Acquired Pure Red Cell Aplasia due to Anti-Erythropoietin Antibodies in a Patient Undergoing Hemodialysis

Me-Ae Kim, M.D.[1], Se-Ho Chang, M.D.[2] and Kook-Young Maeng, M.D.[1]

Departments of Laboratory [1]Medicine, [2]Internal Medicine, Gyeongsang National University Hospital, Jinju, Korea

A 63-year-old man was placed on hemodialysis for the end-stage of renal disease secondary to renal artery stenosis. He was also regularly given epoetin, subcutaneously, for anemia associated with his renal disease. Rapidly progressing erythropoietin (EPO) resistant anemia and reticulocytopenia developed after 1 year of hemodialysis. The patient required frequent red blood cell transfusions. The bone marrow examination demonstrated selective erythroid hypoplasia. A detailed search for the cause of the erythroblastopenia revealed nothing, with the exception of anti-EPO antibodies (Ab). Pure red cell aplasia (PRCA) was suspected due to the anti-EPO Ab. With the immunosuppressive agent and change to the epoetin-therapy, the patient recovered his hemoglobin and reticulocyte counts. Particular attention should be paid for the possibility of PRCA due to anti-EPO Ab in patients undergoing rHuEPO therapy, with an unexplained recombinant human erythropoietin (rHuEPO) resistant anemia, especially via the subcutaneous route. ***(Korean J Hematol 2005;40:45-48.)***

Key Words: Hemodialysis, Anti-erythropoietin antibody (Anti-EPO Ab), Pure red cell aplasia (PRCA)

INTRODUCTION

Chronic anemia is one of the most common features of end stage renal disease. Recombinant human erythropoietin (rHuEPO) has been used successfully to correct the anemia in chronic renal failure (CRF) especially with undergoing hemodialysis. Progressive erythropoietin (EPO) resistant anemia is an important issue in this case because the patient became transfusion dependent. The common causes of EPO resistance are iron deficiency, severe hyperparathyroidism, aluminum toxicity, chronic inflammatory states, and neoplasia.[1)]

Pure red cell aplasia (PRCA) is a rare hematologic disorder characterized by anemia, reticulocytopenia in blood and isolated severe erythroblastopenia with no abnormalities in granulopoiesis and megakaryopoiesis in bone marrow aspirate and trephine biopsy.[2)] Acquired PRCA may present as a primary hematologic disorder or secondary to a variety of conditions such as thymoma, hematologic disorders, autoimmune collagen diseases or carcinoma and viral infections with human parvovirus B19, hepatitis A virus, cytomegalovirus. We report here a case of acquired PRCA due to anti-EPO antibodies (Ab) un-

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교신저자 : 김미애, 경남 진주시 칠암동 90번지
㉾ 660-702, 경상대학교병원 진단검사의학과
Tel: 055-750-8639, Fax: 055-762-2696
E-mail: givmea@hanmail.net

Correspondence to : Me-Ae Kim, M.D.
Department of Laboratory Medicine, Gyeongsang National University Hospital
90 Chilam-dong, Jinju 660-702, Korea
Tel: +82-55-750-8639, Fax: +82-55-762-2696
E-mail: givmea@hanmail.net

dergoing hemodialysis.

CASE REPORT

A 63-year-old man was first presented to the hospital for secondary hypertension due to renal artery stenosis. Progressive renal impairment led to the start of hemodialysis. He was presented to nephrology department in July 2002 for hemodialysis in the end stage renal disease, and periodic hemodialysis was started through the arteriovenous fistula on 3 times per week with subcutaneous epoetin-α (Epocain®) 4000U injection for normocytic normochromic anemia. Initial response to Epocain was excellent; and hemoglobin level was constantly maintained (8.8～9.7g/dL). Thus the red blood cell transfusions were not required. In October 2003 anemia was detected with a rapid decline in hemoglobin values and reticulocyte count unresponsive to high dose of erythropoietin. The blood count revealed 4.8g/dL of hemoglobin, 7.13×10^9/L of white blood cell (59% of segmented neutrophils, 33% of lymphocytes, 5% of monocytes and 3% of eosinophils) and 226×10^9/L of platelets. The corrected reticulocyte count and reticulocyte production index (RPI) was markedly decreased (0.1% and 0.04, respectively). The patient became transfusion-dependent. No evidence of hemolysis was revealed. Serum iron, serum ferritin, vitamin B12 and folic acid were normal range. Autoimmune markers, serologic viral markers (CMV, EBV, parvovirus) and PCR for HPV were all negative. The bone marrow aspiration revealed the absence of erythroid precursors with normal granulopoiesis and megakaryopoiesis (Fig. 1A, B). A detailed search for the cause of the erythroblastopenia revealed nothing. Thus we suspected Anti-EPO Ab mediated PRCA. It was positive finding to the test of anti-EPO Ab via ELISA. Administration of epoetin-α was stopped due to the possibility of epoetin-α induced anti-EPO Ab. In Febrary 2004 bone marrow examination was followed to know the response of epoetin-α therapy. Selective erythroid aplasia was remained and reticulocyte count was very low (corrected reticulocyte count 0.03%). The patient was re-challenged with epoetin-β (Recormon®) known rarely associated with PRCA and prednisolone. Hemoglobin and reticulocyte count was slowly elevated. In September 2004, the reticulocyte count and hemoglobin concentration were showed as 2.1% and 7.8g/dL, respectively. The level of EPO tested via RIA was increased (176mU/mL). In January 2005 the hemoglobin concentration was 6.0g/dL. So cyclosporin therapy is rescheduled to achieve normal

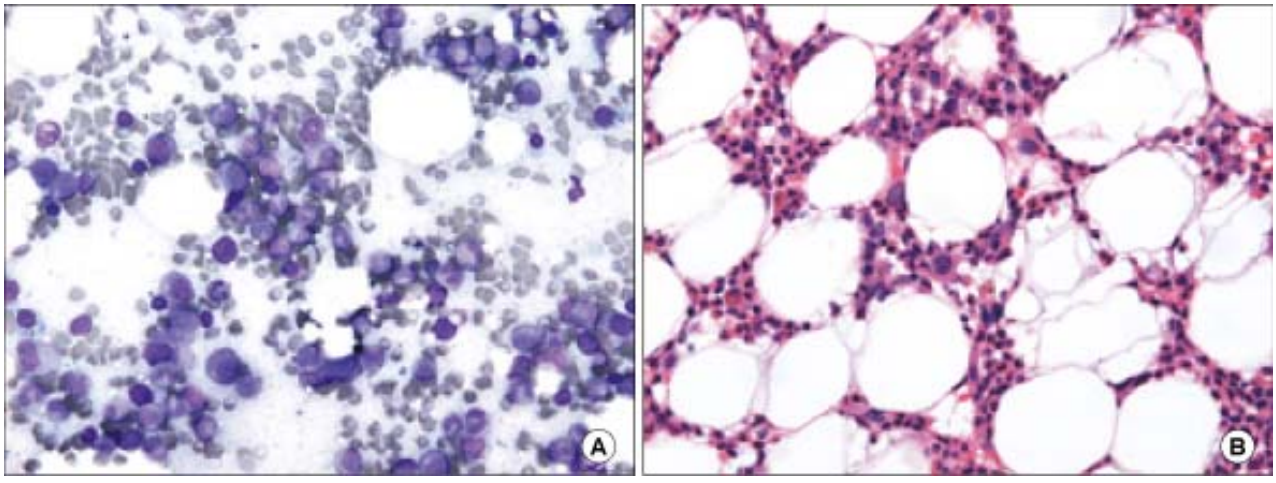

Fig. 1. (A) Normal granulopoiesis with few erythroid precursors on bone marrow aspirate smear (Wright stain, 400). (B) Normal granulocytic and megakaryocytic elements with profound erythroblastopenia are present on bone marrow biopsy section (H&E stain, 400).

level of hemoglobin.

DISCUSSION

It is essential to find underlying hematologic disorders such as PRCA in the case of a hemodialyzed patient who develops an unexplained rHuEPO resistant anemia. Recently, an unexplained rHuEPO resistant anemia by anti-EPO Ab following treatment with rHuEPO has been observed not only in the hemodialyzed patients but also in the patients with anemia with cancer therapy or myelodysplasia.[3,4] In the setting of rHuEPO treatment for patients, epoetin-induced antibodies can generate PRCA. PRCA is an uncommon hematologic disorder in adults. Acquired PRCA may present as a primary hematological disorder or secondary to a variety of conditions such as thymoma, hematological disorders, autoimmune collagen diseases, carcinoma or viral infections. Human parvovirus B19 infection is the infectious agent most often associated with PRCA. In adults, most acquired PRCAs are known as autoimmune-mediated diseases by the antibodies, natural killer cell or T cell mediated lysis and loss of major histocompatibility complex (MHC) class I of erythroid progenitors.[2,5] Most patients with autoimmune form of PRCA have a response to immunosuppressive therapy. The response rate of immunosuppressive therapy in PRCA was 82% in cyclosporine A (CyA), 62% in methylprednisolon and 49% in prednisolon by Mamiya et al.[6] CyA is the most useful immunosuppressive therapy for maintaining remission of PRCA. It needs special considerations to use CyA for hemodialyzed patient because of renal toxicity. So the largest number of patients were treated with oral prednisolone although the response rate is lower than CyA.[6]

A lack of EPO produced mainly by the kidney in adults is the reason for the development of anemia in chronic renal failure. So rHuEPO has been widely used in the patients with anemia caused by CRF since the late 1980s. Progressive anemia is an important issue in the patients with rHuEPO use for anemia caused by CRF, especially in the case of undergoing hemodialysis.[7] The usual causes of progressive anemia after epoetin therapy include iron deficiency, severe hyperparathyroidism, aluminum toxicity, chronic inflammatory states and neoplasia. The abrupt rise in the incidence of PRCA by anti-EPO Ab observed in the last few years in Europe. It had been coincident with a major shift from intravenous (i.v.) to subcutaneous (s.c.) administration of rHuEPO.[8,9] So it has been suggested that the skin plays an important role in immune reaction and the development of anti-EPO Ab. The estimated incidences of PRCA according to the route of administration are 0.67 per 100,000 patient-years for i.v. and 20.66 per 100,000 patient-years for s.c. administration.[9] These patients present with a severe rHuEPO resistant anemia, very low reticulocytes counts, a paucity of erythroid precursors on bone marrow, and absence of other causes of rHuEPO resistance. Our patient had been receiving epoetin-α known to be more associated with PRCA than epoetin-β. There is a consensus in the literature that it is essential to stop rHuEPO in the case with anti-EPO Ab after the development of PRCA. The cessation of epoetin-α alone, without immunosuppressive therapy has not been proved to improve erythropoiesis.[10,11] The bone marrow examination revealed no change in our case. The rHuEPO might be safely re-introduced after a period of immunosupression to reverse anti-EPO Ab.[12,13] Actually, the reticulocyte count of this case was normalized with switching to epoetin-β therapy along with immunosuppressive therapy. So we conclude that anti- EPO Ab to epoetin-α might be the cause of PRCA in this case retrospectively. It is known that serum EPO of the patients with anti-EPO Ab were below the detectable level at the time of diagnosis (serum erythropoietin levels are usually very high in PRCA).[14] Unfortunately, a test for serum erythropoietin at initial presentation was not accessed to our patient. Recently

abrupt rise in the incidence of PRCA cases due to anti-EPO Ab observed in Korea.[15,16] This is the third report of acquired PRCA cases due to anti-EPO Ab undergoing rHuEPO therapy reported in Korea.

In conclusion, we should deserve particular attention through monitoring of the reticulocyte count and anti-EPO Ab when confronted with an unexplained rHuEPO resistant anemia, especially with subcutaneous administration of rHuEPO.

요 약

후천성 진성 적혈구 무형성증(acquired pure red cell aplasia)은 골수에서 백혈구계 및 거핵구계의 성숙이나 수에는 이상이 없이 심한 적혈구계 전구세포의 결핍을 나타내는 드문 혈액 질환이다. 이 질환은 약 반 정도에서 특별한 원인을 찾을 수 없이 특발성으로 발생하며 그 외에 자가면역 질환, 바이러스 감염 및 약제 등에 의해서도 생길 수 있다. 본 증례는 혈액투석과 함께 Recombinant human erythropoietin (rHuEPO) 치료를 병행하던 만성신부전 환자로서 내원시 rHuEPO 치료에 저항을 보이는 심한 빈혈과 망상적혈구수의 심한 감소를 보였다. 골수검사 결과 적혈구계의 심한 감소가 관찰되었으며 후천성 진성적혈구 무형성증을 유발하는 2차적인 원인은 발견할 수 없었으며 ELISA방법으로 실시한 항EPO항체검사에서 양성을 보였다. 저자들은 혈액투석과 rHuEPO 치료를 받아오던 만성신부전 환자에서 항EPO 항체에 의한 후천성 진성 적혈구 무형성증 1예를 경험하였기에 문헌고찰과 함께 보고하는 바이다.

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