

Case Report

Novel Report of a Clonal Myeloproliferative Disorder with Prominent Histiocytic Differentiation

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Abstract

A previously healthy 68-year-old woman presented with constitutional symptoms and pancytopenia. A bone marrow biopsy revealed extensive infiltration by mature histiocytes with no significant cytologic atypia. The residual marrow had active trilineage hematopoiesis and no overt dysplasia in all three lineages. Initial fluorescence in situ hybridization (FISH) studies detected 20q deletion in 84.5% of the marrow cells. Additional FISH studies on Wright-Giemsa stained bone marrow aspirate smears revealed a common 20q deletion between the histiocytes and the granulocytes, whereas the erythroid cells were negative for such a deletion. These findings suggested that the histiocytes and granulocytes arose from the same progenitor cell and were clonal in nature.

INTRODUCTION

A number of reactive and neoplastic disorders may show extensive bone marrow involvement by histiocytes. Reactive diseases include granulomatous infections, lysosomal storage disorders, and hemophagocytic lymphohistiocytosis. Neoplastic diseases associated with bone marrow histiocytosis include Langerhans cell histiocytosis, histiocytic sarcoma, and Erdheim-Chester disease. Metastatic lymphoma or carcinoma in the bone marrow may also induce an abundant histiocytic reaction. We present a case of extensive bone marrow histiocytosis, in which a shared 20q deletion between the histiocytes and the granulocytes revealed a clonal relationship. Therefore, this case reports a novel entity and expands the disease spectrum of bone marrow histiocytosis.

CASE PRESENTATION

A previously healthy 68-year-old female had no significant past medical history, and recently she presented to an outside hospital with a one-month history of fatigue, low-grade fevers and dry cough. She was admitted for these symptoms and treated for presumed aspiration pneumonia. Three days after completing her antibiotic course she developed weakness, nausea and vomiting, and subjective fevers and chills. She was re-admitted to the outside hospital. At that time on physical exam she had no pallor or splenomegaly. Clinical laboratory studies revealed severe anemia (Hemoglobin 79 g/L, reference

range 121-163 g/L), mild leukocytosis (White blood cell count $13.6 \times 10^9/L$, reference range $4.0-11.1 \times 10^9/L$), and marked thrombocytopenia (Platelet count $5 \times 10^9/L$, reference range $150-400 \times 10^9/L$). A peripheral blood smear showed numerous schistocytes. Hematology was consulted and developed a wide differential including thrombotic thrombocytopenic purpura (TTP), idiopathic thrombocytopenic purpura (ITP), acquired hemophagocytic lymphohistiocytosis (HLH), heparin-induced thrombocytopenia (HIT) and leukemia. The patient was treated with steroids, IVIG (2 doses), and multiple transfusions without improvement of her thrombocytopenia or anemia. Per review by the outside hospital the bone marrow biopsy demonstrated histiocytic phagocytosis and trilineage hyperplasia. Flow cytometry was normal. Given the marrow findings in combination with the patient's fevers and splenomegaly the possibility of hemophagocytic lymphohistiocytosis (HLH) was also considered by the outside institution. As the patient was failing to improve she was transferred to our hospital for further work-up and care.

Following admission to our hospital she rapidly developed respiratory distress requiring intubation and mechanical ventilation. She also developed a disseminated intravascular coagulation constellation, including an elevated prothrombin time (29.3 seconds, reference range 11.4-14.4 seconds), low fibrinogen (125 mg/dL, reference range 150-400 mg/dL), elevated D-dimer (7.18 $\mu\text{g}/\text{mL}$, reference range 0-0.5 $\mu\text{g}/\text{mL}$), and elevated lactate dehydrogenase (1,231 U/L, reference range 98-192 U/L). Her

anemia (Hemoglobin 76 g/L) and thrombocytopenia ($2.0 \times 10^9/L$) persisted despite repeat transfusions. On day three at our hospital she developed a fulminant sepsis-like picture with fever, hypotension, tachycardia, and leukocytosis. Clinical image studies revealed multifocal acute infarcts in the brain, gastrointestinal tract, spleen, liver and kidneys. The patient passed away on hospital day five. An autopsy was not performed.

MATERIALS AND METHODS

All immunohistochemical stains were performed on formalin-fixed, paraffin-embedded bone marrow core biopsy sections. The antibodies utilized in this case included CD1a, CD3, CD20, CD30, CD34, CD68, S100, and cytokeratin AE1/AE3. The antibodies, their clones, dilutions, antigen retrieval methods, and manufacturers were summarized in Table 1. Special stains with acid-fast bacilli (AFB), Gömöri methenamine silver (GMS), and periodic acid-Schiff with diastase (PAS-D) were also performed.

Cytogenetic studies were performed on the bone marrow aspirate sample on GTG-banded (Giemsa/trypsin) metaphases and the karyotypes were expressed according to the international guidelines. Interphase FISH analyses were performed on the bone marrow aspirate specimen with the probes covering chromosomal 5, 7, 8, 13 and 20q sequences. Since the initial FISH Studies detected 20q deletion in 84.5% of the marrow cells, we performed additional FISH assays using the 20q probe on the Wright-Giemsa stained bone marrow aspirate smears to map the 20q deletion to specific marrow cell types. Multiple images were taken on the Wright-Giemsa stained marrow aspirate smears to match the cells on the same slides after FISH probe hybridization.

RESULTS

Peripheral blood and bone marrow findings

The peripheral blood smear showed marked normochromic and normocytic anemia, frequent schistocytes, and marked thrombocytopenia. No atypical lymphocytes, dysplastic granulocytes or circulating blasts were noted.

The bone marrow aspirate smears and core biopsy showed a hypercellular marrow (80% cellularity) with infiltration by sheets of histiocytes that accounted for approximately 70% of marrow cellularity (Figure 1a). Residual normal marrow tissue with normal cellularity and active trilineage hematopoiesis was present focally (Figure 1b). The histiocytes did not show

significant cytologic atypia with round to oval nuclei and abundant pale cytoplasm (Figure 1c). Frequent cytoplasmic vacuoles and occasional hemophagocytic activities were present (Figures 1d-1f). On the marrow aspirate smears, the granulocytes, erythroid precursors and megakaryocytes matured in an orderly and complete fashion without overt dysplasia. No metastatic tumor or obvious infectious process was noted.

By immunohistochemical staining, the histiocytes were positive for CD68 and negative for CD1a and S100. No abnormal lymphoid or blastic populations were shown by CD3, CD20, CD30 and CD34 staining. The cytokeratin stain was negative. No infectious organisms or abnormal intracytoplasmic deposits were identified with AFB, GMS and PAS-D special stains.

Cytogenetic and FISH Studies

Conventional cytogenetic studies showed multiple structural chromosomal abnormalities in 18 of the 20 cells analyzed. Eleven cells showed one or more of the following: unknown additional material on the long arm of chromosome 5, an unbalanced translocation between chromosomes 5 and 20 resulting in a deletion in the long arm of chromosome 20, and an unbalanced translocation between the long arms of chromosomes 17 and 21 yielding a deletion of 17p. In addition to the above mentioned abnormalities, 7 cells had an isochromosome 21q.

Karyotype

46,XX,add(5)(q31), der(17;21)(q10;q10), der(20)t(5;20)(q31;q11.2) [11] /46, idem,+21,iso(21)(q10)[7] /46,XX [2]

FISH Studies demonstrated a 20q deletion in 84.5% of marrow cells. Other selected probes detected no genetic alterations on chromosomes 5, 7, 8, or 13. Since it was not clear which population of marrow cells exhibited the abnormal genetic change, additional FISH Studies with a 20q probe were performed on the Wright-Giemsa stained marrow aspirate smears. These studies demonstrated that both the histiocytes (23 out of the 23 cells counted) and the granulocytes (21 out of the 21 cells counted) were positive for the 20q deletion, whereas none of the 26 erythroid cells counted were positive for this deletion (Figures 2a-2f).

DISCUSSION

In our case, the hypercellular marrow had extensive

Table 1: Immunohistochemical stains utilized in this study.

Antibody	Clone	Dilution	Antigen Retrieval	Manufacturer
CD1a	010	1:200	CC1 High pH Ventana	Dako
CD3	Polyclonal	Pre-dilution	CC1 High pH Ventana	Ventana
CD20	L26	Pre-dilution	CC1 High pH Ventana	Ventana
CD30	Ber-H2	Pre-dilution	CC1 High pH Ventana	Dako
CD34	QBend/10	Pre-dilution	CC1 High pH Ventana	Cell Marque
CD68	KP-1	Pre-dilution	CC1 High pH Ventana	Ventana
Cytokeratin	AE1/AE3	Pre-dilution	CC1 High pH Ventana	Ventana
S100	4C4.9	Pre-dilution	CC1 High pH Ventana	Ventana

Abbreviations: DAKO: Dako North America, Inc., Carpinteria, CA; Ventana: Ventana Medical Systems, Inc., Tucson, AZ; Cell Marque: Cell Marque Corporation, Rocklin, CA

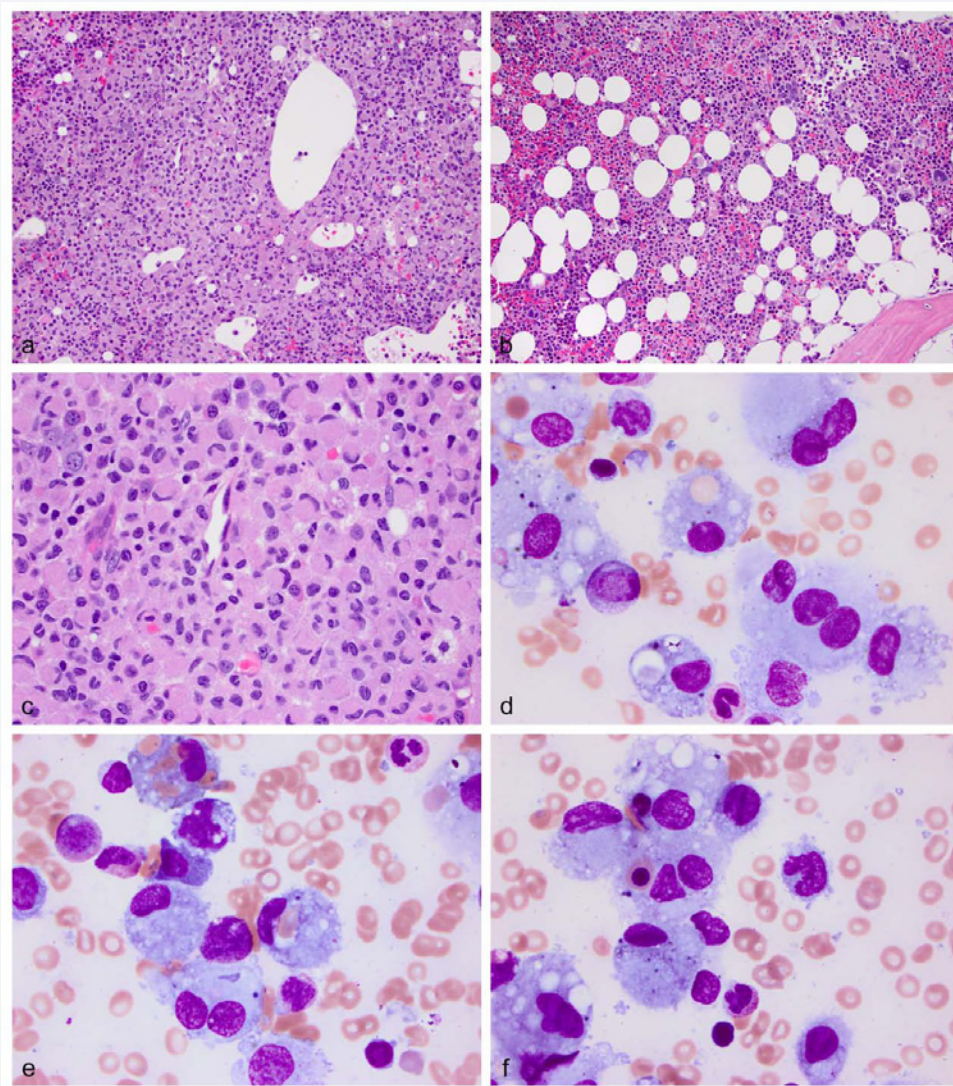


Figure 1 Bone marrow core biopsy and aspirate smear. a, Extensive infiltration by histiocytes (Core biopsy, hematoxylin-eosin, original magnification $\times 100$). b, Residual normal marrow tissue with active trilineage hematopoiesis (Core biopsy, hematoxylin-eosin, original magnification $\times 100$). c, Sheets of histiocytes with abundant cytoplasm. d-f, The bone marrow aspirate smears show many mature histiocytes with frequent cytoplasmic vacuoles and occasional hemophagocytic activities. No significant cytologic atypia is noted (Wright-Giemsa, original magnification $\times 1000$).

infiltration by mature histiocytes with no significant cytologic atypia. Our initial differential diagnosis was divided between a histiocytic neoplasm and a reactive process, due to infection, storage disease or hemophagocytic lymphohistiocytosis (HLH). Negative staining on AFB, GMS and PAS-D in combination with the well-defined clonal genetic changes essentially ruled out the possibility of common infectious and storage disorders. Although the clinical presentation and the presence of scattered histiocytes with hemophagocytic activities raised our suspicion for HLH, the patient did not have many of the clinical laboratory abnormalities characteristic of this entity. Moreover, the presence of clonal genetic changes in both the histiocytes and granulocytes was inconsistent with the diagnosis of HLH.

The morphologic findings may resemble a histiocytic neoplasm, such as Langerhans cell histiocytosis, histiocytic sarcoma, and Erdheim-Chester disease (ECD). The possibility

of Langerhans cell histiocytosis was ruled by negative immunohistochemical stains for CD1a and S100. Only rare cases of histiocytic sarcoma have been reported to primarily involve the bone marrow [1,2]. ECD is a rare systemic disease that typically presents with osteosclerosis and non-Langerhans cell histiocytic proliferation [3,4]. The histiocytes in our case did not show the cytologic atypia characteristic of either histiocytic sarcoma or ECD. Ultimately, both of these entities were ruled out by the shared 20q deletion of the histiocytes and myelocytes.

The clonal genetic findings in both the histiocytes and myelocytes in this case provided strong evidence for a myeloproliferative disorder. Although the presence of the 20q deletion by FISH could be consistent with a myelodysplastic syndrome (MDS), cytogenetic studies demonstrated that the deletion was derived from an unbalanced translocation between chromosomes 5 and 20. Furthermore, the absence of overt

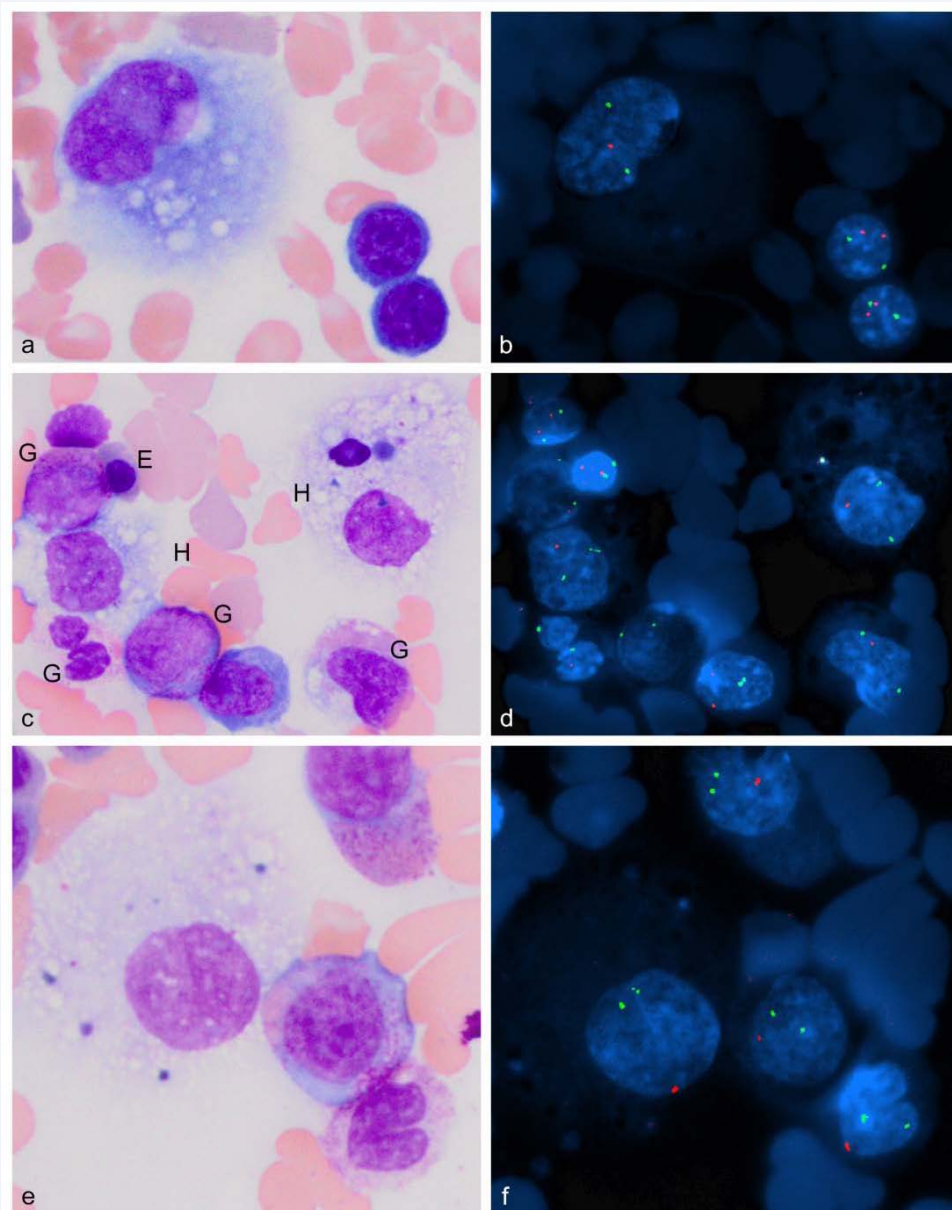


Figure 2 FISH Studies on the Wright-Giemsa stained bone marrow aspirate smears. a and b, One histiocyte positive for 20q deletion, and two erythroid precursors negative for this deletion. c and d, Two histiocytes and four granulocytes positive for 20q deletion, and two erythroid precursors negative for this deletion. e and f, One histiocytes and three granulocytes positive for 20q deletion (a, c and e, Wright-Giemsa, original magnification $\times 1000$; b, d and f, corresponding FISH Studies on the Wright-Giemsa stained bone marrow aspirate smears; H - histiocyte, E - erythroid precursor, and G - granulocyte; green signal - internal reference for chromosome 8, and red signal - probe for 20q).

marrow dysplasia made MDS unlikely. The clinical presentation and bone marrow changes did not fit any specific type of myeloproliferative neoplasm, including chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis. Since the overall findings made precise classification problematic the case was ultimately signed out descriptively as a "clonal myeloproliferative disorder with marked histiocytic differentiation".

This case represents an unusual marrow disorder with recurrent cytogenetic changes and prominent histiocytic differentiation, which, to the best of our knowledge, has not

been documented in the literature. In addition, our work-up exemplifies a useful way to map genetic changes in specific marrow cells by performing FISH Studies on Wright-Giemsa stained aspirate smears.

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