Meningeal Involvement as First Manifestation of Acute Myeloblastic Transformation in Chronic Granulocytic Leukemia

By Hau C. Kwaan, Robert V. Pierre, and Dewey L. Long

IN CHRONIC GRANULOCYTIC LEUKEMIA neurologic manifestations due to leukemic infiltration of the central nervous system occur uncommonly.[1] In acute lymphoblastic leukemia, on the other hand, diffuse leukemic infiltration of the lepto-meninges is frequent and must be differentiated from neurologic involvement due to infection, hemorrhage, or drug toxicity.[2] When acute myeloblastic transformation of chronic granulocytic leukemia occurs, intracranial complications usually manifest as cerebrovascular hemorrhage, but may represent myeloblastic infiltration of the meninges.[3] To our knowledge meningeal leukemia as the single clinical feature of an acute "blastic" phase of chronic granulocytic leukemia has not been previously reported. The purpose of the present paper is to document the course of a patient with chronic granulocytic leukemia who developed myeloblastic involvement of the central nervous system three months before acute myeloblastic transformation was manifested systemically. The diagnosis of meningeal leukemia was confirmed by the demonstration in the cerebrospinal fluid of myeloblasts containing the Philadelphia (Ph^1) chromosome.

Case Report

The patient, T.D., was a 55 year old Negro male mail handler who was in good health until October 1965 when he noticed increasing tiredness and substernal pain. His white blood cell count was found to be 197,000/mm^3. Examination of his peripheral blood and bone marrow established a diagnosis of chronic granulocytic leukemia. In the ensuing three months he received 18 mc of ^{32}P in five doses, the last of which was given on February 1, 1966. His WBC ranged from 65,000 to 143,000/mm^3.

On February 10, 1966, he was admitted to the Veterans Administration Research Hospital because of marked dyspnea on exertion, weakness, tiredness, and frontal headaches for two weeks. These were dull and pounding, were accompanied by dizziness and sweating, and were unrelieved by aspirin. The patient had lost 40 pounds in the preceding five months. He was noted to be thin, weak, and diaphoretic but alert and oriented, with blood pressure 100/60, pulse 100/min, and temperature 101.4 F.

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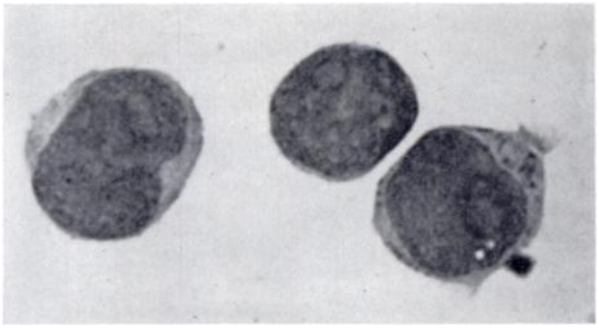

Fig. 1.—Wright's stained films of CSF cellular sediment. Cells possess fine nuclear chromatin pattern and multiple prominent nucleoli characteristic of myeloblasts.

rectally. There were scattered small lymph nodes in all node bearing areas and abdominal distention with liver and spleen each palpable 12 cm. below the costal margins. Neurologic examination revealed hypoactive deep tendon reflexes. No nuchal rigidity nor papilledema were noted. Initial laboratory data included hematocrit 25 per cent, hemoglobin 8.4 Gm. per cent, white count 87,000/mm^3, platelets 250,000/mm^3, BUN 26 mg per cent, alkaline phosphatase 148 units. (King-Armstrong), and trace proteinuria. The white cell differential included myeloblasts 2.0 per cent, progranulocytes 0.5 per cent, myelocytes 4.5 per cent, metamyelocytes 9.5 per cent, neutrophils (bands) 16.5 per cent, neutrophils (segmented) 52 per cent, lymphocytes 2.5 per cent, monocytes 12.0 per cent, and eosinophils 0.5 per cent. There were 5 nucleated RBC's per 100 WBC's. The reticulocyte count was 5 per cent and the leukocyte alkaline phosphatase score was zero. Bone marrow picture was compatible with that of chronic granulocytic leukemia. On the fourth hospital day the patient was afebrile, but had persistant nuchal rigidity and severe headache. Lumbar puncture revealed a cloudy spinal fluid under an opening pressure of 60 cm. H_2O, with protein 100 mg. per cent and sugar 44 mg. per cent. There were 297 cells/mm^3 all of which appeared to be unidentified mononuclear cells; bacterial and fungal studies were negative. A second lumbar puncture was performed on the seventh hospital day, revealing 1986 cells/mm^3 which appeared to be 5 per cent polymorphonuclear neutrophils and 95 per cent unidentified mononuclear cells and no infectious agents could be found. A third lumbar puncture was performed on the tenth hospital day, revealing a cell count of 660/mm^3. For better morphologic definition, the spinal fluid was centrifuged and a drop of the patient's serum added to the cell sediment, which was then stained with Wright's stain. All the mononuclear cells were then identified as myeloblasts (Fig. 1). The patient was treated with methotrexate intrathecally with prompt clinical response. His treatment and cell counts in the cerebrospinal fluid and peripheral blood are summarized in Figure 2. His cerebrospinal fluid cell count remained stable at a level of 34/mm^3, mostly polymorphs and the rest lymphocytes. No myeloblasts were seen on three occasions. There was diminution in the sizes of his liver and spleen. A rise in his white count to 400,000/mm^3 with predominantly mature cells 50 days from first admission was controlled by Busulphan therapy. He was discharged on Busulphan 4 mg. orally per day but was readmitted 90 days from his first admission because a left-sided lower facial paralysis developed. A lumbar puncture was performed, revealing clear fluid with a normal pressure. The cell count was 1178/mm^3, of which 40 per cent were myeloblasts. Twenty ml. of the spinal fluid was collected, incubated, and treated by the direct bone marrow chromosome technic as described by Tjio and Whang.[4] The Ph^1 chromosome was evident in many of the metaphases (Fig. 3). He was again treated with Methotrexate 0.5 mg./Kg. intrathecally, but with little clinical response. X-ray therapy totalling 600 r to each side of the skull was then given with subsequent gradual improvement. On May 6th (105th day) he developed fever and bone pain. The peripheral white count was 187,000/mm^3 with 70 per cent myeloblasts. The patient was then treated for this acute myeloblastic transformation with a combination of chemotherapeutic agents consisting of Vincristine 1.0 mg./M^2 intravenously on days 1 and 5; Methotrexate (Amethopterin) 1.25 mg. every 6 hours for twenty doses; 6-Mercaptopurine

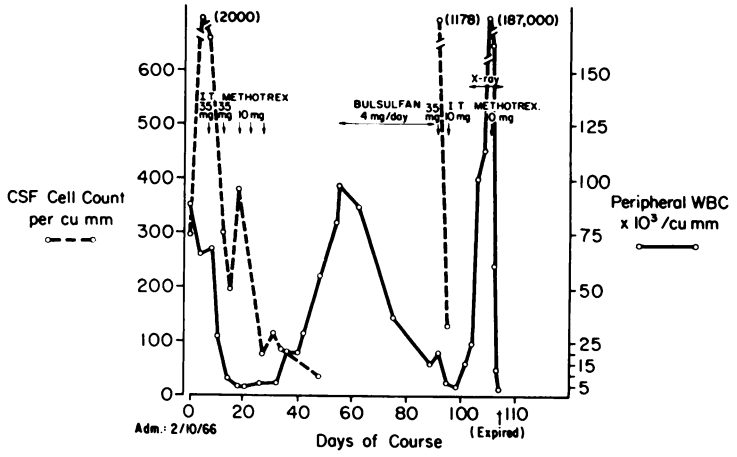

Fig.2.—Changes in CSF cell count and peripheral white blood cell count during hospital course.

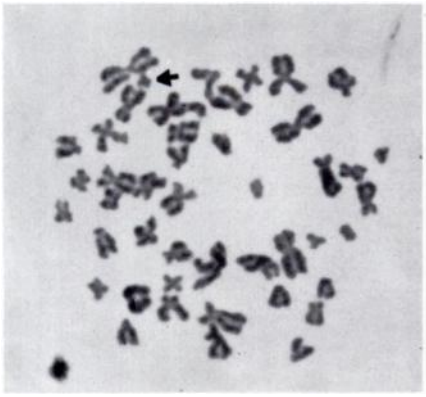

Fig. 3.—Metaphase from CSF cells showing an abnormal small acrocentric chromosome with the features of the Philadelphia chromosome (arrow).

400 mg./M² intravenously, daily times 5; and Prednisone 60 mg./M² daily times 5. He became febrile, confused, and disoriented. A bilateral bronchopneumonia developed and the patient expired on the fifth day of therapy. The last white count was 3,600/mm³ with 9 per cent myeloblasts. Post mortem examination confirmed leukemic infiltration in the brain, spinal cord and meninges.

Discussion

Fever in the course of chronic leukemia may herald infection or advancing disease.[5] In addition, the lethargy, hypoactive reflexes and headache in our patient focused our attention to central nervous system complications. The initial difficulties in identification of the cells in his cerebrospinal fluid delayed the establishment of correct diagnosis. These difficulties arose from the following fact. As the physicochemical composition of the cerebrospinal fluid is different from that of the plasma, white cells passing from plasma to cerebrospinal fluid may be expected to alter their morphologic appearance.

The osmolarity of the two fluids are closely similar but the cerebrospinal fluid is slightly hypotonic due to a lower protein content.[6] Suspending the cerebrospinal fluid cells in serum restored their original morphology and allowed the identification of myeloblasts in the present case.

Acute myeloblastic transformation of chronic granulocytic leukemia generally signifies the terminal phase of the disease.[3,7] Conversion is usually rapid and widespread, commonly involving marrow and peripheral blood simultaneously, and is accompanied by marked constitutional symptoms. We are not aware of any reports in the literature of such an acute conversion being localized in a single tissue of the body. In the present case the acute myeloblastic infiltration was probably confined to the meninges for three months before other clinical or histologic manifestations of transformation were evident. After a brief remission induced by intrathecal Methotrexate, recurrence became manifest as a facial palsy of the infranuclear type. A fullblown myeloblastic crisis with further involvement of the meninges immediately followed.

Residual meningeal infiltration and leukemic depositions in extramedullary sites such as kidney, liver, testes, lung, intestines, and brain are often found in patients dying of acute leukemia during complete blood and bone marrow remission.[8-10] Nies et al.[9] suggested that chemotherapy in acute leukemia does not completely eradicate all leukemia cells at reservoir sites in the body. Shaw and his co-workers[2] found that 8 of their 25 patients with meningeal leukemia had the onset of meningeal signs and symptoms while in partial or complete hematologic remission. They believed that the failure of chemotherapeutic agents (6-Mercaptopurine and Methotrexate) to cross the blood-brain barrier played a role in the development of meningeal leukemia. The course of the present case was unusual in that the acute process was confined locally to the meninges and may have had pathogenic influence on the later generalized spread of acute leukemia. It is also unique that acute myeloblastic involvement occurred first in an anatomic area amenable to local chemotherapy. The prompt clinical improvement and disappearance of leukemic cells in the cerebrospinal fluid after the initial course of intrathecal Methotrexate indicated a therapeutic response. This therapy might have played a part in limiting the disease to the central nervous system for the approximately three month period during which the patient enjoyed relatively good health.

We believe this is the first report of an observation of the Philadelphia (Ph^1) chromosome in the cells of the cerebrospinal fluid. As the Ph^1 chromosome occurs uniquely in myeloid and erythroid cells in chronic granulocytic leukemia,[11] its demonstration in the myeloblasts in nonhemorrhagic cerebrospinal fluid in our patient suggests that they were derived from his chronic granulocytic leukemic cells outside the central nervous system.

Summary

A patient with chronic granulocytic leukemia is presented with documented central nervous system myeloblastic transformation, while in hematologic remission. This transformation was confirmed by the demonstration of myelo-

blasts with the Philadelphia (Ph^1) chromosome in the cerebrospinal fluid. The course of his illness was unusual in that the initial single manifestation of the acute myeloblastic transformation was an acute meningeal leukemia. Intrathecal Methotrexate treatment resulted in a remission for three months, following which general systemic involvement by acute myeloblastic leukemia occurred.

SUMMARIO IN INTERLINGUA

Es presentate le caso de un patiente con chronic leucemia granulocytic con documentate transformation myeloblastic del systema nervose central durante que ille se trovava in remission hematologic. Iste transformation esseva confirmate per le demonstration de myeloblastos con le chromosoma Philadelphia (Ph^1) in le liquido cerebrospinal. Le curso del morbo esseva inusual in tanto que le sol manifestation initial del acute transformation myeloblastic esseva un acute leucemia meningee. Tractamento intrathecal con Methotrexato resultava in un remission de un duration de tres menses, post lo que occurreva le invasion del systema total per acute leucemia myeloblastic.

REFERENCES

1. Schwab, R. S., and Weiss, S.: The neurologic aspect of leukemia. Amer. J. Med. Sci. 189:766, 1935.

2. Shaw, R. K., Moore, E. W., Freireich, E. J., and Thomas, L. B.: Meningeal leukemia. Neurology 10:823, 1960.

3. Morrow, G. W., Pease, G. L., Stroebel, C. F., and Bennett, W. A.: Terminal phase of chronic myelogenous leukemia. Cancer 18:369, 1965.

4. Tjio, J. H., and Whang, J.: Direct chromosome preparations of bone marrow cells. In Yunis, J. J. (Ed.): Human chromosome Methodology. New York and London, Academic Press, 1965, p. 51.

5. Raab, S. O., Hoeprich, P. D., Wintrobe, M. M., and Cartwright, G. E.: The clinical significance of fever in acute leukemia. Blood 16:1609, 1960.

6. Lickint, F.: der Gehalt des Liquor cerebrospinalis an aminosäuren—stickstaff. Z. Ges. Neurol. Psychiat. 120:148, 1929.

7. Haut, A., Abbott, W. S., Wintrobe, M. M., and Cartwright, G. E.: Busulfan in the treatment of chronic myelocytic leukemia. The effect of long term intermittent therapy. Blood 17:1, 1961.

8. Anderson, C. D., and Roberts, G. B. S.: A case of acute leukemia with complete remission and death from subsequent development of chloromas. Glasg. Med. J. 35: 95, 1954.

9. Nies, B. A., Bodney, G. P., Thomas, L. B., Brecher, G., and Freireich, E. J.: The persistence of extramedullary leukemia infiltrates during bone marrow remission of acute leukemia. Blood 26:133, 1965.

10. Mathe, G., Schlumberger, J. R., Schneider, M., Cattan A., Amiel, J. L., Schwarzenberg, L., and Mary, A. M.: Extensive histological and cytological survey of patient with acute leukemia in "complete remission". Abstr. Xth Cong. European Haemat., Strasbourg, 1965, p. 178.

11. Whang, J., Frei, E., III, Tjio, J. H., Carbone, P. P., and Brecher, G.: The distribution of the Philadelphia chromosome in patients with chronic myelogenous leukemia. Blood 22:664, 1963.