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CASE REPORT

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Hypercellular bone marrow in aplastic anemia: A case report of two patients

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Abstract

Aplastic anemia is a disorder of bone marrow failure characterized by a hypocellular bone marrow. We report two cases with an initial hypercellular bone marrow at the time of presentation, suggesting a new phase in the pathogenesis of the disease.

KEYWORDS

aplastic anemia, bone marrow failure, hypercellular bone marrow

1 | INTRODUCTION

Aplastic anemia is a rare bone marrow disorder in which the bone marrow fails after an insult to the hematopoietic stem cell population. Characteristically, aplastic anemia is diagnosed with a hypocellular bone marrow biopsy. Here, we report the cases of two patients who paradoxically presented with initial hypercellular bone marrow biopsies before converting to hypocellular marrows. The mechanisms by which the bone marrow regenerates following myelosuppressive injury to hematopoietic stem cells are not precisely understood, although studies suggest a signaling role in the rich bone marrow microenvironment that may play a role in bone marrow homeostasis. These cases may represent an initial phase in the pathogenesis of aplastic anemia in which the bone marrow shows regenerative potential by producing a hypercellular marrow before eventually failing entirely.

Aplastic anemia is a rare bone marrow disorder characterized by bone marrow aplasia and pancytopenia. The incidence of aplastic anemia is two to three cases per million per year. Median age at diagnosis is 53, although age distribution is bimodal with peaks at 15–24 years and >65 years.[1] Etiologies associated with aplastic anemia

include environmental exposure to benzenes, radiation, infections (EBV, HIV, CMV, parvovirus, and hepatitis), autoimmune disorders such as systemic lupus erythematosus and eosinophilic fasciitis, paroxysmal nocturnal hemoglobinuria, constitutional disorders, and a wide array of medications, including alkylating agents, chloramphenicol, anti-epileptics, anti-protozoals, sulfonamides, and many others.[2–12] Most often, the etiology is unknown.[12] Patients typically present with fatigue, easy bruising, bleeding, and sometimes infection. On laboratory evaluation, patients are pancytopenic.[13] Evaluation for potential etiologies may be extensive and include drug and toxin exposure history, infectious and autoimmune workup, and detailed family history to uncover hereditary constitutional syndromes. Definitive diagnosis is made with a bone marrow biopsy, which characteristically demonstrates a hypocellular bone marrow.[13] Here, we report two patients with aplastic anemia who initially presented with paradoxically hypercellular bone marrow biopsies.

2 | CASE 1

A 49-year-old woman was referred to hematology for pancytopenia with hemoglobin (Hgb) 6.2 g/dl, platelets (plt) 12 K/mm^3 after she complained of dizziness, weakness, and light headedness for 1 week. One month earlier, her complete blood count (CBC) was normal with WBC 7.8 K/mm^3, Hgb 12.5 g/dl, and plt 211 K/mm^3. She denied recent fever or infections or use of new medications/supplements. Her past medical history included morbid obesity for which she underwent gastric bypass 5 years earlier, iron deficiency anemia most likely due to her gastric bypass, and monoclonal gammopathy of uncertain significance (MGUS) with a normal bone marrow biopsy.

Repeat bone marrow biopsy demonstrated a hypercellular marrow (ranging from 30 to 90% cellular with average cellularity of approximately 80%) with no architectural distortion or significant increase in blasts or plasma cells. CD20 and CD3 showed the presence of focal lymphoid aggregates comprised mainly of T cells. CD34, CD117, and TdT did not show a significant increase in blasts, and CD138 did not show a significant increase in plasma cells. Flow cytometry showed a lymphoid population composed predominantly of T cells with occasional B cells and few NK cells. Chromosome analysis was normal. Overall, this was a hypercellular marrow for age without overt dysplasia, B-cell lymphoma, plasma cell dyscrasia or increase in blasts (Figure 1A–C).

Patient was given a unit of packed red blood cells (pRBC), but 1 week later reported heavy menstrual bleeding as well as dizziness, light headedness, shortness of breath, and heart palpitations. CBC showed WBC 1.82 K/mm^3, Hgb 8.6 g/dl, Plt 57 K/mm^3, and absolute neutrophil count (ANC) 0.63 cells/mm^3. Pelvic examination in the emergency department was negative. A pelvic ultrasound revealed a uterus measuring 12.3 × 6.8 × 5.3 cm with a normal endometrial thickness of 6 mm. She was started on daily combined oral contraceptives without improvement in bleeding. CT chest/abdomen/pelvis was negative except for suggestion of a pulmonary embolism, later confirmed with CT angiogram. An IVC filter was placed. The etiology of her pancytopenia remained unclear.

A repeat bone marrow, 1 month after her initial biopsy, revealed "markedly hypocellular bone marrow (<5% cellular) with virtually absent hematopoiesis" (Figure 1D–F).

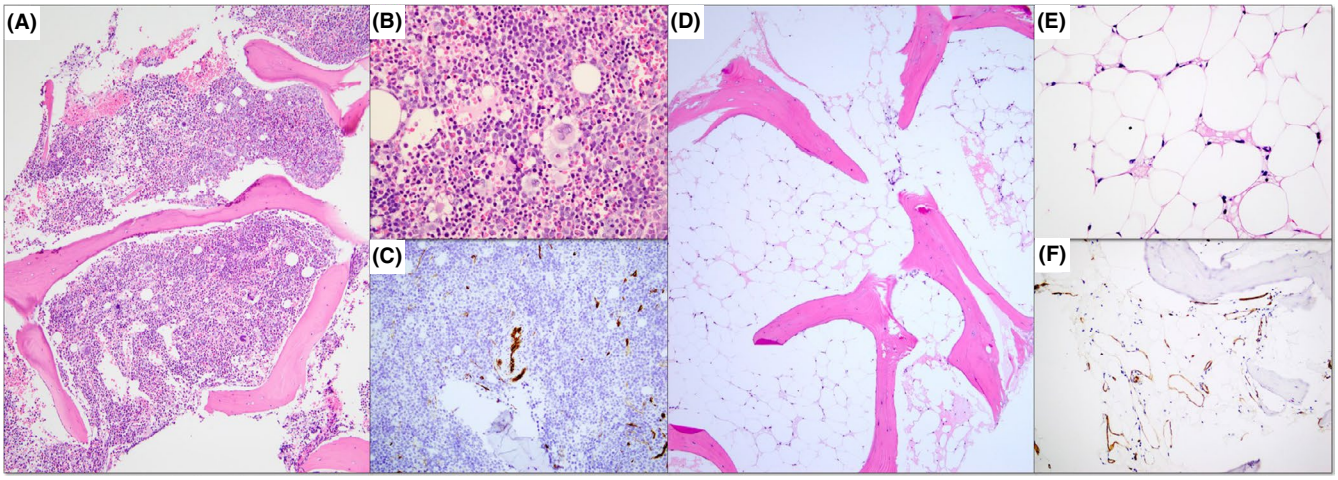

FIGURE 1 The first bone marrow biopsy demonstrates a hypercellular marrow for age (A, H&E stain 10X magnification), with progressive trilineage hematopoiesis (B, H&E stain 40X magnification), and no increase in blasts (C, CD34 IHC stain, 20X magnification). Two months later, the marrow is markedly hypocellular (D, H&E stain 10X magnification), with virtually absent hematopoiesis (E, H&E stain 40X magnification). CD34 IHC staining on this subsequent marrow (F, 20X magnification) highlights marrow sinuses and blood vessels. There is no increase in blasts appreciated

Corrected reticulocyte count was 0.7%. Coombs test was negative. Folate and haptoglobin were within normal limits. Parvovirus and CMV PCR were negative. Genetic analysis of bone marrow revealed variants of uncertain significance in the *CSF3R* and KIT genes. Chromosome analysis was unable to be performed due to absence of mitotic cells in the sample. The patient continued to have progressively worsening menorrhagia and received 5 units of pRBCs and 6 units of platelets over the next month.

She was diagnosed with aplastic anemia and was initiated on anti-thymocyte globulin (ATG), steroids, cyclosporine, and eltrombopag. Her aplastic anemia remained refractory to therapy, and she was given another course of therapy. Seven months after initiation of therapy, she underwent unrelated donor stem cell transplantation. Her CBC continued to show severe pancytopenia, and the bone marrow remained aplastic. She died 2 months later due to septic complications

3 | CASE 2

An 83-year-old woman presented with bilateral lower extremity rash, spontaneous bruising, and dyspnea on exertion. Her past medical history included esophageal dysmotility with strictures requiring multiple balloon dilatations, remote gallstone pancreatitis, pelvic floor disorder complicated by urge incontinence, and gastroesophageal reflux disease. She reported feeling well until 3 weeks prior to presentation, after which she noted dyspnea and fatigue which she attributed to her busy schedule. She also reported dry eyes and blurry vision. The day prior to presentation, she noted multiple spontaneous bruises on her extremities.

She was taking lansoprazole for GERD and a daily multivitamin. She had bilateral lower extremity petechiae and bilateral upper extremity ecchymoses. CBC showed WBC 1.5 K/mm^3, Hgb 7.5 g/dl, and platelet count 6 K/mm^3. Notably, she had a history of mild anemia (>11 g/dl) and mild thrombocytopenia (>120 K/mm^3) for a year prior to presentation.

Bone marrow demonstrated multilineage hematopoiesis with 15–20% marrow cellularity, which was appropriate for her age. There was no evidence of high-grade dysplasia, acute leukemia, or involvement by lymphoproliferative disorder. Staining was negative for CD34 and CD117, and positive for CD138; however, this showed polytypic immunoglobulin light chain expression with kappa and lambda strains. Immunophenotypic analysis by flow cytometry revealed polytypic B lymphocytes and T lymphocytes without evidence of aberrant antigen expression. There was no evidence of increased blasts. She received a total of 4 units of packed red blood cells and 5 units of platelets and was subsequently transferred to our institution for further workup of her pancytopenia. Initial laboratory workup revealed WBC 0.9 K/mm^3, Hgb 9.0, g/dl, platelets 17 K/mm^3, and ANC 0.1 cells/mm^3. Rheumatologic workup was expanded and remained mostly negative. Flow cytometric analysis on granulocytes and erythrocytes did not reveal any significant loss of CD55 or CD59 expression to suggest paroxysmal nocturnal hemoglobinuria. CMV, parvovirus, and EBV PCR were all negative. Hepatitis panel was negative. HIV 1 and 2 antibody and antigen test were non-reactive. LDH was within normal range at 158.

A repeat bone marrow biopsy revealed a hypocellular bone marrow for age (10% cellularity), markedly decreased trilineage hematopoiesis, and blasts <1%. Overall, the findings were consistent with a hypocellular bone marrow without morphological evidence of acute leukemia or myelodysplasia. Our patient was started on immunosuppressive therapy with ATG, cyclosporine, and prednisone with good response (WBC 4.9 K/mm^3, Hgb 9.9 g/dl, and plt count 108 K/mm^3 4 months post-treatment). She continued to follow with hematology/oncology for the next 2 years with few complaints other than easy bruising.

Two years after her initial presentation, she presented with new bruising and bright red blood per rectum. CBC revealed WBC 5.4 K/mm^3, Hgb 10.4 g/dl, and platelet count 11 K/mm^3. Repeat bone marrow biopsy revealed a hypocellular bone marrow (5–10% cellularity) and progressive trilineage hematopoiesis with no significant dysplasia or increase in blasts, consistent with relapsed aplastic anemia. She was started on Romiplostim and continued on cyclosporine. She developed multiple septic complications and died 11 months after the relapse of her aplastic anemia.

4 | DISCUSSION

These cases represent, to our knowledge, the only reports of aplastic anemia with paradoxically hypercellular bone marrow biopsies at initial presentation. The mechanism of bone marrow hypercellularity is unclear in both cases but could represent an initial stage in the evolution of aplastic anemia in which the bone marrow attempts to compensate by aggressively inciting hematopoiesis prior to failing.

Notably, neither bone marrow demonstrated evidence for a malignant or lymphoproliferative process, which also can produce a hypercellular marrow and result in pancytopenia. Moreover, clonal disorders such as paroxysmal nocturnal hemoglobinuria, myelodysplastic syndromes, and leukemias typically develop late in the course of aplastic anemia and often in the context of immunosuppressive therapy.[12] In both patients, the initial hypercellular marrow was noted within days of the onset of pancytopenia.

The mechanisms by which the bone marrow regenerates following injury to hematopoietic stem cells (HSCs) remain unclear, although studies have implicated various signaling pathways within the rich bone marrow microenvironment that may contribute to maintenance of the HSC pool following myelosuppressive injury.[14–23] There is no current literature, suggesting a phase in the pathogenesis of aplastic anemia in which the bone marrow shows regenerative potential by producing a hypercellular marrow, before eventually failing entirely.

While it is possible that an initial hypercellular bone marrow phase could be unique to a small subset of patients with genetic predisposition toward a stronger homeostatic response, recent literature on the role of the bone marrow microenvironment suggest that these findings could represent a physiologic response to marrow damage and a new phase in the pathogenesis of aplastic anemia. In this initial phase, the bone marrow microenvironment responds to insult by promoting HSC regeneration and attempts to recover peripheral blood counts. Ultimately, the bone marrow fails and a hypocellular bone marrow quickly develops. In the case of our second patient, the time course between the hypercellular phase and subsequent hypocellular phase could have been <2 weeks. A further understanding of the time course of aplastic anemia and the physiologic mechanisms at play in response to bone marrow injury could offer greater insight into future treatment possibilities. If the bone marrow's innate regenerative potential could be harnessed and augmented with targeted therapeutic agents, patient outcomes could be improved.

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CONFLICTS OF INTEREST

None of the authors have any conflict of interest to declare.

AUTHOR CONTRIBUTIONS

SN involved in conceptualization of study, interpreting clinical data, and writing the manuscript. FE and RS involved in interpreting clinical data and writing the manuscript. KM involved in obtaining histologic images and writing the manuscript.

ETHICS APPROVAL

The current manuscript is not published elsewhere. Patient-identifying information was not included in the report.

CONSENT

Since the patient passed away before writing this article, written consent was obtained from a family member of the patient.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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