Acute Monocytic Leukemia as an Explanation for “Hiatus Leukemicus” and “Myelo-Monocytic Leukemia”

By Edwin E. Osgood

THE TERM “HIATUS LEUKEMICUS” suggests the appearance in the blood of blast and pro cells of a series, together with mature stages of the same series, but without the intermediate stages of that series. This would be analogous to seeing infants in a human population and adults, with no children of intermediate age.

Such a blood picture can occur in chronic granulocytic leukemia when therapy has interrupted cell division temporarily and cell proliferation begins again before the end of one life span of the series so that segmented neutrophils are still present. It may also be seen at the time when a new somatic genetic change has led to further shortening of the life span of the granulocytic series at the start of the acute terminal phase of a chronic granulocytic leukemia. This is usually preceded in my experience by rapid enlargement of the spleen while the total leukocyte count remains well controlled.

In both of the above instances the immature cells are typical of leukemic myeloblasts and progranulocytes. Theoretically, such a picture might also occur at the very onset of acute granulocytic leukemia, but I have never seen such a patient since the pre-existing normal granulocytic series is usually totally replaced by the time the patient consults a physician.

When such a picture is seen in a previously untreated patient with a short history of symptoms, the diagnosis usually proves to be acute monocytic leukemia. The monoblast and myeloblast are difficult to differentiate from each other, and only search for leukemic promonocytes and disintegrating promonocytes will make the correct diagnosis.

The term “myelo-monocytic leukemia” suggests that a leukemic somatic genetic change occurred almost concurrently in two completely separate series of cells. While this is theoretically possible, the picture is far too frequent for this explanation to be plausible. A few cases so classified are cases of chronic granulocytic leukemia in which Rieder cells or toxic metamyelocytes have been misidentified as cells of the monocytic series. The majority, however, are patients with acute monocytic leukemia in which the large, highly motile promonocytes have chased large numbers of normal marrow cells of the granulocytic and, in some cases, the erythrocytic series into the blood.

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These misinterpretations have led to under-reporting of the true incidence of acute monocytic leukemia and over-reporting of the incidence of chronic granulocytic leukemia. They have led to the impression that maturation arrest or dedifferentiation may occur in leukemias, while in fact early cell death of monoblasts and promonocytes which were interpreted as myeloblasts and progranulocytes gives this appearance. With therapy, the leukemic cells of the monocytic series decrease and the normal granulocytic and erythrocytic series replace them in the marrow. They have, also, led to the belief that the glucocorticoids are of some value in treating granulocytic leukemias. In our experience, acute monocytic leukemias uniformly respond to glucocorticoid therapy while acute or chronic granulocytic leukemias are consistently made worse by such therapy even with maximum dosage. Because some cases of acute monocytic leukemia or histiocytic (reticulum cell) sarcoma chase great numbers of normal nucleated erythrocytes into the blood stream, erythrocytic leukemia is, also, occasionally diagnosed when acute monocytic leukemia or histiocytic sarcoma is the correct diagnosis.

Actually all possible gradations are seen between classic acute monocytic leukemia of the Schilling type and the Naegeli picture that at first glance looks much more like chronic granulocytic leukemia or erythrocytic leukemia. Erythrocytic leukemias do occur, but in these the evidences of large nucleoli, bizarre prorubricytes and cell death at the rubricyte stage are evident.

The features that will usually lead to a correct diagnosis when the patient is first seen are outlined below. Thrombocytopenia is usual in acute monocytic leukemia, but normal or increased numbers of thrombocytes are the rule in chronic granulocytic leukemia. With this to arouse suspicion, look for atypical promonocytes with larger than normal nucleoli and for disintegrated promonocytes with their fine azurophilic granules scattered nearby. Note that the immature cells of the granulocytic and erythrocytic series in the blood look exactly as they would in a normal marrow. Do a peroxidase stain which will show the typical round black granules in the cells of the granulocytic series but only a few scattered rod-shaped granules in the promonocytes.

Note the complete absence of mature monocytes lacking nucleoli because cell death has occurred before this stage is reached. If still uncertain, study the cells under phase microscopy for typical promonocytic motility. A lymph node biopsy with imprint and section will usually reveal the typical picture of histiocytic (reticulum cell) sarcoma which is the usual pathologic diagnosis on lymph node sections from typical cases of monocytic leukemia. A 48 to 72 hour culture of the blood is usually diagnostic if made as described. Figures 3 and 4 in Plate I of Osgood illustrate the cultured appearance of colonies of acute monocytic leukemias and Plate I, Figure 2, Plate II and Plate III illustrate the phase microscopic appearance while Plate IV shows the resemblance to histiocytic (reticulum cell) sarcoma when grown on Leighton’s sponge. The granulocytic series grows in tight colonies and the lymphocytic series grows in similar tight colonies, but with the cells arranged in chords and the lymphocytes show typical tennis racket pseudopods, see Figure 8 in Osgood.

The lysozyme (muramidase) test on the urine may prove to be conclusive.
Plate 1.—All the illustrations are from Wright stained blood smears. Magnification is indicated on the figures. Note that all blood smears show thrombocytopenia. James Beck made the color photomicrographs.

Figs. A and B are from the same blood smear of a white, married female, age 25, who died 19 days after the blood smear was obtained with acute monocytic leukemia of the Schilling type. She is the patient from whom culture J-111 was started. Fig. A illustrates that even in the Schilling type of monocytic leukemia areas can be found that are suggestive of chronic granulocytic leukemia. The toxic metamyelocyte should not be confused with a monocyte, and the three promonocytes should not be confused with Riedel cells. Fig. B shows a diagnostic area. Note the rounded pseudopods and the fine, loose chromatin structure with nucleoli, also the large nucleoli and fine azurophilic granules with beginning disintegration of two of the cells. The neutrophil band cell excludes a diagnosis of acute granulocytic leukemia.

Figs. C and D are from the same slide, from a white, married male, age 73, with an acute monocytic leukemia of the Naegeli type. He died 11 months after the blood smear was taken. Fig. C shows an area typical of those which might be misdiagnosed as chronic granulocytic leukemia. Fig. D shows a diagnostically malignant promonocyte with very large nucleolus. Note that the nucleus is horse-shoe shaped by following the edge of the upper prong in from the notch.

Figs. E, F and G are from the same slide of a white, married female, age 60, who died of the Naegeli type of acute monocytic leukemia 5 days after the slide was taken. Fig. E illustrates an area in which the diagnosis of acute erythrocytic leukemia might be seriously considered, but note that all nucleated erythrocytes look just as they would appear in a normal marrow. Two rubricytes are near the band neutrophil. Three metarubricytes with pyknotic nuclei are present and one with a partially extruded nucleus. All of the erythrocytic series in this field are orthochromatic. Fig. F illustrates a diagnostic area from the same slide and shows the typical appearance of a disintegrated promonocyte as well as two typical malignant promonocytes. A normal appearing polychromatophilic promonocyte with two small nucleoli is in the center of the field. Above it is a polychromatophilic metarubricyte with beginning autolysis and another with pyknotic nucleus only partially in the field is at the bottom. Fig. G illustrates at high magnification the very bizarre appearance of some malignant promonocytes. Contrast the appearance of toxic granules in the metamyelocyte in A with the characteristic azurophilic granules of the promonocytes in F and G.

Fig. H from a white male, age 56, with acute monocytic leukemia of the Naegeli type who died 5 days after this blood smear was made, is a peroxidase stain with Wright's superimposed, showing the contrasting appearance of peroxidase granules in the cells of the granulocytic series and cells of the monocytic series. The typical greenish black rod-shaped peroxidase granules of the monocytic series are best seen in the large promonocyte at upper center. Larger, less typical peroxidase granules are seen in the promonocyte at the extreme left and barely discernible such granules at this magnification in the large promonocyte at lower right. Just to the left and below this cell is a normal appearing progranulocyte with large round black peroxidase granules. Such granules are also visible in the two band neutrophils at the left edge of the field.

So far it has proved reliable in our hands, but not enough typical chronic granulocytic leukemias have been studied so far to be certain it is negative in all.

The accompanying Plate and legends illustrate some of these diagnostic features.

It is noteworthy that those who recognize the monocytic malignancy\(^10\) of most myelomonocytic leukemias report a much higher proportion of acute
monocytic leukemias than is usually reported. This paper\textsuperscript{10} presents more nearly the true proportions of acute leukemias in adult man than any other I have seen. Our own series gives a similar proportion but is smaller and probably less random.

Finding of the Ph\textsuperscript{1} chromosome would favor a diagnosis of chronic granulocytic leukemia, but the Ph\textsuperscript{1} chromosome is not present in all cases of chronic granulocytic leukemia.\textsuperscript{11} In our experience, the neutrophils may show a negative leukocyte alkaline phosphatase test in even the classic Schilling type of acute monocytic leukemia, so this test is of little value in the differential diagnosis. Positive leukocyte alkaline phosphatase tests were present in 8 of our 114 analyzed typical chronic granulocytic leukemia patients\textsuperscript{12} and some had died before this test was available.

Since all leukemias are due to somatic genetic alteration in the alpha-cell,\textsuperscript{13} the only cell that can maintain somatic genetic continuity, resulting in shortening of the life span of the n-cell, it should be obvious that the terms acute or chronic are preferable to myeloblastic or myelocytic, or their equivalents for other series.

**Summary**

The term “hiatus leukemicus” suggests a jump in cell development from an early stage to a late stage with nothing in between, analogous to changing from the appearance of a 10 year old to that of a 60 year old without any intermediate stages. The term “myelo-monocytic leukemia” suggests leukemia involving 2 distinct cell series. Better methods for identification of promonocytes indicate that both of these pictures are usually due to cases of acute monocytic leukemia misdiagnosed as chronic granulocytic leukemia. Monocytic leukemias have a greater tendency than other myelophthisic processes to chase normal immature cells of the granulocytic and erythrocytic series into the blood stream. The result is that blast and pro cells actually belonging to the monocytic series are frequently misinterpreted as myeloblasts and progranulocytes because of the association with normal progranulocytes and myelocytes. These misdiagnoses result in reports of too low a proportion of acute monocytic leukemias among the total leukemic population, account for a belief that leukemia is due to maturation arrest rather than early cell death or shortening of the n-cell life span, and for naming leukemias for cells more mature than the alpha-cell. Only the alpha-cell can maintain the necessary somatic genetic continuity.

**SUMMARIO IN INTERLINGUA**

Le termino “hiato leucemic” suggestiona un salta in le desenvolvimento cellular ab un stadio precoce ad un stadio tardive con nulle phase intermediari, analoge al transition del apparentia de un subjecto de 10 annos de etate ad le apparentia de un subjecto de 60 annos de etate sin stadios intermediari. Le termino “leucemia myelo-monocytic” suggestiona leucemia afficiente 2 distincte series cellular. Meliorate methodos pro le identification de promonocytes indica que ambe le mentionate imagines es usualmente associate con acute leucemia monocytic diagnosticate erroneemente como chronic leucemia granulocytic. Leucemias monocytic ha un plus forte tendencia que altere processos myelophthisic a propeller normal cellulas immatur del series granulocytic e erythrocytic ad in le circulation sanguinee. Le resultato es que formas blastic e pro-formas cellular que pertine de facto al
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serie monocytic es frequentemente misprendite pro myeloblastos e progranulocytos a causa de lor association con normal progranulocytos e myelocytos. Tal erronee diagnoses resulta in reportos de un troppo basse proportion de acute leucemias monocytic in le total population leucemic, illos explica le opinion que leucemia es causate per un arresto in le maturation plus tosto que per un precoce morte cellular o un reduction del longevitate n-cellular, e illos etiam es le base del tendentia de designar leucemias con le nomine de cellular plus matur que le cellula alpha. Solo le cellula alpha pote mantenere le necesse somatic continuitate genetic.

REFERENCES

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