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

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A rare case of primary plasma cell leukemia exhibiting the small-cell variant of plasma cells

TO THE EDITOR: Plasma cell leukemia (PCL) is a rare disease that accounts for approximately 2% of all plasma cell myeloma (PCM) cases. It is defined as the presence of clonal plasma cells (PCs) in more than 20% of the total nucleated cells (TNCs) or when absolute TNC count is higher than $2 \times 10^3/L$ in the peripheral blood. Primary PCL (pPCL) is the initial leukemic presentation of myeloma, which represents 60% of PCL cases [1]. Although patients with PCLs generally have a poor prognosis, early and aggressive chemotherapy and stem cell transplantation (SCT) may improve the prognosis [2]. Clonal PCs can appear in an atypical form, such as small-cell, cleaved, polymorphous, asynchronous, or blastic types, in addition to the Marshalko type, which is indistinguishable from a typical PC [3]. Therefore, the accurate identification of neoplastic PCs in the bone marrow and peripheral blood is important. Herein, we report a case of pPCL that was diagnosed by flow cytometry (FCM) due to morphological similarities between the clonal PCs and small-mature lymphocytes. This study was reviewed and approved by the institutional review board of Soonchunhyang University Hospital in Seoul, South Korea (IRB No. 2021-09-007).

In December 2019, a 65-year-old man visited the emergency room at Soonchunhyang University Seoul Hospital with acute chest pain. No specific abnormalities were observed in the lungs or on cardiovascular examination. The initial complete blood count (CBC) revealed pancytopenia as follows: Hb, 47 g/L (120-160 g/L); WBC, $2.8 \times 10^9/L$ ($4.0-10.0 \times 10^9/L$); and platelet count, $45 \times 10^9/L$ ($130-450 \times 10^9/L$). Peripheral blood smears demonstrated small-mature lymphoid cells, which accounted for up to 20% of the TNCs (Fig. 1A), and bone marrow aspirate smears revealed lymphoid cells comprising 88% of the TNCs (Fig. 1B) together with occasional multinucleated atypical lymphoid cells (Fig. 1C, D). Immunophenotype analysis by FCM (Navios EX flow cytometer and Kaluza analysis software, Beckman Coulter, Inc., Miami, FL, USA) of the bone marrow and peripheral blood specimens revealed abnormal PC populations accounting for 80% and 20% of TNCs, respectively. $CD45^+/CD19^+/CD20^+/CD38^+/CD138^+/CD56^+/CD117^+/cCD79a^+/FMC7^+$ cells and cytoplasmic lambda light chain restriction (Fig. 2) was observed. Serum protein electrophoresis (PEP)

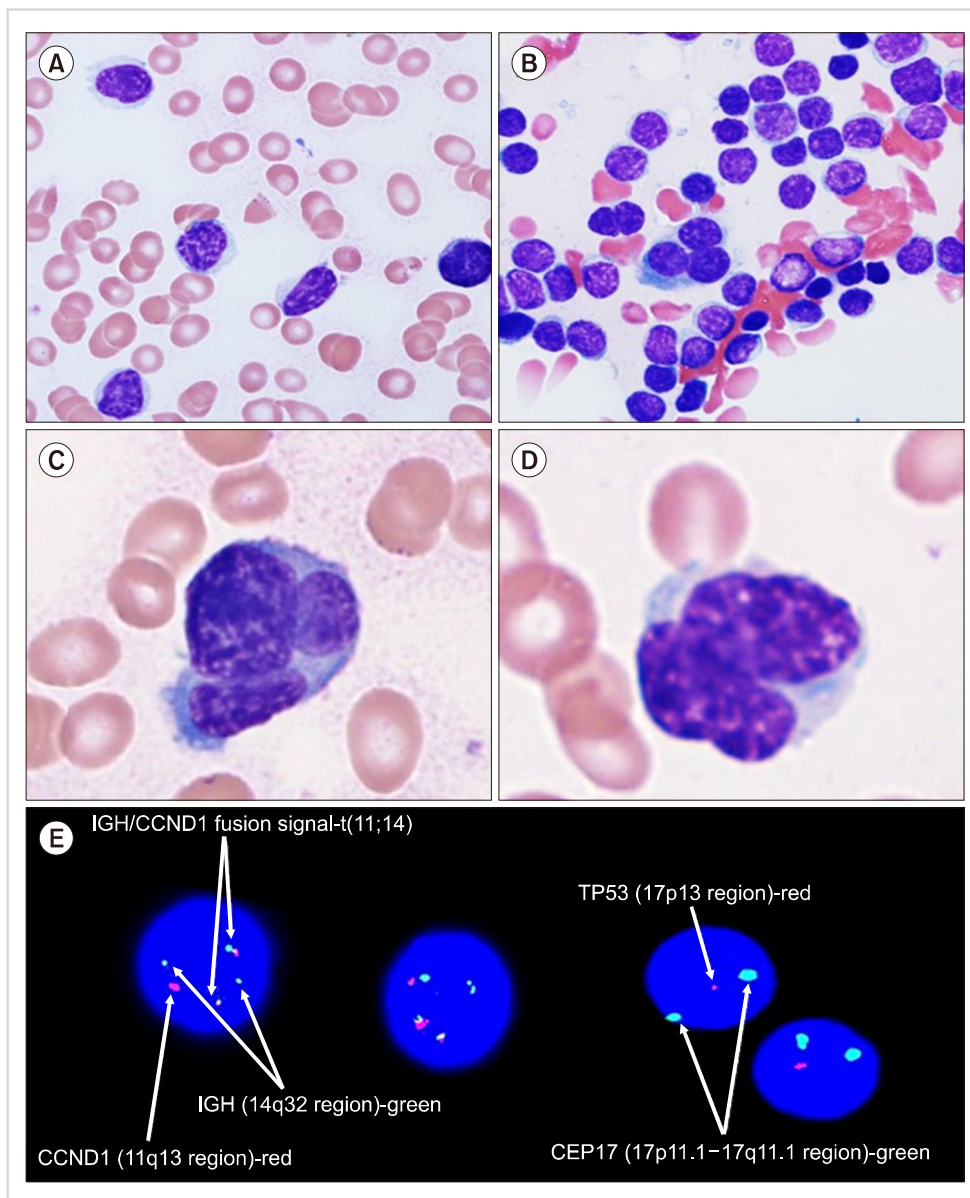


Fig. 1. Microscopic findings and FISH analysis of the small-cell type of plasma cell leukemia. Peripheral blood and bone marrow aspirate smears: small-cell type neoplastic plasma cells and atypical multinuclear plasma cells (A), peripheral blood, Wright-Giemsa stain, $\times 400$; (B), bone marrow, Wright-Giemsa stain, $\times 400$; (C, D) bone marrow, Wright-Giemsa stain, $\times 1,000$. (E) FISH analysis showing an IGH/CCND1 rearrangement and p53 (17p) deletion (white arrow). Abbreviation: FISH, fluorescence in situ hybridization.

and immunofixation electrophoresis (IFE) detected monoclonal gammopathy of the IgA and lambda types (M protein, 4.7 g/L). In the quantitative serum immunoglobulin test by an immunoturbidimetric assay (cobas c702 analyzer, Roche, Ibaraki, Japan; cobas ALB2 reagent, Mannheim, Germany), the IgA and free lambda light-chain were measured as 6.44 g/L (7.0–40.0 g/L) and 0.095 g/L (0.057–0.263 g/L), respectively. In the urine PEP and IFE, lambda-type Bence-Jones proteinuria was detected with an M-protein level of 0.12 g/L. FISH analysis (Fig. 1E) demonstrated *IGH-CCND1* rearrangement and *p53* (17p) deletion (dual-fusion probe, designed by Cytocell, Cambridge, UK and Metafer/Zeiss system, Metasystems, Altlußheim, Germany), and next-generation sequencing (NGS) identified suspected pathogenic mutations of *TP53* (c.490A>G, p.Lys164Glu) (customized panel designed by Celeomics, Inc., Seoul, Korea). On the

basis of these results, the patient was diagnosed with pPCL. Allogenic hematopoietic SCT was performed after the patient achieved complete remission with chemotherapy (carfilzomib, lenalidomide, and dexamethasone). Nevertheless, the patient succumbed to death due to pneumonia 5 months after undergoing the SCT.

Small-cell-type PCs are small (mean size of 13 μm ; compared with 21 μm for the Marschalko type) and have a round shape with only a narrow rim of a cytoplasm. Their nuclei have dense chromatin with rare nucleoli and mitoses resembling those of small lymphocytes [3]. Given their morphological similarities, the microscopic detection of small-cell-type PCL may be challenging to discriminate from small mature lymphocytes. While neoplastic PCs of PCM usually exhibit the $\text{CD19}^{\text{variable}}/\text{CD38}^{\text{+}}/\text{CD56}^{\text{- or +}}$ immunophenotype, neoplastic PCs of PCL exhibit a more-fre-

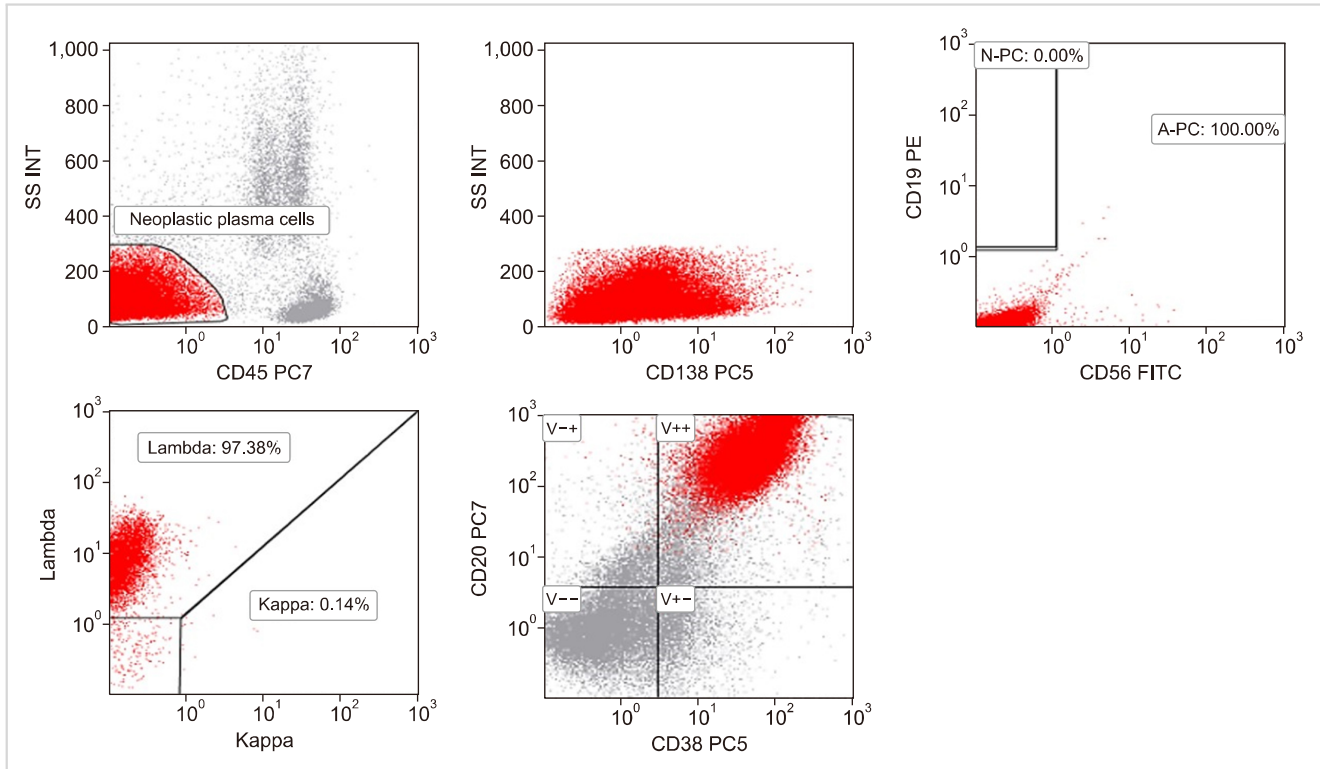


Fig. 2. Flow-cytometric immunophenotyping of the small-cell type of plasma cell leukemia. Clonal plasma cells in the bone marrow exhibited a CD19⁺/CD20⁺/CD38⁺/CD56⁺/CD138⁺ phenotype and cytoplasmic lambda light-chain restriction by CD45⁺ and low side scatter.

Table 1. Basic clinical characteristics of six patients with small-cell-type plasma cell leukemia.

	Present patient	Heerema-McKenney <i>et al.</i> [7]	Heerema-McKenney <i>et al.</i> [7]	Gounari <i>et al.</i> [8]	Loureiro <i>et al.</i> [9]	Teriaky <i>et al.</i> [10]
Sex/age (yr)	M/65	F/59	M/74	M/61	F/77	F/85
Initial CBC	WBC: 2.8×10 ⁹ /L Hb: 47 g/L Platelet: 45×10 ⁹ /L	NR	NR	WBC: 12.3×10 ⁹ /L Hb: 98 g/L Platelet: 89×10 ⁹ /L	WBC: 8.6×10 ⁹ /L Hb: 101 g/L Platelet: 140×10 ⁹ /L	WBC: 28.2×10 ⁹ /L Hb: 92 g/L Platelet: 238×10 ⁹ /L
Plasma cells (BM/PB), %	>80.0 20.0	>80.0 40.0	>80.0 52.0	54.0 22.7	90.0 43.5	75.0 74.0
Immunophenotyping results	CD45 ⁺ /CD19 ⁺ /CD20 ⁺ /CD38 ⁺ /CD138 ⁺ /CD56 ⁺ /CD117 ⁺ /cCD79a ⁺ /FMC7 ⁺ and lambda restriction	CD45 ⁺ /CD20 ⁺ /CD38 ⁺ /CD138 ⁺ /CD56 ⁺ /CD117 ⁺	CD45 ⁺ /CD38 ⁺ /CD138 ⁺	CD45 ⁺ /CD19 ⁺ /CD20 ^{dim+} /CD38 ⁺ /CD138 ⁺ /CD56 ⁺ /CD200 ⁺ and kappa restriction	CD45 ⁺ /CD19 ⁺ /CD38 ⁺ /CD138 ^{dim+} /CD56 ⁺ /CD117 ⁺ /CD28 ⁺ /CD81 ⁺ and kappa restriction	CD45 ⁺ /CD19 ^{partia+} /CD20 ^{dim+} /CD38 ⁺ /CD138 ⁺ and kappa restriction
PEP/IFE	IgA-lambda (5 g/L ^a)	IgG-lambda (4g/L ^a)	IgG-lambda (30g/L ^a)	IgA-kappa	IgG-kappa (44g/L ^a)	kappa
Cytogenetic study	42,XY,-1,-9,-10,? add(17)(p11.2)der(19) t(1;19)(p13;p13.3),-20,-21, +der(?)t(?)21(?)q11.2), +2mar[6]/46,XY [14]	/45,XX,-20[11]	t(11;14)(q12~13.1;q32), del(13)(q14q22), ?del(17)(p12)[cp2] /46,XY[18]	Hyperdiploid clone with trisomy 2, 3, 12, and 18	NR	NR
Molecular study	<i>IGH/CCND1</i> rearrangement, 13q14 deletion, <i>p53</i> (17p) deletion ^b , <i>TP53</i> (c.490A>G, p.lys164Glu) ^c	Overexpression of <i>MS4A1/CD20</i> and <i>CCND2</i> ^d	Overexpression of <i>CCND1</i> ^d	Overexpression <i>CCND1</i> ^e	<i>IGH/CCND1</i> rearrangement ^b	NR
Disease course	Died after 5 months after allo-PBSCT	NR	NR	CR after CTx	Died 3 months after diagnosis	CR after CTx

^a) Amount of M protein. Results of the ^b)FISH, ^c)NGS study, ^d)gene expression profiling (GEP) analysis, and ^e)immunohistochemical staining. Abbreviations: allo-PBSCT, allogeneic peripheral blood stem cell transplantation; CBC, complete blood count; CR, complete remission; CTx, chemotherapy; IFE, immunofixation electrophoresis; NR, not reported; PEP, protein electrophoresis.

quent expression of CD20 and a less-frequent expression of CD56 [4, 5]. Several myeloma studies have shown that CD20 expression is associated with small-cell-type neoplastic PCs and t(11;14) in PCM [6, 7]. As CD56 is an adhesion molecule, PCs with no CD56 expression may reduce cell-to-cell interactions, easily escape from the bone marrow, invade extramedullary organs, including the peripheral blood, and proliferate abnormally beyond immune surveillance [4, 5].

To date, only 5 cases of small-cell-type PCL (Table 1) have been reported, while clonal PCs of the small-cell-type are found only in 3.4% of PCM [7-10]. The median age of the 6 cases including ours was 70.2 years with no demographic preponderance. The 6 cases of small-cell-type PCL demonstrated a variable expression of CD20 and loss of CD56. t(11;14) (*IGH/CCND1* rearrangement), and overexpression of *CCND1* or *CCND2* was detected in 5 cases. Their secreting components were IgG or IgA with lambda or kappa light chains, including only one kappa light chain. The amount of M protein was not associated with the tumor burden. Two patients died within a year of starting chemotherapy.

In summary, we report a rare case of pPCL with t(11;14) presenting as the small-cell type. When diagnosing PCL of an atypical plasma cell type, it is mandatory to use FCM immunophenotyping for the bone marrow and peripheral blood specimens with morphology and IFE.

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Enrichment of TP53 alterations within GCB-like DNA subclassifications of diffuse large B-cell lymphoma after transition from de-novo to relapsed or refractory disease

TO THE EDITOR: Alterations of the tumor suppressor gene *TP53* are frequent in Diffuse Large B-cell Lymphoma (DLBCL), the most commonly diagnosed blood cancer at over 30,000 diagnoses per year, and are associated with poor prognosis [1]. DLBCL has traditionally been divided into three cell of origin (COO) subcategories based on RNA expression profiles or IHC: Activated B-cell (ABC), Germinal Center B-cell (GCB), and Unclassified cases [2]. Patients with ABC tumors are characterized by a more aggressive profile alongside active NF-κB and BCR signaling pathways, while GCB cases are associated with alterations that drive aberrant chromatin-modification, PI3K signaling, and the upregulation *MYC* and *BCL2* through structural variants