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A Rare Case of Chronic Myelogenous Leukemia and Plasma Cell Myeloma in the Same Patient

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Dear Editor

CML and plasma cell myeloma (PCM) arise from pluripotent stem cells and lymphoid cells, respectively [1]. Since different cell lines give rise to CML and PCM, development of both malignancies in one patient is uncommon; only 17 such cases have been reported worldwide [2-5]. Here, we attempt to address questions about the mechanisms of co-existence of these two diseases.

A 76-yr-old Korean male was referred to our hospital in April 2010 with thrombocytosis and leukocytosis with basophilia. Radiographic examination revealed splenomegaly. Using bone marrow (BM) analysis and quantitative reverse-transcription PCR, the patient was diagnosed as having chronic phase *BCR-ABL1*-positive CML. After three weeks of imatinib mesylate (IM) therapy, the patient's leukocyte and platelet counts normalized.

Three years later, examination of the patient's BM revealed normal cellularity, but with plasma cells accounting for 17.5% of all nucleated cells (Table 1). Hypercalcemia, uremia, anemia, and lytic bone lesions were not observed. Serum electrophoresis and immunofixation electrophoresis revealed immunoglobulin (Ig)A lambda type monoclonal protein. The patient was diagnosed as having asymptomatic PCM. No chemotherapy was administered for PCM, but IM therapy achieved maintenance of the CML major molecular response status. Clinical and laboratory findings are summarized in Table 1.

No symptoms or blood tests indicated the presence of PCM at the time of CML diagnosis. However, since it is possible that a PCM clone was present at the time of CML diagnosis, we retrospectively performed immunohistochemical staining of a BM specimen. This staining was positive for CD138 and IgA lambda. We also analyzed Ig heavy chain gene rearrangements (InVivoScribe Technologies, San Diego, CA, USA) in initial and follow-up BM samples. DNA samples from both time points showed gene rearrangement at the same diversity region, indicating that the same PCM clone was present at CML diagnosis.

When we reviewed the previously reported cases of CML and PCM in the same patient (Table 2), we first asked whether the malignancies occurred spontaneously, or whether treatment of the first neoplasm induced the second malignancy. Among the 17 cases, six patients were diagnosed first as having CML, and then PCM. Five of those six patients received IM, while one received busulfan. The mean interval before discovery of the second malignancy was 37.7 months (range, 3 to 88 months). IM has been reported to have both stimulatory and inhibitory effects on PCM cell proliferation [6]. Studies have found no evidence that IM treatment increases the occurrence of any secondary malignancies compared with the lifetime risk of cancer in the general population [7, 8]. There is no clear evidence that IM used for CML treatment caused PCM; however, because IM becomes widely used as an effective target therapy in other

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Table 1. Laboratory findings at diagnosis of CML and PCM

	Initial (April 23, 2010)	Follow-up (June 1, 2013)
Final diagnosis	CML-CP	Asymptomatic PCM
		CML in MMR
Age at diagnosis (yr)	76	79
Splenomegaly	Present	Absent
PB		
WBC ($\times 10^9$/L)	18.8	4.1
Blasts (%)	0	0
Eosinophils (%)	8	3.2
Basophils (%)	12	0.7
Hb (g/dL)	12.9	10.4
Platelets ($\times 10^9$/L)	1,434	154
BM		
Cellularity (%)	90	45
M:E ratio	2.4:1	2.0:1
Blasts (%)	2	0
Plasma cells (%)	1.2	17.5
Karyotype	46,XY,t(9;22)(q34;q11.2)[19]/46,XY[1]	46,XY[20]
BCR-ABL1 transcript level (% IS)	37.29080	0.00033
Serum M protein (g/dL)	ND	0.83
LD (U/L)	238	162
IGH gene rearrangement	Positive (clonal)	Positive (clonal)

Abbreviations: BM, bone marrow; CP, chronic phase; IGH, immunoglobulin heavy chain; IS, international scale; LD, lactate dehydrogenase; M:E, myeloid:erythroid; MMR, major molecular response; M protein, monoclonal protein; ND, not done; PB, peripheral blood; PCM, plasma cell myeloma; WBC, white blood cell.

cancers as well as CML, close investigation of this issue is necessary.

Another five of the 17 patients were diagnosed as having PCM first, and then CML. Two of them were not treated for PCM until their CML diagnosis. The remaining three patients received melphalan, dexamethasone, and other drugs, which have not been reported to cause CML. Two patients with PCM underwent radiation therapy (RT) before their CML diagnosis. In general, irradiation is known to cause leukemia. One study calculated the theoretical probability of an individual exposed to radiation acquiring the t(9;22) translocation to be 0.007/Gy, with a minimum lapse of 5.1 yr [9]. Since the intervals between irradiation and CML development in these cases were less than two years, it seems unlikely that RT induced CML.

Concurrent development of CML and PCM was identified in six of 17 patients, and two patients developed CML before being treated for PCM. Therefore, 8 patients (47%) had a secondary malignancy without having received therapy, so it is difficult to conclude that treatment of the first neoplasm caused a secondary malignancy.

Another important question is whether the two cancers have the same origin. Since CML arises from pluripotent hematopoietic stem cells, it may be possible that CML cells can transform into malignant plasma cells. No Philadelphia chromosomes or *BCR-ABL1* transcripts were found when our patient was diagnosed as having PCM, suggesting that the myeloma cells did not evolve from pre-existing CML cells.

We have described a patient with both CML and PCM. The mechanism of co-existence is unclear. To identify more cases, it is important for clinicians and pathologists to be aware that co-existence of CML and PCM is rare, but possible.

Authors' Disclosures of Potential Conflicts of Interest

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

Table 2. Reported cases of CML and PCM occurring in the same patient

	Age (yr)/ gender	Interval between two diseases (month)	CML		PCM			Reference
			WBC ($\times 10^9$/L)	CT	Type	CT	RT	
Concurrent								
1	58/M	0	140	HU, BU, TG	IgG κ	MP	3,300 cGy	[2]
2	72/F	0	162.4	HU, IFN, BU	IgG κ	IFN, VD, PD	None	[2]
3	81/M	0	28.7	None	IgA κ	MP	None	[3]
4	66/M	0	171	HU, IFN, BU	IgG κ	MP	None	[2]
5	85/F	0	8.1	UK	IgG λ	UK	UK	[2]
6	NS	0	NS	IM	NS	BD	None	[4]
PCM→CML								
7	77/M	33	145	6-MP	BJP	BD, Cy, Len	None	[2]
8	71/M	24	40.8	HU	IgG κ	MP	Yes	[2]
9	70/M	33	25.2	UK	IgG κ	MP	None	[2]
10	47/M	33	23.9	UK	BJP κ	None	UK	[2]
11	64/F	17	14	DA	IgG κ	None	3,000 cGy	[2]
CML→PCM								
12	65/F	88	43	BU	IgG κ	BU, PM	2,000 cGy	[2]
13	68/M	20	NS	IFN, IM	IgG λ	MP	None	[2]
14	71/M	38	NS	IM	BJP λ	UK	UK	[2]
15	76/M	14	NS	IFN, IM	IgA κ	MP	None	[2]
16	72/F	3	31.3	IM	IgG κ	None	None	[2]
17	57/F	65	52.38	IM	IgA κ	Thal, Dox, BD	None	[5]
18	79/M	36	18.8	IM	IgA λ	None	None	The present case

Abbreviations: PCM, plasma cell myeloma; BD, bortezomib and dexamethasone; BJP, Bence-Jones protein; BU, busulfan; CT, chemotherapy; Cy, cyclophosphamide; DA, dasatinib; Dox, doxorubicin; F, female; HU, hydroxyurea; IFN, interferon; IM, imatinib mesylate; Len, lenalidomide; M, male; MP, mercaptopurine; NS, not stated; PD, prednisolone; PM, phenylalanine and mustard; RT, radiation therapy; TG, thioguanine; Thal, thalidomide; UK, unknown; VD, vindesine; WBC, white blood cell.

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REFERENCES

1. Vardiman JW, Melo JV, Baccarani M, Thiele J. Chronic myelogenous leukaemia, BCR-ABL1 positive. In: Swerdlow SH, et al, eds. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC, 2008:32-7.
2. Hehlmann R, Hochhaus A, Baccarani M. Chronic myeloid leukaemia. Lancet 2007;370:342-50.
3. Ide M, Kuwahara N, Matsuishi E, Kimura S, Gondo H. Uncommon case of chronic myeloid leukemia with multiple myeloma. Int J Hematol 2010; 91:699-704.
4. Alvarez-Larrán A, Rozman M, Cervantes F. Simultaneous occurrence of multiple myeloma and chronic myeloid leukemia. Haematologica 2001; 86:894.
5. Romanenko NA, Bessmel'tsev SS, Udal'eva Vlu, Zenina MN, Martynkevich IS, Rugal' VI, et al. The combination of chronic myeloid leukemia and multiple myeloma in one patient. Vopr Onkol 2013;59:103-10.
6. Pandiella A, Carvajal-Vergara X, Tabera S, Mateo G, Gutiérrez N, San Miguel JF. Imatinib mesylate (STI571) inhibits multiple myeloma cell proliferation and potentiates the effect of common antimyeloma agents. Br J Haematol 2003;123:858-68.
7. Pilot PR, Sablinska K, Owen S, Hatfield A. Epidemiological analysis of second primary malignancies in more than 9500 patients treated with imatinib. Leukemia 2006;20:148.
8. Verma D, Kantarjian H, Strom SS, Rios MB, Jabbour E, Quintas-Cardama A, et al. Malignancies occurring during therapy with tyrosine kinase inhibitors (TKIs) for chronic myeloid leukemia (CML) and other hematologic malignancies. Blood 2011;118:4353-8.
9. Holmberg M. Is the primary event in radiation-induced chronic myelogenous leukemia the induction of the t(9;22) translocation? Leuk Res 1992;16:333-6.

http://dx.doi.org/10.3343/alm.2015.35.3.370