# REACTIVE THROMBOCYTOSIS FOLLOWING ACUTE INFECTION AND PANCYTOPENIA

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## INTRODUCTION

Thrombocytosis is classified as either primary or secondary [1]. Primary thrombocytosis is caused by autonomous production of platelets unregulated by the physiologic feedback mechanism to keep the count within the reference range [2]. Reactive thrombocytosis (RT) refers to thrombocytosis in the absence of a chronic myeloproliferative or myelodysplastic disorder, in patients who have a medical or surgical condition likely to be associated with an increased platelet count, and in whom the platelet count normalizes, or is expected to normalize, after resolution of this condition [3]. Here we present a case of reactive thrombocytosis that initially presented with pancytopenia.

## CASE REPORT

A 15-year-old girl was admitted to Military Hospital Rawalpindi in July 2006 with a fifteen day's history of high grade intermittent fever with chills along with passage of loose watery stools, 6-8 times/day, not containing any blood or mucus. There was no associated abdominal pain, vomiting or any other systemic complaints like cough, dysuria, arthralgias, rash etc. On examination, she was thin lean girl, who was markedly pale but fully conscious and well oriented. She was afebrile on admission with the heart rate of 90 beats per minute. Her respiratory rate was 16 breaths per minute; blood pressure 100/70 mm Hg and oxygen saturation of 97% on room air. There was no clubbing, cyanosis and oedema but she had hyperpigmented patches on her forehead and cheeks which had appeared a couple of months ago. There was no pigmentation on mucus membrane. She was not jaundiced. There was no lymphadenopathy or sign of meningeal irritation. On clinical examination, no abnormality was detected in cardiovascular, respiratory and neurological examination. Abdomen was soft, with palpable spleen tip. Initial laboratory investigations were suggestive of pancytopenia with haemoglobin of 4.7 g/dl; white cell count $1.3x10^9$/l and a platelet count of 13x109/l. Mean corpuscular volume (MCV) was 99.3 fl, while peripheral blood film showed macrocytosis, anisocytosis and poikilocytosis. Erythrocyte sedimentation rate was 120 mm at the end of 1st hr and C-reactive proteins were elevated. Her ALT was raised to 70 U/L, bilirubin and alkaline phosphatase were with in normal limits. Serology for Hepatitis B and C was negative. Reticulocyte count was 1%. Her X-ray chest and USG abdomen were unremarkable. Renal function tests, urine and stool were normal. Repeated slides for malarial parasites were negative. Her antinuclear antibody (ANA) was also negative. Her bone marrow aspiration and trephine biopsy showed hypercellularity with megaloblastic as well as dyserythroblastic cells suggesting a differential diagnosis of either myelodysplasia secondary to some infections or aplastic anemia in evolution. She was transfused 2 units of red cell concentrate and 4 units of platelets. Intra-venous Vancomycin was added empirically to the regimen to cover staphylococcal infection. Her blood counts gradually improved and fever and loose stools began to settle. Culture of blood and stool revealed no microbial growth. Echocardiography revealed no vegetation and normal heart valves. Injection Trividox (Vit B1, B6, and B12) and folic acid were also added to treatment because her serum B12 level was found to be at lower normal limit.

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Her blood complete picture repeated 15 days after start of therapy showed haemoglobin of 6 g/dl, WCC 8.6 x$10^9$/l. The notable finding this time was a platelet count of 1610 x $10^9$/l. This high count indicated reactive thrombocytosis confirming bone marrow recovery. The probable cause of this reactive thrombocytosis was recovery from acute infection or Vit B12 supplementation. Her antibiotics were then tapered off and platelet count gradually returned to normal over next four weeks. Her blood counts 2 weeks after discharge showed hemoglobin of 10.7 g/dl, WCC of 7.5 x $10^9$/l and a platelet count of 259 x $10^9$/l.

**Table: Causes of secondary (reactive) thrombocytosis.**

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| **Transient process** |
| Acute blood loss |
| Recovery ("rebound" from thrombocytopenia |
| Acute infection or inflammation |
| Response to exercise |
| **Sustained processes** |
| Iron deficiency |
| Hemolytic anemia |
| Asplenia (e.g., after splenectomy) |
| Cancer |
| Chronic inflammatory or infectious diseases |
| Connective-tissue disorders |
| Temporal arteritis |
| Inflammatory bowel disese |
| Tuberculosis |
| Chronic pneumonitis |
| Drug reactions |
| Vincristine |
| All-trans-retinoic acid |
| Cytokines |
| Growth factors |

## DISCUSSION

The normal platelet count in adults (mean ± 2 standard deviations) ranges from 150,000 to 450,000/uL, thus thrombocytosis can be defined as a platelet count > 500,000/uL once thrombocytosis has been reported, it should be confirmed by repeat testing and examination of the peripheral blood smear. If thrombocytosis is confirmed by repeat testing, the initial step is to perform a comprehensive history and physical examination, and to determine the duration of the patient's thrombocytosis. The initial evaluation alone should be sufficient to exclude many of the common causes of reactive thrombocytosis which are given in table [2]. In a 1994 study by Buss and colleagues [4] of patients with platelet counts greater than 1 million/µL, reactive thrombocytosis was the major cause in 82% and myeloproliferative disorders in 14%; the cause was idiopathic in 4%. The most common cause of reactive thrombocytosis was infection (31%), followed in descending order by splenectomy (19%), malignancy (14%), and trauma (14%).

A recent 1-year prospective study of 777 patients in Kingdom of Saudi Arabia with platelet counts greater than 500,000/µL showed that 21% of the thrombocytosis cases were caused by infection, 19% involved rebound phenomenon (after bleeding, iron deficiency, or cancer chemotherapy), 18% were a result of tissue damage, and 13% were due to chronic inflammation. Malignancy, splenectomy, and myeloproliferative disorders each accounted for fewer than 5% of cases [5].

Thrombopoietic growth factors have been implicated as the cause of Reactive thrombocytosis in various infectious, inflammatory, malignant, necrotic, and traumatic processes. Although the exact mechanism is unknown, reactive thrombocytosis may result from persistent overproduction of one or more thrombopoietic factors that act on megakaryocytes or their precursors [6]. Many cytokines, such as interleukin (IL)-6, IL-1, and tumor necrosis factor (TNF), have been shown to promote in vivo and in vitro megakaryocytopoiesis, or production of platelets. However, the principal regulator of megakaryocytopoiesis is thrombopoietin (TPO), also called megakaryocyte growth and development factor [7]. Megakaryocytes and their platelet progeny have receptors for thrombopoietin (referred to as c-Mpl receptors). Thrombopoietin in plasma binds to c-Mpl on the surfaces of circulating platelets; the remaining, unbound

thrombopoietin in plasma is available to promote megakaryocyte proliferation. Thus, when the platelet count drops, increased plasma levels of free thrombopoietin stimulate megakaryocytopoiesis; conversely, when the platelet count rises, reduced levels of free thrombopoietin slow megakaryocytopoiesis. In this way, the total mass of platelets (and megakaryocytes) can regulate platelet production and maintain it at a steady state. In some cases of reactive thrombocytosis, an underlying inflammatory stimulus may up-regulate the production of thrombopoietin by the liver [8]. Plasma levels of thrombopoietin are high or inappropriately normal in reactive (secondary) thrombocytosis [9]. In cases of acute inflammation, this elevation precedes an increase in the platelet count [10]. Plasma levels of interleukin-6 are also elevated in reactive thrombocytosis: this interleukin, which plays a prominent role in the acute-phase response of inflammatory and neoplastic diseases, up-regulates the expression of thrombopoietin messenger RNA (mRNA) in the liver [11]. Thus, interleukin-6 may be a key mediator of the increased synthesis of thrombopoietin and the consequent reactive thrombocytosis

In most patients of RT, there are clinically apparent symptoms of an active, underlying systemic disease. In others, however, subclinical disorders (e.g., occult cancers) may be responsible for the secondary thrombocytosis. It is the latter group of patients that presents the more vexing diagnostic challenge for the clinician. Before ascribing thrombocytosis to a clonal (myeloproliferative) disorder, which is largely a diagnosis of exclusion and has very different therapeutic implications (see below), the clinician must be confident that the elevated platelet count is not due to an inapparent, but potentially treatable, underlying disease [12].

Bleeding and thrombotic complications which are commonly associated with clonal thrombocytosis are usually not found in secondary thrombocytosis, regardless of the degree of elevation in the platelet count, unless the underlying systemic disorder predisposes patients to them. Their absence in secondary thrombocytosis is presumably due to the fact that the interaction of platelets with the vessel wall remains qualitatively normal [13]. Laboratory tests do not offer clear-cut distinctions between clonal and reactive thrombocytosis. Giant platelets are often found on the peripheral-blood smear in clonal thrombocytosis but not in secondary thrombocytosis. A variety of platelet-function abnormalities also have been described in the clonal but not the secondary form of thrombocytosis. These abnormalities may include acquired von Willebrand syndrome and the absence of epinephrine-induced platelet aggregation. Examination of bone marrow aspirate and biopsy specimens reveals increased numbers of megakaryocytes in both forms of thrombocytosis, but there may be relatively subtle differences in their morphologic features. Megakaryocytes in secondary thrombocytosis appear normal, but in clonal thrombocytosis they may assume giant, dysplastic forms with increased ploidy and may be associated with large masses of platelet debris ("platelet drifts") [14].

The primary treatment should address the underlying cause of the thrombocytosis. In general, no treatment is indicated to directly reduce the platelet count. For patients with platelet counts in excess of 1,000,000 per mL, aspirin 65 mg daily may be considered to minimize the rare development of stroke or thrombosis [15].

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