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Childhood serum sickness: a case report

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Childhood serum sickness is a rare allergic disease that follows the administration of a foreign antigenic material, most commonly caused by injecting a protein or haptenic drug. The disease is a type III hypersensitivity reaction mediated by deposits of circulating immune complexes in small vessels, which leads to complement activation and subsequent inflammation. The clinical features are fever, cutaneous eruptions, lymphadenopathy, arthralgias, albuminuria, and nephritis. Serum sickness is an acute self-limited disease. We report a 3-year-old child who presented with fever and a rash; an invasive bacterial infection was strongly suspected. He was therefore given penicillin and gentamicin and responded well. At day 4 after admission, he developed a serum sickness reaction and showed symptoms of arthralgias, generalized edema, purpura, and gross hematuria. The white blood cell count was 12 190 /mm^3 with 7% eosinophils. Urinalysis revealed red blood cell above 100 per high power field, white blood cell 10 to 15 per high power field, and proteinuria. The antibiotics were discontinued and hydrocortisone (20 mg/kg/d), diphenhydramine HCl (4 mg/kg/d), aspirin (66 mg/kg/d) was administered, plus 1 dose of epinephrine (0.01 mL/kg) administered intramuscularly. On day 7, the 3rd day after withholding antibiotics, his condition dramatically improved. The clinical symptoms resolved progressively and his urinalysis returned to normal.

Key words: Drug hypersensitivity, penicillin, serum sickness

Serum sickness was first described by Von Pirquent in 1905 following the use of antidiphtheria horse serum. The disease was common in the pre-antibiotic era when heterologous antiserum was often used as passive immunization to treat infectious and toxic illnesses. Today, the major cause of the serum sickness syndrome is drug allergy, particularly caused by penicillin or other β-lactam agents [1-4]. Drugs are capable of inducing any of the various types of hypersensitivity reaction. The most common and potentially dangerous reactions are those resulting from the production of specific IgE. Systemic serum sickness is a rare reaction. Typical symptoms of serum sickness include fever, cutaneous eruptions, arthralgia, lymphadenopathy, albuminuria, and nephritis [5]. This study report a child who showed features of serum sickness, including arthralgias, generalized edema, purpura, proteinuria, and hematuria 4 days after treatment with penicillin and gentamicin.

Case Report

A 3-year-old boy presented with fever, purulent tonsillar exudate, edema of the hands and feet, and skin rash was admitted to the Mackay Memorial Hospital. He was conscious on physical examination. Penicillin G, gentamicin, and aspirin were prescribed. His fever subsided and his condition improved.

On admission, the white blood cell (WBC) count was 9200 /mm^3 with 51% neutrophils, 1% band forms, 45% lymphocytes, and 2% monocytes; the hematocrit was 34%, hemoglobin 11.9 gm/dL, and platelet count 223 000 /mm^3; the prothrombin time was 12.2 sec (control, 11 sec), activated partial thromboplastin time 29.5 sec (control, 30 sec), fibrin degradation products above 10 μg/mL, erythrocyte sedimentation rate (60 min) 27 mm, aspartate aminotransferase 30 U/L, and alanine aminotransferase 10 U/L. Total protein was 5.3 gm/dL, albumin 3.1 gm/dL, Epstein-Barr viral capsid antigen (EBVCA) IgG 640x, EBVCA IgM negative, and heterophil antibody negative; throat and blood cultures were negative.

At day 4 after admission, the patient became irritable and lethargic. He developed arthralgias, generalized edema (Fig. 1), purpura (Fig. 2), and gross hematuria. Laboratory data showed WBC 12 190 /mm^3 with 55% neutrophils, 3% band forms, 31% lymphocytes, 2% monocytes, 7% eosinophils, and 2% metamyelocytes; the hematocrit was 29%, hemoglobin 10 gm/dL, platelets 267 000 /mm^3; prothrombin time

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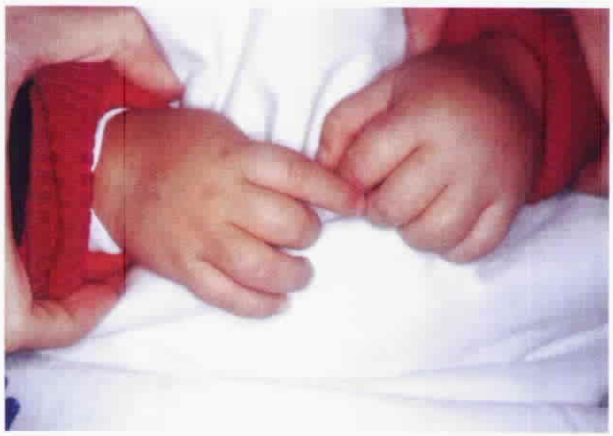

Fig. 1. A 3-year-old boy with serum sickness had suffered from generalized edema.

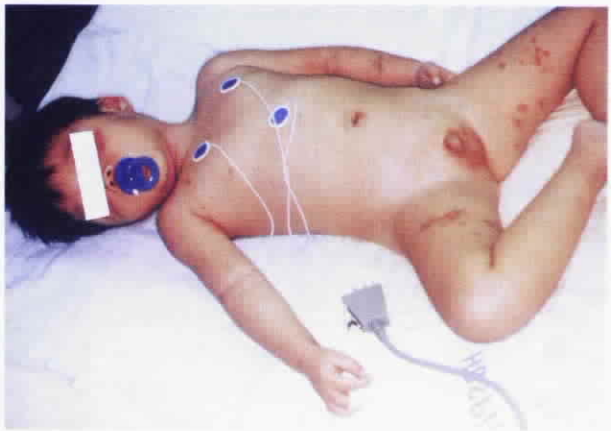

Fig. 2. Same patient with purpura lesions over both upper arms and thighs.

11.4 sec (control, 10.5 sec), activated partial thromboplastin time 29 sec (control, 30.4 sec), fibrin degradation products above 40 μg/mL, erythrocyte sedimentation rate (60 min) 22 mm, blood urea nitrogen (BUN) 7 mg/dL, and creatinine (Cr) 0.9 mg/dL. Results of a urine test for *Neisseria meningiditis* antigen was negative. Urinalysis revealed red blood cell above 100 per high power field (HPF), WBC 10 to 15/HPF, and 3+ proteinuria. Analysis of the cerebrospinal fluid showed results were within normal range. The serum C3 was 140 mg/dL (normal range, 92-160 mg/dL), C4 59 mg/dL (normal range, 14-38 mg/dL), and IgA 231 mg/dL (normal range, 175-315 mg/dL); antinuclear factor and anti-ds-DNA were negative. The culture of cerebrospinal fluid was negative and the throat culture grew only normal flora.

Because serum sickness was highly suspected, the antibiotics were discontinued and hydrocortisone (20 mg/kg/d), diphenhydramine HCl (4 mg/kg/d), aspirin (66 mg/kg/d) were administered, plus 1 dose of epinephrine (0.01 mL/kg) administered intramuscularly. On day 7, all clinical symptoms, including arthralgias, edema, and purpura resolved progressively. Results of urinalysis returned to normal and the patient was discharged.

Discussion

Serum sickness is triggered by the injection of a large dose of foreign antigen, following a slow degradation of the antigen with a concomitant initiation of a primary antibody response [6].

The prevalence of this disease depends on the type of medical treatment used at admission. Serum sickness has been reported more often in children under 5-year-old than in older patients, but the relative risk cannot be assessed in the absence of prescribing information [1].

A number of drugs and agents have been associated with a serum-sickness-like reaction, especially antibiotics of the β-lactam group [1]. Drugs or agents known to cause the disease include cephalosporins (especially cefaclor), penicillin, ciprofloxacin, minocycline, streptokinase, bupropion, barbiturates, carbamazepine, fluoxetine, furazolidone, griseofulvin, hydantoins, hydralazine, indomethacin, iron dextran, isoniazid, lincomycin, nonsteroidal anti-inflammatory drugs, para-aminosalicylic acid, pentoxifylline, quinine, phenylbutazone, procarbazine, quinidine, streptomycin, sulfonamides, thiazides, thiouracils, 6-mercaptopurine, intravenous immune globulin, rabies vaccine, and *Haemophilus* B vaccine [9-16,19]. It is hypothesized that a drug acts as a hapten that binds to a plasma protein; the drug-protein complex is then identified as a foreign body and induces serum sickness [5].

Serum sickness is a type III hypersensitivity reaction. Symptoms occur coincidentally with the appearance of antibody formed against the injected antigen when the latter is still present in the circulation. Immune complexes formed under conditions of moderate antigen excess lodge in small vessels and in filtering organs throughout the body. These complexes activate the complement sequence—the recruitment of granulocytes through adherence of neutrophils to the site of the bound complement, and the chemotactic activity of the C567 complex with the C3a and C5a fragments, giving rise to the clinico-pathological manifestations [7,8].

Lesions are healed after the circulating immune complexes are eliminated. Free antigen is removed more rapidly from the circulation when antibody production and the formation of immune complexes increase. The

circulating complexes shift to antibody excess, thereby decreasing in size and are cleared more rapidly. Free antibody then circulates, no further lesions appear, and healing takes place [2,8].

The clinical manifestations of serum sickness depend on the time of onset in relation to the course of drug administration [17]. Primary serum sickness begins at 4 to 21 days (normal range, 7-10 days) after initial exposure to the causative antigen. Secondary serum sickness occurs in patients previously sensitized to the antigen with a shorter latent period of only 2 to 4 days. The course of the disease may be brief, but the manifestations may be severe [2]. Symptoms include fever, a cutaneous eruption (morbilliform and/or urticaria) in 95% of patients, arthralgias in up to 50%, lymphadenopathy, and myalgias; headache, nausea, and vomiting may occasionally occur. Less common manifestations include arthritis, nephritis, neuropathy, and vasculitis. In severe cases, glomerulonephritis, myocarditis, and hemorrhagic necrosis have been reported [2,14].

Diagnosis of serum sickness is based on the following criteria: timing of symptoms, clinical manifestations, and absence of other immunological and infectious causes [18]. Laboratory studies may reveal leukopenia or slight leucocytosis, elevated erythrocyte sedimentation rate, and low complement levels. Eosinophilia is an inconsistent finding, as in albuminuria [14]. Circulating immune complexes and a reduced level of serum complement components are often detected when the disease is caused by heterologous serum, but they are not usually detected in drug-induced serum sickness. Serum IgG and IgE antibodies specific to the relevant antigen may be detected in the course of the disease [2]. In this case, the onset of symptoms and signs was 4 days after the initiation of antibiotic treatment. The rapid disappearance of symptoms and signs after discontinuation of antibiotics and administration of steroids and antihistamines confirms the diagnosis of serum sickness.

Drug-induced hypersensitivity vasculitis may be difficult to distinguish from other types of vasculitis. Anaphylactoid purpura occurs usually in younger patients, with characteristic large purpuric cutaneous lesions, often on the buttocks. Renal and gastrointestinal involvement is common. Cryoglobulinemia-associated vasculitis has a chronic or recurrent course. Polyarteritis nodosa and Wegener's granulomatosis sometimes manifest with palpable purpura. Most patients with Wegener's granulomatosis have auto-antibodies to neutrophil cytoplasmic antigens; these antibodies are usually absent in drug-induced vasculitis. Drugs cause about 10% of cases of acute cutaneous vasculitis. Infection and collagen vascular disorders can also induce vasculitis [5].

Appropriate therapy includes prompt discontinuation of the offending drug and supportive treatment. Aspirin and antihistamines are effective. A short course of a high-dose corticosteroids is warranted if symptoms are severe [2]. Selection of an alternative antimicrobial agent to treat any underlying infections, proper documentation and reporting of the adverse events, and avoidance of the offending agent are important [15]. Recovery may take about 7 to 30 days.

In conclusion, drug-induced serum sickness is a rare type III hypersensitivity reaction with characteristic clinical features. When fever, cutaneous eruptions, arthralgia, lymphadenopathy, albuminuria, and nephritis are observed in children a few days after receiving a possible offending agent, the diagnosis of serum sickness should be highly suspected.

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