Infectious Mononucleosis in Young Children

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CASE REPORT

A two-year-old black child was brought to the emergency department (ED) by her mother with a chief complaint of neck swelling. On the morning of presentation, the mother had noticed two small masses on the right posterior aspect of the child's neck. The patient was otherwise without complaints. He was very active, with a good appetite. He was not complaining of a sore throat, earache, or headache. There was no history of fever and there had not been any recent nausea, vomiting, or diarrhea. Earlier in the week, the patient did have nasal congestion and an occasional nonproductive cough, but those symptoms had resolved after taking an over-the-counter medication. The patient had no significant past medical problems and immunizations were current. The patient had not traveled out of the local area. There was no history of animal bite or scratch.

The patient's physical examination was significant for a blood pressure of 94/40 mm Hg, pulse of 104 beats/min, respiratory rate of 22 breaths/min, and a temperature of 99°F orally. He was a well-developed and well-nourished two-year-old child. His scalp was free of any lesions, the tympanic membranes appeared normal, and the conjunctiva were not injected. His nose was clear and without drainage. His throat was not erythematous and was without exudate. The uvula was midline. Examination of the neck found multiple enlarged, soft, nontender, nonfluctuant lymph nodes on the right posterior cervical chain. The lungs were clear to auscultation. Examination of the heart found a regular rate and rhythm without murmurs, rubs, or gallops. The abdomen was soft, nontender and without hepatomegaly or splenomegaly. Bowel sounds were present and nonobstructive. His skin was without rash, petechiae, or purpura.

Because the lymphadenopathy was acute and the patient appeared nontoxic, it was decided to treat the patient conservatively. The patient had no significant past medical problems and immunizations were current. The patient had not traveled out of the local area. There was no history of animal bite or scratch.

The patient returned to the ED the following day because of the mother's concern about further neck mass enlargement. The patient had also developed a sore throat. Physical examination found a fever of 101°F orally, with remainder of the vital signs normal. A throat exam demonstrated enlarged tonsils and an erythematous posterior pharynx with areas of exudate. The patient had a "rapid-strep" test as well as a complete blood count and Monospot performed. The rapid-strep test was negative. The patient's white blood cell count was 13,500 cells/µL, with a differential of 75% lymphocytes, 20% polymorphonuclears, and 5% monocytes. The Monospot was positive and a diagnosis of infectious mononucleosis was made. The patient's pediatrician was notified and he expressed surprise that we considered the diagnosis of infectious mononucleosis in a child of this age. The patient's mother was given precautionary instructions regarding mononucleosis and instructed to administer acetaminophen as needed for fever. The patient's symptoms completely resolved within 10 days.

DISCUSSION

The earliest descriptions of the clinical syndrome we know today as infectious mononucleosis (IM) are attributed to Filatov, a Russian pediatrician who published his observations in 1885 and to Emil Pfeiffer, a German physician whose report was published four years later. Pfeiffer described two forms of the process he called "glandular fever," or "Druenfieber." One form was a mild short-lived febrile episode with cervical adenopathy, and the other form was a more protracted illness eight to ten days in duration with fever, lymphadenopathy, sore throat, and organomegaly. In 1920, Sprunt and Evans were the first to use the term "infectious mononucleosis," and they discussed some of the associated hematologic changes, including the presence of atypical lymphocytes. Paul and Bunnell described the heterophil antibody elevation in IM in 1932. This observation continues to serve as the basis for the most widely used diagnostic test for IM today. It was not until the mid-1960s that the Epstein-Barr virus (EBV) was identified as the causative agent of IM.

In developed countries, IM usually presents in older childhood and young adulthood, with a peak incidence in the United States during the teenage years. Salivary tissues are the recognized repositories of EBV and transmission is via the oropharyngeal route ("the kissing disease"). Although the virus has been found to be present in the cervical mucosa and semen, sexual transmission has not been demonstrated. Rarely, EBV can be transmitted to immunosuppressed recipients by blood transfusion or bone marrow transplantation.

After an incubation period of four to eight weeks, patients in the typical age group develop nonspecific symptoms, including malaise, anorexia, chills, fatigue, and sore throat. Ninety percent of patients have fever up to 39°C or 40°C, and 50% have splenomegaly. Other classic findings include an
exudative pharyngitis, lymphadenopathy, and hepatomegally. In typical cases, the patient exhibits an absolute lymphocytosis with at least 10% reactive or atypical lymphocytes and a positive heterophil antibody test result. Although the vast majority of cases of IM are self-limited and resolve in one to four weeks, serious and even fatal complications do occur in the pediatric patient. These complications include (but are not limited to): spontaneous splenic rupture; significant upper airway obstruction (secondary to inflammation, edema, and lymphoid hypertrophy); pneumonia; Alice in Wonderland syndrome (visual metamorphosis); Guillain-Barre syndrome; meningoencephalitis; cerebellar ataxia; Reye syndrome; and virus-associated hemophagocytic syndrome.

In contrast to developed countries, EBV infection in Third World and developing countries is thought to occur early in life. In the United States, however, IM is often considered a rare disease in early childhood, for two reasons: (1) less uniform symptomatology; and (2) a reportedly lower rate of heterophil antibody response in young children compared with teenagers and young adult patients with IM.

Only a few studies have addressed the presentation of IM in early childhood. Tamir et al. prospectively studied 22 children suspected of IM because of the presence of atypical lymphocytosis. Seven of the children were younger than one year old; a total of seventeen patients were younger than four years old. For the patients younger than four years old (young group), 88% had a fever, 76% had splenomegaly, 59% had lymphadenopathy, and 41% had tonsillitis. However, in the very young group, only 71% had fever, 43% had splenomegaly, 57% had hepatomegaly, and 14% had lymphadenopathy and tonsillitis. In addition, these very young children had other symptoms not usually associated with IM: diarrhea (4); otitis media (2); and jaundice (1). Interestingly, none of the patients in the young group had a positive heterophil antibody response, but 16 of the 17 patients had immunoglobulin G antibodies to EBV. The authors concluded that IM should be suspected in the differential diagnosis of children who present with a febrile illness and a large number of atypical lymphocytes on peripheral smear. Furthermore, in view of the low yield of the heterophil antibody test, Tamir and associates recommended that EBV antibody testing be performed if IM is suspected.

Sumaya conducted a seroepidemiologic survey of 209 children in a small parish in southern Louisiana. He found a 6.2% incidence of current or recent primary EBV infection in these patients. Seven of the thirteen children were younger than five years old. The majority of EBV infections in these children were benign, with the most common complaint being a "cold." None of the patients demonstrated a heterophil antibody response.

In a study of IM in 32 patients younger than 49 months old, Horwitz et al. compared the clinical presentation and laboratory findings of two groups: patients 10 to 24 months old (11 cases), and patients 26 to 48 months old (21 cases). They found that the clinical presentations were similar for both groups and compatible with IM. However, the laboratory data disclosed several important differences. Heterophil antibody responses were encountered in only 27.3% of infants younger than two years of age compared with 76% of the children between the ages of 26 and 48 months.

Specific serodiagnostic tests showed current or recent primary EBV infection in all 11 patients younger than 24 months of age.

Sumaya and Ench conducted the largest prospective study to date on the subject, examining 113 children 6 months to 16 years of age with documented EBV-induced IM. For the purposes of analysis, the children were separated into two age groups, those younger than four years old (47 patients) and those four to sixteen years old (66 patients). The incidence of fever, lymphadenopathy, and tonsillitis-pharyngitis was similar for both groups. However, some signs and symptoms occurred more frequently in younger children. A palpable spleen and enlarged liver were more frequent in the younger children. Signs of an upper respiratory infection were found in 51% of the younger children and only 15% of older children. Cutaneous rashes, present in 26% of all cases, occurred more frequently in the younger children than in the older group; those patients that received ampicillin showed an increased trend toward the presence of rash. Some presentations observed in both groups and not normally associated with IM in teenagers and young adults included: failure to thrive, otitis media, recurrent tonsillitis-pharyngitis, and eyelid or periorbital swelling. Evaluation of hematologic findings in each group showed some important differences. Younger children had a significantly greater mean peak total white blood cell count (14.7 ± 5.1) compared with older children (11.1 ± 3.5). Although the relative percent of lymphocytes was similar in both age groups, the younger group had a smaller proportion of atypical lymphocytes on the peripheral blood smear compared with older children. Heterophil antibody testing was performed on the acute sera of 99 of the 113 children (44 in the younger children and 55 in the older children). For the younger children, 31.8% and 18.9% developed serum heterophil antibodies detected by a quantitative method and the rapid slide test, respectively. For this group, the rate of heterophil antibody response appeared to increase progressively with advancing age up to four years, after which the rates remained relatively stable. Of the 55 older children, 83.6% and 80% had these antibodies detected by a qualitative method and the rapid slide test, respectively. EBV-specific serological testing was proved much more sensitive, even for patients in the younger age group. Immunoglobulin antibody to EBV capsid antigen was detected in the acute phase serum of 112 of the 113 children (99.1%). Similarly, 85.8% of the 113 children developed an immunoglobulin M antibody to EBV capsid antigen.

In the United States, IM does not seem to be as rare in young children as it is generally considered to be. Patients older than two years of age will generally present with many of the same signs and symptoms of IM observed in teenagers and young adults. Patient younger than two years old may present similarly or they may present with minimal or atypical symptoms. IM should be considered in the differential diagnosis of young children presenting with fever, lymphadenopathy, sore throat, or nonspecific complaints. Although large number of atypical lymphocytes on the peripheral blood smear should prompt consideration of this diagnosis, IM is by no means the only cause of such a finding. A reactive lymphocytosis can also be observed in cytomegalovirus infection, drug hypersensitivity, viral hepatitis, toxo-
plasmosis, postperfusion syndrome, other viral infections, and even bacterial infections. Heterophil antibody testing will generally not be helpful in patients younger than two years of age. In children older than the age of 4 years, the sensitivity of this test approaches that observed in older children and young adults. For children younger than four years old suspected of IM, when confirmation of the diagnosis is required (ie, because of the presence of serious complications), serological testing for antibodies to EBV should be performed.

REFERENCES