Glatiramer Acetate–Induced Serum Sickness

Paul Ferguson, MD

Multiple sclerosis (MS) is a central nervous system demyelinating disease with a prevalence of approximately 400,000 individuals in the United States. Glatiramer acetate is a frequently prescribed disease-modifying therapy used for the management of relapsing forms of the disease. A 40-year-old woman with relapsing-remitting MS presented with symptomatic concerns of vomiting, fever, diffuse rash, joint and low back pain, and distal lower-limb paresthesia and was subsequently admitted to the hospital for investigation and treatment. She was discharged initially after conservative management with intravenous methylprednisolone and diphenhydramine. She was restarted on glatiramer acetate 3 weeks later and required rehospitalization for similar symptoms 3 days after resumption of the disease-modifying therapy and was diagnosed as having serum sickness. Int J MS Care. 2017;19:263–264.

Case Report

A 40-year-old woman with relapsing-remitting MS presented to the local emergency department with symptoms of acute vomiting, fever, diffuse rash, joint and mild low back pain, and distal lower-limb paresthesia and was admitted for investigation. Physical examination findings were remarkable for new petechial rash and chronic monocular visual decrement and right afferent pupillary defect. She noted arthralgia on joint manipulation, but no obvious deformity or joint abnormalities were observed. During the first hospitalization she was treated with intravenous methylprednisolone and diphenhydramine for symptom mitigation of the rash and pruritus. Laboratory analysis showed mild pancytopenia. Hepatitis panel, peripheral blood smear, cyclic citrullinated peptide, erythrocyte sedimentation rate, C-reactive protein, cytomegalovirus, HIV, and Epstein-Barr virus findings were unremarkable. A brain MRI was ordered, without clear rationale by the primary admitting team, and the results were found to be unchanged from previous examination. Abdominal computed tomography was ordered because of abdominal pain, and the findings were negative. Administration of GA was held during the hospitalization owing to nonformulary status and was not immediately resumed by the patient on discharge. Symptoms improved, and she was discharged without a clear etiology being identified.

The patient was seen in the outpatient neurology clinic, and GA therapy was resumed 3 weeks after her having been discharged from her acute inpatient admission. Within 3 days of subcutaneous administration of 40-mg dosing of GA, her symptoms reemerged and included fever, malaise, petechial rash on the skin and...
mucosal surfaces, pruritus, low back pain, and distal appendage paresthesia. She was again hospitalized and underwent work-up with cerebrospinal fluid analysis for cell count, glucose, protein, Gram stain, and culture, which had negative findings. Serum studies again showed neutropenia and low C3/C4 levels. Urinalysis showed proteinuria. The patient was treated for serum sickness–like syndrome due to GA use and was treated by discontinuation of the therapy, which resulted in gradual symptomatic resolution without recurrence.

Discussion

Glatiramer acetate is a commonly prescribed disease-modifying therapy for relapsing forms of MS. It is a complex mixture of four polypeptides that seems to mimic myelin basic protein structure. It is US Food and Drug Administration approved to be administered subcutaneously in two formulations: 20 mg daily or 40 mg three times weekly. Common adverse effects include injection skin symptoms, including erythema, edema, vasodilation, and rash (19%–20%), and dyspnea with injection (14%).

The patient described herein developed signs, symptoms, and laboratory data diagnostic for serum sickness–like reaction, which was further supported by symptom recurrence with a second challenge 21 days after initial cessation.

Serum sickness is a type III hypersensitivity reaction that results from the injection of heterologous foreign protein or serum. Historically, the condition was described in 1905 by two Austrian pediatricians, Clemens E. von Pirquet and Béla Schick, who published research demonstrating that patients who were repeatedly injected with serum had more intense bouts of sickness with each successive injection, and, in some cases, antitoxin injections resulted in dangerous anaphylaxis.

The clinical presentation of serum sickness is often described as a combination of symptoms, including fever, rash, arthralgia, nausea, vomiting, headaches, and neurologic manifestations, which can include peripheral neuropathy or brachial neuritis. Pathophysiologically, it takes a minimum of 1 to 2 weeks to manifest as an immunologic reaction to the foreign substance after initial exposure, with subsequent exposures resulting in reactivation and symptom recurrence in as little as 3 days. A variety of treatments are used in the management of patients with MS, including monoclonal antibodies, carbamazepine, and bupropion, which have been implicated in causing serum sickness and serum sickness–like reaction; however, to my knowledge, there have been no such reports of GA resulting in the advent of this disease state.

The management of serum sickness centers around cessation of the suspected offending agent combined with conservative symptomatic management with anti-inflammatories, corticosteroids, and antihistamines. Most patients experience complete recovery 7 to 21 days after the implicated medication has been discontinued.

Conclusion

Glatiramer acetate is a frequently prescribed disease-modifying therapy in the United States for relapsing forms of MS. It is composed of a complex mixture of random polypeptides, which in the case of the 40-year-old patient with relapsing-remitting MS described herein resulted in a recurrent atypical serum sickness–like reaction 5 months after dosing was initiated. The role of the GA formulation prescribed (40 mg three times weekly) in the development of the reaction is unknown.

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References


4. Chippis BE. The Béla Schick Lecture: if you don’t know where you are going, you may end up somewhere else. Ann Allergy Asthma Immunol. 2015;114:440–442.


Practice Points

• Glatiramer acetate (GA) is composed of a complex mixture of random polypeptides that mimic myelin basic protein.

• This report details how 40-mg subcutaneous dosing of GA resulted in a constellation of clinical symptoms and laboratory data consistent with a type III hypersensitivity reaction, best termed atypical serum sickness, which was noted to recur on subsequent medication reccommencement.