Alpha-fetoprotein production by a malignant mixed müllerian tumour of the uterus

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An unusual association of Felty syndrome and TCRγδ lymphocytosis

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Abstract
Felty syndrome, comprised of neutropenia, rheumatoid arthritis and splenomegaly, occurs in approximately 1% of patients with rheumatoid arthritis. Up to one third of these patients have an increased number of large granular lymphocytes. The usual immunophenotype of these cells is CD3+, CD8+, CD57+, T cell receptor (TCR) γβ. A patient with Felty syndrome and large granular lymphocytosis, who had an unusual immunophenotype CD3+, CD4−, CD8−, TCRγδ, is described. Her neutropenia responded to treatment with granulocyte colony stimulating factor (G-CSF), which was given in order to raise her neutrophil count prior to bilateral knee replacement surgery. Thus, Felty syndrome with large granular lymphocytosis is a heterogeneous condition, one in which TCRγδ large granular lymphocytosis may be found, and also shows a response to treatment with G-CSF.

Keywords: Felty syndrome, large granular lymphocytosis, TCRγδ.

Felty syndrome is classically defined by the presence of rheumatoid arthritis, neutropenia and splenomegaly. It is reported to occur in about 1% of patients with rheumatoid arthritis, and is known to have close immunogenetic associations with certain HLA alleles.1 The extent of the splenomegaly seems to be variable, and indeed may not be present in an otherwise clinically similar subgroup of patients with neutropenia and rheumatoid arthritis.2 No single cause of neutropenia is known, but it may reflect mechanisms involving disordered granulopoiesis and peripheral consumption. Felty syndrome is also found in association with a form of T cell lymphocytosis, in which the expanded lymphocytes have a large granular morphology.3 These proliferations of large granular lymphocytes (LGL) may be found in up to one third of patients with Felty syndrome, and may be clonal in nature, representing a form of LGL leukaemia.4 The usual immunophenotype of these cells is CD8+, CD57+, T cell receptor (TCR) γβ. The nature of the role of these expansions, whether occult or overt, in the pathophysiology of Felty syndrome (and rheumatoid arthritis in general) is not clear.

Some patients with Felty syndrome and neutropenia may be troubled by recurrent infections, which may further add to the disability imposed by active or longstanding arthritis. Furthermore, the risk of infection due to associated neutropenia may be a relative contraindication to elective orthopaedic surgery indicated in these groups of patients. Treatment of patients with Felty syndrome and noticeable neutropenia in these situations remains unclear and unsatisfactory in many cases, although recent interest has focused on the use of granulocyte colony stimulating factor (G-CSF).5

Case report
This patient, a woman, was first diagnosed as having seropositive rheumatoid arthritis in 1961 when aged 40 years. The arthritis initially affected her small joints but gradually became more severe such that by April 1993, fixed flexion deformities were present in both knee joints. She was also found to have splenomegaly at this time. A full blood count revealed a haemoglobin of 1·1 g/l, with a total white cell count of 3·6 x 10⁹/l, and a significant neutropenia of 0·8 x 10⁹/l, consistent with a diagnosis of Felty syndrome. A small ulcer by the right ankle was also noted at this time. The neutropenia remained at this level, and gen-

Figure 1. Neutrophil counts (×10^9/l) during treatment with G-CSF (300 mg, three times weekly) plotted against time in days. The time of the first knee replacement operation is indicated by the letter A.

Generally below 0.8 × 10^9/l, but was not associated with any recurrent or severe infections. At this stage, discussion was initiated about the feasibility of bilateral knee replacements. In view of the risks associated with the neutropenia, we decided to carry out both operations during a trial of G-CSF therapy. Figure 1 shows how the neutrophil count increased significantly on treatment with G-CSF, during which time the left knee was replaced without complication. The small skin ulcer on the ankle was also found to heal after treatment with G-CSF. Three months later, the second knee was replaced, again without complication following a course of treatment with G-CSF.

A moderate lymphocytosis was noted both before and after surgery. Morphological examination of blood films revealed the presence of increased numbers of LGLs (such that they represented over 50% of the total lymphocyte count, which reached a peak of 6.5 × 10^9/l). On immunophenotyping of peripheral blood lymphoid cells using flow cytometry, we found that most of the expanded population of cells were positive for CD3, CD57, and TCRγδ. (TCRγδ cells usually represent less than 1% of the normal peripheral blood lymphocytes.) The remaining, smaller proportion of lymphocytes were positive for CD4 or CD8 (and TCRζ). Immunophenotyping was repeated on three occasions, over 12 months, giving similar results each time (table 1).

Since both operations, the patient continues to remain well generally, apart from her longstanding arthritis, with no evidence of hepatomegaly or lymphadenopathy; a mild anaemia, neutropenia and lymphocytosis persist.

Discussion
Large granular lymphocytes in the peripheral blood are divided into two main types: those which lack TCRs (natural killer cells), and those which are a subset of CD3+, CD8+ T cells and express rearranged surface TCRs, predominantly of the TCRαβ class. Both cell types, which can be distinguished conventionally by immunophenotyping, together comprise approximately 15–20% of normal blood lymphocytes. However, their physiological roles in vivo have not been defined clearly. There has been considerable discussion in the literature about the nature and significance of persistent clonal and non-clonal expansions of these two groups of cells. A recent review of clonal T-LGL proliferations confirmed that rheumatoid arthritis was the most common associated clinical condition, and that neutropenia was the most frequent haematological finding. These groups of patients may indeed be similar to those with Felty syndrome and LGL expansions, as in the patient described here. It has been suggested that there is a generalised expansion of CD8+ T cells in these patients as part of the response to the underlying pathophysiology of arthritis, from which clonal proliferations may arise.

Other mechanisms may then be the underlying cause of T cell mediated suppression of granulopoiesis, as seen in these patients.

We have reported an unusual case in which lymphocytosis was associated with an expansion of LGLs, with the following immunophenotype: CD3+, CD4−, CD8−, TCRγδ. Similar immunophenotypic findings were documented over 12 months, illustrating the persistent nature of the TCRγδ proliferation, and the likely clonal nature of the expansion. TCRγδ T cell neoplasms are recognised, but have been very infrequently reported unlike TCRαβ proliferations. The nature of the immunological role of TCRγδ bearing T cells remains largely unclear, although there have been some recent interesting advances in our understanding of the ligands recognised by these γδ T cells, which are among the earliest TCR bearing cells to appear during development. In our patient the expansion of LGLs expressing TCRγδ was also associated with neutropenia and splenomegaly, fulfilling the traditional criteria for a diagnosis of Felty syndrome. Further longitudinal studies may establish whether the clonal expansions, bearing TCRγδ in this case, evolved from initial polyclonal lymphocyte responses.

Despite a neutropenia of less than 0.5 × 10^9/l in this patient, recurrent or severe infections were not a common problem. However, the neutropenia was felt to be a relative contraindication to bilateral knee replacement. Therefore, we decided to treat the patient with G-CSF before and after surgery in an attempt to raise her neutrophil count. G-CSF has been used therapeutically in patients after trans-
An unusual association of Felty syndrome and TCR;δ lymphocytosis

plantation and chemotherapy, as well as with primary and secondary neutropenias. As shown in figure 1 for the first operation, the courses of G-CSF were sufficient to raise the neutrophil count above 2 x 10^9/l, enabling both knee joints to be replaced without peri-operative infective complication. The good response to G-CSF in this patient adds to the small numbers of reports found in the literature describing similar favourable responses to treatment of neutropenia. Although the neutropenic conditions associated with either Felty syndrome or expansions of LGL are heterogeneous with respect to severity and cause, it does seem that G-CSF may have a useful role to play in the management of some patients, although longer term studies will be needed to address the issue of possible side effects.

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