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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 (IgMκ) 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-IFNα (80 μg weekly) 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 legs 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 IgMκ (0.26 g/dl), RF positivity (Ra-test, F_{II} latex, Waaler–Rose) and the presence of type II cryoglobulins, $C_4 < 5$ 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 betametasone 4 mg/i.v. and H_1-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 diseases [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(ab′) 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(γ) 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.

The authors have declared no conflicts of interest.

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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 recombinant 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

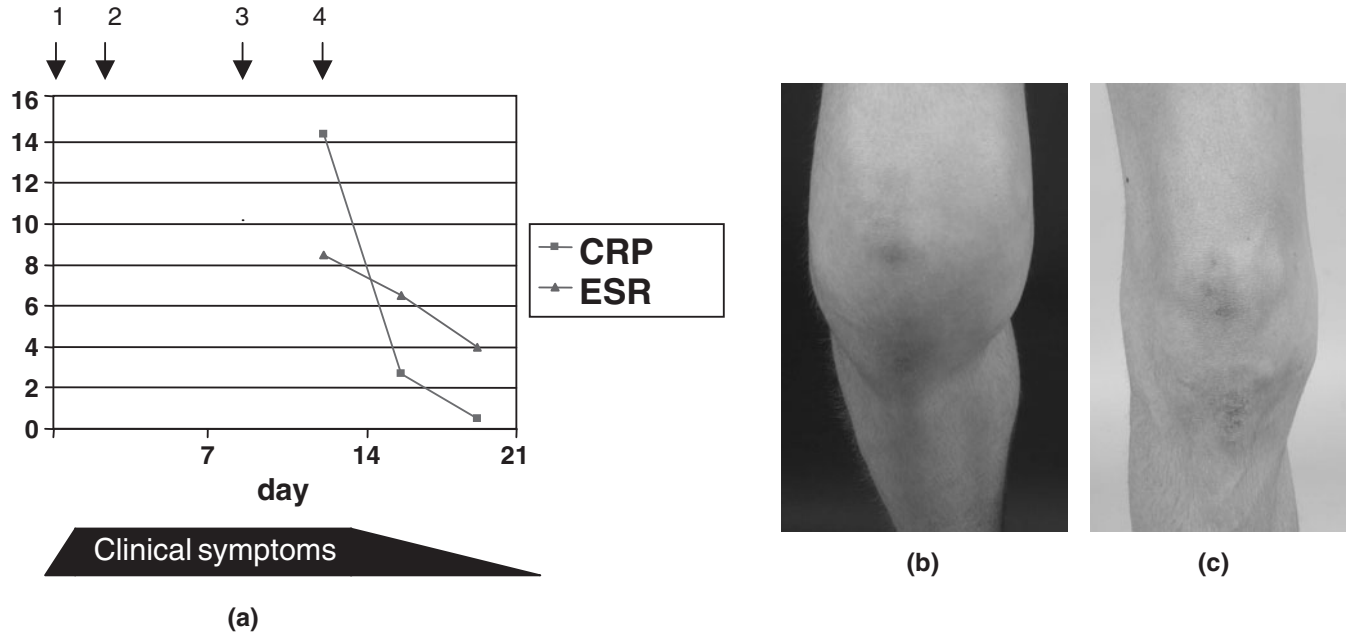

FIG. 1. (a) Clinical symptoms described as pain, swelling, restricted flexion and extension of the right ankle in relation to treatment and laboratory findings. 1 = start of symptoms; 2 = first intra-articular depot (40 mg triamcinolone hexacetonide); 3 = second intra-articular depot; 4 = start of anakinra (1 mg/kg). (b) Right knee at presentation. (c) Right knee 1 week after starting treatment with anakinra. This figure may be viewed in colour as supplementary data at *Rheumatology* Online.

patient was suspected of having a flare of arthritis associated with PAPA syndrome and he received intra-articular steroids (40 mg triamcinolone hexacetonide) twice with a 1-week interval, but without any effect.

He was referred to our paediatric rheumatology department. On examination, the right ankle was swollen and painful, and showed limitation of movement. Besides mild anaemia, an ESR of 85 mm/h and a CRP of 144 mg/l, there were no abnormal laboratory findings. Blood cultures and a culture of an aspirate from the right ankle remained sterile. Since PAPA syndrome is associated with elevated IL-1β production [4], we decided to treat him with anakinra, a recombinant human IL-1 receptor antagonist (1 mg/kg per day subcutaneously for 1 week). After a few days, the swelling and pain diminished, and it resolved completely within 1 week. In addition, laboratory results returned to normal (Fig. 1a). Five and 7 months later, the boy developed acute inflammation of his right knee joint spontaneously and after sports, respectively. Within a day, treatment with anakinra was resumed. Two days later, he was free of symptoms (Fig. 1b and c).

PAPA syndrome belongs to the recently recognized group of hereditary autoinflammatory disorders. Other members include familial Mediterranean fever (FMF), the hyper-IgD and periodic fever syndrome and cryopyrin associated disorders, such as the Muckle–Wells syndrome. Although the precise pathogenesis of these diseases is only partly understood, increased IL-1β production is a common feature [4, 5]. The mutations described in PAPA syndrome result in a mutated CD2BP1 (CD2 binding protein 1, also known as PSTPIP1; proline–serine–threonine phosphatase interacting protein). The function of CD2BP1 is not completely understood, but mutations can lead to decreased apoptosis, explaining the observed accumulation of neutrophil-rich material [6]. In addition, it has been suggested that PAPA syndrome intervenes in the same pathway as FMF. In FMF, there is a mutation in the gene encoding pyrin. The mutated CD2BP1 in PAPA syndrome has increased interaction with pyrin. The effect of this interaction is similar to that of mutated pyrin, resulting in decreased apoptosis and elevated IL-1β levels, as seen in FMF [7]. Recently, anakinra appeared to be highly effective in patients with Muckle–Wells syndrome [8, 9]. We observed that anakinra effectively aborts arthritis flares associated with PAPA syndrome. In the first arthritis flare the improvement could be spontaneous or due to a delayed effect of earlier steroid treatment. However, the speed of amelioration after the first administration of anakinra favours its effectiveness. This was further supported by the immediate clinical response to anakinra at the next two disease flares. PAPA syndrome is exceedingly rare in comparison with, for example, septic arthritis. Therefore the diagnosis rests on the initial repeated exclusion of joint infection in addition to genetic testing. However, when the diagnosis is established the availability of effective systemic therapy spares the patient repeated arthrocenteses for culture and local steroid deposits.

In summary, anakinra appears to be an effective therapy to treat disease flares in PAPA syndrome. Anakinra has previously been employed in other inflammatory diseases for maintenance treatment, but never intermittently to abort disease flares. Our observation shows that further study of intermittent administration of anakinra to treat flares of episodic autoinflammatory disorders is both rational and necessary.

Rheumatology	Key messages
	• Anakinra is an effective treatment for flares in PAPA syndrome.

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Primary obturator pyomyositis

Sir, A 33-yr-old male presented with acute onset bilateral groin pain and fever reaching 40°C. He denied other systemic symptoms. Two days prior to presentation he had played a game of rugby.

On examination, he had several large psoriatic plaques, but none in the groin. Hip movements were painful but not significantly restricted. Spinal movements were unrestricted. A pelvic X-ray showed old calcification, probably representing previous gluteal haematoma. His white cell count was elevated at 15×10^9/l and the CRP was 142 mg/l. An MRI (Fig. 1) of the pelvis demonstrated increased signalling within the left obturators, pectineus and adductors with contrast enhancement, but no abscess. Less marked enhancement was seen in the right obturators. Blood cultures grew *Staphylococcus aureus* sensitive to gentamicin and flucloxacillin.

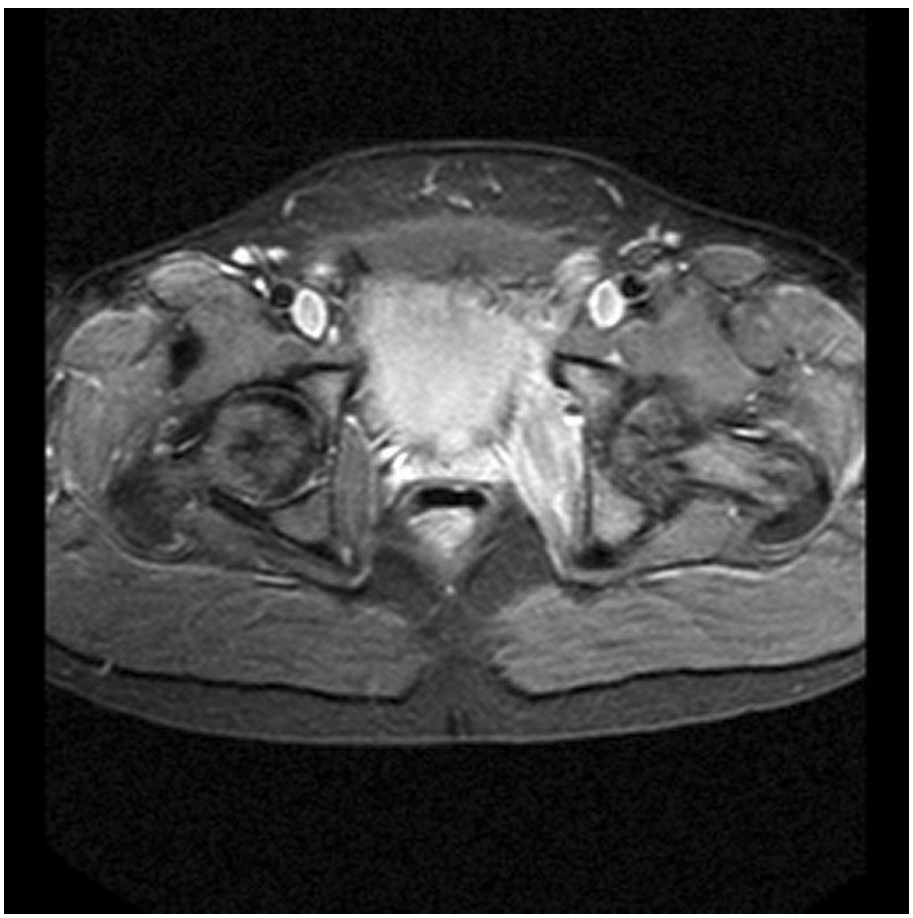

Fig. 1. Gadolium enhancement exhibiting increased signalling within the left obturator internus.