Disseminated intravascular coagulation with renal and liver damage as the predominant manifestations of recurrent relapses in systemic juvenile rheumatoid arthritis

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Abstract

Relapses of systemic juvenile rheumatoid arthritis associated with intravascular coagulation are rare. This paper describes a patient who, over a two year period, had two relapses, each accompanied by evidence of liver and renal damage and disseminated intravascular coagulation. The patient was not receiving non-steroidal anti-inflammatory drugs, and all laboratory and clinical manifestations of her disease rapidly resolved after treatment with prednisone. It is therefore believed that the hepatocellular damage, in addition to the disseminated intravascular coagulation, was a direct manifestation of disease activity. A possible pathogenic role for tumour necrosis factor is suggested.

Juvenile rheumatoid arthritis (JRA) is a chronic disease which can present in three forms: systemic, polyarticular, and pauciarticular. Transformation from one form to another occurs. Intravascular coagulation has been reported as a rare complication of the systemic form. The spectrum of its clinical presentation ranges from prolongation of the prothrombin and partial thromboplastin times only, to a fulminant disseminated intravascular coagulation. The pathophysiological mechanisms causing this complication remain obscure. In this paper, we present a patient with the systemic form of JRA. The interesting features of this patient’s disease are two relapses over a two year period, each predominantly manifested by disseminated intravascular coagulation.

Case report

A 25 year old woman had had systemic JRA since the age of 18 months. At that time she was first admitted to hospital with arthritis of the right knee. Between the ages of 8 and 12 years she had recurrent episodes of remittent fever spiking up to 39°C, often accompanied by diffuse maculopapular eruption and polyarthritis involving both hips, knees, and ankles in addition to metaphyseal and epiphyseal changes, proximal interphalangeal, and wrist joints. At the age of 14 she received a bilateral hip replacement. Since the age of 16 she has been confined to a wheelchair and has had occasional exacerbations of arthralgias, often accompanied by fever and rash. Treatment with gold salts, sulphasalazine, and methotrexate, together with non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, have had no significant effect on the course of her disease. Fifteen months before the admission reported here, she was admitted to hospital with fever, arthralgias, and jaundice. On physical examination she appeared acutely ill. She had a blood pressure of 110/70 mmHg, a temperature of 38.5°C, and a pulse rate of 76/min. A few small, non-tender axillary and inguinal lymph nodes were palpated. The lungs were clear, a 2/6 systolic murmur was heard over the apex, and the liver and spleen were slightly enlarged.

Most of her joints were severely deformed with no signs of active synovitis. The neurological examination was negative.

Laboratory test results were as follows: haemoglobin, 106 g/l; white cell count, 5.8x10^9/l, with 71% polymorphonuclear cells; platelet count, 340x10^9/l. The erythrocyte sedimentation rate was 130 mm/h. The prothrombin time was 17 s (control 11-13 s) and the partial thromboplastin time was 34.3 s (control <35 s). Plasma fibrinogen was 0.9 g/l (normal 1.9-4.7) and the fibrinogen split products 170 mg/l (normal <8). Serum creatinine was 512.7 µmol/l, blood urea 46.8 mmol/l and the creatinine clearance 15 ml/min. Total serum protein was 69 g/l with an albumin to globulin ratio of 2.3, and albumin 35.2 g/l. Serum bilirubin 352-26 µmol/l, of which 188.1 µmol/l was direct bilirubin. The serum alkaline phosphatase level was 156 IU/ml (normal <85), aspartate aminotransferase 417 IU/ml (normal <40), alanine aminotransferase 19 IU/ml (normal <32), γ-glutamyl transferase 109 IU/ml (normal <25), and lactate dehydrogenase 427 IU/ml (normal <320). The direct Coombs’ test was negative and the levels of haptoglobin and glucose-6-phosphate dehydrogenase and the complement components C3 and C4 were normal. The tests for antinuclear antibodies and antiDNA antibodies were negative. Serological tests for hepatitis B virus, Epstein-Barr virus, and cytomegalovirus were negative. Repeat blood and urine cultures were sterile.

Abdominal ultrasonography revealed only slight hepatosplenomegaly. Treatment with cefazidime for seven days gave no response. Soon after, prednisone (60 mg/day) was started, resulting in a dramatic clinical and laboratory improvement. The patient became afebrile and well, and the renal and liver functions, in addition to the coagulation profile, returned to normal. The patient was discharged receiving prednisone 30 mg/day, to be tapered during follow up.

Fifteen months later, while receiving 12.5 mg prednisone every other day, she was readmitted with a spiking fever of up to 40°C and arthralgias. In addition to the physical findings noted on her previous admission, she had a diffuse maculo-
We have derived intestine assumption nated daily infusions of with fulminant laboratory evidence of disease, and et al7 controlling with plasma protein S levels.8-10 These workers have attributed severe microangiopathic plasma fibrinogen to attributing intravascular coagulation abnormalities to those reports, Sbarbaro and Bennet with a prothrombin time, prolonged prothrombin time, and bone necrosis, reported only twice.3 The association of disseminated intravascular coagulation with NSAIDs, has been attributed by the fact that the two previously described patients with this complication were receiving such treatment during each relapse of their disease.3 In contrast, our patient developed both disseminated intravascular coagulation and liver damage in the absence of NSAIDs. Hence, in this instance, other mechanisms are needed to explain the recurrent flare ups characterised by liver damage and disseminated intravascular coagulation.

During these two relapses the activity of the disease itself could have resulted in liver and endothelial damage, both leading to disseminated intravascular coagulation. However, the mediator of this combined damage remains elusive. We suggest a cytokine mediated effect and discuss the possible role of tumour necrosis factor in this. Increased concentrations of tumour necrosis factor have been detected in several rheumatic diseases.14-17 Moreover, tumour necrosis factor has been implicated in the pathogenesis of hepatic failure and disseminated intravascular coagulation.17-19 Several studies have shown an increased bioactivity of tumour necrosis factor in synovial cells and fluid obtained from patients with rheumatoid arthritis. Concentrations of synovial tumour necrosis factor correlate with other indices of disease activity, suggesting that this cytokine may play a part in at least the synovial inflammation and bone resorption characteristic of this disease.15-16 It has also been suggested that tumour necrosis factor is an important mediator of the liver damage associated with fulminant viral hepatitis and alcohol induced hepatitis.18-19 In fact, high plasma concentrations of tumour necrosis factor have been seen in patients with severe alcohol induced hepatitis.18 Tumour necrosis factor has been shown to promote the procoagulant properties of macrophages and endothelial cells and disseminated intravascular coagulation has been induced by tumour necrosis factor given intravenously to healthy volunteers.20

Discussion
We have presented a patient with systemic JRA who developed two flare ups of her disease, each manifested by liver and renal damage and by laboratory evidence of disseminated intravascular coagulation. A possible association between disseminated intravascular coagulation and liver disease has been described previously.5 6 Procoagulant substances released from necrotic hepatocytes and clot promoting intestine derived endotoxins have been incriminated in the induction of disseminated intravascular coagulation.7 Fujiwara et al8 treated 26 patients with fulminant hepatic failure with daily infusions of antithrombin 3, on the assumption that maintaining normal plasma antithrombin 3 levels would prolong survival by controlling intravascular coagulation. D’Angelo et al7 detected decreased concentrations of plasma protein S in patients with severe liver disease, and suggested that this might be the underlying mechanism for disseminated intravascular coagulation under these clinical conditions.

The association between systemic JRA and disseminated intravascular coagulation is extremely rare and has been described only four times.2-4 8 Mukamel et al followed up 79 patients with JRA by repeated coagulation studies for over one year. In spite of active and severe disease in most of these children, coagulation abnormalities developed in only two patients.9 Recurrent disseminated intravascular coagulation in patients with JRA is even less common and has been reported only twice.1 In these two reports, the disseminated intravascular coagulation has been attributed to the use of NSAIDs. Sbarbaro and Bennet described a 17 year old girl with JRA (adult type), who developed microangiopathic haemolytic anaemia with a prolonged prothrombin time, raised plasma fibrinogen split products, and evidence of severe hepatotoxicity.5 The liver damage was attributed to aspirin given at a dose of 3-6 g/day. These workers suggested that the disseminated intravascular coagulation was secondary to continuous activation of the coagulation cascade as a result of the failure of the damaged liver to degrade procoagulant factors. It is not un-

common for the liver to be affected in adult onset Still’s disease and serum liver enzyme abnormalities have been observed in approximately 35% of such patients. These abnormalities were not associated with NSAIDs and have been attributed to the activity of the underlying disease.10 11 In all patients it was not clinically important that the liver was affected, and this was not associated with disseminated intravascular coagulation.

Looking for other mechanisms which might explain disseminated intravascular coagulation in patients with JRA, Scott et al12 have suggested endothelial damage. They found high serum concentrations of factor VIII related protein in patients with JRA. Increased serum concentrations of factor VIII have been suggested as a marker of active vasculitis and have been observed in patients with systemic lupus erythematosus,12 progressive systemic sclerosis, and Raynaud’s phenomenon.13 Active vasculitis in patients with JRA could be a manifestation of the disease itself. In addition, as suggested by Silverman et al,3 it could be aggravated by NSAIDs. A possible role of NSAIDs in the pathogenesis of disseminated intravascular coagulation in JRA is supported by the fact that the two previously described patients with this complication were receiving such treatment during each relapse of their disease.3 In contrast, our patient developed both disseminated intravascular coagulation and liver damage in the absence of NSAIDs. Hence, in this instance, other mechanisms are needed to explain the recurrent flare ups characterised by liver damage and disseminated intravascular coagulation.
To conclude, this case report shows that active systemic JRA might be accompanied by liver damage and disseminated intravascular coagulation, even in the absence of treatment with NSAIDs. Patients with systemic JRA should be more closely monitored for the presence of these complications, which might be initiated by inflammatory cytokines such as tumour necrosis factor. Studies are needed to elucidate further the pathogenic role of tumour necrosis factor in JRA in general, and the pathogenesis of liver damage and disseminated intravascular coagulation in particular. If found to play a major part, intervention to neutralise its effects, such as in vivo treatment with antibodies or purified receptors, might be beneficial in the treatment of systemic JRA and possibly other forms of connective tissue disorders.

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