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Narrative Review on Different Clinical Aspects of Thrombocytopenia

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ABSTRACT

This review article aims to summarize the major causes of thrombocytopenia and characterize the main general symptoms of thrombocytopenia. As well we summarize the diagnosis and treatment methods. We conducted the search using electronic biomedical databases such as; Medline, and Embase, for studies published up to September 2017 in the English language concerning the thrombocytopenia in general. Thrombocytopenia can either be primary or secondary, in that it could go along with a broad spectrum of syndromes and diseases and may be triggered by different systems. Trigger investigation and recognition might be important and sometimes life-saving as in TTP, heparin-induced thrombocytopenia, acute leukemia or perhaps severe ITP. Taking a detailed history and a thorough physical examination can give clues concerning possible underlying illness and clinical treatments. Cautious evaluation of the peripheral blood smear is necessary. When the differential diagnosis is problematic, sometimes a short trial of therapy could help to clarify the reason. For instance, it might be difficult to differentiate inherited thrombocytopenia (without a family history) from immune thrombocytopenia (ITP); in this example, intravenous immunoglobulin infusion will likely have no effect in inherited thrombocytopenia, however, will generally be useful in ITP.

Keywords: Clinical Aspects, Thrombocytopenia, intravenous immunoglobulin infusion.

INTRODUCTION

Although lots feel that a cutoff value of 100 × 109/L is better suited to identify clinically considerable thrombocytopenia. Causes of thrombocytopenia can be subdivided into lowered platelet production, increased platelet damage, increased splenic sequestration, and dilution. The investigation requires a point to consider patient age, baseline platelet count, medical and surgical history, including any kind of bleeding or thrombotic symptoms, family history, medication history, outcomes of any relevant laboratory testing, and health examination findings. A complete blood count (CBC) and peripheral smear testimonial are crucial for first analysis. Ethylene diamine tetraacetic acid (EDTA)-induced pseudothrombocytopenia, a laboratory artifact defined by in vitro platelet clumping in EDTA anticoagulant, need to be omitted [1]. The spleen harbors 30% of the overall platelet mass and splenomegaly could lead to thrombocytopenia due to platelet sequestration. Dilutional thrombocytopenia is seen after the significant surgical procedure or with transfusion of large amounts of non-platelet-containing blood products [2]. Incidental or gestational thrombocytopenia in pregnancy is identified by mild or moderate thrombocytopenia. Although the cause is unidentified, it should be carefully evaluated from other major causes of thrombocytopenia [3].

This review article aims to summarize the major causes of thrombocytopenia and characterize the main general symptoms of thrombocytopenia. As well we summarize the diagnosis and treatment methods.

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials up till November 2017 for published studies in English language concerning the thrombocytopenia in general, Following MeSh terms were used in our search strategy: “thrombocytopenia, pathogenesis and platelets disorders. More relevant studies were searched for in the references list.

- **Data Extraction**

Two reviewers independently reviewed studies, abstracted data, and resolved disagreements by

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consensus. Studies were evaluated for quality. A review protocol was followed throughout.

The study was done after approval of ethical board of King Abdulaziz university.

- **Diagnosis**

Thrombocytopenia is not a disease but is a diagnosis. The detailed knowledge should be acquired from patients that have been suffering from the thrombocytopenia. Detailed examining and the analysis of research laboratory need to be done which belong to etiology. A few of the circumstances concerning thrombocytopenia have to be inspected. Recent new medicines or medicines that are just taken periodically, current infection, previously diagnosed hematologic illness, and nonhematologic illness recognized to decrease platelet counts (eg, eclampsia, sepsis, DIC, anaphylactic shock, hypothermia, large transfusions), positive family history of blood loss and/or thrombocytopenia, recent live virus vaccination, bad dietary condition, pregnancy, current organ replacement from a donor sensitized to platelet alloantigens, current transfusion of a platelet-containing item in an allosensitized recipient. Background pertaining to alcohol consumption and HIV danger factors should be gotten. When confronted with an asymptomatic patient with a low platelet count, the medical professional must originally look for to leave out artifactual or "pseudothrombocytopenia" as the etiology.

Also, the story of the family needs to be questioned for the congenital thrombocytopenia factors [4]. Thrombocytopenia is not only bleeding for the patient, however, it depends on heparin. Disseminate intravascular coagulation and as paroxysmal nighttime hemoglobinuria can be with thrombosis clinic. In checkup the thrombocytopenia which depends upon medical diagnosis petechia, purpura, nose blood loss, gum blood loss, hematuria, and menorrhagia or as cerebral hemorrhage is recognized, likewise, some signs and symptoms which rely on thrombosis can be taken care of. The peripheral smear must be done for every patient who is thrombocytopenia. In regular magnify, there can be seen 3 - 10 platelet in every part. With peripheral smear, pseudothrombocytopenia can be eliminated in the patient or the abnormality which creates thrombocytopenia can be identified [5].

Table 1. Classification of Thrombocytopenia [5].

1.Artificial thrombocytopenia	**3. Increased platelet destruction**
a. Forming of platelet which is relevant to anticoagulant immunoglobulin (pseudothrombo-cytopenia)	a. Immunologic: -Autoimmune, -Primer (Immune thrombocytopenia), -Seconder (Infections, pregnancy, collagen tissue diseases, lymphoproliferative diseases, drugs), -Alloimmune,-Neonatal thrombocytopenia, -Post-transfusion purpura.
b. Platelet satellism	b. Nonimmunologic:-Thrombotic microanjiopaties, -Disseminated intravascular coagulation, -Thrombotic thrombocytopenic purpura, -Hemolytic-uremic syndrome, -Abnormal vascular relevant to the surface of thrombocytopenia, - Others (infection, massif blood transfusion).
c. Giant platelets	**4. Abnormal platelet distribution**
2. Decreased product of thrombocyte	a. The disease that capture spleen (neoplasia,congestive, infiltration)
a.Megakaryocyte hypoplasia or suppression	b. Hypothermia
b. Ineffective thrombopoiesis	
c. Defeat in mechanism which are controlling thrombopoiesis	
c. Herediter trombositopenia	

- **Symptoms**

Mild to serious bleeding causes the primary signs and symptoms of thrombocytopenia. Bleeding could occur inside your body (internal bleeding) or below your skin or from the surface of your skin (external bleeding) [6]. Signs and symptoms can show up unexpectedly or over time. Mild thrombocytopenia often has no indications or symptoms. Many times, it's found throughout a regular blood test. Severe thrombocytopenia could trigger bleeding in almost any part of the body. Bleeding could result in a clinical emergency and must be treated right away. External bleeding usually is the very first sign of a low platelet count. External bleeding might trigger or petechiae . Purpura is purple, brown, and red bruises. This bruising might happen conveniently and often. Petechiae are little red or purple dots on your skin.

Purpura and Petechiae

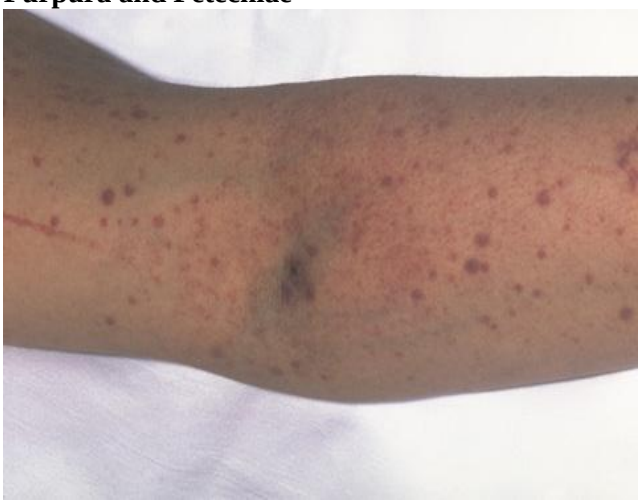

Figure1. The photograph shows purpura (bruises) and petechiae (red and purple dots) on the skin. Bleeding under the skin causes the purple, brown, and red color of the purpura and petechiae.

Other signs of external bleeding consist of [7]:

- Prolonged bleeding, even from small cuts
- Bleeding or oozing from the mouth or nose, especially nosebleeds or bleeding from cleaning your teeth
- Abnormal genital bleeding (especially heavy menstruation flow).A great deal of bleeding after surgical procedure or dental work also may propose a bleeding issue.

Heavy bleeding right into the intestines or the brain (internal bleeding) is severe and can be deadly. Symptoms and signs consist of:

Skin irregularities: unusual skin pigmentation in Fanconi anemia, necrotic skin lesions in HIT patients, eczema in Wiskott-Aldrich syndrome (WAS), "lacy" skin pigmentation connected with unusual development and form of nails in dyskeratosis congenita.

Complete blood count (CBC)

The following issues must be taken into account:

Isolated thrombocytopenia is typically connected with immune-mediated conditions [9] (e.g. ITP, DITP) and acquired disorders (e.g. Bernard-Soulier, TAR disorder), but is unusual in malignant processes entailing bone marrow.

Thrombocytopenia associated with anemia and leucopenia (pancytopenia) can be triggered by bone marrow reductions by numerous medications (typically chemotherapy, rarely antihypertensive medications and anti-biotics e.g. chloramphenicol); viral infections (HIV); bacterial infections (e.g. leishmaniasis); severe folate and B12 shortage; paroxismal nocturnal hemoglobinuria; systemic lupus erythematosus (SLE); inherited disorders (e.g. dyskeratosis congenita, Fanconi anemia); hatred (metastatic disease, leukemia, lymphoma with bone marrow involvement, multiple myeloma, rarely solid tumors) or bone marrow failing (e.g. aplastic anemia, myelodysplastic syndrome).

If thrombocytopenia is related to neutrophilia [10], infection should be thought about or, seldom, chronic myeloid leukemia, usually associated with "left change"-- a raised percentage of premature neutrophils (bands, metamyelocytes and myelocytes). Thrombocytopenia can be accompanied by lymphocytosis suggestive of lymphoid malignancies (e.g. chronic lymphocytic leukemia [CLL], pertussis, or viral infections).

Blood smear

Blood smear has valuable value in the medical diagnosis of thrombocytopenia. Firstly, as discussed, pseudothrombocytopenia ought to be omitted. Secondly, in cases of true thrombocytopenia [11], blood cell morphology ought to be explored completely. Giant platelets can be discovered with various types of hereditary thrombocytopenia (Paris-Trousseau thrombocytopenia, gray platelet syndrome, Bernard-Soulier) and these can result in wrongly reduced platelet counts if the gigantic platelets are not counted as platelets. Microthrombocytes are usually seen in WAS or X-

linked thrombocytopenia [12] and Torch infections (toxoplasmosis, others [such as syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, and herpes infections). Neutrophils with harmful granulation occur in blood smears of patients with sepsis, and Döhle-like bodies in the cytoplasm of neutrophils are seen in the MYH9-related disorders (May-Hegglin abnormality associated with MYH9 gene). Neutrophils with bilobed nuclei recommend Pelger-Huèt anomaly. Atypical lymphocytes are seen in lots of viral infections in children but Epstein-Barr virus is the one typically connected with kind II atypical lymphocytes or Downey cells. Acute leukemia must be considered if there are blasts on blood smear; in this situation unique blood tests (particularly bone marrow goal and biopsy) are the next actions of analysis evaluation. Red blood cell pieces (schistocytes) prevail in microangiopathic hemolytic anemias (such as TTP and DIC). Structure of dacrocytes ("drop" erythrocytes) and nucleated erythrocytes need more bone marrow examination, since these findings are indicative of primary myelofibrosis and myelodysplastic syndrome [13].

Additional investigations

Raised blood lactate dehydrogenase (LDH) and indirect bilirubin, incorporated with reduced haptoglobin level and a positive direct antiglobulin examination (direct Coombs test), prevail in patients with Evans syndrome, a problem presenting with autoimmune hemolytic anemia and thrombocytopenia (both procedures could take place at the same time, or, more frequently, various times) as a consequence of anti-platelet and anti-erythrocyte antibodies. Elevated LDH integrated with kidney function impairment may indicate TTP or hemolytic uremic syndrome (HUS). Blood coagulation examinations disruption: long term prothrombin time (PT), low fibrinogen and elevated D-dimers are regular for DIC.

Elevated liver enzymes with or without elevated bilirubin, LDH and alkaline phosphatase must lead to the examination of hepatic condition (viral hepatitis, drug-induced or harmful hepatitis), cirrhosis, and viral infection such as cytomegalovirus (generally only liver enzymes and LDH are elevated) [12].

Serological tests for viruses, blood cultures, anti-platelet antibodies, bone marrow biopsy and many other diagnostic tests can be performed at the discernment of the medical professional according to the presenting signs and program of the disease One treatment strategy is to direct treatment to the etiology of thrombocytopenia (e.g. discontinuation of the medication that created thrombocytopenia, treatment of the hidden infection, immunoglobulin G (IgG) substitute, radiation treatment routed at CLL). Unfortunately, just in a minority of situations is the etiology of thrombocytopenia clear and the cause is found. Additionally, sometimes "treating" the underlying clinical reason for the ITP may not transform the platelet count.

In a case of serious bleeding, if the etiology of thrombocytopenia is unidentified, however not believed to be immunologic, platelet transfusion can be utilized to supply a prompt platelet rise. On the other hand, if the underlying cause is immune, the result from platelet transfusion may be marginal and at the best is really temporary, and it needs to be scheduled just for serious blood loss (ideally transfused complying with intravenous immunoglobulin to "protect" the platelets). If the cause of thrombocytopenia is unidentified and there are no contraindications, such as infections, corticosteroids may be made use of to increase the platelet count. Much more particular treatment strategies typically depend upon the underlying etiology of the thrombocytopenia.

- **Treatment of thrombocytopenia**

One therapy method is to direct therapy to the etiology of thrombocytopenia (e.g. discontinuation of the medicine that triggered thrombocytopenia, therapy of the hidden infection, immunoglobulin G (IgG) replacement, and radiation treatment directed at CLL). Unfortunately, just in a minority of instances is the etiology of thrombocytopenia clear and the cause found. Furthermore, in many cases "curing" the underlying medical source of the ITP might not transform the platelet matter.

In a situation of severe bleeding, if the etiology of thrombocytopenia is unidentified, however not thought to be immunologic, platelet transfusion can be utilized to provide a prompt platelet boost. On the other hand, if the underlying cause is immune, the impact from platelet transfusion might be minimal and at best extremely temporary, and it ought to be booked just for dangerous bleeding (preferably transfused adhering to intravenous immunoglobulin to "protect" the platelets).

If the cause of thrombocytopenia is unknown and there are no contraindications, such as

infections, corticosteroids might be utilized to boost the platelet count. Much more specific treatment plans generally depend upon the underlying etiology of the thrombocytopenia.

Inherited thrombocytopenia

Patients with inherited thrombocytopenia and their families should be informed concerning their diagnosis to avoid unnecessary examinations and particularly possibly harmful medical/surgical therapy for ITP. In the past, patients with acquired thrombocytopenia have been treated with platelet transfusions (reserved for instances of bleeding or its prevention, e.g. before surgery). While the concern of sensitization has actually controlled restriction of platelet transfusion, the schedule of leukoreduction has greatly decreased this risk. Just recently, one of both thrombopoietin-receptor agonists, eltrombopag, was examined as a possible therapy option in MYH9-related problems (May-Hegglin anomaly connected with the MYH9 gene) thrombocytopenia, with at least some success in 12 of 15 patients [14] Initial outcomes have also been acquired in patients with WAS. Concern of induction of hatred has actually restricted its usage in syndromes where there is myelodysplastic syndrome or a capacity for the development of leukemia, as an example congenital amegakaryocytic thrombocytopenia (CAMT), TAR, GATA-1 (globin transcription factor 1)-related X-linked thrombocytopenia, and domestic leukemia-thrombocytopenia. The option of allogeneic stem cell transplantation is reserved for acquired thrombocytopenias with a high risk of marrow failing or a high risk of acute leukemia [15,16].

Immune thrombocytopenia (ITP)

Lots of situations of ITP can be left neglected, and spontaneous remission in kids is common. However, matters of under 50 × 109/L are typically checked with routine blood tests, and those with counts of under 10-20 × 109/L are usually treated, as the danger of significant spontaneous bleeding, especially intra-cranial hemorrhage, is a lot higher with reduced platelet counts. Any patient experiencing severe bleeding signs secondary to thrombocytopenia must additionally be treated [17,18]. According to the American Society of Hematology 2011 guidelines, treatment initiation is suggested when a grown-up patient is newly-diagnosed with a platelet count <30 × 109/L (grade 2C proof) [19], however in scientific practice numerous elements (e.g. bleeding tendency, age, case history and concomitant medications) should be taken into account.

If therapy is required, the first-line therapy option is typically corticosteroids, with the suggested prednisone dose of 1 mg/kg/day orally for up to 21-28 days relying on action, followed by sluggish tapering. Extra noticeable platelet reactions have been reported with duplicated pulses of high-dose dexamethasone of 40 mg daily for 4 days [20], however no relative data preferring dexamethasone exists.

Thrombotic thrombocytopenic purpura

TTP is a clinical emergency situation, since the death of neglected patients surpasses 80%. The death is believed to be triggered by disseminated microvascular thrombosis which may provoke ischemic injury and numerous body organ failure. Ischemic organ injury can impact all organs, however the brain and heart are generally most impacted. Acute kidney injury requiring dialysis and leading to chronic kidney condition is rare. Central nerve system involvement is typically materialized by transient focal neurologic abnormalities arising from micro-infarcts in the brain, which might create focal neurologic deficiencies.

Drug-induced thrombocytopenia/DITP and heparin-induced thrombocytopenia

In the event of drug-induced thrombocytopenia/DITP, it is global practice to stop the believed medicine right away. Platelet counts generally recuperate within a number of days to 2 weeks. Platelet transfusions may be required to treat patients with extreme thrombocytopenia and blood loss. Various other helpful measures consist of high dosage intravenous immunoglobulin, a brief course of corticosteroids, or perhaps plasmapheresis. Drug-dependent platelet antibodies can persist for several years; thus, patients with a validated diagnosis should be counseled to avoid future direct exposures to the drug (with the possible exemption of heparin). Testing at one of the few experienced research laboratories can be extremely handy in validating a medical diagnosis.

CONCLUSION

Thrombocytopenia is a common disorder with various underlying causes. An important method to the successful treatment of thrombocytopenia is the

understanding of the underlying pathophysiological processes in the development of the illness. Thrombocytopenia can either be primary or secondary, in that it could go along with a broad spectrum of syndromes and diseases and may be triggered by different systems. Trigger investigation and recognition might be important and sometimes life-saving as in TTP, heparin-induced thrombocytopenia, acute leukemia or perhaps severe ITP. Taking a detailed history and a thorough physical examination can give clues concerning possible underlying illness and clinical treatments. Cautious evaluation of the peripheral blood smear is necessary. When the differential diagnosis is problematic, sometimes a short trial of therapy could help to clarify the reason. For instance, it might be difficult to differentiate inherited thrombocytopenia (without a family history) from immune thrombocytopenia (ITP); in this example, intravenous immunoglobulin infusion will likely have no effect in inherited thrombocytopenia, however, will generally be useful in ITP.

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