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Etiologies of Extreme Thrombocytosis: A Contemporary Series

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Abstract

Objective: To describe the multifactorial etiologies of extreme thrombocytosis (EXT) in different care settings and the frequency of finding an occult malignancy.

Patients and Methods: We conducted a retrospective chart review at Mayo Clinic from January 1, 2011, through December 31, 2016. Adult patients who had at least 2 readings of platelet counts greater than 1000×10^9/L within 30 days of each other were included. We determined the causes of EXT on the basis of preset definitions of precipitating factors and identified the dominant causes on the basis of the trend of platelet counts.

Results: A total of 44,490 patients had thrombocytosis, and 305 patients (0.7%) had EXT. In 242 patients (79.3%), EXT was multifactorial. Surgical complications (54.1%) and hematologic malignancies (27.9%) were the 2 most dominant causes. Thirty-eight patients (12.5%) had new diagnoses of malignancies, mostly myeloproliferative neoplasms. In inpatients, surgical complications (71.9%), concurrent/previous splenectomy (50.5%), and infections (44.9%) were the most common causes, whereas hematologic malignancies (56.9%), iron deficiency (36.7%), and previous splenectomy (28.4%) were the most common causes in outpatients. Hematologic malignancy was 3.4 times more likely to be the cause of EXT in outpatients than in inpatients (56.9% vs 16.8%), and a new diagnosis of hematologic malignancy was 1.9 times more likely to be made in outpatients (15.6% vs 8.2%). Eighty-four percent of patients had resolution of EXT within 30 days. One patient died during the period of EXT. Nonsurgical patients with hematologic malignancies had the most prolonged period of EXT.

Conclusion: Extreme thrombocytosis is a multifactorial hematologic condition, and its etiology differs substantially between inpatients and outpatients. Occult hematologic malignancies are uncommon in EXT when other major causes are present.

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The major causes of thrombocytosis can be categorized as reactive (secondary) and clonal (primary).[1] Before the advent of automated blood cell counters, *extreme thrombocytosis* (EXT; defined as platelet count $>1000\times10^9$/L) was once considered a rare event. It was thought that most of the patients with EXT had clonal hematologic disorders on the basis of the assumption that inflammation rarely causes such an extraordinary effect on platelet production.[2] However, 2 subsequent studies suggested otherwise. The first study, a retrospective analysis of 280 patients with EXT seen at an institution from 1964 to 1983, found that only fewer (14%) had hematologic malignancies.[3] A second single institutional series also found that among the 126

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patients identified with EXT from 1994 to 1999, most (55%) had reactive thrombocytosis. However, they reported a much higher proportion of patients with hematologic malignancies (45%).[4] In both studies, each case of EXT was attributed to a single cause and the nature of the patient population and care setting were not taken into consideration. In addition, these studies were conducted several decades ago, and etiologies of EXT may have changed over time. Therefore, this study was performed to determine the contemporary causes of EXT in both the inpatient and outpatient settings. The likelihood of diagnosing an occult malignancy during the evaluation of EXT was also analyzed. We hypothesized that EXT is a multifactorial condition and its pathophysiology depends on the care setting in which a patient is evaluated.

PATIENTS AND METHODS

We performed a retrospective analysis of adult patients (aged ≥18 years) seen at Mayo Clinic, Rochester, Minnesota, from January 1, 2011, through December 31, 2016. Patients who had at least 2 readings of platelet counts greater than 1000×10^9/L within 30 days of each other were identified. Patients who declined bone marrow studies despite physicians' recommendations were excluded (n=3). The causes of EXT for each patient were determined using the following definitions:

1. *Trauma:* Any major trauma requiring surgery under general anesthesia within 30 days before the first reading of EXT.
2. *Surgery:* Major surgery under general anesthesia within 30 days before the first reading of EXT.
3. *Asplenia:* Any history of splenectomy or splenic infarction. We marked "concurrent splenectomy" if the patient received splenectomy within 30 days before the first reading of EXT.
4. *Infection:* (a) Active infection with definitive microbiological evidence within 14 days before the first reading of EXT or (b) receiving therapeutic antibiotics for recent infections at the time of EXT.
5. *Inflammation (noninfectious):* (a) Identifiable inflammatory disorder with active symptoms, abnormal C-reactive protein levels or erythrocyte sedimentation rate, within 14 days before the first reading of EXT or (b) receiving treatment for previously diagnosed inflammatory conditions.
6. *Hematologic malignancy:* (a) Diagnosis of any myeloproliferative neoplasm (MPN) or (b) non-MPN hematologic malignancies which had at least 1 reading of thrombocytosis (platelet count $>450\times10^9$/L) within 12 months before the first reading of EXT that could not be attributed to other causes. Extreme thrombocytosis caused by hematologic malignancies was considered clonal thrombocytosis, whereas EXT not caused by hematologic malignancies was considered reactive thrombocytosis.
7. *Nonhematologic malignancy:* Thrombocytosis at the time of the diagnosis of nonhematologic malignancy that could not be attributed to other causes.
8. *Medications:* (a) Received medications known to be associated with thrombocytosis (eg, romiplostim and eltrombopag) within 14 days before the first reading of EXT or (b) received myelosuppressive chemotherapy resulting in thrombocytopenia within 30 days before the first reading of EXT (rebound thrombocytosis).[5]
9. *Iron deficiency:* Reduced iron stores within 1 year before the first reading of EXT. If patients had received iron supplements since the last report of iron deficiency and mean corpuscular volume had returned to normal before EXT, the previously diagnosed iron deficiency would be considered resolved at the time of EXT.
10. *Hemorrhage:* Symptomatic bleeding in a critical area or region not caused by trauma or surgery, with a fall in hemoglobin level of at least 20 g/L (1.24 mmol/L) or with requirement of transfusion of at least 2 units of red blood cells within 30 days before the first reading of EXT.

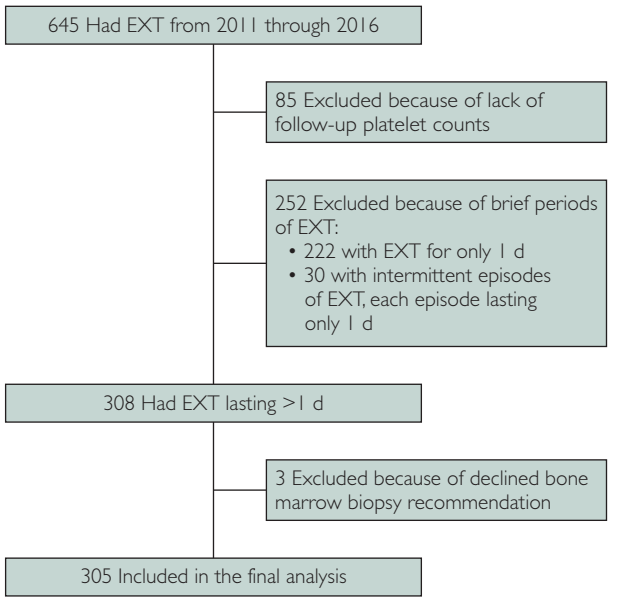

FIGURE 1. Study flowchart. EXT = extreme thrombocytosis.

11. *Electroconvulsive therapy:* Received electroconvulsive therapy within 14 days before the first reading of EXT.

One author (R.W.H.) classified the potential cause(s) for each case of EXT according to the above definitions. Cases not easily defined by the first author were reviewed by a second author (A.R.) and the senior investigator (R.S.G.) and discussed in conferences. The number of causes for each case of EXT was tabulated. For cases with multiple causes, we analyzed the trend of platelet counts to determine the dominant cause. We performed separate analyses for patients who developed EXT in the inpatient and outpatient settings. Lastly, the 30-day trend of platelet counts was analyzed according to the major causes of EXT to determine the natural history. The study was approved and informed consent waived by the Mayo Clinic Institutional Review Board.

RESULTS

Study Inclusion

A total of 44,490 unique patients were found having thrombocytosis (platelet count $>450\times10^9$/L) from 2011 to 2016. Among them, 645 patients (1.4%) had EXT. We identified 305 patients who met the inclusion criteria (Figure 1), including 109 outpatients (35.7%) and 196 inpatients (64.3%). The median age was 57 years (range, 18-95 years; inpatients, 54.5 years; outpatients, 63 years), and the median highest platelet count was 1242×10^9/L.

Causes of EXT

Multiple factors contributed to EXT in 242 patients (79.3%), whereas only a single factor was identified in the remaining 63 patients (20.7%). In total, 210 patients (68.9%) had reactive thrombocytosis alone, 33 patients (10.8%) had clonal thrombocytosis alone, and 62 patients (20.3%) had both. For multifactorial EXT cases, we identified the dominant cause for each case on the basis of the trend of platelet counts as well as the clinical events at the time, and categorized all 305 cases of EXT in Table 1. Surgical complications were the dominant cause (54.1%), followed by hematologic malignancy without recent surgery (27.9%). Although commonly seen in patients with EXT, infection and/or inflammation (8.9%), asplenia (2.0%), or iron deficiency (0.3%) was rarely the dominant cause of EXT, and they usually coexisted with recent surgeries or hematologic malignancies. Medications were the dominant cause of EXT in 19 patients (6.2%). Of these 19 patients, 12 (3.9%) were prescribed medications associated with thrombocytosis whereas 7 (2.3%) had rebound thrombocytosis after myelosuppressive chemotherapy. In the former, medications included gemcitabine (41.7%), romiplostim (25.0%), pegfilgrastim/filgrastim (25.0%), and eltrombopag (8.3%), whereas in the latter, they included antimitotic agents (topoisomerase inhibitors [doxorubicin, daunorubicin, etoposide, and idarubicin] and others [decitabine and bleomycin]; 85.7%), antimetabolites (pemetrexed and cytarabine; 57.1%), and alkylating agents (cisplatin, carboplatin, and ifosfamide; 42.9%). Two patients (0.7%) had EXT caused by hemorrhagic shock after catheterization procedures for portal vein thrombosis. Two patients (0.7%) received electroconvulsive therapy (not shown in Table 1) right before EXT, but both of them also had hematologic malignancies.

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TABLE 1. Major Combinations of Causes of Extreme Thrombocytosis in 305 Patients[a]

Major causes							
Surgical complications	Hematologic malignancy	Infection/ inflammation	Medications	Splenectomy	Nonsurgical hemorrhage	Iron deficiency	n (%)
Surgical complications: 165 (54.1%)							
Trauma		+/−					8 (2.6)
Trauma		+/−		Concurrent			19 (6.2)[b]
Nontrauma		+/−				+/−	47 (15.4)
Nontrauma		+/−		Concurrent		+/−	63 (20.7)
Nontrauma		+/−		Previous		+/−	18 (5.9)
Nontrauma	+	+/−				+/−	3 (1.0)
Nontrauma	+			Concurrent		+/−	6 (2.0)
Nontrauma	+			Previous			1 (0.3)
Hematologic malignancy without surgery: 85 (27.9%)							
	+					+/−	60 (19.7)
	+			Previous		+/−	5 (1.6)
	+	+				+/−	16 (5.2)
	+	+		Previous			4 (1.3)
Infection/inflammation without surgery or hematologic malignancy: 27 (8.9%)							
		+				+/−	19 (6.2)
		+		Previous		+/−	8 (2.6)
Medications: 19 (6.2%)							
			Direct[c]			+/−	4 (1.3)
		+	Direct[c]	Previous			2 (0.7)
			Direct[c]	Previous		+/−	6 (2.0)
			Rebound[d]				5 (1.6)
			Rebound[d]	Previous			1 (0.3)
Nontrauma			Rebound[d]				1 (0.3)
Others: 9 (3.0%)							
				Previous		+/−	6 (2.0)
		+/−			+		2 (0.7)
						+	1 (0.3)
Total							
166 (54.4%)	95 (31.1%)	163 (53.4%)	19 (6.2%)	139 (45.6%)	2 (0.7%)	47 (15.4%)	305

[a]+ = present; − = not present.

[b]Includes 2 trauma cases managed with Gelfoam embolization of the splenic artery, leading to splenic infarction.

[c]Medications associated with thrombocytosis: gemcitabine, romiplostim, pegfilgrastim, filgrastim, and eltrombopag.

[d]Rebound thrombocytosis after myelosuppressive therapy: antimitotic agents (doxorubicin, daunorubicin, etoposide, idarubicin, decitabine, and bleomycin), antimetabolites (pemetrexed and cytarabine), and alkylating agents (cisplatin, carboplatin, and ifosfamide).

Diagnoses of New Malignancies

Thirty-eight patients (12.5%) were diagnosed with new malignancies, including 33 hematologic malignancies (86.8%) and 5 nonhematologic malignancies (13.2%) (Table 2). In most of these patients (20 patients [52.6%]), patients were undergoing clinical evaluation in the outpatient setting. Myeloproliferative neoplasms accounted for 30 of the 33 cases of newly diagnosed hematologic

TABLE 2. New Malignancies Diagnosed During the Evaluation of Extreme Thrombocytosis

Type of malignancy	Setting		
	Inpatient	Outpatient	Combined
Hematologic malignancies	16 (88.9)	17 (85.0)	33 (86.8)
Essential thrombocytosis	7 (38.9)	10 (50.0)	17 (44.7)
Chronic myeloid leukemia	4 (22.2)	2 (10.0)	6 (15.8)
Polycythemia vera	2 (11.1)	1 (5.0)	3 (7.9)
Primary myelofibrosis	1 (5.6)	1 (5.0)	2 (5.3)
Undifferentiated myeloproliferative neoplasms	1 (5.6)	1 (5.0)	2 (5.3)
Diffuse large B-cell lymphoma	1 (5.6)	1 (5.0)	2 (5.3)
Acute myeloid leukemia	0 (0.0)	1 (5.0)	1 (2.6)
Nonhematologic malignancies	2 (11.1)	3 (15.0)	5 (13.2)
Colon cancer	1 (5.6)	1 (5.0)	2 (5.3)
Ovarian cancer	0 (0.0)	1 (5.0)	1 (2.6)
Gastric cancer	0 (0.0)	1 (5.0)	1 (2.6)
Squamous cell carcinoma of the mandible	1 (5.6)	0 (0.0)	1 (2.6)

Data are presented as No. (percentage).

malignancies. Essential thrombocytosis was the most common newly diagnosed hematologic malignancy (44.7%), followed by chronic myeloid leukemia (15.8%) and polycythemia vera (7.9%). All the 5 patients with nonhematologic malignancies had clinical signs and symptoms of malignancies, and EXT occurred during the evaluation of malignancies in either the postoperative (n=4) or the postbiopsy setting that was complicated by hepatic abscess (n=1).

Influence of Care Settings

We calculated the frequency of each factor as a cause of EXT and presented the results based on the care settings in Figure 2A. For inpatients, surgery (71.9%), asplenia (50.5%; including 36.7% with concurrent splenectomy and 13.8% with previous splenectomy), and infection (44.9%) were the most common causes of EXT. Most of the asplenia (72.7%) and infections (77.3%) followed recent surgeries. For outpatients, hematologic malignancy (56.9%), asplenia (36.7%), and iron deficiency (28.4%) were the most common. Hematologic malignancy was 3.4 times more likely to be the cause of EXT in outpatients than in inpatients (56.9% vs 16.8%), and a new hematologic malignancy was 1.9 times more likely to be diagnosed in outpatients (15.6% vs 8.2%).

As most cases of EXT were multifactorial, the 5 most common clinical scenarios for inpatients and outpatients are displayed Figure 2B. For inpatients, all the top 5 most common scenarios were combinations between nontrauma surgery or asplenia and infection or inflammation. For outpatients, 3 of the top 5 most common scenarios were combinations of hematologic malignancy or iron deficiency and infection or inflammation. The remaining 2 were nontrauma surgery from recent hospitalization and medications.

Outcomes

One patient died during the period of EXT. The cause of death was bleeding from portal vein puncture during endoscopic retrograde cholangiopancreatography and not considered as a direct result of EXT. Sixteen patients were lost to follow-up before resolution of their EXT (platelet count $\leq 1000\times10^9$/L). Of the remaining 288 patients, 242 (84.0%) had resolution of EXT within 30 days whereas 46 patients (16.0%) had prolonged EXT (>30 days), with its duration between 31 and 389 days. Only 14 patients (4.9%) had EXT for more than 90 days. If the duration of EXT for those who were lost to follow-up or died was assumed to be until the last platelet count on record, the median duration of EXT and prolonged EXT was 7 days (range, 2-389 days) and 48 days (range, 31-389 days), respectively.

Trends of Platelet Counts

We presented the trends of platelet counts based on different causes of EXT in Supplemental Figure A-F (available online at http://www.mayoclinicproceedings.org). Most of the patients with recent surgeries or infection/inflammation had a steady downward trend of platelet counts within 30 days, whereas many nonsurgical patients with hematologic malignancies had prolonged EXT. Among patients with recent surgeries, those with recent splenectomy had slower resolution of EXT than those without. Of note, patients who received multiple administrations of platelet-stimulating

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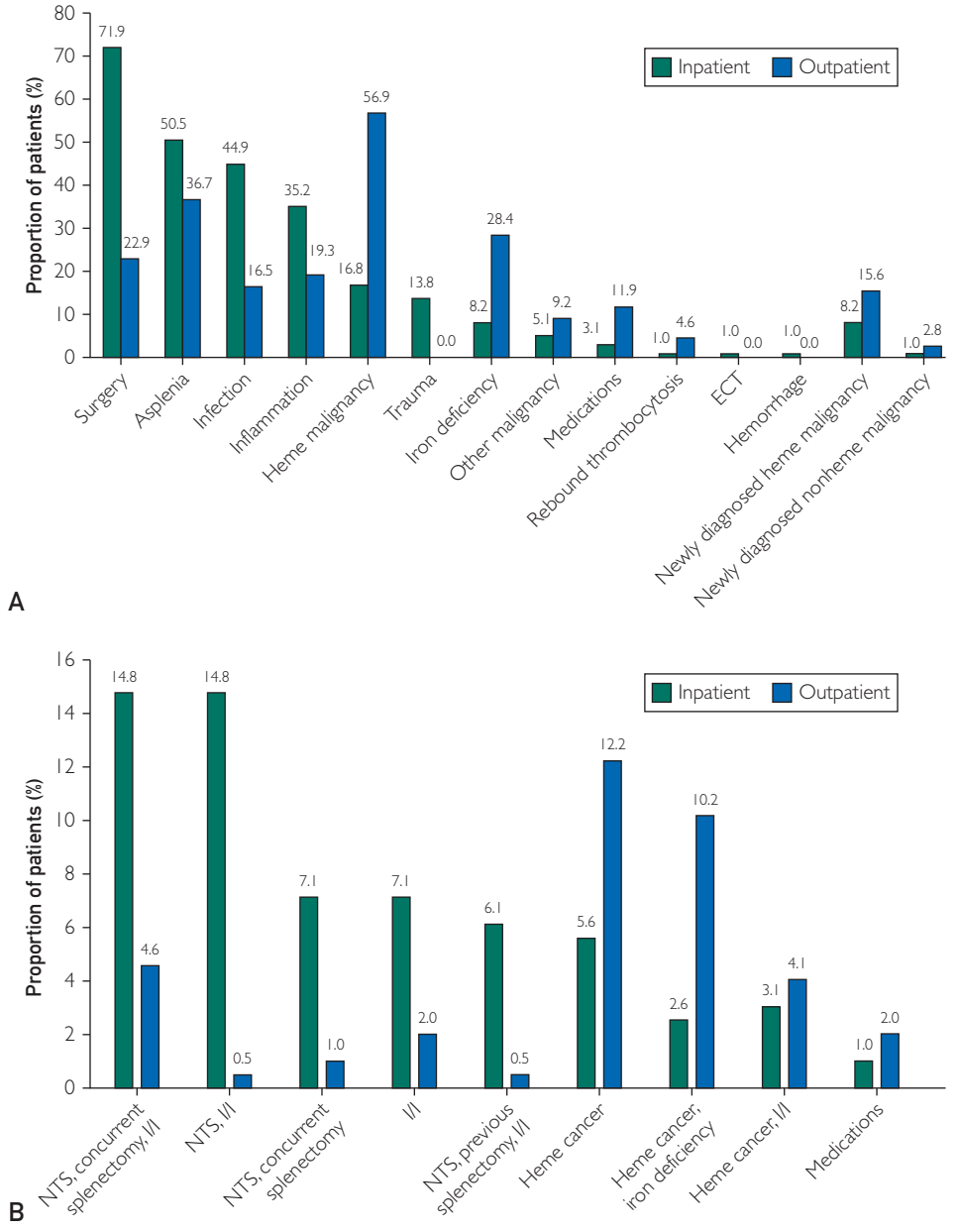

FIGURE 2. A, Factors associated with extreme thrombocytosis in the inpatient and outpatient settings. B, Five most common clinical scenarios for extreme thrombocytosis in the inpatient and outpatient settings. ECT = electroconvulsive therapy; I/I = infection/inflammation; NTS = nontrauma surgery.

medications were susceptible to cyclic thrombocytosis and thrombocytopenia as they received medications on a regular basis.

DISCUSSION

This largest EXT study to date provides a contemporary description of the etiologies of EXT in both the inpatient and outpatient settings. Several findings are notable. Extreme thrombocytosis was a rare occurrence (1 in 100) in unselected patients who had thrombocytosis. In most cases (8 in 10), EXT was multifactorial and likely a result of cumulative "hits" from various

conditions known to cause thrombocytosis. The dominant cause varied on the basis of the care setting, with surgery/surgical complications and MPNs predominating in the inpatient and outpatient settings, respectively. New cancer diagnoses were relatively uncommon (1 in 8 [12.5%]), especially in the inpatient setting (1 in 11 [9.2%]), and they were mostly MPNs. In most cases, EXT resolved within 30 days of its presentation.

Although EXT is common in patients with MPNs, it is extremely rare outside this setting. In our study of nearly 50,000 patients with thrombocytosis, only 1.4% had EXT. The 2 major previous studies focusing on EXT did not report the frequency of EXT in unselected patients with thrombocytosis.[3,4] A relatively smaller study from Germany consisting of patients with thrombocytosis (N=732) reported a similarly low EXT rate of 3.8%.[6] In MPNs, the reported rates of EXT at diagnosis were approximately 50%,[7] 15%,[8] and 4%[9] for essential thrombocytosis, chronic myeloid leukemia, and polycythemia vera, respectively.

Unlike previous studies, which assigned a single etiology for each patient with EXT and did not take into account the setting in which EXT occurred, our study investigated all potential attributable factors that existed during the EXT episode and analyzed them on the basis of whether EXT occurred in the inpatient or outpatient setting. We found that in most of the cases (~80%), EXT could be considered multifactorial and the combination of factors were context dependent. In the inpatient setting, more than half of the EXT cases occurred among those who had major surgeries, mostly in association with secondary factors such as concurrent or previous splenectomy and postoperative infectious complications. In contrast, most patients in the outpatient setting had a previous diagnosis of hematologic malignancy (mainly MPNs) with or without concurrent infection or iron deficiency.

We have summarized the causes of EXT for each case in Table 1 and grouped patients on the basis of the dominant causes. Surgical complications and hematologic malignancies were the 2 most dominant causes. Although previous studies reported infections and splenectomy as the 2 most common causes of EXT, we found that most patients (~70%) who had infections or inflammations had recent surgeries and should be considered surgical complications. Fewer patients (~10%) who had infections had been previously diagnosed with hematologic malignancies. These patients had chronic thrombocytosis because of hematologic malignancies, but platelet counts were not extremely high until they had infections. The increased platelet counts secondary to infections were relatively small as compared with the chronically elevated platelet counts secondary to hematologic malignancies. Two-thirds of our patients who had previous splenectomy had surgeries just before the development of EXT, and they had mild to moderate thrombocytosis before the surgeries. The impact of surgeries on the platelet count appeared to be more substantial than the impact of their previous splenectomy. Hence, our study reported that patients who had infection, inflammation, or asplenia usually had recent surgeries or hematologic malignancies, and infection, inflammation, and asplenia were not as remarkable causes as recent surgeries and hematologic malignancies. These findings suggest that in the absence of myeloid neoplasms, EXT usually occurs as a result of multiple "hits" from several reactive causes of thrombocytosis occurring in sequence. Of note, although iron deficiency was common in outpatients with EXT, most of these patients (~85%) had concomitant hematologic malignancies.

Two common clinical questions are encountered during a hematology consultation for the evaluation of EXT: (1) What is the likelihood of an occult malignancy? and (2) What should be the extent of evaluation to rule out such a possibility? These questions were not addressed by previous studies.[3,4,6] In our study, the discovery of a new malignancy was relatively uncommon (~10%) and most were in the outpatient setting with an abnormal platelet count as the isolated finding—features highly

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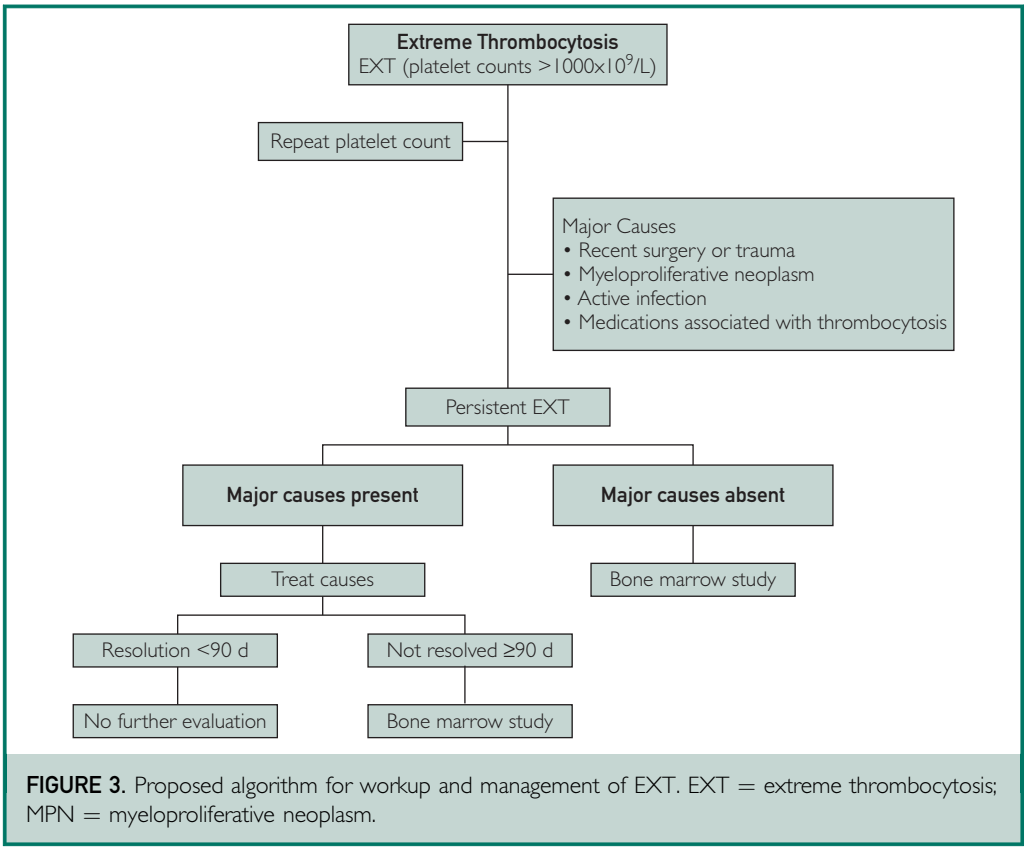

FIGURE 3. Proposed algorithm for workup and management of EXT. EXT = extreme thrombocytosis; MPN = myeloproliferative neoplasm.

suggestive of myeloid neoplasms. Nonhematologic malignancies were discovered in only 5 patients (<2%). Therefore, in our opinion, an extensive search for an occult malignancy, especially solid tumors, is generally not necessary, especially in the inpatient setting. In the outpatient setting, we recommend evaluation for MPNs when an explanation is not evident. A proposed algorithm for work-up and management of EXT is displayed in Figure 3. An observation period of 90 days is defined in Figure 3 on the basis of the fact that less than 5% of patients in our study had EXT for more than 90 days.

There are several limitations of our study. First, the study was conducted at a major academic center well known for its work on hematologic malignancies; thus, referral bias could not be avoided. The proportion of patients with hematologic malignancies in our study (31.1%) was likely higher than expected in the community setting. Second, because our inclusion criteria required cases to have at least 2 readings of platelet counts greater than 1000×10^9/L within 30 days to minimize laboratory error and show persistence, 340 patients were excluded because they had only 1 platelet count revealing EXT. Therefore, patients who had transient EXT, did not require a second platelet count after the initial consultation, or were lost to follow-up were not included in the study. As a result, our patient population could have been sicker, requiring them to be evaluated and followed for a longer period of time, enough to have a second platelet count measured. Third, we did not have clinical outcomes pertaining to thrombotic or hemorrhagic events. We intentionally did not include such outcomes as attribution of causes of thromboses and hemorrhages are difficult to assign. In more than half of our patients, EXT occurred in a postoperative setting, while most of the nonsurgical cases had hematologic malignancies. The largest study of EXT published before our report had attempted to describe these outcomes

but have questioned the reliability of their attribution because many patients had vascular comorbidities and most patients with MPNs received cytoreductive therapy anyway.[3] The remaining question is whether EXT from secondary causes would benefit from antiplatelet therapy. A retrospective study of EXT in the trauma population suggested that antiplatelet therapy may not affect inpatient outcomes including mortality, complications, and hospital stay.[10]

CONCLUSION

The present study reported that other than MPNs, EXT is generally a multifactorial hematologic condition that resolves over time with treatment of the underlying causes. The latter are usually identifiable and related to the clinical context that is generally obvious. An extensive search for an occult malignancy is not necessary unless dictated by other signs or symptoms. We recommend a bone marrow evaluation only if none of the major causes—recent surgery, active infection, history of splenectomy, and MPNs—are present at the time of EXT evaluation.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **EXT** = extreme thrombocytosis; **MPN** = myeloproliferative neoplasm

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