PERNICIOUS ANAEMIA COMPLICATED BY GRANULOCYTIC LEUKAEMIA*

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The coexistence of pernicious anaemia and granulocytic leukaemia is rare. The following three cases showed features of both diseases.

Case 1.—In 1931 a housewife, aged 44 years, presented with general symptoms of anaemia and with tinglings in the feet and hands, difficulty in walking, and a sore tongue. On examination there was pallor and icterus of the mucous membranes, a smooth tongue, cardiomegaly, tenderness of the calves, and diminution of muscle tone, vibration sense, co-ordination, and in sense of position in the legs. The ankle jerks were absent. The peripheral blood showed: Hb 38 \(\%\) (5.6 g. 100 ml.), R.B.C.s 1.50 m. per c.mm., C.I. 1.27, W.B.C.s 1,800 per c.mm., gross anisocytosis and poikilocytosis, macrocytosis, and normochromia. At a later date a gastric test meal showed a histamine-fast achlorhydria. A diagnosis of pernicious anaemia with neurological involvement was made.

She was treated with iron and ammonium citrate and with liquor arsenicalis until July, 1933. As her clinical condition had not improved on this treatment, oral therapy with liver extracts ("filivex" and "hepatex") and "marmite" was substituted. By September, 1933, she had no symptoms, and the blood count was normal. Between 1934 and 1941 she received "campolon" injections followed by parenteral "anaehaemin" until 1954. She remained free of symptoms.

On July 19, 1954, she was admitted to hospital complaining of a sore throat of a few days' duration and of listlessness, dyspnoea on effort, and spontaneous bruising of the arms and legs for a few months. On examination there was slight pyrexia (99° F.), pallor of the mucous membranes, and widespread purpura of the neck, trunk, and limbs. Ecchymoses were seen on the limbs and the fauces were injected. Sternal tenderness was present, but neither the liver, spleen, nor lymph nodes were enlarged. A blood count showed: Hb 57\(\%\) (8.4 g. per 100 ml.), R.B.C.s 2.1 m. per c.mm., C.I. 1.3, W.B.C.s 1,800 per c.mm. (blast cells 1\(\%\), promyelocytes 3\(\%\), neutrophil myelocytes 11\(\%\), neutrophil band cells 12\(\%\), neutrophil polymorphs 20\(\%\), eosinophil polymorphs 1\(\%\), lymphocytes 52\(\%\)), platelets (Lempert) 25,000 per c.mm., marked anisocytosis and moderate poikilocytosis, the overall picture being normochromic and normocytic with slight polychromasia. Iliac marrow smears showed an apparently malignant acute granulocytic reaction (Fig. 1) (blast cells 18\(\%\), promyelocytes 24\(\%\)). The erythron was mainly normoblastic, but some megakaryocytes were seen, while the thrombocyten was hypoloblastic. A diagnosis of acute granulocytic leukaemia was made.

She failed to respond to blood transfusions, cortisone, and supportive therapy, and died one month later. A post-mortem examination showed widespread haemorrhages and leukaemic infiltrations. The liver weighed 1,500 g. and the spleen 480 g.

Case 2.—A housewife, aged 60 years, presented in 1948 with general symptoms of anaemia, numbness in the legs and hands, and unsteadiness on walking. The mucous membranes were pale, the tongue was smooth, and the spleen was just palpable. Her gait was slightly ataxic, while vibration sense was absent in the legs, and the sense of position and co-ordination were diminished. The knee and ankle jerks were diminished and the plantar responses flexor. A blood count gave: Hb 47\(\%\) (7g. 100 ml.), R.B.C.s 1.5 m. per c.mm., C.I. 1.6, W.B.C.s 3,600 per c.mm. (macrogranulocytes), marked anisocytosis and poikilocytosis, macrocytosis and normochromia. At a later date a gastric test meal showed a histamine-fast achlorhydria. A diagnosis of pernicious anaemia and the peripheral type of subacute combined degeneration of the cord was made.

She responded rapidly and completely to parenteral "anaehaemin" therapy, remaining fit on a maintenance dose of 2 ml. monthly until March, 1953. Then she noticed listlessness, anorexia, loss of weight, occasional bruises on the trunk, and fleeting pains in the shoulders and left groin. On June 23, 1953, she suddenly developed a sharp, stabbing pain in the left hypochondrium which was accentuated on deep inspiration. She was admitted to hospital. Small bruises were seen on the limbs and trunk, and there was slight pyrexia (up to 100° F.). The liver was palpable 3 in. below the costal margin, while the spleen almost reached the umbilicus and was tender on palpation. A splenic rub was audible anteriorly. A blood count showed: Hb 65\(\%\) (9.6 g. per 100 ml.), R.B.C.s 3.0 m. per c.mm., W.B.C.s 220,000 per c.mm. (blast cells 3\(\%\), promyelocytes 10\(\%\), neutrophil myelocytes 16\(\%\), band cells 30\(\%\), neutrophil polymorphs 36\(\%\), basophil polymorphs 2\(\%\), monocytes 3\(\%\)), platelets (Lempert) 100,000 per c.mm. The red cells showed moderate anisocytosis and were mainly macrocytic and
normochromic. Examination of marrow smears (left ilium) showed a mixed normoblastic and megaloblastic reaction, while the hyperplastic granulocytic series was mainly represented by myelocytes (Fig. 2). The thrombus was well represented and showed arrested maturation. A diagnosis of chronic granulocytic leukaemia was made.

During the following two and a half years she received parenteral vitamin B₁₂ therapy, and had two courses of deep x-ray therapy to the splenic area and one course of "colcemid" (desacetyl methylcolchicine) by mouth, each treatment causing a satisfactory remission. She died suddenly in her sleep on December 29, 1955. A post-mortem examination showed widespread leukaemic infiltrations. Permission to examine the brain was refused.

Case 3.—A housewife, aged 58 years, was admitted to hospital on February 9, 1953, complaining of general symptoms of anaemia and of a sore tongue. On examination the mucous membranes were pale, the tongue was smooth, and there was oedema of the legs and over the sacrum and pyrexia varying up to 101°F. Her blood pressure was 190/100 mm. Hg, and a loud apical systolic bruit was heard. There was no splenomegaly or neurological abnormality.

A blood count showed: Hb 32% (4.7 g. per 100 ml.), R.B.C.s 1.0 m. per c.mm., C.I. 1.6, W.B.C.s 6,000 per c.mm. (macrogranulocytes), platelets 200,000 per c.mm. (Lempert), marked anisocytosis and poikilocytosis, macrocytosis and normochromia (Fig. 3). The bone marrow (left ilium) was megaloblastic (Fig. 4), and a gastric test meal showed a histamine-fast achlorhydria. The serum bilirubin was 1.9 mg. per 100 ml., the direct van den Bergh reaction was negative, the urine contained an excess of urobilin, and four specimens of stools were free of occult blood. A diagnosis of pernicious anaemia was made.

Vitamin B₁₂, 100 μg. intramuscularly on alternate days, was begun on February 10 and continued until February 26, when twice-weekly injections of 100 μg. were substituted. Ten days after admission she developed a higher pyrexia (102°F.) and scalding and frequency of micturition. The urine, which had previously been free of albumin and organisms, now contained a cloud of albumin and many organisms and pus cells. Cultures of the urine grew Bact. coli. The infection responded well to treatment with sulphamezathine 3 g. stat., then 1.5 g. every six hours and potassium citrate, grains 20 every six hours for seven days.

She had a satisfactory reticulocytosis (maximum 14% —dry method) and by February 26 the haemoglobin had risen to 56% (8.3 g./100 ml.) and the red cells to 2.7 m. per c.mm. As microcytosis then became evident, treat-
ment with ferrous sulph. gr. 6 t.d.s. was begun. She remained on vitamin B₁₂, 100 μg. twice weekly, until May 11, when the Hb was 100% (14.8 g./100 ml.) and the R.B.C.s 5.1 m. per c.mm. The dosage of the vitamin was then reduced to 100 μg. weekly for three months, and then to 100 μg. fortnightly. Throughout this time she remained well.

On July 26, 1954, she complained of malaise and the spleen was palpable 3 in. below the costal margin. Bruises on the arms were seen. A blood count: Hb 93% (13.7 g./100 ml.), R.B.C.s 4.4 m. per c.mm., W.B.C.s 100,000 per c.mm. (promyelocytes 2%, neutrophil myelocytes 12%, neutrophil band cells 24%, neutrophil polymorphs 51%, eosinophils 2%, basophils 3%, lymphocytes 6%), platelets 180,000 per c.mm. (Lempert). Occasional nucleated red cells were seen in the peripheral blood. Examination of left iliac bone marrow showed changes of chronic myeloid leukaemia (Fig. 5). She has responded well to treatment with myleran (1:4-dimethanesulphonyloxybutane) during the past two years.
Discussion

The diagnosis of pernicious anaemia was established in all three cases by the clinical picture, peripheral blood studies, histamine-fast achlorhydria, and adequate erythrocyte and clinical responses to specific therapy (oral liver extracts in Case 1, parenteral liver extract in Case 2, and parenteral vitamin B₁₂ in Case 3). A bone marrow examination was performed in the last case. The patients subsequently developed granulocytic leukaemia (acute in Case 1 and chronic in Cases 2 and 3). The diagnosis in each patient was well substantiated by the clinical course, peripheral blood examinations, bone marrow studies, and, in Cases 1 and 2, by the necropsy findings.

Seven case reports of patients with pernicious anaemia and leukaemia have been found in the literature. In four instances chronic granulocytic leukaemia (Sinek and Kohn, 1930; Sterne, Schiro, and Molle, 1941; Talley, Doherty, and Shukers, 1952; Woolley, 1944), in one acute granulocytic leukaemia (Townsend, 1949), and in two chronic lymphatic leukaemia (Mason and Schwartz, 1949; Rich and Schiff, 1936) were involved. Pernicious anaemia preceded the development of the granulocytic leukaemia by a period of time of the order of years in the above five cases as in the present three patients.

In all the cases quoted leukanaemia appears to have been excluded. This is a condition in which the blood picture resembles both pernicious anaemia and leukaemia. It occurs especially in the later phases of true granulocytic leukaemia and is not a clinical entity in itself (see von Leube, 1900, and Foy, Kondi, and Murray, 1946).

What is the explanation of the occurrence of pernicious anaemia and leukaemia in the same patient? Although pernicious anaemia is a deficiency disease, there is no evidence that this is the case in the leukaemias (Blackburn and Lajtha, 1954, and others). In view of the apparent extreme rarity of the combination, pure chance seems to be the most likely answer to the question. As some of the reported cases have been treated adequately by modern standards, it seems unlikely that improper treatment of pernicious anaemia predisposing the bone marrow to leukaemic changes is a factor. A further tenuous hypothesis is that there is a fundamental defect—possibly hereditary in nature—of the blood-forming organs which makes the individual susceptible to either or both diseases. There are several reports in the literature describing leukaemia and pernicious anaemia, or a pernicious-anaemia-like disease in siblings (Strandell and Lemming, 1931; Bichel, 1940, and others). It is well known that liver extracts, folic acid, and vitamin B₁₂ are capable of correcting the abnormal granulocytic response in pernicious anaemia, and all these treatments in varying combinations were used in reported cases of combined pernicious anaemia and leukaemia. Hence it may be that in a few cases the response of the leucocytes to these agents ultimately becomes exaggerated and uncontrolled with the development of leukaemia. Furthermore, folic acid antagonists are used, sometimes with temporary beneficial effect, in the treatment of leukaemias. This therapy was tried because granulocytopenia develops on diets deficient in folic acid.

Further clinical and laboratory studies on patients with pernicious anaemia over a period of years may ultimately answer the question posed at the beginning of the previous paragraph.

Summary

Three patients who developed granulocytic leukaemia some years after the start of therapy for established pernicious anaemia are described. The literature on the subject of combined pernicious anaemia and leukaemia is reviewed, and possible causes of this very rare association are discussed.

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References