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Multiple Myeloma and Chronic Myelogenous Leukemia
—A case report with literature review—

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This is the case of a 71 year old male who developed multiple myeloma (MM) and chronic myelogenous leukemia (CML) within a two year period. The patient initially presented with osteolytic lesions of the lumbar spine, and following the initial work-up a diagnosis of multiple myeloma with an IgG kappa paraproteinemia was made and appropriate treatment was given. Two years later the patient developed a progressively worsening leukocytosis which was found to be due to Philadelphia Chromosome (Ph^1) positive CML. The occurrence in the same patient of two distinct hematologic malignancies suggests a neoplastic transformation of a pluripotent stem cell. A review of the literature appears to support the existence of a relationship between MM and CML as well as a relationship between MM and the myeloproliferative disorders.

Key Words: Multiple myeloma, chronic myelogenous leukemia

Multiple myeloma (MM) and chronic myelogenous leukemia (CML) are neoplastic processes involving plasma cells and myeloid precursors respectively. These cell types represent distinct but related cell lineages in that plasma cells and myeloid cells are both derived from a common ancestral stem cell. Reported instances of both MM and CML occurring in the same patient are extremely rare. The present case report documents such an occurrence in a 71 year old male who initially developed MM, and subsequently developed CML after an interval of two years. The occurrence of these two malignancies in the same patient supports the concept that both malignancies are derived from a common ancestral stem cell, capable of dif-ferentiating along both lymphoplasmacytic and myeloid cell lines.

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CASE REPORT

A 71 year old white male was hospitalized for back pain, pain and numbness in both legs, and a foot drop on the left. CT scan and bone scan revealed osteolytic lesions of the lumbar spine at the L3-L4-L5 levels and compression fractures of the L4 and L5 vertebrae. Laboratory examination revealed a white blood cell count of 12.3×10^9/L, hematocrit of 42%, hemoglobin of 148 g/L, and platelet count of 376×10^9/L. Serum protein electrophoresis (SPEP) revealed an IgG kappa paraprotein, quantitated by rate nephelometry to be 19.35 g/L. A bone marrow biopsy with aspiration of one of the lumbar lesions was performed, and a cluster of cells with a syncytial arrangement was found in the biopsy (Figure 1) which, despite the benign morphologic appearance of the individual cells, was diagnostic of MM in the presence of a monoclonal gammopathy. The patient was then treated with radiation therapy, melphalan and prednisone. Two years later the patient developed

CML. His peripheral blood exhibited progressive leukocytosis with a white cell count of 40.8 $\times 10^9$/L, a hematocrit of (43%), and a hemoglobin of (14.4 gm/dl). The differential count was as follows: 70% neutrophils, 10% bands, 6% metamyelocytes, 3% myelocytes, 9% lymphocytes and 2% monocytes. The platelet count was 466×10^9/L. A bone marrow biopsy and aspirate from the iliac crest revealed a predominance of mature and intermediate forms of granulocytes consistent with the diagnosis of CML (Figures 2 and 3). Cytogenetic studies on bone marrow cells revealed tae presence of the Ph^1, confirming the diagnosis. The patient was placed on hydroxyurea.

Eighteen months later the patient was again hospitalized for numbness and weakness of the legs, dysarthrosis of the hands and shoulder, and pain radiating from the back. A radiograph showed destruction of multiple upper thoracic vertebrae and extensive paravertebral soft tissue swelling. Serum protein electrophoresis

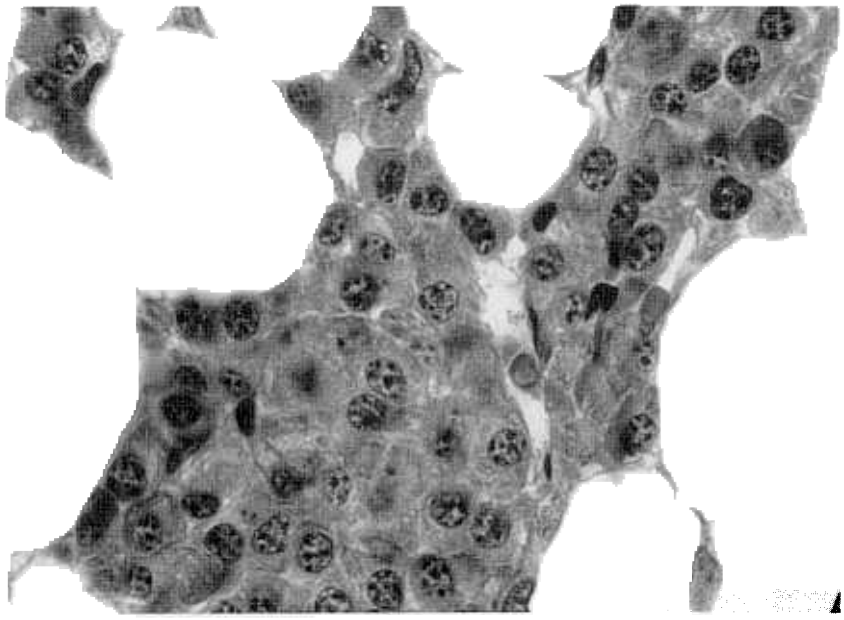

Fig. 1. *Bone marrow biopsy demonstrating syncytial arrangement of plasma cells in MM. (H & E, ×400).*

Table 1. Reported cases of patients with CML and MM

Reference	Ratient	Clinical course
	60M	CML (Ph^1+), IgA lambda monoclonal gammopathy, concurrent
Lewis, *et al* (1986)	62F	CML (Ph^1+), IgA lambda myeloma, concurrent
Ritzmann, *et al* (1966)	72F	CML (Ph^1+), IgA lambda myeloma, concurrent
MacSween, *et al* (1972)	77M	CML (Ph^1+), Bence Jones myeloma, concurrent
Derghazarian & Whittemore (1974)	65F	CML (Ph^1+), treated with busulphan, then IgG kappa myeloma after 3 years
Boots & Pegrum (1982)	58M	CML (Ph^1+), MM, concurrent
Zoumbos, *et al* (1987)	57M	CML (Ph^1-), treated with busulphan, then light chain kappa myeloma after 5 years

(SPEP) with immunofixation for immunoglobulins showed a persistent IgG kappa monoclonal gammopathy (Figure 4). The patient expired from bronchopneumonia after several weeks. An autopsy revealed extensive destruction and fibrosis of the upper thoracic and

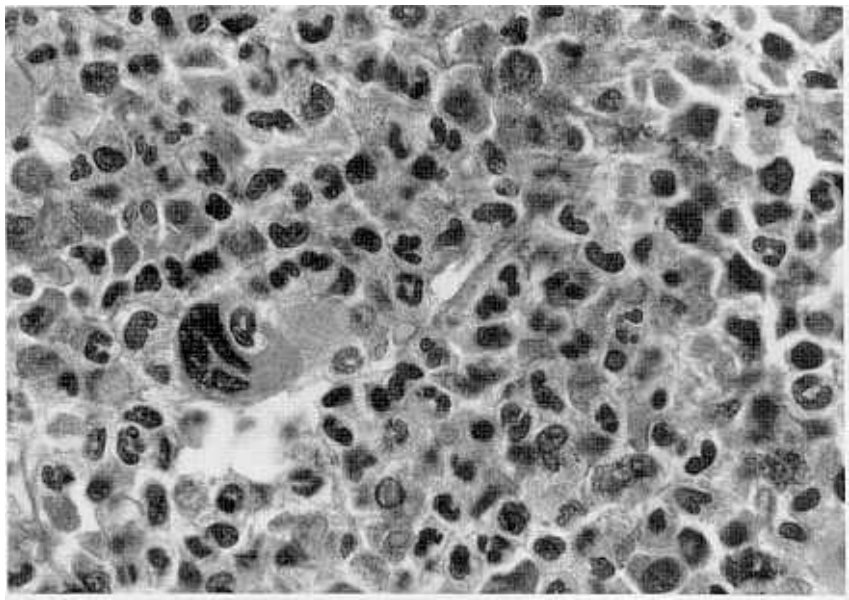

Fig. 2. *Bone marrow biopsy showing a proliferation of mature and intermediate forms of granulocytes in CML. (H & E, × 100).*

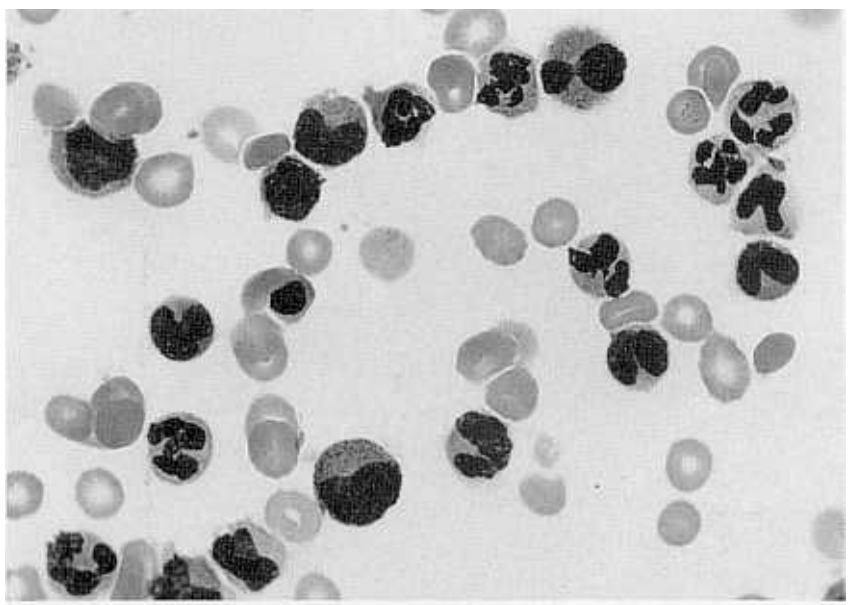

Fig. 3. *Bone marrow aspirate smear showing spectrum of myeloid maturation in CML. Wright-Giemsa stain, × 1000.*

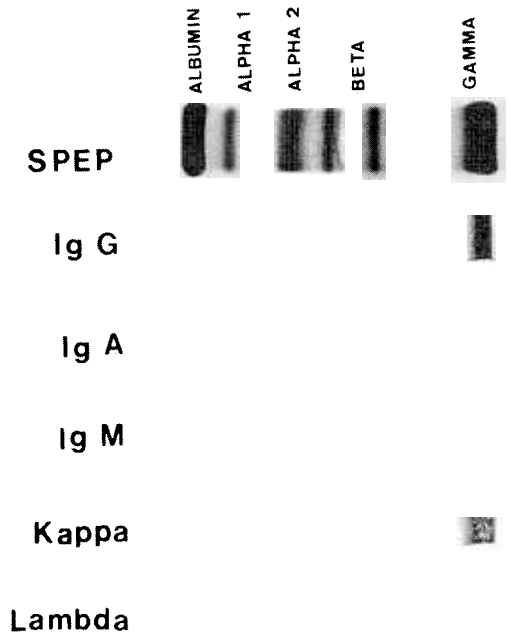

Fig. 4. Serum protein and immunofixation electrophoresis, demonstrating the presence of an IgG kappa monoclonal gammopathy.

lower cervical vertebrae. The bone marrow from these vertebrae demonstrated an incomplete remission of CML. Additionally, one site in the upper thoracic vertebrae contained an ill-defined 50 mm lesion which histologically was almost totally composed of neoplastic plasma cells representing residual MM (Figure 5). These cells appeared more pleomorphic than those from the initial biopsy and were more diffuse and infiltrating with a loss of syncytial pattern. There was an increased nucleocytoplasmic ratio, a loss of the normal "cartwheel" pattern, nucleolar prominence and multinucleation. Furthermore, the neoplastic cells exhibited a monoclonal immunohistochemical staining pattern for IgG kappa immunoglobulins.

DISCUSSION

Multiple myeloma is a neoplastic process involving the B-cell lineage, characterized by plasma cell infiltration of the bone marrow, often resulting in bone destruction, anemia and renal failure (Barlogie *et al.* 1989). The most important diagnostic criterion for MM is the dem-

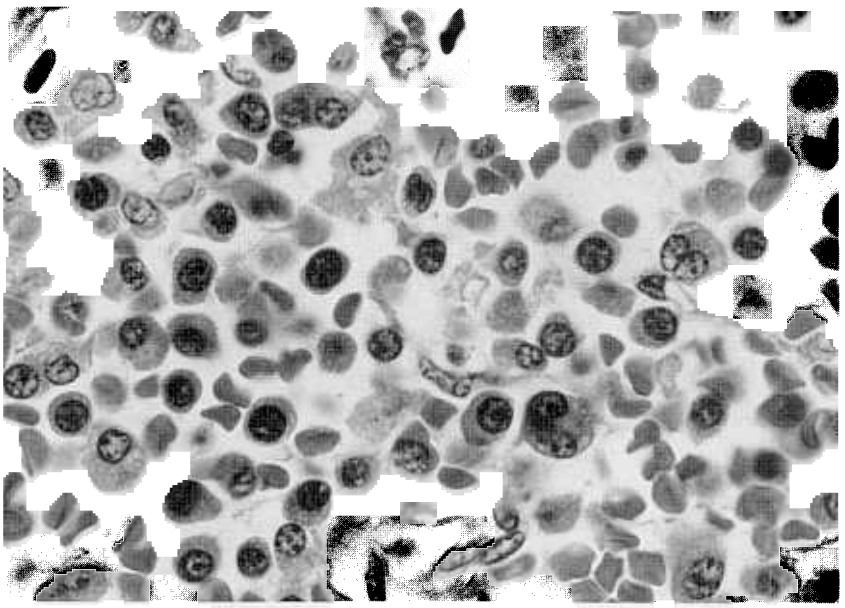

Fig. 5. Bone marrow section from autopsy showing neoplastic plasma cells in MM. (H & E, ×400).

Table 2. Reported cases of patients with MPD and MM

Reference	Ratient	Clinical course
Heinle, *et al* (1966)	80F	PV and MM, concurrent
Spickard (1960)	58M	PV, then MM after 2 years
	49F	AMM and MM, concurrent
Brody, *et al* (1964)	66M	PV and MM *IgA kappa), concurrent
	49F	AMM and MM (IgA kappa), concurrent
Selroos, & Van Ansendelft (1977)	78M	IT and MM (IgA kappa), concurrent
	66F	IT, treated with busulfan, then MM (IgG kappa) after 19 months
Ghosh (1984)	80F	IT and Bence-Jones myeloma, concurrent
Kasimis, *et al* (1981)	62F	AMM and MM, concurrent

onstration of bone marrow plasmacytosis. Plasma cells comprise up to 2% of the nucleated cells of normal bone marrow and are often perivascular in location (Hyun *et al.* 1976; Hyun 1976). The degree of marrow plasmacytosis in multiple myeloma is variable, ranging from 5 to nearly 100%, most often comprising 10 to 20% of the marrow cells (Azar 1973).

The morphology of the individual cells is a significant factor in the differentiation between reactive and neoplastic plasmacytosis. Benign, reactive plasma cells are recognized by the following criteria: a relatively small, distinct, round to oval nucleus with 5 to 8 blocks of chromatin arranged radially about the nuclear membrane in a "cartwheel" fashion; eccentric position of the nucleus; a lighter staining area near the nucleus corresponding to the Golgi zone; and homogenous cytoplasm.

Although the plasma cells in MM can cover the full spectrum of morphologic variations, there usually is a predominance of immature forms. Myeloma cells are generally larger than reactive plasma cells, usually exceeding 20 μm in diameter. The nuclear chromatin is more abundant and dispersed with a loss of the cartwheel pattern typically seen in benign plasma cells. The nucleus is eccentric and the nucleolus is usually prominent (Buss *et al.* 1988). Multinucleation is not a reliable differentiating feature in diagnosing MM. However, the presence of more than five nuclei is often associated with MM.

The plasma cells seen in Figure 1 have a rather benign appearance, with a cartwheel chromatin pattern in the nucleus, whereas those seen in Figure 5, from the autopsy specimen, are more pleomorphic with multinucleation and nuclear atypia. The lytic bone lesions, the plasma cell proliferation, and the monoclonal gammopathy are features diagnostic of MM.

In a small percentage of cases the proliferation of neoplastic plasma cells form an apparently single skeletal or extra-osseous lesion. These lesions are designated as solitary plasmacytomas, however, most patients ultimately develop disseminated disease despite initial treatment by excision or irradiation (Knowling *et al.* 1983).

CML originates from the neoplastic transformation of a pluripotent hematopoietic stem cell which retains a capacity for differentiation into mature myeloid elements. In the peripheral blood, granulocytic leukocytosis is prominent with the leukocyte count ranging from 30×10^9 to $1{,}000 \times 10^9$/L. There is a spectrum of myeloid maturation, usually with fewer than 10% blasts and promyelocytes. Mature granulocytes and metamyelocytes predominate. The relative and /or absolute numbers of basophils, eosinophils, and monocytes are also frequently elevated. Figures 2 and 3 show the histologic and cytologic features of the bone marrow typically associated with the chronic phase of this disease. The characteristic findings include hypercellularity due to a proliferation of granulocytes, megakaryocytosis and a depression of the erythroid series. The mature and intermediate forms of granulocytes predominate in the chronic phase in contrast to the accelerated phase or terminal blastic phase in which blast forms are abun-

dant (Hyun *et al.* 1990).

The Philadelphia chromosome (Ph^1), which represents a reciprocal translocation from the long arm of chromosome 22 to the long arm of chromosome 9 (t(9 22)(q34 q11)) is seen in approximately 95% of patients with CML. The Ph^1 is observed not only in the granulocytes but also in cells of the monocytic, erythroid, megakaryocytic and lymphoid series in patients with CML (Chaplin and Golde 1985). This finding supports the concept of the origin of CML from a pluripotent hematopoietic stem cell. All of the Ph^1+CML cases and approximately half of the Ph^1- ones reveal the *bcr* (breakpoint cluster region) gene rearrangement.

Approximately 75% of patients with CML progress gradually to an accelerated phase, which is characterized by progressive leukocytosis with an increase in intermediate myeloid precursors and blast cells. There is increasing anemia and thrombocytopenia and a gradual failure of response to treatment. Myelofibrosis occurs in approximately one-third of the cases (Hyun *et al.* 1990).

Although the accelerated phase may progress to a blastic phase, in which 30 to more than 90% of the peripheral blood or marrow cells are blasts, approximately 25% of the patients with CML may enter a blastic phase directly, without an intervening accelerated phase. The blast cells are of variable lineages. Approximately 60 to 65% of cases undergo a myeloid transformation with the blasts expressing characteristics of granulocytes, monocytes, megakaryocytes or erythrocytes. In approximately 25% of the cases the blasts are of the lymphoid lineage. Such blasts express antigens seen in early B-cell development such as common acute lymphoblastic leukemia antigen (CALLA; CD10). High levels of terminal deoxynucleotidyl transferase, an enzyme seen in immature lymphoid cells, are also present. (Bettelheim P, *et al.* 1985) The transformation to lymphoid cells in the blastic phase of CML suggests a relationship between the myeloid lymphoid series of cells. A neoplastic transformation of the lymphohematopoietic stem cells, which is capable of both myeloid and lymphoid transformation, would account for this abnormality (Beard *et al.* 1985; Janossy *et al.* 1976).

Reported cases of MM occurring in association with CML are few but significant considering the relative rarity of these diseases. Several such cases reported in the literature are presented in Table I (Naparstek *et al.* 1980; Lewis *et al.* 1986; Ritzmann *et al.* 1966; MacSween and Langley 1972; Derghazarian and Whittemore 1974; Boots and Pegrum 1982; Zoumbos 1987). As can be seen in this table, MM has been reported occurring both at the time of diagnosis of chronic leukemia, and from 3 to 5 years after such a diagnosis.

Because of the relative rarity of MM and CML, their occurrence in the same patient suggests a relationship between these two diseases rather than a chance occurrence of independent events. Such a relationship may originate at the level of the common stem cell for the two cell lineages involved. If a stem cell common to both lymphoid and myeloid cell lineages undergoes a neoplastic transformation and proliferates along the myeloid-granulocytic cell line as well as the lymphoplasmacytic cell line, both CML and MM would develop (Naparstek *et al.* 1980; Lewis *et al.* 1980).

Busulphan is used frequently to treat CML. In the present case, the diagnosis of MM was made first and melphalan was used in treatment. Such drugs have been associated with inducing acute, but not chronic, forms of leukemia (Kyle *et al.* 1970).

There is much evidence supporting the relationship between the myeloid and lymphoid cell lines through an ancestral stem cell. The occurrence of MM and CML in the same patient is comparable to the development of blasts of lymphoid lineage during the blastic phase of CML. It has been shown that Ph^1+ B-lymphoblastoid cells may be observed in patients with CML even during the chronic phase of CML and that they may arise from the CML stem cell clone (Martin *et al.* 1980). Furthermore, there have been cases where the Ph^1, a cardinal feature of CML, was identified in patients with MM (Van Den Berghe *et al.* 1979). Thus, both diseases may originate from an early hematopoietic stem cell disorder which manifests itself in the mature stages of both B-cell and myeloid cell development, resulting in MM and CML.

CML is part of a spectrum of disorders resulting from the neoplastic transformation of hematopoietic stem cells. In addition to producing granulocytes, these stem cells have the capacity to differentiate into erythrocytes and megakaryocytes. When neoplastic transforma-

tion results in the proliferation of erythrocytes the disease is known as polycythemia vera (PV). When the transformation results in a proliferation of megakaryocytes, the result is idiopathic thrombocythemia (IT). Finally, agnogenic myeloid metaplasia (AMM) is characterized by hyperplasia of all three marow elements. These three diseases, along with CML, comprise the myeloproliferative disorders (MPD) which are interrelated in that they result from a clonal expansion of a neoplastic stem cell (Abkowitz and Adamson 1985; Krause 1981).

As with CML and MM, there is an association between the other disorders of the MPD and MM. Table II lists several reported cases of MM occurring with PV, IT, and AMM. (Heinle *et al.* 1966; Spickard 1960; Brody *et al.* 1964; Selroos and Van Assendelft 1977; Ghosh 1984; Kasimis *et al.* 1981). The association of MM and MPD supports the common etiology that these disorders ultimately arise from transformation of a pluripotent stem cell. The resulting neoplastic proliferation would affect not only the myeloid, erythroid, and megakaryocytic cell lines, but also a separate but related lineage involving lymphoplasmacytic cells.

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