Presentation and Outcomes for Children With Bone Marrow Necrosis and Acute Lymphoblastic Leukemia: A Literature Review

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Summary: Bone marrow necrosis is a rare histopathology finding with the majority of cases occurring in the setting of a hematologic malignancy. This article reports a case of diffuse marrow necrosis in a child secondary to acute lymphoblastic leukemia and summarizes the clinical features and outcomes for children with bone marrow necrosis secondary to leukemia from 20 published reports. This review demonstrated that the most common presenting features were bone pain, fever, pancytopenia, and that outcomes were less favorable when compared with those without necrosis. However, contemporary literature suggests that outcomes are similar for children who have bone marrow necrosis secondary to leukemia when compared with overall survival rates for pediatric leukemia.

Key Words: necrotic, myelonecrosis, ALL, pediatric

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Acute lymphoblastic leukemia (ALL) is the most common malignancy seen in childhood, with approximately 3000 new cases diagnosed in the United States each year.[1] A diagnosis of ALL is usually made by documenting the presence of lymphoblasts in peripheral blood and/or $>25\%$ lymphoblasts in the bone marrow. Additional bone marrow findings may include fibrosis, dysplasia, and necrosis. Bone marrow necrosis (BMN) is characterized by necrosis of both medullary stroma and myeloid tissue components of the marrow space.[2] The reported incidence of BMN ranges from 0.3% to 37%.[2–5] However, these studies primarily involved large numbers of autopsied specimens from deceased leukemia patients. Reports from living patients are exceedingly rare and were not described in the literature until 1942.[5] Of reported adult and pediatric cases, anemia (91%), thrombocytopenia (78%), bone pain (75%), and fever (68%) were the most common signs and symptoms, respectively. A malignancy was identified in 90% of the cases with either acute myelogenous or lymphocytic leukemia being the most common underlying diagnosis (41%). Of the nonmalignancy-related cases (22/240), the most common etiologies were infection (6/22), sickle cell disease (6/22), and drug effects (2/22).

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METHODS

We present a pediatric patient who presented with diffuse BMN associated with ALL and the results of a literature search (PubMed) performed using the key terms "bone marrow necrosis," "myelonecrosis," and "acute lymphoblastic leukemia". Our literature search was limited to articles published in English and those which included patients >1 year of age and <18 years of age. We reviewed all peer reviewed published reports of pediatric ALL with BMN described in the literature between 1965 and 2009 and summarized the clinical presentations, reported laboratory values, and outcomes. For all cases reported, BMN was identified either before or at diagnosis of ALL. Laboratory values were considered abnormal based on age-related normal values.

Case Report

A previously healthy 8-year-old female presented to our clinic with repeated attacks of high fever and generalized right lower extremity pain. In addition, she complained of poor appetite and pain with ambulation. Her parents denied the presence of cough, night sweats, and weight loss. Two weeks before this visit she was diagnosed with a viral infection and was noted to have pancytopenia. Physical examination revealed full range of motion of all joints in her lower extremities without reproducible pain. The remainder of her examination was normal, including no evidence of hepatosplenomegaly, petechiae, or lymphadenopathy.

Laboratory studies included a complete blood count which revealed pancytopenia, hemoglobin 10.6 g/dL, white blood cell count 4.2×10^9 cells/L (absolute neutrophil count 786 cells/uL), and platelets 140×10^9/L. Chemistry studies were notable for normal uric acid and electrolytes and an elevated lactate dehydrogenase (LDH) of 256 U/L (normal range, 70 to 230 U/L). Bone marrow was difficult to aspirate with few spicules present. Microscopic review demonstrated a homogenous population of necrotic-appearing cells with indistinct morphology. A bone marrow touch preparation similarly showed necrotic debris and rare blasts. A bone marrow core biopsy revealed few marrow spaces containing necrotic debris (Fig. 1). A reticulin stain showed no fibrosis and flow cytometric analysis revealed $>90\%$ nonviable cells, precluding meaningful assessment of specimen immunophenotype and chromosomal analysis. However, flow cytometry of a peripheral blood sample demonstrated 6% circulating lympoblasts, consistent with a diagnosis of precursor B-cell ALL. A repeat contralateral bone marrow biopsy was difficult to aspirate and again demonstrated significant necrosis (32%). Among the viable

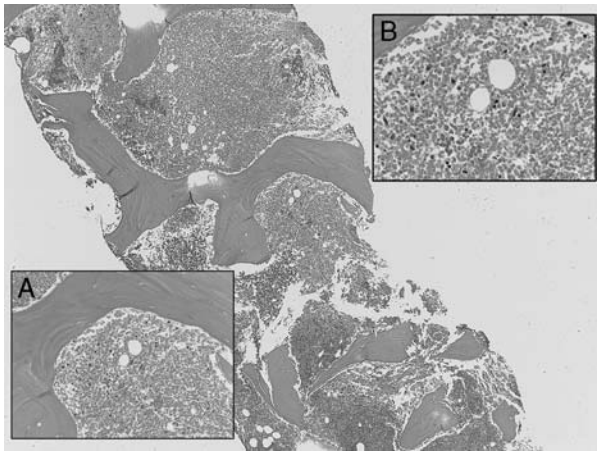

FIGURE 1. A 20× image of the initial bone marrow biopsy demonstrating few cellular elements in an eosinophilic background composed of cellular debris. Inset A (100×) and Inset B (200×) further demonstrate the background of necrotic debris with few interspersed mononuclear and segmented leukocytes.

cells, 90% were lymphoblasts consistent with precursor B-cell ALL. Fluorescence in situ hybridization analysis was positive for TEL-AML and negative for BCR-ABL and MLL rearrangements.

The patient subsequently received 3-drug induction chemotherapy for standard risk precursor B-cell ALL (vincristine, prednisone, and asparaginase) as per the Children's Oncology Group protocol AALL0331, but not on study. A follow-up day 8 induction bone marrow showed persistent BMN with 0.1% lymphoblasts by flow cytometry. Day 29 and all subsequent bone marrows, however, had no evidence of necrosis and no evidence of lymphoblasts. She has remained in remission for 1 year, now, after diagnosis.

RESULTS

A literature search revealed 12 reports of pediatric ALL associated with BMN, which included a total of 20 patients (average age, 6.5 y; range, 1.5 to 16 y). Patient characteristics, presenting symptoms, laboratory values, and outcomes are shown in Table 1. Karyotype was not reported in previous BMN cases described in the literature. The most common presenting characteristics were bone pain (90%) and fever (75%). Abnormal values were determined according to age-based normal values or a reported abnormality in the published report.[18] Among those reported, the most common laboratory abnormalities were anemia (90%) and leukopenia (68%), with 37% of patients presenting with pancytopenia. Although LDH values were reported for only 8 patients, all had an elevated LDH (>2 standard deviations above the upper limit of normal). Outcomes were reported for 18 patients with 14 (78%) survivors at time of publication. The reported duration of follow-up ranged from 7 months to 18 years. The 2 children who died were diagnosed and treated before 1980. Conversely, all patients who presented after 1980 with BMN survived to the time of publication. Three of the patients who died had BMN reported only at time of relapse.

DISCUSSION

Our literature search revealed that pediatric patients with BMN associated with ALL most commonly presented with bone pain (90%) and fever (75%). Interestingly, bone pain is only reported at presentation in 22% of all patients with ALL. In our review of ALL patients with BMN, bone pain was found in 90%. The higher rate of bone pain associated with BMN may reflect the painful nature of the necrotic marrow, in contrast to pain believed to be associated with excess blasts within the marrow space. As described by other researchers, our patient had pain resolved with successful chemotherapy treatment, suggesting a central role of blasts contributing to both necrosis and pain. In children with ALL without BMN, fever (61%) and petechiae or purpura (48%) are most commonly reported at presentation, which is similar to our findings in patients with BMN.[19]

Laboratory findings in patients with BMN revealed anemia (90%) and leukopenia (68%) as the most common abnormalities reported at presentation. This is in contrast to all patients with ALL, where anemia is reported less frequently (60%). In addition, only 20% of patients with BMN had platelet counts below 100,000/mm^3, whereas >70% of all patients with ALL exhibit this degree of thrombocytopenia at diagnosis.[18] Although patients with BMN seem to present with higher red blood cell and platelet counts, our review of BMN found 37% of patients presented with pancytopenia. This is higher than patients without marrow necrosis in which only 1% to 2% of patients present with pancytopenia,[19] which often leads to suspicion of aplastic anemia or bone marrow failure as the initial diagnosis. Furthermore, an elevated LDH was found in all patients in whom it was sought, again this was likely the reflection of necrotic bone marrow.

Before the 1970s, BMN with ALL was initially believed to be a poor prognostic sign.[2,3,20] More recent literature, however, suggests that prognosis is intimately tied to the underlying disease, particularly in children with malignancy. Macfarlane and Tauro[11] presented 4 children with BMN and ALL, of whom 3 presenting in the 1970s died, whereas the child presenting in 1982 remained in remission 40 months after diagnosis. They postulated that the presence of BMN might be a marker for other prognostic factors in ALL with outcome independent of presence of BMN alone.[11] In 1985, Pui et al[10] described BMN in 5 children presenting with bone pain in the setting of ALL. All patients had resolution of symptoms and marrow recovery on repeated marrow biopsy after treatment and remained in remission. Nevertheless, these researchers noted that case numbers were too limited to draw any firm conclusions regarding the prognostic significance of BMN in the setting of childhood malignancy.

Although BMN was initially believed to herald poor prognosis, review of the limited number of reports in the literature suggests that prognosis in patients with BMN in the setting of ALL may not be adversely affected. Although the length of follow-up varied, all reported patients who presented after 1980, remained in remission for an average of 3 years after BMN was identified; as in 2000, the approximate cure rate of standard risk childhood ALL became 80%.[19] The improved survival for BMN ALL patients found in our literature review may reflect superior chemotherapy treatment regimens and use of other prognostic factors to define therapy used after 1980. These factors are possibly prognostically more important than the presence of BMN at presentation in ALL.

TABLE 1. Characteristics of Patients With Bone Marrow Necrosis and ALL in Children From 1965–2009

Age (y)	Sex	Clinical Presentation	WBC	Hgb	Plt	LDH	FAB Classification/ Immunophenotype	Outcome	Year of Publication	Study
16	M	F, P (joint)	3.9	Hct 26	7	NR	NR	Blood cultures positive for *E. Coli* initially. Died 5 mo after BMN with relapse after initial treatment	1972	6
7	M	F, P (inguinal)	7	10.4	150	NR	NR	CR	1977	7
3	F	Night sweats, ear pain, listlessness	0.75	Hct 12	6	NR	NR	CR (diagnosis occurred 10 wk after BMN)	1983	8
2.5	F	F, stomatitis	3.2	Hct 14	235	NR	Null type lymphoblasts	CR 48 mo		
1.5	M	F, P (leg)	8.9	8.8	204	NR	NR	CR 24 mo	1985	9
4	F	F, P (bone)	4.20	6.90	105.00	1189.00	L1 preB	CR 48 + mo	1985	10
5	F	F, P (bone)	2.70	6.50	41.00	775.00	L1 preB	CR 24 + mo		
7	F	F, P (bone)	0.80	8.40	5.00	1290.00	L1 preB	CR 10 + mo		
4	F	F, P (bone)	4.10	6.50	116.00	320.00	L1 preB	CR 51 mo		
4	M	F, P (bone)	6.00	6.90	nl*	NR	L1 preB	Relapse 13 mo, died 3 y after presentation	1986	11
10	F	P (buttock)	3.40	13.00	157.00	NR	L1 preB	Remission initially, relapse 3 y later, died 6 y from presentation		
7	F	P (bone)	10.50	10.00	270.00	NR	L1 preB	Remission initially, relapse at 5 mo, died 1 y from presentation		
4	F	F, P (leg)	4.60	6.60	184.00	NR	L1 preB	CR 40 mo		
3	F	F, P (bone), rigors, anorexia	12	5.6	117	NR	L1 preB	CR 24 mo	1987	12
5	M	F, P (leg, pelvis)	2.5	8.9	19	2765	NR	CR 4 mo	1992	13
14	M	F, P (hip, joint)	NR	NR	NR	NR	NR	NR	1997	14
6	M	F, P (joint)	5.50	10.00	294.00	980.00	CD10/CD19/CD22 positive	NR	2001	15
16	M	P (bone)	nl*	Low*	nl*	High*	L2 ALL	CR 8 mo	2002	16
6	M	F, P (back, leg)	4.10	8.40	160.00	2036.00	L1 preB/TEL-AML +	CR 7 mo	2007	17
3	M	P (back, leg)	9.00	7.20	120.00	342.00	NR	CR 18 y		
8	F	F, P (leg)	4.20	10.60	140.00	256.00	CD10/CD19/CD20/ CD22 positive	Continues on chemotherapy		Present report

*Publication reported normal, elevated, or low.

ALL indicates acute lymphoblastic leukemia; BMN, bone marrow necrosis; CR, complete remission; F, fever; Hgb, hemoglobin (g/dL); Hct, hematocrit; LDH, lactate dehydrogenase (U/L); FAB, French-American-British; nl, normal; NR, not reported; P, pain (site); Plt, platelets ($\times 10^9$); preB, pre-B cell lymphocytic leukemia; WBC, white blood count ($\times 10^9$).

There are however, several limitations of this study. This is a retrospective study of a limited number of patients for whom there is a lack of clinical data such as risk stratification, therapy used, and response to therapy. In addition, It is unknown whether BMN occurs focally or widespread, and therefore the influence of bone marrow sampling is unclear.

In summary, the majority of BMN occurs in the setting of hematologic malignancy, and its finding should trigger an extensive search for malignancy. Among patients with ALL associated with BMN younger than 18 years of age, approximately half were pancytopenic, and most experienced bone pain and fever. This presentation is not typical of the most common presentation for ALL unassociated with marrow necrosis. Finally, prognosis for marrow necrosis associated with ALL was initially thought to be poor. More recent publications, however, support an improved overall outcome for patients diagnosed and treated after 1980, possibly reflecting better chemotherapy treatments. Although findings of marrow necrosis may lead to difficulty in diagnosis, the association of bone pain and fever should warrant further evaluations to determine whether malignancy is the underlying cause.

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