

Case Report

Primary Nonsecretory Plasma Cell Leukemia With Multiple Chromosomal Abnormalities: A Case Report

Satoshi Nakayama, MT¹; Tomohiro Oda, MT¹; Shinya Minabe MT¹; Yukiharu Bamba, MT^{1,2}; Haruko Ukawa, MT¹; Rika Sato, MT¹; Masaki Kawabata, MT¹; Toshikatsu Horiuchi, MD³; Junichi Watanabe, MD, PhD³; Fumihiko Kimura, MD, PhD³; Hideyuki Shimazaki, MD, PhD¹; Sho Ogata, MD, PhD¹; Kuniaki Nakanishi, MD, PhD¹

¹Department of Laboratory Medicine, National Defense Medical College Hospital, Tokorozawa, Japan

²Department of Pathology and Cytology, PCL Japan, Inc., Kawagoe, Japan

³Division of Hematology, Department of Internal Medicine, National Defense Medical College, Tokorozawa, Japan

Abstract

Primary nonsecretory plasma cell leukemia (PCL) is an extremely rare type of multiple myeloma. Here, we report a case of nonsecretory PCL with no previous history of multiple myeloma. The case exhibited extremely low levels of serum immunoglobulin and light chain, no detectable serum M-protein or free light chain restriction, no urine BJP, and no cytoplasmic light chain expression in flow cytometry. In fluorescence in situ hybridization, tumor cells exhibited fusion genes for IgH/BCL1 and IgH/c-Myc, disappearance of the p53 signal, and a split signal for IgK(2p11), but no split signal for IgL (22q11). Therefore, we diagnosed primary nonsecretory PCL with multiple chromosomal abnormalities.

Keywords: Multiple myeloma, Nonsecretory type, Plasma cell leukemia

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Introduction

Plasma cell leukemia (PCL) is an extremely rare type of multiple myeloma, accounting for an estimated 2%–4% of all types of myeloma.¹ PCL is characterized by plasma cells (PCs) making up more than 20% of the white blood cells (WBCs) in the peripheral blood and/or having an absolute number exceeding $2 \times 10^9/L$.¹ It is categorized into 2 types: de novo (primary), and a type found in patients with long standing myeloma (secondary). The majority of cases occur by leukemic transformation of myeloma.¹ Although leukemic PCs usually produce immunoglobulin (Ig), there is a nonsecretory type unable to release monoclonal products (M-proteins) in either the serum or urine in about 1%–5% of myeloma cases.² However, the nonsecretory type of PCL is very rare.³ Here, we report a case of primary nonsecretory PCL with multiple chromosomal abnormalities.

Case Report

A 76-year-old female was admitted to National Defense Medical College Hospital (Tokorozawa, Japan) complaining of general fatigue and weakness for 3 months. She had blood in her stools and hematuria. Also she was found to be anemic upon admission. A complete blood count revealed pancytopenia: hemoglobin level 6.1

g/dL, WBCs $2.8 \times 10^3/\mu L$, platelet count $8.1 \times 10^4/\mu L$. In the peripheral blood smear, PCs were found to be 22.0% of all WBCs. Her laboratory workup demonstrated the following: erythrocyte sedimentation rate 68 mm/h (3–11 mm/h), total protein 5.9 g/dL, albumin 4.2 g/dL, calcium 10.2 mg/dL (8.5–10.3 mg/dL), urea acid 10.4 mg/dL (2.6–6.0 mg/dL), lactate dehydrogenase 208 IU/L (100–225 IU/L), and β_2 -microglobulin 7269 ng/mL (700–2000 ng/mL), blood urea nitrogen 65 mg/dL (8–20 mg/dL), creatinine 1.84 mg/dL (0.44–0.78 mg/dL), and brain natriuretic peptide 198.4 pg/dL (<18.4 pg/dL). Nephrometry identified markedly reduced Ig levels: IgG 530 mg/dL (870–1700 mg/dL), IgA 28 mg/dL (110–410 mg/dL), and IgM 19 mg/dL (35–220 mg/dL). Serum M-protein and urine Bence-Jones protein (BJP) were not identified by immunoelectrophoresis. Restriction of serum free light chain [FLC, FLC ratio; 0.678 (0.248–1.804); κ -chain 10.10 mg/dL (2.42–18.92 mg/dL), λ -chain 14.90 mg/dL (4.44–26.18 mg/dL)] was not detected. The bone marrow (BM) smear revealed a prominent increase (77.6%) of PCs with a high nuclear-cytoplasmic ratio, including an atypical multinucleated form (Figure 1a). The BM biopsy was hypercellular and displayed prominent atypical PC infiltration. Therefore, the nonsecretory type of PCL was diagnosed for this

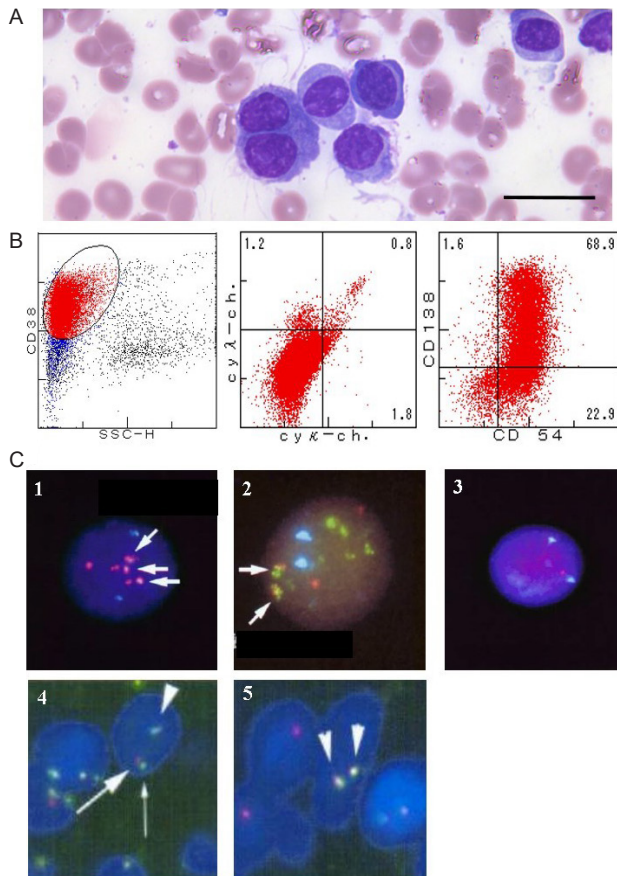


Figure 1. Morphology, flow cytometry (FCM), and fluorescence *in situ* hybridization (FISH) in bone marrow aspiration. **a)** Plasma cells with atypical multinucleated form (bar, 10 μ m). **b)** FCM in gated area obtained from sorting by CD38 showing positive findings for CD138 and CD54, and negative findings for cytoplasmic κ - and λ -chain. **c)** FISH on interphase cells showing 2 green signals for *IgH*, 3 red signals for *CCND1* and 3 red/green fusion signals for *IgH/CCND1* (arrows) (**c-1**), 4 green signals for *IgH*, 2 red signals for *c-Myc*, and 2 red/green fusion signals for *IgH/c-Myc* (arrows) (**c-2**), one red signal for *p53* and 2 green signals for chromosome 17, indicating deletion of *p53* (**c-3**), one yellow fusion signal for *IgK* downstream/*IgK* upstream (arrowhead), one green signal for *IgK* upstream (thin arrow), and one red signal for *IgK* downstream (thick arrow), indicating a split signal for *IgK*(2p11) (**c-4**), and 2 yellow fusion signals for *IgL* downstream/*IgL* upstream (arrowheads), green signal for *IgL* upstream, and red signals for *IgL* downstream indicating no split signal for *IgL* (22q11) (**c-5**).

patient because there was no restriction of serum FLC.

In an immunohistochemical analysis performed using standard techniques, tumor cells were revealed to be positive for CD (cluster of differentiation) 38, CD138, BCL2, Cyclin D1, and CD79acy; weakly positive for CD43; and finally negative for CD20, CD3, CD5, CD10, CD23, CD56, κ -chain, and λ -chain. In flow cytometry (FCM) performed on peripheral blood and BM, tumor cells expressed CD33, CD38, CD138, CD54, and MPC-1, but not CD7, CD19, CD20, CD45, CD49e, CD56, cytoplasmic κ -chain, or cytoplasmic λ -chain (Figure 1b). In fluorescence *in situ* hybridization (FISH), tumor cells exhibited fusion genes for *IgH/BCL1* and *IgH/c-Myc*, monoallelic deletion of the *p53* signal, and a split signal for *IgK* (2p11), but no split signal for *IgL* (22q11). These findings confirmed the t(11;14)(q13;q32), t(8;14)

(q24;q32) and del(17p)i(17)(q10) of the cytogenetic analysis. Polymerase chain reaction performed on BM revealed *Ig* heavy chain (*IgH*) gene rearrangement [positive reaction for *VH(FR1)/JH*, *VH(FR2)/JH*, *VH(FR3)/JH*, and *DH1-6/JH*; negative reaction for *DH7/JH*] and κ -chain gene rearrangement [positive reaction for *V κ /J κ* and *V κ -C κ intron/Kde*].

Discussion

In the present case, we demonstrated the following points: (i) extremely low serum Ig and light chain levels, (ii) no detectable serum M-protein or FLC restriction, (iii) no urine BJP, and (iv) no cytoplasmic light chain expression in FCM. Therefore, we diagnosed a nonsecretory PCL case. The nonsecretory type of PCL is broadly categorized into 2 groups: (i) one unable to excrete Ig (nonsecretor), and (ii) one with a low synthetic capacity for Ig (nonproducer).² Although the evidence in the present case strongly suggested the nonproducer subtype (because there was no cytoplasmic light chain expression in FCM), it is still possible that there would be rapid degradation of abnormal Ig in the cytosol and/or extracellular area.³ Therefore, the nonproducer subtype diagnosis needs to be made carefully, by using findings from cytogenetic investigations. Blade et al demonstrated that cytoplasmic monoclonal protein was detected in approximately 85% of patients with suspected nonsecretory myeloma.⁴

In the FISH examination, the present case demonstrated multiple chromosomal abnormalities.⁵ In a recent FISH study of 23 primary PCLs, *IgH* (14q32) translocations were identified in 87%, including t(11;14) (40%) and t(14;16) (30.5%).⁶ Furthermore, deletion of 17p was evident in 30.5%.⁶ In 14 nonsecretory PCLs examined by Avert-Loiseau et al, the incidence of t(11;14)(q13;q32) was 79%.⁷ They proposed a plausible hypothesis indicating that t(11;14) is mainly observed in clones with low-secreting features.⁷ The present case also exhibited t(11;14)(q13;q32) and t(8;14)(q24;q32).

The mechanism underlying lack of Ig synthesis in the nonproducer subtype has not been fully clarified.⁸ Although a lack of *IgH* transcription was previously suggested as the major cause in a study of 9 *IgH*-negative myelomas,⁹ most myelomas were found to contain chromosomal translocations in a recent study of 12 primary *IgH*-negative myelomas.¹⁰ This led to the idea that aberrations at the DNA level are the major cause of nonsecretory myelomas.⁸ However, a more recent molecular basis study of nonsecretory myeloma (nonsecretor subtype) revealed that abnormal κ -chains resulting from a frameshift mutation, led to an absence of the cysteins required for disulfide bonds. Therefore, the misfolded κ -chains were presumably retained within

the cytosol and then underwent proteolysis.² Further investigations are needed to clarify the pathogenesis of nonsecretory PCL.

In conclusion, we diagnosed primary nonsecretory PCL with multiple chromosomal abnormalities.

Clinical Practice Points

Primary nonsecretory PCL is an extremely rare type of multiple myeloma.

We reported a case of nonsecretory PCL, without history of multiple myeloma, which exhibited no cytoplasmic light chain expression in flow cytometry and multiple chromosomal abnormalities in FISH.

Detailed examination of serum and urine proteins, combined with flow cytometry and FISH studies will be required to establish the exact diagnosis for nonsecretory PCL.

Authors' Contribution

SN carried out the hematologic evaluation, conceived the study and also drafted the manuscript. TO, SM and HS carried out the hematopathologic evaluation. YB, HU, RS and MK carried out the hematologic evaluation. TH, JW and FK carried out the patient treatment and hematologic evaluation. SO and KN helped to draft the manuscript. All authors read and approved the final manuscript.

Conflict of Interest Disclosures

The authors declare that they have no competing interests.

Ethical Statement

This study was conducted along the Helsinki Declaration.

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