LETTERS TO THE EDITOR

IgG rheumatoid factor synthesis in synovial fluid

Sir: Winchester et al two decades ago proposed that IgG rheumatoid factor (RF) could be locally produced in plasma cells that line the synovium.1 We conducted a short study looking at paired samples of synovial fluid (from the knee joint) and serum from patients with definite rheumatoid arthritis to determine if the production of IgG RF is localised in the synovial fluid. Thirty six serum samples and synovial fluids were obtained from patients diagnosed with rheumatoid arthritis, all collected within one day of each other. The synovial fluids were treated with hyaluronidase enzyme2 (Sigma, USA) before testing. Serum samples and synovial fluids were also tested for the presence of IgG antibody to adenovirus. Adenovirus antibody levels have been used to establish local production of antibody in cerebrospinal fluid in syphilis3 and HIV;4 this antibody is common and can be used to determine if non-specific 'leak' of immunoglobulins from serum has occurred. This should be more accurate than comparing total levels of IgG, which are difficult to measure in low concentrations.

An enzyme immunoassay (EIA) was developed for the detection of IgG RF using rabbit IgG on the solid phase and anti-Fab2 to identify bound IgG RF. We measured levels of IgG RF in these serum samples and synovial fluids and determined a ratio of synovial fluid to serum on each patient. A cut off value for the assay was determined from 144 control serum samples from blood donors, and a stringent method of standardisation was used to account for day to day variation that occurs in EIA tests. These values were compared with ratios of synovial fluid to serum of adenovirus IgG antibody. Patients with rheumatoid arthritis positive for IgG RF and normal controls were significantly different (p<0.05). The table shows the results of the ratios for the two antibodies IgG RF and adenovirus IgG in the synovial fluids and serum samples of these rheumatoid patients. A significant difference (p<0.05) was shown between the IgG RF ratios and the adenovirus antibody ratios for the patients with rheumatoid arthritis. This finding strongly suggests that IgG RF had been produced locally. Further work is required to determine if selective accumulation of IgG RF in synovial fluid of other joints correlates with disease activity in rheumatoid arthritis and whether there is selective accumulation in the absence of this disease.

Ratio of IgG rheumatoid factor (RF) optical density to adenovirus IgG optical density in synovial fluid and serum of patients with rheumatoid arthritis

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Ratio adenovirus IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.31</td>
</tr>
<tr>
<td>Range</td>
<td>0.41-2.24</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

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Postpartum autologous plasma transfusion: effect on RA

Sir: A 32 year old white woman with rheumatoid arthritis (RA) for six years affecting many joints had been treated with various drugs, including azuranofin, aurothiochrome, and D-penicillamine, without appreciable benefit. The patient discontinued her drugs and became pregnant, and her disease was moderately well controlled with prednisone 5-7.5 mg/day. By the seventh month of pregnancy the patient was in clinical remission and was taking no drugs. During the third trimester the rheumatoid factor had fallen from 1/320 to 1/80, but the patient had a Westergren erythrocyte sedimentation rate of 39 mm/h and C reactive protein of 8.7 mg/l. She had an uncomplicated delivery and five days postpartum donated a unit of blood from which 300 ml fresh frozen plasma was obtained and stored at −70C. The patient noted gradual relapse of disease activity 10 days postpartum. On the 18th postpartum day the patient demonstrated mild to moderate polyarthritis and consented to autologous plasma transfusion of 250 ml. Within 48 hours after transfusion the patient reported dramatic improvement in her condition, which unfortunately lasted only one to two days (see table). There were no adverse reactions to the autologous transfusion.

The ameliorating effect of pregnancy in patients with RA has been well described.1-5 This patient's case suggests that certain plasma component(s) produced during pregnancy had immunosuppressive properties that also suppressed the rheumatoid factor but did not significantly affect the C reactive protein. As the benefit of autotransfusion on disease activity occurred after storing fresh frozen plasma at −70C and lasted for only one to two days, the plasma factor(s) which suppresses disease preserves well at −70C and has a short half life. A control pregnant patient with no RA and blood drawn during the third trimester showing negative rheumatoid factor, negative C reactive protein, and erythrocyte sedimentation rate 14 mm/h, indicating that pregnancy alone does not affect these disease markers.

Although this is the first known report of a postpartum autologous transfusion in a patient with RA, there are several reports of heterologous postpartum transfusions in rheumatoid patients.6-8 Two reports6,7 showed benefit and one report8 did not. The differences in these studies may reflect the wide ranges in concentration of the pregnancy associated plasma factor(s) responsible for suppressing disease activity in pregnant patients. This study avoided this problem by using autologous postpartum plasma during disease remission. Several reports have been published suggesting that the pregnancy associated αα glycoprotein has disease suppressive properties,9-13 but another report refuted this claim.14 More recent work suggests that some yet unidentified pregnancy associated glycoprotein(s) has immunosuppressive properties.15

In conclusion, this case further supports the possibility that a pregnancy associated plasma factor(s) responsible for suppressing disease activity in treating RA, and further work in identifying this factor(s) should be eagerly pursued.

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Effects of autologous postpartum transfusion on rheumatoid arthritis. Percentage change is shown in parentheses

<table>
<thead>
<tr>
<th>Results of examination:</th>
<th>Before transfusion</th>
<th>Day 3</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of swollen joints</td>
<td>22</td>
<td>6 (73)</td>
<td>22</td>
</tr>
<tr>
<td>Number of tender joints</td>
<td>24</td>
<td>5 (88)</td>
<td>27</td>
</tr>
<tr>
<td>Joint swelling index</td>
<td>6 (75)</td>
<td>6 (75)</td>
<td>25</td>
</tr>
<tr>
<td>Joint tenderness index</td>
<td>5 (85)</td>
<td>3 (85)</td>
<td>29</td>
</tr>
<tr>
<td>Average grip-strength</td>
<td>128/144</td>
<td>236/180</td>
<td>174/154</td>
</tr>
<tr>
<td>Mean grip strength (both hands)</td>
<td>136</td>
<td>208 (172)</td>
<td>164 (28)</td>
</tr>
<tr>
<td>Duration of morning stiffness (h)</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>1/640</td>
<td>1/160</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>22</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>C reactive protein (mg/l)</td>
<td>0.01</td>
<td>3.94</td>
<td></td>
</tr>
</tbody>
</table>

1-6 Eighty nine patients were evaluated.1-7
7 The index assigns a numerical value to the degree of swelling (0 = no swelling; 1 = mild swelling; 2 = moderate swelling; 3 = severe swelling) and represents summation of these values.
8 The index assigns a numerical value to the degree of tenderness; 1 = mild tenderness; 2 = moderate tenderness; 3 = severe tenderness and represents summation of these values.
9 Average of three grip trials per hand.
10 Two months postpartum rheumatoid factor 1/320.
Colchicine myoneuropathy and renal dysfunction*

Sirs: Colchicine has been used in the treatment of gout and other diseases for over 200 years. Usually high dosing regimens have resulted in multiorgan toxicity affecting the haemopoietic, renal, nervous, dermatological, and musculoskeletal systems. 2 Recently, a myoneuropathy has been noted in elderly patients taking low doses of colchicine over months to years.3 All patients had underlying chronic renal insufficiency, which is considered an important component of the syndrome. We report the development of colchicine myoneuropathy in a woman with a transient prerenal illness.

A 75 year old woman presented with a three week history of progressive proximal muscle weakness. The onset of her symptoms followed a 10 day diarrhoeal illness that spontaneously resolved. Her medical history included longstanding hypertension, degenerative joint disease and calcium pyrophosphate deposition disease, for which she had been treated with oral colchicine, 0.6 mg twice daily, over the preceding 16 months. Other drugs included a thiazide diuretic taken three times daily. Physical examination showed an elderly woman weighing 61.4 kg who appeared well. Motor testing disclosed weakness of the shoulder and pelvic girdle muscles with normal distal strength, and results of a neurological examination were normal. Laboratory studies showed a creatine kinase of 646 IU/l (normal range 0–170 IU/l), and a Westergren sedimentation rate of 10 mm/hr. Blood urea was 13.2 mmol/l and serum creatinine 132.6 μmol/l. Renal function studies six months earlier had been within normal limits: blood urea 6.4 mmol/l and serum creatinine 106.1 μmol/l. Electromyography showed myopathic changes characterised by resting membrane instability, positive sharp waves, fibrillations, and decreased amplitude and duration of potentials in proximal muscles. Nerve conduction studies were consistent with a mild polyneuropathy of the legs. A muscle biopsy showed vacuolation of 30% of myofibres without necrosis, inflammatory infiltrates, atrophy, or inclusion bodies (figure). Treatment with colchicine and diuretic was discontinued. Ten days later her motor strength had returned to normal and the serum creatine kinase was 35 IU/l. Blood urea was 6.1 mmol/l and serum creatinine 114.9 μmol/l.

In the nervous system colchicine interferes with neurotubule assembly causing a disruption of axonal transport.4 This probably accounts for the mild polyneuropathy seen in affected patients; however, the mechanism of injury in muscle, is less clear. In rat skeletal muscle an accumulation of ‘large sarcoplasmic membranous bodies’—with presumed autophagic activity—appears two to three days after the intraperitoneal injection of colchicine and is coincident with clinical weakness.5 In the arterial smooth muscle cells of rats colchicine causes structural and functional changes, including the increased appearance of autophagic vacuoles and lysosomes.6 In humans electron microscopy of proximal skeletal muscle from patients with colchicine myopathy shows abnormal accumulation of lysosomes and autophagic vacuoles.7 An anatomical linkage between lysosomes and microtubules has been demonstrated in cultured fibroblast studies.8 It seems likely that colchicine disrupts the microtubular cytoskeleton that directs the movement and function of intracellular organelles including lysosomes and autophagic vacuoles. Ironically, however, microtubules have not been clearly shown in human adult skeletal muscle. Whether colchicine exerts its myotoxic effects through intracellular microtubular disruption or by a yet undiscovered mechanism remains to be shown.

This case of colchicine myoneuropathy was thought to arise in a patient with normal renal function who had transient prerenal azaemia resulting from diuretic abuse superimposed on a diarrhoeal illness. A more careful analysis of her renal function by the Cockcroft-Gault equation,9 however, showed an underlying creatinine clearance of only 46 ml/min, which decreased to 16 ml/min during her prerenal state. It is unclear whether a transient decrease in the renal clearance of colchicine precipitated the development of symptomatic colchicine toxicity. It does suggest, however, that the risk of colchicine myoneuropathy may extend beyond the patient with obvious renal insufficiency to include any elderly patient with normal or near normal serum creatinine concentrations who may be prone to episodes of decreased renal perfusion. Because of partial dependence on hepatic metabolism, underlying liver disease may also predispose to colchicine toxicity.10 Given the increasing application of oral colchicine in a variety of rheumatic and non-rheumatic diseases, increased awareness of its potential toxicities—even in the presence of a ‘normal’ serum creatinine—should not be overlooked.

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*The opinions contained herein are those of the authors and do not necessarily reflect the views of the Department of the Army, Department of Defense, or the United States Government.


Colchicine myopathy. Note the vacuoles and absence of inflammation. (Haematoxylin and cosin.)
Postpartum autologous plasma transfusion: effect on RA.

C D Scoville

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