Extensive Bone Marrow Necrosis in a Case of Acute Myeloid Leukemia Transformed from a Myeloproliferative Neoplasm

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Bone marrow necrosis · Acute myeloid leukemia · Myeloproliferative neoplasm

Abstract
Extensive necrosis affecting more than 50% of the bone marrow is an extremely rare histopathological finding. Relatively little is known about its clinical significance because it is most commonly identified at autopsy – whether it is an independent prognostic marker or whether it is a surrogate marker of underlying disease burden remains unclear. We describe herein a case of a 66-year-old patient with acute myeloid leukemia who presented with acute bone marrow failure and was found to have extensive necrosis. We include presenting clinical features, pathology attained at biopsy, and the challenge of treatment. Bone marrow necrosis is a rare but important clinicopathological entity whose recognition may herald the way for more effective prognostication of underlying disease.

Introduction
Bone marrow necrosis (BMN) is a rare histopathological entity characterized by necrosis of the hematopoietic tissue with disruption of the surrounding bone marrow architecture \cite{1}. The most common cause is hematological malignancy such as acute lymphoblastic leukemia in children and acute myeloid leukemia (AML) in adults \cite{2}. The nonhematological malignancies such as solid gastric adenocarcinomas are less common causes. Approximately 10\% of BMN is due to nonmalignant causes, for example sickle cell anemia, infection, and disseminated intravascular coagulation \cite{1–3}.
The clinical presentation of BMN includes the acute onset of intense bone pain, often localized to the lower back that brings patients to hospital [2, 3]. Patients may, or may not have peripheral cytopenias. Although it is a rare finding in the bone marrow biopsies of living patients, BMN is more commonly identified at autopsy. The degree of necrosis is defined as mild if <25% of the bone marrow biopsy specimen is necrotic, moderate if 25–50% of the biopsy specimen is necrotic, and extensive if >50% of the biopsy specimen is necrotic [1]. Extensive BMN is extremely rare, with available case series describing a prevalence rate of around 0.3–12% of all bone marrow biopsies depending on the population studied and the experience of the pathologist [2]. We report a case of extensive BMN in a patient with AML transformed from a JAK-2+ myeloproliferative neoplasm (MPN).

**Case Presentation**

A 66-year-old lady was transferred to hospital with acute bone marrow failure. She had a past medical history of a JAK-2+ unclassifiable MPN treated with hydroxyurea. One week prior to her transfer, she presented to her local hospital with a 3-week history of progressively worsening back pain, fever, chills, and drenching night sweats. A complete blood count at the time showed cytopenias in multiple blood lineages, with a hemoglobin of 73 g/l, mean cell volume 105 fl, platelet count 38 × 10⁹/l, and white blood cell count 17 × 10⁹/l. Blood film yielded teardrop cells and hypersegmented neutrophils. MRI of the lower back and pelvis revealed evidence of infarction within the bone marrow containing spaces with extramedullary hematopoiesis lateral to the iliac spines.

Bone marrow aspirate and biopsy yielded a fully necrotic sample (fig. 1). The patient continued to develop worsening anemia requiring transfusion support. A second attempt at bone marrow aspirate and core biopsy once again yielded a nondiagnostic necrotic sample, and her peripheral blood contained blast cells. Flow cytometry yielded myeloblast population expressing CD34, CD117, and negative for CD33, CD19, and CD10. After several days in hospital, she developed hepatosplenomegaly, with the spleen measuring 18.4 cm and liver measuring 29 cm on the CT scan of the abdomen. Marked lymphadenopathy was noted in both the peritoneal and retroperitoneal cavities (fig. 2). A third attempt at a bone marrow biopsy once again yielded a necrotic nondiagnostic sample.

The patient’s level of consciousness deteriorated prompting intubation and transfer to ICU. None of the sites of lymphadenopathy were amenable to biopsy given the patient’s worsening functional and hematologic status. She was started on chemotherapy at a dose-reduced 7 + 3 regimen of doxorubicin and cytarabine, with the administration of doxorubicin planned at the end of the 7-day cycle, given the patient’s poor clinical status. Following the initial dose of cytarabine, her blood pressure dropped precipitously requiring fluid bolus support. Her antibiotic coverage was broadened to piperacillin-tazocin and vancomycin. She developed pulmonary edema, and after discussion with immediate family, her goals of care became palliative. She died 3 weeks following her transfer to hospital. Permission to perform an autopsy was attained.

**Pathology**

The bone marrow was completely effaced with diffuse sheets of myeloblasts. Immunohistochemistry failed to identify any discernible staining pattern. Examination of the lymph nodes yielded a pattern similar to the bone marrow, with myeloblasts surrounded by coagu-
lative necrosis. Extranodal extension of neoplastic cells was noted in all lymph nodes. Microscopic examination by a hematopathologist supported the diagnosis of AML likely transformed from MPN.

Discussion

Although BMN is a rare antemortem finding, examination of postmortem pathological specimens may reveal higher prevalence than expected. The mechanism of necrosis in the bone marrow depends on the inciting cause, but shares the common feature of compromise of the bone marrow vasculature [3]. When exposed to a sufficient amount of radiation, for example, the resulting inflammation in the microvasculature causes the blood vessels to disappear from pathological specimens [2]. In sickle cell disease, occlusion of the microvasculature occurs by deposition of sickled red blood cells. In leukemia, necrosis is thought to occur secondary to the deposition of immune complexes within the marrow microvasculature as well as impingement of the vasculature by proliferating blasts [2].

The prognosis with BMN is variable and, once again, depends on the inciting event as well as the extent of necrosis and its complications. In the context of adult acute leukemia, the available literature suggests a poor median survival of patients with BMN compared to those without it [2]. However, whether BMN is an independent prognostic marker or whether it is a surrogate marker of disease burden is not clear from the available data. Interestingly, the presence of BMN does not herald a poor prognosis in children. For example, a study by Pui et al. [4] examined bone marrow specimens from 1,419 children with acute leukemia and bone marrow involvement, finding BMN in 7 of them. Six of these 7 children went on to have cure of their disease or attained long-term remission.

In the patient described herein, extensive BMN developed in the context of acute leukemic transformation from a previous MPN. Cardiorespiratory compromise followed the administration of cytarabine, suggesting the extent of AML burden may have resulted in tumor lysis syndrome upon induction of chemotherapy. As more cases of leukemia-associated BMN are encountered, a diagnostic algorithm for the earlier detection of BMN may be devised potentially heralding the way for more effective treatment.

Statement of Ethics

Written informed consent was obtained from the patient’s family for publication of this case report and any accompanying images.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References


Fig. 1. a HE-stained section of bone marrow core biopsy shows massive necrosis with complete loss of the cellular details. ×100. b The marrow is occupied by granular eosinophilic material containing scattered nuclear debris. ×200.

Fig. 2. CT scan of the abdomen with axial and coronal sections showing marked hepatomegaly and splenomegaly as well as diffuse lymphadenopathy in the gastrohepatic and duodenal compartments.