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A 19-year-old man with oral ulcers, pulmonary infiltrates, and rash

A 19-YEAR-OLD college student presents with fever, chills, sweats, sore throat, and cough productive of white to yellowish sputum. The symptoms began 10 days ago; 4 days later the patient developed painful oral ulcers accompanied by odynophagia. He then noticed itching, tearing, and redness of both eyes.

He has not had any change in vision, sensitivity to light, nosebleeds, earache, or ear discharge. He says he has malaise, fatigue, and vague abdominal discomfort but no nausea, vomiting, diarrhea, or blood in the stools. He had not taken any medications before this illness.

Medical history. The patient had varicella as a child; otherwise, he has been healthy. He says he does not smoke, drink alcohol, or use illicit drugs and has never had sex. He is a member of his college soccer team.

Physical examination. Blood pressure 99/46 mm Hg, heart rate 108 per minute, respiratory rate 24 per minute, temperature 103.5°F (39.7°C), oxygen saturation 99% by pulse oximetry while breathing oxygen at 2 L/minute, and body mass index 24 kg/m^2. He appears uncomfortable and is drooling. He is alert and oriented to time, place, and person.

Both eyes have marked bilateral conjunctival injection with slight bleeding but no purulent discharge (FIGURE 1). His lips are dry, swollen, and erythematous (lower more than the upper) with ulcerations (FIGURE 2). He has multiple shallow ulcers on his tongue, palate, buccal mucosa, and pharynx, but no pharyngeal exudates. He has no palpable cervical lymphadenopathy.

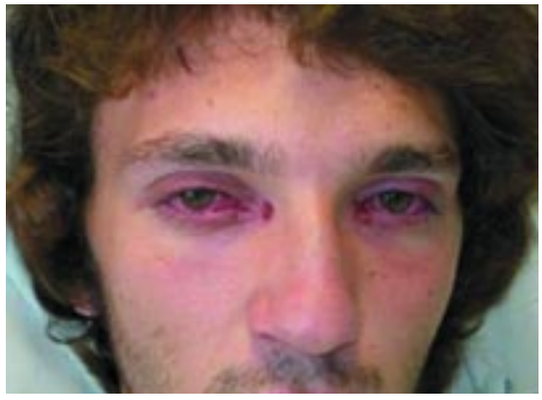

FIGURE 1. Bilateral conjunctival injection with a crusted erosion on the right medial canthus.

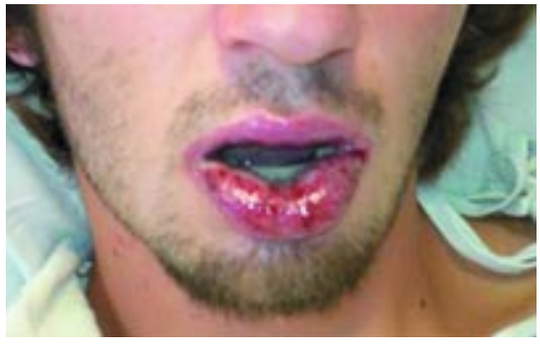

FIGURE 2. Swollen, erythematous lips with ulcerations.

What is the cause of the symptoms in this previously healthy young man?

His chest is clear to auscultation. His heart rate is rapid with a regular rhythm; his heart sounds are normal with no murmurs, rubs, or gallops. His abdomen has no palpable organomegaly or significant tenderness. No skin rash is noted. He has no edema in his legs.

A complete blood cell count and chemistry panel, including liver function tests, are

*Dr. Taege has disclosed that he has received honoraria from Glaxo and BMS for teaching and speaking.

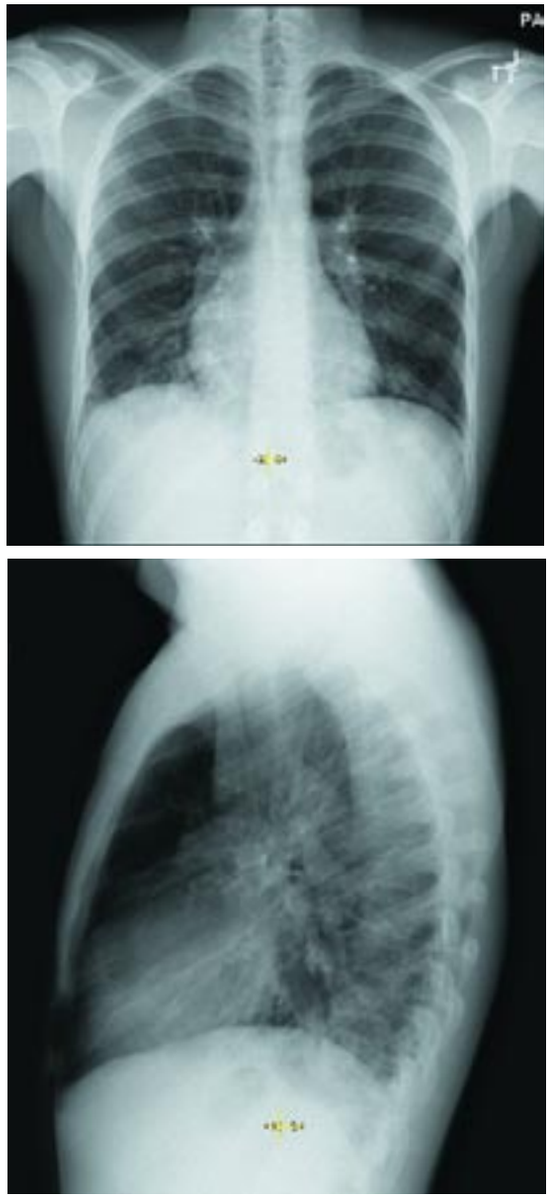

FIGURE 3. The chest radiograph, posterior-anterior view (**top**) and lateral view (**bottom**) both show subtle basilar infiltrates.

Erythema multiforme and Stevens-Johnson syndrome can be viewed as a continuum of severity

normal. Urinalysis shows proteinuria (100 mg/dL) and ketonuria (3+). Chest radiography reveals subtle bilateral alveolar infiltrates (FIGURE 3).

On the second hospital day, the patient begins to experience burning pain on urination but no urgency or frequency. A superficial erosion is noted at the tip of his penis; it is not tender and is not accompanied by any discharge. Subsequently, a few scattered targetoid plaques with vesicles appear on his arms, legs, chest, and back.

A dermatology consult is requested and a skin biopsy is performed on his left arm.

WHAT IS THE LEAST LIKELY DIAGNOSIS?

1 Which of the following is the least likely diagnosis?

- ❑ Infectious mononucleosis
- ❑ Herpes simplex virus (HSV-1) infection
- ❑ Coxsackievirus infection
- ❑ Systemic lupus erythematosus
- ❑ Herpes zoster
- ❑ Erythema multiforme
- ❑ Stevens-Johnson syndrome

Systemic lupus erythematosus is the least likely diagnosis in this case. Although this autoimmune disorder can occur in men, it is more common in women of reproductive age.

Moreover, although this disease can affect nearly any organ system and it can present with fever, myalgia, oral, genital, and nasal ulcers and maculopapular rash (which were present in our patient), the diagnosis requires 4 of the following 11 criteria: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder, and positive antinuclear antibody titer.[1] Our patient has only 2 of these criteria—oral ulcers and mild proteinuria.

The other diagnoses listed above are still possibilities in our patient at this point.

Infectious mononucleosis is an acute illness caused by Epstein-Barr virus in 80% of cases. It develops late in adolescence after intimate contact with someone who is shedding the virus from the oropharynx.

Symptoms and signs include sore throat, fever, generalized lymphadenopathy, headache, and myalgias. Five percent to 10% of patients develop a transient rash that may be macular, petechial, or urticarial. Palatal petechiae are often present, and pharyngitis may or may not be exudative. Cervical lymphadenopathy is prominent, particularly of the posterior lymphatic chain, although lymphadenopathy elsewhere is common. Splenomegaly may be present in 50% of patients. This disease rarely presents with autoimmune

TABLE 1

Drugs associated with Stevens-Johnson syndrome

More frequently
Allopurinol (Aloprim, Zyloprim)
Aminopenicillins
Barbiturates
Carbamazepine (Carbatrol, Tegretol, others)
Hydantoins
Phenylbutazone
Piroxicam (Feldene)
Sulfadiazine (Microsulfon)
Sulfadoxine
Sulfasalazine (Azulfidine)
Cotrimoxazole
Trimethoprim/sulfamethoxazole (Bactrim, others)

Less frequently
Cephalosporins
Diclofenac (Voltaren, others)
Ethambutol (Myambutol)
Fluoroquinolones
Ibuprofen (Advil, Motrin, others)
Ketoprofen (Orudis, Oruvail)
Naproxen (Naprosyn, others)
Rifampin (Rifaden, others)
Sulindac (Clinoril)
Thiabendazole (Mintezol)
Vancomycin (Vancocin)

ADAPTED FROM ROUJEAU JC, STERN RS. SEVERE ADVERSE CUTANEOUS REACTIONS TO DRUGS. N ENGL J MED 1994; 331:1272–1285.

Sulfa drugs cause up to 50% of cases of Stevens-Johnson syndrome

hemolytic anemia, thrombocytopenia, encephalitis, aseptic meningitis, Guillain-Barré syndrome, hepatitis, or splenic rupture. Seventy-five percent of patients have absolute lymphocytosis, and 30% of lymphocytes may be atypical.

The infectious mononucleosis slide (Monospot) test is highly sensitive and specific, with sensitivity ranging from 86% to 94% and specificity ranging from 95% to 99%.[2,3] If the test is positive, no further testing is needed for confirmation. However, if it is negative and the diagnosis is still suspected, testing for immunoglobulin M (IgM) antibody to Epstein-Barr virus establishes the diagnosis of acute infectious mononucleosis.[1]

HSV-1 infection commonly involves the vermillion border of the lips, mouth, and pharynx. Fever, headache, and malaise often precede the appearance of the oral lesion of primary herpes simplex by 24 to 48 hours. The involved areas are swollen, painful, and erythematous. Small vesicles appear and then rupture, leaving shallow, discrete ulcers that may coalesce. Autoinoculation may spread the infection to the eyes and cause herpetic keratitis, which could lead to blindness. HSV-1 can become disseminated in an immunocompromised patient.

HSV-1 infection is diagnosed by Tzanck preparation from the base of the ulcer revealing intranuclear inclusions and multinucleated giant cells. Other diagnostic tests are an immunoassay for viral antigen in the scraping and the direct fluorescent antibody test. Viral cultures are more sensitive but expensive.[1]

Herpes zoster (shingles) occurs as a reactivation of varicella zoster virus infection, usually in immunocompromised patients or those exposed to physiologic stress. Usually, pain or dysesthesia is followed by unilateral papulovesicular lesions in a dermatomal distribution. However, disseminated zoster can occur in severely immunocompromised people.[1]

Coxsackievirus infection can present with enanthems and exanthems. Hand, foot, and mouth syndrome is a common acute illness caused by coxsackievirus A16. It affects mostly children but can also occur in adolescents and adults. In adults, the illness is similar to that in preschool children and is not more severe. The syndrome is characterized by low-grade fever; oral vesicles or ulcerations on the buccal mucosa, tongue, and hard palate; and maculopapular and vesicular lesions on the hands, feet, buttocks, and less commonly, genitalia.[4] The illness is usually benign and resolves in 2 to 3 days without complications.

Erythema multiforme was described by von Hebra in 1866 as acral (peripheral), targetoid, edematous papules or plaques without mucosal involvement. The typical "target" lesions have three zones: a small central erythematous papule that may blister, a raised edematous pale middle ring, and an erythematous outer ring. It is associated with infections, particularly herpes simplex virus.[5]

Stevens-Johnson syndrome is an acute, self-limited disease characterized by severe inflammation and necrosis of two or more mucous membranes. It can be accompanied by systemic symptoms such as fever and malaise.

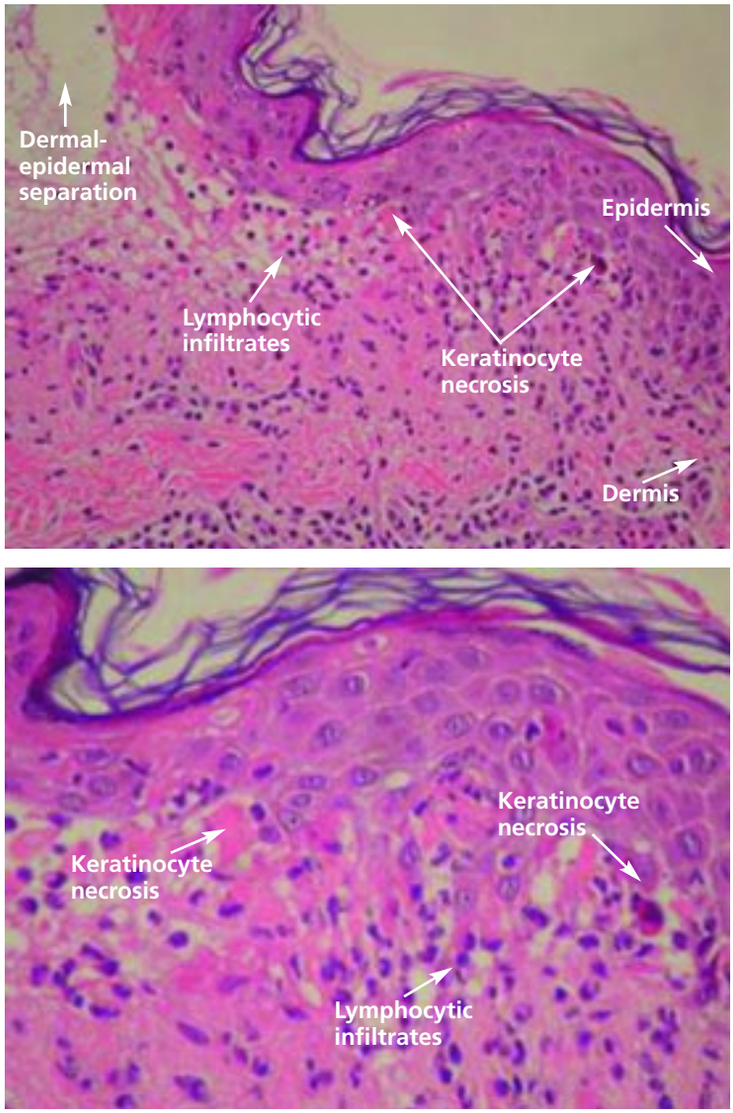

FIGURE 4. Top, skin biopsy at low-power magnification; **bottom,** higher magnification

The term has been used synonymously with erythema multiforme major since the 1950s,[6] and erythema multiforme and Stevens-Johnson syndrome can be viewed as a continuum of severity, with erythema multiforme being milder and Stevens-Johnson syndrome being more severe.

Stevens-Johnson syndrome is commonly associated with drug reactions (**TABLE 1**),[7] most often with sulfa compounds, which cause 30% to 50% of cases. Infections have been linked to 15% to 20% of cases. The remaining cases may be idiopathic or, rarely, associated with malignancies, collagen vascular disease, immunization, or chemicals. The syndrome typically arises 1 to 3 weeks after exposure to an inducing agent.

INITIAL WORKUP

2 Which of the following would be the least helpful for this patient's initial workup?

- ❑ Viral serologic tests
- ❑ HSV-1 direct fluorescent antibody test or culture from lip blister
- ❑ Blood cultures
- ❑ Bronchoscopy
- ❑ Skin biopsy

Given the presentation in this patient (with oral ulcers, skin rash, high fever, and mildly symptomatic pulmonary infiltrates), viral serologic tests, direct fluorescent antibody tests, and blood cultures would be appropriate. Skin biopsy would also be appropriate and may help detect a viral cause.

Bronchoscopy is an invasive procedure, may not offer additional benefit at this time, and would not be used in the initial workup.

CASE CONTINUED

Our patient undergoes testing with an antinuclear antibody titer, blood and urine cultures, a human immunodeficiency virus serologic test, and the test for mononucleosis, all of which are negative. A direct fluorescent antibody test of his lip ulcer is negative for herpes simplex virus, varicella zoster virus, and adenovirus. Cultures of the oral ulcers for cytomegalovirus, HSV-1, and varicella zoster virus are also negative. DNA amplification tests from a urethral swab are negative for *Neisseria gonorrhoea* and *Chlamydia* species.

The patient's serum is negative for coxsackie B antibody; however, it is positive for coxsackie A9. The interpreting laboratory believes this may be a false-positive result due to the presence of anticomplement antibodies and a large number of immune complexes.

Skin biopsy reveals moderately dense superficial perivascular and intervascular infiltrates of small round lymphocytes with epidermotropism, vasculopathy, and keratinocyte necrosis. There is dermal-epidermal separation and mild reactive hyperplasia of the epidermis,

consistent with inflammation. Intranuclear viral inclusions are not seen (FIGURE 4). The pathologic diagnosis of the skin biopsy is consistent with erythema multiforme.

Given the clinical findings of mucosal ulceration, fever, and skin lesions, our patient's case is consistent with Stevens-Johnson syndrome.

WHAT ORGANISMS CAUSE STEVENS-JOHNSON SYNDROME?

3 Which of the infectious agents listed below has been associated with Stevens-Johnson syndrome?

- ❑ Herpes simplex virus
- ❑ Adenovirus
- ❑ *Streptococcus pneumoniae*
- ❑ *Mycoplasma pneumoniae*
- ❑ All of the above

All of the above have been associated with Stevens-Johnson syndrome, but this disease is associated with infection in only 15% of cases.

In case reports, M *pneumoniae* accounted for most of these cases. However, no widespread epidemiologic studies have been conducted. In studies that combined epidemiologic data for infectious causes of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (which are a continuum of diseases), herpes simplex virus accounted for 26% of cases and M *pneumoniae* accounted for 5%. Other infectious associations include urinary tract infection (6%), Epstein-Barr virus infection (3%), viral meningitis (1.6%), viral gastroenteritis (1.6%), cytomegalovirus infection (1.6%), and streptococcal infection (1.6%). Viral pathogens include adenovirus, measles, mumps, influenza, and enterovirus. Other bacteria implicated in Stevens-Johnson syndrome are pneumococci, enterobacteriaceae, enteric pathogens such as *Salmonella* and *Yersinia*, *Mycobacterium tuberculosis*, and *Treponema pallidum*.[8,9]

CASE CONTINUED

In our patient, a serum test for M *pneumoniae* IgM is significantly positive, with an immune status ratio of 6.04 (negative < 0.91); a test for M *pneumoniae* IgG is also significantly positive, with an optical density ratio of 11.20 (negative: ≤ 0.90). These results were obtained approximately 2 weeks after the onset of his illness.

His clinical presentation, physical findings, laboratory results, and radiographic data are consistent with M *pneumoniae* infection complicated by Stevens-Johnson syndrome.

M PNEUMONIAE AND STEVENS-JOHNSON SYNDROME

In 1945, Stanyon and Warner[10] reported the association of M *pneumoniae* and Stevens-Johnson syndrome in 17 young men with atypical pneumonia, fever, conjunctivitis, stomatitis, lesions of the penis, and irregular skin eruptions. In those days this constellation of signs and symptoms was called mucosal respiratory syndrome and had been thought to be due to viral infections.

In 1964, Ludlam and Bridges[11] discovered high titers of antibody to M *pneumoniae* in three patients with Stevens-Johnson syndrome. Since then, at least 70 patients with M *pneumoniae* infection complicated by Stevens-Johnson syndrome were described. The exact incidence of this association is unknown, as most of the literature is in the form of case reports,[6] and no widespread epidemiologic tracking has been performed.

Treatment for Stevens-Johnson syndrome is supportive

Pathogenesis

The pathophysiologic mechanism of Stevens-Johnson syndrome is unclear, but it is presumed to be an immunologic or hypersensitivity reaction to a wide variety of stimuli. The three possible mechanisms for immune-mediated injury are an immune-complex-mediated vascular injury, an autoimmune reaction, and a cytotoxic-T-cell-mediated immune response.[8]

Clinical features

M *pneumoniae*-associated Stevens-Johnson syndrome affects mainly children and young adults (age 5–23 years, mean age 15). A few patients in their 40s have also been described. It is more common in males. However, Lind found the incidence to be similar in males and females.[12]

Prodromal symptoms include fever with or without chills, sore throat, cough, rhinor-

rhea, headache, malaise, and myalgias. Symptoms can arise 2 days to 2 weeks before onset of the skin changes.[6]

The diagnosis of Stevens-Johnson syndrome is based on the following clinical features[5]:

- Mucosal erosion at two or more sites (stomatitis, conjunctivitis, urethritis)
- Skin lesions consisting of small blisters on dusky purpuric macules or atypical target lesions that have rare areas of confluence and detachment covering less than 10% of the body surface area
- Fever
- Respiratory or gastrointestinal involvement.

Laboratory findings are nonspecific and can include leukocytosis, elevated erythrocyte sedimentation rate, elevated aminotransferase levels, and, if urethritis is present, hematuria, proteinuria, and pyuria. Infectious causes can produce elevation of corresponding titers or positive cultures.[5]

Study of skin biopsy specimens reveals a perivascular mononuclear infiltrate with some eosinophils in the papillary dermis, full-thickness necrosis of the epidermis, and variable hydropic degeneration of the basal layer. In severe cases, subepidermal blistering may be seen.[13,14]

The illness can last 1 to 5 weeks. Most patients recover within 2 weeks. However, the mucous membrane lesions may resolve slowly and may take up to 2 months to heal completely.[6] Treatment with corticosteroids is controversial.

***M pneumoniae* causes up to 20% of cases of community-acquired pneumonia in adults and 40% of cases in children**

COMPLICATIONS

4 Stevens-Johnson syndrome is associated with all of the following complications except for which one?

- ❑ A high mortality rate
- ❑ Blindness
- ❑ Recurrent mucocutaneous lesions
- ❑ Respiratory distress

Stevens-Johnson syndrome can be complicated by respiratory distress due to sloughing of respiratory mucosa. Ocular complications can include conjunctival scarring, dry eyes, keratitis, entropion, and blindness. Recurrent mucocutaneous lesions can occur and may be associated with scarring.

Fortunately, few patients die, and the prognosis is generally good.[6] The mortality rate in Stevens-Johnson syndrome is between 1% and 3%; the major cause of death is sepsis.[14]

TREATMENT

5 All of the following are appropriate treatment options for Stevens-Johnson syndrome except for which one?

- ❑ Fluid and electrolyte replacement
- ❑ Adequate nutrition
- ❑ Antibiotics
- ❑ Thalidomide

Treatment for Stevens-Johnson syndrome is supportive, consisting of fluids, adequate nutrition, analgesia, skin care, ophthalmologic care, avoidance of further exposure to the inducing agent, and appropriate antibiotics when infection is the suspected cause.

Conclusive evidence is lacking in support of the use of corticosteroids, cyclosporine, cyclophosphamide, intravenous immune globulin, or thalidomide.[5,6,8]

M PNEUMONIAE INFECTION

M pneumoniae causes atypical pneumonia, and it may be responsible for up to 20% of cases of community-acquired pneumonia in adults and about 30% of hospitalizations for community-acquired pneumonia among the elderly.[15] It also accounts for 40% of cases of community-acquired pneumonia in children, of which 18% may require hospitalization. School-aged children, military recruits, and college students are most commonly affected.[5] *M pneumoniae*-related community-acquired pneumonia is common during the fall and winter, but it can occur throughout the year.

Transmission is via respiratory droplets, and incubation is about 3 weeks.

Clinical features

Mycoplasma infection may be asymptomatic or may produce a mild upper respiratory tract infection or pneumonia. The onset may be insidious, with headache, malaise, and low-

grade fever with or without chills.

Respiratory symptoms include sore throat, earache, and nonproductive cough. Sputum production occurs later in the course of the illness. Patients may present with dyspnea, pharyngitis, rhinorrhea, ear pain (a manifestation of hemorrhagic bullous myringitis), and cervical lymphadenopathy. Physical findings on pulmonary examination are typically far less impressive than the radiographic findings.

Extrapulmonary involvement includes autoimmune hemolytic anemia secondary to cold agglutinins, which are IgM antibodies directed against the red cell basement membrane. When present, skin lesions range from mild maculopapular or vesicular rash to Stevens-Johnson syndrome.

Other rare features, which are more common in children, consist of neurologic manifestations (aseptic meningitis, meningoencephalitis, peripheral neuropathy, transverse myelitis, cranial nerve palsy, cerebellar ataxia), rheumatologic manifestations (myalgia, arthralgia, polyarthritis), cardiac manifestations (arrhythmias, conduction disturbance, congestive heart failure, chest pain, myocarditis), and renal involvement (glomerulonephritis, IgA nephropathy).[16]

Chest radiographic findings commonly include bronchopneumonia, interstitial infiltrates, and atelectasis with predilection for the lower lobes. Nodular infiltration and hilar adenopathy are less common. Pleural effusion occurs in 20% of cases, and empyema is rare.[17]

Macrolide antibiotics are the mainstay of treatment for *M pneumoniae*

TESTS FOR *M PNEUMONIAE*

6 What is the most commonly used test for early diagnosis of M *pneumoniae* infection?

- ❑ Blood culture
- ❑ Sputum culture
- ❑ Serologic testing
- ❑ Cold agglutinin
- ❑ Polymerase chain reaction (PCR)

Serologic testing, using complement fixation to detect early IgM and IgG antibodies, is the most commonly used diagnostic test for M *pneumoniae*. The overall sensitivity of the complement fixation test is 90% in culture-proven cases of M *pneumoniae* pneumonia. Serologic testing is considered positive if there is a fourfold or greater rise in titer of paired sera (sensitivity 53%) or a single titer of greater than 1:32 (sensitivity 90%, specificity 94%). Antibody titers begin to rise 7 to 9 days after infection and peak at 3 to 4 weeks.[18,19]

The white blood cell count is normal in 75% to 90% of cases. In cases of autoimmune hemolytic anemia, the Coombs test may be positive and the reticulocyte count may be high. Cold agglutinins are usually detected 1 week after the onset of symptoms, peaking at 12 to 25 days and rapidly falling after 30 days. They may be elevated in 50% of cases and are nonspecific, as they occur in other conditions such as Epstein-Barr virus, cytomegalovirus, and adenovirus infection, lymphoma, myeloma, and collagen vascular disease.[20]

Sputum culture is not routinely done, as these fastidious organisms require 2 to 3 weeks to grow. The sensitivity of sputum culture is only 60%, but its specificity is 97%.[18]

Antigen detection by enzyme immunoassay (Ag-EIA) is a newer technique for detecting *Mycoplasma* infection. Ag-EIA is usually positive within 7 days of the onset of symptoms.

PCR, performed on a sputum sample, is highly sensitive (92%) and specific (98%). At present, it is used mostly in epidemiologic studies.[21,22]

Treatment of *M pneumoniae* infection

Macrolide antibiotics are the mainstay of treatment for M *pneumoniae*, and most commonly used is azithromycin (Zithromax). Alternative agents are the tetracyclines and fluoroquinolones.

The duration of treatment has not been firmly established. The conventional duration is 7 to 10 days. However, some studies have shown that 3 to 5 days of azithromycin may be adequate.[23,24]

CASE CONTINUED

The patient was treated with azithromycin 500 mg intravenously daily along with supportive care including fluids, nutrition, analgesia, eye care, and skin care. His symptoms improved significantly by the 6th day and he was discharged home. He then completed a course of oral azithromycin. ■

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