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A blinded study of bone marrow examinations in patients with primary immune thrombocytopenia

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Abstract

Objective—The role of bone marrow examinations in patients with primary immune thrombocytopenia (ITP) is uncertain. The objectives of this study were to determine the inter-rater reliability of bone marrow examinations and to identify distinguishing morphological features of ITP bone marrows under controlled conditions.

Methods—Histological slides of bone marrow biopsy specimens and aspirates from 32 adult patients with severe primary ITP who had failed a median of two treatments, and 51 non-thrombocytopenic controls were retrieved from hospital archives. Slides were arranged in random order in a slide box and coded. Blinded to the diagnosis and platelet counts, three independent hematopathologists were asked to identify the ITP bone marrows and to evaluate megakaryocyte number, morphology, and distribution.

Results—Overall chance-corrected agreement on ITP classification among the three raters was poor [κ (κ) = 0.30; 95% confidence interval 0.22–0.38]. Raters were generally unable to

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Author contributions

D. Arnold takes primary responsibility for the paper. D. Arnold, W. Lim, J. George designed the research; V. Mahabir, C. Ross, S. Popovic, M. Sur, J. Bourgeois, L. Toltl, and D. Arnold performed the research, contributed analytical tools, and collected the data; V. Mahabir, C. Ross, G. Wang, R. Cook, J. George, W. Lim, L. Toltl, I. Nazi, J. Kelton, and D. Arnold analyzed and interpreted the data; G. Wang, R. Cook performed statistical analysis; V. Mahabir, C. Ross, J. Kelton, and D. Arnold wrote the manuscript.

Disclosure statement

None of the authors have any conflict of interest to report relevant to this paper.

correctly identify the ITP bone marrows from controls. Increased number of megakaryocytes, while an uncommon finding, was more frequent among ITP patients compared with controls (6/32, 18.8%; vs. 2/51, 3.9%; $P = 0.05$), and abnormal megakaryocyte morphology often led individual raters to reach a diagnosis of ITP. Overall sensitivity and specificity of bone marrow examinations were 24% and 90%, respectively.

Conclusions—This study confirms methodologically that bone marrow examinations are unreliable and frequently non-diagnostic in ITP. Thus, they are not useful for patients with typical disease. Rare subsets of patients with severe ITP demonstrated unique features such as increased number of megakaryocytes.

Keywords

platelets; bone marrow; megakaryocyte; immune thrombocytopenia; reliability

Immune thrombocytopenia (ITP) is a common autoimmune disorder characterized by low platelet counts that can lead to bleeding (1). ITP patients typically have no other physical or laboratory findings to confirm the diagnosis; thus, ITP remains a diagnosis of exclusion. Measurements of platelet turnover and antiplatelet antibodies have been examined in ITP patients; however, platelet turnover studies are not easily applied in practice and current platelet autoantibody testing is insensitive (2, 3). The recent introduction of thrombopoietin (TPO) receptor agonists as an effective treatment for ITP has reaffirmed that ITP may be caused by an impairment in platelet production and has refocused attention on abnormalities of bone marrow megakaryocytes (4).

Bone marrow examinations in ITP have been investigated in studies dating back several decades. Some investigators have found megakaryocyte numbers to be increased (5–7), while others have found them to be normal (8). Similarly, abnormal megakaryocyte morphology including diminished granularity and decreased nuclear ploidy among other findings were observed by some investigators (9, 10) but not others (11, 12). These discrepancies may have arisen because early studies lacked appropriate methodological tools or as a reflection of the subjective nature of bone marrow reporting. Overall, investigators have reached differing conclusions as to whether bone marrow morphology displays unique features in ITP, and the value of bone marrow examinations in ITP in general. Recent guidelines recommend against bone marrow examinations in typical ITP patients (13); however, the evidence in support of this recommendation was weak.

To definitively address the usefulness of bone marrow examinations in patients with ITP, we determined the inter-rater reliability and accuracy of this test based on blinded, independent review of bone marrow specimens by three experienced hematopathologists. The objectives were to determine the agreement between raters and to describe morphological features unique to ITP patients. This study has implications for clinical practice and may shed light on ITP pathogenesis.

Patients and methods

ITP patients and non-thrombocytopenic controls

Bone marrow specimens from adult ITP patients and non-thrombocytopenic controls were retrieved for pathological review. ITP patients had a primary ITP based on American Society of Hematology criteria (13) with isolated thrombocytopenia and a platelet count level below $100 \times 10^9/L$ at the time of the bone marrow procurement. The decision to perform a bone marrow examination was made at the discretion of the treating physician, most often due to disease severity and lack of response to ITP treatment. The pathology report associated with those specimens revealed no underlying bone marrow disorder. Patients were excluded if they had ITP secondary to lymphoma, human immunodeficiency virus (HIV), hepatitis B, or hepatitis C or if they had received treatment with TPO receptor agonists. Control patients had limited-stage lymphoma or monoclonal gammopathy of undetermined significance. Bone marrow specimens were done for staging purposes, and the pathology report associated with those specimens described no disease involvement. Control patients had a normal platelet count ($150\text{--}450 \times 10^9/L$) at the time of the bone marrow procurement and were excluded if they had splenomegaly, HIV, hepatitis B or hepatitis C, or if treatment with hematopoietic growth factors or antineoplastic drugs had been administered. Eligibility of ITP patients and controls was confirmed by duplicate chart review. All bone marrow biopsies and aspirates were performed at one academic hospital using the same technique and the same method of slide preparation. This study was approved by the research ethics boards of Hamilton Health Sciences, McMaster University.

Pathological review

Bone marrow biopsy and aspiration slides were retrieved from hospital archives. Biopsy specimens had been prepared from $0.1 \mu m$ formalin-fixed sections and stained with hematoxylin and eosin. All slides were coded and arranged in random order as assigned by a computer-generated random number sequence generator. Three pathologists, each with at least 5 yr experience in bone marrow reporting, reviewed all slides independently blinded to diagnosis, platelet count, and previous pathology reports. A standardized case report form was used to capture the important domains of ITP bone marrow histology: (i) Bone marrow cellularity (in deciles), (ii) megakaryocyte number (normal, increased, or decreased), (iii) megakaryocyte morphology (normal or abnormal), (iv) megakaryocyte distribution (normal or abnormal clustering), (v) megakaryocyte assessment on aspirate (normal or abnormal), and (vi) final classification (ITP or normal; Fig. 1). These criteria were chosen to reflect the most frequently reported pathological findings in ITP (4). Given the wide range of morphological findings reported in previous studies and to replicate clinical practice, we did not provide pathologists with predefined criteria that would indicate ITP; instead, we asked them to report objectively on each domain, and we summarized the morphological findings descriptively. Agreement among raters on bone marrow cellularity (within two deciles), which was used as a measure of calibration, was excellent [$\kappa = 0.80$; 95% confidence interval (CI) 0.74–0.86].

Statistical analysis

Inter-rater reliability was calculated using overall and pairwise chance-corrected agreement (κ). By convention, κ below 0.40 reflects poor agreement, and κ above 0.75 reflects excellent agreement (14). Accuracy was determined by the proportion of bone marrow specimens correctly identified as ITP by all three raters. Bone marrow features were compared between groups using the chi-square or Fisher's exact test. Logistic regression was used to determine the association between a final diagnosis of ITP and abnormal megakaryocyte number, morphology, distribution, or aspirate findings for each rater. We estimated that 30 ITP patients and 30 controls would provide adequate precision estimates, assuming a baseline sensitivity of 80%, specificity 80%, and precision of 30% for the classification of ITP.

Results

Bone marrow specimens from 32 ITP patients and 51 non-thrombocytopenic controls were retrieved for pathological review. Median age of ITP patients was 57 yr [inter-quartile range (IQR) 31–73], 40.6% were female, and the median platelet count at the time of bone marrow procurement was $21 \times 10^9/L$ (IQR 6–45). Patients had ITP for a median of 1 yr (IQR 0.5–2) and had received a median of two prior treatments (IQR 1–3; Table 1). Control patients had normal platelet counts. ITP patients and controls had normal leukocyte counts and hemoglobin concentrations.

Inter-rater reliability of bone marrow assessments for the diagnosis of ITP was poor ($\kappa = 0.30$; 95% CI, 0.22–0.38). All three pathologists correctly agreed on the diagnosis of ITP for only 2/32 (6.3%) ITP patients, and more frequently overcalled ITP in the control group (Table 2). By logistic regression, abnormal megakaryocyte morphology was associated with a final diagnosis of ITP by any individual rater: The probability of concluding ITP based on abnormal morphology was 82% for rater A; 99% for rater B; and 77% for rater C. The abnormal morphological features that were reported by pathologists included immature forms of megakaryocytes, abnormal clustering, and hyperlobulation; however, no single abnormality was consistently reported. Increased megakaryocyte number was reported by all three raters in 6/32 (18.8%) ITP patients and 2/51 (3.9%) controls ($P = 0.05$; Table 2). The mean sensitivity of bone marrow biopsy across all three raters for the diagnosis of ITP was 24% (95% CI, 15–37%) and specificity was 90% (95% CI, 82–84%). Findings on aspirates did not correlate with the diagnosis of ITP, and the proportion of patients with aspirates reported as abnormal by all three raters was not different between groups.

Discussion

Using a rigorous methodological approach, we found that experienced pathologists were unable to identify ITP patients based on bone marrow examinations. However, a subset of ITP patients with severe disease displayed abnormal megakaryocyte morphology and increased megakaryocyte numbers. Our study provides evidence to support the widely held opinion that bone marrow examinations have limited utility for the diagnosis of ITP and suggests that ITP is a morphologically heterogeneous disease. Our data may also be interpreted as demonstrating a high prevalence of normal or non-diagnostic bone marrows in

patients with clinically diagnosed primary ITP, which is consistent with clinicians' expectations. Either way, our data support the conclusion that bone marrows need not be obtained for typical ITP patients.

Prior investigations of bone marrow features of ITP patients date back several decades. Limarzi and Schleicher (15) reported megakaryocyte hyperplasia with non-granular pseudoplatelet formation. Dameshek and Miller (10) reported diminished megakaryocyte granularity, diminished platelet production, and degenerative changes. Valentine (9) reported decreased megakaryocyte granularity, decreased ploidy, a smooth 'non-budding' cellular membrane, and increased proportion of immature forms. Diggs and Hwelett (11) found no changes or only very subtle changes in bone marrow morphology and megakaryocyte numbers. Harker (16) concluded that ITP patients had megakaryocytes that were more numerous and larger than controls. Overall, investigators reached discrepant conclusions as to the morphological features that may be characteristic of ITP bone marrow. As such the value of bone marrow examinations in typical ITP patients has been a matter of controversy, perhaps because of the methodological shortcomings of previous studies or the subjective nature of bone marrow reporting. Under carefully controlled conditions, our study demonstrates that ITP bone marrows from patients with severe ITP are similar to unaffected controls, except for a subset of patients who demonstrate unique morphological features.

The role of bone marrow examination in thrombocytopenic patients is to exclude hematological disease such as leukemia in children, or myelodysplastic syndrome in adults. It should be performed in patients who present with other cytopenias or hematological abnormalities. However, bone marrow examinations are rarely informative in patients with isolated thrombocytopenia. For example, in a large study of bone marrow samples from 332 children with ITP, none had evidence of underlying leukemia (17). Similarly, in adults, no occult malignancy was found among 86 patients with isolated thrombocytopenia (5), and no underlying hematological disease was found in 61 patients under the age of 65 presenting with isolated thrombocytopenia (18).

Our study raises the possibility that ITP may be comprised of distinct subsets of patients with unique morphological features and possibly distinct mechanisms of thrombocytopenia. For example, approximately 20% of patients in this study had increased numbers of megakaryocytes, which may indicate a disorder caused primarily by peripheral platelet destruction with appropriate bone marrow compensation. This finding fits with the observation that roughly the same proportion (20%) of ITP patients do not respond to TPO receptor agonists (19, 20). Assessments of bone marrow findings beyond gross morphology have become an area of renewed interest (21, 22) and may ultimately help determine whether platelet destruction or underproduction predominates (23, 24). This distinction may allow for individualized treatment strategies and would enable prescribers to restrict the use of expensive medications such as TPO receptor agonists to those patients who stand to benefit most.

Strengths of this study were the selection of clinically similar ITP patients, blinded triplicate pathological review, and adjusted statistical modeling. All bone marrow slides were prepared from one institution, thus ensuring consistency in slide quality. Limitations were that ITP

patients in this study may have had more severe disease than typical ITP patients by virtue of the fact that they had a bone marrow performed. However, because bone marrow examinations are not routinely done at the time of diagnosis, this study was only possible in the cohort of ITP patients selected for bone marrow examinations. To overcome this limitation, we used strict criteria to include only those patients with clinical ITP according to published guidelines (13). In addition, the control group selected for this study was not representative of patients who might typically be confused with ITP, that is, patients with thrombocytopenia due to other causes. Nevertheless, even when compared to non-thrombocytopenic controls, significant differences in bone marrow morphology were not apparent. We cannot exclude that prior ITP treatments may have altered bone marrow pathology; however, we would expect that the effect would be minor because none of the patients had received myelotoxic therapies or rituximab prior to bone marrow procurement. Pathologists may have performed better in this study than in clinical practice simply because they were being observed. In practice, pathologists are provided with the indication for the test which may influence reporting, whereas in this study, slides were coded and raters were blinded to platelet count and other clinical information to avoid confounding.

In conclusion, we found that bone marrow examination cannot be used for the diagnosis of ITP and our study provides evidence to support recent recommendations against its use in typical patients (13). A subset of severe ITP had unique bone marrow features suggesting that it is a heterogeneous disease. Future studies are needed to associate morphologic findings, even subtle changes, with clinical and genetic risk factors that might be associated with treatment responses in ITP.

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INSTRUCTIONS: The objective of this study is to determine the utility and performance characteristics of bone marrow examinations for the diagnosis of immune thrombocytopenia (ITP). Please review the 2 slides provided for each patient (one bone marrow biopsy, and one bone marrow aspirate) and check **one answer** for each question. Each specimen is from either a normal control or a patient with ITP.

Pathologist name: _____
Specimen ID #: _____

1. **Marrow cellularity:** ☐ <20%; ☐ 20–30%; ☐ 30–40%; ☐ 40–50%
☐ 50–60%; ☐ 60–70%; ☐ 70–80%; ☐ >80%

2. **Megakaryocyte number:** ☐ WNL; ☐ Increased; ☐ Decreased

3. **Megakaryocyte morphology:** ☐ WNL; ☐ Abnormal

Describe pertinent findings:

4. **Megakaryocyte distribution:** ☐ WNL; ☐ Abnormal

Describe pertinent findings:

5. **Megakaryocyte assessment on aspirate:** ☐ WNL; ☐ Abnormal;
☐ Aspirate not available

Describe pertinent findings:

6. **FINAL ASSESSMENT- Most consistent with:** ☐ ITP; ☐ WNL

Additional comments:

ITP= immune thrombocytopenia; WNL = within normal limits

Figure 1.

Assessment form for blinded pathological review of bone marrow slides from primary immune thrombocytopenia (ITP) patients and non-thrombocytopenic controls.

Table 1

Characteristics of patients with primary immune thrombocytopenia (ITP) and non-thrombocytopenic controls

	ITP (<i>N</i> = 32)	Controls ¹ (<i>N</i> = 51)
Age (yr)	57 (31–73)	67 (54–75)
Female (number, %)	13 (40.6%)	19 (37.3%)
Total leukocytes ($\times 10^9/L$)	7.7 (6.7–10.7)	6.8 (5.8–9.3)
Hemoglobin (g/L)	137 (123–145)	133 (120–143)
Platelets ($\times 10^9/L$) ²	21 (6–45)	268 (206–323)
Recent ITP treatments ³	Corticosteroids (<i>n</i> = 24) IVIG (<i>n</i> = 16) Immunosuppressants (<i>n</i> = 5) ⁴ Danazol (<i>n</i> = 2)	None

IVIG, intravenous immune globulin.

Median (inter-quartile range), unless otherwise specified. None of the patients had received myelotoxic treatments (such as vincristine or cyclophosphamide) or rituximab prior to bone marrow procurement.

¹ Controls were patients with lymphoma (*N* = 42) or monoclonal gammopathy of undetermined significance (*N* = 9) who had a bone marrow examination performed for staging purposes that showed no bone marrow involvement.

² Platelet counts were measured 3 d (median) before bone marrow procurement.

³ Treatments received in the 4 wk before bone marrow procurement.

⁴ Immunosuppressants refer to cyclosporine, azathioprine, and mycophenolate mofetil.

Table 2

Bone marrow features and final diagnosis agreed upon by all three raters

	ITP (<i>n</i> = 32) (%)	Controls (<i>n</i> = 51) (%)	<i>P</i> -value
Increased megakaryocyte number	6 (18.8)	2 (3.9)	0.05
Abnormal megakaryocyte morphology	2 (6.3)	1 (2.0)	0.56
Abnormal megakaryocyte distribution	0	0	
Abnormal megakaryocyte features on aspirate ^{<i>I</i>}	1 (3.4)	2 (4.0)	1.0
Final diagnosis of ITP	2 (6.3)	37 (72.5)	<0.0001

^{*I*} Bone marrow aspirate slides were missing for two patients with immune thrombocytopenia and one control patient.