

Fever, urticaria, lymphadenopathy, and protracted arthralgia and myalgia resistant to corticosteroid therapy

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ABSTRACT

Allergen immunotherapy is commonly incorporated in the management of allergic rhinoconjunctivitis, allergic asthma, and insect sting hypersensitivity. It is generally safe, but systemic reactions occasionally occur, mainly of the immediate type and rarely of the delayed type. We report a case of a 50-year-old man with allergic rhinoconjunctivitis on immunotherapy for 3 years and then received an injection from another patient's extract. The latter contained a higher concentration of house-dust mite and pollens of grasses, trees, and weeds. It also contained molds that the patient's correct extract did not have. Within half an hour, he developed a systemic reaction that resolved with symptomatic treatment. Two weeks later, he received one-half of his usual immunotherapy dose. Within a week, he developed urticaria, arthralgia, myalgia, fever, and lymphadenopathy. Laboratory abnormalities included leukocytosis, elevated erythrocyte sedimentation rate, hematuria, and elevated liver enzymes. Oral corticosteroid therapy for 3 weeks was ineffective. He developed significant myalgia and apparent mood changes, attributable to corticosteroid intake. After a single plasmapheresis, he felt remarkable improvement within <24 hours. Corticosteroid therapy was gradually withdrawn over 10 weeks without relapse of symptoms. This is a rare case of probable serum sickness after the administration of a wrong allergy immunotherapy extract. However, a causal relationship could not be proven. The response was poor to prolonged corticosteroid therapy but was remarkable to one plasmapheresis.

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CASE PRESENTATION

Chief Complaint

Fever, rash, joint pains, and muscle aches.

History of Present Illness

A 50-year-old man with allergic rhinoconjunctivitis has been receiving immunotherapy with an extract mixture of house-dust mite and pollens of weeds, grasses, and trees for 3 years. After an immunotherapy subcutaneous injection and returning home, his physician discovered that he received the extract mixture of another patient with a similar name. That extract contained a higher concentration of house-dust mite and pollens of grasses, trees, and weeds. It also contained molds that the patient was not originally receiving.

The physician called the patient who reported a large local reaction and was asked to return to the office immediately. On arrival, he had generalized urticaria and facial edema but no respiratory distress. His blood pressure was 120/70 mmHg, pulse rate 92/min, respiratory rate 24/min. He was given diphenhydramine, 25 mg, and triamcinolone, 30 mg, intramuscularly. His symptoms improved during a 3-hour observation and he was discharged to continue diphenhydramine, 25 mg, orally every 4–6 hours.

He continued to have recurrent mild episodes of urticaria and facial edema for a week. After another week, he was given one-half the maintenance dose of his regular immunotherapy extract without any immediate reaction. A few days later, there was recurrence of generalized urticaria and facial edema, accompanied by enlarged cervical lymphnodes, fever, muscle aches, and stiff painful joints, particularly of the shoulders and hands. Immunotherapy was discontinued altogether.

He was started on prednisone, 20 mg, twice a day and after a few days was increased to 20 mg four times a day and then gradually reduced. Laboratory tests (Table 1) revealed leukocytosis, high erythrocyte sedimentation rate (ESR), elevated liver enzymes, and hematuria without proteinuria. Because of persistence of

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Table 1 Laboratory findings in a man with fever, urticaria, lymphadenopathy, and arthralgia after a wrong allergy immunotherapy extract injection

Initial findings

WBC, 17.3 K/mm³ (neutrophil, 85.4%; lymphocyte, 9.4%; monocytes, 5.2%); Hgb, 15.7 g/dL (nl, 13.0–17.8); and platelets, 262 K/mm³ (nl, 140–440)

Erythrocyte sedimentation rate, 35 mm/hr (nl, 0–15)

Sodium, 141 mmol/L; potassium, 3.8 mmol/L; chloride, 104 mmol/L; bicarbonate, 28 mmol/L; glucose, 81 mg/dL; BUN, 13 mg/dL; creatinine, 0.89 mg/dL; and calcium, 8.7 mg/dL

Alkaline phosphatase, 359 U/L; SGOT, 115 U/L; and SGPT, 123 U/L

Urinalysis: WBC, 0–1/hpf; **RBC, 15–20/hpf**; and negative casts, crystals, epithelial cells

IgG and IgM antibody indices to *Borrelia burgdorferi*, <0.90 (negative)

Acute hepatitis panel (hepatitis A IgM, hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core IgM), nonreactive

Subsequent findings

Parvovirus B19 DNA PCR not detected; IgM antibody index, <0.1 (negative); and IgG antibody index, 5.3 (positive)

IgG and IgM antibodies to CMV, negative
ANA, <1:40; rheumatoid factor, <12 IU/mL (nl, <12)

Abnormal values are typed in bold.

symptoms, he was referred to our clinic for further management.

Physical Examination

Patient appeared fatigued, with a temperature of 98.5°F, pulse rate of 55/min, respiratory rate of 20/min, and blood pressure of 150/90 mmHg. His submandibular lymph nodes were slightly enlarged, firm, and mobile, but not tender. Chest was clear to auscultation and heart sounds were normal. There was no significant rash. Muscles of both upper and lower extremities were slightly weak. There was no hypo- or hyperreflexia. The shoulders and wrists were slightly tender but without swelling. The rest of the examination was within normal limits.

Current Medications

At this point, the patient was taking prednisone, 40 mg/day; cetirizine, 10 mg, twice a day; ibuprofen, 600 mg, every 6 hours; and hydrocodone, 10 mg, every 4 hours. He was also taking ropinirole, 1 mg, for restless

leg syndrome; venlafaxine, 75 mg, once a day for depression; and zolpidem, 12.5 mg, at bedtime.

QUESTIONS

What Is the Differential Diagnosis?

The clinical picture (urticaria, arthralgia, fever, and lymphadenopathy) together with the laboratory findings (leukocytosis, high ESR, elevated liver enzymes, and hematuria) were compatible with serum sickness.¹ However, the patient's symptom complex could be the result of other illnesses, such as parvovirus B19 infection, Lyme disease, and hepatitis. Less likely causes are other viral infections (Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus) and rheumatoid arthritis (RA).

Human parvovirus B19 (HPV B19) infection has a varied clinical expression in affected individuals.² Most infected patients are children who may remain asymptomatic or may develop a nonspecific febrile illness. It causes erythema infectiosum, transient aplastic crisis, hydrops fetalis, and arthropathies that may persist for months or years.³ It usually involves the hands, wrists, knees, and ankles. In a series of 22 cases,⁴ elevated liver transaminases were noted in almost one-third, and elevated lactate dehydrogenase in more than one-half. In our patient, IgM anti-parvovirus B19 IgM titer index was <0.1 (negative) and IgG antibody titer index was 5.3 (>1.1 is positive), indicating a past infection. Also, his parvovirus DNA polymerase chain reaction was negative.

Lyme disease, a tick-borne illness caused by *Borrelia burgdorferi*, is commonly manifested as erythema migrans that may be associated with arthralgia, myalgia, and headache, with or without fever.⁵ Our patient lived in a nonendemic area and had no recent travels or tick bites, his rash did not resemble erythema migrans, and he had negative IgM and IgG antibodies to *B. burgdorferi*.

Viral hepatitis infections may present with a serum sickness-like picture. An "arthritis-dermatitis" prodrome has been reported in ~10–30% of patients.⁶ It is characterized by sudden transient polyarthritis or arthralgia of the wrists, hands, knees, and ankles. The joint symptoms precede the jaundice by days or weeks.⁷ Associated skin lesions can include urticaria, maculopapular rash, and petechial rash. Our patient's acute hepatitis serological tests (hepatitis A, B, and C) were all negative.

RA presents with symmetric joint swelling, pain, and morning stiffness, accompanied by symptoms of myalgia and fatigue.⁸ The classic synovitis in RA involves the metacarpophalangeal and proximal interphalangeal joints, but may also affect the wrists, knees, shoulders, ankles, and spine. The onset is usually gradual and symptoms must be present for at least 6 weeks for

diagnosis. Eighty percent of patients have positive rheumatoid factor. Our patient's acute presentation, noninvolvement of small joints, and a negative rheumatoid factor did not support the diagnosis of RA.

What Would Be the Further Management?

Serum sickness remained as the most likely diagnosis. The symptoms improved within 1 week of prednisone therapy and we began to slowly reduce the dose from 40 mg/day by 5-mg decrements every other day. However, within a week, his condition deteriorated. Prednisone was increased to 60 mg/day, without significant improvement for 1 week. Because of significant myalgia and mood changes, we became concerned about continuing corticosteroid therapy that seemingly had failed. We considered plasmapheresis based on a report of good response in a case of serum sickness secondary to wasp venom immunotherapy.⁹ The premise would be the removal of circulating immune complexes. However, the result of testing for circulating immune complexes was negative and the C3 and C4 levels were normal (Table 2), which might be caused by the 6-week lapse since the onset of illness.

Initially, we considered a trial of up to three plasma exchanges. A 1-volume plasma exchange was performed using 5% human albumin for replacement, which amounted to 2.5 L. The following day, the patient reported a dramatic response with considerable decrease in joint and muscle pains and improvement in the patient's general well-being. A week later, the laboratory abnormalities resolved and prednisone was gradually tapered over 10 weeks without relapse.

The patient was living in another state and did not show up for his appointment at our clinic twice during 3 months after plasmapheresis. By telephone, he reportedly had no recurrence of fever, rash, or joint symptoms.

Final Diagnosis

Protracted serum sickness, resistant to corticosteroid therapy, with remarkable response to plasmapheresis.

DISCUSSION

Serum sickness¹⁰ results from the deposition of circulating immune complexes (antigen-antibody-complement) in the postcapillary venules. An inflammatory reaction occurs in the blood vessel wall and surrounding tissue, with the release of proteolytic enzymes and subsequent tissue damage. The symptoms typically occur 1–3 weeks after exposure to the offending antigen, but may occur earlier within days in individuals who had previously been sensitized. The manifestations include fever, malaise, lymphadenopathy, arthralgia, and cutaneous eruption—usually urticaria. Arthralgia or arthritis occurs in 10–50% of cases, usually involving multiple, large joints. Some patients may

Table 2 Levels of serum complement and circulating immune complexes 6 wk after the onset of serum sickness reaction after a wrong allergy immunotherapy extract injection

Laboratory Test	Patient's Result	Normal Level
C3, mg/dL	136	83–239
C4, mg/dL	29	10–63
PEG IgG, mg/dL	<3.5	<3.5
C1q binding assay, μ g/mL	<4	<4
Raji cell assay, μ g/mL	<20	<20

present with nephritis, generalized vasculitis, neuropathy, and cardiopulmonary complications. Laboratory findings may include leukopenia or leukocytosis, with or without eosinophilia; elevated ESR; circulating immune complexes; variable levels of serum complement; hematuria and/or proteinuria; and hypergammaglobulinemia.

Our patient presented with symptoms and signs compatible with serum sickness, with renal and hepatic involvement. Our laboratory evaluation was relatively late in the course, which explains the normal complement levels and lack of increased circulating immune complexes.

Serum sickness is most commonly caused by drugs, infectious agents, vaccines, and blood products. In some series, cefaclor was the most common antibiotic causing serum sickness in children.^{11,12} In the past, animal antisera were common causes but their use has been markedly reduced. The literature contains only a few reports on serum sickness related to immunotherapy. After receiving the wrong high-dose immunotherapy extract, our patient developed an acute hypersensitivity reaction that resolved over 1 week. A week later, one-half of his usual immunotherapy extract dose caused no immediate reaction, but after a few days symptoms of serum sickness began. It is likely that because of the higher antigen concentration in the wrong extract, and possibly its mold content, immune complexes were formed during the following 3 weeks. Whether the subsequent immunotherapy injection of the patient's usual extract contributed to the reaction is unclear. If it had any role, it might be explained by the similarity of some antigens in both extracts.

Serum sickness to insect venom is more commonly caused by an insect sting^{13,14} than to insect venom immunotherapy.⁹ Apparently, it is very rarely caused by immunotherapy with aeroallergen extracts. Anaphylaxis and serum sickness occurred in an 8-year-old boy after his maintenance dose of immunotherapy with an extract containing house-dust mite, mold, and pollens.¹⁵ His serum C3 and C4 levels were normal and

circulating immune complexes were not detectable. In another report,¹⁶ serum sickness developed in two patients undergoing rush immunotherapy. One patient had four episodes of generalized urticaria during immunotherapy with house-dust mite and grass pollen, which was stopped on day 4. That same day, the patient developed joint pains and fever. The other patient's extract was a mixture of wasp and yellow-jacket venoms and he developed urticaria, fever, and arthralgia 3 days after a 4-day rush immunotherapy. In both patients, C3 and C4 levels were normal. Another report was on a 69-year-old man who developed serum sickness while on maintenance immunotherapy with wasp venom for 7 months.⁹ Although immunotherapy was discontinued, he had two relapses at 6 and 11 weeks after the initial episode. The level of circulating immune complexes was slightly elevated during the first episode but normal on the subsequent two.

Most cases of serum sickness are mild and resolve within a few days to weeks.¹⁰ In addition to discontinuation of any causative agent, symptomatic treatment may be in the form of antihistamines and nonsteroidal anti-inflammatory agents. In moderate to severe cases, corticosteroids are often needed. Our patient's symptoms persisted despite 3 weeks of corticosteroid therapy. In a patient with serum sickness to wasp venom immunotherapy, dramatic improvement occurred after plasma exchange therapy on three occasions.⁹ Our patient had remarkable decrease in joint pains and muscle aches within <24 hours after plasma exchange. Plasmapheresis has been reported to be also successful in renal transplant patients who developed polyclonal antibody-induced serum sickness that did not respond adequately to systemic corticosteroids.¹⁷

CONCLUSION

Although a cause-and-effect relationship could not be proven, the development of serum sickness may be related to the administration of a wrong extract mixture or an erroneous high dose. If corticosteroid therapy fails, a trial of plasmapheresis is worth considering.

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