ARTICLE

Is Bone Marrow Aspiration Needed in Acute Childhood Idiopathic Thrombocytopenic Purpura to Rule Out Leukemia?

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Objective: To assess the prevalence of leukemia in a series of bone marrow aspiration (BMA) samples collected to confirm provisional diagnoses of acute idiopathic thrombocytopenic purpura (ITP) in children.

Design: A retrospective cohort.

Setting: All BMA reports at The Hospital for Sick Children, Toronto, Ontario (a tertiary care pediatric hospital), from January 1, 1984, to May 31, 1996, were reviewed.

Patients: Included were BMAs performed to confirm provisional diagnoses of ITP in children (6 months to 18 years of age) with "typical" contemporaneous hematologic features of ITP (platelet count, $\leq 50\times10^9$/L; hemoglobin level, $\geq$100 g/L [6-12 months of age] or $\geq$110 g/L [>1 year of age]; white blood cell count, $\geq 5\times10^9$/L [6 months to 6 years of age] or $\geq 4\times10^9$/L [>6 years of age]; and neutrophil count, $\geq 1.5\times10^9$/L [6 months to 6 years of age] or $\geq 2\times10^9$/L [>6 years of age]). Children with chronic ITP, thrombocytopenia-related chronic conditions, or leukemic blasts on peripheral smears were excluded.

Main Outcome Measure: The finding of leukemia in the BMA report was chosen a priori as the primary outcome for the yield of BMA.

Results: Four hundred eighty-four BMAs were performed to confirm provisional diagnoses of acute childhood ITP. No diagnoses of leukemia were revealed in the 332 children with typical hematologic features of ITP. The risk of missing the diagnosis of leukemia in this setting is less than 1%.

Conclusions: The yield of BMA for leukemia in this setting is low. Routine BMA is not necessary for children with typical acute ITP.

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Editor's Note: In case you need more evidence that bone marrow aspiration is unnecessary for children with a typical history, physical examination, and laboratory evidence of idiopathic thrombocytopenic purpura, here it is via a new method. I hope we can now allow the issue and the children to rest.

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IDIOPATHIC thrombocytopenic purpura (ITP) is a common pediatric hematologic disorder.[1] Although ITP is typically a benign, self-limited condition, bone marrow aspiration (BMA) is often performed in children with acute ITP to rule out leukemia,[2,3] particularly when treatment with corticosteroids is contemplated. The discomfort and expense of a BMA could be avoided if it was proven to be unnecessary in typical acute childhood ITP regardless of treatment plan.

Different approaches have been used to assess whether BMA is needed in children with acute ITP. In 1988, Halperin and Doyle[4] reviewed the medical charts of 127 children with presumed ITP. All 5 patients with abnormal BMA samples had clinical or laboratory features "atypical" of acute ITP; none had leukemia. Dubansky et al in 1989[5] and McIntosh in 1982[6] separately reviewed the initial findings in children with acute lymphoblastic leukemia. Both studies reported that of the children with thrombocytopenia and no peripheral blast cells, none had normal hemoglobin (Hb) levels or neutrophil counts. Although suggesting that BMA may be unnecessary, these studies fail to provide adequate estimates of the yield of BMA in this setting due to small sample sizes and lack of an a priori definition of "typical" ITP.

The objective of this study was to determine whether any diagnoses of leukemia were revealed in a large series of BMA samples collected to confirm provisional diagnoses of acute ITP in children with typical hematologic features of ITP.

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METHODS

The reports of all BMAs performed at The Hospital for Sick Children, Toronto, Ontario, from January 1, 1984, to May 31, 1996, were reviewed manually. The BMA results, and the clinical data (indication, complete blood cell count, age, sex, etc) that the request is based on, are maintained in a uniform, comprehensive, bound registry supervised by one individual (A.P.).

Included were reports of all inpatient and outpatient BMAs performed to confirm the provisional diagnosis of acute ITP. Provisional diagnosis was obtained from clinical information in the BMA report and included "query ITP," "rule out leukemia," "thrombocytopenia," "low platelets," and "ITP." If the report did not provide an indication, the corresponding medical chart was reviewed. Furthermore, if it was not clear from the clinical data on the BMA report that ITP was the primary provisional diagnosis, the corresponding medical chart was reviewed.

The complete blood cell count and a peripheral smear that corresponded closest to the time of, and was taken before, the BMA was obtained, and used to determine whether patients had typical features of ITP. The values for typical laboratory features of ITP were agreed on before the review and consisted of the normal reference range for the hospital (Hb level, total white blood cell (WBC) count, and neutrophil count). A platelet count of $50\,000\times10^9$/L or lower was believed to be the cutoff point at which clinicians would consider the diagnosis of ITP and contemplate investigation. Therefore, a child was deemed to have the typical laboratory features of ITP if the platelet count was $50\,000\times10^9$/L or lower and normal Hb level (≥100 g/L [6-12 months of age] or ≥110 g/L [>1 year of age]), total WBC count ($\geq5\times10^9$/L [6 months to 6 years of age] or $\geq4\times10^9$/L [>6 years of age]), and neutrophil count ($\geq1.5\times10^9$/L [6 months to 6 years of age] or $\geq2\times10^9$/L [> 6 years of age]) were present. The WBC counts, Hb levels, and platelet values were determined using an automated cell counter (Coulter Max M, Coulter Electronics Inc, Miami, Fla) automated counter. Neutrophil counts were determined manually by microscopic examination of peripheral smears. All BMA specimens were reviewed by a single hemopathologist (A.P.).

Exclusion criteria were as follows: the presence of blasts on peripheral smears, age 6 months or younger, chronic ITP, and the presence of a specified condition that may account for thrombocytopenia (ie, Down syndrome, radial aplasia-thrombocytopenia syndrome, or congenital heart disease).

The outcomes of all BMAs performed in children to confirm ITP with typical laboratory features were determined to ascertain the presence of any diagnoses other than ITP. Similarly, the diagnoses of all BMAs performed in children to confirm ITP with atypical laboratory features (ie, platelet count, $\leq5M0\,000\times10^9$/L but values outside the predetermined normal ranges for Hb, WBCs, and neutrophils) were also retrieved.

The Hospital for Sick Children health records database was reviewed to ascertain the number of children admitted from January 1, 1984, to May 31, 1996, with a primary discharge diagnosis of ITP.

Outcome of Bone Marrow Aspirations With "Typical" and "Atypical" Features of ITP*

	ITP Confirmed	Inadequate Specimen	Leukemia	Marrow Aplasia	Other Finding	Total
Typical	324	7	0	1	0	**332**
Atypical	135	6	3	7	1	**152**

**ITP indicates idiopathic thrombocytopenic purpura.*

RESULTS

A total of 7612 BMAs were performed at The Hospital for Sick Children during the study. Review revealed that 484 (6.4%) were performed to confirm a provisional diagnosis of ITP. Of these, 332 had typical and 152 had atypical hematologic features of ITP (see the **Table**). During this same period, 672 children were admitted to The Hospital for Sick Children with the primary diagnosis of acute ITP. Therefore, it is estimated that approximately 72% of children with ITP in this period underwent BMA.

No diagnoses of leukemia were revealed in the 332 children with typical hematologic features of ITP. Given this sample size, these results provide 95% confidence that the risk of missing the diagnosis of leukemia in this setting is no greater than 1%.[7] Bone marrow aspiration did not reveal typical findings consistent with ITP in 2.4% of children with typical hematologic features: 1 had aplastic anemia and 7 were inadequate samples (see the Table).

Results of BMA did not reveal ITP in 11.2% of children with atypical hematologic features of ITP (see the Table). The 3 children with leukemia had 2 or more atypical hematologic values present on complete blood cell count. Furthermore, all 3 patients with leukemia had clinical presentations that were inconsistent with ITP, including presentations with knee pain, an inguinal mass, and fatigue and backache for 1 month. All 8 children diagnosed as having aplastic anemia had abnormally low neutrophil counts; some had additional abnormalities in Hb and leukocyte values.

Random review of 100 medical charts of children with typical and atypical ITP revealed that 98% of the patients included on the basis of BMA reports had acute ITP. Only 2% involved other diagnoses: chronic ITP or acute ITP with relapse. Reproducibility of BMA report abstraction of ITP cases and BMA outcomes was excellent, with 100% agreement in determining inclusion eligibility and BMA outcome.

COMMENT

Recent recommendations about the usefulness of BMA in diagnosing acute childhood ITP have been based largely on opinion.[8-11] Our findings provide some evidence for the low yield and probable lack of significant benefit of BMA in the setting of typical acute childhood ITP. Furthermore, one must consider the cost (US $668 for inpatients and US $808 for outpatients) and the possible morbidity (pain, bleeding, and infection) of this invasive procedure.[2]

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A survey of 322 physicians board certified in pediatric hematology revealed that 74% would perform a BMA in patients with acute childhood ITP.[12] The need to rule out leukemia was the foremost reason cited (78%), followed by the need to rule out aplastic anemia (51%). Trial results have shown that treatment with corticosteroids, intravenous gamma globulin, and intravenous anti-D gamma globulin individually are effective in patients with ITP.[13] The recently reported cases of hepatitis C infection after treatment with contaminated immunoglobulin[14] and a general increased public concern regarding the safety of human blood products potentially could result in increased use of corticosteroids for the treatment of patients with acute ITP. When corticosteroids are chosen to treat patients with acute childhood ITP, it has been proposed that BMA be performed to reduce the risk of obscuring the diagnosis.[15]

Studies,[4] including this one, that demonstrate the low prevalence or absence of leukemia in children with typical ITP, when taken together with studies showing the low incidence of children with normal Hb levels, neutrophil counts, and WBC counts in childhood leukemia presentations,[5,6] provide evidence that a normal Hb level, neutrophil count, and WBC count accurately identify typical ITP.

Given our study's relatively large sample size, we calculated with 95% confidence that the risk of missing the diagnosis of leukemia in this setting is no greater than 1%.[7] This must be considered in light of the concern, but lack of clear published evidence, for bad outcomes in children with leukemia inadvertently treated with corticosteroids.

This study has several limitations. It is retrospective and relies on clinical records. A prospective study, however, would be considerably more difficult; given the systematic nature of collection and recording of the clinical data necessary for this study, a retrospective study approach is justified. Generalizability is not likely to be a problem given the widely available standardized automated hematology technology and certified laboratory technicians. Referral bias is also not a problem because bias would be expected to increase the number of atypical cases and yield, and thus not affect the credibility of these results. The cutoff values arbitrarily chosen for typical hematologic features of ITP are pivotal to this study. The fact that these values were predetermined by consensus and represent accepted normal reference ranges are a strength of this study.

CONCLUSION

The results of this study suggest that BMA is not appropriate for children with typical hematologic features of acute childhood ITP.

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