Case report

Cell mediated autoimmune granulocytopenia in a case of Felty's syndrome

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SUMMARY A variety of mechanisms have been demonstrated or suggested to explain the neutropenia that accompanies Felty's syndrome. This case report presents a patient with Felty's syndrome with recurrent infections who initially had a clinical response to splenectomy. Eleven years later profound neutropenia recurred. In-vitro evidence for cell mediated autosensitisation of peripheral blood lymphocytes to autologous bone marrow cells was found. The cellular abnormalities improved after high-dose corticosteroids but not lithium. However, there did not appear to be a reduction in the incidence of clinical infections. The finding suggests that granulocytopenia in some patients with Felty's syndrome may be an autoimmune phenomenon.

Since Felty's original description1 of 5 patients with rheumatoid arthritis, splenomegaly, and granulocytopenia numerous reports have confirmed the existence of this clinical entity, which occurs in about 1% of patients with chronic rheumatoid arthritis. Variants with 1 or more features of the classic triad probably represent diseases in the continuum of the syndrome. Neutropenia may precede the development of arthritis in some cases, and severe neutropenia may exist without detectable splenomegaly. Reports emphasise that patients with Felty's syndrome frequently have extra-articular manifestations of rheumatoid arthritis.2-4

The mechanisms which have been postulated to explain the neutropenia of Felty's syndrome are summarised in Table 1. The presence of splenomegaly and the beneficial response to splenectomy suggest that sequestration of neutrophils might be a mechanism.5 However, hypersplenism cannot be the only cause, because splenectomy improves the white cell count in only about two-thirds of the cases; and neutropenia may recur after splenectomy.6 7 Recurrence of neutropenia in splenectomised patients also excludes the importance of putative splenic inhibitory factors.8

Others have emphasised abnormalities of granulocyte kinetics. Owing to the lower numbers of granulocyte colony-forming cells in the bone marrow of patients with Felty's syndrome than in patients with idiopathic neutropenia and other causes of splenomegaly, it has been proposed that neutropenia may be the result of decreased production of granulocytes rather than enhanced destruction.9 10 Decreased production of neutrophils due to decreased production or activity of granulopoietic factors might also be important. In support of this

Table 1 Possible mechanisms of neutropenia in Felty's syndrome

<table>
<thead>
<tr>
<th>1. Decreased circulating granulocyte pool</th>
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<tbody>
<tr>
<td>A. Splenic pooling23</td>
</tr>
<tr>
<td>2. Decreased granulocyte production</td>
</tr>
<tr>
<td>A. Low granulocyte production23</td>
</tr>
<tr>
<td>B. Splenic toxic factors24</td>
</tr>
<tr>
<td>C. Decreased activity of granulopoietic factors10</td>
</tr>
<tr>
<td>D. Immunological factors</td>
</tr>
<tr>
<td>I. Autoantibodies12</td>
</tr>
<tr>
<td>II. Cell mediated (present report)</td>
</tr>
<tr>
<td>3. Increased granulocyte destruction</td>
</tr>
<tr>
<td>A. Immunological factors</td>
</tr>
<tr>
<td>I. Cytotoxic autoantibodies17</td>
</tr>
<tr>
<td>II. Opsonising autoantibodies13</td>
</tr>
<tr>
<td>III. Cell-bound antibodies13</td>
</tr>
<tr>
<td>IV. Cell mediated (present report)</td>
</tr>
<tr>
<td>B. Splenic phagocytosis25</td>
</tr>
</tbody>
</table>

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view urinary and serum levels of colony-stimulating activity in patients with Felty’s syndrome are low compared to patients with neutropenic disorder without rheumatoid arthritis. The sum of bone marrow studies seems to indicate that there is no decreased production but compensatory increased production to meet the demand for more neutrophils. Leucopenia secondary to recurring infections is unlikely, since neutropenia is not usually associated with severe infection unless the neutrophil count is 500/mm³ or less.

Plasma factors or autoantibodies might be important. Transfusion of Felty’s plasma into normal individuals has a leucopenic effect. Antigranulocyte antibody has been demonstrated by indirect techniques. A recent report demonstrates quantitatively more immunoglobulin G on human granulocytes in patients with Felty’s syndrome. Another demonstrates quantitative differences in circulating immune complexes in all patients with Felty’s as compared to classical rheumatoid arthritis controls.

This report presents evidence for a cell mediated autoimmune mechanism for the pathogenesis of neutropenia in a patient with recurrent Felty’s syndrome.

**Case report**

A 53-year-old white woman with a strong family history of rheumatoid arthritis (2 maternal uncles, 1 maternal aunt) had the onset of polyarthritis at age 28 and was treated with aspirin and cortisone. In 1964 repeated infections and persistent neutropenia with white blood counts averaging 2·2 × 10⁹/l, with 25% polymorphonuclear cells, necessitated the removal of her spleen, which was enlarged to the pelvic brim. The surgical specimen showed extramedullary haematopoiesis, reactive follicular centres, and many plasma cells within the cords. Postoperatively the white blood cell counts ranged between 5·6 and 8·9 × 10⁹/l, with a normal differential. Infections decreased, and the patient did well. Between 1969 and 1971 she underwent multiple hand surgery for rheumatoid arthritis without complication. Her white blood cell counts were normal.

In 1973 after a dental extraction she suffered fever, weight loss, and recurrent infections of her large toe. Though treated with serial antibiotics she continued to deteriorate. On admission to another hospital her serology showed antinuclear antibody (ANA), and she was started on prednisolone 75 mg a day for the presumed diagnosis of systemic lupus erythematosus. However, she continued to have fever, and subsequently the diagnosis of pulmonary nocardia abscess was made. During this period her white blood cell counts averaged 5·3 × 10⁹/l, with a normal differential. She was successfully treated with sulphonamides and tapering doses of corticosteroids. After Sulphonamide therapy her white blood cell count averaged 10·8 × 10⁹/l with 72% polymorphs.

In 1975, 11 years after her successfully splenectomy, she was seen at Stanford Medical Center. Her clinical evaluation was consistent with seropositive nodular erosive rheumatoid arthritis. Her laboratory studies indicated recurrence of profound granulocytopenia. Her total white blood cell counts varied between 4·7 and 8·8 × 10⁹/l, with a differential of 0–3% polymorphs, 0–6% bands, 11–40% monocytes, 1–23% eosinophils, 0–3% basophils, and 0–17% atypical lymphocytes. Her haemoglobin was between 11 and 12 g/dl, and her haematocrit between 31 and 40%. Her platelet count ranged between 690 and 990 × 10⁹/l. Serological studies showed a rheumatoid factor of 1:2560, antinuclear antibody of 1:320 (diffuse) without anti-DNA or anti-ENA. DNA binding was normal. Determinations of C3 and CH50 were normal. Routine chemical tests and urine analysis were unremarkable. During her absence from Stanford Medical Center she received short courses of sulphonamides and tetracycline. At no time did she receive phenylbutazone, gold, penicillamine, or cytotoxic agents known to cause agranulocytosis. She was restarted on aspirin, and her prednisone was tapered from 15 mg per day.

In 1976 she had osteomyelitis of her large toe requiring antibiotics, local treatment, and finally amputation. Scans for an accessory spleen with chromium labelled red blood cells and rose Bengal were negative. On low-dose prednisone and antiinflammatory levels of salicylates she had recurrent bacterial blepharitis, styes, cellulitis about the eyes and the nose, labial cellulitis, pseudomonas perirectal abscess, and *Hemophilus influenzae* pneumonia, all responding to short courses of antibiotics. Her agranulocytopenia persisted on prednisone 7·5 mg 4 times a day.

In November 1977, after 9 days of prednisone, 30–60 mg a day, her absolute polymorphonuclear count went from 0–21/mm³ to a mean of 1313/mm³ (0·0·02 to 1·3 × 10⁹/l). Thus, mature granulocytes (up to 60%) appeared in the peripheral blood for the first time after agranulocytosis during an observation period of more than 10 months. While on moderate to high doses of prednisone she developed bacterial conjunctivitis, cellulitis around the nares, and a mixed-flora perirectal abscess. In April 1978 lithium carbonate 900 mg a day was added to prednisone, but on this regimen she had no increase in her neutrophils and had another episode of periorbital cellulitis, bacterial conjunctivitis, and cellulitis about
the nose and gingival infection. Prednisone therapy was tapered to 15 mg every other day.

In September 1978 she developed ischaemia in the right leg requiring lumbar sympathectomy and subsequently a transmetatarsal amputation. During her surgery and convalescence high-dose steroids raised her total and absolute neutrophil count. Since her prednisone was tapered to an average of 20 mg every day she has had persistent agranulocytosis and is generally stable. During her recent course she had clinical active synovitis, despite corticosteroids.

RESULTS OF SPECIAL STUDIES
Bone marrow showed a normal megakaryocyte line, increased small lymphocytes, and decreased erythroid elements with normal maturation. The myeloid series was decreased in number with essentially no maturation beyond the myelocyte stage. A serum muramidase test showed a corrected value of 29·8 μg/ml with an index of 28·9. No cytotoxic antibodies were detectable in the patient's serum by means of buffy coat peripheral white cells as targets in a complement dependent microcytotoxicity assay. No serum marrow blocking factors inhibitory for granulocyte precursors were demonstrable by clonogenic assays for human marrow colony forming cells. The proportion of thymus-derived peripheral blood (T) lymphocytes detected by sheep red cell rosette formation and specific goat antihuman thymocytic antiserum was slightly increased over the normal controls (90% versus 70%). In-vitro T cell proliferative responses to phytohaemagglutinin and a one-way mixed lymphocyte reaction were normal.

Table 2 In-vitro studies on the sensitisation of peripheral blood lymphocytes (PBL) to autologous bone marrow (BM) cells in a patient with Felty's syndrome during absolute granulocytopenia and during remission following administration of corticosteroids

<table>
<thead>
<tr>
<th></th>
<th>Responding cells</th>
<th>Stimulating cells</th>
<th>(^{3}H) thymidine uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 × 10⁴ cells</td>
<td>5 × 10⁴ cells</td>
<td></td>
</tr>
<tr>
<td>During granulocytopenia</td>
<td>Patient's PBL</td>
<td>Patient's PBL</td>
<td>2530±110</td>
</tr>
<tr>
<td>Patient's BM</td>
<td></td>
<td>15 017±267</td>
<td></td>
</tr>
<tr>
<td>During remission after corticosteroid treatment</td>
<td>Patient's PBL</td>
<td>Patient's PBL</td>
<td>1269±108</td>
</tr>
<tr>
<td>Patient's BM</td>
<td></td>
<td>1436±124</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Normal's PBL</td>
<td>Normal's PBL</td>
<td>1461±102</td>
</tr>
<tr>
<td></td>
<td>Normal's BM</td>
<td></td>
<td>2005±142</td>
</tr>
</tbody>
</table>

Responding Ficoll Hypaque purified lymphocytes (5 × 10⁴) were cultured with stimulating blood lymphocytes or marrow derived nucleated cells (5 × 10⁴) in 0·2 ml U shaped microculture plates using RPMI 1640 medium enriched with 10% human AB serum, fresh glutamine (2mM), penicillin (100 U/ml), and streptomycin (100 μg/ml). Stimulating cells were inactivated by a single exposure to 6000 rads from a caesium-137 source. Cells were incubated at 37°C with 5% CO₂-air mixture in a humidified incubator for 6 days, and then pulsed for 16 hours with 1 μCi of \(^{3}H\) thymidine per culture. Cells were subsequently collected on paper filters using multiple sample harvester and counted in a Beckman liquid scintillation counter.

Table 2 summarises the in-vitro evidence for auto-sensitisation of the patient's peripheral blood lymphocytes (PBL) to her own marrow cells (P < 0·001).

Discussion

Cytopenic states involving different peripheral blood elements may be seen in a variety of autoimmune disorders. Target specific autoantibodies involving red blood cells, platelets, and lymphocytes are recognised in a spectrum of diseases including autoimmune haemolytic disorders, idiopathic thrombocytopenic purpura, and systemic lupus erythematosus. Recently reliable methods for assaying antineutrophil antibodies have led to characterisation of various forms of autoimmune neutropenic syndromes.Detection of autoimmune mechanisms operative in the development of the cytopenic state occasionally leads to the successful application of cytotoxic immuno-suppressive agents.

In-vitro detection of cell mediated autoimmune phenomena in response to the target cells has previously been reported in association with Coombs-positive idiopathic autoimmune haemolytic anaemia and in aplastic anaemia. This case report gives in-vitro evidence of autosensitisation of peripheral blood lymphocytes to bone marrow cells in 1 patient with severe rheumatoid arthritis and agranulocytopenia. Although the patient probably had recurrence of Felty's syndrome, the possibility that the white blood cell disorder was due to a delayed reaction to sulphonamide therapy cannot be excluded. Whether this is a common mechanism of neutropenia in Felty's syndrome, or represents another possible mechanism, requires additional studies. A recent report suggests cell-mediated inhibition of granulocyte precursors in Felty's syndrome. The existing literature suggests that there may be a number of different mechanisms which produce neutropenia in Felty's syndrome. Understanding which mechanism is operative in a given individual might justify the use of immuno-suppression in the face of potentially hazardous infections. Nevertheless, in this patient immuno-suppression with corticosteroid therapy raised the absolute granulocyte count but did not appear significantly to change the frequency or the type of infections.

Previous studies of neutrophil kinetics in Felty's syndrome present no uniform picture. The half-life of peripheral neutrophils may be shortened with low or normal production of neutrophils; or the half-life may be normal with a kinetic picture suggesting a shift neutropenia. In the subgroup of Felty's
syndrome with shortened half-life of peripheral neutrophils it is possible that increased destruction may result from a number of mechanisms including autoantibody, immune complexes, or cellular.

Another interesting feature of this case is the persistence of synovitis during periods of agranulocytosis. This indicates that neutrophils are not essential for maintaining the inflammatory process in rheumatoid arthritis. Indeed, lymphocyte depleting manoeuvres such as thoracic duct drainage produce transient reduction of disease activity suggesting that lymphocytes play a major role in the pathogenesis of rheumatoid synovitis.\textsuperscript{21} 22

We are indebted to Dr James F. Fries for his permission to study the patient who is the subject of this report.

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References


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