Thrombocytosis in Iron Deficiency Anemia

Key words: thrombocytosis, iron deficiency anemia, thrombosis

Thrombocytosis is observed in many disorders and pathological states. An elevated platelet count may be caused by a reactive mechanism or it may be the result of autonomous (neoplastic) overproduction. A variety of medical and surgical conditions can result in reactive thrombocytosis. These include infections, inflammatory disorders, malignancies, acute bleeding or hemolysis, rebound phase of thrombocytopenia, iron deficiency anemia and post-splenectomy state. On the other hand, autonomous thrombocytosis refers to clonal disorders derived from hematopoietic stem cells. These include essential thrombocytopenia, polycythemia vera, chronic myelogenous leukemia, idiopathic myelofibrosis and myelodysplastic syndrome. The most common myelodysplastic syndrome associated with thrombocytosis is the 5q- syndrome.

As for the frequency, reactive thrombocytosis is much more frequent than autonomous thrombocytosis. In a report of 91 consecutive patients with a platelet count of more than $600 \times 10^9/l$, 64 (70%) had reactive thrombocytosis, 20 (22%) had clonal thrombocytosis, and 7 (8%) had clonal thrombocytosis plus reactive thrombocytosis (1). The most common cause of reactive thrombocytosis was infection, followed by infection & post-surgical, post-surgical, malignancy, splenectomy, acute blood loss and iron deficiency anemia in that order. Of the 20 clonal thrombocytosis, the most common disorder was essential thrombocytosis. Reactive thrombocytosis is a much more frequent cause of thrombocytosis than autonomous thrombocytosis even when cases with extreme thrombocytosis (platelet count $>1,000 \times 10^9/l$) are considered. In one study of 280 patients with extreme thrombocytosis, 231 (82%) had reactive thrombocytosis, 38 (14%) had a myeloproliferative disorder and 11 (4%) had cases of uncertain etiology (2). Of the 231 patients with reactive thrombocytosis, the causes were infection (31%), post-splenectomy (19%), malignancy (14%), trauma (14%), non-infectious inflammation (9%), blood loss (6%), uncertain etiology (4%) and rebound (3%). It is known that the great majority of platelet counts associated with reactive thrombocytosis are less than $1,000 \times 10^9/l$, however, extreme thrombocytosis of platelet counts greater than or equal to $1,000 \times 10^9/l$ should not be considered rare events (2).

Thrombopoietic growth factors including interleukin-6 (IL-6), tumor necrosis factor-α and thrombopoietin have been implicated as the cause of reactive thrombocytosis. Several clinical and laboratory observations support the possible pathogenetic role of elevated IL-6 levels in reactive thrombocytosis. Tefferi A et al evaluated the discriminatory value of plasma IL-6 levels in clonal thrombocytosis and in reactive thrombocytosis (1). They showed that IL-6 levels were undetectable in all the patients with clonal thrombocytosis, whereas they were increased in 60% of the patients with reactive thrombocytosis or clonal thrombocytosis plus reactive thrombocytosis. They suggested that reactive thrombocytosis is either mediated by high plasma levels of IL-6 or associated with high plasma levels of IL-6 in reaction to a common inflammatory process.

Iron deficiency anemia is a cause of reactive thrombocytosis, and the thrombocytosis is usually mild to moderate degree. In one series, the average platelet count was $499 \times 10^9/l$, or roughly twice the controls (3). Extreme thrombocytosis is not so common but in one report of 100 consecutive patients with iron deficiency anemia, platelet counts were above $1,000 \times 10^9/l$ in 7% of the patients (4). Alteration of the bone marrow megakaryocyte count in iron deficiency anemia is not mentioned usually except for two reports (4, 5). In these reports, the authors mentioned that the bone marrow megakaryocyte counts were increased and the plausible explanation of the thrombocytosis might be an increased production of platelets. In this issue, Nagai T et al (6) reported a case of severe iron deficiency anemia with marked thrombocytosis that was complicated by central retinal vein occlusion.

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In this case, the platelet count was $1,020 \times 10^9/l$ and the authors mentioned that the extreme thrombocytosis was involved in the development of central retinal vein occlusion. Although thrombotic and bleeding events are much less likely to occur in association with reactive thrombocytosis than autonomous thrombocytosis (2), thrombotic complications were occasionally reported in iron deficiency anemia (5, 7).

The mechanisms causing reactive thrombocytosis in iron deficiency anemia are also unknown. There are several reports to elucidate the mechanisms of the reactive thrombocytosis from the aspect of thrombopoietic cytokines. Akan et al assayed the serum levels of thrombopoietin, erythropoietin, leukemia inhibitory factor, IL-6 and IL-11, but none of these cytokines had any effect on reactive thrombocytosis in iron deficiency anemia (8). Recently, Bilic and Bilic
reported that the amino acid sequence homology of thrombopoietin and erythropoietin may explain the thrombocytosis in children with iron deficiency anemia (9). Contrary to this report, however, there are two reports suggesting negative participation of erythropoietin and thrombopoietin (10, 11). To clarify the etiology of thrombocytosis in iron deficiency anemia, further investigation will be necessary.

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**References**