GOUT, STEATORRHOEA, AND MEGALOBlastic ANAEMIA

BY

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Liability to gout is a frequent feature of polycythaemia vera, myeloid leukaemia, and myeloid metaplasia (Hickling, 1953), and is a well-recognized though less common event in Addisonian anaemia. Of greater rarity is the association of gout with the anaemia arising from non-tropical sprue. In a comprehensive review, Talbott (1959) found only two examples. The following is a third.

Case Report

In 1949, at the age of 43 years, a man was discovered to have proteinuria. There were no relevant symptoms or signs; his blood-pressure was normal and weight 165 lb. Urine culture, blood urea, and intravenous pyelography were normal.

In 1952 he complained of weight loss for a year, and more recent dyspnoea, thirst, pallor, diarrhoea, and nausea.

Examination in Hospital.—He was febrile and pale with a smooth tongue. No splenic enlargement was detected. There were no significant neurological signs.

The haemoglobin level was 33 per cent., red blood count 1,360,000/c.mm., colour index 1.27, average red cell diameter 7.8 μ , and white blood count 5,800/c.mm. There was marked anisocytosis, poikilocytosis, scanty platelets, and 1 per cent. reticulocytes. The sternal marrow was richly cellular with normal myelopoiesis, and there was marked erythroid hyperplasia with numerous early and intermediate normoblasts, but no megaloblasts or macronormoblasts.

The gastric contents contained free acid. A barium meal reached the caecum in one hour, but showed no clumping or mucosal abnormality.

During his stay in hospital he gave a recent history of gout in his big toes, with attacks lasting up to one week. A radiograph of his feet, however, showed no evidence of gout. He was treated with blood transfusion, liver injections, and vitamin B₁₂, and gradually improved. By June, 1953, his haemoglobin level was 83 per cent.

Progress.—He remained well apart from several attacks of gout each year until November, 1955, when his weight fell to 140 lb. On examination he was underweight with an excessively-pigmented, dry, eczematous skin. He had considerable proteinuria, mainly from

albumin. The haemoglobin concentration was 72 per cent.

Because of doubt over the initial diagnosis of pernicious anaemia, all therapy was stopped, and the patient remained well until April 12, 1956, when he suddenly became pale and had melaena. The haemoglobin level fell to 23 per cent.; the blood smear showed extreme anisocytosis, poikilocytosis, and polychromasia. Sternal marrow aspiration now revealed a mixture of megaloblasts and normoblasts. A gastric test meal contained no free acid.

He was treated by blood transfusion and vitamin B₁₂, and made a slow recovery; his marrow becoming normoblastic in character. Later investigations demonstrated a total bilirubin of 1.4 mg. per 100 ml., and normal values for the serum proteins, thymol turbidity, and alkaline phosphatase. Radiographs of the chest and selected bones showed no skeletal abnormality. A barium meal revealed no cause for the bleeding.

In July, 1956, a fat balance was performed, and on a 40 g. daily fat intake, 12 g. of fat were excreted. A diagnosis of steatorrhoea was made, and folic acid 5 mg. three times daily was added to the treatment with an improved haematological response. He had an attack of gout in September; shortly afterwards the serum uric acid was 5.8 mg. per 100 ml., and a radiograph of the left big toe showed erosive punched-out areas compatible with gout. Because of recurrent pain in the left knee and ankle in July, 1957, he was prescribed 0.5 g. probenecid daily.

He then remained well until February, 1960, when he complained of painful feet and difficulty in walking. No cause was clinically apparent, and the pain worsened over the next year and spread to the hips, knees, and ankles. In September the serum uric acid was 8 mg. per 100 ml., and intermittent courses of colchicine were prescribed without relief. Urine examination in March, 1961, still showed proteinuria, and the serum alkaline phosphatase had risen to 23 King-Armstrong units.

PRESENT STUDIES.—In April, 1961, the patient was referred to the Charing Cross Hospital.

History.—On questioning, he was sure that the severe pain and stiffness in the legs, which he had had for over a year, were unlike those which accompanied his previous

attacks of gout. He denied chest pain, dyspnoea, or symptoms of renal disease. His appetite was good and weight steady, and he had a daily bowel action. He gave no family history of anaemia or gout. By occupation he was a schoolmaster, of temperate habits.

Examination.—He was a thin, grey-haired man of 55 years, with a high-domed forehead, weighing 119 lb., and 71 in. tall. His skin was excessively sun-tanned, and the nails curved. There was no clinical anaemia, glossitis, or gouty tophi. Mild leg oedema was present. He walked with a waddling gait and pronounced limp. His limbs were wasted. The knees had effusions with crepitus; the right hip was restricted in movement by pain. Both shoulders were stiff and painful. No abnormality was found in the heart, lungs, abdomen, or nervous systems. The urine showed a faint haze with the sulpho-salicylic acid test, but none on heating the acidified urine; the stools were semi-formed and light brown.

Laboratory Investigations.—Erythrocyte sedimentation rate 25 mm./hr, haemoglobin 75 per cent., red blood counts moderate anisocytosis, poikilocytosis, and slight anisochromia, mean cell diameter 6.9 μ , white blood count 8,300/c.mm., with normal differential, prothrombin time 27 sec., control time 17 sec. Serum electrolytes sodium 130 mEq., chloride 106 mEq., potassium 4.4 mEq., alkali reserve 17 mEq. The serum uric acid was 7.8 mg. per 100 ml., calcium 8 mg./100 ml., inorganic phosphorus 2.3 mg./100 ml., alkaline phosphatase 20 King-Armstrong units, albumin 4.2 g./100 ml., globulin 3.3 g./100 ml. A glucose tolerance test showed a flat response, the highest value being 90 mg./100 ml. Occult blood tests on the stools were occasionally positive. Absorption studies with radioactive-iodine-labelled triolein showed that the faecal excretion was 14.3 per cent. of the administered dose; this and the low plasma values indicated malabsorption.

Radiographs.—The ribs, right femur, pelvis, and feet showed fractures or pseudo-fractures, and abnormal bone texture. A plain film of the abdomen showed considerable gaseous distension. A barium meal reached the caecum in 3 hours; there was a moderate degree of flocculation and dilation of the small bowel, but no diverticula.

Treatment.—The patient was given vitamins A and D with calcium lactate, in addition to his previous therapy. His pain improved and he was able to walk unaided. Subsequently he was prescribed a gluten-free diet, and gained weight.

Discussion

The first reported case concerned a man with long-standing non-tropical sprue, macrocytic anaemia, and 3 years' intermittent gout (Morlock and Rosenberg, 1944). The anaemia was treated with crude liver infections, but despite the use of colchicine, cinchophen, and salicylates, the gout continued unabated. The authors suggested that treatment of sprue, with improved absorptive ability, might

lead to increased purine absorption and so predispose to further gout.

Zumoff (1953), reporting a second patient with gout, megaloblastic anaemia, and steatorrhoea, was led to consider the possible relation of folic acid to uric acid metabolism. Previous experimental work by Kalckar and Klenow (1948) and Williams and Elvehjem (1949) had shown that folic acid markedly decreased the activity *in vitro* of xanthine oxidase, an enzyme which catalyses the oxidation of xanthine to uric acid. Furthermore, Keith, Broach, Warren, Day, and Totter (1948) had demonstrated that animals on a diet deficient in folic acid had greater xanthine oxidase levels in liver homogenates than controls.

These observations suggested to Zumoff that the hyperuricaemia in his patient might be due to an increased activity of xanthine oxidase, and that the raised serum uric acid was a chemical sign of folic acid deficiency. The ensuing fall in concentration with folic acid therapy supported this contention, as did the work of Machlin, Lankenau, Denton, and Bird (1952), which showed that the blood uric acid in chicks fed on a high glycine diet varied inversely with the intake of folic acid.

Despite the attractiveness of the concept, there is no proof that xanthine oxidase is causally related to the hyperuricaemia. However, under certain conditions, folic acid deficiency has been shown to disturb uric acid metabolism. In cancer chemotherapy the use of anti-metabolites can cause an acute folic acid deficiency (Broquist, 1956; Hiatt, Goldstein, and Tabor, 1958), which is at times associated with an increased production and excretion of uric acid (Sandberg, Cartwright, and Wintrobe, 1956; Lipsett, Bergenstal, and Patten, 1959). The latter authors considered the heightened uric acid excretion in their subjects to be due to the failure of the marrow to use preformed purines.

In steatorrhoea, chronic folic acid deficiency can reasonably be inferred (Girdwood, 1959, 1960), but that this causes increased uric acid production as in acute drug-induced deficiency has not been investigated, though the occasional occurrence of gout raises this possibility. In the present patient as in the two reported previously, the onset of gout coincided with the untreated macrocytic anaemia. In apparent contrast, patients with Addisonian anaemia from vitamin B₁₂ lack are most prone to gout during the initial treatment when increased uric acid production parallels the reticulocyte response, and endogenous uric acid production before is usually normal (Riddle, 1930; Opsahl, 1939).

This difference is paralleled by the experimental

work of Machlin and others (1952), who found that, whereas folic acid usually lowered the serum uric acid, vitamin B₁₂ acted conversely. They suggested that folic acid inhibited uric acid synthesis, and that vitamin B₁₂ accelerated its formation.

In the present patient the gout had continued with little change while vitamin B₁₂ was prescribed, but the patient was convinced that his attacks had decreased in severity and frequency since folic acid was added. The significance of the improvement is debatable since probenecid was also prescribed. It is, however, reasonable to expect some amelioration of gout with combined therapy, since the marrow may remain hyperplastic when vitamin B₁₂ is given alone, and the addition of folic acid leads to a more normal situation.

The cause of the malabsorption was almost certainly idiopathic steatorrhoea and this was responsible for the melaena, and for the osteomalacia which caused the recent bone pain. The long-standing proteinuria was unexplained but, as suggested by Duncan and Dixon (1960), prolonged hyperuricaemia could have been responsible.

At no time was long-term colchicine therapy prescribed. Such treatment may be relevant, for Hawkins (1961) referred to a man with gout treated with colchicine for 10 years who had megaloblastic anaemia, folic acid deficiency, and steatorrhoea. In this case the possibility was considered that prolonged colchicine therapy, by virtue of its cytotoxic action, could have caused jejunal damage, and hence steatorrhoea.

Summary

Details are given of a patient with gout, megaloblastic anaemia, and steatorrhoea. The implications of this association are discussed, especially the relation of folic acid deficiency to uric acid metabolism.

Persistence of gout in a patient treated for megaloblastic anaemia with vitamin B₁₂ may be a pointer to underlying folic acid deficiency, especially if the haematological response has not been complete.

I should like to thank Dr. R. A. Hickling for allowing me to publish details of his patient.

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Goutte, stéarrhée et anémie mégalo-blastique

RÉSUMÉ

On décrit en détail un malade atteint de goutte, anémie mégalo-blastique et stéarrhée. On discute les implications de cette association, surtout en ce qui concerne la carence d'acide folique et le métabolisme de l'acide urique.

La persistance de la goutte chez un malade dont l'anémie mégalo-blastique est traitée par la vitamine B₁₂ peut indiquer l'existence d'une carence d'acide folique, surtout lorsque la réaction hématologique n'est pas complète.

Gota, estearrea y anemia megaloblástica

SUMARIO

Se describe detalladamente un caso de gota, anemia megaloblástica y stearraea. Se discuten las implicaciones de esta asociación, particularmente respecto a la carencia de ácido fólico y al metabolismo del ácido úrico.

La persistencia de la gota en un enfermo con anemia megaloblástica tratada con vitamina B₁₂ puede ser un indicio de la carencia de ácido fólico, particularmente cuando la respuesta hematológica no es completa.