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Henry Ford Hospital Clinicopathological Conference

Metamorphosis in chronic granulocytic leukemia in a 60-year-old man

Participants:

Protocol: Dr. Ellis J. Van Slyck, Department of Internal Medicine, Division of Hematology
Discussant: Dr. Robert K. Nixon, Department of Internal Medicine, Second Medical Division
Radiology: Dr. Mark G. Weingarden, Department of Diagnostic Radiology
Pathology: Dr. John W. Rebuck, Department of Pathology, Division of Hematology

Case Presentation

This 60-year-old white man came to Henry Ford Hospital in December 1975, complaining of increased fatigability over the preceding year. He had also noted mid-abdominal soreness after lifting. His own physician found that his spleen was grossly enlarged and that he had a high white blood count. His past history included a partial gastrectomy for an ulcer in 1960 and a stroke in 1972 with no residual. He was said to be diabetic since 1973 and had been taking 12 units of insulin.

On admission, the pertinent physical findings were blood pressure 142/78, pulse 80 and regular. He was in no distress and mildly obese. There was no lymphadenopathy. Abdominal exam revealed a liver span of 10 cm. The spleen was markedly enlarged, measuring 16 cm below the left costal margin with a total span of 24 cm.

Initial laboratory values revealed a hemoglobin of 10.2 gms, white count 263,000/cu ml. The peripheral smear showed moderate polychromasia of RBCs. The WBC differential was as follows: segmented neutrophils 36%, bands 25%, metamyelocytes 6%, myelocytes 12%, early myelocytes 6%, myeloblasts 1%, eosinophils 5% (3 immature), basophils 7% (immature). Philadelphia chromosome was present. LAP was 0. The platelet count was 637,000/cu ml. Reticulocyte count was 1.2%. Uric acid was 8.7 mg/dl. The LDH was greater than 700 units and the triglyceride was 345 mg/dl. BUN, creatinine, electrolytes, and alkaline phosphatase values were normal. The VDRL was nonreactive. The PT and PTT were within normal limits. Urinalysis was normal. Vitamin B12 level was 7,616 pg/dl. Serum folic acid was 4.9 ng/dl. The bone marrow aspiration and biopsy were consistent with a diagnosis of chronic granulocytic leukemia (CGL). X-ray of the chest showed no acute process. The EKG was considered normal.

The patient was placed on myleran and responded appropriately with a satisfactory reduction of his white cell count, restitution of his hemoglobin, and diminution of his spleen size.

He continued this treatment until he was discharged on December 23, at which time the dose was reduced to 2 mgs three times a day. While in the hospital, his insulin was discontinued. The patient was instructed in a diabetic diet and also given allopurinol.

As an outpatient, his myleran dosage was gradually tapered as the blood counts responded. On February 27, the white count was 40,000 and the platelet count 400,000. On May 10, the white count was 21,000, hemoglobin 13.6% gm, and the platelet count 717,500. In July, 1976, the white count was 28,400, hemoglobin 13.8 gm%, and platelet count 620,000. In August, 1976, the patient was noted to have a white count of 62,000 and a platelet count of 1.2 million. The spleen, although smaller, was easily palpable.

The patient was not seen again until June 1977, having been followed by his local doctor. At this time he reported that he had been hospitalized on several occasions for GI bleeding and that x-rays had demonstrated gastric and duodenal ulcerations. He had continued to take myleran more or less on a continuous basis. A dull, constant aching in the upper quadrant, weight loss, progressive fatigue and some ankle edema had prompted his return to Henry Ford Hospital. On June 16, 1977, his physical examination showed a blood pressure of 130/88. The pulse was 88 and regular. Pertinent findings were generalized hyperpigmentation, bilateral basilar rales, an unremarkable cardiac auscultation, a soft abdomen with splenomegaly 3-4 finger breadths below the level of the umbilicus. There was a small amount of pedal edema. The hemoglobin was 19.4 gm% and white count 78,300. The findings of hyperpigmentation and rales raise the question of interstitial pulmonary changes related to myleran therapy.

After therapy with Rubidazone was started, the white count responded from 78,000 to 4,700. Hemoglobin at this point was 8.4 gm%, and the platelet count was 195,000. On September 6, he had completed three courses of Rubidazone. His blood count was hemoglobin 7.4 gm%, white count 9,900. The nature of the blood and marrow differentials at this time changed dramatically and will be the subject of the discussion and slide presentation.

The patient's course was downhill over the next two to three months with weakness, fever, diffuse bone aching, further enlargement of the liver and spleen, more edema, bilateral calf tenderness, further progression of the anemia, and, subsequently, another marked increase in the white cells to over 200,000.

The patient returned on September 30, weak, febrile, and aching in most of his bones. His temperature was 39.8, blood pressure 85/60, and pulse rate was 92. His skin was dry and hot. Marked

hepatosplenomegaly was noted. There was 2+ edema of the lower extremities and bilateral calf tenderness. There were a few basilar rales. The neck was supple. Pertinent laboratory data included a hemoglobin of 6.8 gm%, and a white count of 280,000. The many bizarre forms in the peripheral blood precluded an accurate platelet count.

The patient died on October 3, after he failed to respond to appropriate antibiotics for the consolidated right upper lobe seen on x-ray. Sputum culture had shown moderate E. coli.

Our task is to try to define the possible complications this patient experienced as a result of his chronic granulocytic leukemia.

Radiology Findings

Dr. Weingarden:

When the patient's first x-ray film (Fig. 1) was taken on December 15, the day after admission, we found no significant abnormalities. This film shows some blunting at the right costophrenic angle, probably due to pleural thickening, but no acute process was seen at this time. Six months later, on June 16, 1977, he was examined again (Fig. 2). Bilateral densities involving the lung fields diffusely were noted, as well as a reticular nodular pattern of an interstitial nature. Dr. Nixon mentioned the possibility that the patient had myleran toxicity, and this is also possible from looking at this film. By the time of the patient's death on October 3, the consolidative changes in the right upper lobe had increased, although the left lung still seemed not to be involved (Fig. 3). The most likely radiographic diagnosis at this point would be a pneumonitis with some atelectasis of the right upper lobe. Also, the trachea may be shifted slightly to the right.

Clinical Discussion

Dr. Nixon:

Our knowledge of the evolution of chronic granulocytic leukemia (CGL) has been greatly enhanced by the study of atomic bomb casualties at the University of Hiroshima. In the earliest proliferative phase, after the presence of a Philadelphia chromosome has been initially ascertained, there is approximately a 6.3 year proliferative period to the point where we can first discern a hematologic change at about a 10,000 white cell count, accompanied by the appearance of basophilia, increase in platelets, and a decrease in leukocyte alkaline phosphatase. At approximately 20,000 white cell count, immature granulocytes, less than 5%, begin to appear, and at a white cell count of 25,000, an increase in serum vitamin B12 is detectable. When the white blood cells increase to between 50,000 and 100,000, the clinical features, including splenomegaly, make the diagnosis evident.

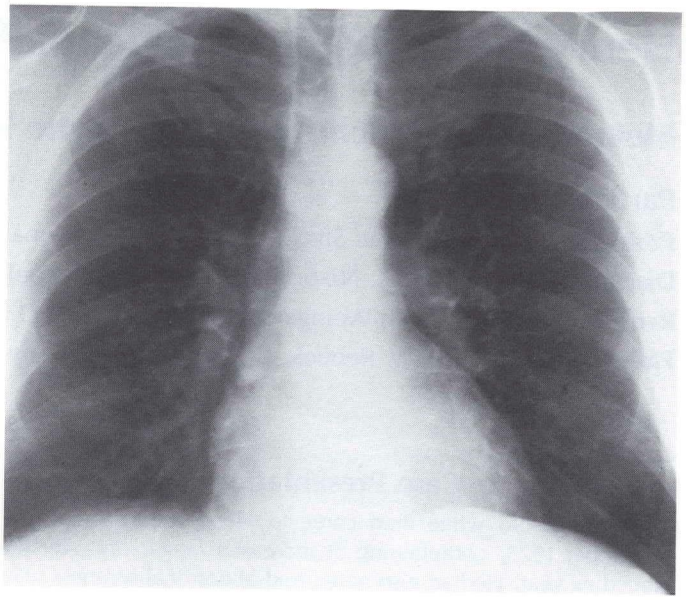


Fig. 1

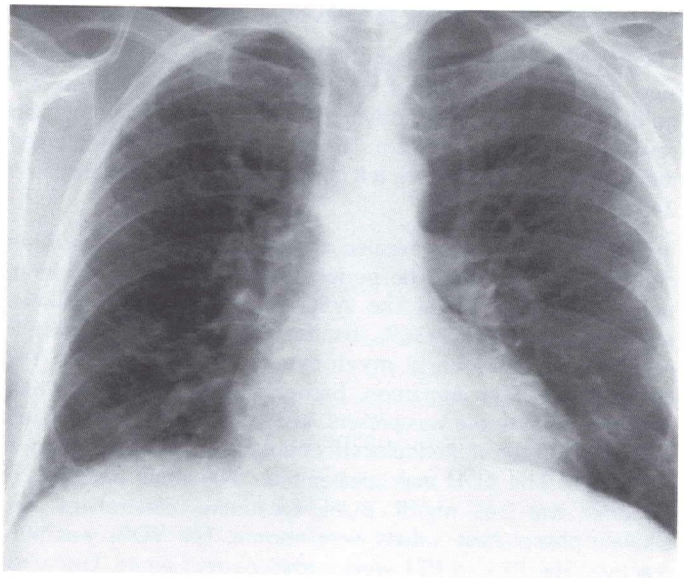


Fig. 2

This patient responded satisfactorily to myleran therapy for five to six months and then underwent a decided change. Over the next three to four months, in spite of a change of chemotherapy, he continued to decline and died with a terminal infection.

What are the possible things that may happen to a patient with chronic granulocytic leukemia and that would seem to pertain best to the patient under discussion? Myelosuppression and a lethal outcome from chemotherapy may

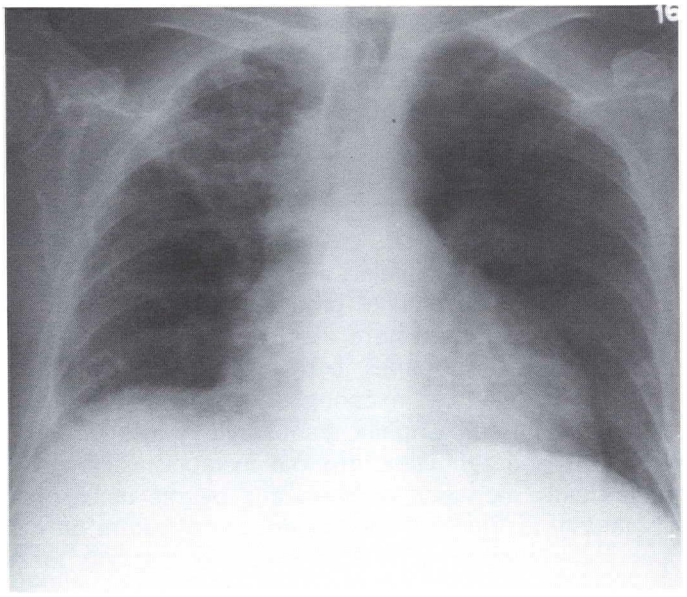


Fig. 3

occur. There may be a transition to myelofibrosis, or non-associated diseases may prevail, particularly those common to middle life, and these may be responsible for death before the final evolution of the leukemia. Most CGL patients (in the range of 70%) move into what is termed an accelerated phase, which terminates in a blast crisis. This transition is characterized by increasing anemia, increased leukocytosis, or cytopenia. Our patient, with increased fatigue, fever, bone pain, as well as further hematologic change occurring some five to six months after initial treatment with myleran, gave evidence that the basic course of his disease had markedly altered in a way compatible with the accelerated phase that precedes a blast crisis. In recent years, we have become aware that just as the Philadelphia chromosome involves not only granulocytes but erythroid elements, megakaryocytes, monocytes and lymphocytes, so the blast transformation that inevitably occurs in practically all CGL patients may actually involve any of these cell lines. Recognition of a terminal lymphoblastic change is clinically important because it demands a change in therapy, which may, for a period, be more effective. Measurement of a terminal transferase (deoxynucleotidyl transferase), a DNA polymerase, facilitates the diagnosis of this lymphoblastic type of crisis.

At this point comments are in order about the unusual multiple duodenal and gastric ulcerations which occurred in our patient when his course was changing hematologically. These alterations may have been a response to a marked histamine stimulus supplied by a basophilia which may accompany a blast crisis. Whether, in turn, this increase in basophils was great enough to qualify for the diagnosis of basophilic leukemia would be speculative, but certainly of interest. Since the symptom expressions of histamine release in basophilic leukemia are not as profound as one encounters with a mast cell origin of histamine release, we may not have the other features that characterize systemic mastocytosis, such as a characteristic flush or other marked symptoms of hyperhistaminemia.

The terminal event of a pneumonia that did not respond to antibiotics would be consistent with this man's disease. In the evolution of chronic granulocytic leukemia, functional changes in granulocytes presumably occur, as suggested by alterations in their phagocytic indices and bactericidal capacity; these, in turn, may make the patient more susceptible to infection.

Student Diagnosis:

The medical students feel that the early clinical course is consistent with the diagnosis of CGL except for three observations: 1) the duration of the disease was less than two years; 2) the elevated platelet count did not decrease with treatment comparable to the decrease in the patient's white count; and 3) the peripheral smear later in the patient's course had a number of bizarre forms which precluded an accurate platelet count. We feel that the hyperpigmentation and the bilateral basilar rales were probably secondary to the myleran therapy. We feel that the platelets are an abnormal and significant part of the picture, first, because of their increased number. Also, the thrombotic and hemorrhagic episodes of the patient's edema, the possible stomach infarct, and the bleeding from the ulcer all suggest abnormal platelet function, as do the bizarre platelet forms. Medical students here suspect that the patient has a megakaryocytic blast transformation of chronic granulocytic leukemia, which is an unusual condition occasionally seen as the terminal event in chronic granulocytic leukemia.

Questions

Are you making any educated guesses about the nature of this pneumonitis? Is it some unusual type of infection? What etiology do you suspect?

Dr. Nixon:

I think it is probably an ordinary bacterial pneumonia. I don't think we need to suspect some unusual organism, which certainly may occur in a variety of hemopoietic diseases and especially with immunosuppressive therapy. I am willing to accept, at this stage of the man's disease, an ordinary bacterial process which didn't respond to antibiotics primarily because the patient had no defenses left to respond with.

In regard to the duration of the disease mentioned by the students, I would answer that from the time of diagnosis to the culmination of the blast crisis the period is generally one to four years.

Pathology Discussion

Dr. Rebuck:

I would like to add a point about the duration of chronic granulocytic leukemia. We should now consider two courses in a disease process: first, the natural evolution of the disease before treatment becomes available, and then, the course of the disease as modified by treatment. Previously, with radiotherapy alone, the median survival of a patient with CGL was 3.1 years. I believe the latest SWOG figures with chemotherapy have a median survival just under that figure. Lest you think there has been no progress, the life quality of such patients has greatly improved, even though we have not increased their survival time.

Well, Dr. Nixon, thank you for focusing on the real problem in this case, namely, the sudden change in the nature of our patient's course in June 1977. I liked your term the "accelerated phase". The term "-blast crisis" generally used in the U.S. to refer to such acceleration of the course of chronic granulocytic leukemia is not nearly as accurate. Gunz' standard text on the leukemias (1) prefers the term "metamorphosis." The reason I like "acceleration" or "metamorphosis" is that in CGL not all the dramatic changes are conversions to a -blast crisis, although I am glad you mentioned a most important conversion recently recognized, that of a truly lymphoblastic crisis, proved by demonstrating lymphoblastic surface markers on the -blasts of some cases. You also mentioned the common myeloblastic crisis or the conversion to an acute myelomonocytic leukemia and, rarely, to an acute erythroblastic leukemia or acute megakaryocytic leukemia, as mentioned in the students' diagnosis.

The nature of our patient's acceleration in June 1977 was none of the aforementioned, as study of his blood smear and bone marrow at the time indicated. Examination of the peripheral blood smear revealed a leukocytic differential count as follows: myeloblasts 8.5%; progranulocytes 4.0%; neutrophilic promyelocytes 0.5%; neutrophilic myelocytes 3.0%; neutrophilic metamyelocytes 2.0%; bands 3.0%; segmented neutrophils 21.5%; eosinophilic promyelocytes 0.5%; eosinophilic myelocytes 3.5%; eosinophilic metamyelocytes 1.0%; eosinophils 3.0%; *immature basophils* 15.5% (Fig. 5); *basophilic granulocytes* 26.0% (Fig. 4); lymphocytes 7.5%; and monocytes 0.5%. Some of the neutrophilic myelocytes had coarse, dark chromatin patterns, the so-called Pelgeroid appearance. In the leukocyte count, 2 megakaryocytic nuclei were encountered per 100 leukocytes, and 1 polychromatophilic normoblast per 100 leukocytes. The mature erythrocytes showed anisocytosis, target cells, burr cells, poikilocytosis, polychromasia, basophilic stippling, blister cells, and rare spherocytes. An occasional platelet was a giant monster in size and appearance, i.e., greater than 8 μm in diameter. Larger than normal platelets are often found as a sign of increased rates of platelet production, but the monster forms that appeared here are found only in the myeloproliferative syndromes, both in chronic granulocytic leukemia as well as in agnogenic myeloid metaplasia. Indeed, increased basophilic granulocytes may be found in both CGL and agnogenic myeloid metaplasia. However, such greatly increased numbers and degree of basophil immaturity as found in this patient are a feature only of granulocytic leukemia and its basophilic variants to be discussed below.

When Paul Ehrlich was a medical student, he used the aniline dyes to discover the tissue mast cell and the peculiar property of the mast cell granule to change the dye color, a property he termed "metachromasia". This was in 1877. Fourteen years later, long after delineating the neutrophilic, eosinophilic and normoblastic and megaloblastic series we know today, he worked out the basophilic granulocytic development in a case of CGL. The basophilic series developed in a fashion parallel to the previously described neutrophilic and eosinophilic series and was similarly derived from the marrow stem cells. The first member of the series he named "basophilic promyelocyte," for the member with the first appearance of metachromatically staining specific granules. The mitotically dividing offspring he designated "basophilic myelocytes," which transformed in turn without further cell division to the "basophilic metamyelocyte," with its broadly indented nucleus, and to the end-stage, mature "basophilic granulocyte" with its poorly segmented, but irregularly lobulated nucleus.

Had we performed the differential only on the predominant basophilic granulocytic series, the basophilic leukocytic differential revealed basophilic promyelocytes 5%; basophilic myelocytes 14%; basophilic metamyelocytes 11%; and basophilic leukocytes 70%. Amid the 5% immature eosinophils in the general differential, we ran across some of the eosinophilic promyelocytes and myelocytes which contained large, refractile, globular, second set lysosomes with both eosinophilic staining in some areas of the cell body intermingled with basophilic staining, similarly structured granules. Ehrlich noted such eosinophilic granulation and correctly gave no great significance in cell identification to such members of the eosinophilic series.

From time to time, they are misinterpreted as signifying a leukemic change per se, which they do not.

From the examination of the peripheral blood slide we diagnosed a "basophilic leukemic conversion" of CGL and not exactly a "-blast crisis," as had been expected clinically. After all, the granulocytic stem cells comprised only 13.5% in the blood slide. To support our interpretation of the peripheral blood, we next examined the bone marrow aspirate at this time. This revealed myeloblasts 13.0%; progranulocytes 4.0%; neutrophilic promyelocytes 3.4%; neutrophilic myelocytes 0.4%; neutrophilic metamyelocytes 2.2%; bands 0.6%; segmented neutrophils 13.6%; eosinophilic promyelocytes 2.2%; eosinophilic myelocytes 1.8%; eosinophilic metamyelocytes 1.2%; eosinophils 4.8%; *immature basophils* 14.6%; *basophilic granulocytes* 28% (Figs. 4 and 5); lymphocytes 6.2%; monocytes 0.2%; megakaryoblasts 2.4%; polychromatophilic normoblasts 0.8%; orthochromatic normoblasts 0.4%; normoblastic mitoses 0.2%. Some of the myeloblasts were micromyeloblasts supporting the leukemic nature of the process. Putting the marrow findings together with those from the blood slide, we made a diagnosis of "subacute basophilic leukemia" complicating CGL, which Dr. Nixon discussed as one possibility. An earlier biopsy of the patient's marrow in April 1977, which had been obtained elsewhere, was made available to us, and a surprising fibrosis of the entire marrow spaces, highlighted only by the presence of entrapped megakaryocytes, intervened at that time. The intervention of marrow fibrosis in a known case of CGL often signifies a severe prognosis, as in this case.

As stated above, Ehrlich himself, as early as 1891, had noted moderate but significant increases in basophilic granulocytes in CGL. In 1906 Joachim (3) was the first to report a variant of CGL such as we see in our study with extreme basophilia. From that time on, sporadic cases of CGL (3-9) with extreme elevation in the basophilic leukocyte count have been reported with the designation of "basophilic leukemia." Forkner, in his 1938 pioneer text on leukemia (3), included a chapter on basophilic leukemia and was able to cite 11 cases in this category. Forkner (3) suggested that "many if not all of the cases recorded of basophilic leukemia in man may represent merely an exaggeration of the basophilia seen not infrequently in patients with straightforward chronic myelogenous leukemia particularly subsequent to treatment." This early view has been confirmed in most respects by more recent reviews (1).

Why, then, our conference case? First of all, one can verify the existence of the various stages of basophilic granulocytic development that Ehrlich described. Beyond that, a number of considerations justify further study. Does the basophilic conversion of CGL alter the prognosis of the disease? Is basophilic conversion a form of "-blast" crisis? Does basophilic conversion require a change in therapy? Is there an acute basophilic leukemia as well as a basophilic conversion of CGL? Finally, does basophilic leukemia differ from tissue mast cell leukemia?

Let us consider the last problem first. In spite of Ehrlich's clear distinction between the "tissue mast cell" with its round, lymphocyte-like nucleus and huge cell body (15 to 30 μm in diameter) and the small basophilic granulocyte of the blood and its marrow precursors, the two cell lines were often lumped together for many years. The fact that both cells contain similar functional constituents (histamine, heparin and a potent chymase, and serotonin in animals) enhanced this tendency. But, properly, they should be separated into dual tissue and blood-borne roles, just as we recognize both tissue macrophages and those arising from migrated mononuclears from the blood. In the basophilic granulocytic leukemias, distinction from systemic mastocytosis and its leukemic counterpart, tissue mast cell leukemia, was never a problem because of the excellent distinction Efrati and his colleagues made in their original description of the tissue mast cell diseases. Although tissue mast cell leukemia (Fig. 6) is rarely confused with the basophilic variant of CGL, it is confused, surprisingly enough, with the more common promyelocytic or progranulocytic variant of acute granulocytic leukemia marked by the coarse and numerous azurophil granules (first set lysosomes) in the cytoplasm of the progranulocytes and promyelocytes. The excessive bleeding that may be a symptom in both tissue mast cell leukemia (on the basis of focal hyperheparinemia) and in the promyelocytic leukemic syndrome (on the basis of granule-induced consumptive coagulopathy) often confuses the distinction. Furthermore, the high heparin content of the leukemic tissue mast cell may lead to needle-like, crystalline precipitates which are then mistaken as "Auer" rods. Another point of confusion is the conversion of the small, round, lymphocyte-like nuclear chromatin pattern of the normal tissue mast cell to the blast-like, finely stippled, chromatin pattern of the leukemic tissue mast cell.

All of this confusion could be settled easily, inexpensively, and promptly by applying *toluidine blue staining with alcoholic fixation* of the marrow or peripheral blood smears to be questioned (Figs. 5 and 7). Modern cytochemists agree with our earlier observations that alcoholic toluidine blue induces a metachromatic (purple) staining of both tissue mast cell and basophilic granulocytic granules but does *not* do so to the azurophilic granules of the progranulocytes and neutrophilic promyelocytes with which they may be confused in Romanowski stains. However, the skilled morphologists (and here we must include

the many hematology specialists among our medical technologists) have an even simpler way of distinguishing between metachromatic granules and the azurophilic lysosomes in ordinary blood or marrow smears. Since the high water content of the Romanowski stains dissolves the metachromatic granular contents in a helpful but haphazard fashion, the metachromatic granules will vary from solid purple to those which are washed out centrally or peripherally with a smudge of pink remaining in their centers or surrounding the granules, to those granules in which the contents are completely dissolved away, with their former sites marked by an empty cytoplasmic vacuole. In contrast, because the azurophilic granules are a hardy lot, they retain their uniform purple stain even in their damaged presentations in the smear.

Next, is there an *acute* basophilic granulocytic leukemia either arising de novo or as a so-called "-blast" crisis of CGL? Hule (11) reported two cases of acute granulocytic leukemia with predominant basophilic granulocytes and Peralta and his associates (12), in the Cuban literature, confirmed the existence of acute basophilic leukemia. In these cases, two problems arise. First, unfamiliarity with the morphology of basophilic promyelocytes may lead to their misdiagnosis as progranulocytes or neutrophilic promyelocytes. Second, failure to employ an alcoholic toluidine blue staining procedure to weed out the acute basophilic granulocytic leukemias from what appears to be an acute myeloblastic leukemia in Romanowki stains appears the most valid criticism of the French American British (FAB) classification of the acute leukemias. The few cases of acute basophilic leukemia I have studied did not respond to therapy considered appropriate for AGL and had an unremitting course. Further study will eventually determine if acute basophilic leukemias should have the same grave prognoses as the acute T-lymphoblastic and B-immunoblastic leukemias currently in the acute lymphocytic leukemia series.

Lest anyone think these remarks are too provincial, at the International Congress of Hematology in Brazil in 1972 the Italian workers (13) reported 37 cases of acute basophilic leukemia in a 15-year period at the Cardarelli Hospital in Naples. Quattrin stated: "The scant number of reported cases of acute basophilic leukemia does not correspond to reality, the main reasons being: (a) the non-performance of the specific toluidine blue or Astra blau stains, on account of which many cases of acute granular leukemia are classified as common myeloblastic leukemia; (b) the very fast fatal course of the disease." He felt that a great many cases attributed to acute promyelocytic leukemia belonged instead to acute basophilic leukemia. According to Quattrin, it is important in diagnosing these cases to distinguish between normal fibrinogen levels in the basophilic leukemias and significantly depressed levels in the acute promyelocytic syndrome.

Another question we raised earlier concerns a change in the prognosis of CGL if the transformation to basophilic leukemia is established. In general, the answer is that the prognosis is worse than average. Gunz and Baikie (1) in their exhaustive leukemia text speculate that the reason may be that it is often detected at what they term "the stage of (leukemic) metamorphosis." Thus, the transformation to basophilic leukemia encountered in this study should also be included in the -blast crises described for CGL. The one known exception to this generalization is cited by Wintrobe in the latest edition of his text (14). He described a patient with 80.0 $\times$ 10^9/L basophils who received busulfan therapy and lived 87 months after the diagnosis had been made. Wintrobe's patient brings us to the final question we asked: Should there be a change in therapy for patients such as the one we are studying? As in all chemotherapeutic trials, the appropriate answers cannot be given until the existence of this change in chronic granulocytic leukemia is widely recognized.

To understand better the possibly pathophysiological consequences of neoplasia of this series, we should know some of the more important properties and functions of the basophilic granulocyte (15):

1. Locomotion
2. Chemotaxis (16)
    a. Lymphocyte dependent
    b. Lymphocyte independent
3. Phagocytosis
    a. For RBC
    b. As host LE cell
4. IgE receptors (appropriate allergen leads to degranulation and/or disruption of the entire basophil, when complexed to IgE.)
5. Heparin content in granules (metachromatic acid mucopolysaccharide)
    a. May lead to local hemorrhage due to heparin excess
    b. Stimulates fibroblasts to increased collagen formation (fibrosis)
6. Chymase content (may lead to local tissue necrosis)
7. Histamine content (complement-induced release)
8. Serotonin content in laboratory animal basophils (not proved for human basophils)
9. Basophil hypersensitivity reaction (as in ulcerative colitis, Hunner's ulcer, penicillin sensitivity, histoincompatibility, etc)
10. Platelet-activating factor derived from IgE sensitized basophils causing platelet function

11. Kallikrein-like activity (compensatory basophilic migration in lesions of patients with Fitzgerald factor deficiency)

Pertinent to a study of this basophilic cell line is the recent report by Juhlin and his colleagues (17) of the case of a 52-year-old patient who, instead of having too many basophils, constantly lacked both eosinophil and basophilic granulocytes. The patient suffered from repeated infections, asthma, and hemolytic anemia. Juhlin et al argued that the lack was due to immunologic destruction of the missing cells. Because of the combined defect with its immunologic etiology, we still do not know what life would be like without basophils alone, but their case affords important clues.

Many years ago, Henry Rappaport reported that the increased reticulin deposition and fibrosis of the bone marrow in chronic granulocytic leukemia were in direct proportion to the absolute basophilic granulocyte count of the marrow. Significantly, the marrow of our patient showed pronounced fibrosis at the time of the "basophilic granulocytic crisis," a fibrosis which became more severe as death approached. Another reason for embarrassment of the microcirculation of the marrow leading to marrow fibrosis is that as greatly increased numbers of megakaryocytes become activated, a cocoon of fibrin (then reticulin) forms around those that have broken out into marrow sinuses, resulting in the classic "entrapped megakaryocytes" of the myeloproliferative disorders. Furthermore, I believe that any marked hyperplasia of cellular elements of any type in the confined marrow cavity leads to some impingement upon the thin-walled marrow sinus microcirculation, with the same resulting fibrosis. Obviously, all these mechanisms were present and potentially operative in our patient. The presence of the Philadelphia chromosome and zero LAP score in this patient on his initial admission in December 1975, along with the original, extremely high white count, confirmed the basic diagnosis of chronic granulocytic leukemia. Fibrosis of the marrow has occasionally been reported in CGL and is being reported more and more frequently as another grave prognostic sign in this disease.

The remainder of the patient's course was as follows. After a third course of Rubidazone therapy, which initially reduced his peripheral white count, his white cell and platelet counts began to rise again in late August without significant reduction in the tumor in his liver and spleen. Hydroxyurea therapy was started, but his leukocytes continued to climb to 180,000 cu mm with 28% mature and immature basophils persisting and an increase in myeloblasts to 21% of the total leukocytes. Death was due to a rapdily developing E. coli pneumonia, as Dr. Nixon indicated, on October 4, 1977, approximately 22 months after CGL had been diagnosed. Important findings in the patient's last marrow report were 32.2% myeloblasts, 17.0% immature basophils, and 18.6% mature basophilic granulocytes. Extensive leukemic infiltration was found in the liver (3,190 gm) and spleen (1,960 gm), as well as in the mesenteric and para-aortic nodes and kidneys. Terminally, the marrow showed 90-100% infiltration of both the myeloblasts and the basophilic granulocytes that had marked his later course, combined with extensive fibrosis, as previously noted.

Dr. Van Slyck:

As part of a CGL treatment protocol, those of us involved in Southwest Oncology Group (SWOG) investigations looked at the fibrosis in marrows before, during, and after myleran therapy, with the idea of trying to obtain useful information on this issue. The study took ten years to complete because of very slow case accrual, and the results were inconclusive. Many of the 100 patients in the study clearly had some fibrosis in their marrows before they were ever treated. The disease itself, as Dr. Rebuck stressed, was associated with an increase in marrow fibrosis as time passed, but how much of a contribution myleran therapy made to the process is speculative. We all suspect that it does something to accelerate fibrosis, but individual cases differ. Thus, we have no clear causal relationship concerning the marrow fibrosis in today's case. So, in summary, we believe that myleran can enhance marrow fibrosis, but the fibrosis can also proceed without myleran.

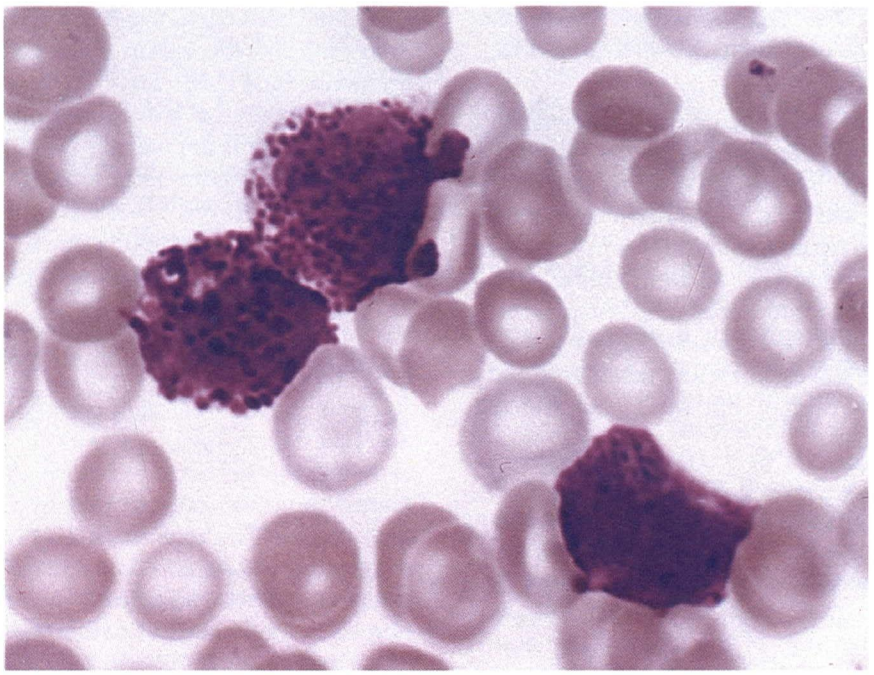


Fig. 4
Basophilic Leukemia Complicating Chronic Granulocytic Leukemia
This photomicrograph represents the patient's blood and marrow picture in June 1977 (mature basophils in the blood 26%; immature basophils 15.5%). The three central cells are mature basophilic granulocytes. This picture should be compared with the morphology of the tissue mast cells in Fig. 6. Leishman's stain (× 1700).

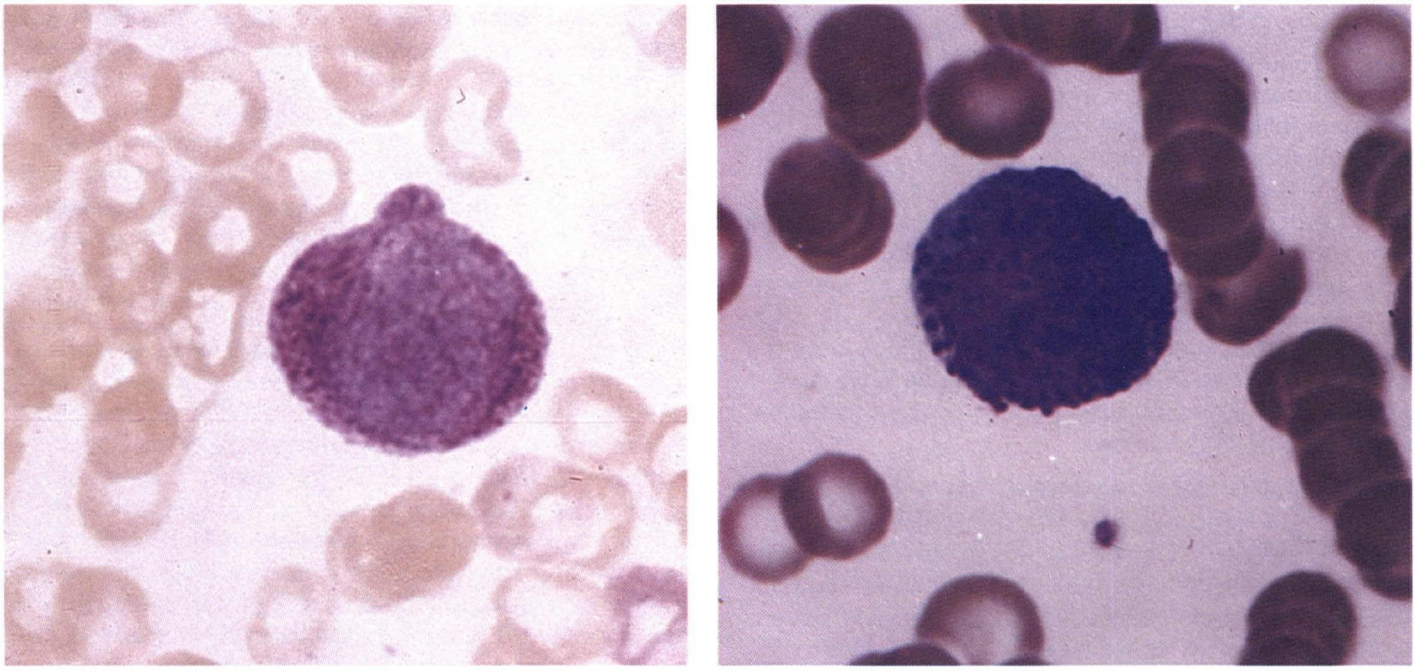


Fig. 5
Deeper Leishman staining on the left (ordinary Romanowski blood staining) of the basophilic promyelocytes contrasted with the identifying paler but definitely metachromatically positive basophilic promyelocyte counterpart in the alcoholic toluidine blue stain on the right. Such metachromatic identification is essential to avoid misinterpretation of the basophilic promyelocyte in ordinary blood stains as a "heavy granular promyelocyte" of the neutrophilic series (× 1700).

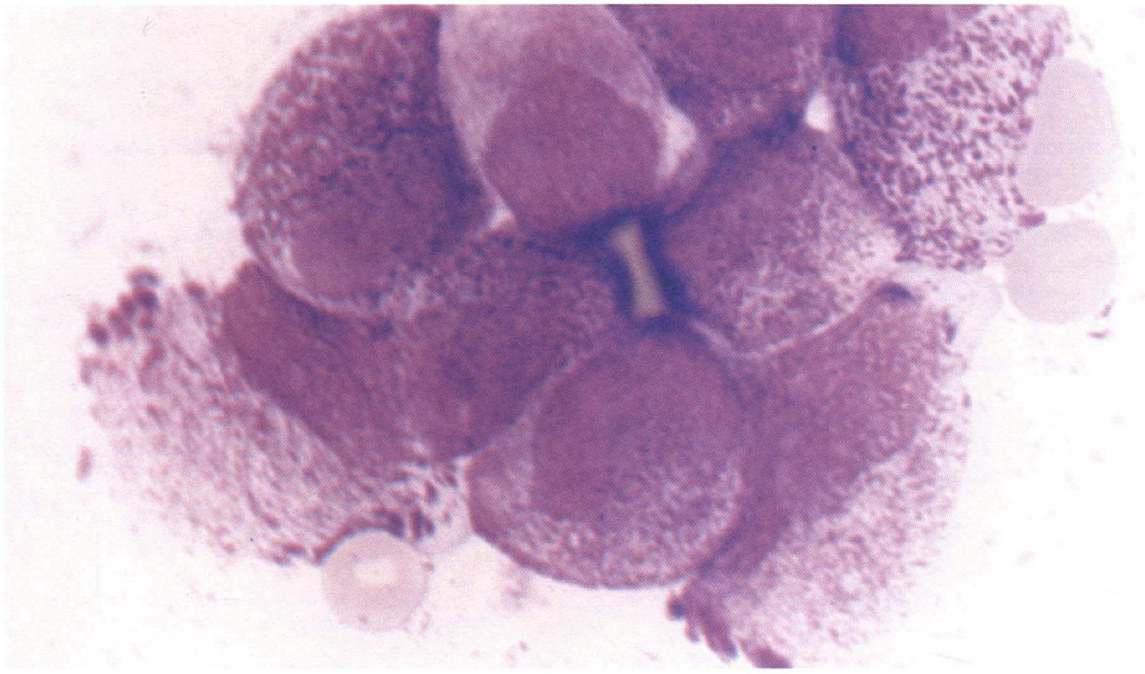


Fig. 6
Tissue Mast Cell Leukemia
Representative field from the blood or marrow of a patient with tissue mast cell leukemia so that the morphology of the leukemic tissue mast cells can be compared with the structure of the leukemic basophilic granulocytes in Figs. 4 and 5. Note the larger cytoplasmic-to-nuclear ratio in tissue mast cells, and the tear-drop secretion of heparin at the edge. Like basophil granules, tissue mast cell granules contain heparin and are truly metachromatic Leishman's stain (× 1700).

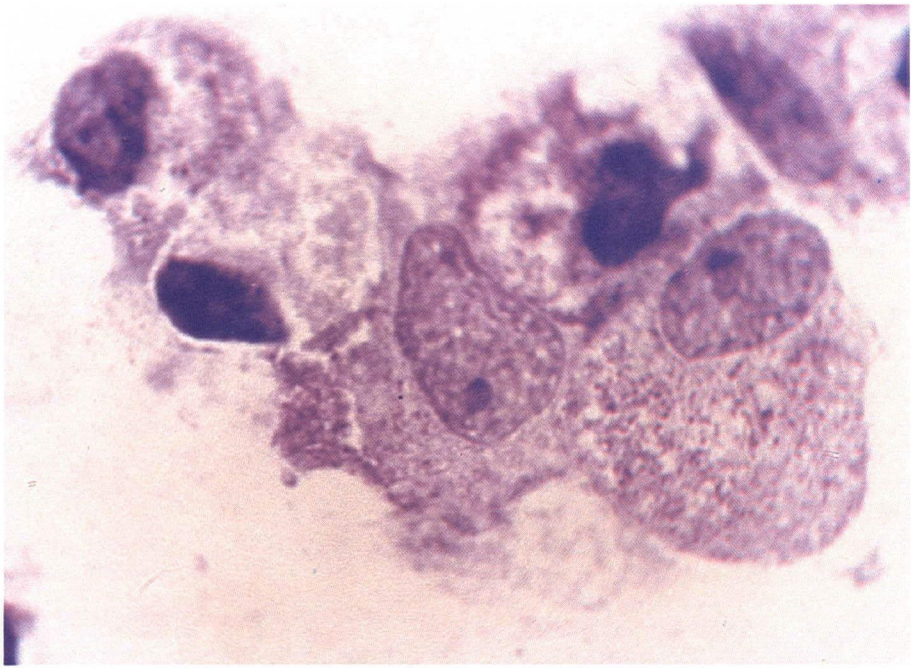


Fig. 7
Alcoholic toluidine blue staining of leukemic tissue mast cells from the same patient depicted in Fig. 6. Note the metachromatic (purple) staining of the granules. The large cell body of the leukemic mast cells can be appreciated here when contrasted with the smaller cytoplasmic rim presented by the basophilic promyelocytes of Fig. 5. Tissue mast cell leukemia is another leukemia that can be misinterpreted as "promyelocytic" leukemia when metachromatic staining is not employed. Alcoholic toluidine blue stain (× 1700).

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