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CASE REPORT

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Secondary polycythemia as a paraneoplastic syndrome of testicular seminoma

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Abstract A 45-year-old man was referred to our hospital because of polycythemia. A physical examination revealed a large tumor in his scrotum enlarged to the size of 13×10 cm. A laboratory examination revealed severe erythrocytosis with a red blood cell count of $6{,}820\times10^9$/L, a hemoglobin concentration of 21.2 g/dL, and a hematocrit of 59.8%. The total red cell volume was increased. A right radical orchidectomy was done with minimum bleeding, and he was diagnosed as having pure seminoma. After the operation, polycythemia improved spontaneously. Polycythemia is a rare complication of seminoma and only two cases have been reported previously. The precise mechanism of polycythemia in our patient could not be clearly evaluated, but clinical course did indicate a close relationship between two distinct disorders.

Keywords Polycythemia · Seminoma · Paraneoplastic syndrome · Orchidectomy

Introduction

There are two subtypes in erythrocytosis, absolute erythrocytosis and relative erythrocytosis. Polycythemia vera, hypoxia, and erythropoietin (EPO) producing tumor are diseases which cause absolute erythrocytosis. Many types of tumor such as renal cell carcinoma [1], hepatocellular carcinoma [2], and gynecological tumor [3] are known as EPO-producing tumor. Here we describe a patient with testicular seminoma complicated by absolute polycythemia. There seemed to be a close relationship between the two distinct diseases because the polycythemia recovered after the resection of the testicular tumor.

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Case report

A 45-year-old man was referred to our hospital in August 2002 because of erythrocytosis that was pointed out at a regular check up. He had no previous history of any kind of disease but had had a feeling of discomfort in his scrotum for about 2 years. A physical examination revealed no abnormality in his chest and abdomen. His right scrotum was enlarged to the size of 13×10 cm. On the laboratory finding, the white blood cell count and the platelet count were within normal range, 5.6×10^9/L, and 178×10^9/L, respectively. The differential leukocyte counts were not disturbed (granulocyte, 60.6%; lymphocyte, 31.2%; monocyte, 6.9%; eosinophil, 1.1%; basophil, 0.2%). However, marked erythrocytosis was found. The red blood cell count was $6{,}820\times10^9$/L, the hemoglobin concentration was 21.2 g/dL, and the hematocrit was 59.8%. In spite of severe erythrocytosis, the reticulocyte count was also elevated to 120×10^9/L. All of the erythrocyte indices were within the normal range, the mean corpuscular volume was 87.7 fL, the mean corpuscular hemoglobin was 30.9 pg, and the mean corpuscular hemoglobin concentration was 35.3%. Serum levels of lactate dehydrogenase and alkaline-phosphatase were increased, 2,000 IU/l and 1,036 IU/l, respectively. Other laboratory data about liver function tests, renal function tests, serological tests, and the serum vitamin B_{12} level were within the normal range. The arterial blood gas study showed no abnormalities. The bone marrow aspiration showed normocellular marrow with the bone marrow nucleated cell count of 102×10^9/L, and the megakaryocyte count of 31×10^6/L. The differential counts from the bone marrow aspirate showed erythroid hyperplasia without any evidence of myeloproliferative disorders (myeloblast, 1.6%; promyelocyte, 5.2%, myelocyte, 2.4%; metamyelocyte, 0.8%; band neutrophil, 7.4%; polymorphonuclear neutrophil, 20.8%; eosinohil, 3.4%; basophil, 0.2%; monocyte, 0.6%; lymphocyte, 11.4%; plasma cell, 0.6%; erythroblast, 45.6%). As a result of erythroid hyperplasia, the myeloid/erythroid ratio decreased to 0.92. The bone marrow biopsy revealed a normocellular marrow with hyperplasia of erythroblast, but did not reveal any evidence of invasion of malignant cells. The total red cell volume was elevated to 32 mL/kg (normal range: 25–30 mL/kg). Unfortunately it was evaluated after the treatment by phlebotomy of 900 mL, so the actual total red blood cell volume before treatment seemed to be higher than this value. The serum EPO concentration was 12.9 mU/mL, which was within the normal range. Abdominal and pelvic computed tomography revealed a huge mass in his right scrotum without other evidence of metastasis. The serum level of human chorionic gonadotropin (hCG) was elevated to 11.8 mU/mL. Serum free testosterone level was low, 11.4 pg/mL (14–40 pg/mL), and levels of gonadotorpins were elevated; follicle-stimulating hormone (FSH) was 17.5 mIU/mL (2.9–8.2 mIU/mL) and luteinizing hormone (LH) was 9.5 mIU/mL (1.5–5.2 mIU/L). No response of testosterone was observed

Table 1 Changes in the laboratory data before and after the orchidectomy are shown. Before the operation, phlebotomy was performed four times and 1600 mL of venous blood was removed

Date	WBC	RBC	Hb	Ht	Plt	Retics
Before operation						
2002.8.12	4100	664	20.4	58.3	16.3	119520
8.19	5600	682	21.1	59.8	17.8	101700
9.5	8400	582	18.3	51.6	19.4	101300
After operation						
9.26	4400	561	17.1	47.9	21.0	56710
10.16	4700	587	17.6	50.1	21.5	98000
2003.2.5	5300	558	17.8	50.7	19.7	69800
3.26	5500	564	17.7	49.6	22.7	98300
5.15	4700	543	17.0	47.9	20.1	92900

after an injection of 4,000 IU hCG, which was compatible with the diagnosis as primary hypogonadism. From these observations, he was diagnosed as having testicular tumor with absolute polycythemia. Before operation, phlebotomy was performed four times and 1,600 mL of venous blood was removed. The hemoglobin concentration decreased to 18.3 g/dl. In September 2002, a right radical orchidectomy was done with minimum bleeding. The bleeding volume was less than 100 mL. The testicular tumor was 904 g in weight, and 130×120×100 mm in size. The entire tumor was seminoma, and he was diagnosed as having pure seminoma. The stage of the disease was T1N2M0 without any metastasis, so no adjuvant radiotherapy or chemotherapy was given. After the operation, the red blood cell count, the hemoglobin concentration, and the hematocrit decreased to $5{,}430\times10^9$/L, 17.0 g/dL, and 47.9%, respectively (Table 1). Although the hemoglobin concentration was still higher than normal range (<16.5 g/dL), the total red blood cell volume was decreased to 30 ml/kg, which was in the normal range. Thus, the increased hemoglobin level was the result of the changes in the distribution of red blood cells in the body, which was different from the initial condition. Hyperplasia of erythroblast in the bone marrow was improved, resulting in the increase of myeloid/erythroid ratio from 0.92 to 1.50. The patient remains in complete remission from these two diseases.

Discussion

There are two types of erythrocytosis, absolute or relative erythrocytosis. In our patient, the total red blood cell volume was elevated above normal range and it was probably higher than the evaluated value because of prior phlebotomy, so the diagnosis as absolute erythrocytosis was compatible. Absolute erythrocytosis can be divided into two categories: neoplastic erythrocytosis like polycythemia vera and reactive erythrocytosis due to an overproduction of EPO secondary to hypoxia and tumor. In our patient, no laboratory data that support the diagnosis as myeloproliferative disorders were observed, and no disturbance was pointed out in the blood oxygen saturation, in the cardiac function, or in the respiratory function. The severe polycythemia improved spontaneously after a resection of the tumor. Thus, it is probable that there was a close relationship between seminoma and polycythemia. In general, polycythemia as a paraneoplastic syndrome is not such a rare event. Many types of tumor such as renal cell carcinoma, hepatocellular carcinoma, and gynecological tumor have been reported as EPO-producing tumors [1, 2, 3]. As for testicular tumors, a human testis germ cell line that produces significant amounts of EPO has been identified [4]. However, there have been only two previous reports about patients with polycythemia and seminoma. In one case, polycythemia was associated with steroid overproduction by the testis, which could be caused by a paracrine mechanism through hCG activity on the Leydig cells [5]. In another case, the testicular tumor seemed to be an EPO-producing tumor because the level of EPO in the tumor tissue was high [6]. Testosterone is known to increase erythropoiesis in many conditions [7, 8]. In our patient, however, the serum level of testosterone was low, so it seemed that serum testosterone had little influence on polycythemia. LH and FSH were high because of the primary hypogonadism, but these two hormones have no positive effect on erythropoiesis [9]. The serum concentration of EPO was not elevated, and kept a stable level after the operation. Concentration of EPO in a polycythemic condition is very variable [10, 11, 12]. Although we could not evaluate the presence of EPO in the tumor tissue, so-called EPO-producing tumor will show a high serum concentration of EPO. It is, therefore, unlikely that the seminoma in our patient was a typical EPO-producing tumor. However, the reticulocyte count was increased in number, although marked polycythemia had persisted, and the bone marrow finding represented hyperplasia of erythroblasts. After the operation these abnormalities resolved spontaneously. These observations indicated the presence of a continuous stimulation of erythropoiesis that was brought by the testicular seminoma. In normal circumstances there should be downregulated EPO levels in a polycythemic condition. Thus, the normal EPO value, in addition to marked Hb-elevation and reticulocytosis, argues for a non-functioning EPO-loop. One possibility was that there may be some paracrine EPO production in this case, but we could not reveal this speculation clearly. The other possibility is that the seminoma produced some kinds of erythropoietic hormones or cytokines other than EPO. For example, it was reported that growth hormone (GH) [13] and transforming growth factor (TGF)-beta [14] were expressed in the seminoma tissue. These substances were reported to have some influence on erythropoiesis [15, 16, 17]. It was possible that seminoma produced such erythropoietic factors in our patient, but this is only a speculation because we could not evaluate the presence of such substances in the tumor tissue or in the blood of the patient. The precise mechanism of polycythemia in our patient could not be clearly evaluated, but the clinical course did indicate a close relationship between these two distinct diseases.

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