RHEUMATOLOGY

Letters to the Editor

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Successful use of tocilizumab in two cases of severe autoinflammatory disease with a single copy of the Mediterranean fever gene

Rheumatology key message

- Tocilizumab may have a role in severe undefined autoinflammatory disease with single-gene FMF mutations.

Sir, Autoinflammatory diseases are heterogeneous hereditary diseases where the main clinical manifestations are a consequence of uncontrolled inflammation. FMF, the most common subtype [1], is classically autosomal recessive. Reports on autosomal dominant FMF exist but are often discounted due to asymptomatic FMF carriers being common in certain populations, giving rise to pseudo–dominant inheritance [2].

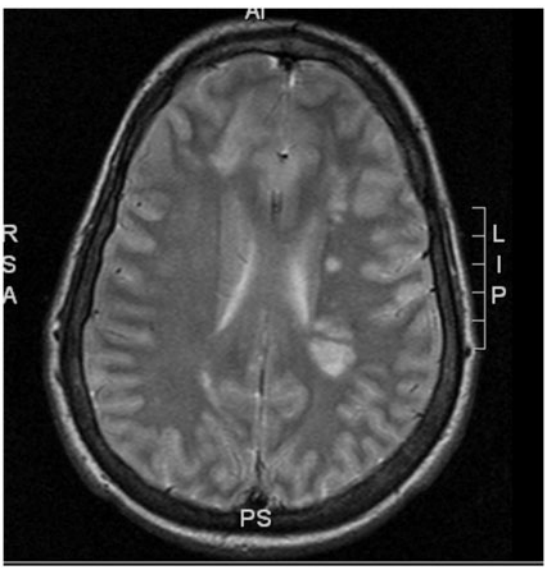
We report two cases of severe autoinflammatory phenotype and heterozygosity to c.2282G>A (p.Arg761His) and c.2177T>C (p.Val726Ala) in the *MEFV* gene, respectively, with excellent response to the IL-6 inhibitor tocilizumab.

The first case is that of a 20-year-old Greek-Cypriot man who at age 4 years presented with fever, spinal pain, splenomegaly and anaemia, leading to a diagnosis of chronic recurrent multifocal osteomyelitis affecting the L1–L2 vertebrae. At the age of 9 years he was diagnosed with aseptic multiphasic disseminating encephalomyelitis. Genetic testing revealed a single mutation for c.2282G>A (p.Arg761His) in the *MEFV* gene. During the course of his illness the patient was treated with corticosteroids and (in sequence) adalimumab (40 mg/15 days), colchicine (2 g/day), mycophenolate (2 g/day) and HCQ (400 mg/day). Despite this, normocytic anaemia (haemoglobin 10 g/dl) and high acute phase response [CRP 100 mg/l (normal <5), amyloid levels 200 (normal <30)] persisted. A trial of anakinra resulted in only partial clinical response, leading to tocilizumab as the next treatment choice. This resulted in rapid clinical and biochemical improvement. After 5 years with ongoing tocilizumab (8 mg/kg/month) and colchicine (1 g/day), he remains well, with normal CRP and amyloid levels.

The second case is that of an 18-year-old Greek-Cypriot man who at age 9 years presented with debilitating headaches, eventually diagnosed with aseptic meningoencephalitis necessitating high-dose steroid treatment. Prior to this he had persisting pyrexia and anaemia. A trial of azathioprine and rituximab proved unsuccessful. There was good clinical response to sirolimus (rapamycin), which was withdrawn after 2 years due to complete symptom resolution. However, this resulted in relapse of pyrexia and anaemia. Microbiological investigations were negative, prompting steroid administration, initially intravenously. A month later he was readmitted with fever and headache. A diagnosis of meningoencephalitis was made (Fig. 1). An intensive workup (including cerebrospinal fluid analysis and microbiological testing) was unremarkable. The patient received corticosteroids (1 g/day over 3 days), resulting in rapid symptom resolution. Genetic testing revealed heterozygosity for c.2177T>C (p.Val726Ala) of the *MEFV* gene. Reintroduction of sirolimus was unsuccessful in controlling symptoms, leading to a trial of tocilizumab (8 mg/kg/week s.c.), which resulted in suppression of CRP and amyloid to normal levels and enabled steroid withdrawal.

Both these patients share similar clinical and genetic characteristics. Pyrexia and CNS involvement were key features and treatment response was best sustained with IL-6 inhibition, suggesting a high IL-6 drive. The clinical picture and response to treatment was atypical for FMF [3], posing significant diagnostic challenges. The possibility of digenic inheritance in autoinflammation-associated genes [4] was considered but ruled out in both patients, who were negative for *NLRP3*, *TNFRSF1A* and *MVK* genes [5]. Whether the single identified FMF mutation at least partly accounts for the above-described clinical pictures remains speculative. The role of epigenetics and/or environmental factors in triggering disease in genetically predisposed individuals and the clinical impact of single-gene mutations in autosomal recessive disease represents an exciting area for research [6]. We hope through these cases to highlight the complexity of

Fig. 1 MRI showing multifocal white matter lesions in the subcortical and periventricular regions



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autoinflammatory disease and provide further insights into mechanistic pathways involved.

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Toxic drug-induced liver failure during therapy of rheumatoid arthritis with tocilizumab subcutaneously: a case report

Rheumatology key message

- Drug-induced liver failure under therapy with tocilizumab can occur even after years of treatment.

SIR, in RA, inflammation is regulated by a complex cytokine and chemokine network, of which TNF-α and IL-6 seem to be most relevant [1]. However, IL-6 is an important inducer of the acute phase response in the liver, modifying infection defence. Furthermore, it is a potent hepatocyte mitogen essential for liver regeneration [2].

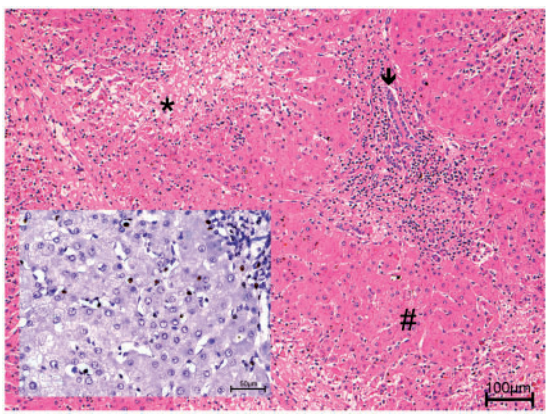
Although MTX still remains the anchor drug, the outcome of patients with RA has dramatically changed with the advent of new therapeutic agents, such as tocilizumab, targeting the IL-6 receptor. Low disease activity and remission are now frequently achieved [3]. However, this highly effective treatment can cause liver damage, and patients at risk cannot be anticipated. Liver failure after years of treatment has not been reported so far.

The patient is a 51-year-old, Caucasian female who was diagnosed with anti-CCP-positive RA in 2008 and was started on different DMARDs during the course of the disease; MTX, among others. Owing to the poor clinical response, the treatment regimen was changed to a monotherapy of toxicilizumab i.v. in 2011. Before administration of tocilizumab her blood counts and biochemical data were all within the normal range, including liver and renal function tests. Clinical response was improved and the patient started on toxicilizumab, 162 mg s.c. once a week.

Five years later, routine laboratory controls demonstrated elevated liver enzymes in the 300–500 U/l range, and tocilizumab was discontinued. At this point, there was no history of potentially hepatotoxic drug intake, especially of no co-medication with any DMARD.

Three months later, the patient experienced increasing fatigue, and physical examination showed jaundice, with a serum bilirubin at 4.9 mg/dl. Repeat laboratory results showed a marked progress of the elevated liver enzymes [Aspartate Aminotransferase (AST) 1049 U/l, Alanine Aminotransferase (ALT) 1415 U/l]. A medical work-up at a community hospital excluded viral hepatitis,

FIG. 1 Histology results



Liver section (Haematoxylin and Eosin stain) of the explanted liver with necrotic tissue (asterisks), remnant of intact liver tissue (hash) and a portal field with infiltration of lymphocytes (arrow). Section: immunohistochemistry of Ki67 in intact liver parenchyma showing proliferating lymphocytes; expression in hepatocytes is almost not detected.