Sinusoidal dilatation: a rare side effect of azathioprine

A M Jacobi, E Feist, B Rudolph, G R Burmester

Hepatotoxicity is an often reported side effect of azathioprine treatment, which requires monitoring of serum transaminases and \( \gamma \)-glutamyltransferase (\( \gamma \)-GT), especially during the first 6 months of treatment. This case report, however, illustrates that side effects of azathioprine can also occur after a longer period of treatment. We report a case of sinusoidal dilatation as a rare side effect of azathioprine treatment in a patient with systemic sclerosis.

CASE REPORT

A 50 year old female patient with systemic sclerosis presented with a rapid increase of body weight (approximately 5 kg within 3 days) and abdominal circumference, diffuse abdominal pain, oedema of the lower extremities, dyspnoea, tachycardia, and low blood pressure (90/60 mm Hg). Because systemic sclerosis with pulmonary involvement had been diagnosed 1\( \frac{1}{2} \) years previously, the patient received azathioprine (2 mg/kg) and prednisone (5 mg) daily. The patient tested positive for anti-PM/ScI (anti-exosomal) antibodies. Furthermore, protein C and S deficiency and occlusions of various finger arteries of the left hand were diagnosed. Therefore she has been treated with warfarin during the past 18 months and received intravenous iloprost intermittently. Treatment was tolerated without any side effects and 3 months before admission to the hospital clinical examination and laboratory measures were completely normal.

The laboratory tests at admission, however, disclosed a pancytopenia (leucocytes \( 2.04 \times 10^9/\text{l} \), platelets \( 44 \times 10^9/\text{l} \), erythrocytes \( 2.02 \times 10^{12}/\text{l} \)) increased \( \gamma \)-GT (90 U/l (normal <38)) and bilirubin (38 \( \mu \text{mol/l} \) (normal <18)), and signs of haemolysis with raised lactate dehydrogenase (323 U/l (normal <247)) and free haemoglobin. Liver function was only mildly impaired (antithrombin III 67% (normal 70–130), pseudocholinesterase normal, slightly reduced albumin). Serum transaminases were moderately raised. Of note, there were no signs of any previous hepatic disease in the patient’s history.

Ultrasound examination of the abdomen showed ascites; a thrombosis of the liver veins or portal vein was excluded. There were no characteristic signs of longstanding portal hypertension in the ultrasound examination (normal diameter of the portal vein and normal size of the spleen). However, ultrasonographic signs of liver steatosis were present. A computed tomographic scan of the abdomen showed fibrosis of the liver and a venous perfusion block.

Warfarin was replaced by heparin. Azathioprine was discontinued. After a mild diuretic treatment (40 mg furosemide and 25 mg spironolactone/day), ascites completely disappeared within 3 days. A slight increase of haemoglobin, leucocyte, and platelet count and decrease of lactate dehydrogenase occurred spontaneously at the end of the first week of observation, whereas the \( \gamma \)-GT remained constant.

After the recovery of platelet counts, bone marrow and liver were biopsied. The histology showed left shifted granulopoiesis and erythropoiesis as well as megablastoid transformed erythrocytes and disturbed megakaryopoiesis. This is in line with bone marrow damage related to drug toxicity with signs of beginning regeneration. The liver tissue was free of inflammation and showed non-continuous infiltrative fibrosis without bridges or remodelling of the liver tissue. Signs of a venous block without central venulitis or clots were reported (fig 1). Sinusoidal dilatation was the predominant pathological finding.

DISCUSSION

Liver biopsy was performed to localise the venous perfusion block in more detail and to rule out Budd-Chiari syndrome, which had to be considered as a differential diagnosis. Sinusoidal dilatation and veno-occlusive disease (VOD) are vascular disorders of the liver associated with azathioprine treatment. Sinusoidal dilatation is assumed to be an early and less severe form of VOD, a liver disease also seen in patients after stem cell transplantation. In contrast with sinusoidal dilatation, VOD is characterised by additional affection of the central venules. Azathioprine possibly causes a depletion of glutathione in the endothelial cells. This mechanism has been described for murine sinusoidal endothelial cells. After endothelial injury subendothelial oedema causes congestion of sinusoids in a non-thrombotic manner. Sinusoidal dilatation has also been seen in patients after kidney transplantation. These patients had been receiving azathioprine for about 16–24 months before the onset of symptoms. After 1–3 years, fibrosis or micronodular cirrhosis had developed.

Figure 1  van Gieson’s stained liver section. *Normal central venule; **sinusoidal dilatation with hyperaemia.

This case illustrates that also after longlasting treatment with azathioprine severe side effects may occur and, therefore, these patients should be continuously monitored.

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LETTERS

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Tick bite fever and arthritis associated with travel to Africa

T Ding, G Lloyd, H Tolley, A Bradlow

CASE REPORT

A 52 year old woman was admitted with fever and acute polyarthritis. She had visited a game reserve in Northern Province, South Africa 5 weeks before admission. Two weeks before admission she developed fever and flu-like symptoms, then mouth ulcers, and a non-itchy, maculopapular rash that covered her whole body and her scalp. Three days after the start of the rash she developed painful and swollen joints—notably, the hands, elbows, wrists, knees, and feet.

On examination at admission she was apyrexial with no visible rash and no lymphadenopathy. She had florid synovitis at elbows, wrists, knees, and dactylitis affecting the right index finger (fig 1A), left thumb, and left 4th toe. Spinal movement was normal. Examination was otherwise unremarkable.

The full blood count and renal function were normal, erythrocyte sedimentation rate 131 mm/1st h and C reactive protein (CRP) 324 mg/l (normal <6 mg/l). A chest radiograph, and x ray examination of hands, feet, and sacroiliac joints were normal. A 99mTc-MDP bone scan showed increased uptake over the elbows, wrists, tars, left 1st interphalangeal joint and 4th proximal interphalangeal joints, and right 2nd and 3rd metacarpophalangeal joints (fig 1B). Antinuclear antibodies, rheumatoid factor, HLA-B27, hepatitis A and B, parvovirus, and arbovirus serology were all negative, as was stool culture for salmonella, shigella, and campylobacter. It was confirmed that the patient’s serum contained anti-rickettsia “spotted fever group” antibody, titre 1/640, by screening using sheep red blood cells sensitised with spotted fever group specific antigen in an immune-haemagglutination assay.

Doxycline was started empirically before the rickettsial serology result was known, and continued for 3 weeks. Intramuscular depomedrone 120 mg produced little improvement in joint symptoms and CRP. After 2 weeks sulfasalazine and oral prednisolone 15 mg daily were started; marked and continuing improvement followed despite rapid tapering of the steroid dosage.

The incubation period of rickettsial disease is 1 to 2 weeks, followed by abrupt onset of malaise, headache, and fever. An eschar is sometimes visible at the site of tick bite. A maculopapular or petechial rash is present usually on days 7 to 10 after the bite.

DISCUSSION

African tick bite fever has been recognised since the beginning of the 20th century as a rural disease, contracted from ticks of cattle and game. Initially, the condition was thought to be exclusively due to Rickettsia conorii. The first human infection with R africae was reported from Zimbabwe only in 1992. Recently R africae has also been identified in Amblyomma ticks from Niger, Mali, Burundi, and Sudan.

Arthralgias occur commonly during rickettsial infections, but arthritis is rare and is usually acute aseptic monarthrits of a large joint. However, pauci- and oligoarthritis have also been described. There have been 12 previous reports of arthritis with Mediterranean spotted fever, caused by R conorii, and there has been only a single case report of arthritis associated with Rocky Mountain spotted fever. As far as we know, this is the first reported case of arthritis in association with spotted fever (R africae and R conorii) originating from South Africa.
Between 1998 and 2002 spotted fever predominately due to \textit{R. africae} was detected in 131 cases (four with arthralgia) returning from southern Africa to the UK. More cases may be seen world wide if southern Africa continues to develop as a tourist destination.

In conclusion, we have described a patient who developed polyarthritis owing to rickettsial disease acquired in South Africa. Diagnosis was made based on the clinical history and the presence of anti-spotted fever group antibodies. Rickettsial infection should be included in the differential diagnosis of acute aseptic arthritis in travellers returning from sub-Saharan Africa; effective treatment with tetracycline may otherwise be overlooked.

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We have no conflict of interest to declare. Dr Ding as corresponding author had full access to all the data in this case report and had final responsibility for the decision to submit for publication.

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REFERENCES


Extracorporeal shock wave therapy in the treatment of inferior calcaneal enthesophytosis: outcome by fan-beam dual x-ray absorptiometry (DXA)

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P lantar fasciitis with heel spurs is a common cause of heel pain, and is often not sensitive to conservative treatment, including insole supports, non-steroidal anti-inflammatory drugs, local steroid injection, and physical therapy. In patients in whom conservative treatment fails, surgical intervention is recommended.

Recently, extracorporeal shock wave therapy has been introduced for the alleviation of painful heel and other conditions such as tennis elbow, calcifying tendinopathy of the shoulder, and non-union of fractures of the long bones.

The presence and size of the heel spurs do not correlate with the clinical symptoms.

Twenty patients aged between 40 and 70 years were treated. Exclusion criteria were degenerative diseases and/or inflammation of the ankle or foot joints, neurological abnormalities, nerve entrapment syndrome, pregnancy, infectious or neoplastic diseases, ulcerations, and bursitis.

Inclusion criteria were painful heel for a minimum of 12 months with heel spur radiologically examined and unsuccessful conservative treatment during the 6 months before referral to our hospital. No other treatment or drug was used during the 4 weeks before the trials began or during the study period, only the use of insole supports was permitted. An electrohydraulic system was used (Orthima; Direx Medical System Ltd).

Five treatments were given (one every 7 days), each treatment comprising 1200 shocks with a frequency of 120 shocks a minute. As the treatment may be initially painful, the energy density used on starting treatment was 0.03 mJ/mm², which was gradually increased to 0.4 mJ/mm².

Variations in the bone mineral content (BMC) of enthesophytosis were evaluated by fan-beam dual x-ray absorptiometry (DXA) using a Lunar-Expert version 1.72, at baseline and 1 month after the end of treatment. This method allows rapid scanning of particular skeletal regions, and provides a radiographic-like image. Scans of 1 mA were applied to the heel, the foot was placed in complete extra-rotation, using a plastic support specific for a DXA evaluation of small bone structures. A region of interest was created in each patient, with a side at the base of the enthesophytosis, to include the enthesophytosis and to exclude the os calcis cortex; this region of interest remained unchanged for later controls (fig 1). The short term precision of the method was 0.5% (coefficient of variation) in vivo, as calculated in 10 patients scanned four times.

Pain levels were evaluated (before treatment, at the end of treatment, and 3 and 6 months later) by visual analogue scale (VAS) ranging from 0 = no pain to 10 = maximum pain.

Figure 1 Fan-beam DXA of the heel.
at rest, after walking on awakening, and after normal daily activity. A significant decrease of VAS (p<0.0001, Wilcoxon test) was seen (table 1).

Dxa analysis of enthesophytosis showed a significant decrease in BMC (p<0.001, paired Student’s t test) from an average of 0.162 g to a mean of 0.111 g.

In conclusion, we found that extracorporeal shock wave therapy significantly improved the painful symptoms; in our study this reduction in pain was accompanied by a significant decrease of the BMC of the heel spur.

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REFERENCES

Clinical predictors of fetal and maternal outcome in Chinese patients with systemic lupus erythematosus

M Y Mok, P Y Leung, T H Lao, Y Lo, T M Chan, W S Wong, C S Lau

A maternal and fetal outcome of pregnancy in patients with systemic lupus erythematosus (SLE) depends very much on the composition of the patient cohort being analysed.

METHODS AND RESULTS
We performed a retrospective study to identify the clinical predictive factors for unfavourable pregnancy outcome in our Chinese patients with SLE from a homogeneous cohort being followed up at the university rheumatology clinic during the period 1982–96. Ninety one pregnancies from 66 patients were identified. Antiphospholipid antibodies (aPL), including lupus anticoagulant (LAC) and/or IgG anticardiolipin antibodies, were present in 18/66 (27%) patients. In 33/80 (41%) pregnancies resulting in live births, patients had a past history of lupus nephritis. Only one patient had impaired renal function, two had significant proteinuria ≥1 g/day, and four had stable hypertension while receiving antihypertensive drugs at conception. Active lupus was present within 6 months before conception in 12/91 (13%) and at conception in 7/91 (8%) pregnancies.

The live birth rate and fetal loss rate was 80/91 (88%) and 11/91 (12%), respectively. Fetal loss was found to be associated with serum anti-Ro (p = 0.04), anti-La (p = 0.007), and significant proteinuria at conception (p = 0.03). aPL were not found to relate to a single episode of fetal loss (p = 0.06), but they were more prevalent in patients with recurrent miscarriages (odds ratio (OR) = 14.3, p = 0.008), of which LAC was the strongest predictive factor (OR = 23.3, p = 0.002). Poor fetal outcome was found in 27/80 (34%) live births. There were 13 premature births and 14 fetuses had intrauterine growth retardation (IUGR). Significant proteinuria during pregnancy (p = 0.006) and flare in gestation (p = 0.001) was found to be related to prematurity. Multivariate analysis identified flare during pregnancy, in particular in the second trimester, as the strongest risk factor (relative risk (RR) = 5.5, 95% confidence interval (CI) 1.4 to 21.9, p = 0.02). Active lupus both within

Table 1 Pain levels

<table>
<thead>
<tr>
<th></th>
<th>Mean VAS at rest (range 0–10)</th>
<th>Mean VAS after walking on awakening (range 0–10)</th>
<th>Mean VAS after normal daily activity (range 0–10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>8.1 (1.5)</td>
<td>8.1 (1.4)</td>
<td>8.3 (1.2)</td>
</tr>
<tr>
<td>End of the treatment</td>
<td>5.9 (1.2)</td>
<td>6.7 (1.6)</td>
<td>5.6 (1.8)</td>
</tr>
<tr>
<td>After 3 months</td>
<td>4.3 (1.6)</td>
<td>6.1 (1.3)</td>
<td>4.1 (1.8)</td>
</tr>
<tr>
<td>After 6 months</td>
<td>4.1 (1.5)</td>
<td>3.9 (1.6)</td>
<td>3.6 (1.7)</td>
</tr>
</tbody>
</table>

Results are shown as mean (SD).
6 months before (p = 0.01) and at conception (p = 0.002) was found to predispose to IUGR. The latter was identified by multivariate analysis as the most predictive factor (RR = 22.1, 95% CI 2.5 to 215.1, p = 0.008). Pre-eclampsia was present in 8/80 (10%) pregnancies and no particular risk factor was found.

Thirty three pregnancies were recorded in the 27 patients with a past history of lupus nephritis. The live birth rate, fetal loss rate, and rate of poor fetal outcome (prematurity in four, IUGR in six) were not particularly different from those in patients with non-renal SLE and were 94%, 6%, and 30%, respectively. Predictive factors for poor fetal outcome in this subset of patients included significant proteinuria at conception (p = 0.004) and during pregnancy (p = 0.01) and active SLE within 6 months before conception (p = 0.007) and at conception (p = 0.03).

DISCUSSION

The fetal loss rate in our cohort lies near the lower end of the 11–46% range which was previously reported.1 This was partly because our patients had a lower prevalence of aPL (27%) than the 34–44% reported in other cohorts2 and partly related to the small proportion of patients with active SLE at conception. Better live birth rates have been reported in patients with inactive rather than active disease at conception.3,4 Our reported rate of poor fetal outcome and the associated risk factors were similar to those previously reported.1,4–9 The fetal loss rate in our patients with a past history of lupus nephritis was, however, lower than those reported (13–46%)6 because the renal disease of our patients was quiescent at conception; active nephritis at conception has been reported to give a higher risk of fetal loss.10 Furthermore, patients in our clinic with impaired renal function were generally discouraged from becoming pregnant.

In conclusion, adverse pregnancy outcome was more common in patients with active disease in gestation. Fetal outcome is favourable in patients with a past history of lupus nephritis if they have normal renal function, no significant proteinuria, and satisfactory blood pressure control.

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REFERENCES


Temporomandibular joint pseudogout: an uncommon site for a familiar condition

F Goldblatt, J Highton, G R Kumara
Antinuclear antibodies are common in an infectious environment but do not predict systemic lupus erythematosus

F Cainelli, C Betterle, S Vento

The reasons underlying the appearance of autoantibodies are poorly understood. The recent proposal that childhood infections prevent both autoantibody formation and occurrence of autoimmune diseases\(^1\)\(^2\) led to the suggestion that widespread vaccination against infectious diseases might favour the development of autoimmune diseases.\(^3\)

To verify whether repeated infections from childhood prevent autoantibody formation we compared the prevalence of antinuclear antibodies (ANA), autoantibodies of infrequent occurrence in healthy controls from Western Europe and associated with systemic lupus erythematosus (SLE) and other autoimmune diseases, in populations with different prevalence of infections throughout the course of life—namely, African immigrants to Italy and Italians.

METHODS AND RESULTS

We obtained written informed consent from 137 Ghanaian or Nigerian apparently healthy immigrants to Italy and living in Verona (northeastern Italy), unrelated to patients with SLE
or other autoimmune diseases, characterised by ANA positivity. We drew blood samples which were first tested for anti-HIV antibodies. Thirteen positive subjects were excluded from the survey. In the remaining 124 (mean age 35, range 8–53 years; 58 women) we looked for the presence of ANA by immunofluorescence on Hep-2 cells. We selected anti-HIV negative subjects to exclude the influence of anti-HIV antibody cross reactivity or HIV infection itself on the results of ANA determination; we also excluded relatives of patients with ANA positive autoimmune diseases because ANA positivity is more common in this subgroup.3,4

All the subjects studied recalled at least four episodes of malaria and three episodes of diarrhoea of at least 5 days’ duration. Hence the immigrant study population had been exposed to repeated infections during their lifetime. The prevalence (reciprocal titres 40–320) of ANA was found to be very high (27.4%, comparable to that of relatives of white Italian healthy controls)5 and even higher in more recent immigrants (table 1). Of the 34 positive subjects, 17 were women and 17 men; their mean (SD) age was 33 (8). As a control population, we used 375 white northeastern Italian subjects matched for age and sex and found an ANA prevalence of 3.5% (p<0.01).

**DISCUSSION**

Our data strongly suggest that living in an “infectious” environment from early life does not prevent, but rather favours, the formation of ANA. Although the reasons underlying their appearance are obscure, a role for a molecular mimicry between nuclear components of normal cells and parasitic or viral antigens cannot be excluded, as this has been demonstrated with the hepatitis B virus DNA polymerase.5

The finding that ANA positivity is far higher in recent immigrants is intriguing, as they are younger and therefore expected to have a lower incidence of autoantibodies than older subjects. Furthermore, although ANA are more frequently detected in women, we did not observe a preponderance in the female immigrant population tested. Although a definitive demonstration would require repeated testing of immigrants and demonstration of loss of ANA positivity over time, the present findings do suggest that the longer a person lives in a “less infectious” environment, the higher is the probability that they will be autoantibody negative.

Interestingly, none of the ANA positive subjects have developed any symptoms of autoimmune diseases in a mean follow up of 18 months.

In conclusion, our data demonstrate that markers of autoimmunity, such as ANA, are frequently found in Africa-born people but tend to be lost if they live for a long time in Western countries. Their presence should not therefore be regarded as predictive of SLE, a conclusion which confirms findings from studies in developed countries.6

Prospective epidemiological studies are needed both in developed and developing countries if the real mechanisms leading to overt autoimmune diseases are to be understood. Meanwhile, vaccination programmes in developing countries can continue without any concerns about a possible increase in the incidence of autoimmune diseases.

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**REFERENCES**


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**Table 1** Prevalence of antinuclear antibodies (ANA) in Italian healthy controls, and in immigrants from West Africa to Italy according to age and length of residence in Italy

<table>
<thead>
<tr>
<th></th>
<th>Italian healthy controls</th>
<th>Subjects who left Africa</th>
<th>Total number of Africa-born subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Age, mean (SD)</td>
<td>3 months–7 years ago</td>
</tr>
<tr>
<td>ANA positive, No (%)</td>
<td>375</td>
<td>30 (15)</td>
<td>31 (7)</td>
</tr>
<tr>
<td>Reciprocal ANA titres, median (range)</td>
<td>13 (3.5)</td>
<td>24 (35)</td>
<td>8 (19)</td>
</tr>
</tbody>
</table>
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