Coexistence of pernicious anaemia and acute erythraemic myelosis

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SYNOPSIS A patient with the apparently unique combination of pernicious anaemia and acute erythraemic myelosis is described. The implications of some of the unusual features together with the difficulties encountered in diagnosis and treatment are discussed.

Acute erythraemic myelosis is a rare condition first defined by Di Guglielmo in 1923 as 'an autonomous pathologic entity, *ie*, a primary and specific disease characterized by a generalized proliferation of the erythropoietic cells of the bone marrow, analogous to the leucocytic proliferation in leukaemia'. Although Di Guglielmo emphasized the 'purity' of the erythroblastic proliferation, Baldini, Fudenberg, Fukutake, and Dameshek (1959) considered this form to be extremely rare and that mixed forms showing proliferation of both erythroblastic and myeloblastic elements were more common. They suggested that the natural history of the disorder may pass through several phases. In the first, erythroid hyperplasia predominates giving the picture of erythraemic myelosis as described by Di Guglielmo; in the second, dual erythroblastic and myeloblastic proliferation produces erythroleukaemia which may proceed in the final phase to predominant myeloblastic proliferation. Several cases have terminated, however, as myelomonocytic leukaemia (Hindmarsh and Wickham, 1955; Sheets, Drevets, and Hamilton, 1963). In regarding erythraemic myelosis and erythroleukaemia as transitory stages in the same pathological entity, Dameshek and Baldini (1958) collectively named these clinical variants the 'Di Guglielmo syndrome' and advocated its classification within the myeloproliferative disorders.

Although the erythroid hyperplasia of erythraemic myelosis has megaloblastoid features and several authors have stressed the clinical and haematological similarities to pernicious anaemia, we have been unable to find any report of the occurrence of both diseases occurring in the same patient. This paper describes the clinical and haematological findings in

such a patient and discusses some of the difficulties encountered in diagnosis and treatment.

CASE REPORT

FIRST ADMISSION A 65-year-old woman was admitted to hospital on 15 June 1966, because of increasing tiredness for one year with loss of weight, progressive breathlessness, and paraesthesiae of the hands and feet for six months. Clinical examination showed pallor of the mucosae with a slight lemon tinge of the skin but no apparent conjunctival icterus. The tongue was smooth and atrophic. The pulse was 108 per minute and blood pressure 150/50 mm/Hg. The heart was not enlarged. A loud ejection systolic murmur was audible in all areas and transmitted into the neck vessels. There were no signs of congestive cardiac failure and the chest was clinically and radiologically normal. The liver edge was felt two fingerbreadths below the right subcostal margin and although the spleen was not clinically palpable, a radiograph of the abdomen revealed significant splenic enlargement. There was no palpable lymphadenopathy. Examination of the central nervous system, including the optic fundi, was normal.

Laboratory investigations Haemoglobin was 4.1 g per 100 ml; PCV 11.4%; MCHC 35.5%; reticulocytes 3%; WBC 3,100 per cu mm, with a normal differential count. The blood film showed anisopoikilocytosis with macrocytosis, erythroblastemia (6 nucleated red cells per 100 white cells) and blue polychromasia. Neutrophils showed nuclear hypersegmentation and occasional giant metamyelocytes were seen. Platelets were adequate.

Sternal marrow examination showed marked erythroblastic hyperplasia with excessive mitotic activity (Fig. 1). There was a marked shift to the left in the erythroid cells the majority being proerythroblasts and basophilic megaloblasts. Many of these immature cells contained 2 to 4 nuclei and many showed prominent cytoplasmic and nuclear vacuolation. Myelopoiesis was distinctly hypoplastic but a fair number of giant metamyelocytes and macropolycytes were present. Megakaryocytes were numerically reduced, showed bulky hyperconvoluted

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nuclei with a finely stippled chromatin pattern. These marrow appearances were regarded as being consistent with megaloblastic haemopoiesis but it was pointed out that in view of the marked dysplasia, Di Guglielmo's disease could not be excluded. An augmented histamine test meal revealed no free acid. Barium meal examination was normal and repeated tests for faecal occult blood were negative. Serum B_{12} was less than $50 \mu\text{g}$ per ml (*L. leichmanii* bioassay, normal range 160 to $800 \mu\text{g}$ per ml). Serum folate was $4 \text{ m}\mu\text{g}$ per ml (*L. casei* bioassay, normal range 3 to $18 \text{ m}\mu\text{g}$ per ml). Serum urea, 50 mg per 100 ml ; serum electrolytes, normal. Immunological tests were positive for parietal cell antibodies but negative for intrinsic factor, antithyroid and antinuclear antibodies. The lupus precipitin test was negative.

The results of the above investigations appeared to substantiate a diagnosis of pernicious anaemia in spite of the atypical features in the marrow, and in view of the clinical condition it was considered justifiable to start vitamin B_{12} therapy while the result of a radioactive vitamin B_{12} absorption test was awaited. Hydroxycobalamin, $250 \mu\text{g}$, was given daily, and a diagnostic reticulocyte response of 24% was obtained on the seventh day of treatment. When discharged for convalescence on 29 June the patient felt generally better. Examination of peripheral blood showed Hb 6.3 g per 100 ml ; PCV 21%; MCHC 30%; reticulocytes, 4%; WBC 6,000 per cu mm. Occasional macrocytes but no nucleated red cells were noted in the film.

SECOND ADMISSION Four weeks later, the patient was readmitted with a recurrence of severe tiredness and listlessness. Clinical examination was essentially as before except that the spleen was now easily palpable and the liver enlargement had increased to four finger-breadths below the right subcostal margin.

Laboratory investigations Haemoglobin was 4.1 g per 100 ml ; PCV 12.3%; MCHC 34%; WBC 4,400 per cu mm (neutrophils 66%, eosinophils 2%, lymphocytes 26%, monocytes 6%). In the film, the red cells showed anisopoikilocytosis with occasional macrocytes. Numerous erythroblasts (16 per 100 white cells), some showing cytoplasmic and nuclear vacuolation, and a very occasional myelocyte were seen. Platelets appeared adequate.

Repeat examination of the sternal marrow showed extreme hypercellularity due to proliferation of erythroblasts, pro-erythroblasts, and haemocytoblasts, many of these cells again showing prominent cytoplasmic and nuclear vacuolation with a tendency for the cytoplasm to 'bud' and fragment. Many also contained multiple nuclei and there was now little or no maturation beyond the erythroblast stage. An unusual feature was the phagocytosis by reticulum cells of erythroblasts, mature erythrocytes, and shed cytoplasmic fragments. Normal marrow elements were almost entirely replaced by the malignant transformation of the erythroid precursors. Periodic-acid-Schiff staining showed positive granules within many of the erythroblasts (Hayhoe, Quaglino, and Flemans, 1960). The morphological appearances of this repeat marrow examination confirmed the original suspicion of Di Guglielmo's disease.

Serum folate was $2.7 \text{ m}\mu\text{g}$ per ml, and liver function

tests showed thymol turbidity, 1 unit; alkaline phosphatase, 5 units; cephalin cholesterol, negative; serum bilirubin, 0.5 mg per 100 ml ; SGOT 90 units; SGPT 40 units; one-stage prothrombin time was 20 seconds (control 15 seconds); serum albumin and globulin, 3.6 and 2.6 g per 100 ml respectively; serum urea, 49 mg per 100 ml ; serum electrolytes, normal.

A radioactive B_{12} absorption test using the hepatic uptake method (Glass, Boyd, Gellin, and Stephanson, 1954) showed a low vitamin B_{12} uptake which was corrected by intrinsic factor.

The results of these further investigations and the haematological relapse occurring while the patient was still receiving vitamin B_{12} indicated the coexistence of Di Guglielmo's disease and pernicious anaemia, an apparently unique combination of disease entities and one presenting special difficulties in management. The use of antimetabolites seemed justified (see discussion) and treatment with pyrimethamine, 25 mg daily, together with Aneurine compound tablets was started. Transfusion of packed cells from five bottles of blood was also given after which peripheral blood examination showed Hb 10 g per 100 ml ; PCV 35.5%; MCHC 28.5%; WBC 2,400 per cu mm. On the tenth day of treatment with pyrimethamine she developed a small epistaxis and blood examination showed a significant thrombocytopenia. The pyrimethamine was stopped and the bleeding tendency controlled by prednisone, 5 mg qid. Five days later she was discharged for two weeks' convalescence.

FINAL ADMISSION On her final admission she was pyrexial and clinical examination showed further enlargement of the liver and spleen and a few bruises were now present over both legs. Examination of the peripheral blood showed Hb 7.3 g per 100 ml ; PCV 22%; MCHC 33%; WBC 4,200 per cu mm. In the film macrocytosis and an occasional erythroblast were present. No immature white cells were seen. Platelets were virtually absent. After a further transfusion, the patient developed a widespread petechial rash and had repeated epistaxes and haematemesis. She developed terminal bronchopneumonia and died on 25 September just 14 weeks from the date of her first admission.

NECROPSY REPORT (Dr I. B. Porteous) The main macroscopic changes were widespread ecchymoses of the arms and legs, multiple petechial haemorrhages of the gastric mucosa, bilateral bronchopneumonia, and extension of red marrow throughout the whole length of both femora. The cut surfaces of the enlarged liver ($2,100 \text{ g}$) and spleen (250 g) showed congestive changes.

The relevant microscopic features were confined to the liver, spleen, and bone marrow. Liver sections showed centrilobular congestion with clumps of primitive erythroblasts and haemocytoblasts within the dilated sinuses. The spleen showed complete loss of its follicular architecture with marked reticuloendothelial hyperplasia and reticulin overgrowth, distension of the sinusoids by proliferating haemocytoblasts and erythroblasts, and focal haemorrhages predominantly subcapsular. Sections of the marrow showed no changes additional to those observed from aspirates obtained during life.

DISCUSSION

In this patient just described, all the criteria for the diagnosis of Addisonian pernicious anaemia appear to have been fulfilled apart from the atypical bone marrow features and the negative intrinsic factor antibody test which is, however, positive in only 57% of cases (Ardeman and Chanarin, 1963).

DIAGNOSTIC CRITERIA The diagnosis of acute erythraemic myelosis is based on clinical and haematological criteria.

Clinical A severe and progressive anaemia is commonly accompanied by irregular pyrexia, hepatosplenomegaly, haemorrhagic manifestations, and death ensues within several months.

Peripheral blood This commonly shows a normochromic macrocytic anaemia with anisopoikilocytosis and a varying degree of erythroblastaemia, and a normal, decreased or slightly increased white cell count with occasional to frequent immature myeloid cells and usually thrombocytopenia.

Bone marrow The picture is that of intense erythroid hyperplasia of megaloblastic or megaloblastoid type with maturation arrest at a primitive level, increased mitotic activity with aberrant nuclear forms, and commonly replacement of myeloid and megakaryocytic elements (Fig. 1). In most instances a variable number of the erythroblasts give a positive PAS-staining reaction (Quaglino and Hayhoe, 1960).

Our case likewise fulfilled these criteria and the diagnosis of erythraemic myelosis was confirmed by the post-mortem findings.

Most previous authors have drawn attention to certain clinical and haematological similarities

between acute erythraemic myelosis and advanced pernicious anaemia which may lead to confusion in diagnosis. This may be extended, however, to include severe megaloblastic anaemias due to vitamin B₁₂ deficiency from any cause. The following investigations have been suggested as being helpful in the differentiation of difficult cases.

THERAPEUTIC TRIAL OF VITAMIN B₁₂ Before the introduction of modern techniques for the study of vitamin B₁₂ and folic acid, a trial of liver extract or vitamin B₁₂ with assessment of the reticulocyte response was suggested as a possible differential test. For obvious reasons, this test must now be considered both inadequate and unsatisfactory.

VITAMIN B₁₂ ASSAY Baldini *et al* (1959) recorded high serum B₁₂ levels in three cases of chronic erythraemic myelosis and suggested that this estimation might be of value in distinguishing the two disorders. High or normal levels have been confirmed by Spray and Witts (1958), Adams and Seaton (1960) and Metz and Klein (1960) exceptions being, however, our own case and that reported by Gibson, Pollock, and Stankler (1963). This estimation cannot therefore, be regarded as a completely reliable means of differentiation. The finding of high serum B₁₂ levels led Dameshek (1958) to postulate that in Dini and Guglielmo's syndrome there is an enzymatic fault in the metabolism of B₁₂ or folic acid, or an inability to utilize these factors, a concept questioned by Gibson *et al* (1963). In our case the diagnostic reticulocyte response and rise in haemoglobin level, although temporary, indicated that the red cell precursors were able to utilize vitamin B₁₂. This finding would appear to invalidate Dameshek's concept but an alternative and probably correct interpretation is that the marrow contained both normal and 'neoplastic' erythroblasts and that response by the former led to the temporary haematological improvement.

BONE MARROW CHANGES Several of the marrow changes in this case merit further discussion because of their apparent rarity yet possible value in distinguishing the megaloblastoid marrow of erythraemic myelosis from megaloblastic haemopoiesis found in other conditions. They may also throw light on some aspects of the pathogenesis of the former, namely, cytoplasmic and nuclear vacuolation of red cell precursors and budding and fragmentation of erythroblast cytoplasm. These changes (Figs. 2 and 3), not recognized in the marrow of B₁₂ or folic acid deficiency, have rarely been reported in erythraemic myelosis but the former were noted in cases 3, 4 and 8 and the latter in case 3 of the series of patient

FIG. 1. Marrow smear showing 'megaloblastoid' hyperplasia with excessive mitotic activity. $\times 600$.

FIG. 2. Marrow smear showing prominent cytoplasmic vacuolation of 'megaloblastoid' erythroblasts. CF = a cytoplasmic fragment showing vacuolation. $\times 600$.

FIG. 3. Marrow smear showing reticulum cell with two ingested normoblasts, one in the prophase stage of mitosis. Several of the erythroblasts show cytoplasmic vacuolation and 'budding'. $\times 600$.

FIG. 4. Marrow smear showing a giant metamyelocyte (GM) and two nucleated red cells with multiple Howell-Jolly body formation (HJ). $\times 600$.

described by Baldini *et al* (1959). 'Knobby cytoplasmic projections' of erythroid precursors were also noted by Martin and Bayrd (1954) in case 1 of their series. None of these authors offered an explanation for the unusual morphological features but it seems reasonable to assume that they are degenerative in nature and a manifestation of defective cell production and development. Phagocytosis of nucleated and mature erythrocytes by reticulum cells, a feature (Fig. 3) described by Di Guglielmo and Quattrin (1942), appears to have been completely neglected by subsequent authors, apart from Metz and Klein (1960) who reported a case terminating in acute monoblastic leukaemia which showed prominent erythrophagocytosis but only in the terminal phase of the disease. Although this patient had a significant haemolytic element, these authors concluded that the degree of erythrophagocytosis did not wholly explain the diminished red cell survival. Erythrophagocytosis, as in familial haemophagocytic reticulosis, may not, however, be demonstrated by examination of the marrow although present in other organs of the reticulo-endothelial system (Goodall, Guthrie, and Buist, 1965). The phenomenon observed in both marrow aspirates in our patient would appear to explain, in part at least, the haemolytic element commonly present in erythraemic myelosis. With no evidence to support an immune mechanism, we would further speculate that the abnormal phagocytic activity results from the reticulo-endothelial proliferation which should be regarded as an integral part of the disorder and not merely as a secondary manifestation of the production of abnormal red cells. This view gains support from the concept which regards erythraemic myelosis as a form of reticulo-endotheliosis (Di Guglielmo and Quattrin, 1942; Schwartz and Critchlow, 1952) and the fact that erythrophagocytosis commonly occurs in this group of disorders. Giant metamyelocytes and macropolycytes are myeloid changes (Fig. 4) which are usually regarded as characteristic of vitamin B₁₂ or folic acid deficiency and are said not to occur in erythraemic myelosis (Israëls, 1963). They have previously been noted, however, in two patients (cases I and III of Schwartz and Critchlow, 1952). In neither of these cases were serum B₁₂ or folate levels assayed and as neither had features of pernicious anaemia it is probable that folate deficiency, analogous to that which may be found in other neoplastic or leukaemic conditions (Rose, 1965), induced the white cell changes. The presence of giant metamyelocytes does not, therefore, exclude the diagnosis of erythraemic myelosis.

In summary, none of the solitary tests previously advocated for the differentiation of pernicious anaemia and acute erythraemic myelosis are

completely reliable, and ultimate clarification can only be achieved by consideration of the overall clinical and haematological picture, including the results of vitamin B₁₂ absorption studies, although as in our case, the marrow changes described should raise a strong suspicion of erythraemic myelosis.

Finally we regard the apparently unique combination of erythraemic myelosis and pernicious anaemia in our patient as being quite fortuitous. It may be pertinent to note, however, that the coexistence of the two diseases is somewhat analogous to the development of polycythaemia vera, also a myeloproliferative disorder, in a small number of cases of pernicious anaemia (Delamore, 1961; Engel and Stickney, 1962; Douglas, Israëls, and Wilkinson, 1964) and that one such case terminated in acute leukaemia (Zarafonetis, Overman, and Molthan, 1957). Also of possible relevance is the occurrence of acute erythraemic myelosis in a small number of patients with polycythaemia vera (Dammert and Kaipainen, 1960; Perkins, Israëls, and Wilkinson, 1964; Scott, Ellison, and Ley, 1964; Watkins, Fairley, and Scott, 1967). The paucity of communications reporting the coexistence of pernicious anaemia and myeloproliferative disorders, including erythraemic myelosis, would indicate that the combination is no more than a chance association, but a definite relationship cannot be completely excluded.

TREATMENT There is no known effective drug treatment for erythraemic myelosis and although transfusion may provide useful supportive therapy, the prognosis is poor and survival is usually measured in months.

In the past, the megaloblastoid appearances of the bone marrow have led to the administration of liver extract, vitamin B₁₂, or folic acid but none has produced recognizable benefit. Their rational use should be limited to cases of proven deficiency but one may question, even in these circumstances, whether they may not accelerate the abnormal cell proliferation. Antimetabolites have provided some temporary benefit especially in the more chronic types of the disease (Sheets *et al*, 1963), but their use in the acute varieties must necessarily depend on the blood and marrow status. In our patient the use of an antimetabolite was considered to be hazardous because of the marked depression of myeloid and megakaryocytic elements but as the abnormal proliferation was purely erythroblastic, pyrimethamine was considered worthy of trial as it has been shown to have a temporary inhibitory action on the red cell hyperplasia of polycythaemia

vera (Isaacs, 1954; Pegg and Ford, 1961) and polycythaemia secondary to hypoxic lung disease (Pengelly, 1966). It proved of no benefit and probably contributed to the thrombocytopenia. Later, in reviewing the literature, we discovered that pyrimethamine had been used in one previous case and although producing an arrest of maturation, led to explosive hyperplasia of extremely large pro-erythroid blast cells (Sheets *et al*, 1963). These experiences seem to contraindicate its further use in erythraemic myelosis.

Steroids have proved of value only in controlling the haemorrhagic manifestations.

Splenectomy has been performed in several cases without beneficial effect and in some instances has been followed by a marked increase in the degree of erythroblastemia.

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