Anticardiolipin antibodies in patients with post-streptococcal reactive arthritis

N Tamura, S Kobayashi, H Hashimoto

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Group A Streptococcus is a common bacterium that induces tonsillitis, pharyngitis, and pyoderma, and, furthermore, its metabolic products cause scarlatina. It is suggested that the molecular mimicry and cross reactivity between human tissues and the micro-organism are associated with immunogenic pathogenesis of well known post-streptococcal manifestations: acute rheumatic fever and acute glomerulonephritis. Recently, non-purulent arthritis after or during streptococcal infection, HLA-B27 unrelated "post-streptococcal reactive arthritis (PSReA)", has been reported as another manifestation associated with streptococcal infection. The pathogenesis of PSReA is unknown, but it is likely that it is an immunogenic disorder similar to acute rheumatic fever.

Anticardiolipin antibodies (aCL) are often detected in patients with autoimmune diseases, especially systemic lupus erythematosus, and they can induce antiphospholipid syndrome. The presence of aCL has also been reported in streptococcal infection—that is, acute rheumatic fever and infectious endocarditis (IE). Here, in 13 patients with PSReA, we determined serum titres of aCL and β2 glycoprotein I (β2GPI) dependent aCL, which is a more crucial antigenic target than cardiolipin itself, in order to evaluate the prevalence of aCL and antiphospholipid syndrome. All patients were treated in the outpatient clinic or ward of the Department of Rheumatology, Juntendo Hospital between 1993 and 1998. Patients with PSReA were diagnosed as having an acute sterile arthritis that developed after or during tonsillitis. All patients with PSReA had high titres of antistreptokinase and antistreptolysin O, and group A Streptococcus was isolated from a tonsillar swab in 7/13 patients. Four of the patients underwent tonsillectomy. The patients were followed up in the outpatient clinic for a minimum of three years (mean (SD) 5.2 (2.0) years). The patients were not recognised in serum samples from patients with SLE and infectious diseases. A study of anti-group A streptococcal monoclonal antibodies cross reactive with myosin. J Immunol 1986;136:293-9.


Successful treatment of SAPHO syndrome with infliximab: report of two cases

I Olivieri, A Padula, G Ciancio, C Salvarani, L Niccoli, F Cantini

The treatment of SAPHO syndrome is empirical and has recently been reviewed. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first choice but have limited efficacy. Second line drugs have been tried with mixed results. Positive effects with pamidronate, which partly works by blocking tumour necrosis factor α, have been reported. Recently, Maksymowych et al suggested that pamidronate is also effective in spondarthritides, which shares manifestations and clinical associations with the SAPHO syndrome. Infliximab, a chimeric anti-tumour necrosis factor α monoclonal IgG1 antibody, has recently been proved to be effective in the treatment of ankylosing spondylitis and psoriatic arthritis.

CASE REPORTS

In view of this information we treated two patients affected by refractory SAPHO syndrome with infliximab. Both patients had chest pain limiting normal activity despite adequate treatment with NSAIDs and second line treatment was unsuccessful. Both patients received three intravenous infusions of infliximab (5 mg/kg) at weeks 0, 2, and 6 and were evaluated at baseline, on days 3, 7, and 14, and then every two weeks.

Patient 1
The first patient was a 35 year old man who had had severe acne and painful ostitis of the left clavicle for 17 years. His family history showed that his mother had psoriasis and his brother had had one episode of acute anterior uveitis. Locus B HLA typing of the patient disclosed the B18 antigen. His disease had been treated with NSAIDs for 12 years. In 1996 he was given cyclosporin at a dose of 3 mg/kg/day, with some benefits for the chest pain only. The drug was stopped after two years owing to a loss of efficacy. In the following months long term antibiotic treatment with azithromycin, which has been suggested to be efficacious in SAPHO syndrome, was tried with no results.

When we decided to start infliximab treatment the patient had had severe pain of his left clavicle for three months despite treatment with nimesulide, the best alternative NSAID for our patient, at a dose of 400 mg/day. The left clavicle was swollen, warm, and tender and florid acne was present on his face and posterior chest wall. Laboratory evaluation was normal except for a C reactive protein (CRP) of 13.5 mg/l (normal <5). The day after the first infusion the chest wall pain disappeared and NSAIDs were discontinued. At the second visit, on day 3, a physical examination and CRP were normal. The disease remained in remission for two and a half months after the third infusion. Pain, swelling, and tenderness on the manubrium sterni and both sternoclavicular joints disappeared in three days after the fourth infusion and have not reappeared so far, two months after the fourth infusion. No side effects of infliximab treatment were seen.

COMMENT
Our study suggests that infliximab is an effective drug in SAPHO syndrome. A larger, controlled, double blind study is required, which should also establish whether improvement of bone scan or magnetic resonance imaging parallels the clinical remission.

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Muscle involvement in childhood sarcoidosis and need for muscle biopsy

A V Ramanan, A D Thimmarayappa, E M Baildam


Sarcoidosis is a multisystem disorder with protean manifestations in childhood. We report on a child with prominent muscular symptoms at presentation. Muscle involvement in childhood sarcoidosis has been described in only two previous reports to our knowledge. We believe that muscle biopsy has a valuable role in aiding the diagnosis of childhood sarcoidosis even in children with no clinical symptoms of muscle involvement.

CASE REPORT

A 10.5 year old girl presented with a nine weeks' history of fever, red eyes, loss of appetite, malaise, florid widespread rash, weakness, and lymphadenopathy. She attended a district general hospital and was diagnosed to have a mycoplasma chest infection and treated with antibiotics. She failed to respond despite three courses of erythromycin and had persistent conjunctivitis, florid rash over her trunk, erythema nodosum over her legs, and weight loss and was therefore referred to our tertiary rheumatology unit.

On review, she was pale, miserable, tired with muscle wasting, weakness, and lymphadenopathy. A complete investigation was carried out and haematological tests showed haemoglobin 102 g/l (normal 114–140 g/l) and white cell count 10.2 (normal 4–11). Her biochemical profile was normal and liver functions showed alanine aminotransferase 263 IU/l (normal 0–45 IU/l). Her autoantibody profile was negative, and inflammatory markers like C reactive protein 190 mg/l (normal <60 mg/l) and erythrocyte sedimentation rate 92 mm/1st h (normal <5 mm/1st h) were raised. Her lactate dehydrogenase 884 IU/l (normal <620 IU/l), serum angiotensin converting enzyme 133 IU/l (normal 15–55 IU/l), and antistreptolysin O titre >800 (normal <200) were all raised. Her creatine kinase was normal. Her chest x-ray examination disclosed bilateral hilar lymphadenopathy with some pulmonary interstitial changes. An echocardiogram, cranial magnetic resonance imaging (MRI), magnetic resonance angiography, dimercaptosuccinic acid (DMSA) scan, and abdominal ultrasound were normal. Her muscle biopsy showed non-caseating, non-necrotising granulomas in fibrous septa and within muscle fascicles. In areas there were granulomas surrounding muscle fibres, the latter showing degenerative features (fig 1). The epitheloid granulomas had some admixed lymphocytes and giant cells. Skin biopsy showed granulomas in debris and subcutaneous tissues. A Mantoux test, gastric washings, and urine examination for acid fast bacilli were negative and bone marrow aspiration was normal. Ocular examination showed evidence of uveitis.

A diagnosis of sarcoidosis was made based on clinical and histological features and treatment was started with high dose methylprednisolone at 30 mg/kg/dose, followed by oral prednisolone. During the course of illness, she developed a tender liver and raised transaminases suggestive of hepatic disease. Currently she is in remission with no symptoms and has been weaned off steroids completely. No symptoms have recurred during the past three years of follow up.
Fever of unknown origin with seronegative spondyloarthropathy: an atypical manifestation of Whipple’s disease

C Várvölgyi, T Bubán, S Szakáll, Z Hargitai, L Galuska, C Jeney, G Kakuk, J Gaál

Many authors emphasise the diagnostic difficulties and point out the multifaceted nature of Whipple’s disease.1,2 Joint symptoms are present in 90% of all cases and may precede other disease manifestations by decades.3 We report here a case with fever of unknown origin accompanied by seronegative spondyloarthropathy with no typical gastrointestinal symptoms and initially negative upper endoscopy. To confirm the diagnosis, the bacterial 16S ribosomal RNA sequence of *Tropheryma whipplei* was determined by polymerase chain reaction (PCR).

**CASE REPORT**

A 58 year old white man had a 12 year history of intermittent arthralgias and seronegative polyarthritis. In 1993, monoliteral stage II sacroiliitis was disclosed with no definite cause. Low dose methyldiphenisolone treatment was started, but there was no clinical improvement. In 1998 the patient became febrile, lost 10 kg of weight but had no gastrointestinal symptoms. He underwent an extensive examination, including radiological examinations of the chest and paranasal sinuses, abdominal sonography, echocardiography, abdominal computed tomography, upper panendoscopy, bone marrow biopsies, whole body gallium-67 citrate scan, multiple blood, stool, and urine cultures, as well as serological investigations for known viruses and autoantibodies. Results of all these tests were normal or negative except for mild splenomegaly, transitory otitis, and temporary antinuclear antibody positivity. Fever of unknown origin was diagnosed. The patient often took antibiotics.

He was referred to our department in October 1999. Physical examination showed limitation in the lumbar spine, bilateral swollen and tender wrists, right sided proximal interphalangeal synovitis of the hand, minimal synovial fluid in the right knee, and bilateral tenderness of Achilles tendons. Radiographic examination showed bilateral stage II sacroiliitis. Non-differentiated seronegative spondyloarthropathy was diagnosed, and meloxicam (15 mg/day) and methotrexate (7.5 mg/week) were started.

In January 2000 the patient’s fever (39°C) reappeared, but no malignant, infective, or autoimmune cause of the disease was shown. The differential diagnosis included rheumatoid arthritis, rheumatic fever, connective tissue disorders, reactive arthritis, adult Still’s disease, sarcoidosis, arthritis with haematological and solid malignancies, familial Mediterranea fever, arthropathy associated with HIV infection, histiocytosis, some fungal infections, other seronegative arthropathies, including inflammatory bowel disease with spondyloarthropathy. Laboratory examinations showed raised C reactive protein level (160 mg/l), increased erythrocyte sedimentation rate (82 mm/1st h), and mild iron deficiency anaemia (haemoglobin, 116 g/l). All other laboratory parameters, including serum albumin, calcium, bilirubin, and HLA-B27
and deparaffinated samples.

cally positive for bacterial 16S rRNA from the formalin fixed
tinal biopsy specimens, numerous periodic acid-Schiff (PAS)
closed small whitish plaques in the duodenum. In the duode-
disease was suspected and repeated upper panendoscopy dis-
accumulation in the small intestinal regions. Whipple's
disorders in macrophages in the lamina propria. In one series,
examination of duodenal mucosa showed PAS positive inclu-
weight loss, and questionable gallium scan report. Histological
panendoscopy in light of the patient's iron deficiency anaemia,
that dyspeptic symptoms were lacking, we repeated the upper
atypical or the disease is oligosymptomatic. Despite the fact
However, difficulties may arise when clinical features are
intensely positive for bacterial 16S rRNA from the native sam-
the diagnosis is recommended.

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Pregnancy has been associated with remission of symptoms in 75% of women with rheumatoid arthritis (RA).\(^1\)\(^2\) This may in part be caused by depression of polymorphonuclear neutrophil (PMN) function, which reduces the degree of synovial fluid (SF) inflammation. This study compared the function of SF and peripheral blood neutrophils from patients with RA and normal subjects, and examined the in vitro effects of pregnancy associated proteins on neutrophil function.

Paired SF and blood samples were obtained from 15 patients with RA (six male, nine female); peripheral blood was obtained from nine normal controls (three male, six female). All patients fulfilled American College of Rheumatology (ACR) criteria for RA.\(^3\) Patients with RA had a mean age of 63 (range 36–81); controls had a mean age of 35 (25–49). Patients with RA had mean disease duration of nine years (1–30); ESR levels mean 50 mm/1st h (SE 6.4) and CRP levels mean 59 mg/l (SE 12.5). In this study, each patient acted as their own control, as both blood PMN and SF PMN were studied. This allowed inclusion of men, and women past child bearing age.

All patients with RA were receiving disease modifying drugs; recruitment of subjects not taking drugs is virtually impossible, so this is a caveat in all studies of PMN function studies in RA.

SF samples were pretreated with hyaluronidase (Streptomyces hyalurolyticus). PMN were isolated as previously described.\(^4\) Superoxide anion production (respiratory burst activity) was determined by lucigenin and luminol enhanced chemiluminescence.\(^5\) Respiratory burst occurs when stimulated PMN convert molecular oxygen to toxic oxygen radicals through activation of NADPH-oxidase. This was measured in response to the physiological receptor agonist n-formylmethionyl-leucyl-phenyalanine (fMLP) and the diacylglycerol analogue phorbol myristate acetate (PMA). We found it was possible to stimulate SF PMN as well as RA blood PMN to initiate a respiratory burst, with greater superoxide anion production than normal blood PMN. SF PMN tended to show greater respiratory burst activity at low agonist concentrations (suggesting priming), although this did not reach statistical significance.

In the joint space PMN undergo degranulation and release their granule contents. Primary and secondary degranulation is demonstrated by increased expression of the integrin CD11b and loss of L-selectin (CD62L).\(^6\) CD11b, CD18, and L-selectin expression were determined by flow cytometry\(^7\) and SF PMN both showed a rise in CD11b expression, but not CD18 expression. This indicates that SF PMN have undergone a degree of both primary and secondary degranulation and that was greater than the degranulation in RA blood PMN. SF PMN lost more L-selectin than RA blood PMN; but neither was significantly different from normal blood PMN. Using fMLP increases CD18 and CD11b expression in normal blood PMN and RA blood PMN, but not SF PMN. SF PMN appear to show maximal CD11b expression without added stimulus and the addition of fMLP did not lead to increased loss of L-selectin. Figure 1 shows these results.

The effect of pregnancy associated proteins was investigated by adding 10 g/ml β-oestradiol; 50 ng/ml α fetoprotein; 10 µg/ml α₁ macroglobulin; 50 U/ml human chorionic gonadotrophin (hCG)

SF PMN showed reduced extracellular superoxide production on incubation with hCG, and when stimulated with fMLP but not with PMA, suggesting a receptor mediated pathway of activation. This inhibitory effect was not observed in RA blood PMN. Production of SF PMN intracellular superoxide was inhibited by α fetoprotein in stimulated and unstimulated conditions; by α₁ macroglobulin in stimulated conditions; and by β-oestradiol in unstimulated and fMLP stimulated conditions. These proteins may be exerting inhibitory effects on the myeloperoxidase dependent part of the respiratory burst pathway. This confirms a previous observation which highlighted the inhibitory effect of β-oestradiol on PMN superoxide production.\(^7\) Figure 2 shows these effects.
In summary, we have shown that SF PMN are more responsive than peripheral blood PMN in RA. It would therefore be logical to target the reduction of activation and priming of these cells as a therapeutic approach to reduce inflammation in RA.

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Authors' affiliations
C Belcher, M Doherty, Academic Rheumatology, Clinical Sciences Building, City Hospital, Nottingham NG5 1PB, UK
S Crouch, David Evans Medical Research Centre, City Hospital, Nottingham

Correspondence to: C Belcher, Academic Rheumatology, Clinical Sciences Building, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK; Carolyn.Belcher@Nottingham.ac.uk

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Figure 2 A comparison of the effects of pregnancy associated proteins on lucigenin enhanced chemiluminescence on unstimulated and stimulated SF and RA blood. Pregnancy associated proteins are β-oestradiol, α fetoprotein, α2 macroglobulin, and hCG. Values are represented as means (standard error).

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