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만성골수성백혈병 환자에서의 형질세포골수종

Plasma Cell Myeloma in a Patient with Chronic Myelogenous Leukemia

이종호 · 김유경
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Dear Editor,

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm that originates from an abnormal pluripotent bone marrow (BM) stem cell. Plasma cell myeloma (PCM) is a neoplasm associated with the monoclonal proliferation of plasma cells differentiated from B-lymphoid cells that secrete a monoclonal immunoglobulin (M-protein). As CML and PCM arise from different cell lines, the coexistence of these two diseases in a single patient is rare. A limited number of cases have been reported worldwide [1]. Here, we report the case of a patient diagnosed with asymptomatic PCM while being treated for CML with imatinib mesylate (IM). We also reviewed the reported cases of combined PCM and CML.

A 61-yr-old male was referred to our hospital in May 2006 due to leukocytosis and splenomegaly. Initial complete blood count (CBC) revealed a white blood cell (WBC) count of 135.4×10^9/L (64% segmented neutrophils, 8% band forms, 3% metamyelocytes, 12% myelocytes, 1% promyelocytes, 2% eosinophils, 1% basophils, 7% lymphocytes, and 2% monocytes), hemoglobin of 13.5 g/dL, and platelet count of 97×10^9/L. The patient was diagnosed with chronic phase *BCR-ABL1*-positive CML. BM aspiration and biopsy revealed typical CML. However, the percentage of plasma cells was not elevated. Cytogenetic analysis of the BM revealed the presence of the Philadelphia (Ph1) chromosome of 46 XY, t(9;22)(q34;q11) in all metaphase cells (n=15). Reverse transcription polymerase chain reaction (RT-PCR) revealed *BCR/ABL1* transcripts. Treatment with IM (Glivec®; Novartis AG, Basel, Switzerland) at the standard dose of 400 mg/day achieved a complete hematologic, cytogenetic, and molecular response in follow up BM studies (July, 2007). At that time, BM aspiration revealed 23% plasma cells. However, M-protein and abnormal serum immunoglobulin (Ig) levels were not examined. Nine months later, BM aspiration revealed 11% plasma cells with a complete hematologic response of CML. The *BCR-ABL1* transcript was detected by RT-PCR. Interphase fluorescence in situ hybridization (FISH) analysis revealed 124 *BCR-ABL1* fusion signals of 200 nucleated cells (62%). Therefore, the dose of IM was increased to 600 mg/day. In May 2014, BM analysis revealed a complete hematologic, cytogenetic, and major molecular response of CML with 12.8% plasma cells. Iron deficiency anemia was detected without other PCM associated end organ damage such as hypercalcemia, uremia, and lytic bone lesions. Serum electrophoresis revealed an M-protein level of 0.88 g/dL in the beta region. The M-protein was identified as IgAλ type by serum immunofixation electrophoresis. The patient was diagnosed with asymptomatic PCM. No chemotherapy was administered for PCM (Table 1).

Multiple factors can result in the coexistence of these diseases [2]. For this patient, it is possible that the IM treatment for CML may have contributed to the development of PCM. However, the following points suggest that it is unlikely IM treatment for CML can induce the development of PCM. From July 2007 to May 2014, the percentage of plasma cells observed in the BM was not ele-

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Table 1. Patient's laboratory findings

	Initial (May, 2006)	(July, 2007)	(April , 2008)	(May , 2014)
Final diagnosis	CML-CP	CML - MR	CML - CHR No MR	CML - MMR Asymptomatic PCM
Age at diagnosis	61	62	63	69
Splenomegaly	Present	Uncertain	Uncertain	Uncertain
PB				
WBC ($\times 10^9$/L)	135.4	5.4	7.4	2.9
Hb (g/dL)	13.5	12.6	14.4	7.3
Platelets ($\times 10^9$/L)	97	210	210	194
BM				
Cellularity (%)	90	25	40	30
M:E ratio	48.5 : 1	1.63 : 1	3.03 : 1	2.79 : 1
Blasts (%)	0	0	1.5	0
Plasma cells (%)	0	23.0	11.0	12.8
Karyotype	46,XY,t(9;22) (q34;q11.2)[15]	46,XY[20]	No interpretable mitosis	46,XY[26]
RT-PCR for *BCR-ABL1* transcript	Positive (b2a2 type)	Negative	Positive (b2a2 type)	Negative
Interphase FISH for *BCR-ABL1* fusion	ND	0% (0/500)	62% (124/200)	0% (0/500)
Serum M protein (g/dL)	ND	ND	ND	0.88
LD (U/L)	1,244	352	ND	431

Abbreviations: CHR, complete hematologic response; CP, chronic phase; Hb, hemoglobin; LD, lactate dehydrogenase; M:E, myeloid:erythroid; MR, molecular response; MMR, major molecular response; M protein, monoclonal protein; ND, not done; PB, peripheral blood; WBC, white blood cell.

vated during IM treatment. To date, there has been no evidence to suggest that IM therapy increases the occurrence of secondary malignancies [3, 4]. Our patient was diagnosed with asymptomatic PCM eight years after the initial diagnosis of CML. However, it is possible that the asymptomatic PCM was already present at the time of follow up BM studies in July 2007 when 23% plasma cells were detected. Unfortunately, the development of PCM was not suspected at the time of the CML diagnosis or the follow up BM analysis; therefore, M-protein and serum Ig levels were not examined. Without this analysis, we cannot exclude the possibility that the patient had PCM at the time of the initial CML diagnosis. Additionally, we performed immunohistochemical staining of BM biopsy specimens from the initial diagnosis of CML to the follow-up BM studies. All BM biopsy specimens (initial, 2007/07, 2008/04, 2014/05) were positive for CD 138, IgA, and lambda, showing monoclonality of PCM cells.

There have been several reported cases of CML diagnosed prior to PCM [1, 5-10], similar to our case. In all these cases, the presence of PCM was not suspected at the time of CML diagnosis. Serum Ig and M-protein levels were either not examined or not stated. All of the cases that describe CML diagnosis preceding that of PCM may in fact be cases of concurrent CML and PCM development. It is difficult to consider the presence of PCM at the time of CML diagnosis, if the number of plasma cells is relatively low due to hypercellularity of other cells and if the patient is negative for PCM-associated symptoms, as is the case with monoclonal gammopathy of undetermined significance and asymptomatic PCM.

The mechanism underlying the coexistence of CML and PCM is currently unclear. To identify the relationship between these two diseases, more research is needed. However, clinicians and pathologists should be aware of the possibility that CML may mask the early diagnosis of PCM.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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