Harry L. Arnold Jr. MD Case of the Month

Chronic Meningococcemia Mimicking Acute Rheumatic Fever

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Chronic meningococcemia is an uncommon feature of meningococcal disease, particularly in childhood. In fact, less than two dozen cases have been previously reported in the English literature. The presentation of chronic meningococcemia is common to a number of infectious and rheumatic diseases. In Benoit's review of 148 cases: all had fever and chills, 138 (93%) had rash, and 104 (70%) had arthritis/arthralgia.[1] A positive blood culture for *Neisseria meningitidis* establishes the diagnosis. The differential diagnosis is considerable and notably includes: Henoch - Scholein purpura (HSP), acute rheumatic fever (ARF), subacute bacterial endocarditis (SBE), Lyme disease, systemic lupus erthematosus (SLE), and systemic juvenile rheumatoid arthritis (JRA). The case of a seven-year-old boy with chronic meningococcemia whose condition completely fulfilled the updated Jones Criteria[2] for the diagnosis of ARF (to include the isolation of a ß-hemolytic streptococcus from his throat), is here reported.

Case Report

A previously healthy seven-year-old white boy presented with pain in his right ankle and a limp. His arthritis subsided over two days only to recur along with fever to 102.5°F. He was hospitalized in a community hospital for eight days during which time he developed evanescent pink, subcutaneous nodules on his extremities. His fever would resolve then recur every two to three days. Six blood cultures were negative. A transient left knee effusion was noted on the seventh hospital day. A radionuclide bone scan was normal. He received no medication other than acetaminophen for fever and was referred on the eighth day of his illness. On admission to the Texas Childrens' Hospital (Houston, TX), he had a temperature of 102° F and appeared moderately ill. Examination of the skin revealed ten round, tender, red nodules on his right leg, buttock, back, occiput, and neck. The nodules varied in size from 5-10 mm. in diameter and were exquisitely tender to touch. He did not have petechiae or purpura. A pericardial friction rub was heard on the first day and resolved spontaneously. He had arthritis with a small effusion of his right ankle. Complete blood count and urinalysis were normal with the exception of a mild thrombocytosis (platelet count was 569,000). His erythrocyte sedimentation rate (ESR) was 50 mm/hour. Rheumatoid factor (RF) was negative as was the antinuclear antibody (ANA, negative <1:10). His C3 (third component of complement) was 150 mg/dl (normal 95-195) and the C4 (fourth component of complement) was 23 mg/dl (normal 15-150). Total hemolytic complement activity (CH_{50}) was 495 u/ml (normal 304-480). His Immunoglobulin G (IgG) was 1100 mg/dl (normal 631-1298), Immunoglobulin A (IgA) 160 mg/dl (normal 70-312), Immunoglobulin M (IgM) 123 mg/dl (normal 56-258). Streptozyme was 400 STZ units, the antistreptolysin 0 (ASO) was 1:333 and antihyaluronidase was 1:512. Serologies for hepatitis A and B viruses (HB_s antigen, HB_c antigen, HB_e antigen, anti-HB_s, anti-HB_c, anti-HB_e, and anti-HA antibody) were negative. A test for circulating immune complexes was normal (Clq binding 9%, normal <13 %). The PPD skin test was negative with a positive tetanus toxoid control. His throat culture yielded a ß-hemolytic streptococcus, later identified as group F. The joint-bone scan, chest radiograph, electrocardiogram, and echocardiogram were all normal. He was afebrile until the third hospital day when he developed a temperature of 100°F, at which time two separate blood cultures were obtained. Penicillin VK (250 mg p.o. qid) and aspirin (80 mg/kg/d in four divided doses) were started on the fourth day when the throat culture was reported positive for a ß hemolytic streptococcus and the diagnosis of ARF appeared to be established. On hospital day six the blood cultures obtained on day three were reported as positive for *N. meningitidis*, type A, establishing the diagnosis of chronic meningococcemia, a full two weeks after the onset of his symptoms. His fever and nodules completely resolved within 24 hours of starting therapy. His right ankle effusion resolved within 72 hours and he had no further joint complaints. Aspirin was discontinued. His family received rifampin prophylaxis, and the patient was treated with a ten day course of oral penicillin. At follow-up, two months after discharge, the child was found to be free of all symptoms.

Discussion

Acute rheumatic fever was the main diagnostic consideration in this child. The presence of migratory polyarthritis, a pericardial friction rub, subcutaneous nodules (including occipital nodules), fever, and an elevated ESR all strongly supported a diagnosis of ARF.[2] The isolation of a ß-hemolytic streptococcus (later shown to be group F) from the patient's throat and positive serologic tests for

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antistreptococcal antibodies confirmed the probable diagnosis of ARF and prompted the institution of penicillin and aspirin therapy. The patient was asymptomatic and had already received 48 hours of oral penicillin when the blood culture results became available. Thus, the decision for continued oral antibiotic therapy was made. Remarkably, T. Duckett Jones, in his classic paper on the diagnosis of rheumatic fever mentions "menigococcic septicemia" as well as "gonococcic arthritis" in the differential diagnosis of ARF.[3]

Chronic meningococcemia is uncommon in children as compared to adults. Conversely, meningococcal disease, overall, is much more common in children and the incidence is the highest in infants less than one year of age. Since 1902, only 20 patients less than 18 years of age with chronic meningococcemia have been described in the English speaking literature.[4,5] Leibel *et al* reviewed 13 of these cases in 1974.[4] The symptoms in children were similar to those in adults, but less severe. However, the duration of illness, prior to diagnosis was shorter in children, and the first positive blood culture occurred earlier in the course of the illness than in adults. Ploysangam and Sheth reviewed the literature and added the twentieth case of chronic childhood meningococcemia in 1996.[5]

Diagnosis is based on the finding of a positive blood culture for *N. meningiditis.* Treatment with penicillin for a 10-14 day course is recommended by most authors. The parenteral route is preferred. Since 1970, there have been several reports of individuals with chronic meningococcemia who were found to have deficiencies of various complement components, including C6, C7, and C8.[6-9] One case of chronic meningococcemia and mild IgM deficiency has been reported.[10] Deficiencies of C3, C5, C6, C7, and C8 have been associated with recurrent episodes of disseminated gonococcal infection and acute meningococcal meningitis.[7,8] A 14 month old boy with IgG_2 subclass deficiency and recurrent acute meningococcemia has been described,[11] as has a 15-year-old French boy with IgA deficiency.[12]

The overall incidence of complement deficiencies in the general population is low with C2 deficiency being the most common, the frequency of C2Q0 being less than 1%. Complete deficiencies of the early classic C components are associated with rheumatic diseases which resemble SLE, vasculitis, and JRA. Homozygous deficiencies of the Membrane Attack Complex (MAC) (i.e. C5b-C9) predispose to recurrent neisserial sepsis. Ellison *et al* identified six patients with complement component deficiencies when they sequentially screened 20 patients presenting with a first episode of meningococcal disease. Thus, 30% of their patients with acute meningococcal disease had an underlying deficiency of a complement component.[8]

The pathogenesis of chronic meningococcemia is not well understood. No predominant strain of meningococcus has been associated with this entity. Chronic meningococcemia appears to be a problem of host defense. One current view is that the disorder represents a serum sickness-like illness with the symptoms occurring secondary to the circulation and deposition of antigen-antibody complexes. Certainly the recent histopathologic demonstration of leukocytoclastic vasculitis in the skin lesions of a 17-month-old boy with chronic meningococcemia lend credence to support that view.[5]

It is not clear why our patient contracted a relatively benign form of meningococcemia. His normal immunoglobulin and complement levels rule out an obvious deficiency of immunoglobulin or complement. This child was clinically and by all laboratory parameters, immunocompetent. There is no known association of chronic meningococcemia and an antecedent streptococcal infection. However, anecdotally, one of us (DAP) has observed recurrences, recrudescences, and/or exacerbations of HSP, JRA, and Kawasaki disease with concomitant group A, ß-hemolytic streptococcal pharyngitis. This child's streptococcal infection certainly compounded the interpretation of his illness and was presumably responsible for the induction of the anti-streptococcal antibodies. The classic syndrome associated with ARF and that seen in our patient with chronic meningococcemia may very well represent the final common pathway of the host-parasite relationship. Immunological reactions are very likely operative and antigen-antibody complexes no doubt play a pivotal role. Only the antigens are different - streptococcal in ARF and meningococcal in chronic meningococcemia. This case, at the very least, illustrates the importance of obtaining several blood cultures in a child with fever, rash, and polyarthritis in order to establish the correct diagnosis.

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