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Erythroleukemia : a review

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ERYTHROLEUKEMIA: A REVIEW

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INTRODUCTION

In 1923, under the designation of erythremic myelosis, Di Guglielmo described a new form of proliferative blood disease involving, not the white cells, but the nucleated red cells.[3] His initial conception of erythroblastic proliferation akin to leukemia was apparently derived from the case of mixed white cell-red cell disorder which he described in 1917 as erythroleukemia. Since that time erythroleukemia (or as Di Guglielmo called it, erythremic myelosis) has become a controversial topic. Its very existence as a specific disease entity has even been challenged. Synonyms which have been proposed for erythremic myelosis are: panmyelosis, sub-leukemic myelosis, polycytene myelogene, and hyperplastic panmyelopathy.[13] The more recent name for this disease is erythroleukemia, suggesting that it is a malignant disease involving both red and white cells.

Although Di Guglielmo early emphasized that erythremic myelosis was an acute, highly specific pathologic entity, his later publications indicated not only some modification of his original views,

but a growing complexity of classification, particularly for the so-called mixed forms. In the meantime, a prolongation of the usual course of the disease by the use of such therapeutic measures as transfusions, antibiotics, etc., has revealed that the end result of most cases is an acute leukemic process.

With these things in mind it is the purpose of this paper to discuss the development of erythremic myelosis as a specific disease entity to its present state of erythroleukemia, the various clinical signs and symptoms, the blood findings--both peripherally and in bone marrow studies, and then to present a few case studies from the University of Nebraska Hospital for comparison with case studies which have been reviewed by other examiners.

HISTORY

In Di Guglielmo's original concept he continually stressed purity of the disorder as an autonomous pathologic entity of the erythropoietic tissue.[3] However, there have been various studies which have indicated that the pureness of this disease is somewhat equivocal and that there are very few unequivocal cases thus far recorded.

Di Guglielmo's original cases suggested that there were increased numbers of erythrocytes, leukocytes, and platelets in the peripheral blood. He therefore maintained that the erythrocytic alteration could not be considered secondary to a leukemic process, but that the lesion was primary in the myeloid tissue and affected all three cytopoietic components. From his study he conceived the idea of a primary erythroblastic proliferation analagous to leukemia and, not incidentally associated with, but the result of the same pathogenetic process. Again in 1923 Di Guglielmo published a case which he considered to be the first example of a true erythremic myelosis. This was followed in 1926 by the report of two more cases--one in a newborn child, the other in a fifty year old man. In 1936 Di Guglielmo recognized about twenty-one cases in the Italian literature which corresponded

to his interpretation of erythremic myelosis. In this article he took cognizance of the work of Cooley in the clarification of the entity known as erythroblastic anemia, or Cooley's anemia.[18]

In 1937 the subject of erythremic myelosis was again reviewed by Storky, and in 1938 by Beserge who collected twenty-nine cases from the Italian literature. The subject was again reviewed by Moeschlin in 1940, and in his opinion did not stand critical evaluation because of either insufficient data or diagnostic errors.[18]

In 1951 Blackburn suggested that erythremic myelosis was an unresponsive anemia associated with a leuko-erythroblastic blood picture. It could be seen in carcinomatosis, leukemia in an early phase, Hodgkin's disease, toxic aplastic anemia, hemolytic anemia, myelosclerosis, myeloma, syphylis, TB, lipidosis, etc. He suggested that the clinical course was short, but failed to mention whether he thought there was a separate entity called erythroleukemia, not associated with any of the above mentioned disease states.[2]

In 1957 Dickenman presented a case which showed a hypercellular bone marrow during life with a great increase in the erythroblastic series during the course of the illness with no significant change in the

granulopoietic or megakaryocytic series. Based on a prolonged course the patient had no demonstrable hemolytic disease.[5] There were increased numbers of polychromatophilic and orthochromic erythroblasts. However, Dickenman concluded that the positive erythroblastic hyperplasia, which was shown to have increased during the course of the disease, was consistent with the diagnosis of erythremic myelosis as suggested by the criteria established by Di Guglielmo in 1923.

During this period of years the idea has gradually developed that erythroleukemia represents a disease that may start with a proliferation of the erythroblastic series of the bone marrow, but if the patient lives long enough the blood picture will terminally represent a picture of acute granulocytic leukemia.[6] In fact, as early as 1928 Myers presented a case report of a forty-two year old white female with a red count of 7,420,000, a hemoglobin of sixty per cent, a white count of 10,400 with twenty per cent myelocytes. During the clinical course Myers did not feel that this was an erythroleukemia and he believed that the increase in red cells indicated that there was no leukemic element present. However, at autopsy he showed that there was an erythroleukemic condition as a result of stimulation of both functions of the

common blast cell. For this reason he suggested the name panmyelosis for this co-existing hyperplasia of the granuloblastic and erythroblastic elements of myeloid tissue.[14]

In 1942 Verloop presented a case study of a twenty-nine year old white male which illustrated the close relationship existing between the pathologic proliferation of erythropoietic and granulopoietic systems. He drew no conclusion, but simply posed the question as to how closely related this disease is to leukemia, Hodgkin's disease, hemolytic anemia, and a hemolytic crises.[21] In this patient Verloop showed a blood picture similar to that of patients reviewed by Martin in 1954. Martin concluded that erythroleukemia was characterized by an excessive hemopoietic activity of bone marrow which may express itself clinically in a polycythemic state at one end, or as a granulocytic leukemia at the other. The blood picture he found most predominant was that of the patient who presented with hypochromasia, polychromasia, microcytosis, thrombocytopenia, and anisocytosis.[13] All of the patients had poikilocytosis. Chief complaints varied from stomach trouble, abdominal cramps, "low blood," anemia, vomiting, rash, weakness, malaise, and weight loss. The various clinical findings were

fever, pallor, edema, dyspnea, paresthesia, blurred vision, heart murmur, splenomegaly, hepatomegaly, and hemorrhagic tendencies. He suggests that, broadly speaking, any combination of polycythemia and leukemia can or possibly should be considered erythroleukemia. He then states that there are two types of erythroleukemia--the acute and the chronic--and that the chronic stage is that originally described by Di Guglielmo. The acute stage is universally fatal in one to two months. It is characterized by anemia, irregular fever, splenomegaly, hepatomegaly, and erythroid hyperplasia. He then suggests that the pattern of the clinical course is at first an acute erythremia which results in an acute leukemia.

In the chronic form the patient may live up to two years. He will probably have orthochromic erythroblasts which are somewhat less atypical than those which appear in the acute cases. Thus, these patients may develop a leukemia at the onset and have a final presentation of polycythemia vera, a leukemia and polycythemia simultaneously, or they may reverse the first case and present early with a polycythemia vera only to have a subsequent development of a full blown acute leukemia, usually of a granulocytic nature.[13]

The one evident factor in many of the articles was the universal appearance of the hyperplastic marrow characterized by an increase in the erythroid series, marked anisocytosis, poikilocytosis, polychromasia, and a decrease in platelets in the peripheral blood.[3,5,18,19,20] However, in 1962 Roath presented twenty-four cases which appeared over a period of twenty years at Manchester University in England. The presenting symptom was anemia, but none showed any hematologic malignancy and he regarded these findings as indicative of a "true anemia". The writer questions whether the chronic erythremic myeloses are linked with chronic leukemia or to a chronic refractory anemia of unknown etiology, as the acute stage of erythremic myelosis is closely related to acute leukemia. He feels that the answer is not purely of academic interest, but is of more interest in regard to the ultimate treatment of the disease because the mitotic arresting drugs used in treatment of leukemia are not suitable for the treatment of refractory anemia. He concludes that the chronic erythremic myeloses are best linked with refractory anemia.[17]

Newmark suggested in 1960 "that the bone marrow, like mesenchymal tissue, may undergo proliferative changes in several ways." He points out that marrow

tissue consists of the erythropoietic, myelopoietic, and megakaryocytic portions. Each may occur alone or in combination. (Damashek had suggested this as early as 1951.) Newmark proposes that the hyperplastic changes which we find in the bone marrow of patients with erythremic myelosis may actually be a combined sect of all three of the mesenchymal elements in the bone marrow reacting when one of the three is diseased. Therefore, if a person had an acute granulocytic leukemia and lived long enough, one would see a very marked proliferation of the erythroid elements of the bone marrow such that its ultimate appearance would be consistent with a diagnosis of erythroleukemia.[15]

Shively presents a case which relates to the conclusions drawn by Newmark in which the patient presented with an anemia which was associated with a leukopenia, thrombocytopenia, and a mild hemolytic anemia. However, examination of the bone marrow definitely suggested that this was an acute granulocytic leukemia. The patient did not respond to cortisone treatment. Blood transfusions were given with minimal results and clinical improvement, and the patient eventually developed an increase in the production of erythroid elements in the bone marrow. He concludes that the patient terminally had an

erythroleukemia, because as the increase in erythroid hyperplasia appeared, there was no particular decrease in the granulocytic hyperplasia. Thus, at the terminal stage, both elements were in a sense competing with each other for dominance.[20]

ETIOLOGY

The etiology of erythremic myelosis is essentially unknown. In the eighty publications which Di Guglielmo reviewed there was no correlation between age and sex, nor did either of these constitute predisposing factors.[18] However, there was a predominance of people over forty years of age in one study by Roath in 1956; twenty-four cases were presented and all but one were over fifty-five years of age.

It has not been substantiated whether there is any relation to infection. Case studies by Copielli and Benadetti indicated that there is no proof that there is.[18]

It seemed evident that, as cases were reviewed, any artificial classification of these into acute and chronic types of disorders was indefinite. It appears that there is no acute or chronic form of erythremic myelosis or erythroleukemia, and that the disease is essentially one, involving two elements of the erythropoietic system.[15,18] Perhaps even a third may be implicated as one realizes the constant relationship of thrombocytopenia associated with this disease.

There are many cases which show overlapping between the increase in both elements of the blood, and the features of each of these, and perhaps of

other conditions as well, will be recognized.[9] This probably characterizes the description of each new disease entity in medicine. At first, the syndrome is described precisely, each point being clearly delineated. As more examples appear the kaleidoscopic nature of the condition is revealed. The rarer the condition, the longer the evolution takes. It becomes evident that Di Guglielmo's original description--although precise, exacting, and having specific diagnostic criteria--was in error. The final answer is not yet obtainable and there is still controversy regarding the actual nature of erythroleukemia. At this time it is not known exactly how they are related, and further investigation is desirable.

PATHOGENESIS

In considering the pathogenesis of this disease one is reminded that Di Guglielmo considers the reactivation of the hematopoietic potential of the RE system as the initial and indispensable phase in the pathogenesis of erythremic myelosis. He does not believe, however, that the disease is primary to the reticulo-endothelial system, but is the consequence of the erythropoiesis resulting in a type of embryonal reticular endothelial genesis wherever reticulum cells of erythropoietic potential exist. He considers the fundamental pathologic characteristics of the disease to be hyperplasia, anaplasia, and dysplasia of the erythropoietic system.[18] He distinguishes the term hyperplasia as a pure proliferation affecting only the erythropoietic cells. The hyperplasia then is primary to another process. It is systemic in that the entire cellular system is eventually affected. It is generalized in that it is not limited to marrow, liver, and spleen, but affects extrahematopoietic organs as well, and it is reversible, regressing neither spontaneously, nor after therapeutic intervention.[11]

By the term anaplasia Di Guglielmo refers to the arrest of cellular maturation of the red cells in the immature primordial phases. This phenomenon is seen

especially in the acute form of the disease in which one may observe a "hiatus erythremicus" or the disappearance of intermediate forms of erythrocytic motivation. By dysplasia, Di Guglielmo refers to the pathologic differentiation of the red cells. The cells exhibiting atypical nuclei in cytoplasm are called paraerythroblasts.

Martin suggested that the pathogenesis of erythroleukemia is probably a bi-directional expression of uncontrolled efforts of the common blast cell. He observes that "Di Guglielmo considered erythroleukemia to be a result of a single force acting on a blast cell producing a simultaneous effect rather than a fortuituous association of polycythemia vera and granulocytic leukemia."[13]

Schwartz states that in analyzing the pathologic changes of erythremic myelosis the problem of extramedullary hematopoiesis must be considered.[18] The question again confronts us: Are the foci of extramedullary blood formations which are found in this condition a result of a metastatic process or of a local hematopoietic transformation of potential cells? He concludes that extramedullary hematopoiesis may occur in a variety of conditions. Its presence does not necessarily mean a neoplastic process.

The question arises as to whether erythremic myelosis should be considered solely as a disorder of erythropoiesis or as a disorder primary to the RE system. Di Guglielmo maintained that a reactivation of the hematopoietic potential of the RE system was the initial and indispensable phase in the pathogenesis of the disorder. In this case lesions would represent a type of reticuloendotheliosis.

Damashek's theory is that the marrow response is not necessarily that of a single type cell but may be non-specific and elicit response along multiple channels.[4] This theory is simplest to comprehend if one accepts the stem cell to be multipotential, and the stimulus for erythremic myelosis, erythroleukemia, leukemia, or transition from one into the other to be non-specific.

Damashek and Baldini have indicated that if the disease runs its full course it passes through several stages: "(1) a predominant erythroblastic proliferation of the bone marrow; (2) mixed erythroblastic myeloblastic growth; and (3) preponderant myeloblastic proliferation."[3] This then supports the theory that the Di Guglielmo syndrome is one of the several myeloproliferative disorders.

Schwartz has long maintained that the various leukemia's represent different form of responses to similar stimuli most likely infectious in nature, the manifestations and course of the disease being governed by host response.

In four cases which Schwartz presented he stated that the erythroleukemia might be considered as a variance of reticulo-endotheliosis for the following reasons: "(1) Hyperplasia of the RE system has been noted in several cases of erythremic myelosis; (2) (2) transitional forms between reticulum cells and primitive erythroblasts are described by Di Guglielmo as a distinguishing feature of erythremic myelosis--Downey's concept that in the leukemic reticulo-endotheliosis, free cells differentiate toward some type of blood cell other than the monocyte; (3)in some of the cases accepted as example of erythremic myelosis a monocytosis was present; (4) the abnormalities in the granulocytes and platelets are more rationally explained in terms of a pathologic disorder of the reticulo-endothelium; and (5) the close relationship between cases of erythroleukemia and erythremic myelosis is more readily understood if both entities are viewed as a variance of reticulo-endotheliosis." [18]

Schwartz concludes that, as more cases are described, the artificial classification into acute and chronic erythremic myelosis and erythroleukemia will not be accurate. However, cases that show overlapping and features of each of these and perhaps even of other conditions will be, and are recognized.

CLINICAL SIGNS AND SYMPTOMS

The chief complaints are not usually very specific--malaise, fatigue, gastrointestinal upset, palpably tender nodes, etc. The diagnosis is not dependent on a definite list of clinical signs and symptoms, nor on clinical history, but rather on what is found in the peripheral blood and bone marrow smears. Physical examination frequently reveals hepatosplenomegaly, palpable lymph nodes usually in the cervical region, evidence of a bleeding tendency, and often anemia.[7,8,10,12,20]

DIAGNOSIS

According to Damashek, "When it is realized that the red cell proliferation may be simply the first stage of the larger more complex syndrome, and that the large number of nucleated red cells in the peripheral blood are by no means essential for the diagnosis, it becomes apparent that some of the refractory anemias and aplastic anemias with hyperplastic marrows are actually examples of the Di Guglielmo syndrome."[3] He lists five things which should be considered in diagnosing erythroleukemia: (1) The anemia is of the normocytic normochromic type with certain indicies suggesting macrocytosis; (2) the bone marrow shows an extraordinary erythroblastic hyperplasia suggesting hemolytic disease where the reticulocytes of the blood are only slightly elevated, indicating an ineffective erythropoiesis; (3) the nucleated red cells of the marrow usually show many bizarre forms with polyploid types and megaloblastoid forms (however, the B-12 concentration of the serum is normal or elevated, and there is no response to Vitamin B-12); (4) the fecal urobilinogen output may be quite high indicating increased hemolysis, but the CR-51 red cell survival time may be only slightly reduced. This may indicate "heme pigment diversion" as seen in pernicious anemia; and

(5) careful inspection of the bone marrow and blood smears show--even in the "pure" red cell proliferations--a sufficient number of myeloblasts to diagnose a myeloblastic, as well as an erythroblastic, proliferation.[3]

He also suggests that recognition of the Di Guglielmo syndrome begins with study of the acute forms where the large number of nucleated red cells in the blood and the highly abnormal marrow picture are quite characteristic. "Quieter" forms may be recognized in which only a few nucleated red cells are seen in the peripheral blood, but with a fairly characteristic marrow picture. If splenectomy is done in such cases, a great increase in nucleated red cells usually takes place without any apparent beneficial effect. Once the diagnosis of the acute form is mastered, the chronic form may be recognized.[3,8]

The bone marrow varied greatly in each case. By adhering to Dameshek's criteria--that even though the picture may present first with a myeloid hyperplasia and follow with an erythroid hyperplasia, or that these might not particularly overlap each other--a definite pattern is presented.[3]

Discussion of PAS positivity and erythroblasts appeared in an article by Quaglind. He showed that

the absence of glycogen from the erythroblasts in some cases (health, pernicious anemia, nutritional macrocytic anemia, aplastic anemia, polycythemia) and the presence of only small quantities of glycogen in low percentages of erythroblasts in others (normal cord blood in fetal hemolytic disease, acquired hemolytic anemia, acute leukemia, chronic granulocytic leukemia, in certain cases of refractory anemia, and in those patients with Hodgkin's disease and lymphosarcoma) accentuate the striking and invariable presence of large amounts of glycogen in iron deficiency anemia and in erythremic myelosis.[16] Consequently, he suggested that the PAS test is a strong diagnostic tool in this disease, as there is no comparable positive reaction in any other disease form.

The diminished red cell survival was present to a slight degree in most cases.[3,6,19] It was due to an intracorpuscular defect of the blood cells. The great increase in fecal urobilinogen as compared with a relatively minor rate of red cell destruction suggests "heme pigment diversion" or increased destruction of precursor red blood cells as in pernicious anemia. The increase in the number of erythroid cells in the bone marrow and the increased rate of

iron turnover as compared with the relatively minor increase in red cell destruction and iron utilization indicate an ineffective type of erythropoiesis. The high degree of ineffective erythropoiesis seen in this disease may be characteristic of an erythroblastic red cell series.[16]

THE ANEMIA OF ERYTHROLEUKEMIA

While the interesting aspect of this disease is the universal appearance of anemia, Baldini and Damashek considered a number of cases to determine the pathology of the anemia of the Di Guglielmo syndrome. They studied this in eleven patients with acute and chronic disease.[1] Again it should be noted that the difference between the acute and the chronic forms of the disease is not universally accepted, and the preponderance of thinking is that no difference exists. Baldini and Dameshek observed that (1) the anemia was normochromic and macrocytic in contrast with the mean corpuscular volume which was elevated, the mean corpuscular hemoglobin was often normal, and in several patients the mean corpuscular hemoglobin concentration was slightly lower than normal suggesting slight hyperchromasia; (2) the reticulocytes were often increased, but bore no relationship to the degree of the anemia nor to the shortening of the red cell life span; (3) the degree of erythroblastemia was highly variable; and (4) the bone marrow showed striking erythroblastic hyperplasia. This was usually of the megaloblastic type, and primitive blast cells were conspicuous. The erythroblastic hyperplasia was out of proportion

to the relatively minor reticulocytosis or the relative diminution of the red cell survival time. The nucleated red cells of the marrow showed variable numbers of megaloblasts and megaloblastoid forms suggesting a Vitamin B-12 deficiency. However, the administration of Vitamin B-12 did not improve the condition.[1]

In conclusion, Baldini points out that the anemia of the Di Guglielmo syndrome is due to a combined disturbance of the following: (1) An "ineffective" type of erythropoiesis of marked degree, perhaps due to an acquired neoplastic defect in the uptake or utilization of B-12 by the erythroblasts; (2) an increased hemolysis resulting from the increased destruction of defective red cells. He also states that most cases which he has studied pass through the following stages: (1) The pure or rather predominant red cell proliferation; (2) the mixture of erythroblastic and myeloblastic proliferation; and (3) the final pure or predominant myeloblastic proliferation--that is, acute granulocytic leukemia.[1] Thus, we have reiterance of the fact that these three stages are, at least at the present time, considered to be almost universally present in the development of erythroleukemia, and the majority of cases reviewed went through these three stages.

BLOOD AND BONE MARROW FINDINGS

The hemoglobin varied from 6.5 to 9 Gm. per cent in most cases; leukocyte count was often below 5000 per cubic mm. In over half of the case studies reviewed nucleated erythrocytes were found; circulating blast cells were reported many times, but incomplete differential countslimited an adequate comparison. An increase in the number of myeloid cells in the peripheral blood was commonly seen. Thrombocytopenia was universally present.[3,5,6,7,12,14,18,19]

Generally speaking, the bone marrow studies revealed hyperplastic changes with an increase in abnormal cells of the erythroid and myeloid series. There was usually an increase in the erythroid elements and oftentimes they exceeded the myeloid elements.[5,6,7,14,18,19] Due to the many varied bone marrow studies it is impossible to review each of them. However, the aforementioned findings are the ones most often seen.

CASE STUDIES

Case 1. This is an eighty-four year old, chronically ill, white male who presented with a chief complaint of severe itching for three weeks duration. He complains of (1) a forty pound weight loss during the past three months; (2) blood in stools four weeks prior to admission: (3) marked bleeding whenever he scratches his skin: (4) a non-productive cough for the past three weeks; (5) pain in the left lateral chest which is made worse by coughing; (6) shortness of breath for three days prior to admission; (7) easy bruising for two weeks accompanied by numerous nose bleeds; and (8) progressive fatigue and malaise. The review of systems, past history, and family history were non-contributory. He had been hospitalized in his local community and was given one blood transfusion, oxygen, and a skin lotion.

Physical examination revealed an eighty-four year old, chronically ill white male who is well developed, poorly nourished, and shows evidence of a considerable weight loss. He is in no acute distress. There are marked excoriations, bleeding, and bruising of the skin, with an ecchymotic anterior thorax. He has jaundiced sclerae, chest is emphysematous,

the heart has a regular sinus rhythm with no murmurs. Liver is palpable 4 cm. below the left costal margin. The remainder of the physical examination was within normal limits.

His admission laboratory studies were as follows: hemoglobin, 4.4 Gm. per cent; erythrocytes, 1.79 million; granulocytes, 6400 with a differential of 18 segs, 16 stabs, 5 bands, 8 myelocytes, 20 promyelocytes, 3 blasts 7 eosinophils, and 5 lymphocytes. There were 5 nucleated red cells per 100 white cells. The sed rate was 55, and PCV was 14. There were 8000 platelets. On the following day studies revealed a bleeding time of 3 minutes, coagulation time of 16 minutes, prothrombin time of 16 seconds with a control of 13 seconds. Prothrombin consumption time was 11 seconds. There were 1400 plateltes and a reticulocyte response of 1.4 per cent. The total serum protein was 7.9 Gm. per cent with an albumin of 3.7 Gm. per cent and a globulin of 4.2 Gm. per cent.

Three days following admission hemoglobin was 7.5 Gm. per cent; erythrocytes, 3.21 million; granulocytes, 6800 with a differential similar to the one on admission. The reticulocyte count was 2 per cent; bleeding time, 1 minute; coagulation time, 14 minutes;

and platelets, 8000. Thirteen days following admission the HB was 4.9 Gm. per cent; erythrocytes, 2.08 million; granulocytes, 5200 with a differential of 15 segs, 26 stabs, 14 bands, 12 myelocytes, 11 promyelocytes, 6 blast cells, and 1 eosinophil. There was basophilic stippling of the red cells and 2+ anisocytosis. There were 3 nucleated red cells, and no platelets were observed on the peripheral smear. Reticulocyte response was 6.3 per cent. Two days later the HB was 5.8 Gm. per cent; erythrocytes 2.2 million; granulocytes, 7100 with a differential of 24 segs, 36 stabs, s0 bands, 8 myelocytes, e promyelocytes, 4 blast cells, and 5 lymphocytes. There was basophilic stippling of the RBC's with 43 nucleated RBC's. There was 2+ anisocytosis with moderate hypochromia. There were fewer than 5000 platelets with a 0.2 per cent reticulocyte response.

Bone marrow examination on the day of admission was markedly hypercellular and showed decreased, immature megakaryocytes. There were some pernicious anemia type changes in erythropoiesis. There was an increase in granulocytes with a left shift and an increase in the progranulocytes and myeloblasts. The initial impression was an abnormal marrow with many characteristics of pernicious anemia and acute

leukemia. There were some differences of opinion regarding the diagnosis, and six days later another examination indicated a number of the immature erythroid series. There was a dark blue foamy cytoplasm and large nuclei with finely clumped chromatin, some of which had nucleoli. The diagnosis at this time was erythroleukemia.

The clinical course of this patient was rapidly downhill. He was started on prednisone, 5 mgm. QID and cobolamine, 30 micrograms twice weekly. Four days later the prednisone was increased to 20 mgm. QID, but then discontinued on the following day.

Eleven days following admission the patient was started on 60 mgm. of 6-MP TID, and he received this dosage each day following until his demise. During his hospitalization he received 7 units of whole blood. Fifteen days following admission the patient had a sudden episode of coughing at which time he passed a large quantity of blood. Five minutes later he was semicomatose with a blood pressure of 230/90. A few minutes later his respiration ceased; he failed to respond to therapy, and was pronounced dead.

A summary of the autopsy report follows:

1. Multiple petechiae and ecchymoses of the skin

2. Cardiovascular hypertrophy
3. Myocardial fibrosis
4. Focal hemorrhages of the myocardium
5. Severe coronary arterial sclerosis
6. Bilateral pulmonary edema
7. Passive congestion of the liver and kidneys
8. Multiple petechiae of the gastrointestinal tract
9. Atrophic gastritis
10. Hepatosplenomegaly

Microscopically there was a leukemic infiltrate of the liver, spleen, and kidneys. There was focal hemorrhage and degeneration of the myocardium, and massive pulmonary hemorrhages bilaterally. The final pathological diagnosis was erythroleukemia with leukemic infiltrate of the liver, spleen, and kidneys.

Case 2. This is a case of a four year old white female who entered University of Nebraska Hospital on August 30, 1960. She had apparently felt well until three weeks prior to admission at which time she noticed swelling in the left mandibular area, particularly at the angle. She also complained of intermittent low-grade fever, anorexia, dark stools three weeks ago, subsiding two days later and recurring on the morning of admission.

She consulted her local physician and a blood test revealed a hemoglobin of 4 Gm. per cent; granulocytes, 310,000; and erythrocytes, 1.2 million. She was immediately referred to University Hospital. Physical examination revealed a pale, weak, poorly

nourished, four year old white female who appeared to be in slight respiratory distress. She weighed 14 kilograms. Her temperature was 38.6° C. HEENT were negative. There were palpable cervical nodes bilaterally. A hard mass was palpated in the right mandibular angle which appeared to be fixed to bone but not to skin. The liver was palpable 4 cm. below the right costal margin; the spleen and kidneys were not palpable. The remainder of the physical examination was essentially normal. On admission the hemoglobin was 3 Gm. per cent with 1.39 million erythrocytes, and 338,000 granulocytes with a differential of 1 seg, 3 lymphs, 1 mono, and 95 blast forms. There were 6 nucleated red cells, and 37,000 platelets. Subsequent CBC's were performed daily until her dismissal on October 13, 1960; these findings are listed in Table I.

Until September 23, nearly a month following her admission, there were never more than 9 nucleated red cells per 100 white cells on a peripheral smear. However, on that day 15 were found. This number gradually increased to a maximum value of 77 six days later. This value gradually decreased until only 2 were seen one week following the hiatus. Radiological examination revealed fluid in the abdomen

with hepatosplenomegaly. There was hilar adenopathy with leukemic infiltrates in both lung fields.

Bone marrow examination on admission revealed a hypercellular marrow, an RBC to WBC ratio of 1 to 40. There was decreased erythropoiesis, and a decrease in granulopoiesis. The primary cell type was the lymphocyte, and the diagnosis was an acute lymphocytic leukemia.

The clinical course of this patient was one of improvement. She received 25 mg. of 6-MP daily and 10 mg. of prednisone six times daily for the first week after admission. This dosage was then decreased to 20 mg. daily. She was dismissed October 13 on 25 mg. of 6-MP daily, and 20 mg. of prednisone daily.

She was readmitted to University Hospital on October 20, 1960, after being seen in hematology clinic where she presented with fever, anorexia, vomiting, and increased cachexia. There was a painful swelling over the lower lip which was apparently there for four days prior to admission. There were 41,000 granulocytes on peripheral smear. Physical examination revealed a pale, weak, four year old child who weighed 17.7 kilograms. Her temperature was 40° C. The mass in the right mandibular angle was somewhat larger than on the previous admission

and was quite tender. There was a tender ecchymotic swelling of the lower lip. The chest was clear to auscultation and percussion. The liver and spleen were palpable at the level of the umbilicus. The remainder of the physical examination was negative. Admission hemoglobin was 9.4 Gm per cent; granulocytes, 41,300 with a differential of 14 segs, 1 band, 9 lymphs, 31 blasts, and 20 promyelocytes. Platelet count was 24,000. Daily CBC's were performed and are recorded in Table II.

A bone marrow revealed a hypercellular consistency with a red cell-white cell ratio of 1 to 10. There was increased granulopoiesis with left shift, and a diagnosis of acute granulocytic leukemia was made. After review of the bone marrows of the previous admission, it was agreed that a diagnosis of acute granulocytic leukemia probably should have been made.

The patient was placed on 12.5 mg. of 6-MP daily and 30 mg. of prednisone daily. She was also treated prophylactically with tetracycline and penicillin. On October 25 the 6-MP was increased to 37.5 mg. daily, and the prednisone was increased to 60 mg. daily. The patient received no transfusions during this hospitalization and was discharged on November 4, 1960 on 20 mg. of prednisone and 25 mg.

of 6-MP daily. Her condition was considered to be improved. The patient returned to hematology clinic twice weekly, and on November 7 complained of severe pain in the right hip at the region of the previous bone marrow aspiration. The patient had a fever of 41° C. and marked epistaxis. Her pulse was 180, and she had slow oozing blood from both nostrils with clotted blood present in the oropharynx. There was a tachycardia of 180 per minute and a grade II/VI systolic ejection murmur. The liver was palpable 5 cm. below the right costal margin and the spleen was palpable 2 cm. below the left costal margin. There appeared to be induration in the area of the right ilium. The initial blood studies revealed 6.4 Gm. per cent hemoglobin, and 37,600 granulocytes with a differential of 54 segs, 18 bands, 2 lymphs, 24 blasts, and 12 nucleated red cells per 100 white cells, 14,000 platelets, and a reticulocyte response of 2.7 per cent. Daily CBC's were performed and are seen in Table III.

A bone marrow was performed on November 21, and at this time there was an increase in the erythropoietic series with a white cell-red cell ratio of 1:1 and a marked left shift. The diagnosis now was erythroleukemia. The dosage of 6-MP was

increased to 37.5 mg. daily and prednisone dosage decreased to 5 mg. every eight hours. She was given 11 blood transfusions totaling 7 units of whole blood.

The patient's clinical course did not seem to improve and on November 25 she had a sudden episode of hematemesis and melena, and expired before any therapy could be administered. No autopsy was permitted. The final clinical diagnosis was erythroleukemia.

Case 3. A fifty-seven year old negro female was admitted to University of Nebraska Hospital on February 26, 1960 with a chief complaint of shortness of breath and exertional dyspnea. She also complains of increased dyspnea over the past three months with easy fatigue. She complained further of left sided chest pain two weeks prior to admission. At that time she was seen by her private physician who diagnosed "heart disease" and gave her a digitalis preparation.

Physical examination revealed a well developed, well nourished fifty-seven year old negro female in no acute distress. Her blood pressure was 130/68 and her heart rate was 108 per minute. She showed evidence of pallor. There was a grade II/VI soft,

blowing systolic murmur, mitral in origin, which was transmitted to the axilla and to the pulmonary and aortic areas. The liver was palpable 1 to 2 finger breadths below the right costal margin.

The initial laboratory work revealed a hemoglobin of 5.1 Gm. per cent, 2,690,000 erythrocytes, hematocrit of 16.5, reticulocyte response of 2 per cent, 250,000 platelets, and 8500 granulocytes with a differential of 98 per cent myeloblastsand 2 per cent segs. The initial bone marrow examination revealed a marked increase in the erythropoietic and myelopoietic series, and the initial diagnosis was erythroleukemia.

The patient's clinical course was one of improvement. She was placed on 25 mg. of purinethol daily. She was dismissed on May 11, 1960 in improved condition. During this time there had been no episodes of bleeding. The patient was eating well, and had lost no weight during the hospitalization.

The patient was followed in the hematology clinic, and on May 19 she had a hemoglobin of 6.9 Gm. per cent and 2000 granulocytes with a differential of 1 band, 1 metamyelocyte, 12 lymphocytes, and 86 promyelocytes. There were 6 nucleated red cells per 100 white cells. She was placed on 15 mg. of

6-MP BID. No further progress is obtainable on this patient as she did not return to hemotology clinic, and was not readmitted to University Hospital. Her final clinical diagnosis was erythroleukemia.

DISCUSSION

Three case studies have been presented, all of which at some time during their clinical course have been diagnosed as erythroleukemia. The ages of the patients ranged from 4 years to eighty-four years. Two of the patients are female and one is a male. Perhaps the only symptom common to all of these patients was fatigue and malaise. Palpable hepatosplenomegaly was the only common physical finding.

The initial studies in our three patients reveal anemia with hemoglobin ranging from 3 to 5.1 Gm. per cent. There were considerable variations in the white counts, ranging from 6400 to 338,000 in cases 1 and 2 with 8500 in case 3.

The clinical course of these patients also varied. Case 1 was a chronically ill man with multiple disease processes who expired shortly after admission, and his course of death was unrelated to erythroleukemia. However, at autopsy the patient had leukemic infiltrate in the spleen, kidneys, and liver, and due to the bone marrow studies which had been made during the clinical course, a final diagnosis of erythroleukemia was established.

Case 2 was a four year old white female who presented initially with an acute lymphocytic leukemia

later believed to be acute granulocytic leukemia. She was treated with 6-MP and prednisone and showed considerable clinical improvement with suppression of the myeloid series early after therapy. However, from the sudden onset of the disease until her demise she was never free of symtomatology.

It is evidenced in Tables I, II, and III that the drugs which were used to suppress the cellular components of this disease were quite successful, particularly early in therapy. On her first admission the WBC's decreased from 338,000 to 47,000. On her second admission she had a white count of 41,000 and was dismissed with 50,000 WBC's. However, there was a hiatus midway during this admission when the white count was over 100,000.

On her final admission the patient's white count was 37,600, and with heavy dosages of prednisone and 6-MP the white count was suppressed to 6300 nine days later. However, at this time there was a precipitous rise in the white count, and at the same time a precipitous decrease in the red count and hemoglobin. At death the patient had a hemoglobin of 2 Gm. per cent, 790,000 erythrocytes, and 152,300 granulocytes 82 per cent of which were blast forms.

It was not until the third admission that a

diagnosis of erythroleukemia was made. This diagnosis was made of the basis of both peripheral blood smears and bone marrow examinations which revealed a marked increase in erythropoiesis with no significant increase in granulopoiesis. This patient also showed a sudden increase in the number of nucleated RBC's in the peripheral blood. On November 16 she had only 3 nucleated red cells and at the time of her death there were 264 nucleated red cells per 100 WBC's. The platelet count at death was 5000.

This case is as classic a description and clinical course of erythroleukemia as one can see if the findings proposed by Baldini and Dameshek are considered accurate. Here is a patient who presented with a full blown granulocytic leukemia and over a period of approximately three months developed an erythroleukemia. At the time of the patient's death Damashek's diagnostic criteria, as previously discussed, were present. Anemia was evidenced by 2 Gm. per cent of hemoglobin, 790,000 RBC's with 264 nucleated red cells per 100 white cells. Thrombocytopenia was also present.

In case 1 the diagnosis was somewhat equivocal in that one examiner believed this to be an acute granulocytic leukemia and a second examiner believed

it to be erythroleukemia. This variation in opinions was never resolved as far as we can determine from the clinic charts. However, the final pathologic diagnosis was erythroleukemia based primarily on microscopic findings at autopsy.

This patient also showed a profound anemia, a decrease in the number of red cells, a gradual increase in nucleated red cells up to 43 per 100 white cells, with only rare platelets seen on peripheral blood smear.

The third case is not as conlusive as the first two because of incomplete follow-up. Her initial laboratory studies reveal low hemoglobin, decreased RBC's and minimal thrombocytopenia. The peripheral blood smear revealed 98 per cent myeloblastic cells. The bone marrow examination was originally thought to be erythroleukemia, but some thirty- five days after admission another examination was done at which time it appeared that she had an acute granulocytic leukemia. Subsequent clinic examination revealed a slow rise in promyelocytes and on her last visit 91 per cent of the peripheral granulocytic series were promyelocytes.

SUMMARY

This paper represents an attempt to review the information which has been written about Di Guglielmo's syndrome. Although the early history was in Europe, the more recent critical reviews have been done in the United States.

No attempt was made in this study to be all-inclusive or to draw any conclusions. At the present time the consensus of opinion is that erythroleukemia is a separate clinical entity. However, the existence of the acute and chronic forms is questioned.

The diagnostic criteria are not unequivocal, and the disease is closely related to acute granulocytic leukemia. In fact, erythroleukemia may be a precursor of acute granulocytic leukemia as stated by Dameshek.

Baldini concludes that his cases go through three stages: (1) the pure or rather predominant red cell proliferation; (2) the mixture of erythroblastic and myeloblastic proliferation; and (3) the final pure or predominant myeloblastic proliferation--acute granulocytic leukemia.

There is considerable evidence that erythroleukemia is one of the myeloproliferative disorders or a variance of reticulo-endotheliosis.

The clinical signs and symptoms are many and

varied, although a few are prominant. However, the ultimate diagnosis is made with blood and bone marrow studies. Dameshek lists the most exacting diagnostic criteria. He concludes, with Baldini's aid, that anemia is the most frequent clinical finding and discusses its nature.

Three case studies have been presented which correlate well diagnostically with cases reviewed in the literature. At some time during the clinical course each case was diagnosed either as an acute granulocytic leukemia followed by erythroleukemia, or with the latter being the first diagnosis. Dameshek's diagnostic criteria appear to be applicable in all cases--particularly case 2.

It was further observed that there is disagree- among clinicians at University Hospital as to the exact diagnostic criteria. This is evidenced in all three cases--particularly case 1. Sufficient evidence is present, I believe, to warrant a diagnosis or erythroleukemia in the cases presented.

Date	HB	RBC	WBC	Segs	Bands	Meta	Lymph	Mono	Platelets	Blast	Nucl. RBC		Retic.
8-30	3	1.39	160,000									23	
8-31	3.8	1.70	338,000	1			3	1	37,000	95	6		3
9-1	6.4		282,000	1	1		3	2		96	9		
9-2	7.4	2.56	307,000								5		
9-4	8.9		270,000	5		1				94			
9-6	8.6		208,000	1				1		98	2		
9-7	8.1		191,000							97	1		
9-8	8.3		166,000							95	4		
9-9	8.9		157,800	2			4			94	1		
9-10	7.7	2.56	51,000	3			95	2	35,000				2.5
9-11	7.6		143,000	3	2		1			94			
9-12	7.8		130,000	2	1		5			92	1		
9-13	7.6		122,500	4			8		10,000	88	2		
9-14	6.9		106,000	2	4		4			90	7		
9-15	7.1		87,800	2			7			91	6		
9-16	6.9		65,000	1			6			93	6		
9-17	6.2		49,000	3	2		4			91	6		
9-19	6.4		29,500		1		7			92	5		
9-20	6.2		35,500	3	4		5			88	8		
9-21	6.4		29,800	3	2		15			80	8		
9-22	6.2		21,000	5	1		6			88	9		
9-23	5.6		19,000	7			15			78	15		
9-24	5.4		16,600	12	5		8			75	17		
9-26	5.8		19,200	7	4		13			76	35		
9-27	6.2		13,400	11	2		30	1		56	60		
9-28	7.1		7,700	14	8		16	1		61	82		
9-29	8.9		6,700	20	10		12	1		57	77		
9-30	10.2	3.23	3,900	26	5		18		13,000	51	37		3.8
10-3	10.0		1,200	23	5		41	2		29	9		
10-4	8.3	2.34	1,600	15	4		58	4	5,000	19	1		
10-5	9.7	2.26	1,200	38	5		51	1	13,000	5	1		
10-6	7.8	2.52	1,600	24	5		66		20,000	5			
10-7	7.8	2.34	1,300	22	7		57	12		2	2		
10-10	8.1	2.65	1,300						18,000				
10-11	8.6	2.65	3,000	21	4		63	1		1			
10-12	9.2		4,700	8	2		79	8	73,500	3			

Table I

Date	HB	RBC	WBC	Segs	Bands	Lymphs	Blasts	Nucl. RBC	Pro Lymph	Platelets
10-20	9.4		41,300							
10-21	9.4	2.61	46,500	14	1	9	31		40	
10-22	8.3		52,300	23	4	5	21		46	24,000
10-24	9.2	2.48	93,000	25	3	4	19	2	48	24,000
10-25	9.7			31	7	3	23	3	34	
10-26	9.2		84,300	22	4	5	23	8	41	
10-27	9.7		108,000	35	4	2	24	5	32	15,000
10-28	9.2		106,800	39	6	3	18	18	31	
10-31	8.9		83,800	44	20	2	31	5		16,000
11-1	7.8		65,800	47	9	4	40	13		
11-2	8.1		66,500	58	9	2	27	11		21,000
11-3	8.3		45,000	63	8	2	24	17		
11-4	8.1		50,300	48	15	2	33	11		

Table II

DATE	HB	RBC	WBC	Segs	Bands	Lymphs	Blast	Nucl RBC	Platelets	Retic
11-7	6.4		37,600	54	18	2	24	12	14,000	2.7
11-8	6.9		28,300	60	15	3	22	11		
11-9	6.9		22,800	61	14	4	20	4	12,000	
11-10	7.4		14,300	52	23	3	21	4		
11-11	9.7		15,900	60	19	1	18	1	5,000	
11-12	10.5		10,500	73	7	3	17	1		
11-14	9.7		7,900	60	5	1	32	1	5,000	
11-15	11.2		7,500	62	8	10	17			
11-16	7.1	2.1	6,300	59	7	6	27	3	5,000	
11-18	4.0	1.17	25,000	56	10	4	27	10	5,000	
11-19	4.8	1.41	33,100	51	5	6	37	50	6,000	
11-21	3.7	1.2	54,300	46	7		46	140	5,000	
11-22	4.4	1.64	65,000	39	9		51	184	5,000	
11-23	4.4	1.20	77,800	25	5	2	63	292	5,000	
11-25	2.0	.79	152,300	12	3		82	264	5,000	

Table III

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