LETTERS

Activation dependent apoptosis of peripheral blood mononuclear cells from patients with rheumatoid arthritis treated with methotrexate

J Swierkot, R Miedzybrodzki, S Szymaniec, J Szechinski


Activation-induced apoptosis is a critical mechanism by which the immune system maintains tolerance to self antigens by the clonal deletion of autoreactive T and B cells.1 The involvement of apoptosis in the mechanism of cell death induced by high doses of methotrexate (MTX) was first demonstrated in Chinese hamster ovary cells.2 Fas mediated apoptosis may have a critical role in the regression of synovial hyperplasia in rheumatoid arthritis (RA).3 Cutolo et al demonstrated the influence of MTX on the proliferation and apoptosis of cultured human monocytic myeloid cells (THP-1).4 Genestier et al investigated the effect of low doses of MTX on human peripheral blood lymphocytes and showed that MTX could induce the in vitro apoptosis of mitogen activated lymphocytes CD4+ and CD8+ but not resting T cells. He also demonstrated that a single injection of MTX during low dose treatment in six patients with RA was sufficient to prime lymphocytes to apoptosis upon subsequent mitogenic activation ex vivo.5

The purpose of our investigation was to examine the influence of MTX on the apoptosis of in vitro phytohaemagglutinin (PHA) activated peripheral blood mononuclear cells (PBMC) from patients with RA subjected to MTX treatment, and its correlation with their clinical response.

PATIENTS AND METHODS

Investigations were carried out on 34 patients (aged 38–76 years) with active RA. MTX, 10–15 mg, was given orally once weekly. An assessment of these patients' clinical response to MTX according to the American College of Rheumatology criteria was made 8 weeks after beginning MTX treatment.6 Patients who had improved >20% compared with the baseline were defined as responders and patients with improvement <20% were classified as non-responders. In the concomitant treatment one non-steroidal anti-inflammatory drug and prednisone (up to 7.5 mg daily) was allowed.

PBMC were isolated according to Böyum before MTX administration, activated with PHA (5 μg/ml) for 72 hours, and then washed and incubated with MTX (0.1–100 μmol/l) in 96 well plates in duplicate.7 Cell death was evaluated using Hoechst 33342 (apoptotic cells) and ethidium bromide (necrotic cells). Three hundred cells from each well were counted and the mean percentage of apoptotic cells calculated.

RESULTS AND DISCUSSION

There were no significant differences in the percentage of the MTX-induced (0.1–100 μmol/l) apoptosis of PHA activated PBMC derived from patients with clinical improvement compared with the patients without improvement (fig 1). These results did not differ when compared with the results in the MTX untreated group. However, as in Genestier's study, MTX increased the specific apoptosis of PHA activated PBMC as compared with cells not activated with PHA (data not shown).5 Lack of differences in the in

Figure 1 Percentage of in vitro MTX-induced apoptosis of PBMC derived from patients with RA (means (SEM)). (A) Apoptosis of PBMC not activated with PHA. (B) Apoptosis of PHA activated cells. *Significant differences in comparison with the control (Wilcoxon matched pairs test). Differences in apoptosis (at the same MTX concentration) between all studied groups were analysed using Kruskal-Wallis analysis of variance test. No significant differences were found either for non-activated or PHA activated cells. MTX untreated = patients with RA before they started MTX treatment (n = 16); responders = patients with improvement of at least 20% according to ACR criteria (n = 13; six patients >20% and seven patients >50%); non-responders = patients without improvement (n = 10).
vitro MTX-induced apoptosis of PHA activated PBMC from MTX treated responding patients compared with the non-responders indicates that this property may not be a good predictive factor for optimising MTX treatment.

Low dose MTX in RA treatment seems to exert anti-inflammatory effects by acting at different levels of the pathophysiologic cascade. Several studies have recently shown that low dose MTX may well induce antiproliferative effects on the immune cells owing to the inhibition of dihydrofolate reductase and folate dependent transmethylation as an independent mechanism of apoptosis. We did not confirm (unpublished data) that low dose treatment MTX was sufficient to prime PBMC to apoptosis upon subsequent PHA activation ex vivo. It is interesting that in Cutolo’s experiments MTX at a concentration of 50μg/ml did not induce apoptosis and did not affect the proliferation of RA synovial macrophages.

It seems that either the apoptosis of cells in the tissue, which is directly involved in the inflammatory process, is more important than that seen in peripheral blood lymphocytes, or that other mechanisms of the MTX action may be responsible for the clinical improvement in patients treated with low doses of MTX.

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Platelet and endothelial activation are requisites for the development of antiphospholipid syndrome
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The antiphospholipid syndrome (APS) is characterised by venous and arterial thrombosis, recurrent fetal loss, and by the presence of antiphospholipid antibodies (aPL). aPL are also present in 2% of the healthy population, and, with the exception of those with high titres of aPL, there is no clear evidence of an increased incidence of thrombosis throughout the follow up. Thus, one of the key questions is: What causes the development of thrombosis in patients with APS? We suggest that in APS, a persistent procoagulant state, a continuous endothelial and platelet activation is present, and this may be detected by raised levels of soluble adhesion molecules.

METHODS AND RESULTS
We prospectively studied the following groups of subjects: (a) 20 patients with APS; 10 with primary disease and 10 associated with systemic lupus erythematosus; all had presented an arterial or venous thrombotic episode, or both; (b) 20 subjects with aPL, but without any clinical finding (aPL WCF); in these subjects aPL were determined by the unexplained presence of an activated partial thromboplastin time inhibitor; (c) 20 healthy controls (HC).

Lupus anticoagulant was analysed by screening tests (dilute Russell viper venom time, dilute one stage prothrombin time, and sensitised partial thromboplastin time) and confirmed by the viper venom time with phospholipid excess and platelet neutralisation tests. Standardised enzyme linked immunosorbent assays (ELISAs) were used to measure serum levels of anticardiolipin antibodies (Oregentec Diagnostika, Mainz, Germany); immunoglobulin G anti-β2-glycoprotein I (anti-β2-GPI) (IMMCO Diagnostic, Buffalo NY, USA); and platelet (P-selectin) and endothelial (E-selectin and intercellular adhesion molecule-1, ICAM-1) adhesion molecules (R&D, Minneapolis, USA). In patients with APS, soluble adhesion molecules were measured at the time of the second determination of aPL (8 weeks after thrombosis or after parturition).

At least the lupus anticoagulant or increased serum levels of one of the isotypes of anticardiolipin antibodies was detected in all subjects with APS or aPL WCF. Serum concentrations of anti-β2-GPI above the normal range were detected in all patients with APS and in 30% of the subjects with aPL WCF.

Those subjects with APS and with aPL WCF all showed increased concentrations of E-selectin, in comparison with HC. P-selectin levels were only significantly increased in patients with APS. ICAM-1 concentrations were similar in each of the groups (table 1). Patients with primary or
secondary APS showed similar concentrations of the adhesion molecules. There was no difference between patients with arterial or venous thrombosis or abortions in respect of these measures (data not shown).

All the patients with APS were treated with dicumarin, maintaining an international normalised ratio of more than 3. During a follow up of 18 months, no significant clinical event was noted. Likewise, no significant change was detectable in the percentage of positivity or in the mean titres of aPL or adhesion molecules.

**DISCUSSION**

These results demonstrate that the presence of aPL, with or without clinical findings, is linked to increased levels of P-selectin, a marker of endothelial activation; however, serum concentration of ICAM-1, a molecule that mediates the firm adhesion of circulating cells, was normal. Owing to the absence of clinical events during the follow up, we cannot rule out the possibility of an increased expression of ICAM-1 in relation to the appearance of new thrombi.

The presence of simultaneously increased levels of P-selectin in patients with APS supports the suggestion of a platelet activation state as the explanation for the clinical findings in this disease. The persistence of raised levels of adhesion molecules rules out an increased expression of these antigens as a consequence of the recent thrombosis or abortions.

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**REFERENCES**

Disease modifying treatment and elective surgery in rheumatoid arthritis: the need for more data

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Disease modifying antirheumatic drugs (DMARDs) have become the cornerstone of treatment for patients with rheumatoid arthritis. The use of these drugs during the perioperative period has caused debate amongst rheumatologists and surgeons. Concerns focus on their potential to increase the risk of infection by affecting the immune response. Rheumatoid patients are at increased risk of infection, and this is of concern after surgery. Orthopaedic surgery in rheumatoid patients is common, and while it may seem prudent to stop DMARD treatment before surgery, this may result in flare up of disease activity. The resultant loss of mobility would adversely affect outcome, particularly after orthopaedic procedures, where mobilisation is crucial for effective rehabilitation.

Early reports suggested that methotrexate should be stopped before rheumatoid surgery, as it was claimed to increase infection rates. Studies have since shown that this is not the case and methotrexate should be continued throughout the surgical period (Table 1). The effect of other DMARDs during surgery has been less well documented. Grennan et al., using logistic regression analysis, showed that penicillamine, indometacin, cyclosporin, antimalarial drugs, and corticosteroids increased postoperative complications in rheumatoid patients. However, they concluded that the clinical significance of these findings was uncertain as their study had not been designed to look at the effects of these drugs on postoperative complications. Recently, we have shown that neither methotrexate nor steroids, when used alone or in combination, affect the postoperative infection rate, and we recommend that these drugs should not be stopped before elective rheumatoid hand surgery.

Increasing numbers of rheumatoid patients are being treated with tumour necrosis factor α (TNFα) inhibitors. TNFα has a pivotal role in host resistance and as a mediator of local inflammation, although etanercept does not appear to alter global immune function, and infliximab treatment restored antigen and mitogen induced lymphocyte proliferation in vitro. There are no clear guidelines on the use of cytokine inhibitors during the perioperative period and data on surgical complications in these patients are scarce. Guidelines for the use of infliximab in Crohn’s disease state that routine use of anti-TNFα cannot be recommended before surgery. However, the authors concede that no formal trial has been undertaken and, based on the opinion or experiences of an expert committee, surgery during and after infliximab treatment appeared to be safe.

Despite the fact that serious infection rates in clinical trials were no higher in those rheumatoid patients taking TNFα inhibitors than in those receiving placebo, concerns remain about infection. With the lack of data on the use of anti-TNFα and surgery, most clinicians would advise a cautious approach. The UK distributors of infliximab recommend that surgery be deferred for 2–4 weeks after the last infusion and close postoperative surveillance maintained, although surgery soon after administration of the drug is not absolutely contraindicated. After surgery, patients should be monitored closely as the long term effects of TNFα inhibition may mask signs of infection. Anti-TNFα treatment could be restarted 3 weeks after surgery, when the incisions should have healed. Like anti-TNFα, trials of the interleukin 1 receptor antagonist anakinra showed that the infection rate was similar to that in patients receiving placebo. Currently there are no specific data on the use of anakinra perioperatively. Therefore, a cautious approach is again warranted, with close postoperative surveillance.

Increasing use of cytokine inhibitors means that more patients receiving these drugs are likely to require surgical procedures in the future, despite improved disease control. Because of the small number of these patients currently being treated by individual surgeons, pooling of data and multicentre trials are essential for the production of meaningful guidelines.

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Table 1  Summary of published reports on the influence of methotrexate (MTX) on postoperative complications

<table>
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<th>Study</th>
<th>Study design</th>
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<th>Number of patients receiving MTX at time of surgery</th>
<th>Percentage complication rate</th>
<th>Should methotrexate be stopped before surgery?</th>
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*Specific data not recorded.*
CONFLICT OF INTEREST STATEMENT
The Kennedy Institute received a research grant and payment (according to the number of patients) for clinical trials of an anti-TNF antibody from Centocor Inc, Malvern, Pennsylvania, USA. Professor Maini has acted as a consultant.

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REFERENCES

Shrinking central nervous system in systemic lupus erythematosus
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Neuropsychiatric manifestations of systemic lupus erythematosus (SLE) are diverse and heterogeneous. We report a patient who experienced a flare of SLE with subacute transverse myelopathy. Magnetic resonance imaging (MRI) showed atrophy of the entire central nervous system (CNS). Apart from psychosis at SLE onset, there had not been any neuropsychiatric relapses. Progressive atrophy of the CNS should be recognised as an evolving feature of SLE, which may occur without overt neurological symptoms.

CASE REPORT
A 22 year old Chinese woman with SLE was admitted because of a 2 month history of progressive weakness in her legs and bladder dysfunction. Her SLE had been diagnosed 5 years previously when she presented with polyarthritis, malar rash, cytopenia, psychosis, positive anti-dsDNA, and anti-Ro. A computed tomographic (CT) scan of the brain and cerebrospinal fluid (CSF) findings were unremarkable. Steroid and cyclophosphamide were given, with complete response. She remained well while receiving prednisone and azathioprine maintenance. Five months before the current episode, she had a mild flare with leucopenia and fever, which was controlled by increasing the steroid dose.

On current admission, examination showed spastic paraparesis (muscle power grade 3/5). The arms were spared. Pain and touch sensation at the S4 and S5 dermatomes had diminished. A neuropathic bladder was present, but there was no optic neuritis or livedo reticularis. A CT scan showed atrophy of the brain and calcification of the basal ganglia (fig 1). MRI showed diffuse thinning of the entire spinal cord without abnormal signals in the intramedullary regions (fig 2). CSF analysis was normal and an oligoclonal IgG band was absent. Her anticardiolipin antibodies and lupus anticoagulant were repeatedly negative. The complement levels and white cell count were both depressed, but the platelet count was normal. High dose steroid, oral cyclophosphamide, and aspirin were given with partial neurological recovery after 4 months. Her urinary catheter was weaned and she could manage to walk with aids.

Figure 1 CT scans of the brain at SLE diagnosis (A) and current presentation (B).
may stimulate endothelial cell proliferation and intimal fibrosis, leading to bland vasculopathy. The most common MRI findings of SLE related TM arecord swelling and longitudinal T2 hyperdense signals crossing multiple spinal levels. Spinal cord thinning has been reported as a late sequela of lupus myelopathy despite successful treatment. Several explanations have been suggested. Ischaemia as a result of vasculitis or vascular thrombosis may mediate damage and demyelination of the cord. Cross reactivity or direct binding of certain existing or as yet unknown autoantibodies to antigens of the CNS may mediate axonal damage and global demyelination. CSF levels of interleukin (IL)1, IL6, and interferon γ are raised in patients with active neuropsychiatric SLE. IL1 up regulates endothelial adhesion molecules and nitric oxide production, which may contribute to vascular inflammation and neuronal injury. IL6 stimulates neurotransmitter release and induces intrathecal synthesis of immunoglobulins. However, the exact role of cytokines in neuropsychiatric SLE remains speculative.

The incidental finding of CNS atrophy in our patient is apparently unrelated to the current episode of myelitis. The gradual evolution of cerebrospinal atrophy, the lack of ischaemic and inflammatory MRI signals, and the absence of antiphospholipid antibodies did not support thrombosis as the chief mechanism. Chronic use of steroids and neuronal insult at disease onset are possible explanations. Although the treatment and prognosis of CNS atrophy in SLE is virtually unknown, empirical aspirin and maintenance immunosuppression may be considered. Follow up MRI scans are needed to monitor the progress of CNS atrophy.

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REFERENCES
Usefulness of glycosylated ferritin in atypical presentations of adult onset Still’s disease

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M any diseases, such as infections, neoplasia, or immune diseases, can mimic adult onset Still’s disease (AOSD). Atypical forms are not so rare, and the search for a diagnosis marker is warranted. Recently, the usefulness of low serum glycosylated ferritin (GF) was suggested.3

**CASE REPORT 1**

An 80 year old woman presented with 4 weeks’ fever, myalgias, polyarthritis, and sore throat. Clinical examination disclosed a fixed generalised maculopapular rash, arthritis of wrists and ankles, and spleen enlargement. C reactive protein was 150 mg/l, haemoglobin level 80 g/l, white blood count 30×10^9/l with 90% polymorphonuclear neutrophils, 10% lymphocytes, and 600×10^9/l platelets. Transaminases were twice the normal value (2N). Ferritinaemia was 40 000 μg/l (normal 50–300). Extensive investigations for infections, antinuclear and antineutrophil cytoplasmic antibodies, and rheumatoid factor were negative. Echocardiography, thoracic and abdominal computed tomographic scan, bone marrow biopsy, lumbar puncture were normal, except for splenomegaly. Skin biopsy disclosed unspecific urticarial lesions. The outcome was marked by high spikes of fever, general malaise with low blood pressure, hypoxaemia, suggesting systemic inflammatory response syndrome, and necessitating admission to an intensive care unit.

Empirical antibiotic treatment was ineffective. The blood white cell count was 42×10^9/l, and ferritinaemia was 80 000 μg/l. The percentage of serum GF was <5%. Corticosteroid treatment improved the syndrome, with normalisation of the white blood count and ferritinaemia in 7 days. No systemic or neoplastic disease occurred with a follow up of 3 years.

**CASE REPORT 2**

A 51 year old woman presented to our department with 5 weeks’ fever, sore throat, and myalgias. Clinical examination showed permanent maculopapular rash, and liver enlargement. C reactive protein was 120 mg/l, haemoglobin 80 g/l, platelet count 30×10^9/l, and white blood cell count 3×10^9/l with 800 polymorphonuclear neutrophils, 1200 lymphocytes, and 800 monocytes. Fibrinogen was 2 g/l, factor V 30%, albuminamia 22 g/l, transaminases 8N, and lactate dehydrogenase 3N. Ferritinaemia was 120 000 μg/l (normal 50–300). Extensive investigations for infections, antinuclear and antineutrophil cytoplasmic antibodies, and rheumatoid factor were negative. Echocardiography, thoracic and abdominal computed tomographic scan, bone marrow biopsy, lumbar puncture were normal, except for splenomegaly. Skin biopsy disclosed unspecific urticarial lesions. The outcome was marked by high spikes of fever, general malaise with low blood pressure, hypoxaemia, suggesting systemic inflammatory response syndrome, and necessitating admission to an intensive care unit.

Empirical antibiotic treatment was ineffective. The blood white cell count was 42×10^9/l, and ferritinaemia was 80 000 μg/l. The percentage of serum GF was <5%. Corticosteroid treatment improved the syndrome, with normalisation of the white blood count and ferritinaemia in 7 days. No systemic or neoplastic disease occurred with a follow up of 3 years.

**DISCUSSION**

Our case reports present atypical presentations of AOSD, with a fixed skin eruption, associated with a life threatening disease outcome in a very old person, and a macrophage activation syndrome in the other. Extensive investigations did not contribute to a diagnosis, and antimicrobial treatments were unsuccessful. Ferritinaemia was very high in both patients. There is no specific clinical or biological marker of AOSD. Low GF led us to the diagnosis of AOSD, and long term follow up validates this conclusion. The normal value of GF is >50%, and the serum level is not significantly modified by inflammation. The usefulness of a low GF value for diagnosis of AOSD was shown by Fautrel et al. In their study the percentage of GF was <20% of the total ferritinaemia for 35 of 44 patients with AOSD, and for only 38 of 113 control patients with other inflammatory diseases. The combination of ferritinaemia fivefold above the upper normal value and a GF value <20% had a specificity of 92.9% and a sensitivity of 43.2% for AOSD. GF could be a powerful diagnostic tool for AOSD, particularly in atypical clinical presentations of the disease.

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www.annrheumdis.com
A 35 year old Afro-Caribbean man was referred by the dermatology department in March 2002. He had a 2 year history of a photosensitive rash, patchy alopecia, and a 1 year history of arthralgia affecting wrists, knees, and shoulders. He also described occasional night sweats. There was no history of thromboembolic events or migraine.

On examination he had two patches of alopecia and a small right knee effusion. His pulse was 64 beats per minute and regular, with a blood pressure of 120/70 and normal heart sounds. Otherwise his examination was unremarkable.

Investigations showed: positive antinuclear antibody (ANA; 1/160 homogeneous pattern); positive double stranded DNA on enzyme linked immunosorbent assay (ELISA) testing (169 IU/ml; negative <40); extractable nuclear antigen negative for Ro, La, Sm, RNP, Jo-1 antibodies; positive IgG antiphospholipid antibody (37 GPLU/ml; negative <14); normal complement C3 and low C4 (0.11 g/l; normal 0.16–0.47); normal full blood count including differential white cell count, renal and liver function, creatine kinase, erythrocyte sedimentation rate, and C reactive protein. His lupus anticoagulant test was also positive on two occasions. A diagnosis of systemic lupus erythematosus (SLE) was made.

Five years previously he had been investigated by the cardiologists for episodes of chest pain and dyspnoea. An initial ECG showed first degree heart block. A 24 hour ECG showed sinus rhythm with first degree heart block throughout, but also significant degrees of second degree heart block, and episodes of third degree block occurring at night with a maximum pause of 3.02 seconds. As he had no syncope symptoms no further action was taken.

There was a family history of SLE in his mother, who had positive ANA and positive Ro and La antibodies.

**DISCUSSION**

Conduction defects in SLE are well described: congenital heart block in infants born to mothers with anti-Ro antibodies is the most widely known. These infants do not seem to have a greater risk of developing adult SLE than that conferred by maternal family history. Conduction disturbances in adults with SLE are rare but documented, in the form of all types of atrioventricular (AV) block, bundle branch block, sinus tachycardia, atrial fibrillation, and atrial ectopic beats. The prevalence of conduction defects may be as high as 10–14%. Third degree block is very rare in adults with SLE—this is only the 11th case described. The pathophysiology as anti-Ro antibodies are thought to be pathogenic in fetal heart block. However, other authors found conduction defects in only two of 33 patients with SLE, neither of whom was positive for Ro or La. The 12 patients with Ro or La antibodies, or both, did not have conduction problems. Although the detection of the antibodies was by differing techniques, overall the pathogenesis does not appear to be related to the presence of Ro or La antibodies.

In the case we describe, possible mechanisms are (a) varying degrees of intermittent heart block since birth and related to maternal Ro positivity; (b) nodal artery occlusive disease secondary to vasculitis; (c) idiopathic fibrosis; and least likely in view of his age, (d) ischaemic heart disease.

This is the first description of high grade heart block predating the diagnosis of SLE. The occurrence of high grade heart block in young adults could prompt a search for other symptoms, signs, or laboratory tests of SLE.

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