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BRIEF REPORT

Serum Sickness-Like Reaction with Clarithromycin

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Serum sickness-like reaction is a rare immunological condition which may develop following exposure to certain drugs such as penicillins, cephalosporins, and trimethoprim-sulfamethoxazole, among many others. It is described classically as a type III hypersensitivity response to heterologous proteins. Its true mechanism is still unclear. We present a case of serum sickness-like reaction to clarithromycin, a commonly prescribed drug for the treatment of respiratory tract infections. The patient had been taking this drug for 3 days when she experienced generalized body aches, rash, arthralgia, and shortness of breath, prompting presentation to the emergency department. Laboratory studies showed decreased C4 and total complement with a slightly elevated sedimentation rate. After exclusion of other possible causes, the diagnosis of serum sickness-like reaction was made. The patient responded well to nonsteroidal antiinflammatory medication, antihistamines, and a short, tapering dose of steroids. To our knowledge, serum sickness-like reaction to clarithromycin has never been reported previously. This case emphasizes the need for increased clinical awareness of such an adverse outcome to clarithromycin use. ***Journal of Hospital Medicine*** **2011;6:231–232.** *© 2011 Society of Hospital Medicine*

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Serum sickness is an immunological condition characterized by fever, rash, arthralgia/arthritis, myalgia, edema, and localized lymphadenopathy. Historically, this syndrome was seen as an immunologic response to heterologous protein components administered for therapeutic purposes, such as in the treatment of diphtheria and scarlet fever. Following the decline in use of such heterologous proteins, this same condition is now seen with equine antitoxins, monoclonal antibodies, and some drugs.[1–3] Specifically, the immunologic response to these drugs is referred to as serum sickness-like reaction (SSLR). The classic serum sickness is described as a prototype Gell and Coombs "type III" or immune complex-mediated hypersensitivity disease.[4] When a foreign protein antitoxin is administered into human serum, immune system recognition and antibody production occurs. Antibodies become attached to antigens and, when there are sufficient antibody/antigen bonds, a lattice-like aggregate called the immune complex forms. Normally these immune complexes are cleared from the blood by the reticulo-endothelial system, but if the system is defective, or the complexes are in a sufficiently large quantity, then deposition into various tissues like the internal elastic lamina of arteries, perivascular regions, synovia, and glomeruli occurs. Following deposition, complement is activated, causing inflammation in these same tissues, resulting in fever, rash, arthralgia, and myalgia.[5] A similar reaction has been seen with certain drug exposures as well. The mechanism for this reaction is less clear, but thought to be similar to haptens attaching to plasma proteins and inciting the immunological response.[6]

Case

A 57-year-old white female presented with rash and generalized body aches. She had no significant past medical history, except for sinusitis several years ago; she was prescribed clarithromycin but did not report any problem with this medication at that time. The patient was diagnosed with acute sinusitis 4 days before this presentation. She had visited a primary care physician for her sinusitis and had been prescribed clarithromycin 500 mg twice daily for 7 days. The patient did not use any prescribed or nonprescribed medications in the last 6 months, except the current use of clarithromycin. She used the medication for 3 days as directed, when she developed a generalized rash. The rash first developed on both arms and then migrated to involve the rest of the body within 1 day. The following day, she developed generalized weakness, muscle aches, and symmetric joint pain in the wrists, arms, fingers, and knees. She stopped taking the medication after her sixth dose because she thought her symptoms might be related to its use. Her rash began to fade away slightly. On the 4th day, her myalgias and arthralgias acutely worsened, limiting her normal activities. She developed shortness of breath, ultimately prompting her visit to the emergency department. On presentation, her temperature was 98°F, pulse 76, blood pressure 115/73, and oxygen saturation 99% on room air. She was in no acute distress, had no signs of acute airway compromise, and was comfortable at rest. On examination, she had a pruritic morbilliform rash which was most prominent on her upper extremities. There was no muscular tenderness elicited on her body. The joint examination was entirely

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normal. Ear, nose, and throat examination was normal; there was no lip swelling, erythema, or swelling in the oral cavity or stridor. The chest was clear to auscultation, and the heart examination was normal. Pertinent labs (and normal ranges) included: C3, 83 mg/dL (79-152 mg/dL); C4, 11 mg/dL (16-38 mg/dL); total complement, 24 mg/dL (30-75 mg/dL); erythrocyte sedimentation rate (ESR), 21 mm/hr (<20 mm/hr); and C-reactive protein (CRP), 0.8 mg/dL (normal, <0.8 mg/dL). Basic chemistries were unremarkable. Serum creatinine was 0.8 mg/dL, and blood urea nitrogen was 11 mg/dL. Creatine phosphokinase was 54 U/L. Liver function tests were normal. Complete blood count with differential showed: Hb, 12.5 g/dL; platelets, 228,000/mm^3; polymorphonuclear cells, 76%; lymphocytes, 15%; and eosinophils, 5%. Given the history, the temporal association of symptoms with medication use, physical examination findings, low complement level, and elevated ESR, the diagnosis of serum sickness-like reaction was made. The patient received intravenous dexamethasone 4 mg once and, following an observation period in the emergency department, was discharged on an oral prednisone taper, with diphenhydramine to use as needed. The patient responded well, and recovered uneventfully.

Discussion

Serum sickness-like reaction has been described for many drugs, especially antibiotics.[7] A clarithromycin-associated reaction has not been reported previously. Diagnosis of SSLR in this case was suggested by several factors, including the temporal association between clarithromycin ingestion, as well as consistent physical examination and laboratory findings. The patient's past history of clarithromycin use caused the reaction to occur within 36 hours of drug ingestion. Important diagnoses that were considered included angioedema, systemic lupus erythematosus, Stevens–Johnson syndrome or other drug eruptions, viral exanthemata, reactive arthritis, and acute rheumatic fever. However, the typical morbilliform skin eruptions with mucosal sparing made both lupus and Stevens–Johnson syndrome unlikely. Without facial or lip edema, angioedema also seemed less probable. Typical features of viral exanthem were also not seen in this patient. The lack of a prior history of a similar reaction and prompt recovery with antiinflammatories also supported a diagnosis of SSLR. Clarithromycin is a very commonly prescribed antibiotic for the treatment of upper respiratory tract infections; this case emphasizes that clinicians should remain aware that its use may rarely be associated with SSLR.

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