

Letter to the Editor

Severe serum sickness-like syndrome after omalizumab therapy for asthma

To the Editor:

It has been stated that—although theoretically possible—no immune complex-mediated pathologic conditions have been observed after omalizumab treatment.¹ We report a case of serum sicknesslike disease caused by omalizumab treatment in a 67-year-old woman with a long history of severe persistent allergic asthma remaining poorly controlled despite Global Initiative for Asthma step 4 treatment including chronic oral corticosteroids. Total serum IgE was 134 kU/L, body weight was 51 kg, and she received a first injection of 300 mg omalizumab as well as telithromycin 800 mg/d for 5 days for a concomitant asthma exacerbation. Five days after omalizumab (last day of telithromycin), she developed arthralgia and swelling of the left wrist and lower extremities, with malaise and generalized pruritus. Examination showed edema with vesicles of the left arm and left-wrist arthritis, pitting edema of the lower extremities with ankle arthritis, and tenosynovitis of the left-hand extensors (with crepitations on palpation). No skin rash was observed. Ultrasound and MRI of the left hand confirmed tenosynovitis of the extensors without evidence of joint effusion. C-reactive protein was increased (2.7 mg/dL), blood cell counts showed mild microcytic anemia (known β -thalassemia trait) and thrombocytopenia, circulating immune complexes were not increased, and complement (C3, C4) levels were normal. Creatinine clearance was reduced (53 mL/min) and proteinuria (1.37 g/24 h) was found, but was stable over the past year and consistent with diabetic nephropathy.

Symptoms resolved almost completely except for slight edema of the left arm and lower extremities, without specific treatment (oral methylprednisolone maintained at 4 mg/8 mg on alternate days), with C-reactive protein normal at 0.8 mg/dL. Symptoms and signs relapsed 6 days after reinjection of 300 mg omalizumab (without any other new drug given concomitantly), with general malaise, arthritis of the right wrist and left ankle, severe right-hand tenosynovitis, and C-reactive protein at 23 mg/dL. These manifestations, worse compared with the first episode, peaked at day 5 after injection and resolved progressively after 1-g methylprednisolone bolus therapy repeated 4 times over 10 days while omalizumab was discontinued. Joint and tendon pain disappeared within 1 week and edema within 2 weeks. Within the next weeks, despite further clinical improvement of joint manifestations and absence of evidence of fasciitis or infection, necrosis of soft tissue and skin developed over the right-hand tendons. Finally, 40 days after the second omalizumab injection, the patient died from acute cardiac failure, with pulmonary edema and liver congestion. Increases in brain natriuretic peptide (738 pg/mL) and troponin I (1.86 ng/mL) were noticed, and a non-Q-wave myocardial infarction in the context of undiagnosed coronary heart disease was considered the most likely diagnosis in the absence of necropsy.

Immediate adverse events to omalizumab are well characterized, with anaphylaxis occurring in approximately 1 in 1000 patients (0.1%). In contrast, delayed anaphylactoid and serum sickness-like reactions have been described,^{2,3} but their relationship to the drug remains uncertain in cases reported so far, and their frequency is unknown. Anaphylactoid reactions described for other mAbs^{4,5} concern mostly non-IgE-mediated immediate events. The 3 cases of serum sicknesslike syndromes described in the 2003 Genentech report to the US Food and Drug Administration for omalizumab³ were self-limiting and did not lead to drug discontinuation. We describe a case of severe, delayed serum sickness-like syndrome with a very particular feature (arthritis with tenosynovitis, progressing to tissue necrosis)⁶ proven by rechallenge to be omalizumab-related. The role of diabetes and pre-existing proteinuria/nephropathy in the development of clinical manifestations on anaphylactoid reaction to omalizumab, as well as in the progression of tenosynovitis to local tissue necrosis, remains elusive. In addition, it is more likely that death occurred as a complication of diabetes and not of omalizumab treatment. This case report does not limit the place and efficacy of omalizumab in poorly controlled severe asthma, but strengthens the need for reporting adverse events in postmarketing surveillance⁷ of mAb-based therapy, as achieved for omalizumab through the ongoing PERSIST study.

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