>
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<tr>
<td>Partially treated bacterial meningitis</td>
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<td>B. recurrentis (relapsing fever)</td>
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<td><strong>Viral</strong></td>
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<td>Echovirus infection</td>
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<td>P. virus infection</td>
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<td>Coxsackievirus infection</td>
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<td>C. virus infection, Rotavirus</td>
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<td>Mumps</td>
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<td>C. virus infection</td>
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<td>St Louis encephalitis</td>
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<td>W. virus infection</td>
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<td>Eastern equine encephalitis</td>
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<td>Western equine encephalitis</td>
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<td>J. virus infection</td>
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<td>California encephalitis</td>
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<td>M. virus infection</td>
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<td>Herpes simplex virus type 1 infection</td>
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<td>V. virus infection</td>
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<td>Herpes simplex virus type 2 infection</td>
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<td>W. virus infection</td>
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<td>HIV infection</td>
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<td>H. virus infection</td>
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<td>Lymphocytic choriomeningitis</td>
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<td>J. virus infection</td>
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<td>Poliovirus infection</td>
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<td>M. virus infection</td>
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<td><strong>Fungal</strong></td>
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<td>Cryptococcosis</td>
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<td>C. ovis infection</td>
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<td>Coccidioidomycosis</td>
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<td>C. ovis infection</td>
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<td>Histoplasmosis</td>
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<td>C. ovis infection</td>
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<td><strong>Parasitic</strong></td>
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<tr>
<td>Angiostrongylus cantonensis infection</td>
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<td>C. ovis infection</td>
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<td><strong>Noninfectious causes</strong></td>
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<td>Neoplastic diseases</td>
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<td>Intracranial tumors</td>
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<td>V. Koyanagi-Harada syndrome</td>
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<td>Lymphoma</td>
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<td>S. Koyanagi-Harada syndrome</td>
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<td>Leukemia</td>
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<td>Metastatic carcinomas</td>
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<td><strong>Systemic diseases</strong></td>
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<td>Neurosarcoidosis</td>
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<td>Behçet disease</td>
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<td>Systemic lupus erythematosus</td>
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<td>S. Koyanagi-Harada syndrome</td>
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<td><strong>Neurosurgical procedures</strong></td>
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<td>Neurosurgery (posterior fossa syndrome)</td>
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Aseptic meningitis continued

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ASEPTIC MENINGITIS continued

meningitis is a diagnosis of exclusion. It is important to obtain a history of medical disorders such as systemic lupus erythematosus, the most frequent underlying condition associated with drug-induced aseptic meningitis. It is also important to make inquiries about recent vaccinations that may be implicated in the development of aseptic meningitis.

Patients with enteroviral meningitis often present with an early neutrophilic pleocytosis, although a shift to lymphocytic pleocytosis usually occurs within the first 48 hours. In normal hosts, enteroviral meningitis occurs within the first 48 hours. It is also important to make inquiries about recent vaccinations that may be implicated in the development of aseptic meningitis.

In normal hosts, enteroviral meningitis is usually characterized by decreased frequency of headaches and stiff neck within the 2-week period. The condition may be diagnosed by polymerase chain reaction testing of the CSF, by viral culture of throat specimens, or by serological tests for enteroviruses. CSF lactic acid levels readily differentiate bacterial from viral meningitis.

Quick resolution of symptoms is an important sign that distinguishes drug-induced aseptic meningitis from viral meningitis, in which recovery usually requires 10 to 14 days. CSF glucose levels are usually normal in drug-induced aseptic meningitis, which may help in differentiating it from bacterial meningitis in which glucose levels usually are low. Analysis of C-reactive protein (CRP) levels also may be helpful in distinguishing bacterial from a drug-induced aseptic meningitis because CRP levels are usually highly elevated in bacterial meningitis compared with drug-induced aseptic meningitis.

The most common cause of drug-induced aseptic meningitis is NSAIDs. The list of medications that cause drug-induced aseptic meningitis continues to increase and currently includes a wide variety of medications (Table 1).

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Clinical Mycology Update

Department Editor
Duane R. Hospenthal, MD, PhD

Diagnostic Nucleic Acid Testing for Invasive Fungal Infections

Rupal Mody, MD and Michael Zapor, MD, PhD

[Infect Med. 2008;25:335-338]

Key words: Nucleic acid testing ■ Polymerase chain reaction ■ Diagnosis ■ Fungal infections

Over the past 2 decades, there has been an alarming increase in opportunistic fungal infections with an associated rise in morbidity and mortality. This trend has been attributed to the growing number of patients who are immunocompromised because of bone marrow or solid organ transplant, immunosuppressive drugs, AIDS, and hematological malignancies. Advances in trauma and critical care medicine that lead to longer survival of more patients with immunocompromising conditions also play a role.

Historically, the most common opportunistic mycotic infections have been those associated with Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans. A number of fungal pathogens, including non-fumigatus Aspergillus species and other septate moulds, as well as members of the Zygomycetes class are emerging as important causes of fungal disease.1,2 These infections are frequently fatal. Early recognition of these pathogens is critical to initiating prompt, appropriate therapy.

Because all antifungal drugs, including the newer agents, have gaps in coverage, most pathogens should be identified at the species level when devising a therapeutic strategy. However, conventional reliance on culture and histopathology for diagnosis of invasive fungal infections is time-consuming and frequently insensitive. For this reason, nucleic acid–based assays are gaining attention as potentially sensitive, accurate, and rapid tests for the diagnosis of fungal infections.

Overview of molecular diagnostics

Methods that are currently used to diagnose fungal infections include direct observation (smears, histopathology); culture of clinical specimens; and antigen/antibody assays for detecting the cell wall components galactomannan (GM) and β-glucan. More recently, polymerase chain reaction (PCR) amplification and its variants (including multiplex PCR, nested PCR, and real-time PCR) have been used to detect fungal pathogens, such as Candida and Aspergillus species, by amplifying genomic sequences unique to each organism.3-6

Multiplex PCR provides increased sensitivity over standard PCR by using multiple primer pairs per reaction to amplify more than 1 target sequence.4 Nested PCR, in which the original target sequence is amplified and then used as a template for additional amplifications with a second set of primers, is more specific than conventional PCR. Nested PCR has been used clinically for the detection of Candida species and Histoplasma capsulatum.7-10 Real-time PCR couples the assay with an amplification product detection system (typically a fluorescent label) and has been used to detect and quantify DNA from several fungal pathogens, including Aspergillus species, Candida species, and C neoformans.11-15

Fungal nuclear, mitochondrial, and ribosomal genes, as well as RNA sequences, have been used as templates in PCR and similar assays.16 The sensitivity of these assays is enhanced when the target sequence has multiple copies within the genome.14,16 Ribosomal targets possess both sequences, which are highly conserved among the fungi and species-specific variable internal transcribed spacer regions. Recent studies have focused on 5.8S, 18S, and 28S ribosomal RNA and DNA genes for the detection of Candida and Aspergillus species.7,8,10,11,13-15,17

Once target sequences are amplified by PCR, the amplicons can be further characterized by other molecu-
lar biology techniques, including restriction fragment length polymorphism analysis, nucleic acid sequencing, Southern and Northern blot analysis, electrophoretic karyotyping, and DNA microarray genotyping.15,18

Clinical application of molecular diagnostics
Although PCR assays can be used to detect any fungi, their clinical application has mostly been applied to the detection of Candida and Aspergillus species.13,15,19,20-26 PCR assays for Candida are very sensitive and can detect DNA from as few as 10 organisms/mL of blood. Similarly, PCR assays for Aspergillus can detect DNA from 10 to 100 conidia/mL of blood.24

Pryce and colleagues13 suggested that real-time PCR testing, which can detect DNA quantity over time, might be useful for monitoring response to antifungal therapy. Klingspor and Jalal15 also found real-time PCR assays to be both sensitive and specific for the detection of Candida and Aspergillus species in clinical specimens. In their study, clinical samples (blood, sputum, tissue, cerebrospinal fluid, bronchoalveolar lavage fluid, pleural fluid, ascites, bile, and urine) from transplant recipients with suspected invasive fungal infections were assayed by PCR. Of 1650 specimens assayed, 114 (6.9%) were PCR-positive for either Candida species (n = 86) or Aspergillus species (n = 28), whereas 62 (3.8%) were culture-positive for either Candida species (n = 57) or Aspergillus species (n = 5). Of the PCR samples positive for Candida, 72% were identifiable to species.

Ahmad and colleagues7 found semi-nested PCR to be 99% specific and more sensitive than culture in diagnosing candidemia. White and colleagues17 found that PCR testing, when compared with latex agglutination and enzyme-linked immunosorbent assay, detected Candida infection earlier, was more sensitive, and was comparably specific.

It has been suggested that environmental contaminants might cause false-positive PCR results when used in the diagnosis of fungal infections.17 This has been substantiated in a study by Ljungman and colleagues21 in which blood samples from patients with leukemia were assayed weekly by PCR for Cytomegalovirus and fungi. Real-time PCR results were positive in 9 samples taken from 8 of 35 patients (3 samples positive for Aspergillus and 5 samples positive for Candida, with 1 sample being positive for both).21 However, only 3 of the 4 samples in which Aspergillus species were detected corresponded with suspicion for Aspergillus infection based on the presence of pulmonary infiltrates on a chest CT scan.21

In the same study, of 3 cases of proven fungemia attributed to Candida species, in only 1 case was the blood PCR-positive for Candida.21 Six samples from 5 patients were PCR-positive for Candida species.21 Two samples came from 1 patient who had bacteremia, 1 sample came from an asymptomatic patient, 1 sample each came from 2 patients with fever of unknown origin, and 1 sample came from a patient with candidemia. Hence, Candida was never recovered in culture of specimens taken from 4 of the 5 patients whose blood was PCR-positive for Candida.21 The PCR test results may represent true positives, although, even in the absence of growth in culture, Candida species are not always recovered from the blood of patients with candidiasis.

Another technique useful for the diagnosis of fungal infections is fluorescent in situ hybridization (FISH). This assay uses fluorescein-labeled peptide nucleic acid (PNA) probes specific for the ribosomal RNA sequences of C albicans.27 The FDA approved 1 of these assays, the C albicans PNA FISH (AdvanDx, Inc, Woburn, Mass), in 2004 for use in rapidly (ie, within 2.5 hours) differentiating albicans from non-albicans Candida species isolated from blood. In one study, the reported sensitivity and specificity of this technique was 99% and 100%, respectively.27 The same company also manufactures a dual color C albicans/Candida glabrata FISH assay for simultaneous identification of both organisms from blood culture. The sensitivity and specificity of this dual assay are similar to those of the C albicans PNA FISH.28

The value of PCR in the diagnosis of invasive aspergillosis has been evaluated in several studies (Table). The sensitivity, specificity, negative predictive value, and positive predictive value are widely varying widely between studies depending on the pretest probability of infection and type of PCR used (eg, real-time vs nested).22-25 The low positive predictive value of PCR assays when bronchoalveolar lavage specimens are used (range, 38% to 83.5%) likely reflects the difficulty in distinguishing airway colonization from infection.22-25

The sensitivity of PCR assays in detecting Aspergillus in serum varies from 40% to 92.3%, with improved sensitivity on serial testing.19,20,26,29 The low sensitivity of the assay described in some studies (especially in early infection) might be attributed to transient fungemia, low-level fungemia (ie, below the detection limits of the assay), and a short half-life of fungal DNA (because of rapid degradation or clearance). PCR testing fares better in detecting Aspergillus invasion of tissue, such as lung tissue, with a reported sensitivity of 100% in one study.26

Comparisons of the GM assay and real-time PCR assay in detecting Aspergillus infections have shown conflicting results. Buchheidt and colleagues28 reported that the nested PCR assay is more sensitive than the GM assay, whereas both Kawazu and colleagues30 and Costa and colleagues31 reported the GM assay to be superior. If valid,
In the findings of the latter 2 studies, the shedding of fungal antigen might reflect greater shedding of fungal antigen relative to the presence of Aspergillus nucleic acid in the blood of patients with fungemia.

**Merits and limitations of molecular diagnostics**

When compared with culture and histopathology for the diagnosis of invasive fungal infections, PCR coupled with various hybridization techniques offers the potential of enhanced sensitivity, specificity, and relative rapidity. Moreover, real-time PCR such as the LightCycler PCR detection system (Roche Applied Science, Mannheim, Germany) confers the advantage of quantifying fungal DNA and potentially might be used to monitor disease progression as well as response to therapy.²⁵,²⁶ PCR testing also permits identification of individual species and strains as well as amplification of specific sequences for further study (eg, nucleic acid sequencing) and manipulation (eg, cloning).

However, there are drawbacks to using PCR testing in the diagnosis of infection. The techniques for extracting and amplifying DNA are not currently standardized, and the reactions are expensive and vulnerable to false-positive results due to contamination. Most important, positive PCR results may not distinguish between contamination, colonization, or true infection, nor between DNA extracted from dead versus viable organisms.³² Lack of recovery of live organisms also removes the option of performing antifungal susceptibility or retrospective virulence or strain testing. Nevertheless, a great potential value of PCR derives from its negative predictive value.

### Table – Reported performance of PCR in the detection of Aspergillus species from clinical specimens

<table>
<thead>
<tr>
<th>Assay</th>
<th>Samples (N)</th>
<th>Source</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real-time PCR²⁵</td>
<td>96</td>
<td>BAL, blood</td>
<td>43%</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Real-time PCR²⁵</td>
<td>&gt; 1522</td>
<td>BAL, blood, other</td>
<td>63.6%</td>
<td>63.5%</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Real-time PCR²⁵</td>
<td>1251</td>
<td>Blood</td>
<td>55%</td>
<td>93%</td>
<td>40%</td>
<td>96%</td>
</tr>
<tr>
<td>Real-time PCR²⁵</td>
<td>16</td>
<td>Blood</td>
<td>69.6% - 82.1% (depending on primers)</td>
<td>80.4% - 91.1% (depending on primers)</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Real-time PCR²⁵</td>
<td>401</td>
<td>Blood</td>
<td>92.3%</td>
<td>94.6%</td>
<td>60%</td>
<td>99.3%</td>
</tr>
<tr>
<td>Real-time PCR²⁵</td>
<td>1193</td>
<td>Blood</td>
<td>100%</td>
<td>65%</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>PCR-ELISA²⁶</td>
<td>241</td>
<td>Blood, BAL, tissue</td>
<td>Proven infection: 40% - 100%; probable infection: 44% - 66%</td>
<td>Proven infection: 100%; probable infection: 100%</td>
<td>100%</td>
<td>44% - 58%</td>
</tr>
<tr>
<td>PCR-ELISA¹⁹</td>
<td>1205</td>
<td>Blood</td>
<td>63.6%</td>
<td>89.7%</td>
<td>63.6%</td>
<td>89.7%</td>
</tr>
<tr>
<td>Conventional PCR²²</td>
<td>197</td>
<td>BAL</td>
<td>93.9%</td>
<td>94.4%</td>
<td>83.8%</td>
<td>98.1%</td>
</tr>
<tr>
<td>Conventional PCR²³</td>
<td>68</td>
<td>BAL</td>
<td>Proven infection: 80%; probable infection: 64%</td>
<td>Proven infection: 93%; probable infection: 93%</td>
<td>Proven infection: 38%; probable infection: 52%</td>
<td>Proven infection: 99%; probable infection: 98%</td>
</tr>
</tbody>
</table>

PCR, polymerase chain reaction; PPV, positive predictive value; NPV, negative predictive value; BAL, bronchoalveolar lavage; NP, not provided; ELISA, enzyme-linked immunosorbent assay.
Conclusions

Studies show PCR assays to be both sensitive and specific in the diagnosis of infections caused by fungi such as *Aspergillus* and *Candida*; sensitivity is typically greater with tissue than with blood. The diagnostic value of PCR testing may be further enhanced in the appropriate clinical setting or when the test is done in conjunction with other tests, such as culture and the GM assay. When done serially, quantitative PCR testing might be useful for monitoring disease progression or response to therapy, and potentially it could be used to differentiate colonization from infection. In addition, PCR testing has shown promise in the diagnosis of infections caused by other fungi, such as *C. neoformans, H capsulatum,* and *Pneumocystis jiroveci.* However, the sensitivity of these assays predominate to false-positive results, and true-positive results may not distinguish between contamination, colonization, and infection. Further clinical studies are needed before PCR testing alone can be advocated for the diagnosis of fungal infection.

REFERENCES


Acute Suppurative Thyroiditis in a Patient With Aplastic Anemia

Yoo Seung Chung, MD, Jun-Ho Choe, MD, Wonshik Han, MD, Dong-Young Noh, MD, Yeo-Kyu Youn, MD, and Seung Keun Oh, MD

Acute suppurative thyroiditis (AST) is a rare inflammatory complication in patients with hematological malignancy. Infection spreads to the thyroid from a distant site through the bloodstream or the lymphatics. Defects such as persistent thyroglossal duct and pyriform sinus fistula are associated with the development of AST. Ultrasonography, barium swallow testing, CT, and fine-needle aspiration are used for diagnosis. Treatment includes the administration of parenteral antibiotics, drainage, and excision. We describe a patient with aplastic anemia and bacteremic AST. [Infect Med. 2008;25:339-342]

Key words: Acute suppurative thyroiditis

A 27-year-old man presented to our hospital with symptoms of general weakness and fatigue. His blood test results were positive for anemia (hemoglobin level, 2.9 g/dL). A bone marrow biopsy specimen showed cellularity values of 0% to 10%, a range that is considered hypocellular for the patient’s age; erythropoiesis, granulopoiesis, and megakaryocyte production were decreased. Aplastic anemia was diagnosed, and the patient was treated with a consecutive 5-day regimen of antithymoglobulin (ATG). At the start of chemotherapy, the absolute neutrophil count (ANC) was 1534/mL.

Five days after the administration of ATG (day 1), sudden fever and sore throat developed. The patient’s temperature was 39.9°C (103.8°F). Blood pressure was 110/70 mm Hg, with a pulse rate of 96 beats per minute. Symptoms of influenza were absent, but the patient complained of a sore throat and right-sided neck pain. No skin change or discoloration of the neck area was observed; however, swelling and tenderness of the neck developed.

The ANC was 252/mL. A thyroid function test revealed high free thyroxine levels (2.37 ng/dL; normal, 0.70 to 1.80 ng/dL), depressed thyroid-stimulating hormone levels (0.12 mIU/L; normal, 0.4 to 4.1 mIU/L), and normal total triiodothyronine levels (91 ng/dL; normal, 87 to 184 ng/dL). A blood culture was performed, and piperacillin and tobramycin were administered empirically.

Radiological examination revealed cystic lesions of the thyroid gland with decreased enhancement; a thyroid abscess was therefore suspected (day 3; Figure 1). No pyriform sinus fistula (PSF) was detected by laryngoscopy or CT. Because the blood culture grew methicillin-sensitive Staphylococcus aureus (MSSA), cefazolin was added to the therapeutic regimen. Despite this antibiotic therapy and ultrasonography-guided aspiration (day 6; Figures 2 and 3), the patient’s condition did not improve.

Acute suppurative thyroiditis (AST) is a rare inflammatory disease. The rarity of this disease can be attributed to several factors. The thyroid is well encapsulated, which may hinder the transmission of infection from surrounding tissue to the thyroid. In addition, a rich blood supply and lymphatic drainage within the thyroid may be protective against bacterial infection. Furthermore, high iodine levels within the thyroid gland may create an environment that is unfavorable to bacterial growth.1 Reports of AST are uncommon in patients who have hematological malignancy. Only 9 cases have been reported in the literature.2,3

Dr Chung and Dr Choe are fellows and Dr Han, Dr Noh, Dr Youn, and Dr Oh are professors of medicine in the department of general surgery at Seoul National University College of Medicine, South Korea.
improve. Surgery was performed to manage the thyroid abscess (day 8).

During surgery, necrotic tissue was discovered in the lower right pole of the thyroid gland. The left side of the gland was lesion-free. We performed necrosectomy of the friable necrotic tissue and drained yellow pus. Ultimately, a right subtotal thyroidec- 

tomy was performed (Figure 4). We irrigated the thyroid bed with normal saline solution and applied a Jackson-Pratt closed-suction drain. The volume of drainage decreased successively from 20 mL to 10 mL to 5 mL over the course of 3 days postoperatively, and the wound was clean. Thyroid tissue culture revealed MSSA, as did cultures of blood and aspirated mucus.

The pathology laboratory reported a chronic active inflammation with an abscess in the base of an adenomatous goiter (AG) (Figure 5). After the operation, the patient’s fever persisted and he reported hip joint pain, which seemed to be caused by bacteremia. A chest CT scan revealed multiple nodules with cavitation in both lungs, which was associated with a ground-glass opacity in both upper lobes and minimal bilateral pleural effusion. These symptoms suggested septic pneumonia and superinfection with Pneumocystis jiroveci. Nafcillin, piperacillin/tazobactam, and trimethoprim/sulfamethoxazole were administered. When the patient’s symptoms improved and the bacteremia resolved, the patient was discharged from the hospital on the 51st postoperative day.

Discussion

Because of its rich blood supply, lymphatic drainage, abundant iodine, and protective fibrous capsule, the thyroid gland is very resistant to infection. However, AST develops in several settings. One setting is when infection spreads from a distant site to the thyroid via the bloodstream or lymphatic system. Also, AST may develop secondary to trauma and persistent thryoglossal duct and by direct extension of infection from a neighboring structure to the thyroid. Preexisting thyroid disease, including AG, nodular goiter, Hashimoto thyroiditis, and thyroid cancer, can precede thyroid infection. AG can be the indirect cause of a thyroid abscess.

In our patient, S. aureus was isolated from blood and thyroid tissue cultures. Bacteremia was attributed to immunosuppression during chemotherapy with ATG. It is recommended that patients in whom fever develops following ATG administration be treated with broad-spectrum antibiotics.
antibiotics. Also, some investigators have recommended that patients at high risk for infection should be given prophylactic antibiotic and antifungal therapy, although there is a concern that this strategy may aggravate emergence of antibiotic resistance. Because of this caveat, our hospital does not use prophylactic antibiotic therapy in neutropenic patients during ATG chemotherapy.

AST is a rare complication of chemotherapy in hematological malignancy: Of the 9 cases reported in the literature, 5 were attributed to fungal infection (all associated with *Candida* species). Of the 4 cases attributed to bacterial infection, a causative bacterial pathogen was confirmed in only 1 case. Blood and tissue cultures yielded *Salmonella*.

Numerous imaging methods, such as ultrasonography, barium swallow tests, and CT, are used to diagnose AST. Ultrasonography is thought to be an important method for diagnosing thyroid abnormalities. PSF, in particular, is considered to be one of the most common underlying abnormalities in AST. Barium swallow is an essential diagnostic tool for confirming PSF. However, Bernard and colleagues have suggested that CT is extremely useful in diagnosing AST in its early phase, claiming that it provides more accurate mapping than ultrasonography. In our case, we used CT as the first-line imaging modality to evaluate the suspected thyroid abnormality and any other pathological cervical lesions. Because laryngoscopy and CT did not detect PSF and because bacteremia was the suspected cause of symptoms, we performed the operation before invaginascence.

Treatment should include administration of parenteral antibiotics, drainage of the abscess, and excision of the affected area. There is no significant difference in the course of disease or survival among patients treated with antibiotics, drainage, or a combination of both. Because the mortality rate of AST is 8.6% and because no improvement was seen after administration of antibiotic therapy and aspiration of exudates, surgical management was an appropriate decision in our case.

Few studies discuss the relationship between hematological malignancy and thyroid disease in long-term follow-up. Moskowitz and colleagues reported that autoimmune disorders such as Graves disease, Hashimoto thyroiditis, toxic multinodular goiter, and idiopathic hy-
Acute Suppurative Thyroiditis continued

... are closely associated with acute leukemia. Toubert and colleagues\textsuperscript{14} reported that hypothyroidism could occur after bone marrow transplant without total body irradiation. Therefore, follow-up thyroid function testing should be performed and hormonal therapy, if needed, should be administered.

\textbf{REFERENCES}


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