Corticosteroids have been the mainstay of treatment for giant cell arteritis (GCA), usually given for at least two years, with the potential for unpleasant consequences. Infliximab, a chimeric monoclonal antibody against tumour necrosis factor α (TNFα), used successfully in the treatment of rheumatoid arthritis (RA) and other conditions, was considered by us, on the basis of pathogenic and pathologic data of GCA, as a potentially effective treatment for this disease. Consequently, we decided to try it in two of our patients with GCA, without concomitant administration of corticosteroids, hoping that if only a few infusions of anti-TNFα cured the disease then the side effects of chronic steroid treatment might be avoided.

Our patients were both male, 85 and 80 years old, respectively, seen six months apart from each other. They had a typical clinical picture of GCA with recent onset of fatigue, weight loss, bilateral temporal headache and low grade fever, mild anaemia, erythrocyte sedimentation rate (ESR) >100 mm/1 h and C reactive protein (CRP) >10 times normal. A temporal artery biopsy was typical for GCA. After approval by the hospital ethics committee and informed consent from the patients, 3 mg/kg of infliximab were given intravenously. Within hours the patients reported dramatic improvement, and their fever and headache disappeared. A second infusion was given after two weeks when the ESR was around 40 mm/1 h and, and a third, one month later when the patients were in excellent condition and had a normal ESR and CRP.

The first patient did well for three months, but at that time symptoms recurred and, despite two infusions at monthly intervals, no significant improvement was noted. Consequently, a decision to stop infliximab was made, and methylprednisolone 16 mg/day was started, with excellent response. He was followed up closely.

Symptoms and a rise in the ESR recurred six weeks after the third injection in the second patient. With the experience of the first patient, we decided to stop infliximab and switch the patient to the conventional treatment, giving methylprednisolone 32 mg/day. He responded well and his ESR was 22 mm/1 h three weeks later. He was then followed up regularly.

As described above, infliximab as monotherapy was extremely effective at the beginning of the treatment of our patients. A favourable response of GCA to this agent was not unexpected. TNFα has been found, in the pathological lesions of GCA. Furthermore, the pathology of the lesions, with the local accumulation of CD4 (+) memory cells, resembles that of RA, for which anti-TNFα is very effective. Finally, an association between GCA with different TNFα microsatellite polymorphisms has been reported.

However, the initial dramatic response of our patients was not followed by a sustained improvement. It may very well be that large doses of infliximab, given monthly for a prolonged time, may be effective. However, such an approach is by no means cost effective, and should not be attempted. This trial was based on the hypothesis that, if three, or at the most, five infusions of infliximab, cured this dangerous but self limiting disease, it might be worth giving it, and avoiding the long term undesirable effects of the conventional approach. This was not found to be the case.

In a recent report infliximab was shown to be effective in three of four cases of GCA resistant to steroid. Furthermore, anti-TNFα treatment of a case of GCA resistant to steroids and immunosuppressive drugs has been reported.

Consequently, we suggest that infliximab should be used in GCA only for patients who are unresponsive to, or intolerant of steroids and/or methotrexate. Probably, a larger dose than that used in RA given for relatively long time will be required. A further conclusion may be that TNFα is one of the major cytokines mediating inflammation in GCA.

References

Correlation between interleukin 10 gene promoter region polymorphisms and clinical manifestations in Japanese patients with Sjögren’s syndrome


Sjögren’s syndrome (SS) is an autoimmune disease characterised by lymphocytic infiltration and glandular tissue dysfunction of exocrine glands such as the salivary and lachrymal glands in genetically susceptible people. Several cytokines, including interleukin 10 (IL10), have been proposed as candidate genes. Recently, Hulkkonen et al reported that in Finnish patients the haplotypes formed on the basis of the IL10 gene alleles (at the -1082, -819, and -592 loci) were related to susceptibility to primary SS. However, no correlation between extraglandular symptoms and IL10 haplotypes was found in that study. In this study we compared the mean age at onset among genotypes of the IL10 gene in patients with SS (fig 1). The age at onset of patients with the ATA/ATA genotype was the highest among patients with SS. The age at onset of ACC haplotype non-carriers was significantly lower than that of ACC haplotype carriers (p<0.001). A younger age at onset of SS was likely to be positively related to the ATA haplotype and negatively to the ACC haplotype (fig 1, lower). The frequency of ACC haplotype was decreased in HIV-1 seropositive patients with SS compared with seronegative patients with SS, though the difference was not significant (data not shown). We failed to detect any association between IL10 gene polymorphisms and any of the following parameters:

| Table 1 | Individual IL10 genotypes, haplotype carrier rates, and haplotype frequencies in healthy controls and patients with Sjögren’s syndrome (SS) |
|---------------------------------|----------------|----------------|----------------|----------------|
| | Sjögren’s syndrome | Healthy controls | Sjögren’s syndrome | Healthy controls |
| | [n=47] | [n=107] | IgG<15 g/l | [n=28] | IgG<15 g/l | [n=9] | χ², p value |
| Genotype No (%) | | | | |
| ACC/ACC | 1 (2) | 6 (6) | 0.313* | 0 (0) | 1 (11) | 0.243* |
| ACC/ATA | 14 (30) | 45 (42) | 0.149 | 6 (21) | 4 (44) | 0.959* |
| ATA/ATA | 24 (51) | 42 (39) | 0.172 | 17 (61) | 1 (11) | 0.012* |
| ACC/GCC | 1 (2) | 4 (4) | 0.516* | 1 (2) | 4 (44) | 0.757* |
| ATA/GCC | 7 (15) | 10 (9) | 0.312 | 3 (11) | 3 (33) | 0.757* |
| GCC/GCC | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | |
| Haplotype carrier, No (%) | | | | |
| ACC carriers | 16 (34) | 55 (51) | 0.047 | 7 (25) | 5 (56) | 0.100* |
| ATA carriers | 45 (96) | 97 (91) | 0.230 | 26 (93) | 8 (89) | 0.578* |
| GCC carriers | 8 (17) | 14 (13) | 0.520 | 4 (14) | 3 (33) | 0.955* |
| Haplotype frequency, No (%) | | | | |
| ACC | 17/94 (18) | 61/214 (29) | 0.053 | 7/56 (13) | 6/18 (33) | 0.988* |
| ATA | 69/94 (73) | 139/214 (65) | 0.145 | 43/56 (77) | 9/18 (50) | 0.033 |
| GCC | 8/94 (9) | 14/214 (7) | 0.537 | 4/56 (7) | 3/18 (17) | 0.385* |

*Value with Fisher’s exact probability. Values underlined indicate p<0.05.
accompanying the tremendous excitement about the introduction of TNF inhibitors into the clinic has been caution about potential adverse events that may be associated with the use of these potent immunomodulators. Increased susceptibility to certain infections, particularly Mycobacterium tuberculosis (TB), has been a particular concern. Data from animal studies suggest that TNF has a central role in host defence against TB, in part related to effective cytokine expression.

Figure 1 The effect of interleukin 10 (IL10) genotypes (upper part) on age at onset in Japanese patients with primary SS. (Lower part) Age at onset (mean and SD) is shown among the carriers and non-carriers of the IL10 ATA haplotype (panel A), ACC haplotype (panel B), and GCC haplotype (panel C), respectively.

Cigarette smoking, TB, and TNF inhibitors

J Bieber, A Kavanaugh

Accompanying the tremendous excitement about the introduction of TNF inhibitors into the clinic has been caution about potential adverse events that may be associated with the use of these potent immunomodulators. Increased susceptibility to certain infections, particularly Mycobacterium tuberculosis (TB), has been a particular concern. Data from animal studies suggest that TNF has a central role in host defence against TB, in part related to effective granuloma formation. For infliximab, 277 cases of TB had been reported worldwide through August 2002 among more than 365 000 patients treated. Interestingly, although about 75% of infliximab use has been in the United States, more than two thirds of the reported TB cases were from outside the USA, mainly from the European Union. Part of the reason for this discrepancy may relate to a higher incidence of latent TB infection in the EU. However, we suggest that cigarette smoking may also be a relevant factor. In 2000, just over 23% of adults in the USA were current cigarette smokers, compared with about 30% of European adults (http://www.cdc.gov/tobacco; http://www.cisid.who.dk/tobacco).
Large synovial cysts originating from the sternoclavicular joints in a patient with rheumatoid arthritis

A P Andonopoulos, N Meimaris, G Yiannopoulos, V Pastromas, P Dimopoulos

Synovial cysts in rheumatoid arthritis (RA), most common in the popliteal fossa,1,2 have also been described in proximity to several other rheumatoid joints,3,4 but never the sternoclavicular joints.

CASE REPORT
We here describe, for the first time, the development of unusually large synovial cysts, from the disproportionately small sternoclavicular joints, in a 58 year old man, with a 27 year history of severe, seropositive, erosive, destructive, deforming, nodular RA. Over the years he had been treated, albeit erratically, with several disease modifying antirheumatic drugs (DMARDs), but he had been poorly followed up.

Seven months ago, while receiving n-penicillamine 500 mg/day and methylprednisolone 2 mg/day, he presented with a 10 cm long and 5 cm thick, fluctuant, non-tender, sausage-like mass over the right clavicle, and a smaller one, about 5 cm long over the left clavicle, developed gradually over one month. Routine haematology and biochemistry were normal. A purified protein derivative (PPD) skin test was negative.

A chest computed tomographic (CT) scan (fig 1A) showed sclerosis and subchondral and marginal erosions in the manubriosternal and both sternoclavicular and first costosternal articulations. The posterior sternal surface was largely eroded, and the cancellous portion transformed to a smooth walled cavity, filled up with soft tissue. The overlying anterior thoracic wall soft tissues contained several cystic lesions, 1–6 cm in diameter, arranged parallel to the two lateral sternal borders. The four upper costovertebral joints (not shown) were similarly affected. Paracentesis of the right mass yielded a turbulent dark yellow fluid, with white blood cells (WBCs) 40.5×10⁶/L (82% polymorphonuclear cells (PMNs)), sugar of 80 mg/l and no malignant cells. Direct evidence of malignancy and negative culture. After a repeat paracentesis with similar results, three months later, an injection, with a long acting corticosteroid preparation, of the right mass yielded a turbulent dark yellow fluid, with white blood cells (WBCs) 40.5×10⁶/L (82% polymorphonuclear cells (PMNs)), sugar of 80 mg/l and no malignant cells. Direct evidence of malignancy and negative culture.

DISCUSSION
The synovial origin of the described lesions was strongly supported by (a) their cystic nature confirmed by CT and...
MRI; (b) the inflammatory character of the fluid they contained; (c) the exclusion of any infectious or malignant process; (d) the biopsy of the cystic wall, typical for synovial cyst; (e) the favourable response to the local steroid injection.

Interestingly, imaging did not succeed in demonstrating any communication between the cysts and the sternoclavicular or the upper costosternal joints, a feature which even arthrography may not disclose. Nevertheless, the arrangement of the cysts along the sternal borders, and their close proximity to the severely affected sternal joints, led us to presume that they originated in the latter.

This unusual case emphasises the possibility of synovial cyst formation from any inflamed rheumatoid joint, no matter how small it may be, and the fact that such presentations may appear in very atypical locations, posing important and sometimes difficult diagnostic problems.

Authors’ affiliations
A P Andonopoulos, N Meimaris, G Yiannopoulos, Department of Medicine, Division of Rheumatology, University of Patras School of Medicine, Patras, Greece
V Pastromas, P Dimopoulos, Department of Radiology, University of Patras School of Medicine, Patras, Greece

Correspondence to: Professor A P Andonopoulos, Division of Rheumatology, University of Patras School of Medicine, 26 500 Rio, Patras, Greece; andandon@med.upatras.gr

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Figure 1 First (A) and second (B) CT scans through the manubriosternal articulation, show several cysts (arrows) with thin, contrast enhanced walls, lying under both major pectoralis muscles, mainly on the right. The number and size of the cysts are decreased in (B).
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