Multiple myeloma superimposed on chronic myelocytic leukemia

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Summary: A 65-year-old woman with chronic myelocytic leukemia and multiple myeloma is described. Cases of acute leukemia complicating multiple myeloma have been reported in recent years, but to our knowledge this is the first case where multiple myeloma developed in a patient who had pre-existing chronic myelocytic leukemia.

Résumé: *Un cas de myélome multiple surajouté à une leucémie myéloïde chronique*

L'article présente un cas de leucémie myéloïde chronique compliqué de myélome multiple chez une femme de 65 ans. Depuis quelques années, on a signalé des cas de leucémie aiguë venant compliquer un myélome multiple, mais, à notre connaissance, ce présent cas est le premier où un myélome multiple s'est développé chez un malade souffrant déjà d'une leucémie myéloïde chronique.

Multiple myeloma has been reported in association with a variety of hematologic and non-hematologic diseases, both benign and malignant. Association with the myeloproliferative syndromes has occurred rarely, but to our knowledge no cases of multiple myeloma developing in patients with chronic myelocytic leukemia have been reported.

Case report

A 65-year-old Greek woman was well until April 1963 when she developed generalized weakness and dizziness. Investigations were undertaken in Greece, but unfortunately the physical findings and the results of the bone marrow examinations were not available to us. The leukocyte count in peripheral blood was 43,000/mm³ with 59% mature neutrophils, 14% band neutrophils, 15% myelocytes and 12% monocytes. The patient was begun on 2 to 4 mg of busulfan per day. She remained in Greece until November 1968, during which time the leukocyte count ranged from 5000 to 84,000/mm³ with myeloid immaturity and an occasional nucleated erythrocyte. Urinalyses in 1963 and 1964 yielded normal findings.

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Upon returning to Canada in 1969 she was maintained on busulfan by her family physician. The hemoglobin ranged from 6.4 to 11.0 g/dl and the leukocyte count from 11,000 to 86,000/mm³. Radiographs of the right hip and pelvis were taken in August 1970 because of pain in this area; lytic lesions were present in the upper third of the femur and were believed to be due to chronic myelocytic leukemia. Radiotherapy was begun, but after one week a pathologic fracture of the right femur occurred. A compression plate was inserted but had to be replaced in May 1971 because of nonunion. Unfortunately no tissue from either surgical procedure was available for pathologic examination. During hospitalization in May 1971 the hemoglobin varied from 7.4 to 10.0 g/dl, the leukocyte count from 7700 to 12,400/mm³, and immature myeloid cells were again present. A bone marrow aspirate showed marked myeloid hyperplasia with a shift to the left (i.e. greater proportions of cells in earlier stages of development) and 9% plasma cells. Nine months later a skeletal survey revealed numerous lytic lesions. A repeat bone marrow aspirate showed normal granulopoiesis, slightly depressed erythropoiesis and 12% plasma cells, some of which were binucleated and trinucleated. The total serum protein was increased to 9.1 g/dl, but unfortunately serum protein electrophoresis was not done. The patient had been continued on busulfan throughout this period.

This lady was first admitted to The Montreal General Hospital in September 1972 because of fatigue, dizziness and pain over the sternum, ribs and neck of approximately one year's duration. Nausea and vomiting without abdominal pain or change in bowel habits had been present for two months prior to admission. She was slightly obese, afebrile and in moderate discomfort. The blood pressure was 110/70 mm Hg, the pulse 84/min and regular, and the respirations 24/min. The lungs were clear. There was a short ejection systolic murmur along the left sternal border. The abdomen was obese and soft. The liver edge was palpable 3 cm below the right costal margin. The spleen was not palpable. There was no significant lymphadenopathy. There was slight tenderness over the sternum. Results of neurologic examination were within normal limits.

The hemoglobin was 9.0 g/dl, leukocyte count 3600 to 5000/mm³ and platelet count 205,000/mm³. The peripheral blood smear showed metamyelocytes, myelocytes and the occasional promyelocyte, but no blast cells. The bone marrow was hypercellular with active granulopoiesis but no significant myeloid immaturity, which excluded a morphologic diagnosis of chronic myelogenous leukemia. Plasma cells, some of which were multinucleated, constituted 9% of the marrow cells. The leukocyte alkaline phosphatase score was normal. The serum alkaline phosphatase was 16 KA units and the uric acid was 7.8 mg/dl. Serum calcium, SGOT, BUN, creatinine and creatinine clearance were normal. Serum protein electrophoresis revealed an albumin level of 3.57 g/dl, and a gamma globulin of 3.63 g/dl with a sharp monoclonal peak. By immunoelectrophoresis IgG was found to be 5520 mg/dl, IgA 90 mg/dl and IgM 20 mg/dl. Total 24-hour urinary protein was 2.4 g, and immunoelectrophoresis revealed kappa-type light chains with a trace of albumin. On chest radiography cardiomegaly and a prominent left ventricle were evident. A skeletal survey, including the skull, showed diffuse osteoporosis with numerous osteolytic lesions, compatible with multiple myeloma (Fig. 1). Cytogenetic studies, including four complete karyotypes, seven mitotic analyses by photography with partial karyotype of G-group chromosomes and one mitotic analysis under microscopy, revealed a 46, XX, Gq⁻ chromosome complement. Gq⁻ represents a deletion of the long arms of chromosome 22, commonly referred to as the Philadelphia chromosome. Seven other mitotic analyses examined by microscopy with partial karyotypes of G-group chromosomes were hypodiploid and all displayed the Philadelphia chromosome (Fig. 2); the hypodiploidy was thought due to random loss of chromosomes.

Busulfan was discontinued on admission. Because of constant pain over the neck and imminent fracture of the fifth cervical vertebra, this area was irradiated (2000 rads over 14 days) with relief of pain. Phenylalanine mustard (PAM) 4 mg/day was started, but the dosage was decreased to 2 mg/day after three weeks because of mild leukopenia. On discharge the patient was still complaining of nausea, vomiting and weakness, and discontinued her medications shortly afterwards because of these symptoms. Their persistence led to her readmission to hospital in November 1972. Examination revealed no change from the previous findings, except for rales at both lung bases. The hemoglobin was 10.5 g/dl, the platelet count 165,000/mm³ and the leukocyte count 5400/mm³, and an occasional myelocyte was noted. The leukocyte alkaline phosphatase score was again normal. The serum alkaline phosphatase was 25 KA units, 5'nucleotidase 16.7 units, SGOT 64 units, and uric acid 8.7 mg/dl. Serum calcium, phosphorus, creatinine, bilirubin and LDH were normal. A chest radiograph revealed prominent pulmonary veins, indicative of pulmonary hyperten-

sion, Kerley B lines (distended interlobular lymphatics), and blunting of both costophrenic angles. An upper GI series was normal.

Dixogin, diuretics and allopurinol produced little change in symptomatology but some improvement in the clinical and radiologic findings in the chest was noted. Further investigation was not pursued and the patient was discharged on the above medications. She refused to return to hospital for further evaluation.

Comments

This patient appeared to have two distinct diseases concomitantly, chronic myelogenous leukemia and multiple myeloma. Some of the classical manifestations of multiple myeloma have been described in chronic myelogenous leukemia, and hence some of the features which may be common to these entities are reviewed.

Chronic myelogenous leukemia may be defined as a neoplastic disease, often associated with a unique chromosomal abnormality, in which the major clinical manifestations are attributed to the abnormal, excessive and apparently uncontrolled proliferation of granulocytes in the bone marrow. Characteristically, large numbers of immature myeloid cells circulate in the peripheral blood, and extramedullary myelopoiesis often produces gross enlargement of the liver and spleen.

The Philadelphia chromosome is an abnormal G 22 autosome with its large arms significantly shortened. Although reciprocal translocation between the long arms of two G chromosomes has been postulated as a mechanism for the formation of the Philadelphia chromosome,[1] it has not yet been determined whether the long arms of the chromosome have been deleted or translocated to another chromosome. These chromosome rearrangements may be a common pathway by which carcinogenic factors induce malignant growth.[2] Since Nowell and Hungerford[3] described this abnormality numerous studies have shown that a large percentage of patients with chronic myelocytic leukemia have the Philadelphia chromosome, and its presence has been of prognostic value.[4,5] The specificity of the Philadelphia chromosome has been questioned since it has been reported in other myeloproliferative disorders such as polycythemia rubra vera, myelofibrosis and essential thrombocythemia. It has been suggested that cases of Philadelphia-chromosome-positive myelofibrosis are secondary forms derived from chronic myelocytic leukemia, and that other myeloproliferative disorders with a positive Philadelphia chromosome are forms in transition to chronic myelocytic leukemia.[6]

In classical adult chronic myelogenous leukemia the neutrophil alkaline phosphatase (NAP) is absent or very low in almost all cases. With remission the NAP may return to normal. In our case the NAP score was determined when the disease was in remission.

Bone tenderness, especially over the sternum, was present on admission. This symptom often occurs in chronic myelogenous leukemia when a rapid increase in bone marrow cellularity occurs, producing increased pressure, erosion of the bone or elevation of the periosteum with consequent pain. In this case it was perhaps due to numerous lytic lesions of the skeleton rather than myeloid hyperplasia since there was no evidence of the latter on bone marrow aspiration at that time.

In summary, the clinical onset of the disease with weakness, the presence of marked leukocytosis with immature myeloid cells in the peripheral blood and bone marrow, the presence of the Philadelphia chromosome, and a satisfactory response to busulfan therapy for many years, all confirmed the diagnosis of chronic myelogenous leukemia.

Multiple myeloma is the most common clinical plasma cell dyscrasia. It may be defined as: (a) the proliferation of immunologically competent cells, usually identifiable as plasma cells, in the absence of a recognizable antigenic stimulus; (b) the elaboration of large quantities of monoclonal-type gamma globulin with a characteristic electrophoretic homogeneity and/or excessive quantities of comparable homogeneous polypeptide subunits of these proteins, usually of the light-chain type; and (c) a decrease in the production of normal immunoglobulins. The marrow usually contains 5 to 10% or more plasma cells, many of which are large, immature and multinucleated. The term myeloma implies that the presenting and usually predominant clinical features are those related to marrow infiltration and bone destruction by the neoplastic cells.

Neither monoclonal gammopathy nor the presence of destructive bone

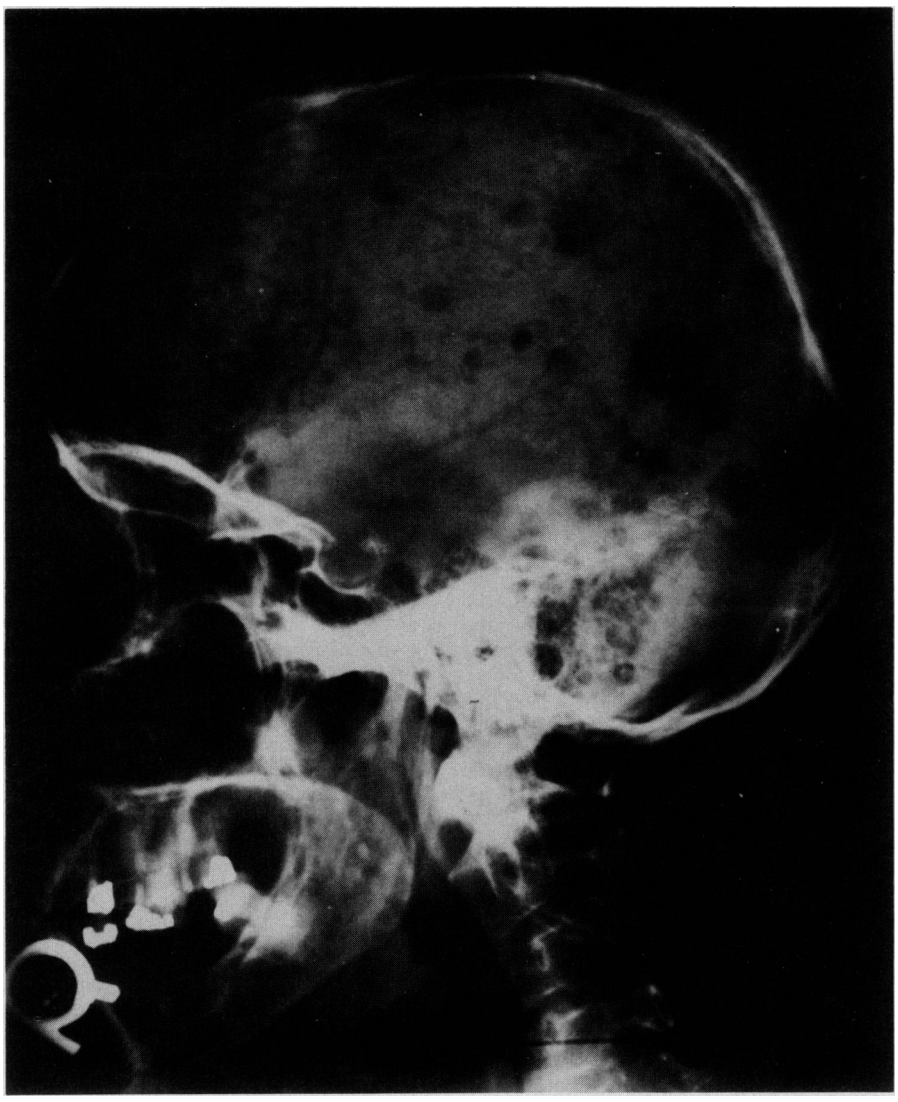

FIG. 1—Radiograph of the skull showing osteolytic lesions compatible with multiple myeloma.

lesions alone is diagnostic of multiple myeloma and each may be seen in chronic myelogenous leukemia. Monoclonal gammopathy has been reported in a variety of myeloproliferative disorders including polycythemia rubra vera,[7] myelofibrosis[7] and chronic myelogenous leukemia.[8] The most interesting cases are those described by Osserman and Takatsuki[9] and Hollard *et al.*[10] These cases had unequivocal clinical and hematologic features diagnostic of chronic myelogenous leukemia with an abnormal gamma globulin identified as an IgG in one case and a paraprotein in the β_1-globulin range in the other. None of the cases showed osteolytic lesions.

A quantitative analysis of IgG, IgA and IgM in acute and chronic myelogenous leukemia (22 and 8 cases, respectively) showed that the mean values of IgG and IgA were not significantly different from those of healthy controls. The IgM levels were elevated in acute myelocytic leukemia but not in chronic myelocytic leukemia. In polycythemia rubra vera the IgA and IgM levels were significantly elevated, and in myelofibrosis the levels of all three immunoglobulin classes were increased.[11] Michaux and Heremans[12] studied 30 cases of monoclonal immunoglobulin disorders not classified as multiple myeloma or Waldenstrom's macroglobulinemia, and the only leukemic case was one of chronic lymphatic leukemia. Hence monoclonal gammopathy is a rare finding in chronic myelogenous leukemia, although figures of its incidence are not available.

Destructive bone lesions have been reported in the leukemias. Most cases have been in patients with acute leukemia and hypercalcemia.[13,14] In some the presenting symptoms were related to the hypercalcemia, and radiographic evidence of bone disease was not always present. No pathologic fractures have been reported in these cases. Occasional cases of chronic lymphocytic leukemia with hypercalcemia and destructive bone disease have also been observed.[13] Chabner, Haskell and Canellos[15] reviewed 205 patients with chronic myelogenous leukemia seen at the National Cancer Institute between 1961 and 1969 and found only six cases with skeletal involvement. In three patients bone involvement occurred during the blastic phase of the illness, and in two the bone lesion was the initial manifestation of this transformation. Two other patients with osseous lesions remained in the chronic phase of their disease, one with multiple sites of involvement. In a more recent case hypercalcemia in association with multiple skeletal myeloblastomas preceded transformation to an acute myelocytic leukemia.[16] Destructive bone lesions are relatively rare in chronic myelogenous leukemia, and in approximately 50% of these the lesions have preceded or occurred concomitantly with blastic transformation.

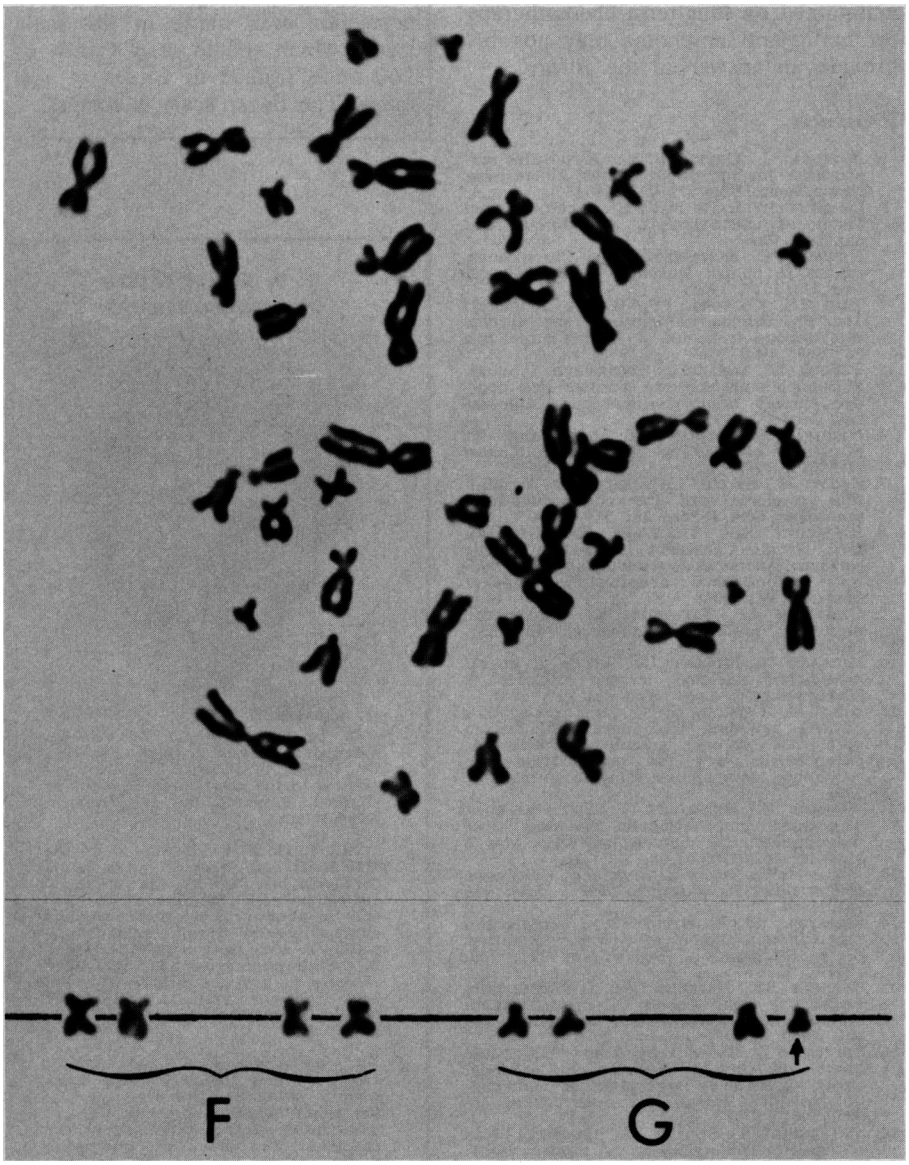

FIG. 2—Metaphase with partial karyotype showing Philadelphia chromosome — from bone marrow chromosome studies.

Different chromosomal abnormalities have been reported in multiple myeloma, viz absence of one small acrocentric autosome, either 21 or 22, an abnormal submetacentric marker, aneuploidy, pseudodiploidy and polyploidy.[17-19] No marker chromosome other than the Philadelphia chromosome has been described.

Hence, considering the other features compatible with multiple myeloma in our patient, it appears unlikely that the bone lesions can be attributed to chronic myelogenous leukemia. Our patient had 9 to 12% plasma cells, some of which were immature and multinucleated, markedly increased levels of IgG, a decrease in the production of normal immunoglobulins, proteinuria consisting of kappa light-chains, and numerous skeletal lytic lesions, all of which support the diagnosis of multiple myeloma.

There is an unequivocal relationship between some neoplastic diseases and the subsequent development of another malignant disease. An association between multiple myeloma and leukemia may be an example of such a relationship. Nordenson[20] described two cases of acute myeloblastic leukemia in a clinical review of 310 cases of myelomatosis. In 1970 Kyle, Pierre and Bayrd[21] reported four cases of acute myelomonocytic leukemia developing in patients with multiple myeloma who had been on PAM for 30 to 57 months. Because of the remote likelihood of chance association of these two entities, the known effect of alkylating agents on deoxyribonucleic acid, and the long period of treatment with PAM, a possible etiological role of PAM therapy in the development of

acute leukemias was suggested. The same year four other patients were described by Andersen and Videback;[22] two of these patients had been on PAM, one on cyclophosphamide, and one on both agents prior to the development of leukemia. Numerous other cases have been reported in the past two years. Most have been on PAM, but some have been treated with other alkylating agents in combination with radiotherapy.

Radiation-induced cancer[23] and radiation leukemogenesis[24] have been recently reviewed and it is believed that ionizing radiation may induce cancer in man. Prolonged exposure to chlorinated hydrocarbons and benzene may produce leukemia in man. However, the case for chemical leukemogenesis is much weaker than that for ionizing radiation. Although alkylating agents cause chromosome damage in experimental animals,[25] their leukemogenic action is not well established, but the increased number of reported cases of leukemia in patients on prolonged chemotherapy makes the cause-and-effect relationship more probable. This possible leukemogenic action is not limited to the alkylating agents; procarbazine has been shown to induce neoplasms of the hematopoietic system in non-human primates.[26]

Two cases, one of chronic lymphatic leukemia and one of lymphosarcoma terminating in multiple myeloma, have been reported. The patient with chronic lymphatic leukemia was on long-term chlorambucil therapy when multiple myeloma developed. The authors concluded that transformation from malignant lymphocytic disease to myeloma had occurred,[27] but the possible carcinogenic action of chlorambucil in this transformation cannot be excluded.

In our case chronic myelocytic leukemia was complicated by superimposed multiple myeloma and, surprisingly, with the progression of the latter, the manifestations of the leukemia were minimal. Whether long-term busulfan therapy had a role in inducing the plasma cell dyscrasia, or whether the association of the two conditions is coincidental, remains to be established. The increasing population of patients maintained on long-term chemotherapy for malignant lymphoma may possibly provide an answer in the future.

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Erratum

When the map in Fig. 1 of the article "Human botulism in Canada (1919-1973)" (*Can Med Assoc J* 110: 191, 1974) was reduced to two-column width from the original diagram, no correction was made in the scale legent which should read 1 inch = 260 miles instead of 1 inch = 140 miles. The linear scale is correct.