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Occasional Survey

Acute Promyelocytic Leukaemia

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Summary

Acute promyelocytic leukaemia (A.P.L.) is a rare but important type of acute myeloid leukaemia characterized by major bleeding in association with thrombocytopenia, a specific peripheral blood and bone marrow picture, low plasma fibrinogen, and the presence in the serum of fibrin degradation products. These last abnormalities are related to the disseminated intravascular consumption of coagulation factors with secondary fibrinolysis. A.P.L. requires early recognition and urgent treatment. With optimal management up to half of the patients may achieve complete remission of two years or more. Undoubtedly patients with A.P.L. do especially well when treated in special centres and some patients with A.P.L. now die before the nature of their disease is recognized. Increased familiarity with the problem, which has been known for nearly 20 years, should yield great dividends for those few patients who have this disease.

Abundant evidence indicates that erythrocytes, granulocytes, platelets, and probably monocytes have a common stem cell in the adult bone marrow and the term "acute myeloid leukaemia" (A.M.L.) is often used to embrace all types of acute leukaemia thought to arise from this cell—myeloblastic, myelomonocytic, monocytic, erythroleukaemic, and promyelocytic. The term "acute promyelocytic leukaemia" (A.P.L.) describes a special type of A.M.L. characterized by severe bleeding manifestations which are frequently fatal, the presence in the peripheral blood and bone marrow of atypical promyelocytes containing large azurophilic granules, thrombocytopenia, and abnormalities in clotting test results that reflect disseminated intravascular coagulation. Recently the treatment of A.P.L. has improved greatly and the incidence of complete remission now approaches or equals that seen in other types of A.M.L. Generally these remissions appear to be much longer than those in other types of A.M.L. and are frequently measured in years. The analogy with acute lymphoblastic leukaemia, in which cure appears to

depend on adequate chemotherapy during remission and to be closely related to the total duration of disease-free survival suggests that it may prove easier to eradicate residual disease in patients with A.P.L. in remission than in other types of A.M.L.

The first description of acute leukaemia associated with hypofibrinogenaemia is attributed to Croizat and Favre-Gilly.¹ Eight years later Hillestad² described a special type of A.M.L. characterized by the presence of atypical promyelocytes, hypofibrinogenaemia, and a severe bleeding tendency and introduced the term "acute promyelocytic leukaemia." Later the low fibrinogen was found to be due to rapid destruction and the idea that the clinical picture was due to fibrinolysis or to increased intravascular consumption was formed.³⁻⁴

Many cases have now been diagnosed and A.P.L. probably represents about 6% of all cases of acute leukaemia or 13% of all cases of A.M.L.⁵⁻⁷ This review summarizes the clinical, haematological, and coagulation features of A.P.L. and the important improvements in treatment and prognosis that have recently occurred.

Clinical Features

There are no clinical criteria for a positive diagnosis of A.P.L., yet it differs from other varieties of A.M.L. in the frequency of bleeding manifestations and the relative absence of enlarged viscera. Thus, a high proportion of patients present with purpura, epistaxis, haematuria, or bleeding from gums or other gastrointestinal sites. Death often results from cerebral haemorrhage. The liver and spleen are less frequently palpable in A.P.L. than in other types of A.M.L. and lymphadenopathy is usually absent. Gum hypertrophy and infiltration of the skin are unusual in A.P.L.

Haematological Features

The total peripheral blood leucocyte count is variable but low counts are much commoner at the time of presentation of A.P.L. than in other types of A.M.L. This may reflect relatively earlier diagnosis and the leucocyte count may rise rapidly after diagnosis if treatment is not started. Blast cells are usually present in the peripheral blood but the predominant cell is frequently an atypical promyelocyte. This cell differs from a normal promyelocyte in that nucleoli are often inconspicuous; the nucleus is more likely to be indented, folded, or bilobed and is frequently double; while the cytoplasm contains many large densely-staining azurophilic granules which may overlie and occlude the

nucleus yet occasionally leave some of the cytoplasm clear. These granules are much larger and stain more densely than those of the normal promyelocyte—hence the suggestion (not yet widely accepted) that the disease is better named “hypergranular promyelocytic leukaemia.” A variable proportion of these promyelocytes have elongated crystalline cytoplasmic inclusions that may have pointed or tapered ends and so resemble splinters; these are often multiple and may be arranged in sheaves.⁷ These splinter-like inclusions stain positively for peroxidase and acid phosphatase and thus have cytochemical properties identical to the Auer rods that may characterize acute myeloblastic and myelomonocytic leukaemias. Electron microscopy, however, shows a substructure consisting of a hexagonal arrangement of tubes with a periodicity of 25 nm which differs from the periodicity of typical Auer rods.⁸⁻⁹ They also differ from ordinary Auer rods in that the latter are very rarely multiple. The erythrocytes in the peripheral blood show no consistent abnormality and red cell fragmentation is less commonly seen in A.P.L. than in association with some other causes of disseminated intravascular coagulation. The peripheral blood

platelet count is usually much lower than in other types of A.M.L. and is often about 10,000 to 30,000/mm.³

Examination of the bone marrow may be difficult because the aspirated material clots very rapidly and hence satisfactory films are not easy to prepare. With this stipulation the film is usually hypercellular and shows more or less complete replacement of normal myeloid tissue by abnormal promyelocytes and blasts. Cells containing splinter-like cytoplasmic inclusions may be identified in films of marrow as of peripheral blood and these may occasionally rupture, leaving the intact inclusions lying free (fig. 2). These cells disappear rapidly after treatment is started.

Patients with well-differentiated myeloblastic leukaemia may be seen in whom only normally granulated promyelocytes are conspicuous in the peripheral blood and bone marrow. Splinter-containing cells are not seen and these patients do not usually have concomitant disseminated intravascular coagulation. Conversely, this abnormality is occasionally seen in types of A.M.L. other than A.P.L. but the association is rarely of clinical importance.

The serum vitamin B₁₂ level and B₁₂-binding capacity are noticeably raised in some patients with A.P.L. who are not suffering from liver damage.¹⁰ This contrasts with other forms of A.M.L., in which the levels of vitamin B₁₂ and B₁₂-binding proteins are usually normal. These proteins, especially transcobalamin I, appear to be synthesized in granulocytes and are released from them into extracellular compartments. Probably the atypical promyelocytes of A.P.L. are a rich source of transcobalamin I and so lead to the increased serum vitamin B₁₂ level and B₁₂-binding capacity.

Coagulation Findings

The early recognition of the association of A.P.L. with low plasma fibrinogen levels led to the assumption that the severe bleeding tendency was due to excessive fibrinolysis; it is now known to be a consequence of disseminated intravascular coagulation. Plasma fibrinogen is reduced, often greatly, and fibrin degradation products are increased in the serum. Assays of other clotting factors may show reduction, especially of factors V and VIII and prothrombin. Other tests, including the thrombin-fibrinogen time, the prothrombin time, and the activated partial thromboplastin time may not be helpful in the diagnosis for the results may be normal, prolonged, or even accelerated at the time of diagnosis. These findings, together with the low peripheral blood platelet counts and the frequent thrombi in small blood vessels at necropsy, provide ample evidence that the basic coagulation abnormality is disseminated intravascular coagulation and that the fibrinolysis occurs as a secondary event. With minor degrees of disseminated intravascular coagulation the results of all the tests mentioned above may be normal but activated fibrinogen (fibrin monomer) may still be found in the plasma by using the very sensitive protamine sulphate or ethanol gelation tests.¹¹ When significant disseminated intravascular coagulation is present the promyelocytes have these distinctive morphological features in almost every case.⁷ With successful treatment abnormal promyelocytes disappear from the blood and the bone marrow and the results of the coagulation tests return to normal. Haematological relapse is associated with recrudescence of disseminated intravascular coagulation.

Normal leucocytes contain a tissue factor that may play a part in the Schwartzman reaction or intravascular coagulation.¹² The proteolytic and fibrinolytic activity of promyelocytes from patients with A.P.L. is somewhat increased compared with normal leucocytes, but their procoagulant activity is enormously increased and resembles that of tissue thromboplastin.¹³ This procoagulant property appears to be especially associated with the granular fraction of the abnormal promyelocytes and helps to explain the pathogenesis of the disseminated intravascular coagulation.

FIG. 1—Chart showing the treatment and haematological progress of a patient with A.P.L. Daunorubicin (average dose: 80 mg/m²/day) and cytosine arabinoside (average dose: 120 mg/m²/day) were given in repeated courses lasting up to five days until remission was obtained. Intravenous heparin was administered for 15 days until a rising platelet count and falling level of fibrin degradation products (FDP) showed diminution of the disseminated intravascular coagulation. Successive bone marrow biopsy specimens (B.M.) showed relapse (■), partial remission (□), and full remission (□). Each arrow represents the transfusion of two or three units of blood or of platelet concentrates from 5 or 10 donors or more. A FDP titre of above 1/4 is abnormal.

FIG. 2—Photomicrographs of bone marrow showing densely staining granules and crystalline inclusions in cells of the myeloid series. The membrane of the cell on the right has ruptured and the inclusions are lying free. (May-Grünwald-Giemsa. $\times 1,120$.)

Treatment

A.P.L. responds to the same drugs that are effective in treating other types of A.M.L., but most clinicians think that the treatment of A.P.L. must be initiated urgently and that rapidly acting drugs are to be preferred. At least one group¹⁴ treats A.P.L. differently from other types of A.M.L.: this means that treatment must begin on the day of diagnosis and the use of daunorubicin, a non-cycle-active drug capable of producing rapid aplasia of bone marrow, seems to be crucial. It may be given alone or in combination with other drugs such as cytosine arabinoside and best results seem to be obtained with high dosage. In one series the standard initial dose of daunorubicin was 300 mg/m² given over three days.⁶

The start of treatment is frequently associated with an exacerbation of the clinical signs and the laboratory features of disseminated intravascular coagulation and steps should be taken to prevent this, which probably results from the lysis of many promyelocytes with release of their granular constituents with procoagulant activity. The mainstay of supportive therapy is probably the transfusion of donor platelets, which may be required in very large quantities. The aim should be to increase the peripheral blood platelet count to at least 50,000/mm³ and this may require platelet concentrates from as many as 30 donors daily. Antibiotics may be given as indicated. It is logical to try to suppress the intravascular coagulation with an agent such as heparin, but opinions are divided whether it is clinically useful^{6, 14, 15} and it should never be given without adequate platelet support. Most clinicians favour its use though its administration is difficult to monitor. The object of heparin administration in disseminated intravascular coagulation which is complicated by bleeding should be to produce less than full anticoagulation and somewhat less heparin may be required than is conventionally used to anticoagulate the haematologically-normal patient. The daily dose of heparin may be between 10,000 and 25,000 units (100 to 250 mg) and a reasonable target is to hold the thrombin-fibrinogen time at twice normal and the activated partial thromboplastin time at somewhat less than twice normal, provided these lengthened times are not already present as the result of disseminated intravascular coagulation and fibrinolysis. In this case, the correct dosage of heparin becomes even more empirical; adequate support with platelets, and possibly fresh blood, fibrinogen, or cryoprecipitate is then absolutely essential. Once started, heparinization should be continued until the signs of disseminated intravascular coagulation have disappeared and this may take eight days or more.¹⁴ The investigations described may have to be carried out twice daily or more often until the correct dosage of heparin is established. They may be repeated daily after this.

Caution is required in the interpretation of bone marrow biopsy specimens obtained after treatment has begun. An excess of promyelocytes, presumably without procoagulant activity, may persist for some time and should not by themselves lead to prolongation of treatment with cytotoxic drugs.

Prognosis

The chance of obtaining remission of the disease is good in patients who do not die before treatment begins or in the period immediately afterwards. Bernard⁶ obtained complete remission in 19 out of 44 patients (43%) treated with daunorubicin, which compared with a complete remission rate of 11% in the period before this drug was available. This improved incidence of complete remission is similar to that in other types of A.M.L. The remissions that do occur, however, tend to be prolonged and the median duration of complete remission in Bernard's series was 26 months, which is substantially better than the seven months' median duration seen in other types of A.M.L. Four of his patients were in full remission for more than four years. These exceptionally long remissions make this variety of A.M.L. especially rewarding to treat and contrast most dramatically with the rapidity of death in those cases in which treatment fails.

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