

## Prolonged Extreme Thrombocytosis in a Postsplenectomy Patient with Hereditary Spherocytosis

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We report a case of prolonged extreme reactive thrombocytosis in a post-splenectomy patient with hereditary spherocytosis. A 29-year-old female patient presented with gall stones detected incidentally by abdominal ultrasonography. Her laboratory findings showed hemolytic anemia with spherocytosis on the peripheral blood smear and increased osmotic fragility. She was diagnosed with hereditary spherocytosis and underwent a laparoscopic cholecystectomy and splenectomy. After undergoing surgery, the hemolytic anemia was resolved but thrombocytosis was newly detected. Nineteen months after the splenectomy, the thrombocytosis was still persistent and extremely high. To our knowledge, this is the first report of a prolonged extreme reactive thrombocytosis after a splenectomy in Korea. (*Korean J Hematol* 2009;44:298-303.)

**Key Words:** Reactive thrombocytosis, Postsplenectomy, Hereditary spherocytosis

### INTRODUCTION

Thrombocytosis is frequently encountered as an incidental laboratory finding.<sup>1)</sup> The common etiologies of reactive thrombocytosis are infection, trauma, surgery, and occult malignancy. Splenectomy was found to be one of the main causes of thrombocytosis. The probability of thrombocytosis in patients who have had splenectomy is about 75~82% and about 9% of all reactive thrombocytosis occurrences are caused by this procedure. The platelet count in reactive thrombocytosis is expected to normalize after the resolution of the underlying condition.<sup>2)</sup>

We experienced a patient of prolonged extreme

thrombocytosis for more than 19 months after splenectomy with hereditary spherocytosis without any complications such as bleeding or thrombosis.

### CASE REPORT

In June 2007, a 29-year-old female patient presented with incidentally detected gall stones by an ultrasound of the abdomen. She had no significant past medical or surgical history and denied any medications. Her family history was unremarkable. Physical examination showed no tenderness or rebound tenderness in the palpation on right upper quadrant but her spleen was palpable. Laboratory values were significant

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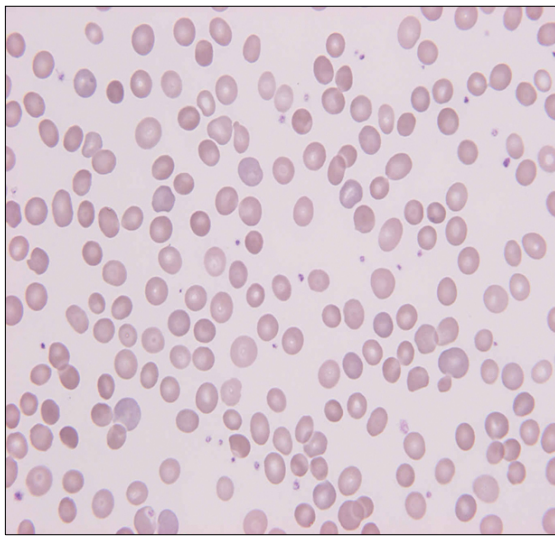
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for a hemoglobin (Hb) level of 10.0 g/dL, a hematocrit (Hct) of 27.7%, white blood cell count (WBC) of  $11.54 \times 10^9/L$  (neutrophil 69.5%, lymphocyte 26%) and a platelet count of  $374 \times 10^9/L$ . The reticulocyte count was 14.9% and corrected reticulocyte count was 9.2%. The peripheral blood smear (PBS) showed spherocytosis (Fig. 1). The total bilirubin was 4.7 mg/dL with 3.6 mg/dL of indirect bilirubin and AST, ALT were 17 U/L and 22 U/L. The LDH was 366 IU/L, the alkaline phosphatase 39 IU/L, and the gamma-GT 23 IU/L. And direct and indirect Coombs' tests and anti-nuclear antibody test were negative but the patient's osmotic fragility was increased. Computed tomography (CT) of the abdomen showed multiple gall stones and splenomegaly of largest diameter 155 mm (Fig. 2). She was diagnosed as

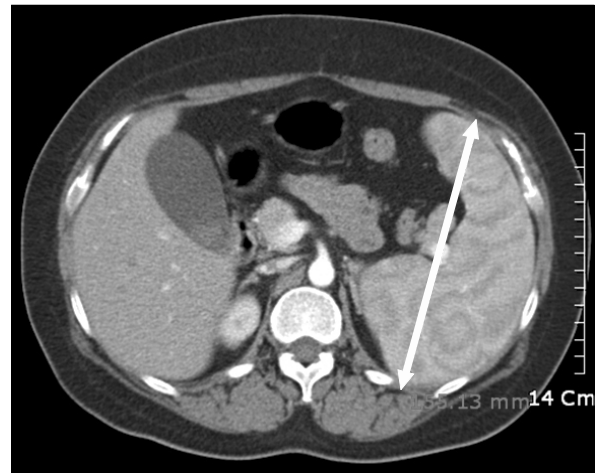


**Fig. 1.** Peripheral blood smear shows normocytic normochromic anemia with spherocytes which are small hyperchromatic cells without the usual clear area in the center (Wright stain,  $\times 400$ ).

hereditary spherocytosis and underwent laparoscopic cholecystectomy and splenectomy.

Her platelet count was  $266 \times 10^9/L$  immediately after the splenectomy but abnormally elevated to  $1,496 \times 10^9/L$  two weeks after the surgery. Other laboratory findings showed Hb level of 12.8 g/dL, a Hct of 40.3%, WBC of  $8.59 \times 10^9/L$  and we did not detect the spherocytes on the PBS any more. Hemolytic anemia is improving but thrombocytosis, which was not present prior to splenectomy, was noted and persistent. There is no evidence of infection or trauma by the medical history and physical examination.

Four months after the splenectomy, her platelet count was still elevated at  $867 \times 10^9/L$  with Hb level of 13.5 g/dL. She hadn't taken any medication or show any symptoms, signs of trauma, infection or inflammation (Table 1). We per-



**Fig. 2.** Abdominopelvic computed tomography shows subtle high density in gall bladder suggesting GB stone and splenomegaly of 155 mm.

**Table 1.** Characteristics of blood count in relation to hospital course

|                           | Admission | Postoperative duration (months) |       |       |       |       |       |       |       |       |       |       |
|---------------------------|-----------|---------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                           |           | 0.5                             | 1     | 2     | 4     | 6     | 8     | 10    | 12    | 14    | 16    | 18    |
| PLT (X10 <sup>9</sup> /L) | 374       | 1,496                           | 718   | 839   | 867   | 584   | 947   | 739   | 773   | 1,021 | 940   | 1,051 |
| WBC (×10 <sup>9</sup> /L) | 11.54     | 8.59                            | 18.03 | 16.50 | 16.61 | 15.96 | 18.05 | 16.23 | 14.60 | 17.61 | 16.12 | 11.29 |
| Hb (g/dL)                 | 10        | 12                              | 13.2  | 13.9  | 13.5  | 13.4  | 13.8  | 13.1  | 13.2  | 12.5  | 37.2  | 37.9  |
| Hct (%)                   | 27.7      | 40.3                            | 39.8  | 40.8  | 38.9  | 40.6  | 42.3  | 41.0  | 40.0  | 40.4  | 11.1  | 11.3  |

Abbreviations: PLT, platelet; WBC, white blood cell; Hb, hemoglobine; Hct, hematocrite.

formed chest X-ray, chest CT and abdominopelvic CT to rule out any other causes of secondary thrombocytosis such as acute or chronic inflammatory conditions including post operative inflammatory lesions, infectious focuses, or occult malignant lesions. But the test results did not show any other specific abnormal findings. Therefore, we performed bone marrow aspiration and biopsy to rule out myeloproliferative disorders. However, variable cellularity for her age as 20~50% (overall 30%), with normal megakaryocytic count and morphology was revealed. Also, the erythroid and granulocytic elements were normal in proportion and maturation. It revealed adequate storage of iron without any pathologic ringed sideroblasts.

At the first period of thrombocytosis, she complained of headaches, dizziness, and a digital tingling sensation, and consequently, she received anagrelide 0.5 mg qid per day for cytoreduction with an aspirin 100 mg per day for antiplatelet agent. After the anagrelide therapy, platelet count was decreased and it showed  $584 \times 10^9/L$  after 2 months receiving anagrelide (Table 1). The symptoms were resolved and anagrelide treatment was discontinued but the antiplatelet agent was continued. After the discontinuation of the ana-

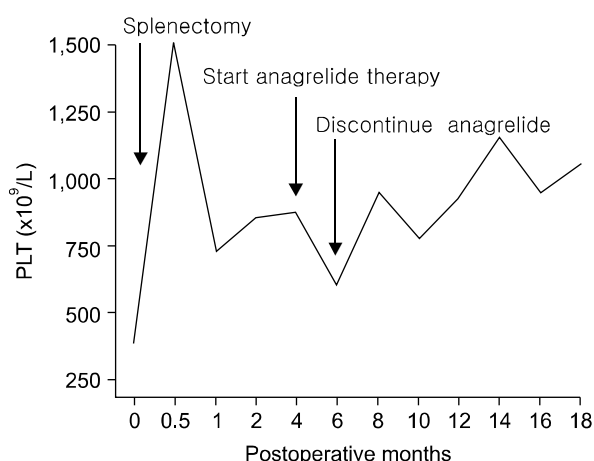
grelide therapy, the platelet count began to increase again (Table 1, Fig. 3). At 8 months after the splenectomy, we performed second bone marrow aspiration and biopsy because thrombocytosis was persistent but there were no abnormal findings.

Now it is 19 months after undergoing splenectomy, and extreme thrombocytosis is persistent. But now, with only the help of the antiplatelet agent, she has been asymptomatic and working full-time with no complications, despite her peripheral blood platelet count being over  $1,000 \times 10^9/L$  for more than 12 months.

## DISCUSSION

The definition of thrombocytosis varies among authors but is most commonly defined as a platelet count  $>500 \times 10^9/L$ .<sup>2)</sup> and extreme thrombocytosis defined as platelet counts  $>1,000 \times 10^9/L$ .<sup>3)</sup> Thrombocytosis generally either is a reactive process (secondary thrombocytosis) or is caused by a clonal bone marrow (myeloproliferative) disorder; the latter category includes essential thrombocythemia.<sup>1)</sup>

Reactive thrombocytosis is a common cause of thrombocytosis, the response to infection, trauma, or surgery.<sup>4)</sup> In one study of patients with thrombocytosis, reactive thrombocytosis was diagnosed in 70% and primary thrombocytosis in only 22%.<sup>5)</sup> Similarly, in patients with extreme thrombocytosis, reactive thrombocytosis is a more common cause of thrombocytosis than primary or essential thrombocytosis. In another study of 280 patients with a platelet count  $>1,000 \times 10^9/L$ , reactive thrombocytosis was the cause in more than 80% and myeloproliferative disorder in only 14%.<sup>3)</sup> In that study the etiologies of extreme reactive thrombocytosis are infection (31%), post-splenectomy or hyposplenism (19%), malignancy (14%), trauma (14%), non infectious inflammation (9%), blood loss (6%).<sup>3)</sup> Therefore, splenectomy was found to be one of the main causes of extreme reactive thrombocytosis. Another study



**Fig. 3.** The platelet count was increased after splenectomy. After the anagrelide therapy, the count was decreased, but after the discontinuation of the anagrelide therapy, it began to increase again. 19 months after having underwent splenectomy, extreme thrombocytosis is persistent.

shows 75% of individuals without myeloproliferative disorders developed thrombocytosis after splenectomy.<sup>6)</sup>

The spleen plays a major role in platelet regulation, as it is the primary site of destruction of platelets, which is why thrombocytosis is seen with hyposplenism.<sup>7,8)</sup> Reactive thrombocytosis is a predictable finding after splenectomy, with the platelet count peaking at 1 to 3 weeks and returning to normal levels in weeks, months, and rarely, years.<sup>2)</sup>

Regardless of cause, a high platelet count has the potential to be associated with vasomotor (headache, visual symptoms, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia), thrombotic, or bleeding complication.<sup>9)</sup> The association of thrombocytosis with thrombosis and hemorrhage appear to be related to qualitative rather than quantitative platelet abnormalities.<sup>10)</sup> Clonal involvement of megakaryocytopoiesis is regarded as the main origin of thromboembolism in myeloproliferative (MPD) disorder and results in abnormal platelet production. These platelets show increased size heterogeneity and ultrastructural abnormalities, and their function in vitro is in many ways impaired with a high degree of individual variability. Elevated levels of platelet-specific proteins, increased thromboxane generation, and expression of activation-dependent epitopes on the platelet surface are common on chronic MPD, and may reflect an inappropriate state of platelet activation. Although a variety of platelet receptor deficiencies and some defects of intracellular signaling pathways have been identified, the different platelet defects in MPD could not be traced back to an underlying general pathogenetic mechanism. On progression of chronic MPD to more advanced stages of the disease, the number of platelet abnormalities tend to increase.<sup>11)</sup>

Postsplenectomy venous thrombosis is usually associated with platelet counts  $>600 \times 10^9/L$  to  $>800 \times 10^9/L$ ,<sup>12)</sup> and occurs in approximately 5% of patients.<sup>13)</sup> Less commonly, postsplenectomy

thrombocytosis results in arterial thrombosis that leads to stroke or myocardial infarction.<sup>10)</sup> But these hemostatic events infrequently occur in patients with reactive thrombocytosis.<sup>3,14)</sup> This is presumably due to the fact that the interaction of platelets with the vessel wall remains qualitatively normal in secondary thrombocytosis.<sup>1)</sup> Neurologic complications including chronic headache or dizziness, or focal neurologic sign occur in about 25 percent of patients with essential thrombocythemia, and may be manifested as non-specific symptoms.<sup>15)</sup> Neurologic complications are presumably caused by platelet-mediated cerebrovascular ischemia.<sup>1)</sup>

The first step in managing a patient who presents with elevated platelet count is to determine if the etiology is a primary process or a reactive response,<sup>1)</sup> because the platelet count in reactive thrombocytosis is expected to normalize after resolution of the underlying condition.<sup>7)</sup> Furthermore because their abnormal platelet count itself does not place them at risk for hemostatic or vascular events, patients with reactive thrombocytosis generally do not require platelet-lowering or antiplatelet treatment.<sup>1)</sup> If it is a primary process including essential thrombosis, the immediate risk to the patient from the increased platelet count and additional risk factors for thrombotic complications include advanced age, a history of thrombosis, hypercholesterolemia and cigarette smoking should be assessed.<sup>1)</sup> Thereafter, management of the thrombocytosis and prevention of complications should be initiated. Some pharmacologic agents used for this purpose are acetyl salicylic acid, ticlopidine, enoxaparin, hydroxyurea, anagrelide, interferon alpha along with associated adverse effects such as hemorrhage, myelofibrosis, leukemic transformation.<sup>7)</sup> Anagrelide is a newer platelet-lowering agent, an orally administered quinazoline derivative that inhibits megakaryocyte proliferation and differentiation. It has been approved in patients with essential thrombocytosis, and now has been established as alternative first-line therapy to reduce the plate-

let count.<sup>1,7)</sup> Anagrelide is nonleukemogenic and is therefore a particularly reasonable initial option in young patients who require long term platelet count control.<sup>1)</sup> Common side effects include fluid retention, palpitations, and arrhythmias, heart failure, headaches, and anemia.<sup>1)</sup> Long-term data on the side effects and complications of anagrelide are lacking, however, preliminary data suggest it is well tolerated, with mild to moderate anemia as a frequent side effect.

So after weighing the benefits versus the risks of various treatment plans, determine whether reduction of platelet numbers or simple observation is indicated. Although the degree of elevation in the platelet count does not correlate with the risk of thrombosis, control of the platelet count by cytoreduction does reduce the frequency of thrombosis in some patients.<sup>1)</sup> Our patient showed extreme thrombocytosis after the splenectomy and the first period of postsplenectomy thrombocytosis, she complained of headaches, dizziness and a digital tingling sensation, and consequently she received cytoreductive therapy and antiplatelet therapy.

But 2 months after cytoreductive therapy, it was discontinued because the symptoms were resolved. Now it is 19 months after the splenectomy, and she has been asymptomatic and working full-time without any complications, despite her peripheral blood platelet count being over  $1,000 \times 10^9/L$  for a long duration. To our knowledge, this is the first report of a prolonged extreme reactive thrombocytosis in postsplenectomy patient in Korea.

## 요 약

혈소판증가증은 흔히 관찰되는 검사소견이다. 특히 극도의 혈소판증가증의 경우 이차성 혈소판증가증이 대부분을 차지하며 이의 흔한 원인으로 는 감염, 외상, 수술, 종양 등이 있다. 이차성 혈소판증가증은 원인 질환이 해결되면 대부분 호전되어 치료를 요하는 경우는 흔하지 않다. 비장절제술 또한 이차성 혈소판증가증의 주된 원인이며

비장절제술을 받은 환자들 중 약 75~82%에서 나타날 수 있지만 수년간 지속되는 경우는 매우 드물다. 저자는 우연히 발견된 담석과 용혈성빈혈을 주소로 내원한 환자에서 유전구형적혈구증을 진단하고 이에 대한 치료로 비장절제술을 시행한 후 용혈빈혈은 호전되었으나 19개월 이상의 장기간 극도의 혈소판증가증이 지속되는 환자를 경험하였기에 문헌고찰과 함께 보고한다.

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