Platelet-lowering Therapy with Anagrelide as an Adjuvant Therapy for Treatment of Primary Pulmonary Neoplasm-associated Extreme Thrombocytosis

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INTRODUCTION

Thrombocytosis is a common paraneoplastic syndrome in patients with lung cancer. However, complications associated with malignancy-related thrombocytosis, including thrombosis and hemorrhage, have rarely been reported. In this case, we describe a 57-year-old man with unresectable adenocarcinoma of the lung who presented with a platelet count over $100 \times 10^4/mm^3$. In addition, deep venous thrombosis of the left femoral vein was found during admission. The circumference of the left lower leg and platelet count progressed during the period without chemotherapy and anticoagulants; however, with the addition of anagrelide they improved. We provided an adjuvant therapy with platelet-lowering therapy to treat cancer-induced thrombocytosis during the period without chemotherapy.

Key words: lung cancer – paraneoplastic syndrome – thrombocytosis – anagrelide
fixed point to determine the extent of edema and were found to be 36 and 37 cm for the right and left legs, respectively. Laboratory tests showed a white blood cell count of \(8.9 \times 10^3/\text{mm}^3\), with 74% neutrophils, thrombocytosis \((60 \times 10^4/\text{mm}^3)\) and elevated plasma D-dimer (3038 ng/ml). Additional laboratory investigations showed a C-reactive protein level of 2.36 mg/dl (reference value, \(<0.5 \text{ mg/dl}\)) and negative blood culture findings. Color Doppler ultrasonography of the left lower leg demonstrated thrombus formation in the left common femoral, posterior tibial and peroneal veins. Other studies to evaluate the hypercoagulable state including factor V Leiden mutation, protein C and S, antithrombin activity and fibrinogen plasma levels, as well as lupus anticoagulant and anticardiolipin antibodies, were all negative.

Low-molecular-weight heparin (enoxaparin) was administered subcutaneously every 12 h with no changes observed in the patient’s status. During this period, the administration of chemotherapy was maintained to control the adenocarcinoma.

Approximately 50 days after admission, subsequent laboratory investigations revealed a persistently elevated platelet count of \(~87–120 \times 10^4/\text{mm}^3\). The Janus Kinase 2;9p24 (JAK2V617F) mutation test was negative. Bone marrow aspiration and a biopsy were performed on day 65 after hospitalization. The results showed normal cellularity and no increase in megakaryocytes with normal maturation. In addition, the interleukin-6 (IL-6) plasma level was elevated compared with the normal range (576 vs. \(<12.5 \text{ pg/ml, respectively}\)). A platelet-lowering therapy consisting of oral hydroxyurea (500 mg twice daily) was administered on day 75 after two cycles of chemotherapy; however, the patient was unable to tolerate the side effects of hydroxyurea (severe nausea and vomiting), and oral anagrelide (0.5 mg twice daily) was subsequently prescribed after 5 days of treatment. During this period, the tri-weekly administration of chemotherapy was continued, and the platelet count declined to \(~40–65 \times 10^4/\text{mm}^3\). The serum IL-6 level also decreased to an undetectable level (0.1 pg/ml). Edematous skin changes indicated an improvement over the initial presentation. The lower leg fully recovered, and subsequent vessel studies revealed no residual thrombus. A line and bar chart summarizing the therapeutic management and relationship between the platelet count and the circumference of the affected limb throughout the entire treatment period are shown in Fig. 2. Four months after hospitalization, the patient had finished six cycles of chemotherapy. No life-threatening toxicity was noted, except for sensory neurotoxicity (WHO grade I) during this period. His serum carcinoembryonic antigen level was 14.72 ng/ml at
Thrombocytosis is a common paraneoplastic manifestation that can occur in lung cancer. The incidence rates of thrombocytosis among non-small cell lung cancer and small cell lung cancer patients are ~45 and 35%, respectively (1). The mechanism of thrombocytosis remains unclear. Various humoral cytokines, such as IL-1β, IL-3, IL-6 and thrombopoietin, have been shown to be involved (2,3). Although several factors regulate thrombocytosis and megakaryocytosis, plasma IL-6 levels seem to be dependent on the platelet count of the patient (4). In previous studies, primary lung cancer has been shown to produce IL-6 resulting in thrombocytosis (5,6). However, thrombocytosis can also occur in patients without elevated plasma IL-6 levels (7), and the relationship between IL-6 and thrombocytosis remains unclear.

Anagrelide hydroxide is a reversible platelet-lowering agent used to treat thrombocytosis in myeloproliferative disorders. Based on pharmacological characteristics, anagrelide does not directly inhibit megakaryocyte production or increase platelet destruction (8). A recent study showed that anagrelide-related thrombocytopenia may occur due to a reduction in receptor binding through inhibition of the thrombopoietin-mediated intracellular pathway (9). However, no obvious suppression of IL-6 levels was reported after anagrelide therapy. In our patient, a higher IL-6 plasma level was recorded before anagrelide was administered, but was reduced to an undetectable level after chemotherapy and anagrelide therapy. Therefore, the effects of anagrelide on IL-6 remain unclear.

In contrast to essential thrombocytosis and other myeloproliferative states, complications associated with malignancy-related thrombocytosis such as thrombotic events and hemorrhage have rarely been reported. The management of malignancy-related reactive thrombocytosis should be aimed at treating the underlying neoplasm, since appropriate control of the tumor can lead to expeditious improvements of the thrombocytosis. In our case, swelling of the left thigh and platelet count were not alleviated in the first two courses of chemotherapy. The possible causes may be a high tumor burden associated with higher paraneoplastic hematologic effects, or that the chemotherapeutic effects did not appear in the first two courses of chemotherapy. Subsequently, the platelet count declined and the circumference of the left lower leg decreased after the therapeutic effects of the chemotherapy appeared combined with the platelet-lowering effect of anagrelide. We hypothesize that anagrelide played an adjuvant role in treating the reactive thrombocytosis and deep venous thrombosis in our case. Chemotherapy is still a cornerstone in treating this disease entity. While further surgical intervention was not suitable due to the advanced stage of the underlying malignancy in our patient, in cases of poor performance state and ongoing infection, anagrelide can be considered as another adjuvant therapeutic strategy for managing the thrombotic events related to reactive thrombocytosis.

**Conflict of interest statement**

None declared.

**References**