leucocytes (total white cell counts around $3.1 \times 10^9/l$). In 2003, his bone marrow showed active marrow and normal granulocyte precursors, and he was started on methotrexate. He demonstrated a good initial response to methotrexate 7.5 mg weekly, but this was stopped due to neutropenia of $0.9 \times 10^9/l$. Cyclosporin was unsuccessful (gum hypertrophy and hypertension). Methotrexate was restarted, but with persisting asymptomatic neutropenia varying between 0.57 and $0.93 \times 10^9/l$. Methotrexate proved ineffective for the arthritis 6 months later. He was started on etanercept. He had an excellent clinical response, but with persistent neutropenia. Six months later, he presented to clinic with weight loss and left upper quadrant pain. Total white cell count was $8.9 \times 10^9/l$, with neutrophils of $6.79 \times 10^9/l$ (very high for him). Ultrasound and CT scan showed multiple splenic abscesses. Blood cultures grew Staphylococcus aureus. Despite intensive intravenous antibiotics his C-reactive protein continued to rise and repeat CT showed no improvement. He had an elective splenectomy, complicated by post-operative sepsis and bleeding requiring repeat laparotomy and a 5-day ICU stay. Splenic histology confirmed staphylococcal abscesses. He made a full recovery, and is currently well, on no medication, with normal neutrophil counts.

There have been previous reports of neutropenia with anti-TNF agents. We have found only one other report with etanercept in an ankylosing spondylitis patient, with two positive rechallenges [6]. The patient also developed neutropenia after an infliximab infusion. Agranulocytosis and neutropenia have been described with infliximab [6–8], one case requiring inpatient stay for intravenous antibiotics until the cultures were negative. A recent study of 130 patients on anti-TNF showed a cytopenia rate of 12%, mainly leucopenias, with none leading to serious infection [9].

Our first patient had no sepsis, but the second showed a rapid and dramatic neutropenia, and though cultures were negative she behaved as if septic. The third patient had pre-existing neutropenia, and developed a dramatic and life-threatening infection with staphylococcal abscesses in a most unusual location. All three patients had normal bone marrow examinations, suggesting that the neutropenia may be due to peripheral consumption rather than a primary marrow disorder. All three patients were strongly positive for IgG ANA (1/1280, 1/5120 and $>1/5120$, respectively), though a previous analysis showed no evidence of an association between ANA and neutropenia in RA anti-TNF patients [5]. None of the patients had symptoms of Sjögren’s syndrome. All three are negative for anti-neutrophil cytoplasmic antibodies, but we have not tested for other anti-leucocyte antibodies. The first patient has tolerated adalimumab far better than etanercept from a neutrophil perspective. The third patient has had a normal neutrophil count since his splenectomy. All three patients had episodes of neutropenia prior to their anti-TNF treatment, which significantly worsened with etanercept. We advise that all patients on anti-TNF agents should be monitored with regular full blood counts, with particular care for those with previously documented neutropenia [5]. We are not alone in this recommendation [9].

**Rheumatology key message**

- Etanercept can be associated with significant neutropenia.

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**Cholesterol crescents and plates in shoulder effusion of a rheumatoid patient**

SIR, While the occurrence of cholesterol effusions in patients with inflammatory arthropathy is a recognized phenomenon, the aetiology of this complication is not known. Whether there is any relationship to hyperlipidaemia remains speculative although a previous report has described clinical response to statin therapy [1]. We would like to report our experience of a patient with seronegative, erosive rheumatoid arthritis, whose disease was unresponsive to sequential DMARD monotherapy and also to oral steroid/DMARD combination treatment. In June 2005, he was commenced on etanercept and methotrexate combination therapy but stopped it perioperatively in December 2006 whilst he underwent knee replacement surgery. Later that month, he developed a large left shoulder effusion and aspiration yielded small quantities of turbid fluid. Ultrasound confirmed a large subacromial effusion with increased echogenicity suggesting partially solid material. Examination of the aspirates (by polarizing microscopy) demonstrated cholesterol crystals and cholesterol crescents (Fig. 1). The finding of cholesterol crescents is rare and they usually occur only in shoulder effusions (J. Denton, personal communication). Fasting serum cholesterol was normal.

He was commenced on simvastatin 20 mg daily in February 2007 and methotrexate was switched to subcutaneous administration at a dose of 7.5 mg/week in March 2007. There was no improvement in disease status or in the shoulder effusion. His CRP was 41 mg/l. In May 2007, he suffered a further disease flare and oral prednisolone was increased from 5 mg daily to 20 mg daily temporarily. This resulted in an excellent clinical response...
with marked improvement in the shoulder effusion and normalization of CRP. Attempted re-aspiration of the shoulder was unsuccessful at this point.

The finding of cholesterol in rheumatoid arthritis is usually seen in the context of disease activity. Freemont and Denton [2] state that cholesterol is found in any blind-ended sac and is usually evidence of a previous long-standing inflammatory arthropathy. Cholesterol plates are found in aspirate from para-articular bursal sacs, and are evidence of long-term inflammatory arthropathy, most commonly rheumatoid disease. The lack of response in our patient to therapeutic doses of statin therapy and the marked improvement once the disease control was achieved is in keeping with this. Our experience suggests that cholesterol effusions are a manifestation of rheumatoid arthritis disease activity and resolution can be achieved by optimizing disease control. Cholesterol plates and crescents are only sporadically seen in rheumatoid arthritis and this may be due to doctors not requesting that the aspirate be examined for cholesterol crystals, or because the aspirates are from joints (as opposed to para-articular bursal sacs), or because of a lack of laboratory expertise in looking for these features.

**Rheumatology key message**

- Cholesterol crescents are an uncommon feature in synovial fluid and reflect rheumatoid disease activity.

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**Hypoglycaemia induced by hydroxychloroquine in a non-diabetic patient treated for RA**

Sir, Anti-malarial drugs have become one of the most commonly prescribed drugs in the treatment of many rheumatic diseases such as RA and SLE. Anti-malarials may improve glucose tolerance. Hypoglycaemia is a rare but well-recognized adverse effect of antimalarial therapy [1–3].

Here we described a non-diabetic patient with RA who developed hypoglycaemia under hydroxychloroquine (HCQ) treatment. We also discussed the possible mechanisms of hypoglycaemia due to HCQ.

A 62-yr-old man was admitted to our hospital with symmetric polyarthritis and morning stiffness for more than 2 h in 2005. He had a history of pain and swelling in his fingers, wrists, elbows and shoulders for 3 yrs. He had been diagnosed as having RA in another hospital and treated with sulphasalazine (SSZ) 2 g/day, methotrexate (MTX) 7.5 mg/week, prednisolone 7.5 mg/day and NSAIDs.

On examination, swelling and pain in the wrists, metacarpophalangeal joints and proximal interphalangeal joints was found. He had also subcutaneous nodules around the elbow joints. The blood count, liver function and urinalysis tests were normal. RF was 632 IU/ml and ESR was 102 mm/h. The dose of MTX was increased to 12.5 mg/week and prednisolone 15 mg daily was started. SSZ was continued and leflunomide 10 mg daily was added to treatment.

He was lost to follow-up 2 yrs after his last control. In April 2007, he was admitted with symmetric polyarthritides. Leflunomide was increased to 20 mg/day. SSZ, MTX were continued and HCQ 200 mg daily was started.

In June 2007, he was brought to the emergency department because of unconsciousness. Blood analysis showed hypoglycaemia (10 mg/dl; reference range 70–110 mg/dl). He rapidly responded to i.v. dextrose. Serum insulin and C peptide levels were determined during 72 h of the fasting test. Fasting test was stopped at 40th h due to hypoglycaemic symptoms. Glucose, insulin and C peptide levels were found to be 39 mg/dl, <2 µU/ml and 0.7 mg/dl, respectively at the end of the test. These results were not consistent with insulinoma. Cortisol and growth hormone levels were in normal ranges. Oral glucose tolerance test (oGTT) was normal. HbA1c and BMI were 5.09% and 22.9, respectively. Abdominal ultrasonography for the evaluation of the pancreas was normal. HCQ was stopped. MTX, leflunomide and prednisolone were continued. Ten days after his discharge from the hospital, hypoglycaemic attack recurred and his hypoglycaemic symptoms including perspiration and unconsciousness were treated with i.v. dextrose. Carbohydrate-rich diet as well as frequent meal was advised to patient for avoiding a possible hypoglycaemia.

In the literature, our patient is the first non-diabetic case with RA who developed hypoglycaemia secondary to HCQ. Anti-malarials are well-tolerated and safely used drugs. Hypoglycaemia is a rare adverse effect of anti-malarials. Although, some cases in the literature about hypoglycaemia related to chloroquine (CQ) is reported [1, 2], there is only one RA patient with diabetes mellitus who developed hypoglycaemia due to HCQ [3]. Our patient had no predisposing disorder that will lead to hypoglycaemia such as insulinoma, ethanol intake, oral anti-diabetic and exogenous insulin usage. There were also no clinical and laboratory manifestations of starvation, liver failure or sepsis that can lead to hypoglycaemia.

In vitro evidence has shown that CQ reduces intracellular insulin degradation, increases intracellular insulin accumulation, slows receptor...