ORIGINAL RESEARCH

Clinicopathological study of reactive thrombocytosis in a tertiary care hospital

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ABSTRACT

Background: Raise in platelet count called thrombocytosis, which is mostly an incidental laboratory finding may be primary (essential thrombocytosis) or secondary (reactive thrombocytosis). The reactive thrombocytosis can be caused due to malignant or non-malignant hematological conditions; acute or chronic inflammatory conditions and tissue damage. This study, was aimed to analyze the clinical spectrum of reactive thrombocytosis, grade thrombocytosis according to the etiologies and analyze the distribution of platelet indices in various clinical settings of secondary (reactive) thrombocytosis. **Objectives:** The objective of this study was to analyze various clinical patterns and etiologies causing reactive thrombocytosis, to grade reactive thrombocytosis based on various clinical settings and etiologies, to analyze the distribution of platelet indices in various clinical conditions and to analyze the associated peripheral smear findings observed in various clinical settings of secondary thrombocytosis. **Methodology:** An observational study done among the patients attending the OPD of General Medicine Department of Trichy SRM medical college for a period of 6 months. All patients found to have thrombocytosis (platelet count >4.5lakhs/mm^3) were included, while those with primary thrombocytosis after complete clinical evaluation and corelating with the laboratory parameters, known case of myeloproliferative disorders and those who did not consent for the study were excluded. Thus, a total of 289 samples, were studied to identify the clinical spectrum, grade of thrombocytosis and analyze the distribution of platelet indices in various clinical settings of secondary(reactive) thrombocytosis. **Results:** The mean age of the study participants was found to be 40.16±20.34 years (range 1 to 83 years). 11.4% of who had reactive thrombocytosis were children <10 years. Reactive thrombocytosis was more prevalent among those in 3rd and 4th decade of life, as 36.3% belonged to this age group and 19.1% more than 60 years. The major cause of reactive thrombocytosis was infection (52.3%), inflammation (14.2%), iron deficiency anemia (13.8%) and 15.9% being idiopathic. Around 75% of the reactive thrombocytosis were mild and only 4.2% and 1.7% had severe and extreme reactive thrombocytosis. Majority (47.5%) of iron deficiency anemia had giant platelets compared to infection (47.02%) who mainly had small platelets. While 75.61% of the patients with inflammation had small platelets and 58.70% of idiopathic conditions presented with small platelets. All the patients who had thrombocytosis due to the effect of drugs had giant platelets. **Conclusion:** Though the reactive thrombocytosis per se doesn't result vascular and hemostatic complications, the underlying cause should be found and treated. The grading of thrombocytosis serves a good purpose in analyzing the severity of infection, inflammation and malignant conditions thus facilitating in adequate modification of management techniques.

Key words: Secondary thrombocytosis, platelet indices, myeloproliferative disorder, hemogram, peripheral smear finding

INTRODUCTION

Thrombocytosis, a condition where platelet count raises above 4,50,000/µL, is mostly an incidental abnormal laboratory finding. It can present either as a reactive process (secondary thrombocytosis) or may be caused by clonal bone marrow, myeloproliferative disorder, includes essential thrombocythemia (primary thrombocytosis) which is difficult to differentiate just with the clinical findings or laboratory test results [1, 2]. Plasma levels of thrombopoietin are high or inappropriately normal in reactive thrombocytosis [3, 4]. In cases of acute inflammation, this elevation precedes an increase in the platelet count [5, 6]. Thrombocytosis is graded as mild (500-700x10^3/µL), moderate (700-900x10^3/µL), severe (900-1000x10^3/µL) and extreme (>1000x10^3/µL) [7, 8]. Plasma levels of thrombopoietin are high/inappropriately normal in reactive (secondary)

thrombocytosis. In cases of acute inflammation, this elevation precedes an increase in platelet count [1].

The causes of secondary thrombocytosis are

1. Non-malignant hematological conditions like Acute hemolytic anemia, Iron deficiency anemia, Acute bleeding and Post treatment of vitamin B12 deficiency.
2. Malignant hematological conditions like Metastatic cancer, Lymphoma and Post treatment with myelosuppressive drugs.
3. Acute or chronic inflammatory conditions like Connective tissue disorder (vasculitis), Inflammatory bowel disease, Autoimmune disease (celiac disease), Post-splenectomy or functional asplenia and POEMS syndrome.
4. Tissue damage like Myocardial infarction, Severe trauma, Acute pancreatitis and Thermal burns [9].

The hemogram of thrombocytosis patients show peculiar pattern of platelet indices that can be used to differentiate between primary and secondary causes [10]. In this study, we attempt to analyze the clinical spectrum of reactive thrombocytosis, grade thrombocytosis according to the etiologies and analyze the distribution of platelet indices in various clinical settings of secondary (reactive) thrombocytosis.

The objective of this study was to analyze various clinical patterns and etiologies causing reactive thrombocytosis, to grade reactive thrombocytosis based on various clinical settings and etiologies, to analyze the distribution of platelet indices in various clinical conditions and to analyze the associated peripheral smear findings observed in various clinical settings of secondary thrombocytosis. The lacunae in literature regarding these aspects of thrombocytopenia in Indian setting was one of the factors inspiring us carry out this study.

MATERIALS AND METHODS

An observational study was done among the patients attending the OPD of General Medicine department in a Trichy SRM medical college for a period of 6 months. All patients who were found to have thrombocytosis (platelet count >4.5lakhs/mm^3) were included in the study. Those who were identified with primary thrombocytosis after complete clinical evaluation and corelating with the laboratory parameters, known case of myeloproliferative disorders and those who did not consent for the study were excluded. Thus, a total of 289 samples, which fit into the inclusion criteria were studied to identify the clinical spectrum, grade of thrombocytosis and analyze the distribution of platelet indices in various clinical settings of secondary (reactive) thrombocytosis using relevant statistical methods. All relevant clinical and laboratory investigations done were documented.

The study was started after obtaining approval from the institutional ethical committee. A written informed consent was obtained from each participant before including them in the study. The purpose of the study was clearly explained to the participants and the right to withdraw from the study at any given point of time without any loss in patient care was also explained. The data obtained was maintained confidentially. The data collected was entered in MS excel and SPSS software was used for analysis. Frequency of each variable was calculated and chi square test was used to find the association of the disease with basic demographic details like age and gender and with peripheral smear findings.

RESULTS

The mean age of the study participants was found to be 40.16±20.34 years, with the range from 1 year old to 83 years. 33(11.4%) of participants who presented with reactive thrombocytosis were found to be children <10 years of age. Reactive thrombocytosis was more prevalent among those in 3rd and 4th decade of life, together being 105(36.3%) and 55(19.1%) of the participants were aged more than 60 years.

Table 1: Frequency distribution of age and gender among study participants

Characteristics		Frequency N (%)
Age	<10 years	33(11.4)
	11-20 years	16(5.5)
	21-30 years	34(11.8)
	31-40 years	52(18)
	41-50 years	53(18.3)
	51-60 years	46(15.9)
	61-70 years	36(12.5)
	>71 years	19(6.6)
Gender	Male	152(52.6%)
	Female	137(47.4%)

The etiology of majority of reactive thrombocytosis was found to be infection (52.3%), followed by inflammation (14.2%), iron deficiency anemia (13.8%) and 15.9% being idiopathic. Around 75% of the reactive thrombocytosis were mild and only 4.2% and 1.7% had severe and extreme reactive thrombocytosis.

Table 2: Frequency distribution of etiology and grading of reactive thrombocytosis

Characteristics	Frequency N(%)
Etiology	
Iron deficiency anemia	40(13.8)
Infection	151(52.3)
Inflammation	41(14.2)
Hemorrhage	1(0.3)
Hemolysis	4(1.4)
Malignancy	2(0.7)
Splenectomy	1(0.3)
Drugs	3(1)
Idiopathic	46(15.9)
Grading	
Mild (500-700x10^3/µL)	218(75.4)
Moderate (700-900x10^3/µL)	54(18.7)
Severe (900-1000x10^3/µL)	12(4.2)
Extreme (>1000x10^3/µL)	5(1.7)

In our study samples MPV was found to be <5.9 femtoliters in in 13(4.5%), 6-6.9 femtoliters in 103(35.6%), 7-7.9 femtoliters in 108(37.5%), 8-8.9 femtoliters in 60(20.8%) and in 5(1.7%) cases was 9-9.9 femtoliters. The mean value of MPV was found to be 7.31±0.79 in females and 7.13±0.81 in males, thus a total mean of 7.22±0.81. Majority of the samples had microcytic hypochromic RBC 128(49.1%) followed by normocytic normochromic 142(44.3%). Analysis of the nature of WBC's showed that 48(16.6%) were normal whereas 178(61.6%) polymorphs, 32(11.1%) toxic changes, 107(37%) shift to left, 63(21.8%) reactive lymphocytes and 2(0.7%) eosinophilia. Only 62(21.5%) of the samples studied had normal platelets, with 86(29.8%) having giant platelets and 141(48.8%) presenting with small platelets. On examination of the peripheral smear 2(0.7%) samples were found to have roulex formation, 1(0.3%) had Target cells with microcytic hypochromic cells, 1(0.3%) had sepsis with leucoerythroblastic blood picture and 16(5.5%) had signs of sepsis.

Table 4: Association of peripheral smear findings with etiology

Etiology	Characteristics of white blood cells							p value
	N	P	PL	RL	PL, RL	PLT	EO	
Iron deficiency anemia	7	11	9	8	1	3	1	0.22
Infection	24	46	30	33	0	17	1	
Inflammation	6	6	15	7	0	7	0	
Hemorrhage	0	0	0	0	0	1	0	
Hemolysis	2	1	1	0	0	0	0	
Malignancy	0	0	1	1	0	0	0	
Splenectomy	0	1	0	0	0	0	0	
Drugs	0	0	3	0	0	0	0	
Idiopathic	9	5	14	13	1	4	0	

N-Normal, P-Polymorphs, T-Toxic changes, L-Shift to left, RL-Reactive lymphocytes, PLT-Polymorphs, shift to left, toxic changes, EO-Eosinophilia

Table 5: Morphology of platelets among different etiologies

Etiology	Normal platelets	Giant platelets	Small platelets
Iron deficiency anemia	11	19	10
Infection	35	45	71
Inflammation	8	2	31
Hemorrhage	0	0	1
Hemolysis	1	3	0
Malignancy	1	0	1
Splenectomy	0	1	0
Drugs	0	3	0
Idiopathic	6	13	27

Majority (47.5%) of iron deficiency anemia had giant platelets compared to infection (47.02%) who mainly had small platelets. While 75.61% of the patients with inflammation had small platelets and 58.70% of idiopathic conditions presented with small platelets. All the patients who had thrombocytosis due to the effect of drugs had giant platelets.

Table 6: Association of peripheral smear finding with grade of thrombocytosis

Peripheral smear findings		Thrombocytosis grading				p value
		Mild	Moderate	Severe	Extreme	
MPV	5-5.9	9	0	4	0	0.01*
	6-6.9	73	22	4	4	
	7-7.9	86	19	2	1	
	8-8.9	45	13	2	0	
	9-9.9	5	0	0	0	
RBC	Normal	105	17	6	0	0.064
	Macrocytic	5	2	0	0	
	Microcytic hypochromic	103	28	6	5	
	Polycythemia	0	2	0	0	
	Dimorphic anemia	2	2	0	0	
	Hemolysis	3	1	0	0	
	Target cells with microcytic hypochromic	0	2	0	0	
WBC	Normal	37	9	1	1	0.234
	P	50	13	6	1	
	P, L	55	13	3	2	
	RL	48	14	0	0	
	P, L, RL	1	0	1	0	
	P, L, T	26	4	1	1	
	EO	1	1	0	0	
Platelets	Normal	51	10	0	1	0.035*
	Giant platelets	65	19	2	0	
	Small platelets	102	25	10	4	

P-Polymorphs, T-Toxic changes, L-Shift to left, RL-Reactive lymphocytes, PLT-Polymorphs, shift to left, toxic changes, EO-Eosinophilia.
*p value <0.05 is considered to be significant

In the peripheral examination, roulex formation was observed in 2 cases of thrombocytosis due to inflammation. 14 cases of signs of sepsis were due to known infection and 2 cases were due to idiopathic. 1 case of thrombocytosis due to splenectomy had target cells with microcytic hypochromic cells.

Table 7: Grades of thrombocytosis in different etiologies

Etiology	Thrombocytosis grading			
	Mild	Moderate	Severe	Extreme
Iron deficiency anemia	28	8	4	0
Infection	119	24	6	2
Inflammation	31	8	0	2
Hemorrhage	1	0	0	0
Hemolysis	3	1	0	0
Malignancy	1	1	0	0
Splenectomy	1	0	0	0
Drugs	1	2	0	0
Idiopathic	33	10	2	1

Severe cases of thrombocytosis were observed only in 10% of iron deficiency anemia, 3.97% of infection and 4.35% of idiopathic condition. Whereas extreme cases of thrombocytosis were seen in 1.32% of infection, 4.88% of inflammation and 2.17% in idiopathic cases. In our study both the malignant case only presented with mild and moderate thrombocytosis.

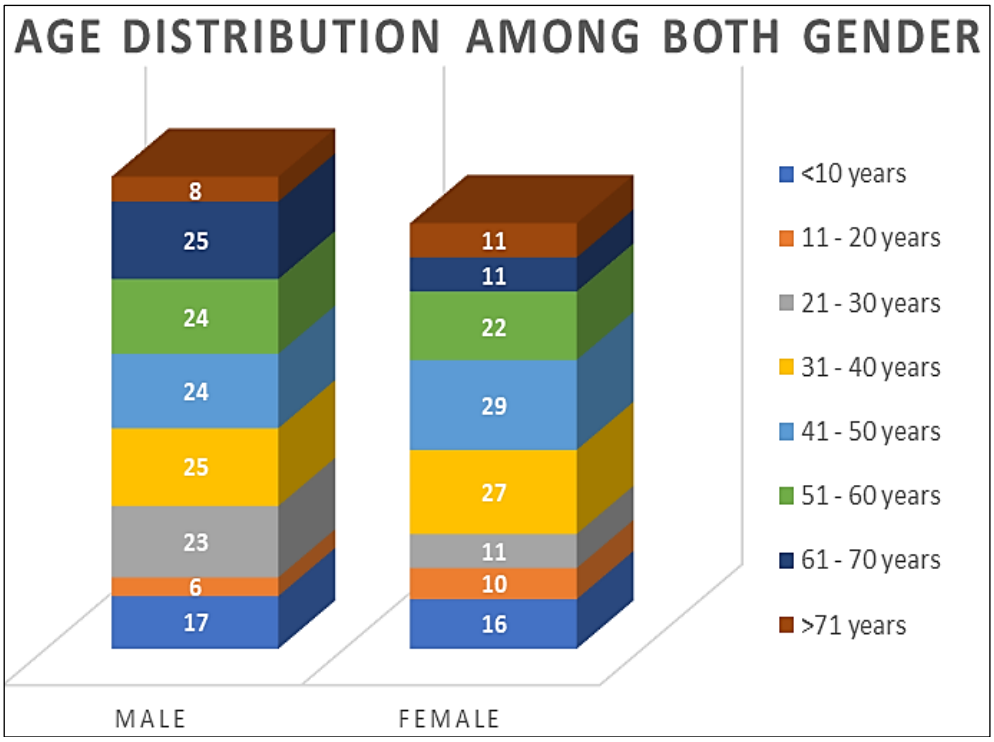

Figure 1: Age distribution among both genders of study population

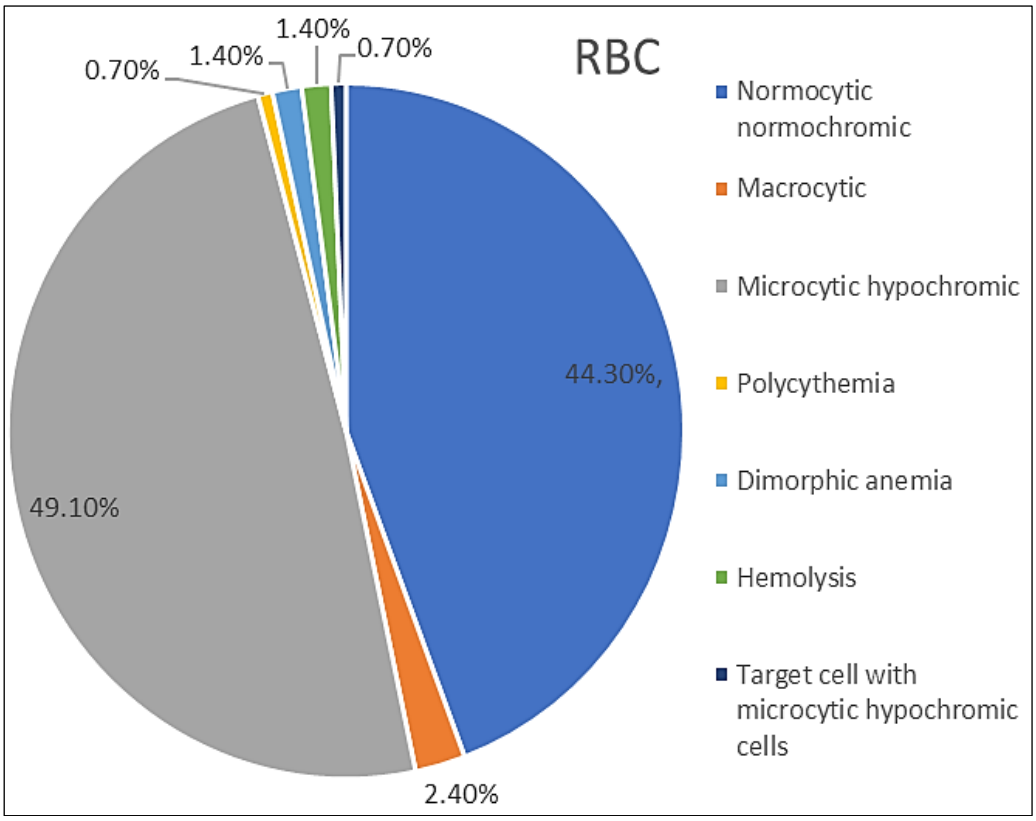

Figure 2: Nature of RBC in peripheral smear

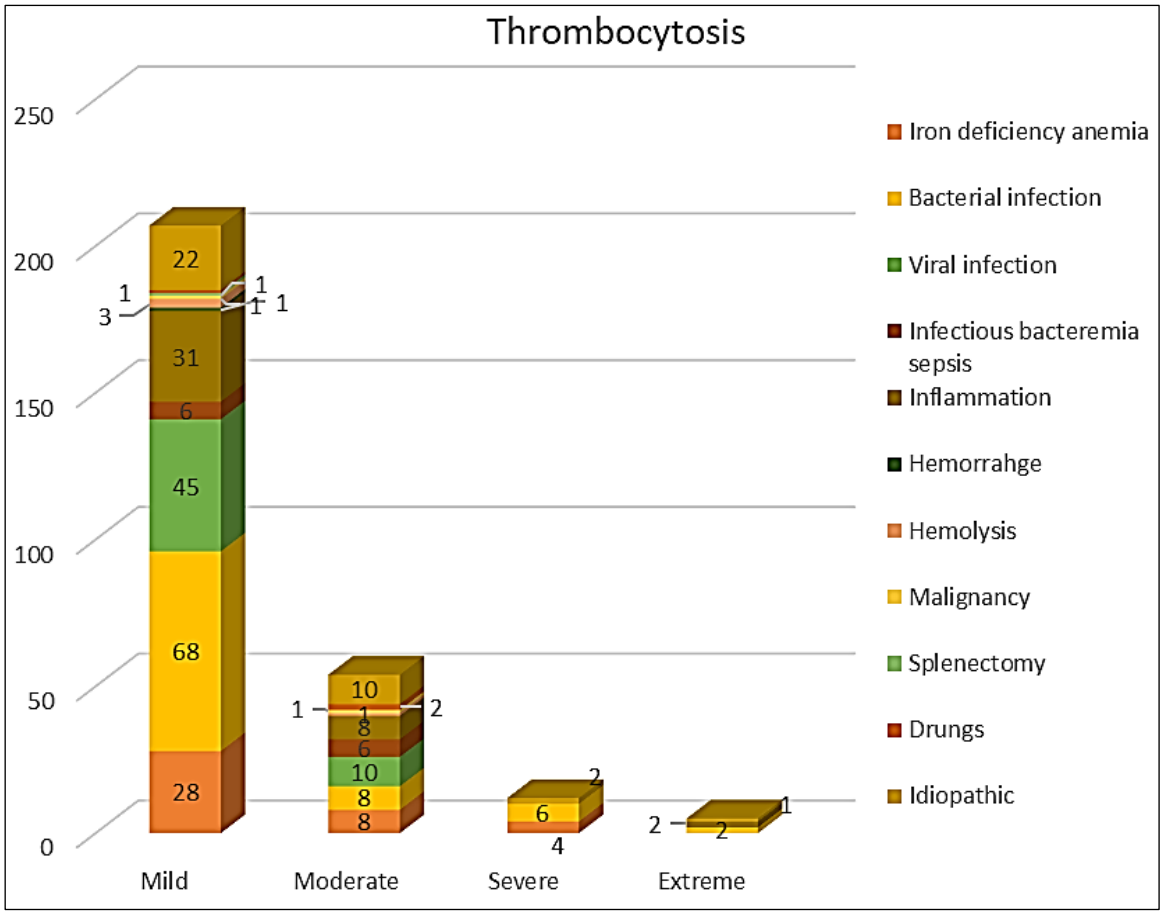

Figure 3: Grading of reactive thrombocytosis based on ETIOLOGY

DISCUSSION

In our study the mean age of the participants found to have thrombocytosis was 40.16±20.34 years (range 1 – 83 years), with 11.4% being children <10 years. Reactive thrombocytosis was most prevalent in 3rd and 4th decade of life and a slight preponderance was seen among males compared to females. 75% of reactive thrombocytosis was mild in nature, 18.7%, 4.2% and 1.7% had moderate, severe, and extreme thrombocytosis. This was similar to a study done by Chiarello P *et al.*, among children which showed mild in 72-86%, moderate in about 6-8% and extreme in 0.5-3% [8]. Showing not much of variability in severity depending on the age groups. Severe cases of thrombocytosis were observed only in 10% of iron deficiency anemia, 3.97% of infection and 4.35% of idiopathic condition. Whereas extreme cases of thrombocytosis were seen in 1.32% of infection, 4.88% of inflammation and 2.17% in idiopathic cases

In a study done by Syed NN *et al.*, Frequent causes of reactive thrombocytosis were infections (44.9%), tissue injury (11.4%) and rebound thrombocytosis (10.2%) [11]. While in our study majority (52.3%) had an infective etiology followed by 14.2% and 13.8% of inflammation and iron deficiency anemia respectively. Diagnosis of reactive thrombocytosis resulting from infection, cancer and connective tissue/autoimmune disease is by identification of specific disease etiology. The prognosis of these is primarily driven by the underlying disease [9]. In a study done by Xue Li *et al.*, it was said that there had been few case studies showing the thromboembolic risk in both arterial and venous system in association with iron deficiency anemia induce thrombocytosis. It was also proved that the administration of iron supplements reduced the thrombocytosis level below 450 × 10^9/L in almost half of the study population in 2 weeks [12, 13].

Also, in a study done by Vasiliki Vlacha *et al.*, thrombocytosis is was a common finding among clinically severe condition of lower respiratory tract infection like pleural effusion among children, thus can be considered as a clinical marker associated with severity of lower respiratory tract infection [14]. In our study 6(7.14%) of the patients who presented with bacterial infection had sever thrombocytosis and 2(2.38%) had extreme thrombocytosis. In a study done by Mishra D *et al.*, among febrile infants it was found that serious bacterial infection was associated with thrombocytosis and c-reactive protein. The sensitivity and specificity of thrombocytosis was found to be 53.3% and 90% respectively, while elevated CRP had 81.4% sensitivity. Thus, the combination of thrombocytosis, elevated c-reactive protein, leukocytosis and pyuria had sensitivity of 93% which was better compared to considering each parameter alone [15].

Only 2 patients with malignancy had participated in the study and happened to have mild and moderate

thrombocytosis. An in-depth study of these patients may reveal various features as in the study done by Crasta JA *et al*., on ovarian cancer, it is seen that thrombocytosis is associated with advanced stage disease and higher histological grade, thereby supporting the hypothesis that platelet plays a role in tumor growth and progression, thus thereby reflecting the tumor burden and aggressive nature [16]. Tranum BL *et al*., had also discussed about the relationship between thrombocytosis and negative prognostic factors and shortening of overall survival in several malignant disease like breast, lung, pancreatic cancers, etc [17]. The diahnosis of thrombocytosis among the malignant cases play a vital role as Honn KV *et al*., had shown anti-platelet agents/anticoagulants have inhibitory effects on tumor cell-platelet interactions and also on spontaneous or experimental metastasis. Thus interfering in the steps of tumor cell-platelet interactions lead to diminished platelet aggregation due to tumor cells and blocked cancer metastasis [18].

CONCLUSION

Analysis of hemogram and peripheral smear findings in combination with clinical parameters can identify secondary thrombocytosis and its etiology. Though differentiating the clonal from secondary thrombocytosis can be extremely difficult the distinction plays a good role in the therapeutic implications. Though the reactive thrombocytosis per se doesn't result vascular and hemostatic complications, the underlying cause should be found and treated. A severe or extreme case of thrombocytosis gives a good heads up regarding the state of infection, inflammation and malignant conditions thus facilitating in adequate modification of management techniques.

LIMITATION

More elaborate details regarding the clinical picture of the disease were not obtained to corelate with the severity of thrombocytosis to get a clear picture. As it is a single centric study, the external validity of the study might be affected.

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