Ulcerative colitis complicated by a leucoerythroblastic anaemia

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Summary

Two cases of biopsy-proven ulcerative colitis are described, and both developed a leucoerythroblastic anaemia during the course of the acute illness. Despite intensive investigation for the presence of bone marrow infiltration, no neoplasm was demonstrated. The leucoerythroblastic anaemia remitted in each case on medical treatment of the ulcerative colitis. The possible mechanisms underlying the development of reversible leucoerythroblastic anaemia are discussed.

Case reports

A 58-year-old woman gave a six-month history of progressive anaemia, lethargy, increased stool frequency with watery diarrhoea and for 6 weeks had noticed rectal blood loss on defaecation. There was no weight loss, no other systematic symptoms and no family history of inflammatory bowel disease.

On examination she was markedly pale with mild bilateral pitting ankle oedema. Abdominal examination was unremarkable but sigmoidoscopy revealed a friable, granular mucosa with contact bleeding and a moderate amount of blood in the bowel lumen. Rectal biopsy showed changes of acute ulcerative colitis.

A blood count on presentation revealed a leucoerythroblastic anaemia—(haemoglobin (Hb) 7.6 g/dl, mean corpuscular volume (MCV) 102 fl, white cell count (WCC) 4.6×10^9 /litre, neutrophils 46%, lymphocytes 38%, monocytes 12%, eosinophils 4%, promyelocytes 1%, myeloblasts 1% with occasional nucleated red cells). Platelet count 320×10^9 /litre. The leucocyte alkaline phosphatase score was normal as were the serum folic acid and vitamin B12 levels. The bone marrow aspirate was hypercellular but showed active normoblastic erythropoiesis. Granulopoiesis was also active but maturing normally. There were normal iron stores. A trephine bone marrow biopsy confirmed the hypercellularity of the marrow with reduced fat spaces. There was no evidence of infiltration by adventitial tissue. Liver function tests

showed an elevated serum bilirubin at 45 μ mol/litre with normal transaminases. A liver biopsy showed extra medullary haemopoiesis within a normal hepatic lobular pattern. The elevated bilirubin level was thought to have been due to the several blood transfusions this patient had already required due to the chronic persistent rectal blood loss. There had been no single acute loss at any time and there was no evidence of active haemolysis, urobilinogen and haptoglobin levels being normal. Orosomucoid protein levels were elevated at 1.45 g/litre (normal < 1.2 g/litre). Immunoglobulin levels C3 and C4 were all normal.

Barium meal and follow-through showed a normal small bowel and terminal ileum. Barium enema showed the changes of ulcerative colitis affecting the whole colon and evidence of rectal disease. Additionally there was diverticulosis of the sigmoid colon. After initial transfusion she was treated with hydrocortisone acetate (Colifoam) enemas, sulphasalazine and parenteral steroids. She responded well and following active treatment of her inflammatory bowel disease required no further transfusions. The appearances of leucoerythroblastosis cleared from her blood film and have not returned. She is at present well with a haemoglobin of 13.8 g/dl, WCC 5.3×10^9 /litre with a normal differential, sulphasalazine 1 g four times a day.

Case 2

A 52-year-old woman was initially investigated in 1977 with symptoms of diarrhoea and rectal blood loss. Rectal biopsy showed a non-specific proctitis and barium enema confirmed the presence of distal colitis. She was treated with Colifoam enemas and oral sulphasalazine 1 g three times daily.

In 1978 she was admitted with a widespread maculopapular rash, pyrexia and peripheral lymphadenopathy. A blood count revealed a leucocytosis of 20.0×10^9 /litre with 74% neutrophils. Liver function tests showed elevated serum transaminases and alkaline phosphatase. Lymph node biopsy was non-

diagnostic. Liver biopsy showed changes compatible with resolving acute hepatitis. Neither hepatitis B antigen or antibody was demonstrated; other viral studies and the Monospot test were negative. She recovered completely and was discharged. No leucoerythroblastic picture developed during this illness.

In 1979 she was admitted with an exacerbation of her colitis, rectal biopsy again showing changes of active ulcerative colitis. She developed toxic dilatation of the transverse colon and splenic flexure but this settled with conservative management. A blood count at this time showed a neutrophilia of $9.3 \times 10^9/\text{litre}$. No immature forms were seen. She was maintained as an out-patient on prednisolone and sodium cromoglycate.

She was re-admitted in March, 1980 with a further exacerbation of her colitis. There was no weight loss and no systemic symptoms. Investigations at this time revealed Hb 10.7 g/dl, WCC $6.9 \times 10^9/\text{litre}$, neutrophils 55%, lymphocytes 24%, monocytes 10%, eosinophils 5%, myelocytes 5%, myeloblasts 1% and nucleated red cells were seen. Platelet count $66 \times 10^9/\text{litre}$. A bone marrow aspirate showed markedly increased cellularity due to very active granulopoiesis with a left shift. Fat spaces were reduced. Erythropoiesis showed some megaloblastoid features and iron stores were depleted. Leucocyte alkaline phosphatase score was normal and there was no evidence of haemolysis. Orosomucoid levels were elevated at 1.76 g/litre. IgG was mildly elevated at 17.2 g/litre and polyclonal but IgA and IgM were normal.

The leucoerythroblastic features remitted on medical treatment for her ulcerative colitis. At present she is well, Hb 14.1 g/dl, WCC $5.3 \times 10^9/\text{litre}$ with a normal differential count.

Discussion

The term leucoerythroblastic anaemia was first coined by Vaughan (1936) and describes the presence in the peripheral blood of nucleated red cells and immature cells of the neutrophil myeloid series. The major textbooks (Wintrobe *et al.*, 1975; De Gruchy, 1978; Hoffbrand and Lewis, 1981) have given prominence to the neoplastic causes of a leucoerythroblastic anaemia, whereas several studies (Burrett, Cox and Fields, 1965; Werck, Hageborn and Linman, 1974) have demonstrated that up to half of the conditions underlying a leucoerythroblastic picture are of a benign nature. Leucoerythroblastic anaemia also has been demonstrated in animals (Madewell and Feldman, 1980). However, there are no reports in the literature of a reversible leucoerythroblastic anaemia occurring in association with ulcerative colitis. Retief (1964) showed that conditions such as acute rheumatic fever and haemorrhagic pancreatitis

produce a leucoerythroblastic reaction and commented that the degree of normoblastosis was no guide to the probability of bone marrow infiltration. However, normoblastosis occurring during the course of an illness confers a worse prognosis (Schwartz and Stansbury, 1954).

The pathological process occurring in the bone marrow in conditions producing a leucoerythroblastic anaemia is uncertain. The earliest speculations included suggestions of a direct stimulus to the bone marrow by invading neoplastic cells (Hill and Duncan, 1941), but hyperplasia of the marrow tissue had been noted and an accompanying deficiency of a factor essential for normal haemopoiesis was considered likely. Intramedullary endothelial damage allowing larger immature cells to leak out into the peripheral blood has also been proposed (Hilts and Shaw, 1953), and a third mechanism suggested that immature cells in abnormal locations may be intravascular and therefore easily washed into the circulating blood (Heck and Hall, 1939). Mechanisms put forward to explain the severe leucoerythroblastic reactions seen in the presence of localized primary cancer of parenchymal organs included a selective chemotactic effect of toxic substances on an haemopoietic cell type (Arneth, 1937), possibly a tumour product (Sonnenfeld, 1929). In a non-infiltrative condition, active bone marrow replaces the marrow fat spaces and extends into the yellow marrow of the long bones. It seems reasonable to postulate that if the stressing stimulus is of a severe nature or occurs as an acute exacerbator of a chronic condition, the marrow will release immature cells into the peripheral blood. Acute infections, haemolysis or persistent blood loss are all examples of such reversible stimuli and once decreased or removed the peripheral blood will soon clear of immature forms.

In longstanding ulcerative colitis the development of a leucoerythroblastic anaemia may be taken to be the manifestation of an occult colonic carcinoma, a well recognized complication of chronic ulcerative colitis (Dawson and Pryse Davies, 1959; Edwards and Truelove, 1964). In our two cases, no such neoplasm was found and the leucoerythroblastic anaemia remitted entirely with medical treatment directed at the ulcerative colitis. Both have remained well with no recurrence during follow up for over 12 months.

Anaemia occurring in association with ulcerative colitis is commonly secondary to blood loss from inflamed colonic mucosa. Chronic gastrointestinal haemorrhage is not a recognized cause of a leucoerythroblastic anaemia and it is likely that the combined effect of blood loss together with a chronic inflammatory condition unduly stressed the bone marrow. Neither case demonstrated evidence of haemolysis, infection or acute massive haemorrhage.

In addition, neither had received drugs with recognized toxic effects on bone marrow. Patient 1 had received no drugs and Patient 2 had been maintained for 9 months on prednisolone and sodium cromoglycate, and this treatment regime was maintained throughout the recovery period.

These two cases demonstrate bone marrow stress of the 'acute on chronic' type, resulting in the typical changes of a leucoerythroblastic anaemia. The reversible nature of these changes has not been previously described in relationship to ulcerative colitis.

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References

- ARNETH, J. (1937) Über die akute lymphatisch—leukaemoide reaktion ('acute myeloische leukaemie') bei sepsis—Ersatz der organpunctionen durch die qualitative Blutuntersuchung. *Deutsches Archiv für klinische Medizin*, **180**, 620.
- BURKETT, L.L., COX, L.M. & FIELDS, M.L. (1965) Leucoerythroblastosis in the adult. *American Journal of Clinical Pathology*, **44**, 494.
- DAWSON, I.M.P. & PRYSE DAVIES, J. (1959) The development of the carcinoma of the large intestine in ulcerative colitis. *British Journal of Surgery*, **47**, 113.
- EDWARD, F.C. & TRUELOVE, S.C. (1964) Course and prognosis of ulcerative colitis. Part IV: Carcinoma of the colon. *Gut*, **5**, 15.
- DE GRUCHY, G.C. (1978) In: *Clinical Haematology in Medical Practice*. (Ed by Pennington, D., Rush, B. & Castaldi, P.), 4th edn, p. 491. Blackwell Scientific Publications, Oxford.
- HECK, F.J. & HALL, B.E. (1939) Leukaemoid reactions of myeloid type. *Journal of the American Medical Association*, **112**, 95.
- HILL, J.M. & DUNCAN, C.N. (1941) Leukaemoid reactions. *American Journal of Medical Science*, **201**, 847.
- HILTS, S.V. & SHAW, C.C. (1953) Leukaemoid reaction. *New England Journal of Medicine*, **249**, 463.
- HOFFBRAND, A.V. & LEWIS, S.M. (1981) *Postgraduate Haematology*. 2nd edn, p. 414. William Heinemann Medical Books, London.
- MADEWELL, B.R. & FELDMAN, B.F. (1980) Characterisation of anaemias associated with neoplasia in small animals. *Journal of the American Veterinary Medical Association* **176**(5), 419.
- RETIEF, F.P. (1964) Leucoerythroblastosis in the adult. *Lancet*, **i**, 639.
- SCHWARTZ, S.O. & STANSBURY, F.S. (1954) Significance of nucleated red blood cells in peripheral blood. *Journal of the American Medical Association*, **154**, 1339.
- SONNENFELD, A. (1929) Leukaunsche reaktionen bei carcinom. *Zeitschrift für klinische Medizin*, **111**, 108.
- VAUGHAN, J.M. (1936) Leucoerythroblastic anaemia. *Journal of Pathology and Bacteriology*, **42**, 541.
- WEICK, J.K., HAGEDORN, A.B. & LINMAN, J.W. (1974) Leucoerythroblastosis. Diagnostic and prognostic significance. *Proceedings of Staff Meetings of the Mayo Clinic*, **49**, 110.
- WINTROBE, M.M., LEE, G.R., BOGGS, D.R., BITHELL, T.C., ATHENS, J.W. & FOERSTER, J. (1975) *Clinical Haematology*, 7th edn, p. 1787. Lea & Febiger, Philadelphia.