

## Idiopathic Thrombocytopenic Purpura in a Patient with Carcinoma of the Uterine Cervix

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We describe here the case a patient with advanced cervix carcinoma and who developed idiopathic thrombocytopenic purpura (ITP). A 63-year-old woman with stage IV squamous cell carcinoma of the uterine cervix and that was complicated by hydronephrosis was treated palliatively with 45Gy of external beam radiation to the pelvis. About 3 years later, she developed hematochezia and severe thrombocytopenia. The laboratory examinations showed no evidence of thrombotic thrombocytopenic purpura or disseminated intravascular coagulopathy, and she was positive for serum anti-platelet antibodies. On the bone marrow examination, there was a normal number and morphology of megakaryocytes with no evidence of malignant cell infiltration. We made the clinical diagnosis of ITP, and the intravenous immunoglobulin and steroid therapy was successful. This case suggests the possibility that ITP can occur in association with advanced cervix carcinoma. (*Korean J Hematol* 2009;44:58-61.)

**Key Words:** Autoimmune thrombocytopena, Idiopathic thrombocytopenic purpura, Cervix carcinoma

### INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is known to be occasionally associated with lymphoproliferative disorders such as chronic lymphocytic leukemia, lymphoma.<sup>1)</sup> In patients with solid tumors, common causes of thrombocytopenia are myelosuppression secondary to chemotherapy, bone marrow infiltration with malignant cells. However, various solid tumors, including breast, lung, prostate, skin, and ovarian cancers, have been reported to be associated with ITP.<sup>2-7)</sup>

Here we describe a patient with advanced cervix carcinoma who developed ITP as a possible paraneoplastic syndrome.

### CASE REPORT

In February 2005, a 63-year-old woman was diagnosed with stage IV squamous cell carcinoma of the uterine cervix. She had no allergies or significant past medical history, and her family history was unremarkable. The initial complete blood counts (CBC) were within normal ranges: hemoglobin (Hb) of 12.7g/dL; white blood cell count

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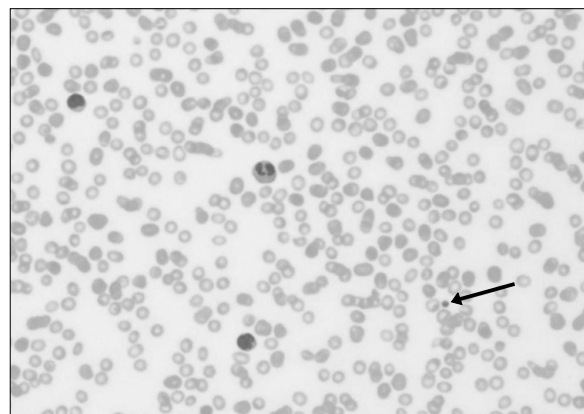
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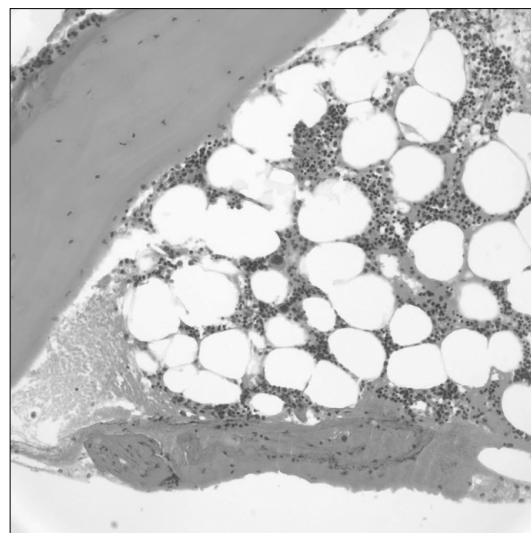
(WBC) of  $7.48 \times 10^9/L$ ; platelets count of  $361 \times 10^9/L$ . Because her disease was complicated by hydronephrosis she received palliatively 45Gy of external beam radiation to the pelvis followed by ureteral stent (Double J catheter) insertion in the left ureter. Thereafter she was recommended systemic chemotherapy but refused. She was followed-up with ureteral stent changes every 2 to 3 months. In March 2008, her CBC showed WBC of  $4.3 \times 10^9/L$ , Hb of 10.3g/dL, platelets count of  $477 \times 10^9/L$ .

In August 2008, she presented with hematocchezia developed abruptly. She was not taking any medication and herbs. Physical examination revealed petechiae on her legs and no evidence of splenomegaly. On hematologic examination, Hb was 5.6g/dL, WBC count  $4.96 \times 10^9/L$ , and platelet count  $8 \times 10^9/L$ . Serologic tests for Hepatitis B virus, Human immunodeficiency virus, and anti-nuclear antibody were negative. Chest radiology newly revealed multiple hematogeneous metastases in the lung. Abdomen CT showed multiple low attenuated lesions in spleen and metastasis to spleen was suggested. Biochemistry showed a normal kidney and liver function, and coagulopathy parameters were within normal ranges. The direct Coombs' test and anti-nuclear antibody test were negative, and serum anti-platelet antibodies were positive on immunofluorescent assay. Peripheral blood smear showed severe thrombocytopenia with the presence of megaplatelets and lack of schistocytes (Fig. 1). Transfusions of 16 units of platelets, with together 3 units of red blood cells, were immediately administered after initial laboratory evaluation. A transient rise in platelet count after transfusion was observed, but the number decreased again to reach to  $4 \times 10^9/L$ . Bone marrow examination revealed a slight hypocellular marrow (about 30%) with no evidence of neoplastic infiltration. Marrow megakaryocytes were normal in number and morphology (Fig. 2).

Clinical diagnosis of ITP was made, and therapy with intravenous immunoglobulin (400mg/kg per day for 5 days) and steroid (intravenous



**Fig. 1.** Peripheral blood smear shows severe thrombocytopenia with the presence of megaplatelets (arrow) and lack of schistocytes (Wright stain, 400 $\times$ ).



**Fig. 2.** Bone marrow examination reveals a slight hypocellular marrow with no evidence of neoplastic infiltration. Marrow megakaryocytes are normal in number and morphology. (Hematoxylin-Eosin, 400 $\times$ ).

methylprednisolone 125mg per day followed by prednisone 40mg per day) was started and platelet counts increased gradually. Four weeks after administering steroid her platelet count was  $234 \times 10^9/L$ . Thereafter prednisone was tapered to 10mg per day and subsequent platelet count remained stable at levels over  $200 \times 10^9/L$ .

## DISCUSSION

ITP is an autoimmune bleeding disorder char-

acterized by the development of autoantibodies against platelets, which resulted in phagocytosis by spleen and thrombocytopenia. The majority of autoantibodies are directed against the GPIIb/IIIa structural complex on the surface of the platelets.<sup>1)</sup> The common causes of immunologic thrombocytopenia are viral infection, drugs, and chronic autoimmune disorders. However, Immune-mediated thrombocytopenia is occasionally encountered in patients with lymphoproliferative disorders, especially malignant lymphoma, chronic lymphocytic leukemia.<sup>1)</sup>

In patients with solid tumor, the most common cause of thrombocytopenia is myelosuppression secondary to systemic chemotherapy or radiotherapy. Especially in patients with advanced cancer, thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulopathy (DIC), and bone marrow infiltration with malignant cells (myelophthisis) can be considered as a possible cause of thrombocytopenia. In this case, patient did not receive systemic chemotherapy. On laboratory examinations, she showed no evidence of DIC or TTP. We initially thought that thrombocytopenia would be resulted from myelophthisis secondary to bone marrow infiltration with malignant cells. In myelophthisis, the blood smear is characterized by leukoerythroblastosis (immature granulocyte, nucleated red cells, and teardrop-shaped red cells). However, there was no evidence of leukoerythroblastosis on the peripheral blood smear of our patient. Moreover, serum anti-platelet antibodies were positive, and massive platelet transfusions failed to increase circulating platelet counts. Therefore, we also considered that other factors may have caused thrombocytopenia in our patient. On bone marrow examination, megakaryocytes were normal in number and morphology, although marrow cellularity was slightly decreased. In ITP, the marrow is usually normal, although megakaryocytes may be increased in number. Because marrow hypocellularity in our patient was thought to be associated with the history of pelvic irradiation, clin-

ical diagnosis of ITP could be made. Therapy with intravenous immunoglobulin and steroid was successful.

A literature review showed that various solid tumors, including breast, lung, prostate, skin, and ovarian cancers, have been reported to be associated with ITP,<sup>2-9)</sup> and the diagnosis of ITP was based on the clinicopathologic findings of positive platelet antibody, normal number of megakaryocyte in BM, and treatment responses to steroid, immunoglobulin, and splenectomy. In relation to carcinoma of the uterine cervix, there were two cases of autoimmune thrombocytopenia developing after cisplatin and radiation therapy.<sup>10)</sup> In case 1, patient developed pancytopenia ten days after administrating the last course of cisplatin. Leukopenia improved immediately with granulocyte colony stimulation factor, but thrombocytopenia was not ameliorated in despite of massive platelet transfusion. In case 2, thrombocytopenia alone was developed two months after chemotherapy. In both cases, the diagnosis of autoimmune thrombocytopenia was made on the results of elevated platelet-associated IgG, increased numbers of megakaryocytes on marrow examination, and the response to prednisone therapy. Because these patients had received chemotherapy recently before developing thrombocytopenia, platelet-associated antibodies might be induced by drug (cisplatin or paclitxel). On the other side, our patient had no history of chemotherapy.

There are two explanations for the development of ITP in cervix cancer.<sup>6-9)</sup> First, as described in other solid malignancies,<sup>6,7)</sup> paraneoplastic ITP may be triggered by the formation of anti-platelet antibodies in our patient who had newly developed distant metastases. The fact that many cases including our case had stage IV cancer<sup>6,8,9)</sup> suggest that a high tumor burden or metastasis to other organ via blood stream may produce an immune-response resulting in platelet destruction.<sup>8)</sup> Second, the involvement of spleen by tumor may change the splenic environmental

milieu producing an ITP and may be heralded by ITP.<sup>9)</sup>

In conclusion, we have treated a patient with carcinoma of the uterine cervix complicated by ITP, which was not related to the chemotherapeutic agent. To our knowledge, this is the first ITP case developed in a patient with advanced cervix carcinoma in Korea.

## 요 약

진행성 고형암 환자에서 혈소판 감소의 원인은 대부분 항암치료나 종양의 골수 침범에 의한 골수억제에 기인한다. 하지만, 다양한 진행성 고형암에서 특발혈소판감소자색반병에 의한 혈소판 감소의 보고가 있었다. 저자 등은 최근 진행성 자궁경부암 환자에서 발생한 특발혈소판감소자색반병을 진단하였고, 면역글로불린과 스테로이드로 성공적인 치료를 한 증례를 경험하였기에 문헌 고찰과 함께 보고하는 바이다.

## REFERENCES

- 1) Bussel JB. Autoimmune thrombocytopenic purpura. *Hematol Oncol Clin North Am* 1990;4:179-91.
- 2) Chehal A, Taher A, Seoud M, Shamseddine A. Idiopathic thrombocytopenic purpura and ovarian cancer. *Eur J Gynaecol Oncol* 2003;24:539-40.
- 3) Kim HD, Boggs DR. A syndrome resembling idiopathic thrombocytopenic purpura in 10 patients with diverse forms of cancer. *Am J Med* 1979;67:371-7.
- 4) Schwartz KA, Slichter SJ, Harker LA. Immune-mediated platelet destruction and thrombocytopenia in patients with solid tumours. *Br J Haematol* 1982;51:17-24.
- 5) DiFino SM, Lachant NA, Kirshner JJ, Gottlieb AJ. Adult idiopathic thrombocytopenic purpura. Clinical findings and response to therapy. *Am J Med* 1980;69:430-42.
- 6) Bir A, Bshara W, George M, Fakih MG. Idiopathic thrombocytopenic purpura in a newly diagnosed pancreatic adenocarcinoma. *JOP* 2006;7:647-50.
- 7) Demirer T, Celebi H, Arat M, et al. Autoimmune thrombocytopenia in a patient with small cell lung cancer developing after chemotherapy and resolving following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1999;24:335-7.
- 8) Porrata LF, Alberts S, Hook C, Hanson CA. Idiopathic thrombocytopenic purpura associated with breast cancer: a case report and review of the current literature. *Am J Clin Oncol* 1999;22:411-3.
- 9) Cummings OW, Mazur MT. Breast carcinoma diffusely metastatic to the spleen. A report of two cases presenting as idiopathic thrombocytopenic purpura. *Am J Clin Pathol* 1992;97:484-9.
- 10) Mitsuhashi A, Yamazawa K, Tanaka N, Sekiya S. Autoimmune thrombocytopenia in women with carcinoma of the uterine cervix developing after cisplatin and radiation therapy. *BJOG* 2002;109:103-4.