Atypical measles: A diagnostic conundrum

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Atypical measles syndrome has been reported extensively in the pediatric medical literature. However, the clinical picture in the adult is similar to that of many other diseases, making the diagnosis elusive. The case reported here was unusually morbid. The patient, a young man, had been in excellent health until the onset of a perplexing syndrome. When seen by the author, he had been ill for 1 week with chills, pharyngitis, and vomiting; later, a nonpruritic, maculopapular rash developed. Symptoms progressed to pneumonitis and hepatitis. A rubeola titer was obtained and was found to be considerably elevated. Because of the high titer and the fact that the patient had been immunized against measles in early childhood, the diagnosis was atypical measles syndrome. Two theories are offered to explain the pathogenesis of this disease.

(Key words: Atypical measles syndrome, rubeola, pneumonitis, hepatitis, maculopapular rash, killed measles virus vaccine)

Since atypical measles syndrome was originally reported by Rauh and Schmidt[1] in 1985, it has been extensively described in the pediatric medical literature. Cases were reported in the internal medicine literature during the mid- to late-1970s[2-5]; however, few cases have been reported since 1982.[6] Because the clinical picture of atypical measles syndrome is so similar to that of many other diseases, the diagnosis may be elusive unless the practitioner keeps this syndrome specifically in mind.[7]

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The syndrome is generally considered to include fever, malaise, myalgia, headache, nausea, and vomiting, followed by coryza, sore throat, conjunctivitis, photophobia, nonproductive cough, and pleuritic pain. The characteristic rash is erythematous and maculopapular, possibly progressing to vesicular, petechial, or purpuric lesions. The rash initially involves the palms of the hands and the soles of the feet. It subsequently spreads to the proximal extremities and the trunk, sparing the face.[8,9] Hepatitis and pneumonitis with considerable hypoxia are also seen. The case described here was associated with greater morbidity than is generally reported.

Report of case

A 22-year-old Mexican-American man was admitted to Mesa (Ariz) General Hospital after being ill for 1 week. Illness began with chills, followed by mild pharyngitis, mild dysphagia, and one episode of vomiting. The patient had been seen by his family physician, who started amoxicillin therapy. A nonpruritic, macular rash then developed, first appearing on the knees, elbows, and thighs, and then the chest, hands, and feet. Antibiotic therapy was then switched to erythromycin, which the patient continued taking until the time of admission. He had had sweating and chills, weakness, and severe myalgia, but he denied having symptoms of arthritis.

The patient had gone wading in a local lake several weeks before becoming ill. He was unaware of having had a tick bite, and he had not consumed any raw foods. He had lived in Arizona since 1979,

and had previously lived in Florida and Texas. The patient's pet dog was healthy. The patient had not had close contact with children who might have been recently vaccinated, nor had he been in contact with persons with active tuberculosis. He had not been sexually active, he had not used intravenous drugs, and he had never received a blood transfusion.

The patient's parents stated that they had followed the recommended immunization schedule, but they could not produce specific records. They said that the patient had had measles and chickenpox as a child. The patient had not had surgery, had never been hospitalized, took no medications, and was a nonsmoker and a nondrinker. The family history was noncontributory for significant illness.

Physical findings

The findings of a review of systems added nothing to the preceding history. Until the present illness, the patient had been in excellent health.

Physical examination revealed pharyngeal lymphoid hyperplasia. The neck was supple with tender anterior cervical adenopathy. The heart rate and rhythm were regular at 110 beats per minute; the respiration rate was 14 per minute. The patient had a III/VI systolic ejection murmur without radiation that was best heard at the apex. The patient had no previous awareness of this murmur. The liver was tender to percussion at approximately 14 cm. A fine, reticular, maculopapular, erythematous rash covered the whole body, but was fainter on the palms of the hands and soles of the feet.

Laboratory findings

Laboratory studies during the patient's first hospitalization yielded the following values for serum components: albumin, 3.0 g/dL; alkaline phosphatase, 324 units/L; alanine aminotransferase, 196 units/L; aspartate aminotransferase, 127 units/L; total bilirubin, 1.5 mg/dL; blood urea nitrogen, 12 mg/dL; creatinine, 0.8 mg/dL; and lactate dehydrogenase (LDH), 509 units/L. Blood component values were as follows: hemoglobin concentration, 14 g/dL; hematocrit, 40%; white blood cell (WBC) count, 29,000/mm^3, with a differential count of 60 segmented neutrophils, 24 band neutrophils, 9 lymphocytes, 4 monocytes, many Döhle bodies, and toxic granulation; erythrocyte sedimentation rate, 77 mm/h; prothrombin time, 16.4 seconds, with a control of 11.7 seconds; and partial thromboplastin time, 30.1 seconds. The findings of these laboratory studies did not change markedly during the hospital stay, but the WBC count did reach as high as 39,000/mm^3, with 37 segmented neutrophils, 59 band neutrophils, 2 lymphocytes, and 1 eosinophil.

Table
Additional Serology Test Results

Test	Titer
Toxoplasmosis	
Immunoglobulin G	<1:16
Immunoglobulin M	<1:8
Herpes simplex	
Immunoglobulin G	<0.25
Immunoglobulin M	<0.22
Coxsackie virus	<1:8
Complement fixation	<1:2
Cytomegalovirus	
Immunoglobulin G	<0.22
Immunoglobulin M	<1:18
Antinuclear antibody	<1:40
Epstein-Barr virus antibody by indirect fluorescent antibody test	<1:10
Legionella	<1:64
Mycoplasma	<1:2

The following tests yielded negative results: buffy-coat preparation for cytomegalovirus; serologic tests for antibodies to *Leptospira*; direct antiglobulin test; serologic tests for antibodies to hepatitis A and B; *Clostridium difficile* toxin; latex agglutination test; serologic test for antistreptolysin-O; antibodies to human immunodeficiency virus; stool cultures for ova and parasites; cultures of blood and urine; and smear and culture of the urine for acid-fast bacilli. Urinalysis revealed 20 to 25 WBCs. Results of a febrile agglutinin series were within normal limits, and a latex agglutination test for coccidioidomycosis was nonreactive. Additional serology test results appear in the Table.

An echocardiogram showed mitral valve prolapse without vegetations. Results of the electrocardiogram indicated Wolff-Parkinson-White syndrome, type B. Findings of abdominal ultrasonography were unremarkable, and a liver and spleen scan showed a fairly normal-sized liver with a reversed ratio to the radioisotope. The chest roentgenogram obtained on admission was clear.

Hospital course

Antibiotic therapy was started with cefazolin sodium, gentamycin sulfate, and trimethoprim/sulfamethoxazole. The patient had febrile episodes, with fever as high as 40.6°C. Despite antipyretic therapy, the patient's temperature never went be-

low 38.9°C. When 3 days of antibiotic therapy had not produced positive cultures or a response, all antibiotic therapy was discontinued.

By the fourth day, some pitting edema had developed in the lower extremities and the patient's serum albumin level had dropped to 1.9 g/dL in spite of aggressive nutritional supplementation. Erythromycin therapy was started. On the sixth day, a dry cough developed; it did not respond to antitussives. A chest roentgenogram obtained at this time showed lower lobe bilateral infiltrates; the patient had a PO_2 of 58 mm Hg on room air. The next day, the patient was dyspneic, with a PO_2 of 52 mm Hg on 2 L of oxygen delivered by nasal cannula, and there was further progression of infiltrates. The patient was then transferred to Good Samaritan Hospital to obtain infectious disease consultation.

On arrival at Good Samaritan Hospital, the patient had a temperature of 41.1°C, a respiratory rate of 40 per minute, and a pulse rate of 120 beats per minute. Bronchoscopy revealed a nonspecific interstitial pneumonitis that was thought to be consistent with a viral infection. Erythromycin therapy was continued. The patient had progressive respiratory failure and was eventually placed on a ventilator at 100% inspired fraction of oxygen with a PO_2 of 71 mm Hg.

Bronchoscopic washings and brushings revealed no organisms, and all cultures were negative for acid-fast bacilli; silver stain for *Pneumocystis carinii* was also negative. An effusion of the left knee developed; it was tapped and found to be sterile. A pleural effusion was found to be exudative and sterile, with a WBC count of 980/mm^3, an RBC count of 4340/mm^3, serum protein level of 3.86 mg/dL, and LDH of 402 units/L.

The patient was able to be weaned gradually from the ventilator and oxygen. He continued to have marked leukocytosis (25,000/mm^3) with fewer band neutrophils (8). The patient had persistent temperature spikes, but it was thought that he was ready for discharge from the hospital. He was dismissed on the 26th day, a stay that included 8 days at Mesa General Hospital. At an infectious disease conference, it was agreed that his course was consistent with atypical measles. A rubeola titer was measured by immunofluorescence, and it was found to be considerably elevated (1:4096).

The high rubeola titer and the fact that the patient was immunized against measles in 1965 or 1966 led to the belief that this case was surely atypical measles syndrome with resultant pneumonitis, hepatitis, and maculopapular rash.

Discussion

Although atypical measles syndrome was described in the pediatric literature as early as 1965,[9-12] internists may not be familiar with this syndrome. It can appear as a diagnostic conundrum. The differential diagnosis of atypical measles includes Rocky Mountain spotted fever, rubella, *Mycoplasma pneumoniae* infection, varicella, viral pneumonia, generalized viral infection, collagen vascular disease, infectious mononucleosis, infective endocarditis, coccidioidomycosis, and Kawasaki's disease.[8,13]

Formalin-inactivated (killed) measles virus vaccine and attenuated live-virus measles vaccine (Edmonston B strain) became available in 1963. Killed measles virus vaccine was not distributed after 1967, in part because the immunity it conferred was short-lived and also because of the increasing awareness of atypical measles.[8,14]

Two major explanations have been suggested for the pathogenesis of atypical measles. One theory holds that humoral immunity, in the form of antigen-antibody complexes is responsible for the atypical rash and other manifestations of the syndrome. A second theory is that of enhanced cell-mediated immunity. The cellular immunity conferred by the vaccine appears to persist even though the humoral immunity is short-lived. This cellular immunity may not be responsible for the manifestations of the syndrome.[8]

Comment

Although the atypical measles syndrome has interested pediatricians for years, the disease comes increasingly within the province of the internist as the population at risk ages.[15] As many as 1,836,300 doses of killed measles virus vaccine may have been administered between 1963 and 1967.[8] Of perhaps even greater importance have been reports of atypical measles occurring in patients who had received only live attenuated measles virus vaccine.[16-18] These observations suggest that the population at risk may encompass most young adults. Therefore, internists should add "atypical measles" to the differential diagnosis of the syndrome consisting of rash, hepatitis, and pneumonitis.

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