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Original Article

Reactive thrombocytosis in acute infectious diseases: Prevalence, characteristics and timing

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ABSTRACT

Background: Reactive thrombocytosis is known to occur in infectious, inflammatory and neoplastic diseases. However, the characteristics of its association with acute infections (ID) has not been systematically studied.
Setting: A department of internal medicine in a general teaching hospital.
Methods: Retrospective chart review of admitted patients with a confirmed diagnosis of community-acquired pneumonia (CAP), urinary tract infection (UTI) or skin and soft tissue infection (SSTI). Key clinical and laboratory data were retrieved and patients with platelet counts > 400 × 10^9/L who had no alternative cause of thrombocytosis were studied longitudinally and compared to patients with acute infections who had no thrombocytosis.
Results: Thirty two of 421 patients with acute infections (ID) had infection-associated thrombocytosis (7.6%): 11/125 patients with CAP (8.8%), 13/205 patients with UTI (6.3%) and 8/91 (8.8%) patients with SSTI. Their median ages (77–78 years), gender (48% males), admission temperature, Hb, and WBC were not significantly different from ID patients without thrombocytosis. However, patients with thrombocytosis had longer hospital stays (P = 0.001), more bacteremias (P = 0.048) and in 4/32 (12/5% vs. 2%) significantly increased combined mortality or suppurative complications (P = 0.0006). The ESR (median 70 vs. 40 mm/h, P = 0.000) and CRP (median 214 vs. 114 mg/dL, P < 0.0001) were found to be increased in ID-associated thrombocytosis patients, similarly for each ID. Platelets increase was already found on admission in 18 patients (56%), was mild in most cases (median 492.5 × 10^9/L, range 401–917 × 10^9/L) and resolved after recovery in all survivors. The median time to thrombocytosis was 1 day in patients with CAP, 4 days in UTI and 7.5 days in SSTI. No thrombotic complications were found.
Conclusions: Approximately 8% of patients with acute ID examined had thrombocytosis which was mostly mild, transient, and not usually indicative of an infectious complication. However, these patients had enhanced acute-phase response, increased length of hospital stay, more bacteremia and increased mortality/suppurative complications albeit affecting a minority of patients.

1. Introduction and background

Reactive thrombocytosis (i.e. thrombocytosis in the absence of a myeloproliferative or myelodysplastic disorder) has diverse etiologies including inflammatory, neoplastic and infectious diseases [1]. The latter association is predominantly considered in the context of chronic long-standing infections such as chronic osteomyelitis, abscesses or suppurative chest infections and active tuberculosis [2–4]. However, in most patient series, acute infections represent the most common cause of reactive thrombocytosis [5,6]. The same observation was made when patients with extreme thrombocytosis (> 1000 × 10^9/L) were studied [7]. Nevertheless, the prevalence, characteristics, timing and impact of thrombocytosis in common acute infections are not well known.

2. Patients and methods

We retrospectively examined the charts of all patients with a discharge diagnosis of one of three acute infectious diseases who were discharged from one department of medicine in a teaching hospital in central Israel over one year. The conditions studied were community-acquired pneumonia [CAP], urinary tract infection/acute pyelonephritis [UTI]; and skin-soft tissue infections [SSTI] - erysipelas or cellulitis. Co-morbidities, key clinical data, laboratory test results, and cultures were noted. Imaging studies (chest X-rays, abdominal ultrasound, chest and/or abdominal CT) were individually reviewed by a radiologist (KJ). Hospital stay and outcome were recorded (in-hospital mortality, infectious complications). In patients who had

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thrombocytosis (defined as platelets $> 400 \times 10^9$/L over at least two consecutive blood counts) (8), the time of its appearance since the onset of symptoms was recorded and platelet counts in all the patient's blood tests were noted.

Patients who had primary thrombocytosis (e.g. myeloproliferative disorder) or alternative causes of reactive thrombocytosis prior to the acute infection (e.g. iron deficiency anemia, chronic inflammatory disease, splenectomy, tissue damage, acute bleeding) were excluded. Patients who developed chronic complications of their acute infection (e.g abscess or empyema, osteomyelitis, infective endocarditis) were identified. Post-discharge blood counts in the HMO charts of infection-associated thrombocytosis patients were checked in all cases to verify normalization of platelet counts after recovery.

Data is presented as mean and standard deviation for continuous variables and as numbers and percentage for nominal parameters. Cases (patients with thrombocytosis) were compared with controls (patients whose platelets were not elevated) for the whole group as well as separately for each of the three diagnoses. Nominal variables were compared using χ^2 (Chi-Square) test or Fisher's exact test and continuous variables such as laboratory characteristics were compared using *t*-test or the Mann-Whitney test (each when appropriate). *P* value < 0.05 was considered significant. All statistical analyses were done with SPSS-25 software (IBM, Armonk, NY, USA).

3. Results

Over the course of the study, 441 patients with the index discharge diagnoses were identified. Twenty patients were excluded due to pre-existing thrombocytosis (primary and reactive) as described above or an alternative acute cause, including 2 patients in whom the index diagnosis was not confirmed (no infiltrate on chest imaging). The ICD-9 coded primary diagnosis was confirmed by the authors' chart and imaging review in all remaining cases. Altogether, 32 of 421 patients with acute infections had infection-related thrombocytosis (7.6%). They included 11/125 patients with CAP (8.8%), 13/205 patients with UTI (6.3%) and 8/91 (8.8%) patients with SSTI.

The characteristics of all patients who had thrombocytosis ($n = 32$) compared to those without increased platelets is presented in Table 1. Mean peak platelet counts were $527 \pm 120.6 \times 10^9$/L among cases (median 492.5×10^9/L) vs. $225 \pm 57 \times 10^9$/L (median 212.5×10^9/L) among 'controls. Their median ages (77 and 78 years), gender (48% males), admission temperature (median 38 °C and 38.2 °C), hemoglobin levels (median 10.7 and 11 g/dL), and WBC (median 14.4×10^9/L and 13.9×10^9/L) were not significantly different. Their main co-morbidities and medications were also similar. However, patients with acute infections who had thrombocytosis had significantly longer hospital stays (median 7 vs. 4 hospital days, $P = 0.001$) and more bacteremias ($P = 0.048$) (Table 1). Pathogens isolated from blood cultures in the two groups are presented in Table 2. Acute-phase reactants were found to be increased in ID-associated thrombocytosis patients, including the ESR (median 70 vs. 40 mm/h, $P = 0.000$), CRP (median 214 vs. 114 mg/dL, $P < 0.0001$) and serum albumin, a negative acute-phase reactant (2.9 vs. 3.1 g/dL, $P = 0.001$) (Table 1). When data was analyzed for each acute infection separately, essentially the same results were obtained (not shown). Patient's outcomes included 2/32 (6.25%) mortality (both in the CAP group) vs. 8/389 (2.0%) among patients with acute infections who had no thrombocytosis. In addition, an abscess was diagnosed in 2 patients with thrombocytosis (both in the UTI group). These adverse outcomes combined were significantly increased in the ID-associated thrombocytosis group ($P = 0.0006$) but affected only 12.5%. The remaining 87.5% had no adverse outcome despite their thrombocytosis. No thrombotic complications were found.

Looking at the *timing* of the thrombocytosis vis-a-vis the onset of symptoms of infection, two groups could be identified. We found that 18/32 (56%) patients *presented* with thrombocytosis on admission (Table 3). This included 7/8 SSTI patients (87.5%), 5/13 patients with UTI (38.5%), and 6/11 CAP patients (54.5%), including 2 patients who died and were admitted with thrombocytosis despite a short 1-day symptomatology. Illness duration at home prior to admission for the whole group was short and varied between 1 and 6 days (median 1 day,

Table 1
Demographic, clinical, and laboratory data of 421 patients hospitalized with acute infections, comparing patients with and without thrombocytosis.

	Cases Ac. ID, +Thrombocytosis N = 32	Controls Ac. ID, No Thrombocytosis N = 389	Statistical significance
Variable*			
Age, Years	76.3 ± 16 77 33–94	71.3 ± 20 78 18–108	NS
Gender, % Male	47.6	49.6	NS
Hemoglobin, gr/dL	10.5 ± 1.2 10.7 7.5–12.5	10.9 ± 1.0 11 7.7–12.9	NS
WBC, $X10^9$/L	15.9 ± 4.0 14.4 11.1–23	14.5 ± 4.3 13.9 2.3–31	NS
Platelets, $X10^9$/L	527 ± 120.6 492.5 410–917	225 ± 57 212.5 102–394	0.000
Temperature, °C	38.0 ± 1.0 38 37–40	38.2 ± 1.0 38.2 34–40	NS
Length of stay, days	8.2 ± 6.0 7.0 2–31	5.1 ± 3.7 4.0 1–34	0.001
ESR, mm/h	79 ± 32 70 5–130	48 ± 30 40 1–140	0.000
CRP, mg/dL	213 ± 112 214 40–436	148 ± 123 114 6–827	< 0.001
Albumin, gr/dL	2.7 ± 0.3 2.9 2.0–3.3	3.0 ± 0.3 3.1 2.0–5.1	0.001
Bacteremia, No. (%)	4 (12.5)	23 (5.9)	< 0.05
Mortality, No. (%)	2 (6.25)	8 (2.0)	0.006 for combined mortality/abscess
Abscess, No. (%)	2 (6.25)	0	

* Presented as mean ± S.D, median, and range. ID = Infectious disease, acute; WBC = White blood cells; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein.

Table 2
Pathogens isolated from blood cultures of patients with and without thrombocytosis.*

Cases Ac. ID, +Thrombocytosis N = 4/32	Controls Ac. ID, No Thrombocytosis N = 23/389
A. *Streptococcus pneumoniae* [1] *Staphylococcus aureus* [1]	A. Streptococcus pneumoniae [8] Staphylococcus aureus [4] Escherichia coli [4] *Klebsiella pneumoniae* [1]
B. *Escherichia coli* [2]	B. *Escherichia coli* [4] *Proteus mirabilis* [1]
C. –	C. *Staphylococcus aureus* [1]

* P < 0.05. ID = Infectious disease, acute (A = Community-acquired pneumonia; B = Urinary tract infection; C = Skin-soft tissue infection). Some of the patients had been partially treated with antibiotics prior to admission and first set of blood cultures.

Table 3
Platelet values on admission and throughout hospitalization in 32 patients with acute infection-associated thrombocytosis, in relation to days of illness prior to admission, and preceding the first appearance of increased thrombocyte values.

Patient	Illness duration before admission (Days)	Platelets on admission ($\times 10^9$/L)	Hospital day of 1st increased platelets	Symptom onset to 1st thrombocytosis (Days)/1st PLT↑ value ($\times 10^9$/L)	Thrombocytosis, Range ($\times 10^9$/L)	Comments
A2	1	**411**	#1	1/411	404–411	
A3	6	**436**	#1	1/436	414–436	
A4	1	**429**	#1	1/409	429–446	
A5	1	**424**	#1	1/424	424–**562**	Died
A6	1	**635**	#1	1/635	499–**917**	Died
A7	3	367	#3	6/467	443–**733**	
A8	7	359	#3	10/478	478–**568**	
A9	4	299	#7	11/412	412–452	
A10	1	393	#5	6/447	447–**774**	
A11	1	**694**	#1	1/694	522–**694**	
A12	7	369	#2	9/408	408–**624**	
B1	2	301	#6	8/420	420–491	
B2	6	355	#3	9/401	401–461	Abscess
B3	1	**453**	#1	1/453	453–**569**	
B4	1	262	#3	4/419	419–496	
B5	1	**404**	#1	1/404	404–410	
B6	1	273	#3	4/437	437–460	
B7	1	**478**	#1	1/478	427–478	
B8	3	**436**	#1	4/421	421–436	
B9	2	331	#9	11/415	415–497	
B10	3	190	#6	9/419	419–**511**	Nephronia
B11	3	382	#3	6/433	433–437	
B12	1	**432**	#1	1/432	410–432	
B13	3	297	#6	9/431	431–**571**	
C1	3	392	#4	7/435	435–**509**	
C2	3	**565**	#1	4/565	450–**711**	
C3	6	**432**	#1	7/432	432–447	
C4	3	**430**	#5	8/430	430–494	
C5	4	**410**	#6	10/410	410–470	
C6	2	**438**	#1	3/438	410–438	
C7	4	**423**	#6	10/423	414–423	
C8	1	**444**	#9	10/444	444–**505**	

PLT = Platelets; A = CAP, B = UTI and C = SSTI patients. Bold type represents patients with > 400 × 10^9/L on admission (n = 18) or value > 500 × 10^9/L at any time (n = 13), respectively.

mean 2.2 ± 1.7) (Table 3). The mean time elapsed from the start of symptoms to the first appearance of thrombocytosis in the remaining 14 patients (whose admission platelet counts were normal), was 7.7 ± 2.3 days (median 8.5 days, range 4–11 days) at home and in the hospital. The median time to thrombocytosis in the whole group (n = 32) was 1 day in patients with CAP, 4 days in UTI and 7.5 days in SSTI, but the difference was not statistically significant.

Acute infectious-diseases-associated thrombocytosis was usually mild with an overall mean of 527 ± 120.6 × 10^9/L and median 492.5 × 10^9/L for the peak value of each patient. The highest count did not surpass 917 × 10^9/L, only 13 patients' thrombocytes were > 500 × 10^9/L during their hospital course (40.6%) and most of the counts were far less (Table 3). On admission, 14 of the patients had normal platelet counts and in the remainder, thrombocytosis was mild in the majority of the patients (< 480 × 10^9/L in 77.77%). Values exceeding 20% increase over baseline (565–694 × 10^9/L) were found in just 3 patients (9.4%). Looking at the *whole* duration of hospitalization, values > 20% increase over the baseline of 400 × 10^9/L were observed in just 17/32 patients and platelet levels were only mildly increased (median 568 × 10^9/L; range, 491–917 × 10^9/L). Despite the association with longer hospitalizations and more bacteremias (Table 2), the presence of thrombocytosis was not usually indicative of infectious complications in the majority of patients. Only 2/32 (6.25%) patients with thrombocytosis had paranephric abscess or lobar nephronia, vs. none in the remaining patients. Their thrombocytosis was not marked. The 2 patients who died in-hospital (6.25% vs. 2.0%) had thrombocytosis already on admission which peaked later to > 500 × 10^9/L and both suffered from CAP.

Finally, thrombocytosis was transient in all surviving patients and ambulatory blood counts performed after discharge showed normal platelet counts in all 30 cases.

4. Discussion

Our first finding is that thrombocytosis in acute infections is far less common than previously supposed. < 8% of the patients with either CAP, UTI or SSTI had thrombocytosis (Tables 1, 3). Most of the published patient series of thrombocytosis agree that reactive ('secondary') thrombocytosis outnumbers primary 'clonal' thrombocytosis by a ratio of approximately 7:1 [9] and that infections (predominantly acute infections) constitute its most common cause [5–7] One prominent study of 643 inpatients with reactive thrombocytosis found that 21% had infections, which emerged as a frequent cause of increased platelet counts, second only to tissue damage [9] In contrast with these studies, thrombocytosis in patients with acute infections had been seldom investigated. Secondly, the degree of platelet increase found in our cohort was often mild, with a mean of 527 ± 120.6 × 10^9/L for peak values (median 492.5 × 10^9/L, range 410–917 × 10^9/L) (Table 2). We have chosen 400 × 10^9/L as a cutoff, based on the study from Italy demonstrating that only 99/10,000 population cohort had a platelet count > 400 × 10^9/L, which persisted in just 8/99 [8]. Indeed, our confirmation through the patient's HMO charts that thrombocytosis normalized in all cases, supports our choice. Had we selected ≥450 × 10^9/L as some authorities recommend [1], just 22/421 (5.2%) would have acute-infection-associated thrombocytosis. If defined as ≥500 × 10^9/L [9], the incidence would further decline to 3.0% (13/421).

Third, the association we found of ID-associated thrombocytosis with significantly increased acute-phase reactants (Table 1) is self-explanatory since reactive thrombocytosis is thrombopoietin- and

cytokine-driven [1,10,11] and cytokines are an important determinant of the ESR and CRP. We could not examine cytokine levels in our patients due to the retrospective nature of the study. However, infections lead to substantial increases in the plasma concentrations of many acute-phase proteins such as CRP due largely to hepatic overproduction [12]. Interleukin-6 plays a pivotal role in both CRP induction and the thrombocytosis of inflammation [13], together with other inflammation-associated cytokines produced primarily by WBC at inflammatory sites. Our finding of longer hospital length of stay (LOS) among ID-associated thrombocytosis patients is a new observation. The increased LOS together with more bacteremias and either mortality or infectious complications observed in 1: 6–7 patients (4/32, 12.5%) suggest that thrombocytosis in acute ID patients identifies a subset of patients who need enhanced treatment and monitoring, even when platelets' increases are not at all striking. Our observation is strongly supported by studies that consistently identified thrombocytosis as a marker of poor outcome in CAP. For example, 204/2423 consecutive patients with CAP studied prospectively had thrombocytosis (i.e. 8%, similar to our findings) and these patients had more respiratory complications, longer hospital stays, and higher 30-day mortality [14].

Our results also reveal the kinetics of thrombocytosis in ID. About half of the patients (SSTI > CAP > UTI) already had it on admission, even though their symptomatology was quite a short one (median 1.5 days). Two of these patients died and none had an abscess. Thus, thrombocytosis when present can be an additional clue to an acute ID. A second clinical pattern includes patients whose thrombocytosis develops gradually, in-hospital, despite appropriate antibiotic treatment (median 8.5 symptomatic days). This pattern was only seldom associated with an infectious complication and no mortality occurred (Table 3).

Thrombocytosis was transient and resolved spontaneously with the cure of the infection in all surviving patients, constituting an additional laboratory marker of full recovery.

Limitations of our study include those derived from its retrospective design and the question of generalizability. However, the latter is supported by observations in CAP patients done in Europe, Brazil and the US [14,15]. Strengths are the fairly large sample studied, the sequential information on platelet levels in individual patients with multiple determinations, and the correlation examined with multiple laboratory and clinical variables including length of stay, infectious complications, and outcome

In conclusion, reactive thrombocytosis was found in 7–8% of patients with varied acute ID in our cohort, associated with acute-phase reactants. It was often mild and yet associated with longer hospital length of stay and increased incidence of bacteremia as well as infectious complications/mortality.

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Conflict of interest/competing interests

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