

[ CASE REPORT ]

## Oligosecretory Primary Plasma Cell Leukemia with Atypical Morphological Abnormality

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### Abstract:

Plasma cell leukemia (PCL) is a rare variant of multiple myeloma. The detection of plasma cells in the peripheral blood and monoclonal protein in the serum or urine is important for the diagnosis of PCL. However, it is sometimes difficult to diagnose PCL in patients with atypical plasma cell morphology and/or those without detectable monoclonal protein. We herein report a case of oligosecretory PCL showing atypical morphology in leukemic cells with a convoluted nucleus and basophilic cytoplasm but without detectable monoclonal protein, except for serum free light chain. A flow cytometric analysis and pathological analysis were useful for the early diagnosis of PCL.

**Key words:** primary plasma cell leukemia, non-secretory type, oligosecretory type, atypical morphology

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### Introduction

Plasma cell leukemia (PCL) is a rare subtype of multiple myeloma (MM), accounting for 1-2% of all MM cases. Its diagnosis requires the identification of  $\geq 2,000/\mu\text{L}$  of monoclonal plasma cells in the peripheral blood (PB), comprising  $\geq 20\%$  of the total white blood cell (WBC) count. PCL is divided into two subtypes: primary (pPCL) and secondary (sPCL). Abnormal plasma cells are observed in the PB at the initial presentation in pPCL, whereas they are observed in the PB during the clinical course of MM in sPCL (1-3). The prognosis of pPCL has been reported to be very poor, and the median overall survival (OS) has been reported to be four to six months (4, 5). Thus, the early, accurate diagnosis is required for the proper management of PCL. The detection of plasma cells in the PB is important for diagnosing PCL, and that of monoclonal (M) protein in the serum or urine is often a determining factor diagnosing PCL/MM.

MM without M-protein in the serum or urine, known as

non-secretory type MM, is rare, accounting for only a small proportion of MM cases (6). With advances in examination sensitivity, small amount of monoclonal light chain can be detected with a serum free light chain (SFLC) assay in some non-secretory type MM patients. Thus, oligosecretory type MM has been recently proposed as a subtype of non-secretory type MM for patients with monoclonal light chain detected only with the SFLC assay (7, 8). Thus, non-secretory type (and also oligosecretory type) PCL is a very rare subtype of MM. When abnormal cells in the PB show atypical morphology and M-protein is not detected in either the serum or urine, the differential diagnosis of PCL from other leukemic diseases becomes extremely difficult.

We herein report a case of oligosecretory pPCL with atypical morphology of leukemic cells.

### Case Report

An 81-year-old man suffering from bilateral lower leg edema visited a nearby clinic. A 70-mm tumor was detected

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**Table 1. Laboratory Data at Diagnosis.**

[Peripheral Blood]		[Biochemistry]		[Serological test]	
WBC	5,700 / $\mu$ L	BUN	37.0 mg/dL	IgG	572.0 mg/dL
Seg	40 %	Cre	1.6 mg/dL	IgA	28.0 mg/dL
Stab	11 %	Ca	12.7 mg/dL	IgM	10.1 mg/dL
Lymph	21 %	UA	14.3 mg/dL	IgE	54.1 mg/dL
Mono	0 %	T-Bil	2.0 mg/dL	IgD	<0.6 mg/dL
Eosino	2 %	D-Bil	0.5 mg/dL	FLC $\kappa$	590 mg/L
Baso	0 %	LDH	224 U/L	FLC $\lambda$	9.1 mg/L
Abnormal cells	26 %	TP	6.4 g/dL	FLC $\kappa/\lambda$ ratio	64.9
RBC	2.4 $\times$ 10 <sup>6</sup> / $\mu$ L	Alb	4.1 g/dL	$\beta$ 2-MG	7.3 mg/L
Hemoglobin	8.4 g/dL	NT-proBNP	4,728 pg/mL		
Platelet	64,000 / $\mu$ L	Intact PTH	10.9 pg/mL		

WBC: white blood cell, Seg: segmented neutrophil, Stab: band neutrophil, Lymph: lymphocyte, Mono: monocyte, Eosino: eosinophil, Baso: basophil, RBC: red blood cell, BUN: blood urea nitrogen, Ca: calcium, Cre: creatinine, UA: uric acid, T-Bil: total bilirubin, D-Bil: direct bilirubin, LDH: lactate dehydrogenase, TP: total protein, Alb: albumin, NT-Pro BNP: N-terminal pro-brain natriuretic peptide, Intact PTH: intact parathyroid hormone, Ig: immunoglobulin, FLC: free light chain,  $\beta$ 2-MG: beta 2-microglobulin

on the left kidney via abdominal sonography. Renal cell carcinoma was suspected; he was therefore referred and admitted to the Department of Urology in our hospital. A blood analysis revealed anemia and thrombocytopenia, and abnormal cells with convoluted nuclei were also observed in the PB; he was therefore referred to the Department of Hematology for a further examination. His primary medical history included atrial fibrillation, chronic heart failure, hypertension, and chronic renal failure. He was alert, with an Eastern Cooperative Oncology Group performance status of 1. Bilateral lower leg edema was observed. The blood analysis showed a WBC count of 5,700/ $\mu$ L with 26% abnormal cells (Table 1), which showed morphological atypia with a convoluted nucleus and basophilic cytoplasm (Fig. 1a). Anemia, thrombocytopenia, and hypercalcemia were also observed in the blood analysis, as shown in Table 1. In the serum and urine, M-protein was not detected via electrophoresis or immunofixation electrophoresis (Fig. 2, 3). The SFCLC assay showed  $\kappa$  590 mg/L,  $\lambda$  9.1 mg/L, and a  $\kappa/\lambda$  ratio 64.9.

A flow cytometric (FCM) analysis showed that the abnormal cells in the PB were negative for CD20 and positive for CD38, CD138, and cytoplasmic (cy) immunoglobulin (Ig)  $\kappa$  (Table 2a). A bone marrow (BM) analysis also showed increased abnormal cells in the smear (Fig. 1b), with CD20 negativity and CD38, CD138, and cyIg  $\kappa$  positivity in a FCM analysis (Table 2b). In the pathological analysis of the BM clot section, the morphology of abnormal cells was compatible with that of the plasma cells, with CD20 (L26) negativity and CD138 positivity on immunohistochemistry (Fig. 1c and d). A chromosomal analysis of the BM cells revealed a normal karyotype in 17 dividing cells using the Giemsa banding method; however, t(11;14)(q13;q32) was detected in the fluorescence *in situ* hybridization (FISH) analysis. The frequency of deletion p17 was in the normal range (2%), according to the FISH analysis. Computed tomography showed a mass lesion, which was suspected of being renal cancer, in the left kidney; however, no other pathological

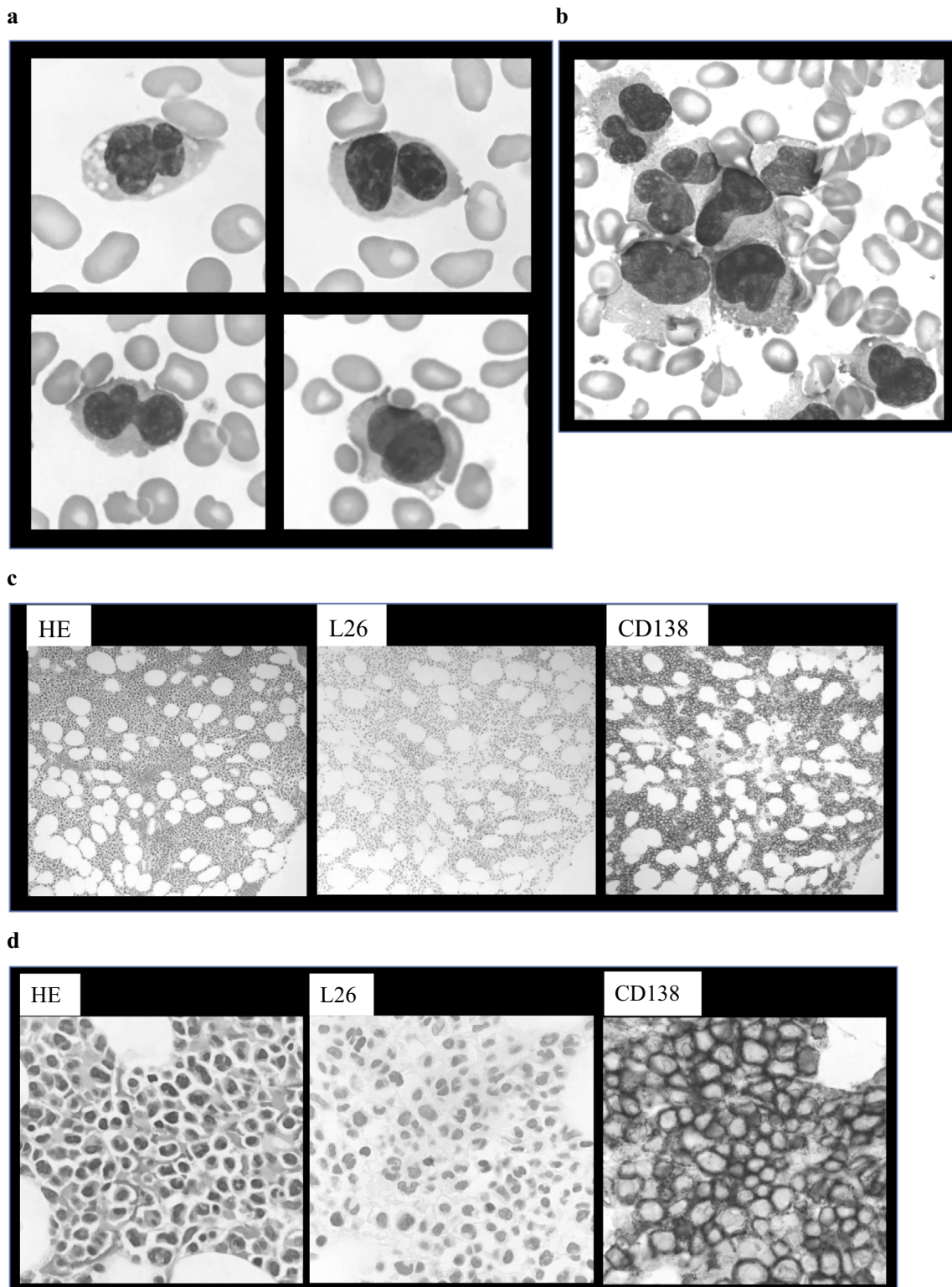
findings, such as bone lesions or lymphadenopathy, were detected. The patient was therefore diagnosed with oligosecretory pPCL, stage IIIA in the Durie and Salmon criteria, complicated with left renal tumor.

No cytological or pathological analysis was carried out for the diagnosis of the left renal tumor. Complication with renal cancer was suggested based on the imaging findings; however, the possibility of an extramedullary lesion of PCL/plasmacytoma could not be excluded. Treatment with weekly administration of bortezomib and dexamethasone was initiated. After 10 days of treatment, the proportion of abnormal cells count in the PB decreased to 2-4%. However, the left renal tumor did not show any changes in size. Calcium levels were normalized after three weeks, and abnormal cells in the PB disappeared after four weeks of treatment. Six weeks after starting treatment, the anemia and thrombocytopenia were improved, and the patient was referred to a nearby hospital for the continuation of treatment.

## Discussion

In this patient, plasma cells in the PB accounted for >20% of the total WBC count but measured <2,000/ $\mu$ L. In some reports, meeting only 1 of the 2 criteria (>20% and >2,000/ $\mu$ L of plasma cells in the PB) was considered sufficient for the diagnosis of PCL, as meeting both criteria might underestimate the real frequency of PCL (9). Furthermore, the diagnostic effects of the criteria have recently been proposed to be similar even in cases with plasma cells  $\geq$ 5% of a total WBC count and/or  $\geq$ 500/ $\mu$ L in the PB (9). Thus, the present patient was diagnosed with pPCL.

Atypical morphology in plasma cells has been reported in some case reports of pPCL (10-16), such as blastoid, prolymphocytoid, lymphoplasmacytoid, and monocytoid, among others. In a previous case report, significant morphological abnormality with multi-lobulated nucleus, resembling adult T-cell leukemia-lymphoma, was also reported (12). The

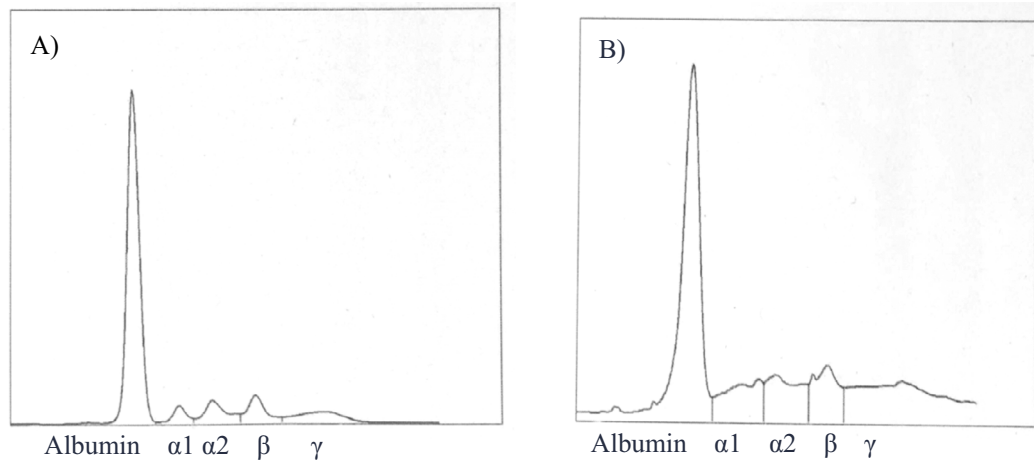


**Figure 1.** (a) Leukemia cells in the peripheral blood at the diagnosis (May-Giemsa stain,  $\times 1,000$ ). (b) Leukemia cells in the bone marrow at the diagnosis (May-Giemsa stain,  $\times 1,000$ ). (c) HE and IH of the bone marrow clot section ( $\times 200$ ). (d) HE and IH of the bone marrow clot section ( $\times 1,000$ ). L26 is the same as CD20. HE: Hematoxylin and Eosin staining, IH: immunohistostaining

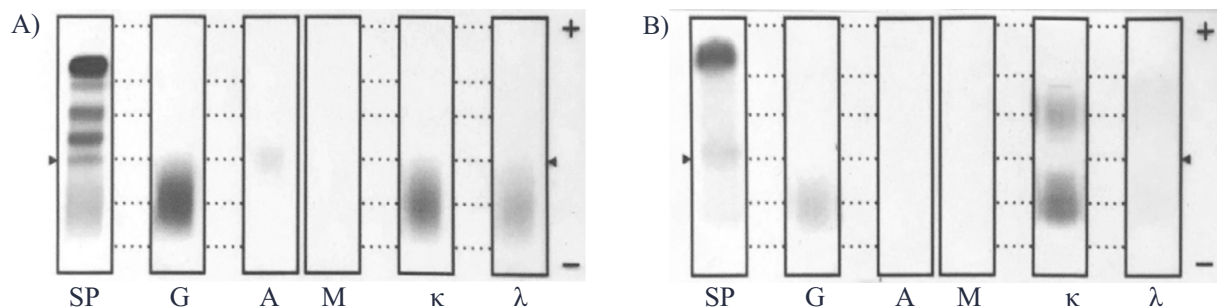
clinical significance of morphological atypia in plasma cells remains unclear; however, its association with a poor prognosis has been suggested.

The proportions of immunoglobulin subtypes of PCL were reported as follows: Bence Jones protein (BJP) type in

35%, IgG type in 33%, IgA type in 20%, non-secretory type in 8%, IgD type in 3%, and IgE type in 1% cases. Non-secretory type is therefore considered a rare subtype of PCL (2). Our literature review found only six previously published case reports on non-secretory pPCL with atypical



**Figure 2.** M-component was not detected. (A) Electrophoresis of the serum protein, (B) electrophoresis of the urine protein.



**Figure 3.** M-protein was not detected. Immunofixation electrophoresis. (A) Serum, (B) urine.

**Table 2a.** Flow Cytometric Analysis of Peripheral Blood at Diagnosis.

CD38 gating (21.2%)			
CD 3	0.8 %	cyIgG	0.3 %
CD 4	0.9 %	cyIgA	0.1 %
CD 8	1.2 %	cyIgM	1.1 %
CD10	0.3 %	cyIgD	0.3 %
CD16	4.9 %	cyIgκ	95.9 %
CD19	0.1 %	cyIgλ	0.8 %
CD20	0.0 %		
CD56	0.7 %		
CD138	97.7 %		

CD: cluster of differentiation, cy: cytoplasmic, Ig: immunoglobulin

**Table 2b.** Flow Cytometry of Bone Marrow at Diagnosis.

CD38 gating (81.8%)			
CD 3	0.2 %	cyIgG	0.5 %
CD10	0.0 %	cyIgA	0.2 %
CD19	0.1 %	cyIgM	0.7 %
CD20	0.2 %	cyIgD	0.0 %
CD56	0.2 %	cyIgκ	98.9 %
CD138	97.9 %	cyIgλ	1.8 %

CD: cluster of differentiation, cy: cytoplasmic, Ig: immunoglobulin

morphology (Table 3) (11-16). Leukemic plasma cells were CD38- and CD138-positive but CD56-negative in most cases. Regarding the chromosomal analysis, only our case was positive for t(11;14)(q13;32) in the FISH analysis, although the results were not described in half of the previously reported cases. The results of an SFLC assay were not available in most of the reports, and the frequency of oligosecretory type PCL was not mentioned. Non-secretory (including oligosecretory) pPCL with atypical morphology is a rare disease; however, its existence should be recognized in

order to ensure the appropriate management. When abnormal cells are observed in the PB, an FCM analysis of the PB (and BM) and a pathological analysis of the BM and an SFLC assay can aid in the differentiation.

We encountered a case of oligosecretory pPCL with atypical morphology in plasma cells that was effectively diagnosed through FCM and pathological analyses and an SFLC assay. The recognition of such cases and performance of appropriate examinations are important for the early diagnosis of this rare MM subtype.

**The authors state that they have no Conflict of Interest (COI).**

**Table 3. Review of the Literature about Primary Plasma Cell Leukemia with Cell Morphological Abnormality.**

Reference	This report	(11)	(12)	(13)	(14)	(15)	(16)
Age, Sex	81, Male	79, Male	51, Female	85, Male	60, Female	69, Male	49, Male
Cell morphology	Convolved nucleus with basophilic cytoplasm	High N/C ratio, dispersed, open chromatin, nuclei with one or more nucleoli	Bi-to-multinucleated and multilobulated cells	Lymphoplasmacytoid cells	Lymphoplasmacytoid cells	Atypical large lymphocytes resembled prolymphocytes	Multinucleated large cells
IH	CD38+ CD138+ CD20- CD56-	CD38+ CD138+ CD20+ CD56-	CD138+ CD43+ CD20- CD56-	CD38+ CD138+ CD20- CD56-	CD38+ CD138+ CD20- CD56-	CD38+ CD56+ CD20-	CD38+ CD13+ CD44+ CD56-
FLC (mg/L)							
κ	590	NA	NA	0.3	NA	NA	NA
λ	9.1			5.1			
Karyotype	46, XY	Complex karyotype	NA	46, XY	NA	NA	NA
FISH	t(11;14)(q13;q32)	Negative for t(4;14), t(14;16), and t(11;14)	NA	NA	NA	NA	NA
Extra-medullary	none (or Kidney)	Kidney	none	none	none	Spleen	Liver, Spleen Gastric tract
Bone lesion	none	none	Skull, pelvic, vertebral body, rib	none	vertebral	none	none
OS (after diagnosis)	≥3 months	few months	not reached	1 month	unknown	unknown	16 months

IH: immunohistostaining, FLC: free light chain, FISH: fluorescence *in situ* hybridization, OS: overall survival, N/C ratio: nuclear/cytoplasm ratio, CD: cluster of differentiation, NA: not analyzed

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