Serum sickness associated with rituximab in a patient with hepatitis C virus-related mixed cryoglobulinaemia

Sir, We report the case of a 60-yr-old woman who developed serum sickness after rituximab.

At the age of 56 yr, a routine blood test showed a moderate increase of transaminases. Anti-hepatitis C virus (HCV) antibodies were demonstrated, the genotype was subtype 1b and the virus actively replicated (600,000 IU/mL). In spite of persistent elevation of transaminases, the patient refused liver biopsy. Within 18 months lower limb sensory polyneuropathy developed, followed by motor involvement. Transaminases were still high and rheumatoid factor (RF) and a small serum monoclonal component (IgM) were present in the absence of Bence-Jones proteinuria. A liver biopsy was performed showing signs of chronic active hepatitis while a bone marrow biopsy excluded a lymphoproliferative disease. Prednisone (1 mg/kg/day) and pegylated-Fc\((\alpha)\) associated with ribavirin (1 g/day) were started with clinical improvement and normalization of transaminases. Nevertheless, any effort to taper steroids induced a flare of neuropathy. Within 1 yr the patient developed a cushingoid aspect and severe osteoporosis. At the age of 59 yr, deep skin ulcers of the leg appeared; initially the patient was treated with plasmapheresis and subsequently i.v. immunoglobulins with little clinical benefit. After 2 yr of treatment, antiviral therapy was stopped due to progressive leucopenia and anaemia, both improving within 1 month of withdrawal.

At the age of 60 yr, the patient was admitted to our division; she was still taking prednisone (37.5 mg/day). Physical examination showed a steppage walk, livedo reticularis and wide skin ulcers of the leg involving the right calf, right external malleolus and left heel; the patient refused skin biopsy. Laboratory examinations showed high erythrocyte sedimentation rate, C-reactive protein and fibrinogen, normal renal and liver function, low viral activity (HCV RNA <3000 IU/mL), IgM 453 mg/dl with a monoclonal component IgM\(\kappa\) (0.26 g/dl), RF positivity (Ra-test, F\(\gamma\) latex, Waaler–Rose) and the presence of type II cryoglobulins, C\(3\) < 5 mg/dl (normal range 20–55).

Rituximab is an anti-CD20 human–mouse chimeric monoclonal antibody that showed encouraging results in two series including 35 patients with mixed cryoglobulinaemia resistant to traditional approaches [1, 2]. Therefore, we performed a first infusion of the drug (375 mg/m\(^2\)), which was well tolerated. However, 7 days after, shivering fever (38.5°C) and polyarthralgias presented. The next day fever was higher (39.3°C) and associated with diffuse urticaria. Symptoms and signs completely remitted after administration of betamethasone 4 mg i.v. and H\(\gamma\)-blockers. Haemoculture and urinoculture were sterile.

We hypothesized an acute serum sickness which, as far as we know, has never been reported in association with rituximab in patients with lymphoproliferative disorders [3] while it has been previously described in three cases of autoimmune diseases (autoimmune polyneuropathy, autoimmune thrombocytopenia, systemic lupus erythematosus) [4–6]. It is possible to speculate that some factors related to autoimmune disorders are involved in the pathogenesis of serum sickness such as a reduced clearance of immunocomplexes and/or an increased production of autoantibodies. As a matter of fact, high titres of antibodies directed against the murine F(\(\alpha\)b') fragments were detected in the first reported case of serum sickness after rituximab [4]. On the other hand, patients with lymphoproliferative disorders are usually treated with polychemotherapy, which could prevent the development of serum sickness. This is the first case of serum sickness associated with rituximab in a patient with HCV-related mixed cryoglobulinaemia. In this condition RF could bind to the human Fc(\(\alpha\)) fragment of the chimeric antibody and form immunocomplexes, possibly inducing a third-type immune reaction. A further possible pathogenetic factor is the previous administration of i.v. immunoglobulins, which might have sensitized our patient, explaining the occurrence of serum sickness after the first infusion of rituximab. With the expansion in the therapeutic use of monoclonal antibodies in a widening spectrum of disorders, it is advisable to take into consideration not only immediate reactions but also delayed ones.

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Anakinra for flares of pyogenic arthritis in PAPA syndrome

Sir, Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome (MIM no. 604416) is an autosomal dominant autoinflammatory disease caused by mutations in the PTSTPIP gene [1]. Historically, it had been described as streaking leucocyte factor disease [2]. PAPA syndrome is characterized by recurrent sterile arthritis that usually occurs after minor trauma, but also spontaneously [3]. It is a self-limiting disease, but can lead to serious joint destruction. No effective treatment has been published so far, although steroids have been effective in some cases. Here we describe the effect of recombiant human interleukin (IL)-1 receptor antagonist (anakinra, Kineret®) in a case of PAPA syndrome-associated arthritis refractory to steroids.

A 16-yr-old boy presented in a local hospital with a swollen and painful right ankle 2 weeks after a minor traffic accident resulting in a superficial laceration on his knee. He, his father and three of his six siblings suffer from recurrent sterile arthritis. In addition, they have mild acne, mainly around the nose. Recently, this family was diagnosed as having PAPA syndrome, confirmed by a heterozygous A230T mutation in the PTSTPIP1 gene (the genetic confirmation kindly performed by I. AkSENTIJEVICH, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH Bethesda, MD, USA). Therefore, the