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Case Report

Serum sickness-like syndrome after immunoglobulin M-enriched polyclonal immunoglobulin

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Abstract

Medication reactions, infectious etiologies, graft vs. host disease, serum sickness, and serum sickness-like reaction are the most common conditions that cause skin fever and rashes in immunosuppressed patients. In addition to this long list of diseases, severity of the primary disease and deterioration in the patient's health status can make the diagnosis difficult. Furthermore, cutaneous and histological similarities in these mentioned conditions can be confounding. Here, we present a 16-year-old male patient with acute myeloid leukemia suffering from skin rashes and fever that appeared following a chemotherapy course leading to bone marrow suppression. We aim to discuss the differential diagnosis and share the diagnostic challenges that we already have experienced after immunoglobulin M-enriched polyclonal immunoglobulin.

Keywords: immunoglobulin M-enriched polyclonal immunoglobulin; immunosuppressed; serum sickness; serum sickness-like reaction.

Introduction

Acute myeloid leukemia (AML) accounts for 11% of childhood leukemias, and both the disease and its management can provoke myelosuppression (1). Conditions that lead to skin rashes and fever in immunosuppressed patients could be serious and immediate management is required. Medication reactions, infectious etiologies, and graft vs. host disease (GVHD) are included in the differential diagnosis in immunosuppressed patients; cutaneous and histological similarities can be confounding. The majority of medication reactions are mild morbilliform or exanthematous eruptions of little clinical consequence. Identifying the suspect medication can be difficult owing to the many medications used in this population. Features that could help identify suspect medications include rash onset relative to exposure, character of distribution and spread, associated symptoms, and laboratory data. Medications eruptions begin on the trunk 7–10 days after exposure, spread peripherally, and are associated with pruritus, and, less commonly, fever, arthralgia, and lymphadenopathy. Eosinophilia can support a diagnosis of drug eruption but can be absent in the setting of bone marrow suppression. Penicillin, sulfa drugs, cephalosporins, nonsteroidal anti-inflammatory agents, anticonvulsants and, on occasion, aminoglycosides are common offenders (2). Medication eruptions can resolve despite continued use of the offending agent or they can progress to more severe involvement. A careful drug history, elimination of all nonessential, suspect medications or change to medications of dissimilar class, and treatment of pruritus with emollients, topical steroids, antihistamines, and antipruritics are indicated (3). Skin biopsies are rarely useful in distinguishing medication eruptions from infectious exanthemas, although GVHD, if sufficiently advanced, can have signature histopathological findings. Serum sickness is a systemic, immune complex-mediated hypersensitivity vasculitis classically attributed to the therapeutic administration of foreign serum proteins (4). The availability of alternative medical therapies, modified or bioengineered antibodies, and biological materials of human origin have supplanted the use of nonhuman antisera. Reactions originally described as serum sickness-like are now attributed to drug allergy, triggered in particular by antibiotics (penicillin, cefaclor) and rarely to other agents such as human immune globulin, humanized monoclonal antibodies, and insect venom (5–7).

Case presentation

A 16-year-old male patient was diagnosed with CD 19 aberrant (+) AML and was on Children's Oncology Group AAML0531 chemotherapy protocol. Febrile neutropenia occurred following the second reinduction chemotherapy. His blood count revealed white blood cell count of 600/mm^3, hemoglobin of 92 g/L, and platelet of 5000/mm^3 at that time. Pneumonia was the source of fever and empirical wide spectrum antibiotics including ceftazidime (150 mg/kg/day) and amikacin (15 mg/kg/day) were initiated in terms of neutropenia. Despite the treatment, his condition worsened. Respiratory failure and sepsis occurred and thus he required intensive care and was transported to the intensive care unit. His body temperature was 38.7°C, heart rate was 158/min, breath rate

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was 38/min and he was confused. Laboratory investigations, cultures, serological tests did not help to identify the causing agent, the antibiotics were replaced by meropenem (100 mg/kg/day), amikacin (15 mg/kg/day), vancomycin (60 mg/kg/day), amphotericin B (1.5 mg/kg/day). Pancytopenia persisted and furthermore his anemia deepened and thus required transfusion. Ig M-enriched polyclonal immunoglobulin was administered for 5 days. And some other supportive therapeutic approaches such as total parenteral nutrition, inotropic agents, and oxygen were used. Finally, he was improving until the fever returned a week after Ig M-enriched polyclonal immunoglobulin infusion, rising up to 41.5°C. Swelling on the face and hands, erythematous maculopapular rashes on shoulders and back, diarrhea, thrombocytopenia intractable to multiple transfusions and mildly elevated serum transaminases accompanied the fever in the following days. These findings suggested serum sickness since his serum C3 and C4 levels were in normal ranges and serum sickness-like reaction was considered. He was empirically treated with methylprednisolone for symptom relief. Body temperature dramatically decreased and the rashes disappeared. He recovered from sepsis and pancytopenia and underwent bone marrow transplantation.

Results and discussion

Leukemia patients show various cutaneous manifestations such as leukemia cutis, septic eruptions, viral exanthemas, fungal eruptions, and drug eruptions. Furthermore, serum sickness, serum sickness-like reaction, and systemic hypersensitivity reactions are rare conditions caused by drugs. Because multidrug therapies are required for leukemia patients, to find the exact cause of skin rashes is very difficult. Serum sickness is a type III hypersensitivity reaction presumably involving complement fixation and deposition of antigen-antibody complexes in small vessels, especially of the skin and joints. Clinically, serum sickness usually presents 1–12 days following exposure to a foreign substance, and occasionally, it occurs as much as 3 weeks later. Serum sickness is most commonly associated with fever, malaise, and cutaneous eruptions. Edema, arthritis, myalgia, and gastrointestinal complaints can also occur. Serum complement levels are usually decreased (4–6). Our patient meets all the clinical criteria except for the low complement levels. Clinical syndromes that resemble serum sickness but do not meet all the diagnostic criteria are termed serum sickness-like reactions. These reactions usually occur 7–21 days after administering the offending agent, most often an antibiotic. On laboratory workup, circulating immune complexes and decreased complement levels are lacking (8). Our patient was already on antibacterial, antifungal, antiviral therapy, while the clinical findings described above occurred. Also, there was a history of Ig M-enriched polyclonal immunoglobulin infusion 7 days before the findings. Both antibiotics and the Ig M-enriched polyclonal immunoglobulin could be the causing agent (3). He had been treated with these antibiotics in the earlier febrile neutropenia periods; however, there was no similar reaction. All laboratory workup failed to establish any bacterial, viral, or fungal agent. All cultures were negative. Cytomegalovirus PCR was negative in urine and serum. We excluded all possible infectious etiologies, and subsequently decided to put the patient on methylprednisolone therapy for symptom relief and to maintain the empirical antibiotic therapy because of his critical clinical course. Enhanced cellular sensitivity has been demonstrated to be a component of adverse reactions to several drugs, including antimicrobials, anticonvulsants, and antipsychotic agents (8). Significant symptom relief and decrease in body temperature immediately after methylprednisolone therapy suggests an immunology-mediated disorder such as enhanced cellular sensitivity, more likely than the other possible causes. Leukemia patients are candidates of multidrug therapy including chemotherapeutics, antibiotics, blood products, etc. Furthermore, they require long and recurrent drug therapies that make them susceptible to adverse drug reactions and hypersensitivity syndromes. Although serum sickness-like reaction is a rare complication, it should be considered in patients with fever and skin rashes as a differential diagnosis.

References

1. Clark JJ, Smith FO, Arceci RJ. Update in childhood acute myeloid leukemia: recent developments in the molecular basis of disease and novel therapies. Curr Opin Hematol 2003;10:31–9.
2. Wilson SM. Temperature dysregulation. In: Tisdale JE, Miller DA, editors. Drug induced diseases prevention, detection, and management. Bethesda, MD: American Society of Health System Pharmacists, 2005:421–54.
3. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–45.
4. Buhner D, Grant JA. Serum sickness. Dermatol Clin 1985;3:107–17.
5. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272–85.
6. Naguwa SM, Nelson BL. Human serum sickness. Clin Rev Allergy 1985;3:117–26.
7. Heckbert SR, Stryker WS, Coltin KL, Manson JE, Platt R. Serum sickness in children after antibiotic exposure: estimates of occurrence and morbidity in a health maintenance organization population. Am J Epidemiol 1990;132:336–42.
8. Martin J, Abbott G. Serum sickness like illness and antimicrobials in children. NZ Med J 1995;108:123–4.