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Trans-differentiation of plasma cell neoplasm to acute myeloid leukemia with monocytic features: Case report of divergent phenotype with identical genotype

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ABSTRACT

Myeloid malignancies following treatment for plasma cell neoplasms (PCN) are infrequent but is a serious complication, often exhibiting complex karyotype and *TP53* mutations. Plasma cell myeloma lineage switch to a myeloid malignancy with evident clonal relatedness is seldomly reported. Here, we report a unique case of acute myeloid leukemia with monocytic differentiation that shares clonal features with an antecedent plasma cell myeloma with t(4;14)(*FGFR3::IGH*). This phenomenon differs from therapy-related myeloid neoplasm arising from an unrelated clone and underscores the need to elucidate the role of mutations in pathways such as MAPK (e.g., *BRAF* and *KRAS*) into lineage plasticity.

1. Introduction

Standard therapeutic modalities for PCN, including autologous hematopoietic stem cell transplantation (auto-HSCT), have been associated with increased risk for therapy-related myeloid neoplasms (t-MN) such as acute myeloid leukemia (t-AML) [1–3]. The etiology for the development of these myeloid neoplasms is multifactorial [3]. In this context, emerging myeloid neoplasms that are clonally related but phenotypically divergent from the antecedent PCN are rarely reported [4]. This phenomenon is known as trans-differentiation and principally reported in the context of the transformation of B-cell lymphoma to histiocytic neoplasm [5].We report herein detailed clinicopathologic characteristics of a patient with a long-standing history of PCN who underwent trans-differentiation to clonally related AML with monocytic features involving bone marrow and extramedullary tissue.

2. Case

The patient was a 70-year-old female with a PCN diagnosed about 5 years before the AML presentation. The patient presented with cytopenia. She had a white blood cell count (WBC) of 1.7 $\times$ 10^3/mcL, hemoglobin (Hgb) level of11.7 g/dl and a normal platelet count. A bone marrow (BM) biopsy was notable for 22 % kappa-restricted monoclonal plasma cells. There was no evidence of myelodysplastic syndrome/neoplasm (MDS) by morphologic and cytogenetic assessments. The karyotype was normal. Serum protein electrophoresis revealed a kappa paraprotein of 1.5 gr/dl with free kappa/lambda ratio of 56.3; renal function and calcium were reportedly normal. There were no lesions in the skeletal survey. Overall, the presentation was consistent with a smoldering multiple myeloma (SMM).

Over time, the paraprotein levels increased, and a repeat BM biopsy a year following the initial one, revealed an increase of the monoclonal kappa-restricted plasma cells (54 %). Mutational analysis of the BM was notable for a *BRAF* mutation; however, further details such as exact variant mutation and variant allele frequency (VAF) are not available to us, and the patient was initially treated with trametinib. Ultimately, the patient underwent induction treatment with 4-cycles of revlimid, velcade, and dexamethasone. The patient achieved good partial response and proceeded to auto-HSCT conditioned with Melphalan 140mg/m^2. The patient achieved at day 60 post-auto-HSCT near complete remission (nCR) and positive serum immunofixation electrophoresis (SIFE). The patient received ixazomib as maintenance for two years. The patient was then transitioned to daratumumab(monthly), lenalidomide (day 1–21), and dexamethasone due to disease progression. Lenalidomide was discontinued due to myelosuppression. Pancytopenia was persistent, and a PET scan revealed innumerable lytic lesions and the presence of

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hypermetabolic lymph nodes. Patient received radiation treatment to the femur for pain management.

Hematological parameters worsened; it was noted that her WBC was 1.40 × 10^3/mcL, Hgb 10.5g/dL, MCV 104fL, and platelet count 42.0 × 10^3/mcL and the differential showed circulating blasts. Further workup, including BM biopsy (5 years from the initial diagnosis of smoldering myeloma) was consistent with AML with monocytic features without evidence of residual PCN. Concurrent skin biopsy demonstrated infiltration by AML cells.

Serum immunofixation was notable for a faint IgG kappa band; the free kappa/lambda ratio was 28, and beta-2-microglobulin level was normal.

Given the patient's low-performance status (ECOG score-2) status and cytopenia, the patient was treated with a combination of hypomethylating agent (azacitidine) and venetoclax. After the first cycle of treatment, the bone marrow biopsy was hypocellular with residual AML by morphology (5–10 % blasts), had two metaphases with residual complex karyotype, and initial resolution of skin involvement. The patient received a second cycle of azacitidine and venetoclax and a subsequent bone marrow biopsy revealed persistent AML (50 % blasts). Eventually, the patient was transitioned to supportive care/hospice.

The malignant plasma cells in initial and follow up marrow samples were of IgG/kappa secretory type and exhibited the following immunophenotype: CD19-, CD27-, CD38+, CD56+, CD81+, CD117+, CD138+, and kappa+, and harbored a normal karyotype. - Fluorescence *in-situ* hybridization (FISH) performed on CD138-enriched BM samples identified genetic abnormalities including t(4;14) (*FGFR3::IGH*) and deletion 13q. *BRAF gene* mutation was detected by next generation sequencing (NGS) molecular test. Of note, del(13q) was detected only in the first BM seen at our institute but not thereafter, and deletion *TP53* and t(14;16) were not detected (see supplementary figure-1 for a detailed timeline). The leukemic cells of AML exhibited prominent monocytoid cytomorphology including large cell size, irregular nuclei with prominent nucleoli, abundant cytoplasmic vacuoles (Fig. 1 a-b), expressed CD11b,CD11c, CD13 (partial),CD56,CD64, and HLA-DR (partial), and were negative for CD34,CD117, and CD33 by 10-color multiparameter flow cytometry assay performed on the BM sample at presentation. Immunohistochemistry (IHC) was performed on BM core biopsy (Fig. 1 c-d)and abdominal skin biopsy the same leukemic cells harboring identical disease and showed the following staining pattern: CD30-,CD43+,CD56+,CD68+,CD138-,CD163-, cytokeratin AE1-3 (-), IgG-, lysozyme+, MUM1-, myeloperoxidase (MPO)+, OCT2+ (partial), PAX5-, and TdT-. The karyotypic analysis of the AML BM sample showed an abnormal complex karyotype that was significant for t(4;14)(p13; q32) (Fig. 2) and multiple numerical and structural changes (table 1). NGS assay, 75 myeloid neoplasm-related genes, performed on the BM showed *BRAF* c.1397G>C (p.G466A) detected in ~14% of alleles and *KRAS* c.35G>T (p.G12V) in ~27% of alleles.

3. Discussion

Trans-differentiation or lineage switch of hematologic neoplasms is an uncommon phenomenon and rarely reported in the context of PCN/PCM. The myeloid neoplasms, and seldomly B lymphoblastic leukemia, that are encountered in the context of post-therapy, including post-auto-PBSCT, for PCN represent therapy-related/clonally unrelated hematolymphoid neoplasm [6]. The combination of chemotherapy that includes melphalan, utilized within the auto-HSCT therapy, is a key risk factor for t-MN. Commonly, Therapy-related MNs are often associated with a complex karyotype and *TP53* mutation [3]. Studies have suggested that t-MN evolves from a pre-existing hematopoietic clone harboring a leukemic driver single nucleotide variant (SNV) that escapes high-dose melphalan conditioning prior to auto-HSCT [2]. Whether t-MN derived from a pre-existing hematopoietic clone prior to chemotherapy or an acquired hematopoietic clone after treatment, clonality relatedness between t-MN and PCN is not typical.

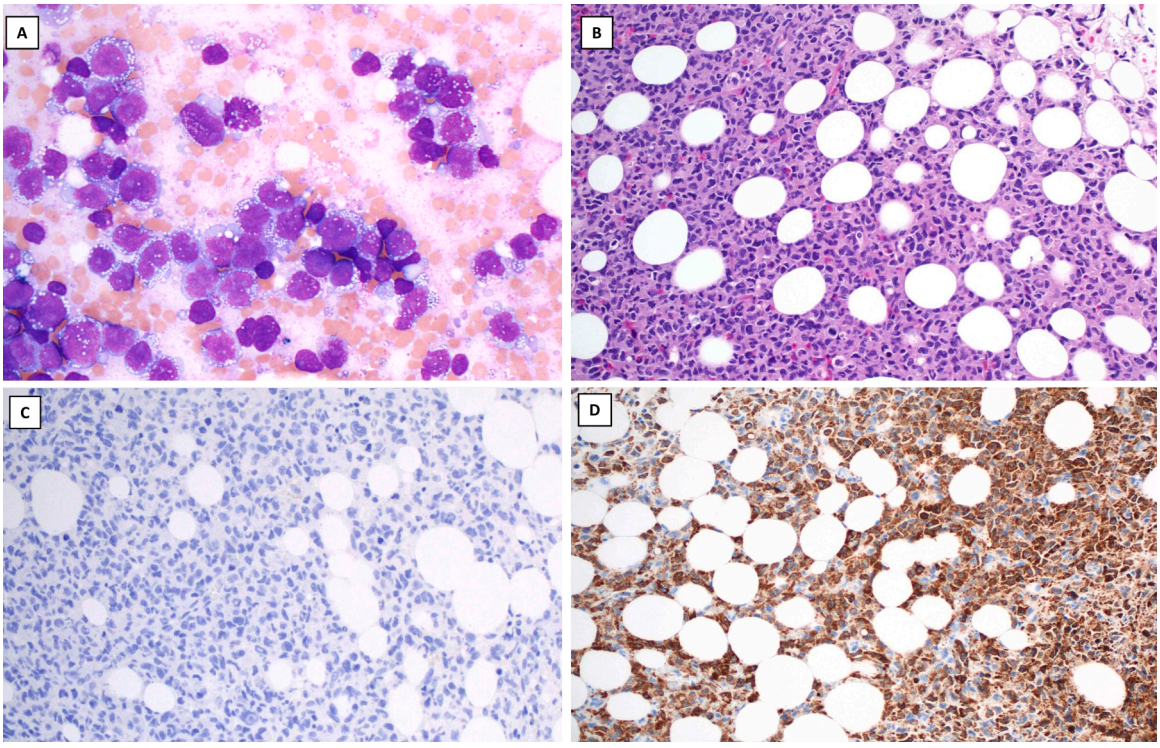

Fig. 1. The leukemic cells of AML exhibited a prominent monocytoid appearance, including large cell size, irregular nuclei with prominent nucleoli, and abundant cytoplasmic vacuoles (A), and are the dominant population of the hypercellular marrow occupying 90 % of the core cellularity (B). These cells are negative for CD138 (C), and strongly express MPO (D). Bone marrow biopsy: Wright-Giemsa-stained bone marrow aspirate (40X) **(A),** H&E stained core section (20X)**(B),** CD138 IHC (20X)**(C),** and MPO IHC (20X)**(D)**.

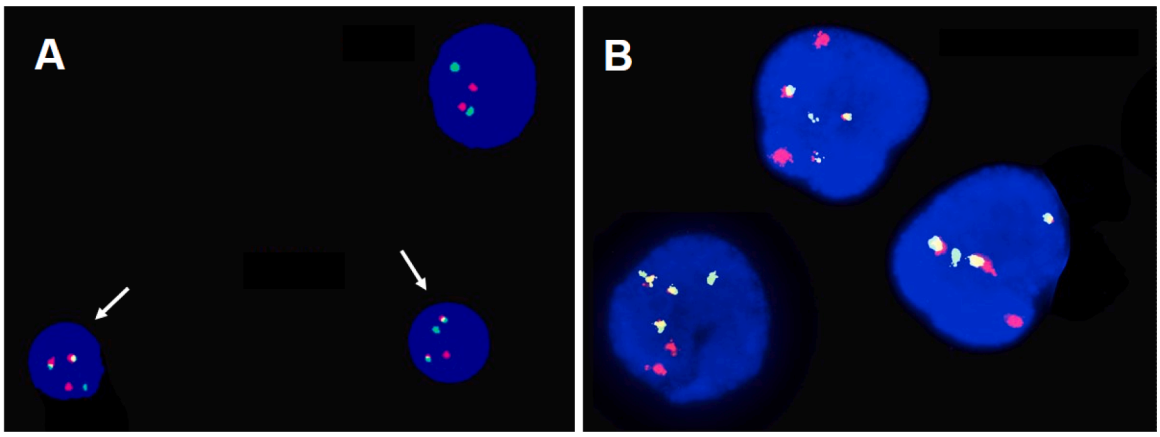

Fig. 2. Dual color, dual fusion probe for t(4;14)(p13;q32) (*FGFR3::IGH* fusion) on plasma cells (previous plasma cell myeloma marrow sample)**(A)** and acute myeloid leukemia cells (most recent transdifferentiated AML marrow sample) **(B).** Nuclei are stained by 4′,6-diamidino-2-phenylindole (DAPI, blue). Anaphase FISH using dual fusion probes for 4p and 14q showed a t(4;14)(p16;q32) corresponding to a rearrangement involving the *FGFR3* gene on chromosome 4 and the IgH gene on chromosome 14. Yellow fusion signals are seen on the rearranged chromosomes 4 and 14, which reflects a balanced translocation. **(A)** The abnormal cells containing the *FGFR3::IGH* fusion are detected in 60 % of CD138+ enriched plasma cells (arrow). A normal cell consists of two red (*FGFR3*) and two green (*IGH*) signal pattern. The round nuclei appearance reflects plasma cells origin. **(B)** The abnormal cells containing *FGFR3::IGH* fusion (three fusion signals) and gain of one extra copy of 4p *FGFR3* (red) are seen in 76 % of cells. These cells represent the evolution of the original plasma cell abnormality with additional clonal changes. The nuclei with irregular and folded appearance represent blasts. Microscope objective at 100X.

The patient had a long-standing history of high-risk PCM with t(4;14) *FGFR3::IGH* fusion and mutations affecting the mitogen-activated-protein-kinase (MAPK) pathways including *BRAF* and *KRAS*. The disease was treated with standard therapeutic modalities including auto-HSCT 5 years before the presentation of AML with dominant monocytic features and similar genetic abnormalities. Interestingly, t(4;14) was identified in the initial PCN cells as well as the subsequent AML blasts supporting a clonal relatedness and emergence from the same hematopoietic stem cell clone in a process known as trans-differentiation. We do not know the exact *BRAF* mutation variant at the time of PCN diagnosis, but given the presence of t(4;14), it could be inferred the possibility of the same *BRAF* mutation existed in both. Studies have shown that clonal stem cells with *BRAF* mutation can evolve into multiple *de-novo BRAF* mutated neoplasms with different lineages that manifest either simultaneously or at different time points [7].

Lineage-plasticity between B-lineage cells and myelomonocytic/histiocytic cells with *BRAF* mutation was demonstrated in prior studies [7]. The environmental milieu and the upregulation and downregulation of lineage-specific genes would determine the lineage switch. For example, the downregulation of B-cell transcription factors including PAX5, E2A, and EBF, and the upregulation of PU.1 leads to myelomonocytic lineage commitment [7,8]. CD19 positive B220^{-} cells from adult mouse bone marrow can transform into macrophages when cultured in the presence of IL-3, IL-6, and GM-CSF [7,8]. There are several reported cases of secondary trans-differentiated histiocytic/monocytic disorders arising from B-cell lymphomas with genetic mutations enriched in the *BRAF*/MAPK pathway [5]. However, such trans-differentiation of PCN has been rarely reported. Gralewski *et.al.* reported a patient with PCN that transdifferentiated into a "myeloid sarcoma" (extramedullary involvement by myeloid neoplasm) with "tumor cells derived from monocyte-macrophage-lineage" [4]. Interestingly, the reported and current patients shared similar findings; both had PCN carrying high-risk cytogenetic profile and *BRAF* mutation, which may have role in this lineage switch. Both cases had evidence of extramedullary involvement, raising the possibility that the molecular aberrations leading to trans-differentiation also led to the infiltration of organs by leukemic cells. However, the pathways leading to myeloid sarcomas are currently not well understood. Of note, response to HMA and venetoclax was only transient, underscoring the aggressive features of the myeloid neoplasm.

In addition, *BRAF* mutation is uncommonly associated with AML [9], and the *BRAF* mutations observed in both patients (G466A and G469V) differ from the V600E typically found in hairy cell leukemia, histiocytosis, and melanoma. The clinicopathologic and genetic features of both patients are summarized in Table 1.

KRAS, NRAS and *BRAF* mutations are observed in a sizeable percentage of patients with PCNs and are associated with reduced time of response/probability of complete remission [10]. BRAF inhibitors have shown efficacy in some *BRAF* (V600E) mutated neoplasms such as hairy cell leukemia or melanoma. BRAF inhibitors are not standard of care in the treatment of PCN, but studies with RAS-RAF-MEK pathway inhibitors have been reported [10]. We acknowledge the limited records of diagnosis and early treatment of the PCN, lack of detailed molecular data, and details regarding trametinib (MEK-inhibitor) use.

4. Conclusion

Myeloid/monocytic trans-differentiation of PCN is rarely encountered. The recognition of overlapping features, including molecular and chromosomal aberrations, highlights the importance of elucidating lineage plasticity and molecular pathways that promote extramedullary tissue infiltration. Regardless, this phenomenon appears to be associated with dismal outcomes. Vigilance in studying this phenomenon could further provide prognostic information and inform the best therapeutic strategies.

CRediT authorship contribution statement

Saja Asakrah: Writing – original draft, Methodology, Investigation, Data curation. **Kristin K. Deeb:** Writing – review & editing, Data curation. **Nikolaos Papadantonakis:** Writing – review & editing, Investigation, Data curation. **George Deeb:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 1
The clinicopathologic and genetic features of plasma cell neoplasm/myeloma (PCN/PCM) underwent trans-differentiation to myeloid sarcoma (MS) and acute myeloid leukemia (AML) in two patients.

	Patient reported by Gralewski et al	Current patient
Patient	60 Y/O M	74 Y/O F
PCN immunophenotype (IHC and MFC)	CD20+ (partial) CD38+ CD138+ MUM1+ lambda+ / CD19- CD27- CD45- CD56- CD81-	CD38+ CD56+ CD81+ CD117+ CD138+ kappa+ / CD19- CD27- CD45-
PCN karyotype	Anormal complex	Normal karyotype
PCN FISH	Not available	del(13q) (in 17 of 50 cells) and t(4;14) (in 30 of 50 cells)
PCN molecular genetic testing	*IGH*::*MAF* gene rearrangement, *BRAF* G469V and G466A, *KRAS* A146V, *MAP3K6* Q943, *CDKN2A/B* loss, *TRAF3* R505, *PTPRO* E379K	*BRAF* (no further characterization available)
PCN therapy	Induction → cytoreduction → melphalan-based auto-HSCT	Induction → cytoreduction → Trametinib →RVd → auto-PBSCT conditioned with Melphalen → Ixazomib maintenance
Time to trans-differentiation post-auto-HSCT	12 months	~ 51 months
Trans-differentiation diagnosis	MS (monocyte-macrophage derived) (essentially extramedullary involvement)	AML with monocytic features (medullary and extramedullary involvement)
Trans-differentiation immunophenotype (IHC and MFC)	CD11b+ (bright) CD14+ (bright) CD33+ CD36+ (variable) CD45+ CD68+ CD163+ HLA-DR+ MPO+ (subset) lysozyme+ / CD34- CD56- CD117- CD138- PAX5- P53- MUM1- S100-	CD11b+ CD11c+ CD13+ (partial) CD43+ CD45+ (dim) CD56+ CD64+ CD68+ HLA-DR+ lysozyme+ MPO+ OCT2+ (partial) / CD3- CD20- CD30- CD33- CD34- CD117- CD138- CD163- cytokeratin AE1/3- IgG- MUM1- PAX5- TdT-
Trans-differentiation karyotype	Normal (limited by low mitotic index)	Abnormal complex, including t(4;14)(p13;q32), in 10 cells, and normal in 1 cell
Trans-differentiation FISH	t(14;16)(q32;q23) [*IGH*::*MAF*]	t(4;14) [*IGH*::*FGFR3*] (76% of cells)
Trans-differentiation molecular genetic testing	*IGH*::*MAF* gene rearrangement, *BRAF* G469V *KRAS* A146V, *MAP3K6* Q943, *CDKN2A/B* loss, *NF1* R2450	*BRAF* c.1397G>C (p.G466A) (VAF: 14%), KRAS c.35G>T (p.G12V) (VAF 27%)
Trans-differentiation therapy	induction chemotherapy (7 + 3 regimen of cytarabine and idarubicin)	Hypomethylating agent (HMA)-Azactidine and Venetoclax
Follow up	Persistent/refractory disease with soft tissue involvement and the patient died shortly after 2 months	Persistent/refractory disease with extramedullary involvement and last follow-up about 4–5 months after the AML presentation

HSCT = Hematopoietic stem cell transplantation. MPO = Myeloperoxidase. VAF = Variant allele frequency.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2025.100504.

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