

Serum sickness following a first rituximab infusion with no recurrence after the second one

Sirs,

Rituximab is a chimeric monoclonal antibody targeting the CD20 cell surface molecule, initially developed for the treatment of B cell lymphomas, then recently used in the treatment of various autoimmune disorders: autoimmune cytopenia, systemic lupus and rheumatoid arthritis (1, 2). Among adverse events reported, different infusion reactions have been described (3, 4). These early events differ from delayed reactions which were less frequent, such as serum sickness that has been exceptionally reported (4-7). We report the case of a 30-year-old woman who developed a serum sickness after a first infusion of rituximab. This patient presented a 12-year history of mixed connective tissue disease associating symmetrical destructive polyarthritis, Raynaud's phenomenon, sclerodactyly and pericarditis. She was unsuccessfully treated by hydroxychloroquine, methotrexate, etanercept and finally mycophenolate mofetil. Considering the severity of her symptoms, a treatment by rituximab was initiated. The first infusion was performed after a conventional premedication (1000 mg paracetamol, 100 mg prednisolone, and 5 mg dexchlorpheniramine). Thirteen days later, the patient was readmitted because of a non pruriginous morbilliform skin eruption, myalgias and arthralgias. Laboratory investigations revealed a decrease of complement C3 (0.64g/l, with normal ranges between 0.8 and 1.6g/l) and C4 (0.02g/l, with normal ranges between 0.15 and 0.35g/l), normal IgE level (titer 46 kUI/l), an increase of inflammatory markers (CRP=43.1mg/l, ESR=36 mm/h), no sign of renal involvement.

In this context, according to the nature of the eruption and the delay of occurrence after the rituximab infusion, the disease was described as serum sickness. The patient was given an oral antihistamine treatment, but no corticosteroids were administered because of lack of severity. The eruption recovered progressively in three days. According to the facts that: 1) the reaction was mild and recovered rapidly, and 2) a large number of previously used treatment failed to demonstrate any efficacy, we decided to perform a second infusion 6 weeks after the first one (4 weeks after the serum sickness recovery). The premedication was not modified and the infusion was performed over three hours and half. The prednisone treatment was slightly increased, up to 20 mg per day for 14 days. No immediate or

delayed reaction was observed after this second infusion. The polyarthritis progressively improved during the following months (7 months of follow-up).

Serum sickness is a type III hypersensitivity reaction resulting from the infusion of heterologous or foreign protein (8). Primary serum sickness occurs 6-21 days after the administration of the inciting antigen. The classic clinical manifestations consist of fever, arthralgia, lymphadenopathy and skin eruption. Usually, laboratory investigations reveal an increase of ERS, a proteinuria, a hematuria, a decrease of C3 and C4 levels, and mixed cryoglobulinaemia. Such events have been reported after rituximab infusion. These observations were generally described in autoimmune disorders: thrombocytopenic purpura (9, 10), Sjögren's syndrome (6, 11, 12), hepatitis C virus-related mixed cryoglobulinemia (5), systemic lupus (13), autoimmune neuropathy (14) and patient treated for a lymphoma (7, 15). These observations have suggested that patients affected by autoimmune disorders characterized by high levels of auto-antibodies in the serum, the B-cell lysis induced by anti-CD20 antibodies may lead to serum delivery of intracellular antigens, and consequently to antigen-antibody complex formation and precipitation (16, 17). D'Arcy and Mannik proposed a second hypothesis (14). They showed that the murine component of rituximab induce human antibodies formation. In a patient treated with rituximab who developed a serum sickness, the analysis of serum samples showed human antibodies binding to IDEC-C2B8 (rituximab). Such a hypothesis could not, however, explain serum sickness occurring after a first infusion of chimeric monoclonal antibodies.

In previously reported cases, no indication of on going rituximab therapy was described. Our observation indicates that, at least in mild case of serum sickness occurring after rituximab therapy, the treatment can be repeated with no recurrence of the serum sickness. This suggests that, in mild serum sickness occurring in patients treated with rituximab, treatment withdrawal is not necessary. Serum sickness can be managed with anti-histamine treatment. A further infusion can be done under strict medical care and an adequate dose of prednisone.

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References

1. COHEN S, EMERY P, GREENWALD M *et al.*: Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy : results of multicenter, randomized, double blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty four weeks. *Arthritis Rheum* 2006; 54: 2793-806.
2. EDWARDS J, SZCZEPANSKI L, SZECHINSKI J *et al.*: Efficacy of B-Cells-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004; 350: 2572-81.
3. HERISHANU Y: Rituximab-Induced Serum Sickness. *American Journal of Hematology* 2002; 70: 329-34.
4. HELLERSTEDT B, AHMED A: Delayed-type hypersensitivity reaction or serum sickness after rituximab treatment. *Ann Oncology* 2003; 14: 1792.
5. CATUOGNO M, REZAI S, PRIORI R, MAGRINI L, VALESINI G: Serum Sickness associated with rituximab in patient with hepatitis C virus-related mixed cryoglobulinemia. *Rheumatology* 2005; 44: 406.
6. SCHUTGENS REG: Rituximab induced serum sickness. *Br J Haematol* 2006; 135:147.
7. TODD D, HELFGOTT S: Serum sickness following treatment with rituximab. *J Rheumatol* 2007; 34: 430-3.
8. CLARK B, KOTTI G, SHAH A, CONGER N: Severe serum sickness reaction to oral and intramuscular penicillin. *Pharmacotherapy* 2006; 26: 705-8.
9. BENNETT CM, ROGERS ZR, KINNAMON DD *et al.*: Prospective phase 1/2 study of rituximab in childhood and adolescent chronic immune thrombocytopenic purpura. *Blood* 2006; 107: 2639-42.
10. WANG J, WILEY JM, LUDDY R, GREENBERG J, FEUERSTEIN MA, BUSSEL JB: Chronic immune thrombocytopenic purpura in children : assessment of rituximab treatment. *J Pediatr* 2005; 146: 217-21.
11. PIJPE J, IMHOFF GWV, SPIJKERVET FKL *et al.*: Rituximab treatment in patients with primary Sjögren's syndrome. *Arthritis Rheum* 2005; 52: 2740-50.
12. DEVAUCHELLE-PENSEC V, PENNEC Y, MORVAN J *et al.*: Improvement of Sjögren's syndrome after two infusions (anti CD 20). *Arthritis Rheum* 2007; 57: 310-7.
13. GOTTENBERG J-E, GUILLEVIN L, LAMBOTTE O *et al.*: Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. *Ann Rheum Dis* 2005; 64: 913-20.
14. D'ARCY CA, MANNIK M: Serum sickness secondary to treatment with the murine-human chimeric antibody IDEC-C2B8 (rituximab). *Arthritis Rheum* 2001; 44: 1717-8.
15. DISPERRATI P, HICKS L, BUCKSTEIN R: Rituximab-induced serum sickness in a patient with follicular lymphoma. *Leuk Lymphoma* 2007; 48: 1633-5.
16. FINGER E, SCHEINBERG M: Development of serum sickness-like symptoms after rituximab infusion in two patients with severe hypergammaglobulinemia. *J Clin Rheumatol* 2007; 13: 94-5.
17. YOUINOU P, JAMIC C, SARAUX A: B cell: a logical target for treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2007; 25: 318-28.