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Case Report

B-lymphoblastic leukemia/lymphoma arising in treated plasma cell myeloma: A rare second malignancy

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ABSTRACT

Plasma cell myeloma (PCM) is a neoplasm of plasma cells, end-stage post germinal center B cells, which shows a variable clinical spectrum from asymptomatic to aggressive; the nature of the disease is generally progressive. Rarely, leukemia arises treated plasma cell myeloma. Acute myeloid leukemia/Myelodysplastic syndrome (AML/MDS) is most common, but rare cases of B lymphoblastic leukemia/lymphoma (B-ALL) have been described. The diagnosis of transformation or secondary B-ALL is supported by ancillary studies such as flow cytometry, immunohistochemistry, and molecular studies. Once the diagnosis of a B-ALL is made, consideration should is given as to whether the malignancy is a clonally related transformation of the original PCM or treatment related second leukemia. We present a case of B-ALL after PCM which does not appear to show a clonal relationship with the original PCM suggesting a treatment related B-ALL.

1. Introduction

B-ALL arising in patients with PCM is extremely rare. We describe one case of PCM with subsequent B-ALL diagnosed by histologic, immunophenotypic, and molecular evaluation. PCM is a plasma cell neoplasm typically seen in the middle-aged to elderly. Symptomatic cases present with high calcium, renal insufficiency, anemia, and bone lesions (CRAB criteria). The bone marrow exhibits plasmacytosis with sheets or aggregates of atypical cells. Immunophenotypically, plasma cells characteristically are positive for mum1, CD38, CD138, CD56, cytoplasmic kappa or lambda, and PCA1, and tend to be negative for CD45, CD19, CD20, CD21, CD22, and sIg [1]. The nature of disease is progressive, and it has been described to transform into high-grade lymphoma [2] or, rarely, to plasmablastic lymphoma [3], a rare subtype of diffuse large B-cell lymphoma. Although there is an increased risk of acute myeloid leukemia and myelodysplastic syndromes after treatment for PCM [4–6], transformation to B-ALL is uncommon [3,7–11]. Rarely other mature B-cell lymphomas such as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and follicular lymphoma are reported to undergo lymphoblastic transformation [12–14]. Plasma cell neoplasms are mature terminally differentiated B cell neoplasms composed of long-lived plasma cells, which have undergone somatic mutation in the germinal center. Transformation to an immature B cell neoplasm is very unusual and, in the rare cases reported [9–11,15–19], the clonal relationship between plasma cell myeloma and the subsequent B-ALL has not been well studied. Of two previous cases studied by molecular techniques comparing clones, neither showed a clonal relationship of the B-ALL to the original plasma cell myeloma [9,11]. Here we report a patient with treated PCM developing subsequent B-ALL which has been studied by molecular and cytogenetic techniques.

2. Clinical history

A 55-year-old Hispanic female was diagnosed with PCM in June 2009. (Bone marrow aspirates were examined using Wright –Geimsa stains; hematoxylin and eosin staining with formalin fixation was used to examine the biopsies.) This diagnosis was supported by laboratory studies including fluorescence *in situ* hybridization (FISH) showing an abnormal t(11;14) and *IGH* gene rearrangement with no deletion of 17p or 13q. Conventional cytogenetic studies at that time were normal. She had elevated lambda free light chains. A subsequent bone marrow biopsy showed 30–40% plasma cell involvement by immunohistochemical stains (Fig. 1a, b and c). Immunoglobulin heavy chain (*IGH*) gene rearrangement studies (PCR method based on BIOMED-2 consensus guidelines) demonstrated predominant peaks at 266 base pairs (bp) in FR2-JH and at 131 bp in FR3-JH, consistent with clonal gene rearrangements (Fig. 3). She received Revlimid (lenalidomide) and Dexamethasone, with an initial decrease in lambda light chains. Bortezomib was later added. She eventually had a chemotherapy holiday in July 2012 due to cumulative toxicities. A subsequent bone marrow biopsy in September 2012 demonstrated 2–5% plasma cells by manual differential (1–2% by immunohistochemical staining) with polytypic light chain expression by chromogenic *in situ* hybridization

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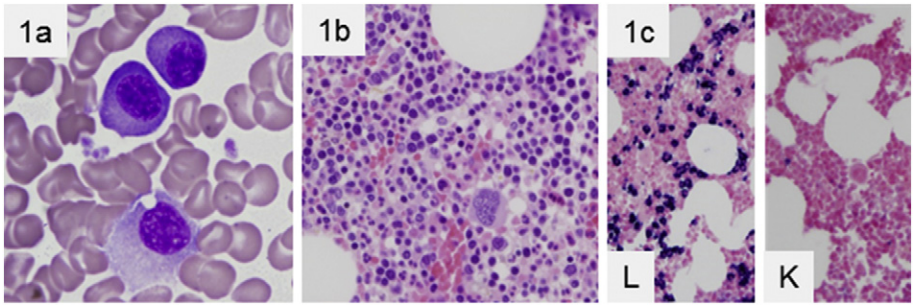

Figs. 1. Plasma cell myeloma. a) Bone marrow aspirate showing increased plasma cells (Wright-Giemsa 400× oil); b) Bone marrow biopsy showing trilineage hematopoiesis with increased scattered plasma cells (hematoxylin-eosin 20×); c) Kappa (K) and lambda (L) *in situ* hybridization showing lambda restriction (*in situ* hybridization 20×).

(CISH). FISH and cytogenetics were normal. She was started on Revlimid as a single agent; however, her disease appeared to progress so she was started on pomalidomide. A skeletal survey in December 2013 showed no lytic lesions.

In November 2014, she was seen for another bone marrow biopsy, which showed a hemodilute aspirate but variably cellular marrow biopsy (10–70%) with involvement by sheets of medium to large immature lymphoid cells with a high nuclear to cytoplasmic ratio and fine chromatin (Fig. 2a and b). A reticulin stain showed moderately to markedly increased reticulin fibrosis. The immature lymphoid cells were strongly and uniformly positive by immunohistochemistry for CD45, Tdt, CD20, CD10, bcl-2, and pax5 with variable CD34 (Fig. 2c, d and e), and negative for bcl-6, CD23, CD117, cyclin D1, CD123, lysozyme, and myeloperoxidase. Ki-67 labeled approximately 80% of neoplastic nuclei. CD138 showed only rare plasma cells (Fig. 2f). Kappa and lambda CISH showed no evidence of light chain restriction. Flow cytometry demonstrated no definitive evidence of a plasma cell neoplasm. A FISH panel for PCM showed no abnormal cytogenetic findings. Conventional cytogenetics studies could not be performed as the specimen lacked dividing cells.

The patient had a subsequent repeat bone marrow biopsy in December 2014 showing a hemodilute aspirate but variably cellular bone marrow biopsy (30–50%) with scattered immature lymphoid cells. Diffuse sheets of immature lymphoid cells were not identified, but the scattered cells were strongly, uniformly positive for Tdt, CD20, CD10, and pax5, and demonstrated variable expression of CD34, CD79a, and CD99. The cells were negative for CD117, CD123, and myeloperoxidase. A CD 138 and stain highlighted scattered plasma cells, but there did not appear to be any increase in the number of plasma cells. Ki-67 labeled approximately 80% of the atypical cells. Kappa and lambda CISH showed no evidence of light chain restriction. A reticulin stain highlighted moderately increased reticulin fibrosis. Flow cytometry demonstrated no definitive evidence of mature B lymphocytes or myeloid blast population. A FISH panel for acute leukemia showed no abnormal findings. Cytogenetics revealed a normal female karyotype. *IGH* gene rearrangement studies performed on the bone marrows (both biopsies) revealed peaks in DH-JH at 138 and 228 bp only (Fig. 3). *IGH* clonality studies on peripheral blood at the time of the B-ALL diagnosis demonstrated the two peaks found in the B-ALL bone marrow specimen DH-JH at 138 and 228 bp and additional peaks in FR1-JH at 325 bp, FR2-JH at 260 bp, FR3-JH at 125 bp (not shown). The significance of the additional three peaks is uncertain. The PCR product sizes were compared between specimens to determine clonal relationship.

3. Discussion

Sequential bone marrow biopsies from this patient revealed a population of immature B cells expressing CD45, Tdt, pax5, CD20, and CD10

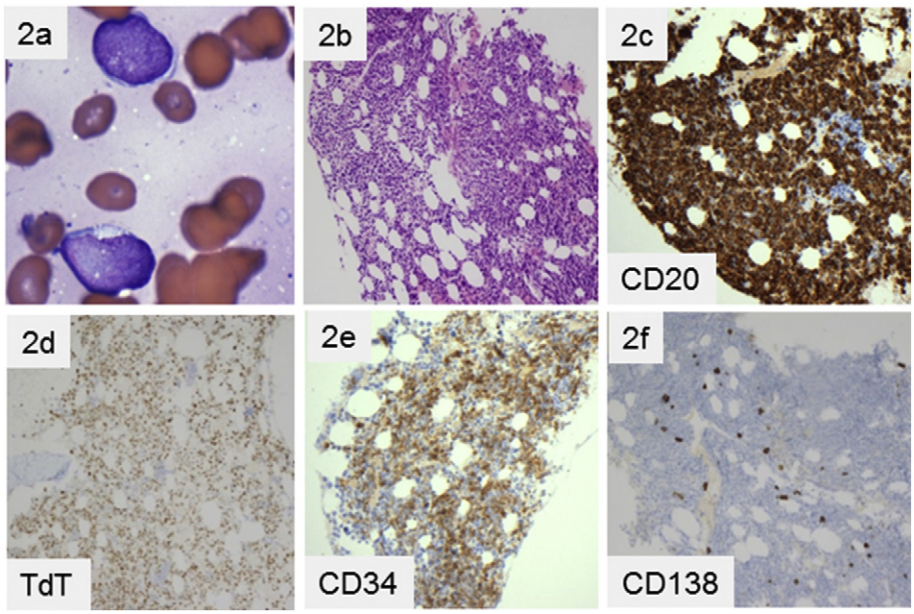

Fig. 2. B-Lymphoblastic leukemia/lymphoma. a) Bone marrow aspirate showing B-lymphoblasts (Wright-Giemsa 400×.; b) Bone marrow biopsy showing sheets of blasts (hematoxylin-eosin 20×); c) Bone marrow biopsy with CD20 expression in blasts (immunohistochemistry CD20; 20×); d) Bone marrow biopsy with diffuse nuclear positivity for Tdt (immunohistochemistry Tdt 20×); e) Bone marrow biopsy with diffuse CD34 positivity (immunohistochemistry CD34, 20×); f) Bone marrow biopsy showing only rare CD138-positive plasma cells polytypic by light chains (immunohistochemistry CD138; 20×).