Structured approach to the investigation of anaemia in patients with rheumatoid arthritis

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Abstract

A group of 28 patients with rheumatoid arthritis who were severely anaemic were investigated for iron deficiency. On the basis of bone marrow studies, the patients were divided into two groups, those with and those without signs of stainable iron in the marrow. This grouping did not distinguish between the severity of their rheumatoid arthritis measured by clinical parameters.

Measurement of the red cell count and biochemical parameters in the peripheral blood showed a statistical difference in red cell size, haemoglobin content, and iron binding capacity between the two groups. The statistical variation of these parameters, however, did not allow these measurements to predict bone marrow iron deficiency in any subject. Investigation of the upper gastrointestinal tract by endoscopy showed that acute macroscopic lesions were infrequently associated with anaemia.

It was concluded that anaemia in association with rheumatoid arthritis may mimic iron deficiency anaemia, and that simple investigations of the peripheral blood do not accurately show the iron status of the reticuloendothelial system in the presence of a chronic inflammatory disease. For the investigation of severe anaemia in rheumatoid arthritis, bone marrow assessment of iron status should be performed as the initial investigation. In addition, iron deficient patients require investigation of the lower and the upper gastrointestinal tract.

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Anaemia is a common extra-articular manifestation of rheumatoid arthritis. It is often mild to moderate in severity, is normochromic and normocytic, and correlates with disease activity. Investigation of the cause may be made by the measurement of biochemical indices of iron status in samples of peripheral blood. These parameters are confused in rheumatoid arthritis, however, because the acute phase response alters indices relating to anaemia. Blood loss from the gastrointestinal tract is often suspected in rheumatoid arthritis. This may be caused by drugs or the disease process, but findings in the upper gastrointestinal tract do not always explain the anaemia.[1] The investigation of anaemia in such a confused setting requires a logical approach if the anaemia of iron deficiency is to be differentiated from other causes, particularly that caused by a chronic inflammatory disease.

In a group of 28 patients with rheumatoid arthritis, all of whom were anaemic, we determined the bone marrow iron status for subsequent comparison with measurements of red cell and biochemical parameters of the peripheral blood. On the basis that iron absorption by the gastrointestinal tract is normally inversely proportional to body iron stores, a low dose iron absorption test was performed.[2 3] In addition, an upper gastrointestinal endoscopic examination was performed in those patients found to have an iron deficient bone marrow.

This study examines the clinical usefulness of these methods of assessing iron status in patients with rheumatoid arthritis using bone marrow iron as the standard test for iron deficiency.

Patients and methods

PATIENTS

Twenty eight patients with definite or classical rheumatoid arthritis were investigated. Patients were considered for the study when their haemoglobin concentration was 90 g/l or less, or when there was a decrease in the haemoglobin content of 10 g/l per month without obvious cause. Patients were excluded if they had received iron treatment within one month, had a macrocytosis due to treatment with cytotoxic drugs, or had a disease that may have contributed to the anaemia, although one patient with clinically inactive ulcerative colitis was included in the study. All patients had normal serum B-12, red cell folate, thyroid stimulating hormone, and renal function. The history of the patient was considered and physical examination was performed with an emphasis on possible sites of blood loss.

IRON STATUS

Haemoglobin concentration, mean red cell volume, mean red cell haemoglobin, platelet count, plasma viscosity, serum iron, serum iron binding capacity, and serum ferritin were measured using routine laboratory methods. Bone marrow iron was assessed using Perls's Prussian blue stain. An absence of stainable iron was interpreted as indicating iron deficiency. Iron, if present, was not graded.

LOW DOSE IRON ABSORPTION TEST

Following an overnight fast, 10 mg of elemental iron (a paediatric elixir of iron(II) sulphate, 50 mg per 10 ml) was given by mouth. Serum iron was measured at time zero and after one hour, and the percentage increase was calculated. Care was taken to ensure that the iron solution

was fresh and that patients receiving D-penicillamine did not receive the drug for at least 12 hours before the test.

RESPONSE TO IRON GIVEN BY MOUTH

Iron deficient patients were treated with iron given by mouth (equivalent to 105 mg elemental iron daily) for three months. The initial and final haemoglobin concentrations were compared and an increase of 20% was considered significant.

INVESTIGATION OF IRON DEFICIENCY

Patients with an iron deficient bone marrow were questioned and investigated for a site of possible blood loss. Investigations were pursued until a lesion considered to be responsible was discovered. Upper gastrointestinal endoscopy was performed and a jejunal biopsy sample was taken before colonoscopy.

ASSESSMENT OF DISEASE ACTIVITY

The activity of the rheumatoid disease was assessed using a visual analogue scale for early morning stiffness and joint pain, the Ritchie index, a health assessment questionnaire score, platelet count, and plasma viscosity. A 20% change in the same direction in two or more parameters was taken to indicate a change in disease activity over the three month follow up period. All parameters were measured by one observer (AD).

STATISTICAL METHODS

Significance was assessed using Student's t test for parametric data, the Mann-Whitney U test for non-parametric data, and the product moment correlation coefficient between indices.

Results

Of the 28 patients studied, 14 patients had iron present in the bone marrow and 14 patients were iron deficient. The two groups were similar with respect to age, sex, presence of rheumatoid factor, and disease duration. The iron deficient patients tended towards less active disease, although statistical significance was obtained only on the visual analogue scale for early morning stiffness and plasma viscosity (table).

Drug treatment was similar in the two groups. All patients were receiving a non-steroidal anti-inflammatory drug (NSAID) and equal numbers in each group were receiving slow acting disease modifying drugs (seven), steroids (two), and cytotoxic drugs (four in the iron deficient group; three in the group with iron present). One patient in each group was receiving long term treatment for the replacement of vitamin B-12.

HAEMATOLOGICAL AND BIOCHEMICAL PARAMETERS

Haemoglobin concentrations were similar in the two groups with no significant difference between the median value for the iron deficient patients (86 g/l, range 58–94 g/l) and the patients without iron deficiency (86 g/l, range 71–93 g/l). Although the median values of mean red cell volume and mean red cell haemoglobin were lower in the iron deficient patients (69 fl, range 60·6–83·9 fl and 21·8 pg, range 18·6–28·9 pg v 76 fl, range 63·5–88·3 and 26·5 pg, range 20·8–32·1 pg) than in the group without iron deficiency ($p<0·05$ for both indices), significant overlap of values occurred (fig).

The serum iron concentration was similar in the two groups (median 5 μmol/l, range 1–22 μmol/l in the iron deficiency group compared with 3 μmol/l, range 2–7 μmol/l in the group without iron deficiency). The serum iron binding capacity was higher in the group with iron deficiency (median 63 μmol/l, range 47–88 μmol/l) compared with the iron replete group (median 44 μmol/l, range 27–53 μmol/l, $p<0·001$). Serum ferritin was lower in the iron deficient group (median 15 ng/ml, range 5–65 ng/ml) compared with the iron replete group (median 85 ng/ml range 17–270 ng/ml, $p<0·001$) (fig).

The low dose iron absorption test produced a greater percentage increase in serum iron in the iron deficient patients (median 334%, range 0–1600% compared with median 19%, range 0–32%) than in the patients without iron deficiency ($p<0·01$; fig).

For all these parameters many values fell within the laboratory reference range and approximately one third of the values in each patient group overlapped.

Comparison of demographic data and measures of disease activity between patients with and without iron in the bone marrow. Unless stated, values are medians (range)

	Iron absent	*Iron present*	*p Value**
Women:men	11:3	12:2	
Seropositive	12	10	
Mean age (range) (years)	66 (40–84)	62 (38–87)	NS**
Disease duration (years)	15 (1·5–40)	10 (3–33)	NS
Duration of early morning stiffness (minutes)	22·5 (0–120)	120 (0–300)	NS
Visual analogue scale			
Early morning stiffness	27 (0–70)	58 (0–86)	<0·05
Joint pain	32 (0–86)	57 (0–98)	NS
Ritchie index	14 (0–40)	21 (2–36)	NS
Health assessment questionnaire score	2·38 (0·5–3·0)	2·25 (0·5–3·0)	NS
Platelet count ($\times 10^9$/l)	479 (239–810)	518 (305–988)	NS
Plasma viscosity (cP)	1·81 (1·62–2·32)	2·03 (1·68–2·96)	<0·05

*All analyses by Mann-Whitney U test, except **, which used Student's t test.

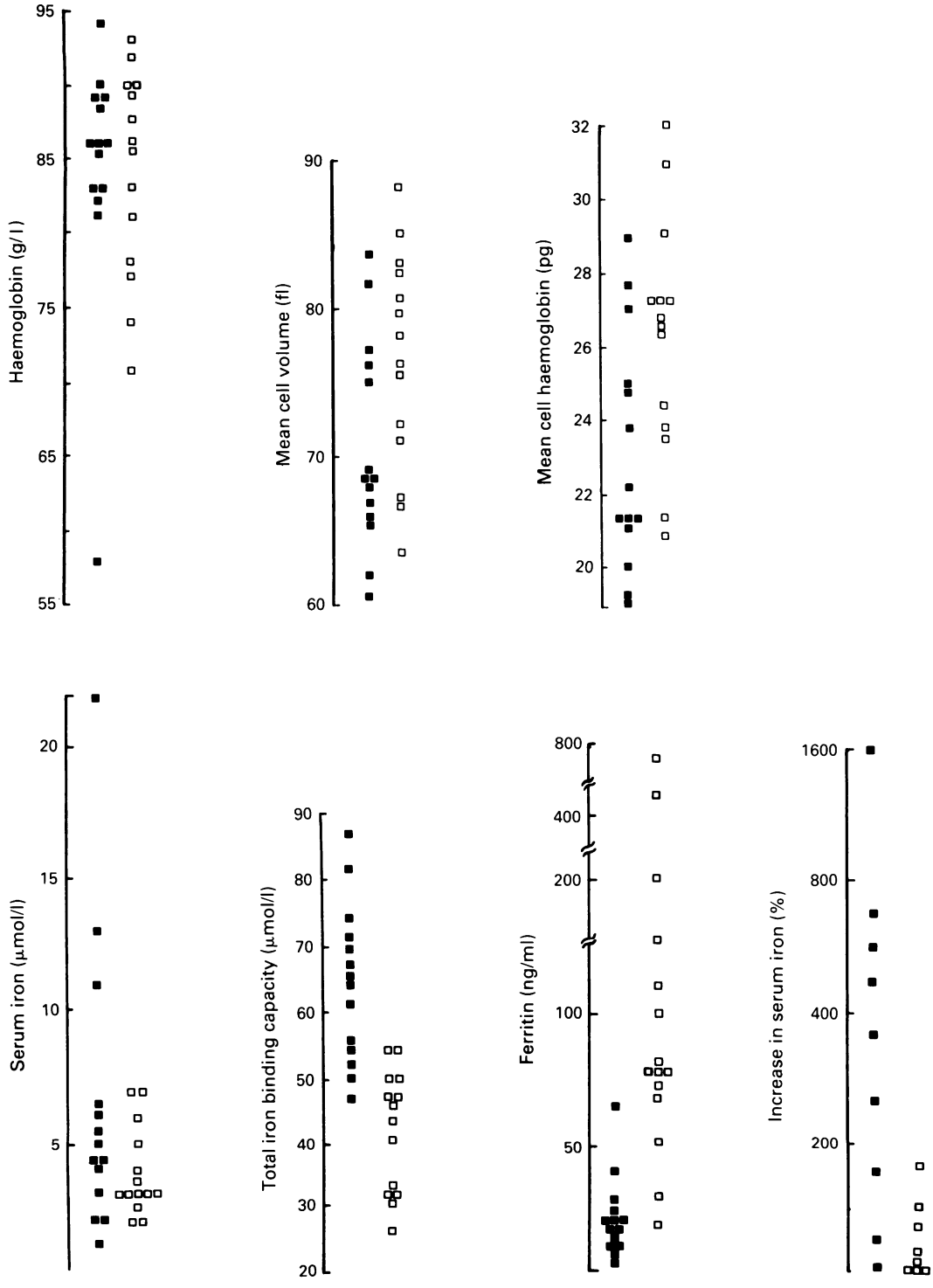
GASTROINTESTINAL INVESTIGATIONS

Thirteen of the 14 patients with iron deficient bone marrows were investigated for a source of gastrointestinal blood loss. One patient refused investigation. An upper gastrointestinal endoscopy and jejunal biopsy were performed on 11 patients. All jejunal biopsy samples were normal. One patient had normal results on a barium meal study and one patient had active ulcerative colitis on colonoscopy. Eight patients had a normal upper gastrointestinal tract and three were abnormal (one severe lower oesophagitis, one haemorrhagic duodenal ulcer, one small prepyloric ulcer). Colonoscopy was not performed on any patient. One patient with a

normal upper gastrointestinal tract refused further investigation and one patient was considered too frail for colonoscopy. Colonic lesions were found in four patients (one angiodysplasia, one vascular malformation, one diverticular disease, one ulcerative colitis).

RESPONSE TO IRON GIVEN BY MOUTH

Twelve of the 14 iron deficient patients received iron replacement treatment for three months. One patient was intolerant of iron given by mouth and one patient received a blood transfusion because of symptomatic anaemia. Seven patients responded with a greater than 20% increase in their initial haemoglobin concentration. Disease activity altered over the three month period in nine patients. Seven patients had an improvement in their disease activity (defined as a 20% or greater change in two or more indices of disease activity). Two patients deteriorated and two remained the same. Of the seven patients whose haemoglobin content responded to iron given by mouth, four had an improvement in their disease activity, one deteriorated, one remained the same, and one



Comparison of haematological indices in 28 patients with rheumatoid arthritis. The population was differentiated into two groups; those with iron present in samples of bone marrow (□) and those who were iron deficient in this respect (■). Local laboratory ranges were: serum iron, 13–32 μmol/l; total iron binding capacity, 45–70 μmol/l; mean red cell volume, 75–95 fl; ferritin, 10–250 ng/ml; mean red cell haemoglobin, 27–32 pg.

patient's disease activity status was unknown at three months.

Discussion

The significance and differentiation between the anaemia of chronic disease and iron deficiency anaemia in patients with rheumatoid arthritis has recently been reviewed.[3] The anaemia of chronic disease states correlates with the progression of bony erosions[4] and its early presence is associated with a poor prognosis.[5 6] In the long term, deaths related to rheumatoid disease are more common in patients who are anaemic at the time of diagnosis.[6a] Iron deficiency anaemia requires explanation, but investigation may be time consuming, uncomfortable, and potentially hazardous. In patients with inflammatory diseases, the diagnosis of iron deficiency is complicated by the influence of the acute phase response, particularly on serum indices of iron status. For example, the prediction of bone marrow iron stores from measurements of serum ferritin concentrations is unreliable.[7-9] In addition, our data show that indices such as the serum iron and serum binding capacity also have a poor ability to predict iron status in this clinical setting.

This study shows that the anaemia of chronic disease may be severe and may mimic iron deficiency with microcytic, hypochromic red cells, supporting a similar observation made in a small number of children with juvenile chronic arthritis.[10] It has been suggested that a serum ferritin concentration of 55 ng/ml is an appropriate lower limit of normality in inflammatory diseases,[11] and that concentrations of less than 60 ng/ml suggest iron deficiency with a sensitivity of 86% and a specificity of 88%.[12] Reliance on these criteria would have led to an incorrect diagnosis in one third of our patients whose anaemia was not associated with iron deficiency, resulting in unnecessary investigation of the gastrointestinal tract. In addition, the severity of the disease activity may not have been appreciated in these patients, resulting in less than optimum treatment.

The overlap of values shown by this study emphasises the difficulty in assessing iron status in rheumatoid arthritis. The response of anaemia to treatment by mouth can be predicted in 83% of patients where the serum ferritin concentration is less than 60 ng/ml.[12] Iron can, however, induce changes resembling the synovial response to antigens[13] and can exacerbate synovitis.[14] Thus inappropriate iron treatment in patients with a synovitis should be avoided. The low dose iron absorption test did not differentiate between the two groups.[2]

The ability of the haemoglobin concentration to increase over a three month period after treatment by mouth with iron has been used as an indicator of iron deficiency in rheumatoid arthritis.[9] Our data show that patients with iron deficiency have a variable ability to respond to iron given by mouth. No patient studied could be shown to have blood loss, and all had normal jejunal biopsy samples, thus excluding gluten enteropathy as a cause of iron deficiency. Intestinal absorption of iron in patients with rheumatoid arthritis in one study has been reported as normal,[15] but in another group of patients treated in hospital for persisting rheumatoid activity, iron absorption was decreased, regardless of initial bone marrow iron stores.[16] Most of our patients whose anaemia responded to iron given by mouth also had an improvement in their disease activity over the three month period. This major confounding factor limits the value of a trial of iron given by mouth to differentiate between the causes of anaemia in rheumatoid arthritis.

The gastrointestinal investigations performed on the iron deficient patients in this study indicated that upper gastrointestinal lesions, attributable to NSAIDs, are infrequently associated with iron deficiency. Of the upper gastrointestinal lesions shown, only one (a small prepyloric ulcer) was attributable to ingestion of NSAIDs. Colonic lesions were common and the need to perform colonoscopy was emphasised by the nature of the lesions found.

As the anaemia of chronic disease can mimic iron deficiency, with important implications for patients, we consider that the bone marrow evaluation of iron stores plays a central part in the investigation of severe anaemia in patients with rheumatoid arthritis. Patients with documented iron deficiency deserve careful gastrointestinal investigation, often including colonoscopy. Patients without iron deficiency needed careful assessment of their disease activity. The unjustified use of iron treatment should be avoided.

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