Occult Hemorrhage in Immune Thrombocytopenia

Adolfo Flores and George R. Buchanan

Assessing clinical bleeding in patients with immune thrombocytopenia (ITP) and predicting future risk of major hemorrhage has proven to be a complicated task given the heterogeneity in bleeding manifestations. Although bleeding scales have been used for this purpose, they fail to account for occult or subclinical hemorrhage. Little is known about the frequency and clinical significance of occult hemorrhage in ITP and no formal investigations have been published on the subject. However, determining the prevalence and incidence of occult hemorrhage may shed light on our understanding of bleeding severity in both children and adults. This review explores the potential clinical significance, sites and methods of testing of subclinical microbleeding in ITP.

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Hemorrhage in immune thrombocytopenia (ITP) is extremely variable with regard to body site and clinical severity. Platelet count has often been used as a surrogate marker to define bleeding severity and to predict future risk of hemorrhage in persons with ITP. Despite having a low platelet count (< 20,000/μL), the great majority of children with ITP do not have major bleeding at diagnosis or during the following 28 days. Yet it is difficult if not impossible for even the most experienced hematologist to predict which children with severe thrombocytopenia will develop life-threatening hemorrhage upon presentation or later in the course of their disease.

Over the past 30 years, hematologists have relied on bleeding scales not only to grade or quantify bleeding that is already apparent but also to help gauge whether a particular patient may be at risk of impending life-threatening hemorrhage. However, there are many limitations and imperfections in the bleeding scales currently in practice, particularly the use of broad, subjective categories to define and grade hemorrhage. The characteristics of these bleeding tools have been extensively reviewed in work previously published by Koreth and Key. One of the constraints of most bleeding scales is that they only measure readily observable bleeding. Most hemorrhage in patients with ITP is external and easily appreciated on physical examination. On the other hand, bleeding in some ITP patients may also be “occult” or “silent” and not readily determined by history and/or physical examination. Such hemorrhage, if it were felt to be important, would have to be evaluated through laboratory tests and/or imaging studies.

THE POTENTIAL IMPORTANCE OF ASSESSING OCCULT HEMORRHAGIC SITES

Occult hemorrhage can theoretically occur in any internal organ in ITP patients with severe thrombocytopenia. Although most hematologists will ask their patients whether they have noticed gross blood in the urine or stool, many do not routinely test for the presence of microscopic bleeding in these sites. This is largely because it is not felt to occur or to be important. Moreover, most previous ITP guidelines do not specify whether the use of laboratory assessments to test for microscopic blood should be employed as means to guide patient management. Unfortunately, little is actually known about the frequency and clinical relevance of occult hemorrhage in ITP. No formal investigations exist in the literature regarding how often occult hemorrhage indeed occurs in ITP and whether or not it is...
clinically significant. Currently, there is much interest in developing better methods of assessing clinical bleeding in ITP, largely by implementing more sensitive bleeding scales. Since measurement of disease manifestations remains one of the most important tools of physicians (especially in a complex disease such as ITP), determining the prevalence and incidence of occult hemorrhage may shed light on our understanding of bleeding severity in both children and adults.

Four sites of occult hemorrhage deserve special attention, ie, microscopic hematuria, fecal occult blood, retinal hemorrhage, and silent (subclinical) intracranial hemorrhage (ICH). Table 1 provides a review of potential tests and imaging methods that might be used to assess each of these sites of occult hemorrhage, along with their potential limitations.

### CASE REPORTS IN THE LITERATURE

Occult bleeding in ITP is infrequently reported in the literature. Retinopathy is a frequent finding in persons with severe thrombocytopenia, especially when they are anemic as well. Accordingly, retinal hemorrhages have been reported largely in patients with leukemia, aplastic anemia, or myelodysplastic syndromes. It is noteworthy that very little has been written about ocular complications in children or adults with ITP except for a few single case reports in the ophthalmology literature. While some cases of asymptomatic vitreoretinal hemorrhage have been reported in chronic ITP patients, sudden loss of visual acuity secondary to retinal bleeding has also been reported as the first presenting clinical feature in ITP. Two case reports (one adult and one pediatric) have described retinal hemorrhage at diagnosis or shortly thereafter in the absence of previous trauma occurring prior to or concurrently with ICH.

### HEMATURIA AND OTHER BLEEDING MANIFESTATIONS

In 2009, Psaila et al reported a study of intracranial hemorrhage in children with ITP identified from 1987 to 2000. Forty patients with ICH and 80 matched ITP control subjects without ICH were evaluated. Bleeding manifestations from diagnosis of ITP to occurrence of ICH were distinguished and compared between the two study populations. Hematuria (22.5%) and head trauma (33%) were identified to be the most prominent features in children with ICH, whereas none of the control subjects were reported as having hematuria and only one had previous head trauma. Of the nine children (22.5%) with ICH and urinary tract bleeding, five had macroscopic while three had microscopic hematuria, and one child the nature of the bleeding was unspecified. Additionally, bleeding beyond petechiae and ecchymoses, including wet purpura, epistaxis, and gastrointestinal bleeding, were described to be linked to ICH, but this finding was not statistically significant. Although this study may be among the largest primary case series of ICH in children with ITP, it is not without limitations. While reporting biases are certainly a consideration, perhaps the most important limitation of this study is that the number of patients in the control population who had urinalyses performed to determine the presence or absence of microscopic hematuria is unknown. Therefore, while an association between hematuria and ICH was suggested in this study, the limited data

<table>
<thead>
<tr>
<th>Bleeding Site</th>
<th>Potential Method</th>
<th>Test Detection</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Guaiac</td>
<td>Heme (peroxidase activity)</td>
<td>Dietary interference (plant peroxidases, red meat, vitamin C)</td>
</tr>
<tr>
<td>Urinary</td>
<td>Immunochemical</td>
<td>Globin (erythrocyte peroxidase activity)</td>
<td>Only detects colonic bleeding, false positive results (myoglobinuria, dehydration, exercise)</td>
</tr>
<tr>
<td>Retinal</td>
<td>Microscopy (3 RBCs/hpf)</td>
<td>RBC visualization</td>
<td>Patient cooperation required, time-consuming</td>
</tr>
<tr>
<td>Brain</td>
<td>MRI</td>
<td>Brain microbleeds (hemosiderin deposits)</td>
<td>Possible sedation in younger children, costly</td>
</tr>
</tbody>
</table>

Abbreviations: RBC, red blood cell; hpf, high-power field; MRI, magnetic resonance imaging.
regarding microscopic hematuria in the control group makes this association less convincing.

Upon examining large pediatric ITP cohort studies that reported gastrointestinal, urinary and intracranial hemorrhages, it appears that there has been a marked increase in bleeding prevalence in these sites during the past ten years (Table 2).1,22–24 Unfortunately, none of these studies specified whether the gastrointestinal and urinary bleeding events were occult (ie, microscopic) or gross (visible to the patient and clinician) in nature. Nevertheless, this apparent increase in bleeding frequency, particularly in sites where bleeding has historically been perceived as being less common, raises several questions: (1) Are children with ITP now experiencing more bleeding in these sites than previously thought? (2) Does the potential for prior underreporting of gastrointestinal and urinary bleeding exist given that ICH has received so much attention as the only clinically relevant site of “internal” bleeding? (3) Is it possible that some hematologists have been more recently supplementing their findings on physical examination with laboratory tests and imaging in order to screen for occult hemorrhage?

THE POSSIBILITY OF MINUTE CEREBRAL CAPILLARY HEMORRHAGES IN ITP

One important site of occult bleeding that merits further discussion is silent intracranial hemorrhage. Subclinical intracranial bleeding was first hypothesized to occur in a 1971 report by Matoth and Zaizev, who described children with chronic ITP as possibly having “minute cerebral capillary bleeding.”1,25 These authors observed that there was a high incidence of minimal cerebral dysfunction (MCD) in their chronic ITP patients. This led to an investigation in which the authors compared 20 children with chronic ITP to two control groups each consisting of 19 subjects—one with rheumatic fever and the other a combination of healthy children and children suffering from chronic abdominal pain of uncertain etiology. Neurological and psychological examinations were completed on all subjects, with electroencephalographic (EEG) tracings obtained for the chronic ITP population. According to the study’s findings, 20% of chronic ITP patients were diagnosed with MCD and 50% of them were reported to have mild diffuse EEG changes thought at the time to be consistent with MCD. Consequently, the authors speculated that acquired organic brain lesions might explain these findings, which were possibly the result of multiple minute cerebral capillary hemorrhages. Although this report has several flaws in its methodology, to our knowledge it is the first to speculate that subclinical intracranial hemorrhages might occur in ITP and have potential deleterious consequences.

BRAIN MICROBLEEDS AS FUTURE PREDICTORS OF ICH

Subclinical intracranial hemorrhages, also known as brain microbleeds, are currently being studied by neurology and neuroimaging specialists in adults with hypertension and previous stroke as prognostic markers for risk of developing future brain hemorrhages.26–28 Brain microbleeds are a radiologic construct visualized through magnetic resonance imaging (MRI) that represent perivascular collections of hemosiderin-laden macrophages and are considered to be silent lesions resulting from previous petechial hemorrhages. These lesions are small (<5 mm in diameter) and are reported to occur in 5% of healthy adults.12 Because this field of study is relatively young, to date no consensus has been reached regarding a specific imaging protocol that would allow for optimal identification.

Studies reporting an association of overt ICH in patients with brain microbleeds are conflicting. While some reports suggest that the presence of microbleeds following stroke increases a patient’s risk of developing future ICH,29 others have indicated that the risk of ICH remains low.30 Some data suggest that location, such as cortical microbleeds, may better predict future risk of symptomatic ICH.31 Microbleeds and their prognostic value have yet to be studied in children and/or in patients with bleeding disorders. Nevertheless, future study of microbleeds in selected patients with severe ITP

### Table 2. Bleeding Frequency in Large Prospective Pediatric ITP Cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Evaluated Children (N)</th>
<th>Gastrointestinal (%)</th>
<th>Urine (%)</th>
<th>Intracranial (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICIS Registry I22</td>
<td>2031</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Nordic Cohort23</td>
<td>501</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ICIS Registry II1</td>
<td>863</td>
<td>8 (0.9)</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>PARC ITP Registry24</td>
<td>1784</td>
<td>52 (2.9)</td>
<td>44 (2.5)</td>
<td>10 (0.6)</td>
</tr>
</tbody>
</table>

Abbreviations: ICIS, Intercontinental Childhood ITP Study Group; PARC, Pediatric and Adult Registry on Chronic ITP.
may uncover the sequelae of occult bleeding and should be considered.

CONCLUSION

Little is known about occult hemorrhage in ITP. Characterizing sites and prevalence of occult hemorrhage may provide greater understanding of the heterogeneity in bleeding propensity among ITP patients and its relationship to serious hemorrhagic events, such as intracranial hemorrhage. Brain imaging has revolutionized our management approach to patients with many conditions, and the same could hold true for patients with severe bleeding disorders, including ITP. Although such testing for occult bleeding should not yet become part of standard care, this subject certainly merits future study.

REFERENCES


