Case Reports

DI GUGLIELMO'S SYNDROME WITH LOW SERUM VITAMIN B₁₂

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Di Guglielmo's syndrome is a rare myeloproliferative disorder characterized by malignant erythroid hyperplasia with megaloblastoid features. Di Guglielmo, who first described it, regarded it as a pure disorder of the erythropoietic tissue. Further work, notably by Dameshek and his colleagues, has shown this concept to be too narrow (Baldini and Dameshek, 1958; Baldini, Fredenberg, Dameshek and Fukutake, 1959; Dameshek, 1958; Dameshek and Gunz, 1958). The syndrome is now regarded as one that passes through three phases. In the first phase there is excessive erythroid proliferation of the marrow, the erythremic myelosis of Di Guglielmo. The second phase is one of erythroleukaemia involving both red and white cell series, which finally passes into the third phase, an acute myeloblastic leukaemia. The disease may present at any stage, the second being the most frequent, and may run a total course of a few weeks to several years, being fatal at any stage. An erythremic forms may occur in which few or no nucleated red cells are found in the peripheral blood, and in these cases diagnosis depends on the appearances of the marrow, which also differentiate leukaemia presenting with some nucleated red cells in the blood. In this paper another case of Di Guglielmo's syndrome is presented, with features of unusual interest.

Case Report

History. A man of 66 was admitted to the Victoria Infirmary on November 1, 1960, with a history of progressive loss of energy, dyspnoea, angina of effort and ankle oedema of one month's duration. He had been diabetic for seven years, well controlled on diet alone. Three months before admission he was passed as fully fit at medical examination before going to Canada, where he was in excellent health for two months until the onset of the above symptoms. One week after these started there was recurrence of glycosuria and a general practitioner prescribed tolbutamide and vitamin B complex tablets, with apparent improvement of his diabetic control. However, his general condition deteriorated so rapidly that within another week he was too weak to dress and undress himself. There was no history of exposure to ionizing radiation or to chemicals, and no family history of blood dyscrasias. There had been no obvious blood loss or purpura.

Examination. On admission the patient was extremely pale. There was ankle and sacral oedema and crepitations were detected at both lung bases. The liver, spleen and lymph glands were not enlarged. Purpura was not present but the capillary fragility test was positive. Retinal examination showed bilateral hemorrhages and exudates. The other systems were normal.

Investigations. Hb. 4.5 g./100 ml., r.b.c. 1.83 mill./cu. mm., PCV 18%, MCV 100 cu.mm., MCHC 25%. The initial 'white cell count' was 103,400/cu.mm., but examination of a stained film showed no mature white cells. The nucleated cells were in fact almost all red cell precursors. Differential count: Undifferentiated cells 8% (including a few myeloblasts and others which could not be identified), nucleated red cells 92% (basophilic 9%, polychromatic 41%, orthochromatic 42%). Many of these were megaloblastic. The red cells were hypochromic with moderate anisocytosis, slight poikilocytosis, and marked polychromasia. Reticulocyte count 3.2%, platelet count 59,000/cu.mm.

Sternal puncture revealed an intensely cellular marrow, containing many very primitive stem cells. There was extreme erythroid hyperplasia, with many pro-erythroblasts and early basophilic forms. At the later stages both normoblasts and megaloblasts were present. Many cells in mitosis could be seen, including some large polydiploid forms. In the granular series there were a few myeloblasts and promyelocytes but no more mature forms, and no Auer rods were present. No megakaryocytes and no myeloma or other tumour cells could be seen. The periodic acid Schiff (PAS) reaction (Hayhoe, Quaglino and Flemans, 1960) was strongly positive in the erythroid precursors. Paraffin sections of the marrow confirmed the hypercellularity and the absence of megakaryocytes and tumour cells. Perls' reaction showed free iron to be reduced.

Direct and indirect Coomb's tests, Donath-Landsteiner, and Ham's acid serum tests were negative. Paper electrophoresis and alkali denaturation of haemoglobin gave normal results. The blood group was A, Rh. positive. Bleeding time by Duke's method was 7 min., and clotting time by Lee and White's method 7 min. Hess's capillary fragility test was strongly positive. Prothrombin time by Quick's one-stage method was 16 sec., control being 14 sec. Serum vitamin B₁₂ level was 20 μg./ml. on two occasions. An augmented histamine test meal (Kay, 1953) showed hyperchlorhydria. The direct serum bilirubin reaction was negative, but the indirect serum bilirubin was 2.4 mg./100 ml. Other liver function tests and plasma protein levels were normal. Urobilinogen, urobilin,
and bilirubin were absent from the urine. Faecal uro-
bilirubin level was 43.2 mg./100 g. wet faeces, and repeat-
ed examinations for occult blood were negative. Micro-
scopic examination of the faeces showed no abnormality.
Serum electrolytes normal, blood urea 49 mg./100 ml.,
ESR 52 mm./1 hr. (Westergren). Chest X-ray was
normal. ECG showed left ventricular strain.

Clinical Course and Treatment. Tolbutamide was
discontinued, the diabetes was well controlled on soluble
insulin for ten days, and thereafter with 28 units lente
insulin per day. Transfusions of packed cells and
whole blood were given. Crystalline penicillin, 1 million
units twice daily, was administered for nine days. This
was followed by oral penicillin until 9.12.60, when
tetracycline, 1 g./day, was started. A good diuretic
response was obtained to mersalyl but improvement
was transient. In view of the low serum vitamin B\textsubscript{12}
level he was given 1,000 μg. cyacobocobalamin daily for
ten days and on 28.11.60, three weeks after admission, the
serum B\textsubscript{12} level was over 1,000 μg./ml. Reticulo-
cyte counts repeated during the course of the illness
never rose to more than 4\%.

The anemia progressed and on 7.11.60, after transfusion of 1 1/2 pints of packed
cells, total nucleated cell count had fallen to 8,400/
cu. mm. in the peripheral blood, of which 1,386 were
lymphocytes. The remaining cells were nucleated red
and blast cells. This picture remained fundamentally
unchanged until the patient died. Epistaxis and further
retinal hemorrhages occurred and petechiae became
evident. Predniadione, 30 mg./day, was started four
weeks after the patient's admission but did not effect
any improvement. Pyrexia continued and blood culture
revealed a B. coli septicemia. The patient died on
9.12.60.

Permission for autopsy was refused but further
sternal marrow tissue obtained post mortem confirmed
the findings from two marrow aspirations made during
life.

Discussion

Dameshek and his colleagues have proposed
certain criteria in the diagnosis of this disease.
The marrow should show erythroid hyperplasia
with maturation arrest at a primitive level, megaloblastoid features, increased mitoses with frequent
abnormal figures, degenerative features, and a vary-
ing degree of myeloblastic proliferation. The blood
picture is that of a macrocytic anemia, with aniso-
cytosis, poikilocytosis and erythroblastosia, normal,
decreased or slightly increased white cell count and
occasional to frequent myeloblasts. The disease is
invariably fatal and, although supportive therapy
may prolong life, no specific treatment is effective.

In addition, Quaglino and Hayhoe (1960) have
pointed out the importance of the periodic acid
Schiff test for glycogen and related mucopolysaccharides in the diagnosis of this disease. They
found that the erythroblasts were strongly positive.
A similar reaction was found in iron-deficiency anaemia and thalassemia major, but in no other
megalooblastic anemia apart from Di Guglielmo's
disease. In the case presented all the features of the
blood and bone marrow were as described by
Dameshek and the periodic acid Schiff reaction
was strongly positive.

In the pathogenesis of this disease toxicity or
sensitivity to drugs did not seem possible, since
tolbutamide was the only drug which he had been
given. No blood dyscrasias have been reported
with this and symptoms had actually started before
therapy was commenced.

It is interesting to compare this marrow picture
with that found in Addisonian pernicious anemia
in which there is also erythroid hyperplasia and
megalooblastosis, and without treatment this disease
also has a fatal outcome. It is, of course, known that
the marrow changes in pernicious anemia are due to
defective absorption of vitamin B\textsubscript{12} with consequent
low serum vitamin B\textsubscript{12} levels.

In six cases of Di Guglielmo's syndrome serum
vitamin B\textsubscript{12} levels have been normal or high. The
levels recorded were 1,100 μg./ml., 1,180 μg./ml.,
2,544 μg./ml. (Baldini and others, 1959); 1,800
μg./ml., 510 μg./ml. (Spray and Witts, 1958);
150 μg./ml. (Adams and Seaton, 1960). Spray and
Witts used microbiological assay by Lactobacillus
leichmanii, as in this case, while Euglena gracilis
was the organism used by the others. Although
the results given by the two methods are not
strictly comparable, they are of the same order
(Girdwood, 1960). The unusual feature in this case
was the extremely low vitamin B\textsubscript{12} level, which was
repeated with identical result. The possibility of
inhibition of the microbiological assay by penicillin
was considered, since the patient had received one
million units twice daily for three days before the
first estimation was made. Bruce (1961) has shown
that penicillin may affect the estimation, but only
appreciably when serum B\textsubscript{12} levels are normal or
high, when active growth of the organism is possible
and penicillin can exert its bactericidal action. In
the method used to estimate the serum B\textsubscript{12}
the penicillin was diluted beyond its effective
concentration. The very low levels found in this case could
not be accounted for by the antibiotic.

Di Guglielmo's disease is a megaloblastic anemia,
which is known not to respond to vitamin B\textsubscript{12}.
The high serum vitamin B\textsubscript{12} levels found in other
cases have led to the suggestion that there is a
defect of utilization at the cellular level (Dameshek,
1958). This case throws some doubt on this con-
cept, since the problem posed here was that of a

Fig. 1.—Showing megaloblasts and normoblasts in
peripheral blood. \times 860.
megaloblastic anaemia, with low serum B₁₂, unresponsive to parenteral cyanocobalamin therapy. Although the patient’s serum vitamin B₁₂ level was raised from 20 to 1,000 μg./ml. by therapy, there was no clinical or haematological response. Further study of vitamin B₁₂ metabolism in this disease is clearly required.

Summary

A case of Di Guglielmo’s syndrome has been described, in which megaloblastic anæmia was associated with low serum vitamin B₁₂ level. The case is compared with others previously described. The need for further study of vitamin B₁₂ metabolism is emphasized.

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Addendum

Since this paper was prepared work has been published (Boczarow, 1961) suggesting that penicillin will invalidate B₁₂ assay by the L. leichmannii method. Previous work by Dr. L. G. Bruce, in the clinical laboratories of the Victoria Infirmary, did not suggest this and estimations of serum vitamin B₁₂ levels in our patient were done by his methods, which differ slightly from those of Boczarow. The validity of the results was confirmed by further studies, which will shortly be published.

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LIFE FROM A COUVELAIRE UTERUS

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As a result of the use of human fibrinogen in the treatment of the blood coagulation defect associated with abruptio placentæ, for which the work of Weiner and Schneider was mainly responsible, it is now widely appreciated that, until the correction of this coagulation defect, active interference of any sort is fraught with danger. On the subject of the method of delivery, however, there appears to be a great divergence of opinion.

The fetal mortality rate in the more severe degrees of abruptio placentæ is reported by almost all authors to be 100%. In the presence of a Couvelaire uterus a living infant is even more rare.

Case 1

A gravida three, aged 29, was admitted to St. Paul’s Hospital, Hemel Hempstead, as an emergency case of ante-partum haemorrhage, on July 3, 1961. On admission a history of a sudden painless blood loss of approximately 10 oz. was obtained. The pregnancy had been uneventful. The estimated date of delivery was June 9, 1961. The previous pregnancies had been 43 weeks and
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