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Case Report Open Access

The Diagnostic Challenge of Therapy-Related Pure Erythroid Leukemia Arising in the Setting of Multiple Myeloma

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Abstract

We report two interesting cases of patients with multiple myeloma, who developed a therapy-related myeloid neoplasm in the form of pure erythroid leukemia. In both cases, it was difficult to differentiate the erythroid blasts from plasma blasts by morphology alone. The diagnostic picture was further confounded by the presence of a hyperdiploid karyotype (case 1), which is a frequent cytogenetic abnormality in multiple myeloma but distinctly uncommon in acute myeloid leukemia. These cases highlight the diagnostic challenge encountered with pure erythroid leukemia in the setting of multiple myeloma, and underscore the importance of immunohistochemistry, cytogenetics, and gene rearrangement studies in resolving the diagnostic conundrum. To the best of our knowledge pure erythroid leukemia with a hyperdiploid karyotype arising in a background of pre-existing multiple myeloma, has not previously been reported.

Keywords: Leukemia; Myeloma; Cytogenetic; Tumors

Introduction

Pure Erythroid Leukemia (PEL) is a rare form of acute myeloid leukemia (AML) characterized by neoplastic proliferation of immature cells restricted to the erythroid lineage [1-3]. Most published papers that discuss this rare entity are case reports or small patient series [1,2,4]. The majority of the reported cases were classified as AML with myelodysplasia-related changes either because they evolved from a previous Myelodysplastic Syndrome (MDS), or because they had cytogenetic abnormalities frequently associated with MDS. It is uncommon for PEL to occur as a therapy-related Myeloid Neoplasm (t-MN); PEL as a t-MN has been described in patients previously treated for precursor B-lymphoblastic leukemia [5], chronic lymphocytic leukemia [6], solid tumors [7], and myeloma [8]. The rarity of PEL coupled with the lack of erythroid-lineage-specific markers, frequent occurrence of early myeloid antigens on erythroid precursors, and an undifferentiated morphology makes distinction from minimally differentiated AML (M0) challenging. The very immature or early erythroid precursors may resemble immature cells of other hematopoietic lineages including plasmablasts/immature plasma cells [9], large cell lymphoma cells, and megakaryoblasts, as well as undifferentiated carcinoma cells. An awareness of the relationship of PEL to other entities that show morphological and immunophenotypic overlap with it is required for accurate diagnosis of PEL. In this paper we present two morphologically and clinically challenging cases of PEL in a therapy-related setting following treatment for multiple myeloma (MM), both having a sudden onset—one where the karyotype added to the diagnostic dilemma, and the other where the karyotype helped to confirm the diagnosis.

Case Presentations

Case 1

The patient is a 73-year-old woman with a diagnosis of IgG kappa MM that had a normal karyotype by Conventional Metaphase Cytogenetics (CMC) at diagnosis. She received melphalen-based autologous stem cell transplantation followed by maintenance with thalidomide for 6-months. Thalidomide was discontinued due to peripheral neuropathy, and replaced by lenalidomide and dexamethasone, with which she achieved a partial remission for 2-years. Bortezomib-based therapy was given at disease progression, which was stopped after 3 cycles due to development of painful peripheral neuropathy. She remained in remission while being off therapy for 1 year, but subsequently relapsed. After relapse she was started on a clinical trial with carfilzomib. A Bone Marrow (BM) examination performed 46-months after the initial diagnosis demonstrated a hypercellular marrow with 15-20% kappa-restricted mature plasma cells that expressed the following antigens: CD138 (CD: cluster of differentiation), CD20, CD117, CD56, and CD52. The karyotype was normal. Fluorescence In-Situ Hybridization (FISH) analysis showed no evidence of gain of 1q21, deletion 13q, t(4;14), deletion 17p13.3, or translocations involving the Immunoglobulin Heavy Chain (IGH) gene.

Six months later when she was noted to be anemic (hemoglobin (HgB) 7.4 g/dL and platelet count 53 K/uL), Carfilzomib was stopped. Two months later when Hgb and platelet count dropped further to 6.5 g/dL and 19 K/μL respectively, a BM was performed. At this time the lactate dehydrogenase (LDH) was high at 11,242 U/L. The Complete Blood Count (CBC) revealed WBC 2.8 L/uL, Hgb 6.5 g/dL, hematocrit 19.1%, and platelet count 53 K/uL. WBC differential: neutrophils 63%, lymphocytes 18%, monocytes 10%, and eosinophils 5%. A BM

examination revealed large atypical cells with round and often eccentrically located nuclei, coarse chromatin, prominent nucleoli, and basophilic cytoplasm with occasional cytoplasmic vacuoles (Figure 1a). The cells were negative for myeloperoxidase, Sudan black, and nonspecific esterase; few showed Periodic Acid Schiff (PAS)-positive staining in the cytoplasmic globules. Flow cytometry identified a population of high-side-scatter (large size) cells with dim CD45 expression, which expressed CD71 (bright), CD235a (dim, in a small subset), CD33 (subset), and HLA-DR, and were negative for all other myeloid and all lymphoid markers. The core biopsy showed a hypercellular marrow with maturation in the granulocytic and megakaryocytic lineages, but not in the erythroid series. Multiple cohesive clusters of large atypical cells were identified within the sinusoids, resembling metastatic carcinoma (Figure 1b). By immunohistochemistry, these cells were positive for CD43 and CD71 (Figure 1c), and had weak and focal expression of glycophorin A; they were negative for CD45, hemoglobin A, CD138, kappa, lambda, CD56, CD20, CD34, CD117, pancytokeratin, and S100. Immunohistochemistry identified a small population of CD138 positive plasma cells (~3-5% of the cellularity) that were polytypic for light chains by in-situ hybridization. Although negative by morphological and immunophenotpic criteria, serum electrophoresis and immunofixation revealed a small M-protein spike of 0.4 g/dL, consistent with partial remission based on the International Myeloma Working Group criteria [10,11]. IgH gene rearrangement studies by Polymerase Chain Reaction (PCR) did not identify a clonal B-cell population. Of note, a prominent clonal population was detected by a PCR study performed retrospectively on the previous BM sample in which the neoplastic plasma cell population had been identified by morphology and immunohistochemistry.

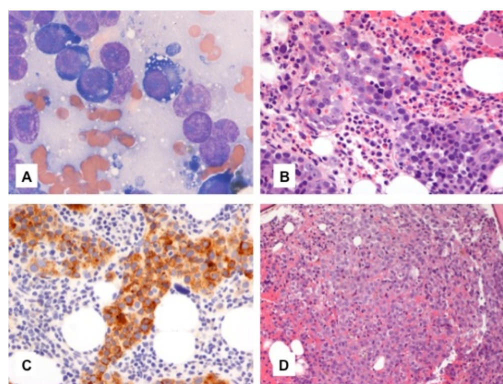

Figure 1: Bone marrow morphology in Case 1. A) Bone marrow aspirate with erythroid leukemic blasts, morphologically similar to plasmablasts (Wright-Giemsa, 1000X). B) Bone marrow core biopsy section with sinusoidal clustering of malignant erythroid precursors (Hematoxylin and Eosin, 400X). C) Bone marrow core biopsy section showing expression of CD71 by malignant erythroid cells (400X). D) Follow-up bone marrow core biopsy with diffuse replacement of normal elements by erythroid blasts (Hematoxylin and Eosin, 200X)

Karyotypic analysis revealed hyperdiploidy in all 20 metaphases examined (Figure2):57,X,–X, +1,+2,+6,+8,+10,+13,+15,+15,+21,+21,+2mar. The clone showed trisomy of chromosomes 1, 2, 6, 8, 10, and 13; tetrasomy of chromosomes 15 and 21; and gains of two marker chromosomes of unknown origins. Interphase FISH analysis confirmed the presence of trisomies 1, 8, and 13 in 65-69% of the cells examined. No structural abnormalities were identified.

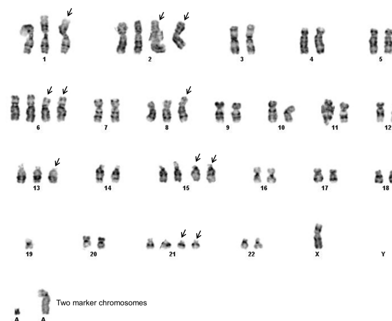

Figure 2: G-banding karyogram in Case 1 showing a hyperdiploid karyotype at the relapsed sample. Arrows point to abnormal chromosomes with gains of a variety of chromosomes and two marker chromosomes.

Based on these results, a diagnosis was made of t-MN, morphologically of the pure erythroid leukaemia type. The patient was started on decitibine. A day-33 BM biopsy showed a markedly hypercellular marrow that was almost completely replaced by erythroid blasts (Figure 1d). The patient elected to receive palliative and supportive treatment, and expired shortly.

Case 2

The patient is a 64-year old male with a diagnosis of stage III-A IgG kappa MM that had a hyperdiploid karyotype: 53,XY, +3,+5,+9,+11,+15,+15,+19[2]/46,XY[18]. He was treated on a total therapy 2 regimen 12 followed by bortezomib, lenalidomide, and dexamethasone maintenance. After two years, he returned to the clinic with extreme fatigue. The CBC revealed WBC 4.29 K/μL, haemoglobin 9.7 g/dL, platelet count 32 K/μL. A BM evaluation at this time revealed dyserythropoiesis in addition to persistent involvement by MM. Metaphase cytogenetics demonstrated the previously identified hyperdiploid MM karyotype. FISH studies were not performed at this time. Maintenance therapy was withheld and he was treated symptomatically. The patient returned after 4-months with worsening symptoms at which time the laboratory tests showed WBC 2.51K/μL, Hgb 7.7 g/dL, platelet count 28 K/μL, LDH 8,397 IU/L, AST 376 IU/L, ALT 96 IU/L, Alkaline phosphatase 176 IU/L. Magnetic Resonance Imaging (MRI) and Positron Emission Tomography-ComputedTomography (PET-CT) scan studies revealed hepatosplenomegaly with possible extramedullary MM involvement.

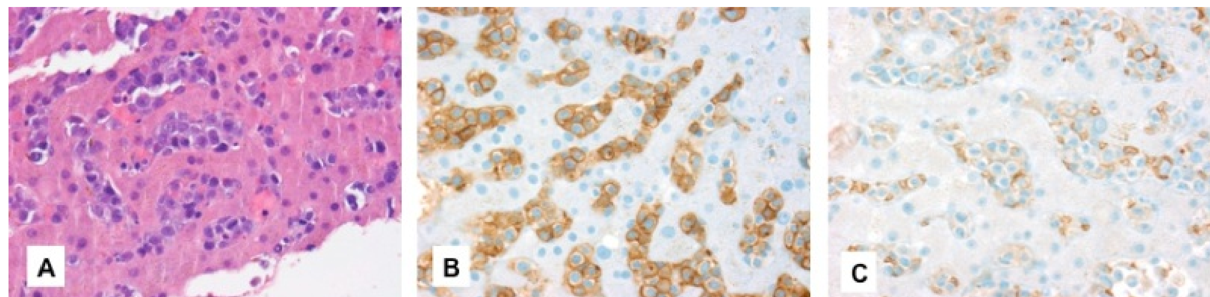

Figure 3: Liver biopsy morphology in Case 2. A) Liver with sinusoidal infiltration by leukemic blasts (Hematoxylin and Eosin, 400X). B) CD117 expression on leukemic blastsin the liver (400X). C) Glycophorin A expression on the leukemic blasts within the liver sinusoids (400X).

A liver biopsy showed sinusoidal infiltration by large cells with a blastic morphology (Figure 3A). By immunohistochemical staining the cells were CD138 negative, but marked with CD117 (Figure 3B) and focally with glycophorin A (Figure 3C). A BM biopsy showed a hypercellular marrow with extensive (~70% of the cellularity) involvement by large blastic cells (Figure 4A) that expressed CD117, glycophorin A (weak and variable expression) and E-Cadherin (strong and uniform) (Figure 4B). A PAS stain demonstrated intense PAS-positive cytoplasmic globules. The remaining cells (~30% of the cellularity) had a plasmablastic appearance (Figure 4C), and were CD138 positive (Figure 4D) with kappa light chain restriction. On the aspirate smear, there was an intermingling of leukemic blasts and immature-appearing plasma cells (Figure 4E).

Bonemarrowkaryotypeshowed2clones:52~53,XY,+3,+5,del(6)(q25),+9,+11,+15,+15,19[cp13]/43~45,XY,del(1)(p13p22),?t(1;2)(p32:q33),del(7)(p12p15),add(8)(p22),del(9)(q12q22),add(13)(p11.1),-16,add(16)(q?22),add(19)(p13.1),del(?20)(p11.2), del(?21)(q21)[cp6]. One clone was hyperdiploid consistent with the patient's known MM clone (Figure 5A), and the other had complex anomalies including multiple deletions involving chromosomes 1, 7, 9, 16, 20 and 21(Figure 5B). Cytogenetics analysis of the liver biopsy revealed a karyotype similar to the second clone (Figure 5C). The second clone apparently represents the leukemia clone. A diagnosis of t-MN, morphologically of the pure erythroid leukaemia type was rendered. Based on IMWG criteria 10,11, he had stable MM at the time of onset of t-MN.

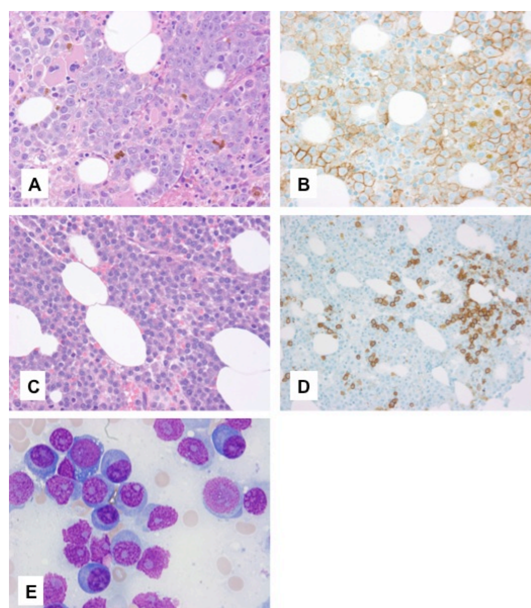

Figure 4: Bone marrow morphology in Case 2. A) Bone marrow core biopsy with erythroid leukemic blasts (Hematoxylin and Eosin, 200X). B) Bone marrow core biopsy section; expression of E-Cadherin by malignant erythroid cells (400X). C) Bone marrow core biopsy with sheets of plasmablasts (Hematoxylin and Eosin, 200X). D) Bone marrow core biopsy; CD138 positivity in plasmablasts (400X). E) Bone marrow aspirate showing admixed population of leukemic erythroblasts and neoplastic plasmablasts (Wright-Giemsa, 1000X).

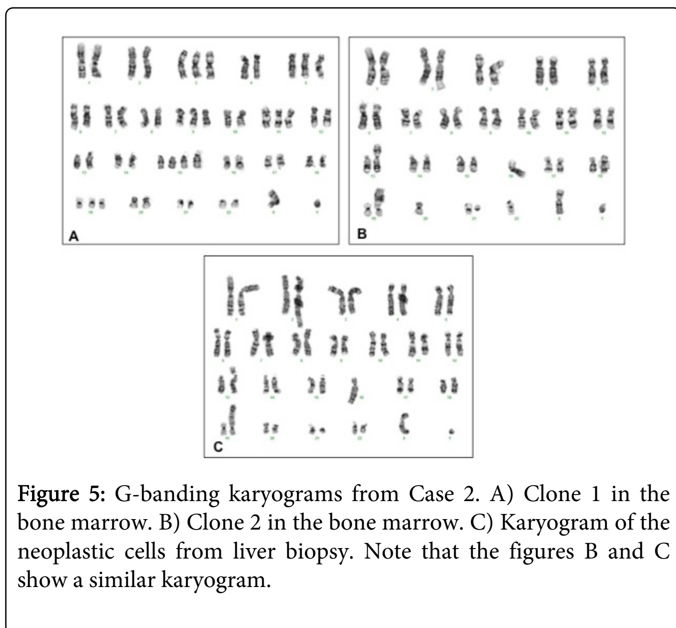

Figure 5: G-banding karyograms from Case 2. A) Clone 1 in the bone marrow. B) Clone 2 in the bone marrow. C) Karyogram of the neoplastic cells from liver biopsy. Note that the figures B and C show a similar karyogram.

Discussion

Presence of cytopenia, morphological evidence of dysplasia, and characteristic cytogenetic abnormalities allows easy recognition of t-MDS even when the primary neoplasm is another hemato-lymphoid malignancy. When morphological dyspoiesis is equivocal, or when blasts are not increased, clonal cytogenetic abnormalities, especially those commonly described in myelodysplasia [13], are evidence of development of t-MN. Coexistent primary and therapy-related neoplasms can be difficult to distinguish especially when their morphologies overlap such as in t-AML following ALL, t-ALL following AML, or t-AML following AML. The plasma cells in MM can have diverse morphologies [14] including the easily recognizable mature or 'Marshalko-type", small lymphocyte-like type, or the immature plasmablastic morphology. The mature 'Marshalko-type', with their eccentric nuclei, condensed clock-face chromatin, deep blue cytoplasm, and perinuclear hoff, closely resemble basophilic erythroblasts, whereas the plasmablastic myeloma cells can be virtually indistinguishable from proerythroblasts.

PEL developing as t-MN in patients treated for MM is very unusual [9]. The distinction of a PEL-morphology from MM can be challenging, particularly in cases where the neoplastic plasma cells have a blastic morphology, or when the MM progresses from a low-grade to a high-grade neoplasm [9,15,16]. In such instances demonstration of erythroid lineage can be facilitated by immunohistochemistry. Erythroid antigens include hemoglobin A [16], glycophorin A [17], CD71 [17,18], E-cadherin [19] and spectrin [20]. Hemoglobin A and glycophorin A are expressed by non-nucleated red blood cells and more mature erythroid precursors, but not by early erythroblasts. CD71 is an integral homodimeric membrane glycoprotein expressed on a variety of cells including placental syncitioblasts, basal keratinocytes, myocytes, endocrine pancreatic cells, hepatocytes, and erythroid cells [21], and is involved in the uptake of iron-transferrin complexes by the cells. The density of transferrin receptors is highest on the erythroid precursors, including the early, intermediate and late normoblasts, and is decreased in the reticulocytes [22]. This high expression of CD71 on the erythroid precursors makes it a particularly useful immunohistochemical marker for evaluating erythroid precursors in the BM [18]. In a study that compared immunohistochemical expression of CD71, glycophorin A, and hemoglobin A on 65 BM biopsies from normal and a variety of hematolymphoid neoplasms and metastatic carcinoma, found that CD71 was expressed exclusively on the erythroid precursors, and not on myeloid or lymphoid leukemic blasts, or neoplastic plasma cells [18]. In comparison with the other erythroid markers, CD71 did not mark mature red cells resulting in a clean background that facilitated identification of erythroid precursors. In our paper, the neoplastic cells in Case 1 were identified by strong CD71 expression by immunohistochemistry and by flow cytometry, whereas the other erythroid-lineage markers were either not detected (hemoglobin A), or expressed only focally and weakly (glycophorin A). Additionally, PCR studies excluded the presence of clonal plasma cell or B cell populations. These combined findings confirmed the erythroid lineage of the neoplastic cells. This pattern is consistent with the abnormal maturation arrest in the malignant cells. One caveat in solely relying on CD71 as an erythroid marker is that it can also be expressed by some other highly proliferative neoplasms such as diffuse large B-cell lymphoma [23-25], in particular, by flow cytometry phenotyping. Therefore, additional erythroid markers are recommended for confirmation of erythroid lineage initially identified by CD71. Other sensitive and robust markers for the erythroid lineage are E-cadherin [26], and more recently, ALDH (Aldehyde Dehydrogenase), CA I (carbonic anhydrous isoenzyme1), and CD2AP (CD2-associated protein) [27]. E-cadherin exclusively marks proerythroblasts, and is particularly useful when erythropoiesis is left-shifted with an increased number of proerythroblasts that may be negative for glycophorin A and hemoglobin A. This situation is reflected in Case 2 wherein the blasts were strongly positive for E-cadherin, but negative for glycophorin A. Similar to CD138, which is specific for plasma cells only in the context of the hematopoietic lineage, E-cadherin is specific for the (early) erythroid precursors only in the context of the hematopoietic lineage. Therefore, when the neoplasm is very poorly differentiated, other lineage markers including cytokeratins should be part of the panel of antibodies used for immunohistochemistry.

The two cases presented in this report exemplify the role of cytogenetics in the diagnostic process. In the first case, presence of a hyperdiploid karyotype added to the diagnostic challenge by misdirecting the focus towards high-grade transformation of MM. To the best of our knowledge, PEL with hyperdiploid karyotype occurring as a t-MN following MM has not been previously reported. This association is noteworthy because whereas hyperdiploidy, especially high hyperdiploidy (>49 chromosomes) is rare in AML, occurring in <1% of patients [28-30], nearly 50%-60% of MM patients have a hyperdiploid karyotype. Out of 44 reported cases of AML with hyperdiploidy where FAB subclassifiction was provided [31-33], only one is described as erythroleukemia (AML-M6) [32]. Conversely, in a series evaluating 75 patients with erythroleukemia, including both de novo and therapy-related forms, 11 patients (19%) had a hyperdiploid karyotype [34]; two were therapy-related, but none had a prior history of MM.

The patterns of chromosome gains in AML and MM are different and non-random. In AML, chromosomes 8, 21, and 13 are reported as the most frequently gained chromosomes, and chromosomes 5, 7, 16, and 17 are least likely to be gained [29]. In MM, hyperdiploidy occurs due to multiple trisomies of the odd numbered chromosomes 3, 5, 7, 9, 11, 15, and 19. Trisomy 8 and trisomy 21 are much more common in

AML than in plasma cell neoplasms. In MM trisomy 8 usually indicates development of a therapy-related myeloid neoplasm, or a concurrent myeloproliferative neoplasm [36-38]. Identification of specific trisomies is important in the distinction of hyperdiploidy of MM from those occurring in AML. Importantly, in contrast to AML, hyperdiploidy in MM is generally associated with longer survival [35].

Both the patients described in this paper received lenalidomide. Whereas no causal association can be inferred from two isolated cases, this therapeutic history is important, especially in the context of several studies suggesting a higher incidence of second malignancies following lenalidomide maintenance [39-41]. The exact mechanism(s) by which lenalidomide might contribute to development of secondary malignancies remain largely unknown; results of a recent meta-analysis show an increased risk with lenalidomide in combination with oral melphalen [42]. Whether genetic variation in drug metabolism and other host-related factors that are known to effect influence of other cytotoxic therapies [43] contribute to the effect of lenalidomide as well is currently unclear. Data from a large population-based study [44] has demonstrated however, that in addition to the extrinsic (drug-), and intrinsic (host-) related factors, there may be disease- related factors that predispose some treatment naïve patients with monoclonal gammopathy of uncertain significance, or certain molecular subtypes of MM to develop t-MN.

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