Short Communication

Plasma Cell Leukemia with Myelofibrosis

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Keywords: plasma cell leukemia, myelofibrosis, plasmacytosis, myeloma, splenomegaly

Myelofibrosis, which is usually observed as one of the primary forms of chronic myeloproliferative disorders, is characterized by splenomegaly and fibrotic bone marrow. The disease is observed in 10 to 30% patients with multiple myeloma.1 The degree of the marrow fibrosis tends to correlate with the magnitude of plasma cell infiltration and therefore seems to be associated with prognostic significance. On the other hand, plasma cell leukemia which is an infrequent manifestation of multiple myeloma develops in 1-2% of patients with multiple myeloma.1 Therefore, it seems to be a very rare case to observe the coexistence of plasma cell leukemia and myelofibrosis in the same stage of disease. Moreover, it has not been clearly demonstrated whether coexistent of myelofibrosis in untreated bone marrow with plasma cell leukemia is dependent on the secondary effect of this leukemia. Here, we report a case of plasma cell leukemia with myelofibrosis, which showed a rapid development into a fatal outcome.

A 59-year-old man was admitted to our hospital because of fever and progressive general fatigue on July 2, 2000. The patient had remained asymptomatic until 3 months prior to his hospitalization. The findings on admission showed that the abdomen was slightly distended and both the liver and spleen were palpable at about 8 cm below the costal margin. Laboratory findings were as follows: white blood cells, 5.1 × 10⁹/L (myelocyte, 0.5%; metamyelocyte, 0.5%; neutrophil, 37.0%; lymphocyte, 25.5%; monocyte, 16.0%; plasma cell, 20.5%; and erythroblast, 2.0%); hemoglobin, 6.5 g/dL; platelets, 27 × 10⁹/L; lactate dehydrogenase (LDH), 1,875 IU/L; calcium, 4.9 mEq/L; albumin, 3.0 g/dL; uric acid, 12.4 mg/dL; BUN, 20.3 mg/dL; creatinine, 1.5 mg/dL; CRP, 1.7 mg/dL; β2-microglobulin, 15.9 mg/dL; IgG, 5,060 mg/dL; IgA, 6 mg/dL; and IgM, 6 mg/dL. Immunelectrophoresis revealed a monoclonal component of IgGλ in the patient’s serum. X-rays of cranial and appendicular bones presented no punched out lesions. Abdominal computed tomography scan showed marked hepatosplenomegaly. A bone marrow aspiration was dry tap. A bone marrow biopsy showed marked myelofibrosis (Fig. 1) and infiltration of plasma cells, which manifested the same phenotype as circulating plasma cells in peripheral blood.

Immunophenotypic analysis showed that plasma cells were positive for CD38, CD40, CD44, CD49d, and CD54, and negative for CD19, CD20, CD49e, CD56, CD62L, CD126, and HLA-DR. Chromosomal study using peripheral blood revealed complex karyotypic abnormalities such as 41, X, -Y, +1, der(1;3)(pter → 9q27?, 1p11 → 1qter), der(1;17)(q10; q10), der(3)(t;3;7)(q27;q11), ins(3;?)(q27;?), del[5](q21), -7, -8, der(8)(t;8)(p13;q24), -10, -13, -16, -22, +mar1, +mar2, and +mar3 in all 20 analyzed cells. Based on these laboratory data, the patient was diagnosed as having plasma cell leukemia with myelofibrosis. After the patient received combination chemotherapy consisting of vincristine (0.4 mg/body day 1-4), doxorubicin (15 mg/body, day 1-4), and dexamethasone (40 mg/body, day 1-4), the circulating plasma cells gradually decreased. However, he died of acute renal failure, possibly due to tumor lysis syndrome and myeloma kidney on day 14.

Plasma cell leukemia is characterized by the existence of the increased numbers of plasma cells both in peripheral blood and common organ sites (tissue infiltration), and the prognosis of this disease is very poor. This leukemia, which is defined as a condition that circulating peripheral blood plasma cells exceeding 2 × 10⁹/L or 20% of peripheral blood white cells, is classified into two groups; the “primary” and the “secondary” plasma cell leukemia. The secondary plasma cell leukemia is usually observed as a terminal complication during the course of multiple myeloma.2 Although it is widely accepted that there is a relationship between multiple
myeloma and myelofibrosis, only few cases that primary plasma cell leukemia coexists with myelofibrosis are reported.\textsuperscript{3-7} Most cases of myelofibrosis complicated by multiple myeloma are secondary myelofibrosis and this is mostly caused by anticancer drugs, such as melphalan. The finding that myelofibrosis is improved after successful treatment for multiple myeloma or plasma cell leukemia suggests that myelofibrosis appears to be pathogenetically associated with the infiltration of plasma cells into bone marrow. Therefore, the myelofibrosis in these cases may be a secondary clinical state after multiple myeloma or plasma cell leukemia. Kawaguchi \textit{et al.}\textsuperscript{8} suggested that cytokines, such as interleukin-6, derived from leukemic cells stimulate the secretion of fibroblast proliferation factors including platelet derived growth factor (PDGF), transforming growth factor (TGF)-\(\beta\), or epidermal growth factor (EGF), which are contained in platelets or bone marrow. Extracellular matrix protein derived from fibroblasts resulted in bone marrow fibrosis. Moreover, in the cases of myeloma which are complicated by primary myelofibrosis, myeloma cells may easily recruit to the peripheral blood.\textsuperscript{8} The current study shows that a high proportion of patients with myeloproliferative disorders, including primary myelofibrosis, carry a dominant gain-of-function mutation of JAK2.\textsuperscript{9} Popat \textit{et al.}\textsuperscript{10} suggested that high levels of circulating CD34\(^+\) cells and JAK2 mutations can differentiate myelofibrosis with myeloid metaplasia from other myeloproliferative disorders, including secondarily developed myelofibrosis. Further studies on the specific alterations in these molecules may be helpful to explain why increased numbers of plasma cells coexist with myelofibrosis in this patient.

As for the mechanisms which explain the coexistence of myelofibrosis and plasmacytosis, there are at least three hypotheses worthy of consideration. The first hypothesis is that secondary myelofibrosis occurs after primary plasma cell leukemia. The second is that secondary myelofibrosis occurs after multiple myeloma with or without antecedent chemotherapy. The third is a coincidence of the primary myelofibrosis and plasma cell leukemia. Our patient revealed hepatosplenomegaly, leukoerythroblastosis, and high level of serum LDH. These clinical manifestations were quite different from those of typical non-leukemic multiple myeloma and were similar to those of primary myelofibrosis. In addition, the usual clinical signs of multiple myeloma were not observed in this case and, therefore, the patient had not received any chemotherapeutical agents. Moreover, since the patient did not achieve complete remission and had a progressive course, we could not examine whether chemotherapeutical agents could improve myelofibrosis in this case. Therefore, we presume that plasma cell leukemia might be incidentally complicated by the antecedent primary myelofibrosis in the present case. Although plasma cell leukemia that coexists with myelofibrosis is an interesting condition in terms of clinical sign and course, the pathogenesis of relationship between myeloma and plasma cell dyscrasias with myelofibrosis has not been determined. Further investigations are required in order to improve the poor outcome of these patients.

**REFERENCES**
