Outcomes in Mild to Moderate Isolated Thrombocytopenia

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abstract

OBJECTIVES: Incidental isolated mild to moderate thrombocytopenia is a frequent laboratory finding prompting a referral to pediatric hematology-oncology. We tested the hypothesis that patients with isolated asymptomatic mild thrombocytopenia would not progress to require an intervention from a pediatric hematologist–oncologist.

METHODS: This is a 5-year retrospective review of 113 patients referred to pediatric hematology–oncology for isolated thrombocytopenia. Initial, lowest, and current platelet counts along with clinical course and need for interventions were recorded. Thrombocytopenia was categorized as mild (platelet count: 101–140 $\times 10^3/\mu L$), moderate (platelet count: 51–100 $\times 10^3/\mu L$), severe (platelet count: 21–50 $\times 10^3/\mu L$), and very severe (platelet count: $\leq 20 \times 10^3/\mu L$).

RESULTS: Eight of 48 patients (17%) referred for initial mild isolated thrombocytopenia progressed to moderate thrombocytopenia at 1 visit. At present, 2 of these patients have moderate thrombocytopenia, 17 remain with mild thrombocytopenia, and 29 patients have resolved thrombocytopenia. Nine of 65 patients (14%) referred for moderate thrombocytopenia progressed to severe or very severe thrombocytopenia on 1 occasion. At present, no patients have severe thrombocytopenia, 18 remain with moderate thrombocytopenia, 14 improved to mild thrombocytopenia, and 33 have resolved thrombocytopenia. Only 3 patients required interventions from a hematologist, whereas 10 patients required therapy from other subspecialties.

CONCLUSIONS: We only identified 3 patients (3%) with mild to moderate thrombocytopenia who required an intervention from a hematologist to improve platelet counts. Patients with isolated mild thrombocytopenia with a normal bleeding history and physical examination findings frequently have normalized their platelet counts within 1 month.

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Dr Lebensburger conceptualized and designed the study and drafted the initial manuscript; Drs Schlappi, Kulkarni, and Palabindela designed and coordinated data collection, conducted the initial analyses, and reviewed and revised the manuscript; Drs Bemrich-Stolz, Howard, and Hilliard participated in the design of the study, reviewed the analyses, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Isolated thrombocytopenia is a common pediatric laboratory finding among patients with a bleeding or bruising history as well as being an incidental laboratory finding. The outcomes and need for referral to pediatric hematology–oncology have not been established.

WHAT THIS STUDY ADDS: The majority of patients with mild or moderate thrombocytopenia normalized platelet counts within 3 months. Mild isolated thrombocytopenia without a bleeding history or abnormal physical findings did not require interventions from pediatric hematology–oncology; moderate isolated thrombocytopenia cases rarely required interventions.

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A broad differential diagnosis exists for pediatric patients diagnosed with isolated thrombocytopenia, defined as a platelet count <140–150 × 10^3/μL.[1,2] When platelet counts drop to <30–50 × 10^3/μL, patients may develop petechiae, bruising, and epistaxis, prompting primary care providers to obtain a complete blood count.[3,4] Isolated thrombocytopenia may also be incidentally identified by a primary care provider who performs a complete blood count for other indications, including concerns for anemia, leukopenia and/or leukocytosis, or as part of a routine health screening with hemoglobin and/or hematocrit.[5] Once isolated thrombocytopenia is identified, a primary care provider may further evaluate or refer that patient to a pediatric hematologist–oncologist on the basis of either the primary care provider's concern or parental desire.[6] Parents and patients referred for isolated mild to moderate thrombocytopenia may experience emotional distress either during the wait for their referral visit and/or the time spent in a waiting room at a pediatric hematology–oncology clinic. Often, this distress is due to concern by the patient and/or parent that the child has cancer. In addition, current health economics necessitates improved use of health care specialists. Therefore, having a clear understanding of which patients with mild to moderate thrombocytopenia require evaluation or intervention from a pediatric hematologist–oncologist would help primary care providers make the most beneficial referrals.

Although we hypothesize that pediatric patients with mild to moderate thrombocytopenia, no clinical symptoms, or any abnormal physical findings may not warrant an immediate referral to a pediatric hematologist–oncologist, there is minimal literature that can support this hypothesis. We could not identify any pediatric reports of outcomes for patients with mild or moderate thrombocytopenia and identified only 1 adult study of patients with mild persistent thrombocytopenia. Among the 191 adult patients with mild persistent thrombocytopenia, 60% remained with mild thrombocytopenia, 7% normalized their platelet counts, 7% developed an autoimmune disorder, and 6% were diagnosed with immune thrombocytopenia (ITP); 6 patients developed adult-specific malignancies (including breast, lung, and colorectal cancers and myelodysplasia).[7] To better understand the outcomes for pediatric patients with isolated mild to moderate thrombocytopenia, we conducted a retrospective chart review to assess the incidence, outcomes, and need for intervention from a pediatric hematologist–oncologist among all patients referred for thrombocytopenia over a 5-year period. We tested the hypothesis that patients with isolated mild thrombocytopenia without bruising and/or bleeding symptoms would not progress to require an intervention from a pediatric hematologist–oncologist.

METHODS

We conducted an institutional review board–approved retrospective study of all outpatient referrals to the University of Alabama at Birmingham (UAB) Pediatric Hematology Oncology Clinic from June 2012 to June 2017. We excluded patients initially admitted to the hematology oncology service at Children's of Alabama for thrombocytopenia who required additional follow-up in our outpatient clinic. The diagnosis and demographics were recorded for every patient. We recorded the date and platelet count at the time of the first episode of thrombocytopenia and the referral visit, lowest platelet count, and the most recent platelet count (as of January 2018). We categorized patients as having mild (platelet count: 101–140 × 10^3/μL), moderate (platelet count: 51–100 × 10^3/μL), severe (platelet count: 21–50 × 10^3/μL), and very severe (platelet count: ≤20 × 10^3/μL) thrombocytopenia at the time of referral on the basis of the lowest platelet count and current platelet count. We included 1 patient as mild at the time of referral despite being referred for thrombocytopenia with a platelet count of 143 × 10^3/μL; this patient had a previous clinic history of mild thrombocytopenia and an initial in-clinic platelet count of 123 × 10^3/μL. History of bruising at the time of referral, age, sex, and referring provider were recorded from clinic and referral notes. Therapeutic interventions and reason for intervention were recorded from pediatric hematology clinic notes. Finally, antineutrophil antibody, antinuclear antibody, platelet antibody, and immunoglobulin G levels were recorded. Descriptive statistics and univariate analysis were conducted by using JMP Pro 12 (SAS Institute, Inc, Cary, NC).

RESULTS

Among 2820 patients referred to the outpatient UAB Pediatric Hematology Oncology Clinic over a 5-year period, 2256 patients were referred for evaluation of a hematologic disease. The most common hematologic referral to our clinic was for sickle cell disease (*n* = 296; 13%) and the second most common referral was to evaluate thrombocytopenia (*n* = 204; 9%). Among the 204 patients with an outpatient referral for thrombocytopenia, 113 of these referrals were for isolated moderate or mild thrombocytopenia. The incidence of referrals for mild to moderate isolated thrombocytopenia was 23 patients per year. The mean age at referral was 10.6 years, and younger age was associated with a lower platelet count at the time of referral

TABLE 1 Referral Platelet Counts

Variables	*n*	Mean Platelet Count at Referral	Range
Categorical platelet count at time of referral			
Mild (101–140 × 10^3/μL)	48	120	103–143
Moderate (51–100 × 10^3/μL)	65	75	52–100
Sex			
Male	63	98	54–143
Female	50	89	52–139
Referral			
Pediatrician	91	96	52–143
Family medicine	12	88	54–139
Subspecialist (orthopedics, rheumatology, infectious disease)	5	81	58–106
Internal medicine	4	89	77–100
Hematology–oncology	1	122	
Bruising			
Positive	29	89	53–140
Negative	84	96	52–143

(*P* = .02). More patients were of male sex, and the majority of practitioners making referrals were pediatricians (Table 1). There were no statistical differences in the mean referral platelet count among 29 patients (26%) referred with a parent or referral report of increased bruising and/or bleeding as compared with 84 patients without a reported history of bruising and/or bleeding history (*P* = .2).

Among the 113 patients with isolated thrombocytopenia evaluated in our pediatric hematology clinic, 48 (42%) had isolated mild thrombocytopenia at the time of referral. Among the patients with isolated mild thrombocytopenia, 8 (17%) progressed to the moderate range during at least 1 point of follow-up, but no patients progressed to the severe or very severe ranges (Table 2). Twenty-nine (60%) of these patients currently have normal platelet counts, 17 (35%) have persistent mild thrombocytopenia, and 2 (4%) have moderate thrombocytopenia. Among those patients who had resolved thrombocytopenia, 23 resolved within 1 month and 3 additional patients resolved between 1 and 2 months. Two patients remain with moderate thrombocytopenia, 1 patient continues to be monitored by pediatric hematology for a RUNX1 mutation (familial platelet disorder with predisposition to acute myelogenous leukemia), and the other patient is being treated in rheumatology for juvenile idiopathic arthritis.

Sixty-five patients were referred with isolated moderate thrombocytopenia. Eight patients (12%) progressed to the severe thrombocytopenic range, and 1 patient (2%) progressed to very severe thrombocytopenia on at least 1 occasion (Table 2). For these patients with moderate thrombocytopenia at the time of referral, 33 (51%) currently have a normal platelet count, 14 (22%) are in the mild range, 18 (28%) have moderate thrombocytopenia, and no patients have severe thrombocytopenia on the basis of their most recent blood count.

To determine the role of monitoring of complete blood counts before

TABLE 2 Outcomes for Patients With Isolated Mild to Moderate Thrombocytopenia That Progressed to a Lower Platelet Category

Change in Category	Referral Platelet Count[a]	Lowest Platelet Count[a]	Current Platelet Count[a]	Therapeutic Intervention	Outcomes
Mild thrombocytopenia that progressed to moderate thrombocytopenia (*n* = 8)	111	74	78	No intervention	RUNX-1 mutation; monitoring for progression to AML (FPD AML)
	106	89	89	Methotrexate, etanercept	Juvenile idiopathic arthritis
	125	78	106	Steroids	Immunology managing for likely CVID
	125	53	107	Infliximab	Crohn disease
	109	88	112	No intervention	Resolved
	106	86	146	No intervention	Resolved
	127	93	147	No intervention	Viral illness, resolved
	129	74	150	No intervention	Resolved
Moderate thrombocytopenia that progressed to severe thrombocytopenia (*n* = 9)	77	35	58	No intervention	Concern for ALPS
	80	38	58	IVIG for sports participation	ITP; immunology managing for low immunoglobulin
	71	5	64	IVIG, steroids	ITP
	81	44	70	No intervention	Thrombocytopenia
	56	47	89	No intervention	Thrombocytopenia ANA-positive
	61	41	93	No intervention	Thrombocytopenia
	60	44	158	IVIG, steroids for sports	ITP
	68	41	191	No intervention	Resolved
	70	46	241	No intervention	Resolved

ALPS, autoimmune lymphoproliferative syndrome; AML, acute myelogenous leukemia; ANA, antinuclear antibody; CVID, chronic variable immunodeficiency disease; FPD, familial platelet disorder; IVIG, intravenous immunoglobulin.

[a] Platelet count units ×10^3/μL.

referral, we analyzed the time to normalization for platelet counts. Among 62 patients who had normalized platelet counts, 43 (69%) normalized at their initial referral visit to pediatric hematology–oncology. In total, 50 (81%) patients had a normalized platelet count within 1 month of their referral visit, and 55 (89%) normalized within 2 months. Next, to evaluate outcomes on the basis of the length of time patients had thrombocytopenia before the primary care provider referral, we reviewed the 2 most common clinic visits resulting in a diagnosis of thrombocytopenia: (1) acute illness (n = 32) and (2) well-child evaluations (n = 18). Thirty-one of these patients were evaluated within 2 months of their first episode of thrombocytopenia. Twenty-three (74%) currently have normal platelet counts, including 14 whose counts had normalized at the time of the referral and 19 who resolved within 2 months after referral. In contrast, of the 19 patients with thrombocytopenia identified during an acute illness or well-child evaluation who had thrombocytopenia for at least 3 months before the referral visit, only 10 (53%) have normal platelet counts.

The majority of patients were not identified with a specific diagnosis for their mild to moderate thrombocytopenia. Several of these patients presented with viral symptoms at or around the time of referral, and the symptoms either resolved before the clinic visit or soon thereafter. Specific viral etiologies were not commonly tested for, and only 2 patients were formally diagnosed with Epstein-Barr virus infection during their evaluation for thrombocytopenia. Fourteen patients referred with moderate thrombocytopenia were diagnosed with ITP, but only 3 patients required interventions. Twelve patients were diagnosed with a drug-induced thrombocytopenia (4 for valproic acid, 2 for methylphenidate, 2 for dexmethylphenidate, 2 for risperidone, 1 for valganciclovir, and 1 for sertraline). Five patients were diagnosed with rheumatologic diseases (3 for systemic lupus erythematous [SLE] and 2 for juvenile idiopathic arthritis). Two of these 5 patients presented with joint pain and thrombocytopenia; 1 patient developed joint pain 1 month after the thrombocytopenia referral; 1 patient developed fever, rash, and joint pain 20 months after the thrombocytopenia referral; and 1 patient with a history of lupus developed thrombocytopenia 6 years after the lupus diagnosis. Finally, we identified 1 patient with a clinical history of bruising and moderate isolated thrombocytopenia who was diagnosed with a rare, qualitative platelet defect (Table 3).

TABLE 3 Current Diagnoses for Referred Patients

Current Diagnosis	*N*	Mean Referral Platelet Count[a]	Range
Thrombocytopenia, unspecified	61	100	53–140
ITP	14	77	54–121
Drug-induced thrombocytopenia	12	84	52–124
Viral-induced thrombocytopenia	5	93	59–111
Systemic lupus erythematosus	3	101	70–143
Inflammatory bowel disease	2	102	78–125
Juvenile idiopathic arthritis	2	123	106–139
Neonatal alloimmune thrombocytopenia	2	59	58–59
Concern for immunodeficiency	1	84	75–92
RUNX1 mutation	1	111	—
Henoch-Schonlein purpura	1	132	—
End-stage renal disease	1	100	—
DiGeorge syndrome	1	82	—
ADP receptor deficiency	1	63	—
Common variable immune deficiency	1	125	—
Autoimmune lymphoproliferative syndrome	1	77	—
Hypothyroidism	1	59	—
X-linked thrombocytopenia	1	122	—
NICU, premature	1	97	—

ADP, adenosine diphosphate; —, not applicable.
[a] Platelet count units $\times 10^3/\mu L$.

Among the 115 cases of mild and moderate isolated thrombocytopenia, we identified 13 patients (11%) who required an intervention. Only 3 patients required therapy from a hematologist for ITP (1 for bruising and 2 for sports participation). The remaining 10 patients who required an intervention for thrombocytopenia received those interventions from another subspecialist (Supplemental Table 4).

DISCUSSION

Few patients with newly diagnosed isolated mild to moderate thrombocytopenia progressed to very severe thrombocytopenia in this cohort, and only 3 patients required interventions prescribed by a pediatric hematologist for moderate chronic ITP. One patient with a history of bruising and moderate isolated thrombocytopenia was diagnosed with a rare, qualitative platelet defect. No patients with an initial outpatient referral for isolated mild to moderate thrombocytopenia progressed to leukemia.

Many patients referred for mild to moderate isolated thrombocytopenia had a recent history of virallike symptoms. The majority of these patients had a normalization of their

platelet counts within 1 to 2 months. Pediatric patients with congenital or acquired viral infections may develop thrombocytopenia because of alterations in platelet production or platelet destruction. Prevalent viruses linked to thrombocytopenia include HIV, hepatitis C, cytomegalovirus, varicella virus, Epstein-Barr virus, and others. In patients presenting with viral symptoms, isolated thrombocytopenia, and normal physical examination results (including lack of hepatosplenomegaly), the isolated thrombocytopenia may continue over the course of the viral illness. Although there is concern that thrombocytopenia and fever might be a presentation of leukemia, our results mirror those in other large reviews of children with leukemia demonstrating that isolated thrombocytopenia with a normal hemoglobin, white blood cell count, and physical examination results and no symptoms of bone pain is unlikely to be leukemia.[8–11]

Drug-induced thrombocytopenia was the second most common diagnosis for patients in this cohort with mild to moderate thrombocytopenia. An established database for medications with a high incidence for drug-induced thrombocytopenia is available at http://www.ouhsc.edu/platelets/ditp.html. We also identified several potential additional diagnoses, such as SLE. Juvenile idiopathic arthritis and Crohn disease and/or ulcerative colitis should be considered by a primary care provider when patients present with mild to moderate thrombocytopenia. Although anemia is the most common hematologic manifestation of SLE, identified in up to 90% of cases, 40% of case patients with SLE present with a platelet count of $<150 \times 10^3/\mu L$ and 27% present with a platelet count of $<100 \times 10^3/\mu L$.[12,13] Our data is used to support screening patients with thrombocytopenia for SLE by clinical history and physical examination, and in patients with high clinical suspicion, further testing with antinuclear antibody is warranted. A second nonhematologic diagnosis to consider in patients with thrombocytopenia is Crohn disease or ulcerative colitis as an extraintestinal manifestation of these diseases. Similar to SLE, anemia is the more common hematologic manifestation of Crohn disease or ulcerative colitis, yet our group and others have identified thrombocytopenia as a rare presenting hematologic manifestation.[14,15] Finally, we identified 1 referral for a patient who was diagnosed with a rare, inherited functional platelet defect. These patients often present with manifestations of bruising, epistaxis, and/or menorrhagia in the setting of mild to moderate thrombocytopenia and a family history of mucocutaneous bleeding or menorrhagia.

The most common diagnosis for all referred patients with thrombocytopenia was ITP. However, these patients frequently presented with severe or very severe thrombocytopenia rather than mild or moderate isolated thrombocytopenia. In addition, several case patients with ITP presented to the emergency department rather than in referral to our outpatient clinic. Patients with mild to moderate thrombocytopenia that progress to very severe thrombocytopenia during ITP typically present with acute onset of bleeding or significant bruising.[16]

As a retrospective study, some limitations are worth noting. One limitation is that we analyzed history of a bleeding disorder from the referral clinic notes rather than using a validated bleeding score. Therefore, to fully assess the risk for disease-specific progression of thrombocytopenia among patients with mild to moderate thrombocytopenia, assessing bleeding history in a more comprehensive and standardized manner is helpful. There are several pediatric bleeding questionnaires designed to help distinguish between children with and without von Willebrand disease.[17–20] A second limitation exists because patients could develop progressive thrombocytopenia that was not identified. Because patients may not experience clinical signs of thrombocytopenia until a platelet count is very low, we may have missed patients with platelet counts $<50 \times 10^3/\mu L$ between clinic visits. Third, we continue to follow some patients with persistent mild to moderate thrombocytopenia without clinical signs or symptoms who lack a defined diagnosis. These patients may have a mild autoimmune thrombocytopenia or platelet antibodies not yet identified, but because they are not progressive in their current disease course, more expensive and invasive testing has been deferred. Thus, an ultimate diagnosis may not have been made. Fourth, we diagnosed several patients referred with 2 cell line abnormalities with a bone marrow failure syndrome or aplastic anemia. We acknowledge that some patients with bone marrow failure syndromes may initially present with isolated mild to moderate thrombocytopenia and require continued serial blood count monitoring for progression to additional cytopenias. Finally, we do not have a systematic referral system in place in which all thrombocytopenia cases in Alabama are referred to a pediatric hematologist–oncologist at UAB. Therefore, we would expect that several case patients with isolated mild to moderate thrombocytopenia were not referred to us by their primary care providers. However, we expect that the majority of those missing cases would have resolved

rather than progressed without referral. Therefore, this missing data are unlikely to change our findings.

CONCLUSIONS

The study shows that few patients with isolated mild to moderate thrombocytopenia require interventions from a pediatric hematologist. Interestingly, the majority of patients who needed an intervention after referral for mild to moderate thrombocytopenia received treatment from subspecialties other than hematology. Sixty percent of patients with mild isolated thrombocytopenia and 50% of patients with moderate thrombocytopenia resolved. Among those patients with resolved thrombocytopenia, ~90% resolved within 2 months. We also identified autoimmune disorders or drug-induced thrombocytopenia as potential diagnoses in patients with persistent mild to moderate thrombocytopenia. Repeat serial histories, physicals, and complete blood counts can be used to differentiate an acute versus chronic course of thrombocytopenia. These measures are needed to rule out progressive cytopenias, macrocytosis, and organomegaly as well as to assess for any clinical manifestations of thrombocytopenia.

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ABBREVIATIONS

ITP: immune thrombocytopenia
SLE: systemic lupus erythematous
UAB: University of Alabama at Birmingham

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