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Review

A Scopic Review on Reactive Thrombocytosis

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ABSTRACT

Thrombocytosis, also called thrombocythemia, is generally defined as platelet count greater than a defined upper limit of normal. The most common cut off for normal is <450,000/µl. Elevated platelet counts are often an incidental or unexpected finding on a complete blood count conducted to evaluate an unrelated condition. The causes of thrombocytosis are separated into two categories: autonomous (primary) thrombocytosis and reactive (secondary) thrombocytosis. Autonomous thrombocytosis occurs as a result of myeloproliferative disorders, myelodysplastic disorders, or rarely as a result of a hereditary condition. Reactive thrombocytosis is most often a normal physiologic response to coexistent chronic inflammatory conditions. Distinction between these two categories is important since autonomous thrombocytosis is associated with a significantly increased risk for thrombotic or hemorrhagic complications whereas reactive thrombocytosis is not. The most common reason for an elevated platelet count is reactive thrombocytosis. The present review will discuss about the association of reactive thrombocytosis with different clinical conditions and the possible underlying mechanism.

KEYWORDS: Thrombocythemia, Autonomous thrombocytosis, Platelet granules

INTRODUCTION

Historical Aspect - Discovery of Platelet

Brewer traced the history of the discovery of the platelet[1]. Although red blood cells had been known since van Leeuwenhoek (1632–1723), it was the German anatomist Max Schultze (1825–1874) who first offered a description of the platelet in his newly-founded journal Archiv für mikroscopische Anatomie[2]. Max Schultze describes "spherules" to be much smaller than red blood cells that are occasionally clumped and may participate in collections of fibrous material. He recommends further study of the findings.

Giulio Bizzozero (1846–1901), building on Schultze's findings, used "living circulation" to study blood cells of amphibians microscopically in vivo. He is especially noted for discovering that platelets clump at the site of blood vessel injury, a process that precedes the formation of a blood clot. This observation confirmed the role of platelets in coagulation[3].

PLATELET[4]

Platelets have been described as the smallest cell fragment in the human body[5] (Jurk & Kichrel, 2005). The normal platelets are small, disc-shaped cells without a nucleus, normally measuring 1 to 2 µm in diameter and 0.5 to 1.0 µm in thickness with a volume of about 6µl. Platelets are derived from the cytoplasm of megakaryocyte, primarily located in the bone marrow. Normally, a platelet is released to the blood stream and circulates for about 10 days before its removal, largely by the spleen. Platelets circulate freely without adhesion to the vessel wall or aggregation with other platelets. If stimulated, platelets become spherical, extend pseudo pods, and adhere to vessel walls and to each other. It participates with the blood vessel, coagulation factors, and other platelets in the initiation of haemostasis.

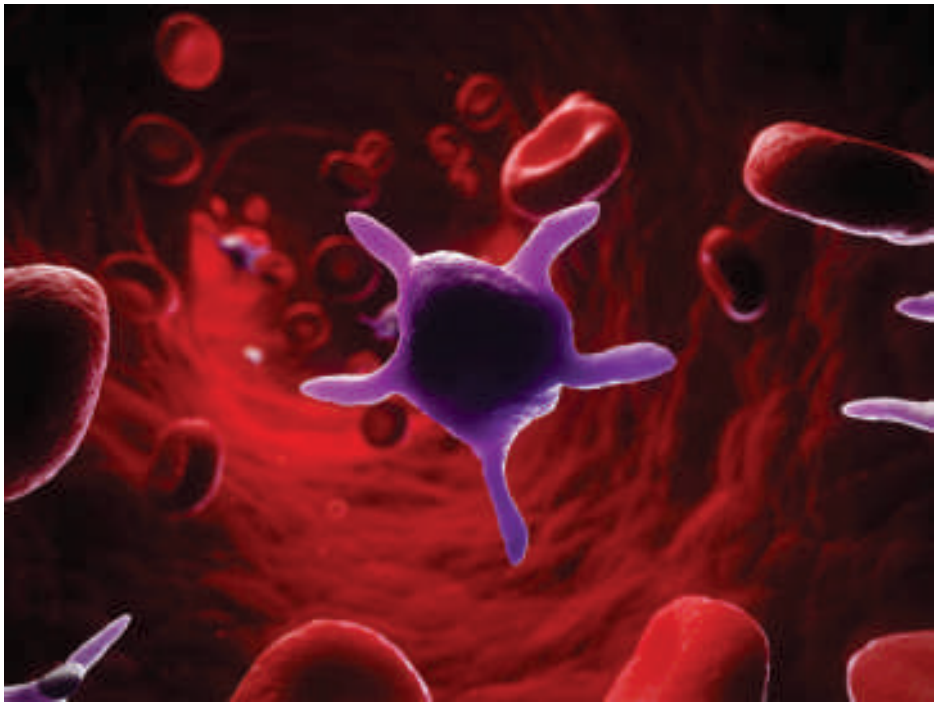

Figure 1: Platelet

Platelet Production and Release[4]

The megakaryocyte, parent cell of the platelet, is derived from pluripotential cells in the bone marrow. Individual megakaryocyte have been estimated to produce as many as 1000 platelets per cell, and apparently very efficient system facilitated by the absence of nuclei in platelets. IL-6 and IL-11 are thought to increase platelet production by megakaryocyte. There are two possible mechanisms whereby platelet achieves the transition from being stationary constituents of megakaryocyte cytoplasm in the bone marrow to circulation cells in the bloodstream. One theory is that megakaryocyte themselves are released from the bone marrow and are carried to the pulmonary capillaries, where they fragment into individual platelet. Another is that the bone marrow endothelium has special properties that encourage formation of pseudopods extending from mature megakaryocyte to bone marrow sinuses and thereby directly release platelets into the blood.

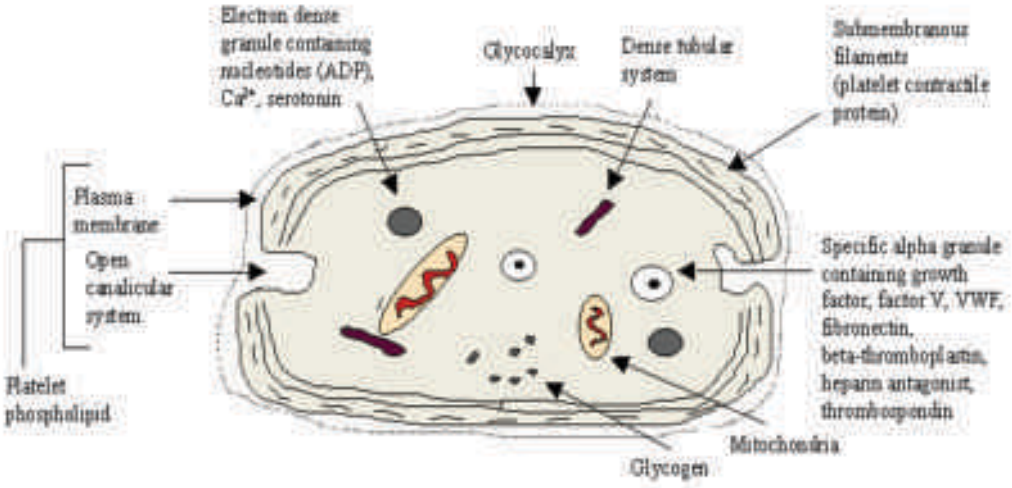

Figure 2: Ultra Structure of Platelet

Platelet Structure[4]

Platelets are composed of three principal components: membrane structures, microtubules, and granules. Platelet membrane, overlying glycocalyx, and submembrane structures mediate responses to platelet stimulation and express specific antigenic characteristics. The surface glycoprotein's variously serve as receptors, facilitate platelet adhesion, contraction, and determine expression of specific platelet antigens. Platelet canalicular system is created by numerous invaginations of the platelet surface and, interspersed among these structures; a set of narrower channels termed the dense tubular system. The canalicular system provides a direct connection between the interior and the surface of the platelet, providing entrance of plasma ingredients into the platelet as well as exit of its own ingredients in connection with the release reaction. The dense tubular system, on the other hand, is entirely enclosed and is the major site for storage of Ca^{2+} and the location of cyclooxygenase, the critical enzyme for conversion of membrane-derived arachidonic acid to unstable endoperoxide precursors of prostaglandins and thromboxanes. The major inner structures of the platelet are the cytoskeleton, the microtubules, and a system of contractile proteins. The cytoskeleton provides a framework to anchor the platelet membrane and allow signal transduction to take place. Furthermore, it is a framework against which the contractile proteins of the platelet can operate to initiate shape change and protrusion of pseudopodia at the onset of spreading. Actin, actin-binding protein, talin, vinculin, stectrin, a-actinin, and several membrane glycoproteins make up the cytoskeleton. Actin-binding protein binds both actin and GPIb-IX. In resting platelet this maintains the discoid shape of the platelet. With activation and calcium influx, calpain is activated, severing the link of actin-binding protein to GPIb-IX. The microtubules are arranged in the form of an inner ring beneath the surface of the platelet and are distinct from the canalicular and dense tubular systems of the membrane zone. The microtubules provide structural support of the platelet, maintain its discoid shape in the resting state, and influence the character of its contractile functions. Contractile proteins largely consist of myosin and submembrane actin filaments that are anchored to the surface of the platelet by the Tran membrane glycoprotein a-actinin. On stimulation of the platelet, the cytoplasmic concentration of Ca^{2+} rises and calmodulin is activated and combines with myosin light-chain kinase; this enzyme phosphorylates myosin, leading to the combination of myosin with actin to form contractile act myosin, which mediates the initial changes in shape of the platelet and ultimately, retraction of the formed clot.

The three types of storage granules dominate the central cytoplasm are the dense granules, alpha granules and lysosomal granules.

In general, platelet aggregation is associated with release but at least in vitro certain "strong" agonists, i.e., collagen and thrombin, can trigger release without aggregation. P selectin or GMP140 is a component of the a-granule membrane. Release involves the granules nearest the platelet surface being transported to the platelet membrane and fusing with it so that a

Content of Platelet Granules[6]

Dense Granules	Alpha Granules	Lysosomal Granules
Adenosine triphosphate	PF-4	Galactosidase
Adenosine diphosphate	Beta-thromboglobulin	Fucosidase
Glucuronidase	Fibrinogen	Hexaminidase
Calcium	Factor V	Thrombospondin
Serotonin	Fibronectin	Cathepsin
Pyrophosphate	Plasma inhibitors	
P-selectin(CD-62)	P-selectin(CD-62)	
Transforming growth factor beta-1	Platelet derived growth factor inhibitor(PDGF)	
Catecholamines	Alpha-2 macroglobulin	
Nor-adrenaline/adrenaline		
Guanosoine-5diphosphate		
GDP/guanosine-5(GTP)		
Triphosphate		

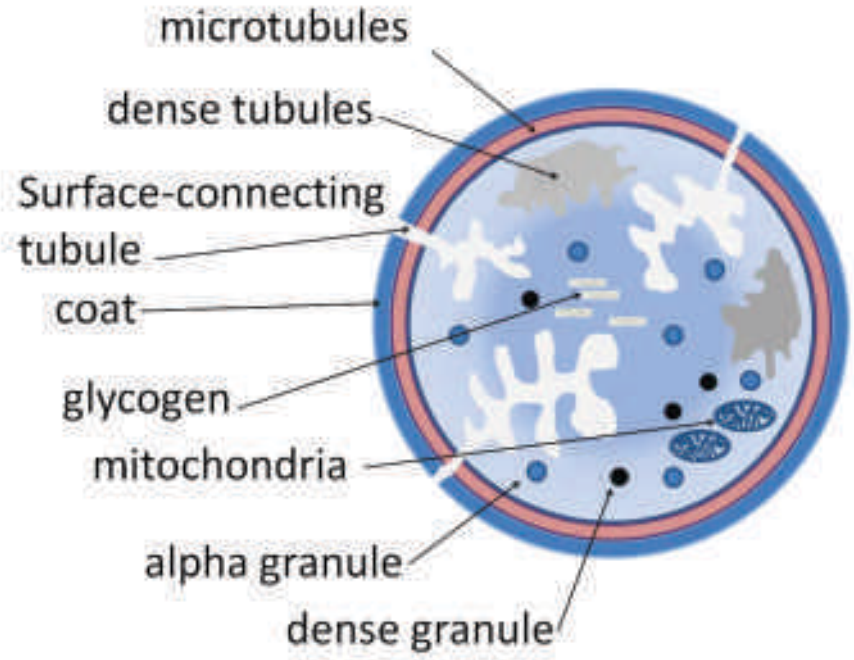

Figure 3: Platelet Structure

small portion of the post release external platelet membrane is made up of the inner membrane of theca-granule, including GMP140.

Dense bodies are granules characterized by high electron density and are fewer in number than a-granules. These structures serve as a depot for non-metabolic substances that are extrinsic to the platelet and may be picked up or released as indicated. On their release, these substances are particularly critical to platelet aggregation.

Lysosomal granules are also present in platelets, perhaps representing the original role of the platelet as a white blood cell. These granules contain at least seven acid hydrolyses. These enzymes may contribute to the intracellular effects of phagocytosis of may create an uncertain amount of damage extracellularly at the site of platelet release.

The contents and functions of the non-granular organelles of the platelet may be summarized as follows: mitochondria contain enzymes for oxidative metabolism and thereby provide a major source of energy through the generation of ATP, and peroxisomes contain catalase, which protects the platelet from oxidative damage in connection with periodically intense metabolic activity. Platelets also contain occasional ribosomal particles and small amounts of RNA.

On films made from blood anticoagulated with the strong calcium chelating agent ethylenediamine tetra acetic acid (EDTA) and stained with Wright's stain, platelet appears as small bluish-gray, oval-to-round with several purple-red granules. When anticoagulated blood is used to prepare blood films, platelet undergo variable activation and spreading and thus platelet aggregate are commonly seen: platelet from specimens may demonstrate three to four very long and thin processes extending out from the body of the platelet (filopodia).

Normal Range, Life Span and Physiological Variation of Platelet Count

The platelet count in the peripheral blood is maintained at a fairly constant level, which is in the range 150,000 to 450,000/cmm of blood in normal subjects. A somewhat lower range is seen in the newborn, normal adult level being achieved by about 3 months. Considerable fluctuation may occur during the course of menstrual cycle, lowest level being found at or just prior to menstruation. Heavy exercise and adrenergic stimulation tends to increase the platelet count transiently, possibly by mobilization of the splenic pool. There are some racial differences in platelet count for e.g. Mediterranean races' platelet count is as low as 80,000/ cmm of blood are sometimes found in normal individuals.

However in such cases the mean platelet volume is increased so that over all platelet mass is unaltered. Apart from this so called "Mediterranean Macrothrombocytopenia"[13] which is not clinically significant. There may be sex difference: thus in women, the platelet count have been reported to be about 2% higher than man. There is no evidence that oral contraceptives affect the platelet count. There are some ethnic differences and in healthy west Indians and Africans platelet counts may on average be 10-20% lower than those of Europeans living in the same environment. Strenuous exercise causes a 30-40% increase in platelet count. The normal life span of platelet ranges between 8 to 14 days[7].

Platelet Morphology and Number in Peripheral Blood Smear

Platelet appears in normal stained blood as small blue or colourless bodies with red or purple granules. Normal platelet average about 1-3 micrometer in diameter but show wide variation in shape, from round to elongated, cigar shaped forms. A rough estimate of the platelet count can be made by observation of the stained blood film. If the platelet count is normal, approximately 8 to15 platelet (individual or in small clumps) should be visible in each oil immersion field. There should be one platelet for every 10-30 erythrocytes[8].

The occurrence of giant platelets or platelet masses may indicate a myeloproliferative disorder, or absence of the spleen or improper collection of blood sample. Estimation of platelet concentration is best determined from EDTA anticoagulated blood, where the platelets generally do not aggregate[8].

Giant platelets and abnormal platelet granulation are characteristic features of idiopathic myelofibrosis[9].

Platelet morphology show large, pale-staining, hypo-granular platelet in essential thrombocythemia in peripheral smear. Characteristic morphological platelet features are seen in two platelet inherited disorders associated with bleeding. The Bernard- Soulier syndrome in which there are giant platelet with defective ristocetin response and Gray Platelet syndrome in which platelet lacks granules and have ghost like appearance on blood stained film[10]. In about 1% of patient EDTA anticoagulated blood causes platelet clumping and thus resulting in pseudo-thrombocytopenia.

Role of Platelet in Infection and Inflammation

Blood platelets are presented as active players in antimicrobial host defence and induction of inflammation and tissue repair in addition to their participation in hemostasis. Megakaryopoesis is inhibited after the acute infection with viruses or bacteria. In addition chronic inflammation is often associated with reactive thrombocytosis. Platelets can bind and internalize pathogens and release microbicidal proteins that kill certain bacteria and fungi. By making cell-cell contacts with leukocytes and endothelial cells, platelets assist white blood cells in rolling, arrest and transmigration. On stimulation by bacteria or thrombin, platelets release the content of their alpha granules, which include an arsenal of bioactive peptides, such as growth factors for endothelial cells, smooth muscle cells and fibroblast. This integral to innate immunity, the tiny little platelets may become bombshells when irritated by pathogens[11].

Thrombocytosis

Thrombocytosis is the presence of an abnormally high number of platelets in the circulating blood. It may result from various physiological stimuli and pathological processes[12].

Classification

A) Primary Thrombocytosis (Essential thrombocytosis) - This is due to a failure to regulate the production of platelets (autonomous production) and is a feature of a number of myeloproliferative disorders. About a third of patients are asymptomatic at the time of diagnosis[13].

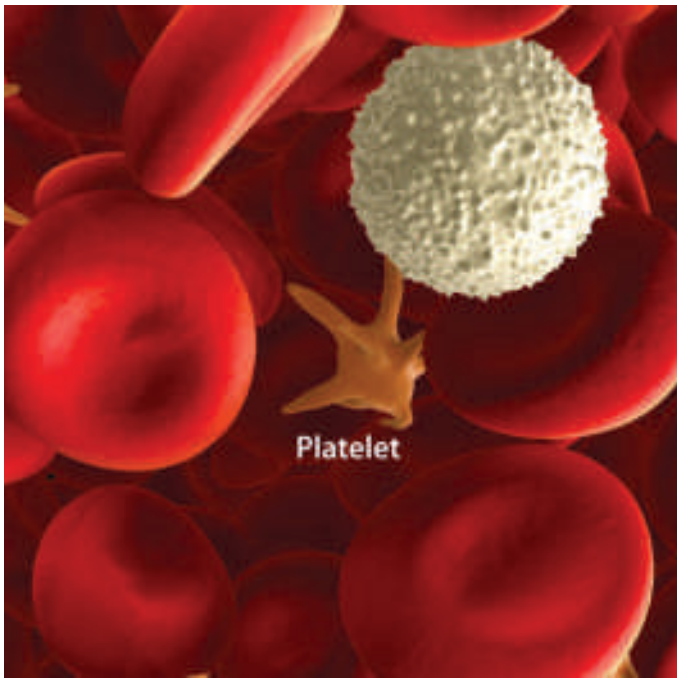

Figure 4(a): Low Platelet Count

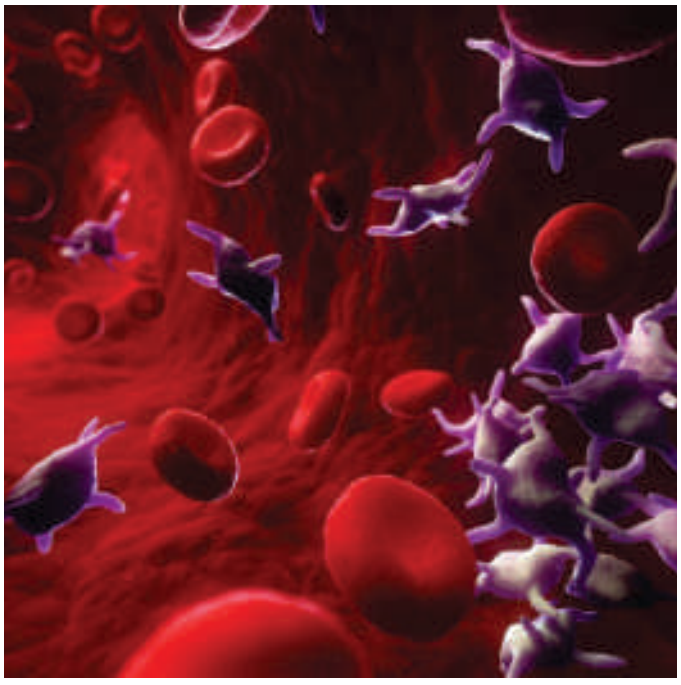

Figure 4(b): High Platelet Count

B) Secondary Thrombocytosis (Reactive thrombocytosis) - This can be secondary to a number of conditions. It is an exaggerated physiologic response to a primary problem, such as an infection. The trigger factor (e.g. infection) results in the release of cytokines which mediate an increase in platelet production. It is often a transient phenomenon which disappears when the underlying cause is resolved[14].

C) Non-specific Thrombocytosis - A recent "expert panel" has recommended that a platelet count of 400-450,000 needs no further evaluation.[15] Any platelet count > 450,000 does need evaluation. If there is no evidence of a "reactive" thrombocytosis, then Janus Kinase 2 mutations (JAK-2) testing should be done. A bone marrow biopsy should also be done, which would include testing for the Ph+ chromosome. Commonly, if these tests are negative, the individual platelet count is between 450,000/µl and 600,000/µl, and no evidence of reactive process then the individual is labeled "non-specific thrombocytosis."

Causes of Thrombocytosis[12]

I. Physiological: Exercise, Parturition, and Epinephrine

II. Pathological:

A) Primary Thrombocytosis

1) Myeloproliferative disorders.
   - Polycythemia vera
   - Chronic myeloid leukemia (CML)
   - Chronic idiopathic myelofibrosis
   - Essential thrombocytosis

2) Myelodysplastic disorders

3) Hereditary thrombocytosis

B) Secondary Thrombocytosis

1) Infection
   - Meningitis,
   - Infections of the upper and lower respiratory tract,
   - Urinary tract infections,
   - Gastroenteritis,
   - Septic arthritis,
   - Osteomyelitis and Generalised sepsis.

2) Chronic inflammations and vasculitis
   - Rheumatoid arthritis,
   - Kawasaki syndrome,
   - Henoch-Schonlein purpura,
   - Inflammatory bowel disease.

3) Tissue damage
   - Postsurgical,
   - Burns,
   - Trauma,
   - Fracture.

4) Rebound thrombocytosis
   - Iron deficiency anemia,
   - Bleeding,
   - Cancer chemotherapy,
   - Recovery phase of idiopathic thrombocytopenic purpura (ITP)

5) Postsplenectomy

6) Haemolytic anemia

7) Renal disorders (for example nephrotic syndrome, nephritis)

8) Malignancy (especially soft tissue sarcoma, osteosarcoma)

9) Low birth weight/ preterm infants.

Pathophysiology of Reactive Thrombocytosis[12]

Reactive thrombocytosis is usually mediated by increased release of numerous cytokines in response to infections, inflammation, vasculitis, tissue trauma, and other factors. Thrombopoietin (TPO), the primary cytokine for platelet production and maturation, and interleukin (IL)-6 levels are usually initially elevated in response to the primary events mentioned earlier; they stimulate an increase in platelet production.

It may be due to the overproduction of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and IL-11, that occurs in chronic inflammatory, infective, and malignant states. The presence of elevated IL-1, IL-6, C-reactive protein (CRP), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) in individuals with these conditions suggests that these cytokines may be involved in secondary thrombocytosis (reactive thrombocytosis).

However, serum or plasma levels of these cytokines do not seem to be correlated with degree of thrombocytosis. Other cytokines may participate in the stimulation of platelet production. They include IL-3, IL-11, granulocyte-macrophage colony-stimulating factor (GM-CSF), and erythropoietin. These cytokines are directly or indirectly released during the primary events. When the original stimulation stops, the platelet count then returns to the reference range.

In severe infections, such as bacterial meningitis, one of the causes may be a rebound phenomenon after initial thrombocytopenia due to rapid consumption of platelets. This most commonly occurs in neonates and infants, indicating the labile nature of platelet count control in these subjects.

The most common infection associated with thrombocytosis is

pneumonia. In some instances, such as chronic haemolytic anemia, the stimulus (hypoxia) to produce cytokines persists, causing long-term elevation of platelet counts. Although thrombocytosis in association with iron-deficiency anemia is well documented, the mechanism remains unclear. Although elevated erythropoietin levels are observed in patients with thrombocytosis who have iron-deficiency anemia, a recent study showed that these elevated levels had no correlation with platelet count. Levels of other cytokines potentially responsible for thrombocytosis, such as IL-6 and TPO, were not elevated.

The spleen is the major organ for the destruction of platelets; therefore, after splenectomy, a sharp rise in the platelet count is routinely observed, although the count subsequently slowly decreases to the reference range. Similarly, functional asplenia that may occur after splenic artery embolisation results in thrombocytosis.

Laboratory Findings in Reactive Thrombocytosis

There was no specific laboratory finding in patients with reactive thrombocytosis, and the diagnosis ultimately depends on diagnosing the underlying problem. Serum IL-6 concentrations measured by activity assay of ELISA are increased in majority of patients believed to have reactive thrombocytosis and in of the patient with clonal megakaryopoesis, but these tests are not clinically available. Hollen found increased serum concentrations in 80% to 100% of his patients with malignancy, inflammation or recent surgery. Only 50% of the anaemic patients had increased concentration of IL-6 and only one of five patients were in this group[12].

Elevated fibrinogen levels are found in patients of reactive thrombocytosis, presumably as a part of acute-phase reaction, and may be helpful in differentiating primary from secondary thrombocytosis[16].

Serum obtained from patient with thrombocytosis may contain elevated concentration of acid phosphates or potassium. In blood samples containing increased number of platelets, the PaO_2 may be significantly reduced due to consumption of oxygen by the platelet, particularly if the blood sample is stored at the room temperature[16].

In one study done by Perez Encinas et al[36] in 1995, they found the most potent stimulator for the hepatic synthesis of C-reactive protein is interleukin-6. Also, interlukin-6 is endowed with thrombopoietic activity and its level increases in most of the reactive thrombocytosis where as they remain normal in primary thrombocytosis. They had concluded that Quantitation of C-reactive protein could thus prove useful in differentiating between primary and reactive thrombocytosis[17].

Differential Diagnosis of Thrombocytosis

Clinical and laboratory features that distinguish between primary (ET) and secondary thrombocytosis (RT)[12].

Features	ET	RT
1. Thrombosis and haemorrhage	+	-
2. Splenomegaly	+	-
3. Increased acute-phase reactants (IL-6, CRP and plasma fibrinogen)	+	-
4. Bone marrow reticulin fibrosis	+	-
5. Bone marrow megakaryopoesis clusters	+	-
6. Clonal haematopoiesis	+	-
7. Spontaneous colony formation	+	-
8. Abnormal cytogenetic	+	-

Prognosis

Most patients with reactive thrombocytosis do not have significant problems caused by thrombocytosis, and the prognosis of the basic disease is not usually significantly affected.

Thrombocytosis in Childhood[18]

Thrombocytosis is a frequent finding in hospitalized and ambulatory children due to the widespread use of automated blood cell counters. Reactive thrombocytosis is very common and is due to a variety of conditions

Causes of Secondary or Reactive Thrombocytosis in Children[18]

1. Infections (e.g., of the respiratory tract, gastrointestinal tract, urinary tract infections central nervous system, skeleton and others)
2. Iron deficiency anemia, haemolytic anemia
3. Bleeding
4. Connective tissue diseases (juvenile rheumatoid arthritis, small and large vessel vasculitis including Wegener's granulomatosis, polyarteritis nodosa and others)
5. Kawasaki's disease
6. Inflammatory bowel diseases
7. Langerhan's cell histiocytosis
8. Malignancies (mostly solid tumours, such as hepatoblastoma, hepatocellular carcinoma, neuroblastoma, and rarely acute lymphoblastic leukaemia)
9. Drugs (adrenaline, corticosteroids, vinca alkaloids, iron, miconazole, antibiotics, haloperidol, narcotics, and non-narcotic psycho pharmaceutical agents)
10. Trauma, burns, tissue injury
11. Intense exercise
12. Splenectomy (surgical or functional e.g., sickle cell anemia)

It seems to affect up to 15% of hospitalized children[19-25]. It is more common in neonates, particularly premature ones, and infants up to 2 years of age and less common in older children. In most children with reactive thrombocytosis, platelet counts

are moderately elevated up to 700,000/µl. Moderate thrombocytosis (platelets between 700,000 and 899,000/ µl) occur in 6-8% of children with reactive thrombocytosis, while platelets >1,000,000/µl occur in less than 2-3% of children with reactive thrombocytosis[22].

Presently, **infections** of the respiratory tract account for 60-80% cases of secondary thrombocytosis in children[20,22-27], followed by infections of the urinary[28] and gastrointestinal tracts, and of the bones[22-24,27,29].

From the **non-infectious** causes of secondary thrombocytosis, iron deficiency anemia is a common one, since it is the single most common nutritional deficiency worldwide[30,31]. The fact that thrombocytosis is more frequent in children up to 2 years of age is partly due to the higher incidence of iron deficiency in this age group.

In patients with **systemic-onset JRA,** serum IL-6 levels correlate with platelet counts and with the extent and severity of joint involvement[32]. Regarding **Kawasaki's disease (KD),** thrombocytosis typically occurs in the second week of the illness, and it is therefore not helpful in making a timely diagnosis. Moreover, the absence of thrombocytosis during convalescence does not exclude the disease. TPO in conjunction with IL-6 contributes to the thrombocytosis of patients with KD. TPO serum levels are also increased in patients with inflammatory bowel diseases, irrespective of disease activity, platelet counts and clinical characteristics of the patients[33].

The association between **liver tumours** and thrombocytosis is likely due to the increased production of hepatic TPO in these patients. Reactive thrombocytosis has also been described in children with other small, blue round cell tumours of childhood, such as **neuroblastoma**[34].

Reactive thrombocytosis can also be related to treatment with several drugs. **Adrenaline and corticosteroids** are known to cause transient thrombocytosis, as a result of release of stored platelets from the spleen into the blood circulation[35]. Various antibiotics such as **carbapenems and cephalosporins** are also claimed to cause thrombocytosis in children[36-43]. In the first week, when platelet counts are normal, circulating TPO concentrations rise and then gradually decrease. When platelet counts peak during convalescence, TPO concentrations are back to normal. Hence, the development of thrombocytosis during the recovery phase after appropriate antibiotic therapy for an infection is consistent with the bone marrow response to TPO and not the result of the antibiotic[43,44].

Miconazole, ciprofloxacin and tazobactam/ piperacillin caused thrombocytosis in a single patient18 since the platelet count started to increase immediately after initiation and dropped immediately after discontinuation of the drug[39].

Neonatal reactive thrombocytosis has been described from **maternal narcotic drug abuse,** but may also occur in infants born to mothers treated during pregnancy with non-narcotic psycho pharmaceutical agents[45,46]. Finally, reactive thrombocytosis may be due to multiple, simultaneous, causative factors. In one paediatric series, 9% of cases of secondary thrombocytosis were multi-factorial[47].

Reasons for reactive thrombocytosis in different clinical conditions:

1) Inflammations and Infections:

Thrombopoietin (TPO), the primary cytokine for platelet production and maturation, and interleukin (IL)-6 levels usually stimulate an increase in platelet production. Thus, it may be due to the overproduction of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and IL-11, that occurs in chronic inflammatory, infective, and malignant states.

2) Iron Deficiency Anemia:

Reactive thrombocytosis is usually of mild to moderate degree. Extreme thrombocytosis is not so common but in some patients it can occur. Thrombopoietic growth factors including interlukin-6(IL-6), tumour necrosis factor-alpha, and thrombopoietin have been implicated as the cause of reactive thrombocytosis. Several clinical and the laboratory observation support the possible pathogenic role of elevated IL-6 in reactive thrombocytosis. An alteration of the bone marrow megakaryocyte count in iron deficiency anemia is not mentioned except for the two reports. In these reports authors mentioned that the bone marrow megakaryocyte count was increased and the plausible explanation for the thrombocytosis must be increased production of the platelet. The mechanism causing reactive thrombocytosis in iron deficiency anemia is unknown.

3) Tissue damage from trauma or surgery (postoperative):

The platelet count increases when a relatively large amount of body tissue is damaged either intentionally following surgery or after an accident. This is because of body natural defence mechanism to ensure adequate clot formation and prevent fatal bleeding.

4) Blood loss:

In event of an injury, the response of the bone marrow to blood loss is to produce more red blood cells and more platelets.

5) Post-splenectomy:

The splenectomised patients are expected to have high postoperative platelet counts because of reduced platelet storage in the spleen. The increase may remain for a long time, but usually it settles back into the normal range.

6) Haemolytic anemia:

Haemolytic anemia is another frequent cause of thrombocytosis. Sickle cell anemia is a congenital haemolytic anemia associated with thrombocytosis due to increased bone marrow platelet production, but also due to functional asplenia from the repetitive splenic autoinfarcts. Patients with sickle cell anemia and thrombocytosis are at

increased risk for vaso-occlusive complications, such as brain infarcts, painful crises, while they have highly impaired full scale IQ[48,49].

7) Malignancy:

Malignancy causes high platelet count either by causing damage to tissues, causing blood loss (for example from the bowel) or by erroneously producing a response from the immune system that stimulates the bone marrow to produce platelets.

8) Tuberculosis:

The pathogenesis of reactive thrombocytosis in tuberculosis is not clear. It has variously been attributed to increase thrombopoietin[50] or production of platelets in pulmonary vasculature by fragmenting proplatelets[51].

CONFLICT OF INTEREST: None

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