

PostScript

MATTERS ARISING

Refractory leg infection as an inducer of the catastrophic antiphospholipid syndrome

In their report Yoo *et al* describe a 72 year old woman who presented with fever and symmetrical gangrene of the fingers and toes despite intact peripheral arterial pulses.¹ *Klebsiella pneumoniae* grew both from blood and liver biopsy aspirates. Treatment with antibiotics, prostacyclin, tissue plasminogen activator followed by warfarin and aspirin was beneficial and led to the regression of almost all the lesions. The authors state that "Although Amital *et al* reported that amputation could induce remission of the systemic illness, some reports have recommended that non-surgical management is preferable if there is an intact pulse in the affected limb".

The term "catastrophic" antiphospholipid syndrome (CAPS) is used to define an accelerated form of antiphospholipid syndrome (APS) resulting in multiorgan failure. These patients have clinical evidence of multiple organ involvement, which develops within a short period of time, in addition to histopathological evidence of multiple small vessel thrombotic occlusion and high titres of antiphospholipid antibodies. The most common precipitating factor of CAPS is infection, appearing in 35% of patients.²

We previously described two patients with APS with severe leg infections who developed a fulminant course of CAPS with acute renal failure, adult respiratory distress syndrome, central nervous system involvement, and the emergence of gangrenous lesions in both legs. After conservative treatment failed both patients had both legs amputated and recovered.³ Recently, we encountered two patients with systemic lupus erythematosus and secondary CAPS who were less fortunate. Both had severe leg infections refractory to antibiotic, vasodilator, and anticoagulant treatment. Both refused bilateral leg amputation and after a short period died owing to multiple thrombi and multiorgan failure.

CAPS differs from APS by its systemic involvement and down hill progression ending in multiorgan failure and death. Kitchens reasoned that a "fibrinolytic shutdown"

might be caused during infections as they induce a transitory increase in plasminogen activator inhibitor concentrations.⁴ This especially when another thrombophilic conditions is present may lead to a "thrombotic storm".

We believe that the patient described by Yoo *et al*¹ does not comply with the definitions of CAPS. Therefore their citation of our previous work, underlining the importance of eradicating the source of infection even at the cost of amputating both legs (in case the infection cannot be conservatively controlled), is inaccurate. The two unfortunate new cases we mentioned clearly demonstrate how critical these conditions may be and how essential it is to reach a decisive mode of action.

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Authors' reply

We thank Dr Amital and his colleagues for their valuable opinions about important guidelines for treatment of catastrophic antiphospholipid syndrome (CAPS). We think there are two points which were raised by Dr Amital and colleagues: one is whether our case is strictly consistent with the criteria of CAPS, the other is to decide between the surgical and non-surgical intervention in cases of gangrenous extremities.

CAPS was initially defined as an accelerated APS with multiorgan failure.¹ This definition has been refined to be classified as the definite and probable category through the consensus workshop of the 10th International Congress on antiphospholipid antibodies (aPL) on 29 September 2002.²

According to these new preliminary criteria, the patient presented by us³ belongs to the category of probable CAPS: shock, acute respiratory distress syndrome, stuporous mentality, and liver failure as well as the gangrenous extremities were the initial manifestations shown simultaneously (we had to omit these findings from the initial manuscript owing to the length of letters allowed in this journal). The presence of aPL was confirmed on two occasions 6 weeks apart. However, histopathological confirmation was

not obtained. Therefore, there is no doubt that the patient had probable CAPS.

As Asherson *et al* commented in the new preliminary criteria,² the optimal management of CAPS is not yet firmly established. In fact, we agree with Dr Amital's opinion that it is important to eradicate the infectious source even at the cost of amputation in case the infection is intractable.⁴ However, we do not think that amputation should be performed in all cases of CAPS. If peripheral arterial pulses are intact, as they were in our patient, non-surgical management may be initially preferred to allow the chance that the patient's lesion may improve. In addition, the new treatment algorithm presented by Asherson *et al* also recommends medical management as an initial treatment (anticoagulation plus high doses of steroid plus intravenous immunoglobulin and plasma exchange).² In our opinion, there is no absolute rule for the management of gangrenous condition in CAPS. We also think that the decision to amputate should be individualised and remains to be elucidated in the further consensus study.

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Hepatic manifestations of autoimmune rheumatic diseases

We read with interest the recent review by Abraham *et al*.¹ Other uncommon conditions of the liver have been described in association with rheumatic diseases.

One case report detailed the presence of rheumatoid nodules in a patient with active rheumatoid arthritis complicated by amyloidosis and chronic renal failure.² Postmortem findings disclosed numerous nodules scattered throughout the liver of maximum diameter 5 mm. Histological examination of these showed a central zone of cell necrosis

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with surrounding histiocytes in a palisade arrangement with peripheral fibrosis and a chronic inflammatory cell infiltrate. These nodules were identical to subcutaneous nodules found in the same patient near joints.

Landas *et al* reported another distinct histopathological entity involving the liver in patients with rheumatoid arthritis who had been treated with gold compounds.³ Each of these patients was biopsied after their gold treatment had been stopped for at least 3 months and before they started treatment with methotrexate. Twenty three of 41 (56%) patients had well formed lipogranulomas in the lobules compared with a 5% incidence in the control biopsy group. In 20 of these cases pigment was noted in the lipogranulomas and in seven patients it was found in lipid droplets in portal triads. The black to brown pigment was confirmed as gold in three cases by energy dispersive spectroscopy. The presence of gold pigment in the liver did not appear to have any serious immediate pathological consequences or other long term effects as judged in 12 patients who were followed up over a period of 10 years.

Spontaneous rupture of the liver has been reported in association with rheumatoid arthritis and systemic lupus erythematosus.^{4,5} This condition has been described in rheumatoid arthritis complicated by extra-articular features and high titre rheumatoid factor. Petterson *et al* have also described spontaneous liver rupture in a patient with mild seronegative inflammatory arthritis.⁶ A generalised necrotising arteritis may also complicate many of the rheumatoid and connective tissue diseases. Hepatic involvement may be part of the arteritis, with resultant nodular regenerative hyperplasia and hepatic rupture occurring as a consequence.

Hepatic involvement therefore can occur not only as part of the disease process but also as Abraham *et al*¹ point out as a result of drug treatment.

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Authors' reply

We thank Drs Sandhu and Jawad for highlighting additional hepatic pathologies

associated with rheumatoid arthritis. Our review was specifically aimed at highlighting liver involvement primarily due to autoimmune rheumatic disease and not as a result of pharmacotherapy.

The presence of hepatic rheumatoid nodules or gold pigmented lipogranulomas is of histopathological interest but has not definitively been associated with an adverse clinical outcome in rheumatoid arthritis. Spontaneous rupture of the liver and hepatic necrotising arteritis are rare, but nevertheless life threatening, complications of autoimmune rheumatic disease.

We reiterate that the physician should remain vigilant to liver pathology using serum liver enzyme markers and clinical examination for hepatomegaly.

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Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis

We read with interest the article by Fathi *et al*.¹ We agree with the main message indicating that interstitial lung disease is a common early clinical manifestation in patients with polymyositis (PM) and dermatomyositis (DM). The prevalence in their study was much higher than commonly reported. However, for the sake of objective information, some important methodological insufficiencies and disputable data in the article need to be highlighted.

The immunoserological profile of the patients with myositis studied seemed to be peculiar in light of previous reported data. The very unusual serological finding was the high frequency of anti-La antibodies. To our knowledge, it was in only one multicentre study by Brouwer *et al*,² that anti-La antibodies were detected in 6% of patients with PM and 3% with DM, using an enzyme linked immunosorbent assay (ELISA) and western blot analysis. Otherwise, neither in earlier studies^{3,4} nor in more recent ones,^{5,6} has any anti-La activity been reported despite several different techniques used for the detection of antibodies against intracellular antigens.

Further, the authors reported positive anti-Ro antibodies in 44% of the patients with PM and in 25% of the patients with DM, which differs considerably from the data on the prevalence of anti-Ro in patients with pure idiopathic myositis described by others. Those studies, using counterimmunoelectrophoresis or an immunodiffusion technique, found antibodies against native Ro antigens in 0–14% of the examined sera,^{3–6} while relevant ELISAs showed antibodies to recombinant Ro60 in 0–6%⁵ of the tested sera, and with a higher frequency of 17–70%^{4–8} to Ro52, along with anti-Jo1 antibodies, constituting the so called antisynthetase syndrome.^{7,8} The prevalence of autoantibodies against La and Ro antigens in patients with PM and DM in the study by Fathi *et al*¹ was thus not in agreement with the majority of published data and should have been discussed more extensively.

Unfortunately, the authors did not present any details of the antibody detection methods, which are of the utmost significance. Owing to many different to the detection of autoantibodies against intracellular antigens, several options are available, ranging from “in-house” methods to commercial kits. The choice may be crucial in considering those patients/cases where an autoantibody profile can substantially influence the final clinical decision. It has been suggested that in such situations two independent techniques should be employed to confirm the presence of specific autoantibodies in the patient serum,⁹ which is especially applicable to the family of antibodies against Ro antigens.

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Authors' reply

We thank Dr Rozman and coauthors for their interest in our study presented in the *Annals* and their thoughtful reflections on the autoantibody profile in patients with polymyositis and dermatomyositis.¹ As Dr Rozman *et al* comment, we found that anti-SSA/Ro antibodies were detected in 35% (6/17) and anti-SSB/La antibodies in 12% (2/17) of our patients with poly- or dermatomyositis. We

agree that these numbers are higher than expected in comparison with most previously published myositis cohorts.^{2,3} Notably, we had excluded patients with other defined rheumatic diseases.

The analyses for anti-SSA/Ro and anti-SSB/La antibody detection that were used in our study were performed with an enzyme linked immunosorbent assay (ELISA) containing both Ro52 and Ro60 recombinant antigen. These autoantibody tests were performed at the time of the diagnostic check up for each person as part of the routine procedure at the Karolinska University Hospital, Solna, Sweden. The laboratory procedures were performed at the Department of Clinical Immunology, which is ISO/IEEC certified for autoimmune analyses.

To further confirm the anti-SSA/Ro positive results we have retested the anti-SSA and anti-La positive sera with two other assays—immunodiffusion from Immuno-concepts and line immunoassay from Innogenetics. We could confirm the anti-SSA/Ro positivity from the ELISA tests with immunodiffusion in three of the six cases. The three additional cases were negative for anti-SSA using immunodiffusion, but were positive for Ro52 with the immunoblot technique. None of the six cases was positive for Ro60. Two cases had anti-La antibodies, both in addition to anti-SSA antibodies, using the ELISA test. The anti-La positivity was in one case confirmed by immunodiffusion, the other was not.

The discrepancy between the results in our patients and previously presented data is likely to depend on the different methods that have been used in different studies.² The patient cohort presented in our study is small, which makes analyses from stratified patient groups into subgroups such as polymyositis or dermatomyositis uncertain. Both ELISA and the line immunoassay are generally more sensitive than immunodiffusion and counter-immunoelectrophoresis.⁴ Moreover, the sensitivity threshold of various immunodiffusion tests varies with the manufacturer's content of specific antigens, like the Ro52 antigen. The assay used for immunodiffusion is, in our hands, less likely to detect Ro52 positive sera than other assays and, consequently, likely to oversee anti-SSA autoantibody reactivity if used alone. On the other hand, the higher sensitivity of ELISA and the line immunoassay may be at the cost of a weaker clinical specificity for the detection of anti-SSA antibodies associated with disease.

We still believe that our data are valid as similar results were achieved by both the ELISA and the line immunoassay using recombinant Ro52 antigen from different sources and even confirmed by immunodiffusion in three of the six cases. Another possible explanation for the lower frequency of anti-SSA antibodies in patients with polymyositis in older studies might be that patients with inclusion body myositis were not excluded, as autoantibodies seem to be less common in this disease entity.

Based upon the validating laboratory procedures presented above, we believe that anti-SSA/Ro and anti-SSB/La antibodies may be more common in pure polymyositis and dermatomyositis than previously recognised. This hypothesis remains to be tested in

a larger cohort of patients with myositis, particularly with regard to Ro52 alone.

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