Case report

Felty's syndrome associated with high levels of IgA rheumatoid factor

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SUMMARY A 64-year-old woman with rheumatoid arthritis developed Felty's syndrome. Her serum contained large amounts of IgA rheumatoid factor (RF) but insignificant levels of IgM-RF and IgG-RF. It is postulated that the high levels of IgA-RF may have contributed to the neutropenia.

The association of chronic (rheumatoid) arthritis, splenomegaly, and leukopenia was first described by Felty in 1924.¹ Most patients with Felty's syndrome have high levels of IgM rheumatoid factor (RF) in their sera,² a condition which, although not part of the syndrome, has been implicated as one of the causes of the leukopenia.³ We report here the case of a patient with Felty's syndrome whose serum contained large amounts of IgA-RF but insignificant levels of IgM-RF and IgG-RF. We postulate that the high levels of IgA-RF may have contributed to the neutropenia in this case.

Case report

A 64-year-old Caucasian woman presented to the rheumatology clinic with a 6-month history of pain in the left shoulder. Subsequently she developed synovitis in the knees, wrists, and hands. She had marked morning stiffness lasting for one hour and complained of anorexia and 2 kg loss of weight over this period. Investigations revealed a haemoglobin (Hb) of 13.0 g/dl a white cell count (WCC) of $5.6 \times 10^9/l$, and an erythrocyte sedimentation rate (ESR) of 57 mm in the first hour. Protein electrophoretic strip showed a raised gamma globulin. Immunoglobulin levels were: IgG 16.6 g/l (6-16), IgA 1.35 g/l (1.2-4), IgM 1.15 g/l (0.5-2). X-rays of the hands and feet were normal. She was managed initially with various anti-inflammatory agents, but as the response

to these was poor she was started on prednisolone 5 mg at night. After the introduction of prednisolone there was a marked improvement in function. The ESR returned to normal and all drugs apart from prednisolone were stopped.

Two years after diagnosis a routine blood count showed the following: Hb 13.2 g/dl leucocytes $1.9 \times 10^9/l$, with neutrophils $1 \times 10^9/l$, lymphocytes $1.5 \times 10^9/l$ and monocytes $2 \times 10^9/l$, and a platelet count of $194 \times 10^9/l$. Examination of the patient at this time revealed splenomegaly of 2 cm below the left costal margin. Apart from classical joint changes of rheumatoid arthritis (RA) there were no other abnormal signs. A bone marrow examination showed active, normoblastic erythropoiesis, active myelopoiesis with a marked shift to the left, and normal megakaryocytes. Studies of the peripheral blood lymphocytes showed a normal distribution of T suppressor and T helper phenotypes. Bone marrow studies showed that 30% of the nucleated cells were T lymphocytes with equal numbers of T suppressor (OKT8+) and T helper (OKT4+) phenotypes. We have a detailed record of the level of serum RFs measured by enzyme-linked immunosorbent assays (ELISA) throughout this patient's illness.

RF ASSAYS AND PROFILES

Serum RF levels of IgM, IgG, and IgA isotypes were measured by an indirect ELISA technique developed in our laboratory. Briefly, flat-well microplates were coated with rabbit IgG, saturated with 1% bovine serum albumin (BSA) in PBS-Tween, and incubated with serum dilutions. The samples tested

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for IgG-RF were digested with pepsin as described previously.⁴

The F(ab')₂ fraction of rabbit antihuman IgA (raised and prepared in our laboratory), goat antihuman IgG (TAGO Inc) and the F(ab')₂ of goat antimouse IgG (TAGO Inc) were conjugated to alkaline phosphatase by glutaraldehyde.⁵ Following serum incubations, microplates were reacted with the antihuman IgM (for IgM-RF) and antihuman IgA (for IgA-RF) conjugates. In the IgG-RF assay, the plates were first incubated with a monoclonal mouse antihuman Fab-gamma (Miles Laboratories), followed by the goat antimouse conjugate.

Finally, the plates were reacted with *p*-nitrophenyl phosphate (Sigma, London) and read in a Titertek Multiskan. The results were expressed as units/ml by referral to dilution curves for internal standard sera. The internal standards were sera from patients with classical RA found to react exceptionally strongly in the RF tests. The internal IgM-RF standard was calibrated against the international RF standard and contained 875 U/ml. Since there are no international standards for IgG-RF or IgA-RF, the other internal standards were each assigned a value of 1000 U/ml. The upper limits of normal for IgM-RF, IgA-RF,

and IgG-RF, determined on sera from 102 healthy individuals, were 20 U/ml, 10 U/ml, and 80 U/ml respectively.

Fig. 1 shows the serum RF profiles of the patient described. The 11 samples collected during 1980-2 were stored at -80°C and assayed simultaneously. The IgA-RF levels rose above the normal limits during the latter half of 1981 and still remain significantly elevated, but the IgM-RF and the IgG-RF remained normal throughout. Conventional test for IgM-RF (latex and rheumatoid arthritis haemagglutination assay (RAHA)) also remained negative throughout this patients illness.

Discussion

It is not clear why certain patients with RA develop Felty's syndrome. The cause of the leucopenia is unknown, by a number of theories have been proposed: excessive margination of neutrophils,⁶ phagocytosis by the spleen,⁷ decreased marrow production due to a splenic humoral effect,⁸ autoimmune neutrophil destruction,^{9, 10} and simple splenic pooling.¹¹ Although some workers have tried to attribute the neutropenia to a single cause,⁶ it seems more likely that several different mechanisms may be involved. Neutrophils from patients with Felty's syndrome have been shown to be coated with IgG,^{12, 13} and an increased incidence of this syndrome has been reported in RA patients with high levels of IgM-RF.³ It therefore seems reasonable to postulate that, at least in some patients, the neutrophil destruction may be mediated by an RF-amplified IgG autoantibody activity. However, Felty's syndrome has been described in patients who did not have raised levels of IgM-RF, and in these patients there could have been selective increases in the IgG or IgA-RF isotypes. We postulate that these high levels of IgA-RF may have contributed to the neutropenia demonstrated in this patient.

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Fig. 1 The serum profiles of IgM RF, IgG RF, and IgA RF as measured by ELISA during 1980-2. Upper limits of normal: IgM RF, 20 U/ml; IgG RF, 80 U/ml; IgA RF, 10 U/ml.

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