ERYTHRAEMIC MYELOSIS (DI GUGLIELMO'S DISEASE) OCCURRING IN AN INDIAN — CASE REPORT

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INTRODUCTION

Erythraemic myelosis is sufficiently rare to warrant the reporting of a single case. Cases have been reported in Argentina, Belgium, England, France, Germany, Italy, Japan, Sweden, Switzerland and the United States. In a search of the literature we have been unable to find a report of this disease in an Indian, so that we presume that this is the first case report of the disease occurring in a member of the Indian race.

In retrospect, it appears that the first genuine case of erythraemic myelosis to be reported in the medical literature was a case reported by Copelli in 1912. In an article entitled, "A Systemic Hemopathy with Erythroblastic Hyperplasia", he described a case which presented clinically with weakness, anaemia and splenomegaly. The peripheral blood showed a normocytic normochromic anaemia and leukopenia. Autopsy revealed abnormal erythroblastic cells in hepatic sinusoids, splenic pulp, bone marrow and lymph nodes. The predominant cells in the lesions were large primitive erythroblastic cells, which Copelli likened to the primitive blood cells of Maximow with smaller numbers of "atypical megaloblasts" and "normoblasts" being present. Copelli considered that the lesions represented neoplasia of the early erythropoietic cells and he termed this disorderly hyperplasia of erythropoietic cells "atypical erythromatosis".

In 1917, Di Guglielmo reported a case designated by him as "eritoleucemia" (-erythroleukemia-). He considered that this case showed abnormal proliferation of both erythropoietic cells and leukopoietic cells, and that the abnormal erythropoiesis was an integral part of the disease process and not merely secondary to the abnormal proliferation of the leukopoietic cells. In 1923, Di Guglielmo published a case which he termed "eritremia acuta" (-acute erythraemic myelosis-). He believed that this case represented pure abnormal proliferation of erythropoietic cells and considered that this abnormal proliferation was similar in nature to the leukaemic process which affects leucopoietic cells. In 1926, Di Guglielmo reported two further cases of erythraemic myelosis, one in a new-born infant and the other in a man aged 50 years. In a publication in 1928, Di Guglielmo reviewed these three cases of erythraemic myelosis. It is worthy of note that only the third of these three cases can stand critical examination. In 1936, Di Guglielmo reviewed the subject and considered that 21 cases in the Italian literature conformed to his concept of erythraemic myelosis.

In 1940, Moeschlin reviewed the subject and accepted only five published cases as true examples of erythraemic myelosis. He considered that many cases could not be accepted because of inadequate data or diagnostic errors. This is not surprising when one remembers that Di Guglielmo for many years considered that cases, which we now recognise as Cooley's anaemia, were varieties of erythraemic myelosis. Also many of the cases reported in the earlier literature showed persistent extreme elevation of the reticulocyte count. Such cases are not acceptable, as one of the rigid criteria for diagnosis of this disease is the presence of a marked degree of maturation arrest of erythropoiesis. Such persistently high reticulocyte counts are clearly incompatible with such a maturation arrest and these cases almost certainly represented primary haemolytic anemias. It is not denied that a secondary haemolytic element may be present, in this disease, but if such a secondary haemolytic element is present, then it is certain that the abnormal erythropoietic cells cannot respond so as to produce persistently high levels of reticulocytes.

In 1946, Di Guglielmo reviewed the subject once more and redefined his concepts of erythraemic myelosis and laid down new diagnostic criteria.

The following are Di Guglielmo and Moeschlin's concepts of erythraemic myelosis.

Erythraemic myelosis is a disease characterised by generalised hyperplasia of erythropoietic cells. This hyperplasia is irreversible, unaffected by any known therapy and always terminates fatally. This hyperplasia is present not only in bone marrow but in hepatic sinusoids, splenic pulp, lymph nodes and in other extramedullary sites where reticulum cells of erythropoietic potential occur. The erythropoietic cells show anaplasia with a marked degree of maturation

arrest and dysplasia with nuclear and cytoplasmic abnormalities. In many cases the dysplasia is manifested by the presence of cells resembling true megaloblasts and the adjective "megaloblastoid" has been used to describe these cells. There is a frequently evidence of hyperplasia of primitive reticulum cells and transitional forms between these reticulum cells and proerythroblasts (rubriblasts) are frequently seen.

Erythroleukaemia is a disease characterised by exactly the same generalised anaplastic and dysplastic hyperplasia of erythropoietic cells as is seen in erythraemic myelosis. The same hyperplasia of primitive reticulum cells and the same transitional forms between reticulum cells and proerythroblasts (rubriblasts) are frequently seen. However, in addition there is leukaemic proliferation of myeloblasts in the lesions side by side with the abnormal erythroblastic proliferation.

We regard both erythraemic myelosis and erythroleukaemia as proliferative disorders of the reticulo-endothelium or to use a more frequently used term, myeloproliferative disorders.

In 1958, Dameshek and Baldini pointed out in a timely editorial, that there is no valid distinction between erythraemic myelosis and erythroleukaemia. They reported that cases, which on initial examination showed pure erythroblastic proliferation, later showed mixed erythroblastic and myeloblastic proliferation and that some cases finally terminated with predominant myeloblastic proliferation, which was indistinguishable from acute myeloblastic leukaemia. These authors used the term "Di Guglielmo Syndrome" to embrace both so-called pure erythraemic myelosis and erythroleukaemia. These views of Dameshek and Baldini are confirmed by the findings in five cases of erythroleukaemia reported by Martin and Bayrd in 1954. Therefore it would appear that erythraemic myelosis and erythroleukaemia together constitute one variety of myeloproliferative disorder termed the Di Guglielmo Syndrome and that if the survival of cases of "pure" erythraemic myelosis can be prolonged then the mixed picture of erythroleukaemia will often be seen.

The case to be presented is one of "pure" erythraemic myelosis but it must be realised that the patient was only under medical observation for three days and that the time elapsing from the onset of the first symptom till death was only seventeen days.

CASE REPORT

R.K., a male Indian of 41 years was admitted to the General Hospital, Singapore, on 25th June, 1958, with irregular fever, vague abdominal pains, increasing weakness and increasing breathlessness. All these symptoms were of only two weeks' duration, the patient maintaining that he had felt well until two weeks prior to admission. The vague abdominal pains were experienced in the upper half of the abdomen and accompanying these pains there was marked anorexia. No nausea or vomiting was experienced. The weakness and breathlessness both became progressively worse so that on the day of admission he could not walk due to severe general weakness and he felt quite breathless even when sitting or lying in bed. The patient had one attack of malaria 14 years previously but without subsequent attacks. He had no other serious illnesses.

Clinical examination revealed a well nourished man of average build. Extreme pallor and extreme dyspnoea were present. The respiratory rate was 30 per minute. The oral temperature was 101.8°F. and the pulse rate was 128 per minute, regular. The skin was hot and dry and showed no evidence of a rash, telangiectasia, echymoses or purpura. No jaundice of skin or sclera could be detected. The oral cavity and tongue were normal apart from marked mucosal pallor. The blood pressure was 110 mm. Hg. systolic and 50 mm. Hg. diastolic. The heart, on clinical examination was slightly enlarged both to the left and to the right. A soft blowing haemic systolic murmur was present in all areas of the precordium. The lungs were clinically clear. The cervical, axillary and inguinal lymph nodes were not enlarged. The liver was slightly enlarged, the edge being palpable 3.0 cm. below the right costal margin. The spleen was moderately enlarged and palpable 2.0 cm. below the left costal margin. The patient showed no neurological abnormality.

The capillary resistance test of Hess was negative.

INVESTIGATIONS

Chest X-ray: The heart showed moderate diffuse enlargement, the appearances being consistent with the cardiac dilatation seen in severe grades of anaemia.

Peripheral Blood: 28th June, 1958 (Day of admission): Haemoglobin 3.1 Gm%; Red cells 1,200,000 per cu. mm.; Leukocytes 6,700 per cu. mm.; Platelets 1,500 per cu. mm.; Reticulocytes 0.6%; Differential Leukocyte Count (To include Normoblasts) Neutrophils 82%; Eosinophils 0%; Basophils 0%; Lymphocytes 12%; Monocytes 4%; Normoblasts 2% (the normoblasts present were basophilic and polychromatic normoblasts); Total Normoblasts 134 per cu. mm.

Red cell morphology: The red cells were normocytic and normochromic; moderate anisocytosis was present but no distinct macrocytosis was present. The normoblasts present in the peripheral blood showed the same features as those present in the bone marrow aspirate to be described below.

Sternal bone marrow aspiration on June 25, 1958 (day of admission) revealed an extremely hypercellular marrow, the marrow fragments in the tails of the films being composed entirely of haemopoietic cells with no evidence of adipose tissue cells being present.

The following myelogram was found:

Primitive Reticulum Cells	2.0%
Proerythroblasts (Rubriblasts)	45.0%
Basophilic Normoblasts (Basophilic Rubricytes)	33.5%
Polychromatic Normoblasts (Polychromatic Rubricytes)	5.0%
Orthochromatic Normoblasts (Metarubricytes)	3.0%
Proerythroblasts (Rubriblasts) and Basophilic Normoblasts (Basophilic Rubricytes) in Mitosis	5.0%
Myeloblasts	0.5%
Promyelocytes	0.5%
Neutrophil Meylocytes	0.5%
Neutrophil Metamyelocytes	1.0%
Neutrophil Band Forms	1.0%
Mature Neutrophils	3.0%
Eosinophil Myelocytes	.0%
Eosinophils	.0%
Plasma cells	.0%

Megakaryocytes: None seen despite a careful search.

Erythroid: Myeloid Ratio 14:1.

As can be seen above, the hypercellular marrow was composed almost entirely of erythropoietic cells, which constituted 91.5 per cent of the cells present. Cells which appeared to represent transitional forms between the primitive reticulum cells and the proerythroblasts (rubriblasts) were seen. The proerythroblasts and basophilic normoblasts showed the following features. Large size; these cells ranged from 15 μ to 45 μ in diameter; the cytoplasm was deeply basophilic and frequently showed numerous small empty vacuoles; an occasional cell showed basophilic granulation of the cytoplasm. Many cells were multinucleated showing from two to eight nuclei; the chromatin pattern of the nuclei was finely stippled, the proerythroblasts (rubriblasts) showing one to four large nucleoli while the basophilic normoblasts (basophilic rubricytes) were devoid of nucleoli. Mitoses were numerous (5.5 per cent of total erythropoietic cells present) and were often abnormal. Several tripolar mitoses were seen. Amitotic division of nuclei was frequently observed in the multinucleated cells.

The polychromatic and orthochromatic normoblasts (basophilic rubricytes and metarubricytes) numbered only 8.7 per cent of the total erythropoietic cells indicating a severe degree of maturation arrest. In addition these cells showed "megaloblastoid" features being from two to three times normal size, showing an immature chromatin pattern in the nuclei when considered in relation to the degree of haemoglobinisation of the cytoplasm and showing bizarre convolution and bizarre lobing of nuclei. Occasional extremely large non-nucleated red cells measuring from 20 μ - 25 μ in diameter were seen in the marrow. As these cells were not seen in the peripheral blood it is presumed that they were either not released into the peripheral blood or having been released, survived in the peripheral blood for only a short period.

Granulocytes and their precursors accounted for only 6.5 per cent of the total cells present. These cells showed no abnormalities and there was certainly no evidence of myeloblastic proliferation. No megakaryocytes could be found despite a careful search.

Briefly the marrow may be described as showing marked hyperplasia of erythropoietic cells with dysplasia and anaplasia with severe maturation of these cells, depression of granulocytes and their precursors and absence of megakaryocytes.

On the basis of the bone marrow findings a diagnosis of "pure" erythraemic myelosis was made.

CLINICAL COURSE

On the day following admission the patient was given a blood transfusion of 1 litre of whole blood. However his clinical condition deteriorated, dyspnoea and weakness increasing in severity. The irregular pyrexia continued the temperature fluctuating between 99°F. and 103°F. The patient's deterioration continued, death occurring on 28th June, 1958, seventy two hours after admission.

AUTOPSY (Performed 19½ hours after death)

The significant findings only are given:

Microscopic:

Extreme pallor of all organs.

Fatty degeneration of cardiac muscle ("thrush's breast" appearance).

Liver (1,625 Gm.) slightly enlarged, appeared normal on cut surface.

Spleen (345 Gm.) moderately enlarged; splenic substance soft, diffluent in consistence, deep red in colour.

Bone Marrow (sternal, vertebral, femoral)

deep red in colour; soft, diffluent in consistence.

Lymph nodes: Normal size and appeared normal.

Occasional small petechiae were present in the visceral and parietal pericardium and in the endocardium of the left ventricle.

No true haemorrhagic manifestations were found.

MICROSCOPIC

Sections of bone marrow, spleen and liver were available for study.

The bone marrow showed complete replacement by hypercellular tissue composed almost entirely of large primitive erythroblastic cells. These cells showed large oval or round nuclei, often with large eosinophilic nucleoli, and a small amount of deeply basophilic cytoplasm. Many erythroblasts in mitosis were seen and occasional multinucleated erythroblastic cells were seen. Occasional haemoglobinised erythropoietic cells were present.

The spleen showed almost complete replacement of the splenic pulp by erythropoietic tissue identical with that seen in the bone marrow.

The liver showed accumulations of similar abnormal erythropoietic cells in the hepatic sinusoids. The centrolobular zones of the liver lobules showed fatty degeneration, numerous small droplets of lipid being present in the cytoplasm of the hepatic parenchymal cells. This latter change is frequently seen in patients dying with a severe degree of anaemia.

SUMMARY OF CASE REPORT AND DISCUSSION

The patient presented with fever, breathlessness and weakness of two weeks' duration. Examination revealed pallor, cardiac dilation, slight hepatomegaly, moderate splenomegaly, complete absence of haemorrhagic manifestations and a negative capillary resistance test of Hess.

The peripheral blood showed a severe normocytic normochromic anaemia (Hb. 3.1 Gm. per cent), normal total leukocyte count, normal differential leukocyte count, a small number of normoblasts (134 per cu. mm.) and severe thrombocytopenia (1,500 per cu. mm.).

Sternal bone marrow aspirates revealed an intensely hypercellular marrow composed almost entirely of erythropoietic cells showing anaplasia with a severe degree of maturation arrest and dysplasia. The granulocytic elements appeared morphologically normal and were reduced in number. Megakaryocytes were absent.

A diagnosis of "pure" erythraemic myelosis was made and a blood transfusion was given, but the patient died 72 hours after admission.

Autopsy revealed abnormal erythroblastic proliferation in bone marrow, splenic pulp and hepatic sinusoids. Changes due to severe anaemia (fatty degeneration of cardiac muscle and liver; pericardial and endocardial petechiae) were present. No true haemorrhagic manifestations were present.

Certain features of interest were present in this case:

(1) This case is considered to be an acute form of erythraemic myelosis on the basis of the short duration of symptoms, the short survival time and the morphological criteria of the severe degree of maturation arrest of erythropoietic cells and the marked atypical and dysplastic changes in the erythropoietic cells. Of the total erythropoietic cells present in the bone marrow polychromatic and orthochromatic normoblasts (polychromatic rubricytes and metarubricytes) constituted only 8.7 per cent, emphasising the severe degree of maturation arrest.

Two points of difference between this case and many of the previously reported cases of acute erythraemic myelosis are present. Firstly this case showed only a small number of normoblasts in the peripheral blood (134 per cu. mm.), whereas most of the previously reported cases of acute erythraemic myelosis have shown extremely large numbers of normoblasts in the peripheral blood. It is thus apparent that in true examples of this disease "erythroblastosis" of the peripheral blood may be very minor in degree. Dameshek and Baldini further point out that "anerythroblastic" forms with no normoblasts in the peripheral blood do occur. Secondly, this case showed complete absence of haemorrhagic manifestations during life and at autopsy, whereas many of the previously reported cases of acute erythraemic myelosis have shown prominent haemorrhagic manifestations. It is thus apparent that haemorrhagic manifestations are not always present in acute erythraemic myelosis.

(2) The combination of marked thrombocytopenia (1,500 per cu. mm.) with complete absence of haemorrhagic manifestations during life and at autopsy is of interest. This combination is frequently seen in some cases of aplastic anaemia and is occasionally seen in other haematological disorders. The presence of this combination in this case further supports the well established view that haemorrhagic manifestations in thrombocytopenic states are sometimes due to capillary abnormality and may not be

related to the accompanying thrombocytopenia. These views have been well expressed by Macfarlane, whose extensive work on this subject is well known.

The occasional small pericardial and endocardial petechiae found at autopsy are not to be regarded as haemorrhagic manifestations. They are frequently found in patients dying with severe grades of anaemia and are manifestations of capillary damage due to anaemic hypoxia.

(3) With regard to diagnosis and differential diagnosis, little difficulty was experienced in this case. Acute haemolytic anaemia, which often figures prominently in the differential diagnosis of acute erythraemic myelosis, could be readily discarded because of the normal reticulocyte count and the severe degree of maturation arrest and dysplasia of the erythropoietic cells of the bone marrow. However, Owren has shown that haemolytic anaemias during crises may show a severe degree of maturation arrest of erythropoietic cells in the bone marrow. This gives rise to little difficulty in diagnosis, as while the marrows from such cases of haemolytic anaemia in crisis may show severe degrees of maturation arrest, there is absence of the severe atypical and dysplastic changes in the erythropoietic cells, which are such prominent features of the erythropoietic cells of acute erythraemic myelosis.

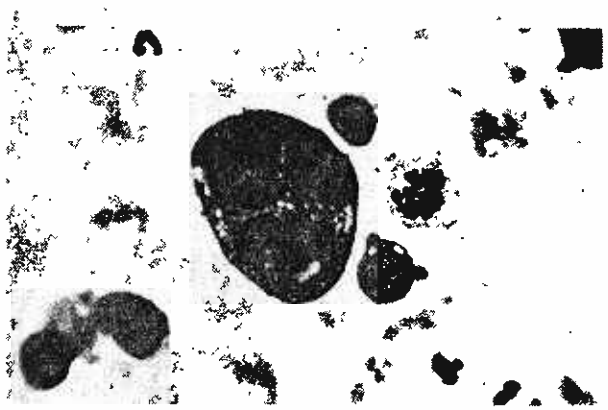
Megaloblastic anaemia could be readily discarded as a diagnosis because of the absence of macrocytosis of the peripheral blood and the bone marrow morphology. While megaloblastoid changes were present in the polychromatic and basophilic normoblasts (polychromatic rubricytes and metarubricytes), the anaplasia with severe maturation arrest and the atypical features of the erythropoietic cells and the absence of giant metamyelocytes readily enabled true megaloblastic erythropoiesis to be discarded as a possible cause of the bone marrow changes.

A careful search of the bone marrow revealed no evidence of myeloblastic proliferation, so erythroleukaemia could be discarded as a diagnosis.

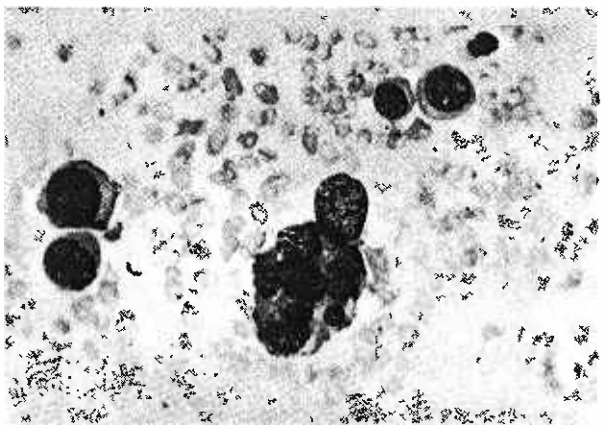
We consider that the changes present in the aspirated bone marrow were so clear cut that any diagnosis other than acute erythraemic myelosis could not be seriously considered.

SUMMARY

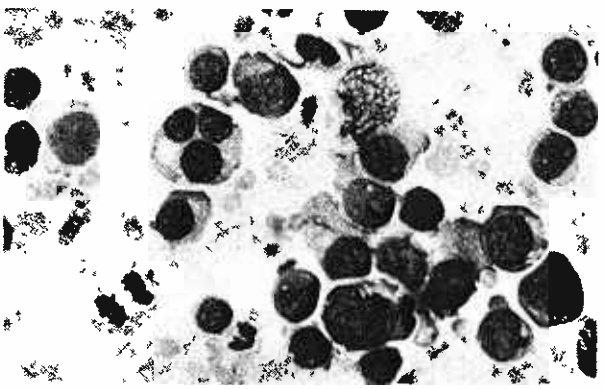
A case of acute erythraemic myelosis is presented. It is believed that this constitutes the first report of erythraemic myelosis occurring in a member of the Indian race. While agreeing with the unitarian concept that erythraemic myelosis and erythroleukaemia together represent one variety of myeloproliferative disorder and with the view that many cases of "pure" erythraemic myelosis eventually evolve into erythroleukaemia, we present this case as one of "pure" erythraemic myelosis with no evidence of myeloblastic proliferation.



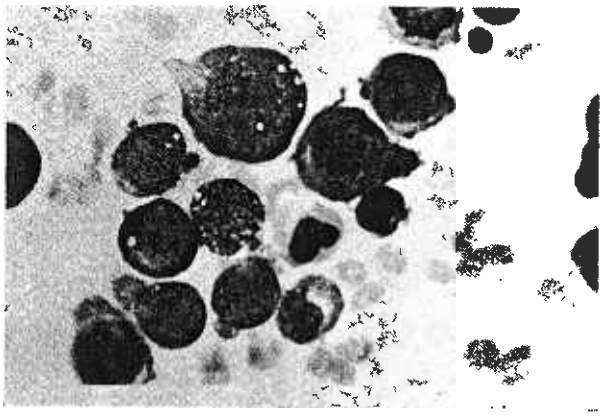
Bone marrow aspirate: Showing a large trinucleate basophilic normoblast (basophilic rubricyte) with a deeply staining cytoplasm and prominent cytoplasmic vacuolation. X 1400.



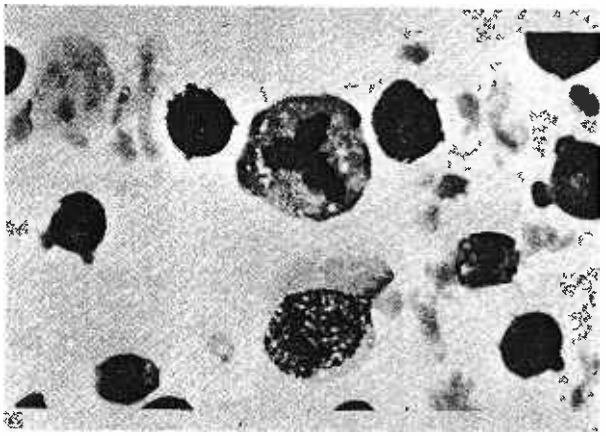
Bone marrow aspirate: Showing a huge, atypical, basophilic normoblast (basophilic rubricyte) with seven nuclei and deeply staining cytoplasm. X 1400.



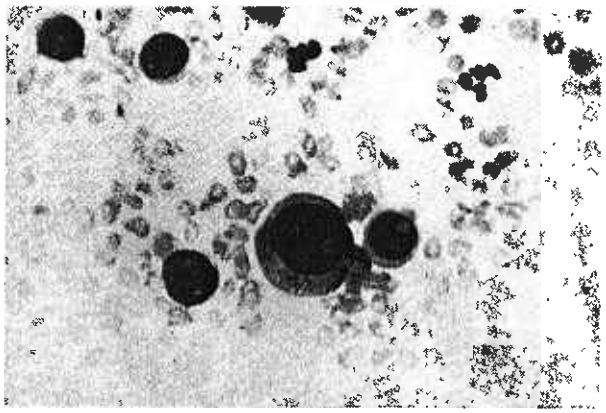
Bone marrow aspirate: Showing a trinucleate polychromatic normoblast (polychromatic rubricyte), an erythroblastic cell in mitosis and proerythroblasts (rubriblasts) and basophilic normoblasts (basophilic rubricytes). X 640.



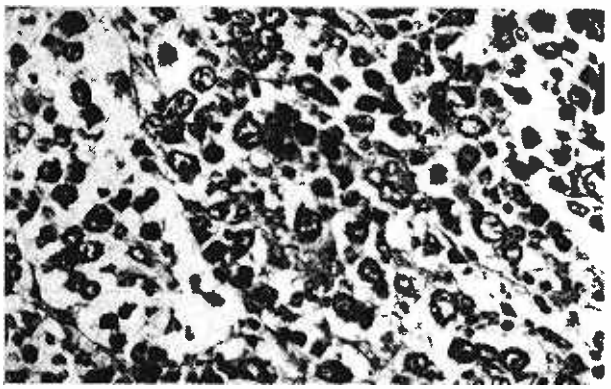
Bone marrow aspirate: Showing several basophilic normoblasts (basophilic rubricytes) and one orthochromatic normoblast (metarubricyte) with megaloblastoid features. X 1400.



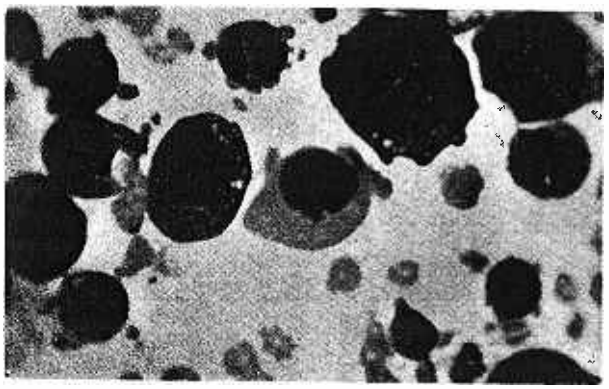
Bone marrow aspirate: Showing tripolar mitosis in a cell which is either a proerythroblast (rubriblast) or a basophilic normoblast (basophilic rubricyte). X 1400.



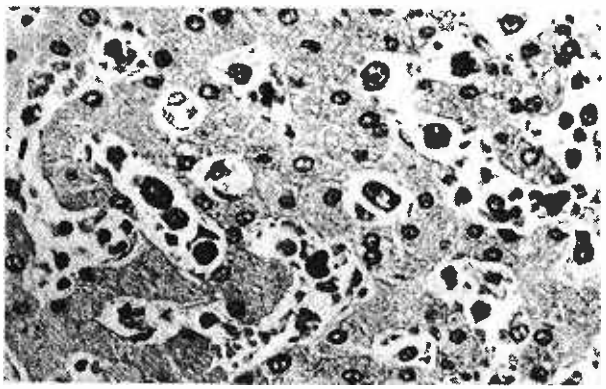
Bone marrow aspirate: Showing two proerythroblasts (rubriblasts) with finely stippled chromatin and prominent nucleoli; fine vacuolation of the cytoplasm of the larger cell is seen. X 640.



Splenic pulp (Autopsy): Showing virtual complete replacement of normal pulp tissue by abnormal, erythroblastic cells with deeply staining cytoplasm. A binucleate primitive erythroblastic cell is well shown. X 280.



Bone marrow aspirate: Showing an orthochromatic normoblast (metarubricyte) with basophilic stippling. Two extremely large, atypical, basophilic normoblasts (basophilic rubricytes) are present showing cytoplasmic vacuolation. X 1400.



Liver (Autopsy): Showing numerous large, abnormal, erythroblastic cells in hepatic sinusoids. X 280.

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