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CASE REPORT

Synchronous plasma cell neoplasm and B lymphoblastic leukemia/lymphoma at initial presentation: first report of an unusual association with a good outcome

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Abstract
A synchronous diagnosis of a plasma cell neoplasm (PCN) and a non-plasma cell hematologic malignancy is very rare. We report what we believe is the first instance of a synchronous PCN and B lymphoblastic leukemia/lymphoma (B-ALL) diagnosed at initial presentation. The patient underwent laboratory evaluation for an underlying plasma cell neoplasm, including immunology studies, bone marrow biopsy, and flow cytometry immunophenotyping. Serum lambda free light chain and serum IgG were elevated, with an IgG lambda M-protein identified by serum protein electrophoresis and immunofixation. The clinical working diagnosis was plasma cell myeloma. Bone marrow biopsy was positive for a composite PCN and B-ALL. The patient received treatment with VDT-PACE chemotherapy followed by autologous stem cell transplant and maintenance therapy with bortezomib/daratumumab and is in complete remission for both diseases 3.5 years after diagnosis. This case not only adds to the known repertoire of hematologic neoplasms that can occur in association to a PCN, but also demonstrates that patients presenting with this rare combination of hematopoietic neoplasms can be effectively treated simultaneously with excellent responses. Additional research is warranted to understand the pathophysiology, to identify potential prognostic factors, and to develop specific therapeutic plans for these patients.

Keywords Composite lymphoma · Bone marrow · Plasma cell myeloma · Immunohistochemistry · Hematologic malignancy · VDT-PACE

Introduction

A synchronous diagnosis of plasma cell neoplasm (PCN) and a non-plasma cell hematologic neoplasm is very rare. Only sporadic reports of B lymphoblastic leukemia/lymphoma (B-ALL) developing after treatment of plasma cell myeloma or the latter arising after therapy for B-ALL have been described in the literature [1–6]. To the best of our knowledge, this is the first report of a patient with synchronous PCN and B-ALL diagnosed at initial presentation and that was successfully treated.

Clinical history

A previously healthy 69-year-old woman presented to our institution with back pain, low-grade fever, weight loss, and fatigue. Physical examination was only remarkable for left proximal leg weakness. Complete blood count showed a WBC of 6.03×10^3/µL, RBC: 3.46×10^6/µL, hemoglobin: 10 g/dL, hematocrit: 32.6%, and platelet count: 351×10^3/µL. Bone survey and magnetic resonance imaging demonstrated multiple lytic lesions throughout the lumbar spine and pelvic bones, with the largest focal lesion (9.5 cm) involving the left iliac bone and extending into the soft tissue. Additional laboratory serologic studies included the following: kappa free light chain of 1.84 mg/dL, lambda free light chain of 21.59 mg/dL, IgG of 1878 mg/dL, IgA of 118 mg/dL, and IgM of 47 mg/dL. Serum protein

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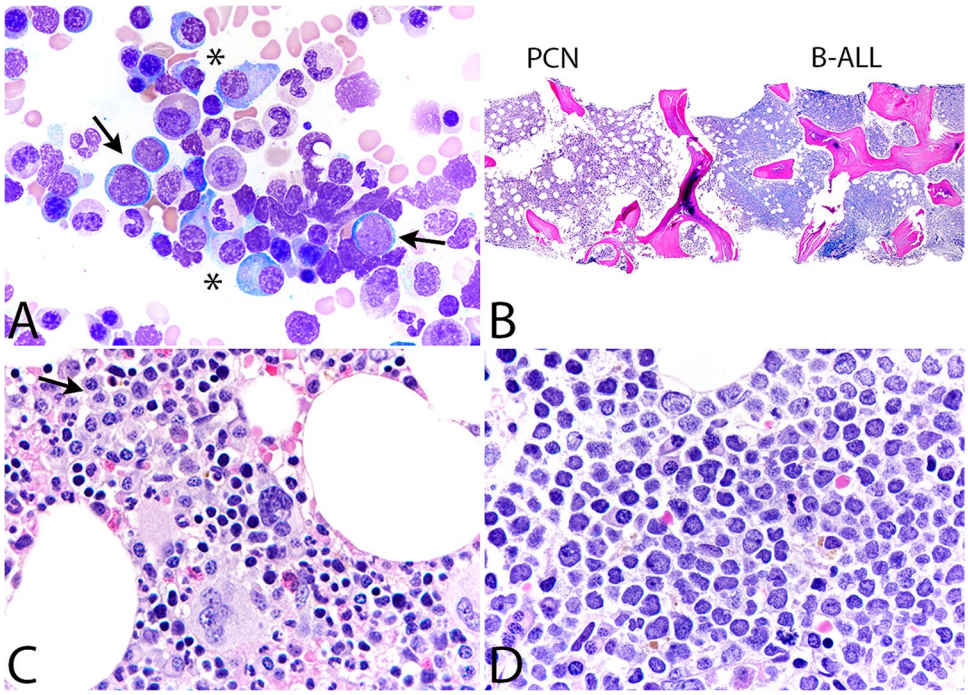

Fig. 1 **A** The bone marrow aspirate shows increased mature-appearing plasma cells (asterisks) and increased blasts (arrows) (Wright stain, 60×). **B** Low magnification of the core biopsy shows areas of hypercellular marrow for age that were involved by plasma cell neoplasm (PCN) with adjacent areas entirely replaced by acute lymphoblastic leukemia (B-ALL) (H&E stain, 2×). **C** Higher magnification of the area labelled "PCN" on panel **B**. There are plasma cells with interstitial distribution (arrow) (H&E stain, 40×). **D** Higher magnification of the area labelled "B-ALL" on panel **B**. Sheets of blasts with irregular nuclei, fine chromatin, and scant cytoplasm. Only rare plasma cells are seen (**D**, H&E stain, 40×)

electrophoresis showed a M-protein of 1200 mg/dL with an IgG lambda M-protein identified by immunofixation. Urine protein electrophoresis showed a M-protein of 260 mg/24 h with an IgG lambda M-protein plus a free lambda light chain detected by immunofixation. The clinical working diagnosis was plasma cell myeloma.

Materials and methods

A bone marrow biopsy was performed. Wright-stained aspirate smears and 4-µm tissue sections of the core biopsy stained with hematoxylin and eosin were evaluated. Immunohistochemical stains using antibodies against CD138, PAX5, TdT, CD79a, CD10, CD20, CD34, MPO, and cyclin D1 were performed on paraffin-embedded tissue sections from the bone marrow biopsy, following the manufacturer's instructions (VENTANA ultraView Universal DAB Detection Kit using the BenchMark XT instrument; Tucson, AZ).

For flow cytometry immunophenotyping, EDTA-anticoagulated bone marrow aspirate specimens were washed with phosphate-buffered saline (PBS) and resuspended in PBS containing 2% fetal calf serum. Cell suspensions were then incubated for 15 min with various cocktails of fluorochrome-conjugated antibodies. These antibodies included CD5, CD10, CD19, CD20, CD27, CD34, CD38, CD45, CD56, CD81, and CD138. All antibodies were obtained from BD Biosciences (San Jose, CA). Isotype controls were included in all analyses. RBCs were then lysed with FACS Lyse (BD Biosciences) or ammonium chloride solution, rinsed with PBS, and resuspended in PBS containing 1% formaldehyde. Analysis was performed on a FACSCanto II flow cytometer using FACSDiva software (BD Biosciences). Gating on lymphoid cells and lymphoblasts was based on CD45 vs side scatter analysis. Plasma cells were identified based on CD138 vs. side scatter analysis.

Chromosome analysis was performed on trypsin-Giemsa banded metaphase cells from 24-, 48-, and 72-hour harvests of unstimulated bone marrow aspirate cultures at the 400 band level of resolution. Twenty-one cells were analyzed and imaged, and nine complete cells were karyotyped. Fluorescence in situ hybridization (FISH) specific for myeloma was performed as follows: CD138 + magnetic cell sorting was utilized to enrich for plasma cells in the sample. FISH analysis of interphase nuclei was performed using commercially available FISH probes specific for *CDKN2C* (1p32), *CKS1B* (1q21), *FGFR3* (4p16.3), *D13S319* (13q14.3), *LAMP1* (13q34), *IgH* (14q32), *CEN 17*, *p53* (17p13.1), *CCND1* (11q13), *MAF* (16q23), and *MAFB* (20q12) loci. This test was scored using a combination of an automated image analysis platform and manual counting. A quality control review was performed on the results. Interphase FISH analysis was also performed in archival available bone marrow aspirate smears with a dual color, break apart *JAK2* (9p24) probe set used to detect various translocations that involve the *JAK2* gene in Ph-like B-ALL. A total of 200 interphase nuclei were scored. FISH analysis for *MYC* (8q24), *KMT2A* (11q23), *CRLF2* (Xp22.33, Yp11.32), and *ETV6/TEL* (12p13)-*RUNX1/AML1* (21q22) probes could not be performed due to limited cellularity.

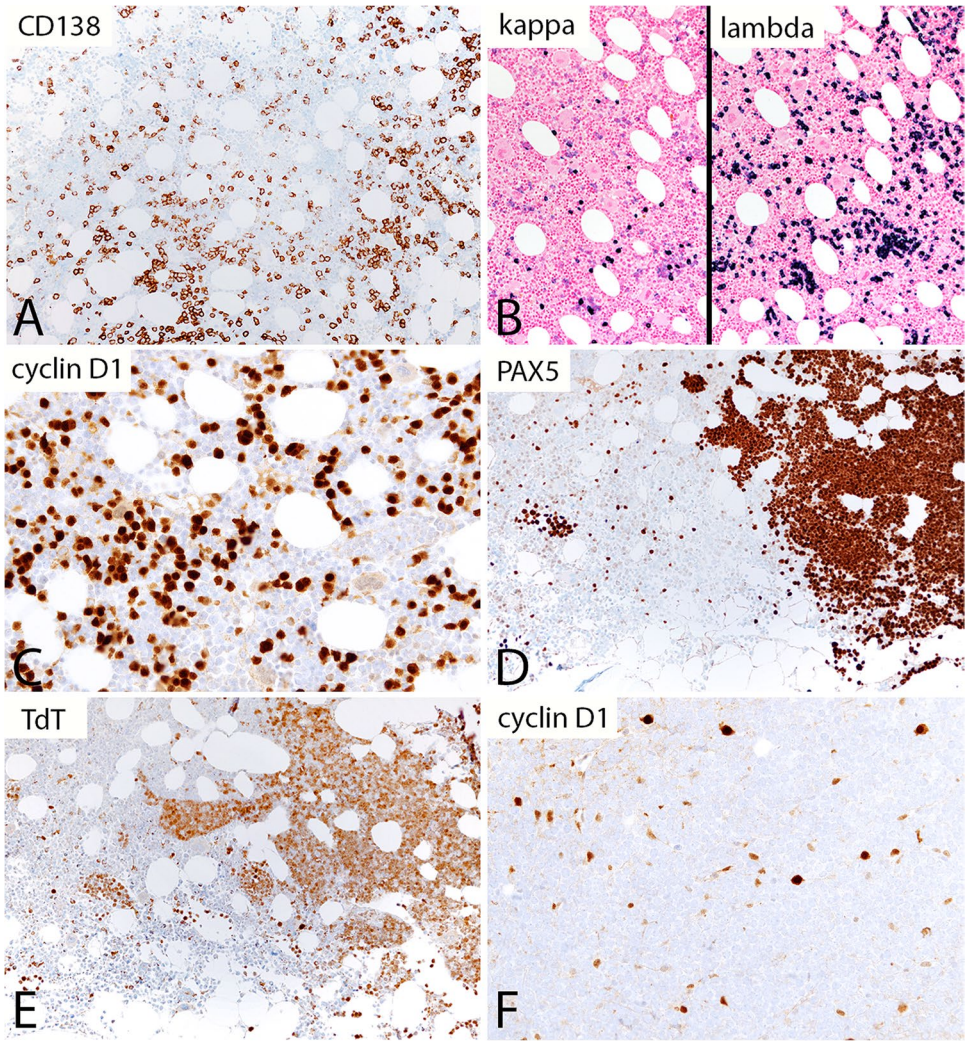

Fig. 2 Immunohistochemistry. **A** CD138 highlights 20–30% plasma cells in the areas labelled "PCN" in Fig. 1B (10×). **B** By in situ hybridization, the plasma cells are predominantly positive for lambda (right panel, 10×) as compared to kappa (left panel, 10×). **C** The plasma cells are positive for cyclin D1 (20×). **D** PAX5 and **E** TdT are positive in the areas labelled "B-ALL" in Fig. 1B (10×). **F** The blasts are negative for cyclin D1, whereas rare plasma cells interspersed among the blasts are strongly positive for this marker. Marrow stromal cells show weak nuclear positivity for cyclin D1

Results

A peripheral blood smear showed no significant abnormalities and no circulating blasts or plasma cells. The bone marrow aspirate smear showed trilineage hematopoiesis and increased plasma cells (37% of nucleated cells) with occasional prominent nucleoli. Additionally, increased blasts (40% of nucleated cells) of small to intermediate size and high nuclear-to-cytoplasmic ratio were identified (Fig. 1A). The core biopsy showed areas of hypercellular marrow for age (70%) with trilineage hematopoiesis and 20–30% plasma cells with interstitial distribution (Fig. 1B and 1C). In addition, other areas of the biopsy comprising ~ 50% of the intertrabecular space were entirely replaced by sheets of blasts with irregular to oval nuclei, vesicular chromatin, scant cytoplasm, and rare interspersed plasma cells (Fig. 1B and 1D). By immunohistochemistry, the plasma cells were highlighted with CD138 (Fig. 2A) and by in situ hybridization studies, the plasma cells were predominantly positive for lambda as compared to kappa (Fig. 2B). The plasma cells were also positive for cyclin D1 (Fig. 2C). By immunohistochemistry, the blasts were positive for PAX5 (Fig. 2D), TdT (Fig. 2E), CD79a, and CD10, and were negative for CD20, CD34, MPO (not shown), and for cyclin D1 (Fig. 2F). Flow cytometry immunophenotyping of the marrow aspirate detected a population of plasma cells (3.2% of total events) with an aberrant immunophenotype, positive for CD138, CD38, CD20 (heterogeneous), CD27 (heterogeneous), and CD81 (dim/heterogeneous) and negative for CD45, CD56, and CD19, and an atypical population of B-cells (4% of analyzed events) expressing CD45 (dim), CD19, and CD10, and negative for CD5, CD20, CD34, and surface light chains (Fig. 3). With all these findings, the diagnosis of composite PCN and B-ALL was established. Cytogenetic analysis showed a complex karyotype 47 ~ 48,XX,der(6)t(1;6)(p32;p23), + 8, + 8,der(18)t(1;18)(q21;q23)

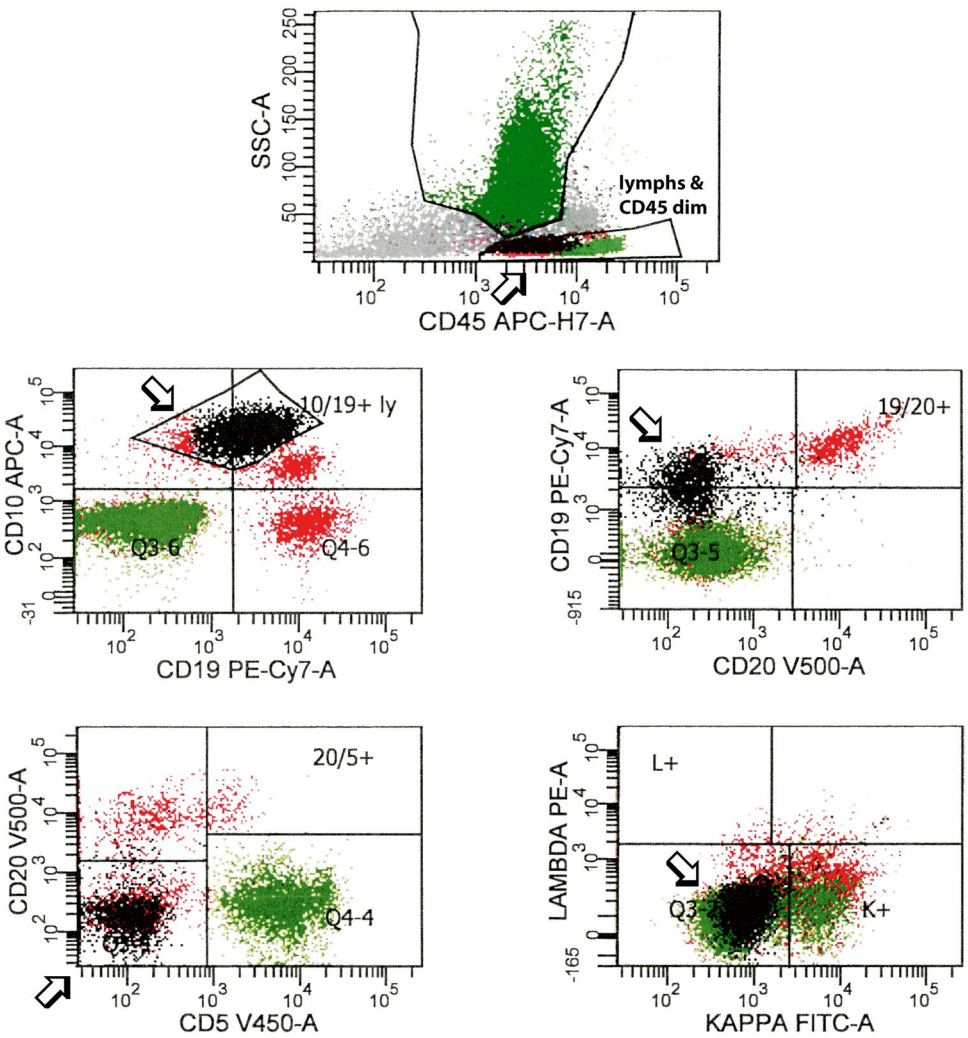

Fig. 3 Flow cytometry immunophenotyping of the marrow aspirate detected an atypical B-cell population colored in black that is dim positive for CD45 as compared to the rest of brightly CD45-positive lymphocytes (all gated under "lymphs & CD45 dim"). This dim CD45 population is positive for CD19 and CD10, while negative for CD5, CD20, and surface light chains (white arrows). Mature B-cells and hematogones are shown in red. T-cells are shown in green

[cp10]/49,idem, + 5,del(5)(q13q33),-8, + der(18)t(1;18)[2]/52 ~ 55,idem, + X, + 2, + 5, + der(18)t(1;18), + 20, + 21, + 22[cp2]/46,XX7]. FISH specific for myeloma alterations detected t(11;14)(q13;q32)(*CCND1/IGH*) associated with deletions of 14q32 (*IGH*) and 16q23 (*MAF*). Additional FISH specific for B-ALL alterations performed in archival bone marrow aspirate smears showed no *JAK2* rearrangement, and the rest of probes could not be tested due to limited cellularity.

The patient received induction chemotherapy with two cycles of bortezomib/dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (VDT-PACE) followed by high-dose melphalan conditioning with autologous stem cell transplantation and maintenance therapy with bortezomib/daratumumab with an excellent response. She achieved complete remission with negative minimal residual disease for both PCN and B-ALL 11 months after diagnosis and remains in complete remission for both diseases 3.5 years after diagnosis.

Discussion

Synchronous cases of plasma cell myeloma and other hematologic malignancy are very rare. Reported cases in the literature include plasma cell myeloma and acute myeloid leukemia [7–9], plasma cell myeloma and non-Hodgkin (T-cell) lymphoma [10–12], and plasma cell myeloma and a myeloproliferative neoplasm [13, 14]. Only sporadic reports of B-ALL developing after treatment of plasma cell myeloma or plasma cell myeloma arising after therapy for B-ALL have been described in the literature [1–6]. To our knowledge, no prior case of synchronous PCN and B-ALL at

first presentation has been reported to date. The rarity of all these composite cases — excluding those where a secondary neoplasm developed after therapy — suggests that most of them may be coincidental. However, the pathogenesis of these simultaneous occurrences is not well understood. Since both PCN and B-ALL derive from a B-cell, it is possible that synchronous cases of PCN and B-ALL may originate from a same clone, from different clones, or from PCN "de-differentiation/transformation" into B-ALL [3, 6]. The karyotype in the current case contains abnormalities that have been rarely reported in B-ALL, such as der(18)t(1;18)(q21;q23) [15], but other detected abnormalities overlap with those previously reported in plasma cell myeloma [16, 17]. Therefore, these findings do not support or exclude the possibility of a clonal relationship of these two processes. FISH specific for B-ALL was limited to establish further conclusions. An uncertain finding in this case is that the karyotype did not detect the t(11;14) present in the myeloma FISH panel, which might suggest a potential sample bias from an area rich in B-ALL cells. Given these findings, we evaluated the expression of cyclin D1 at the protein level in both processes and were able to demonstrate overexpression of cyclin D1 in the PCN (Fig. 2C) but not in the B-ALL (Fig. 2F), supporting the findings detected in the myeloma FISH panel.

The patient presented here showed an excellent response to standard chemotherapy for plasma cell myeloma, followed by autologous stem cell transplant, and myeloma-based maintenance therapy. This suggests that this treatment regimen might be sufficient to achieve a complete remission for both PCN and B-ALL in this kind of patients.

This unique case not only adds to the known repertoire of hematologic neoplasms that can occur in association to a PCN, but also demonstrates that patients presenting with this rare combination of hematopoietic neoplasms can be effectively treated simultaneously with excellent responses. Additional research is warranted to understand the pathophysiology, to identify potential prognostic factors, and to develop specific therapeutic plans for these patients.

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Declarations

Not applicable.

Consent for publication This case is exempt for the need of approval from the University of Arkansas for Medical Sciences (UAMS) Institutional Review Board according to Policy Number 1.4, Principles and Authority as stated below:

"**Case Reports**: For the purpose of this policy, a case report is defined as the collection and/or presentation of existing clinical information from three or fewer patients to illustrate an interesting or unique situation. Activities meeting this definition are not considered Human Subject Research by the UAMS IRB and do not require IRB Review or Approval."

Conflict of interest The authors declare no competing interests.

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