# Pheochromocytoma, Polycythemia, and Venous Thrombosis

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**Polycythemia is rarely associated with pheochromocytoma. A patient with a 22-year history of malignant pheochromocytoma is presented in whom major complications developed as a result of long-standing polycythemia, apparently due to secretion of erythropoietin by the tumors. Despite attempts to reduce tumor burden by surgery, chemotherapy, and large doses of I-131-metaiodobenzylguanidine, polycythemia persisted. Extensive venous thrombosis developed requiring hospitalization and anticoagulation. Thus, polycythemia itself may be a cause of major morbidity in patients with pheochromocytoma, and prophylactic measures may be warranted. Review of the 130 patients with benign and malignant pheochromocytoma studied since the introduction of I-131-metaiodobenzylguanidine in 1980 revealed another six patients with hematocrits over 50 but only one had a hematocrit greater than 55 and required regular phlebotomy. In contrast, anemia (hematocrit less than 35) due to variety of causes was present in 18 cases.**

The deleterious effects of pheochromocytoma are usually directly attributable to the excessive secretion of catecholamines [1,2]. More rarely, pheochromocytomas may secrete other hormones including ACTH, growth hormone-releasing hormone, somatostatin, vasoactive intestinal polypeptide, and possibly substance P and motilin, which may themselves cause additional syndromes [3–8]. We present a patient with malignant, widespread pheochromocytoma in whom major complications developed as a result of long-standing polycythemia, apparently caused by erythropoietin produced by the tumor.

## CASE REPORT

A 32-year-old black man experienced palpitations, diaphoresis, hypertension, and epistaxis at the age of 10 in 1964. The hemoglobin level was 21.8 g/liter (**Table I**). Multiple abdominal pheochromocytomas were excised and further excisions were attempted two years later. Hemoglobin and hematocrit subsequently declined. Pulmonary metastases developed, followed by skull lesions five years later. In 1975, the patient underwent a chemotherapeutic trial of streptozotocin, carmustine (1,3-bis-[2-chloroethyl]-1-nitrosourea), and vincristine. In 1977, polycythemia was again noted. In 1980, his hematocrit rose to 73. Arterial blood gases on room air at pH 7.42 were as follows: oxygen partial pressure of 80 mm Hg, carbon dioxide partial pressure of 40 mm Hg, and oxygen saturation of 95 percent. Bone marrow examination showed increased cellularity, of which 58 percent was erythropoietic, 41 percent was granulopoietic, and 1 percent was lymphoid (myeloid: erythroid ratio 0.7, normal 3:1 to 4:1) [9], indicating marked expansion of the erythron. Megakaryocytes were normal and trace amounts of iron were found in the bone marrow. Hemoglobin electrophore-

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**TABLE I Hematologic Profile**

| Clinical Course | | Age | Hemoglobin | Hematocrit | White Blood Cell Count | Platelet Count | Erythropoietin |
|---|---|---|---|---|---|---|---|
| Presentation | 1964 | 10 | 21.8 | — | 5.5 | — | — |
| Repeat abdominal surgery | 1966 | 12 | 15.4 | 51 | 8.1 | — | — |
| Repeat abdominal surgery | 1967 | 13 | 12.2 | 39 | 5.5 | — | — |
| Repeat abdominal surgery | 1969 | 15 | 11.9 | 36 | — | — | — |
| Chemotherapy | 1977 | 23 | 19 | 58 | 3.2 | 265 | — |
| 131-I-MIBG | 1981 | 27 | 22 | 70 | 2.5 | 136 | — |
| 131-I-MIBG | 1982 | 28 | 22.6 | 70 | 2.3 | 117 | — |
| | | | | 68 | | | 56 |
| | | | | 70 | | | 50 |
| 131-I-MIBG | 1984 | 29 | 21.2 | 66.5 | 2.5 | 135 | — |
| Edema, venous thrombosis | 1986 | 31 | 19.1 | 60 | 4.2 | 126 | — |
| (Discharge) | | | | 46* | | | |

MIBG = metaiodobenzylguanidine.
* Following therapeutic phlebotomy.

sis was normal (hemoglobin $A_1$ 97.5 percent and hemoglobin $A_2$ 2.2 percent); the oxygen dissociation curve showed a P50 of 29.2 mm Hg (normal, 27.2 ± 1.8 mm Hg, ± 2 SD) [10], which was believed to be normal. Red blood cell mass, determined by chromium-labeled red blood cells, was 4,054 ml (normal, 1,673 to 2,045 ml), plasma volume by radioiodinated albumin was 2,900 ml (normal, 2,048 to 2,944 ml), and whole blood volume was 6,950 ml (normal, 4,082 to 4,990). The patient subsequently received high-dose I-131-metaiodobenzylguanidine in an attempt to reduce the tumor burden and catecholamine production [11]. **Figure 1** shows the multiple sites of metastatic involvement detected following the second therapeutic dose. A total of 606 mCi of I-131-metaiodobenzylguanidine was administered in four treatments from 1980 to 1984. Plasma and urine catecholamine levels were very high (**Table II**). In 1982, the erythropoietin level was 56 μU/ml (normal, 7 to 33 μU/ml; Bioscience, Van Nuys, California) at which time the hematocrit was 68. The repeat erythropoietin level was 50 μU/ml, while the hematocrit was 70. Blood pressure was controlled with 100 mg of phenoxybenzamine daily. The patient irregularly presented for follow-up but maintained two jobs. However, frequent calls from pharmacists questioning the dose of phenoxybenzamine and the frequent prescription refills suggested compliance with the antihypertensive regimen.

At age 31, the patient experienced right lower quadrant pain and returned for follow-up. Blood pressure was 120/74 mm Hg, and the pulse was 70 beats/minute. Nodules were palpable over the right and left parietal regions of the scalp. The abdomen was tender to palpation of the right lower quadrant, but guarding and rebound were absent. The spleen was not enlarged. The extremities were not edematous. Chest radiographs showed multiple pulmonary nodules consistent with metastatic pheochromocytoma. The admission hematocrit was 60. The following day, edema of the right lower extremity developed. Ultrasonography showed extensive venous thrombosis including the infrarenal inferior vena cava, right common femoral, and right inferior epigastric veins. Computed tomography showed bilateral parietal skull metastases. The patient was treated with intravenous heparin, phlebotomy, and subsequently warfarin. The hospital course was unremarkable. Discharge hematocrit was 46. He returned to the emergency services area five days later complaining of lower extremity edema after standing several hours at work. His legs were

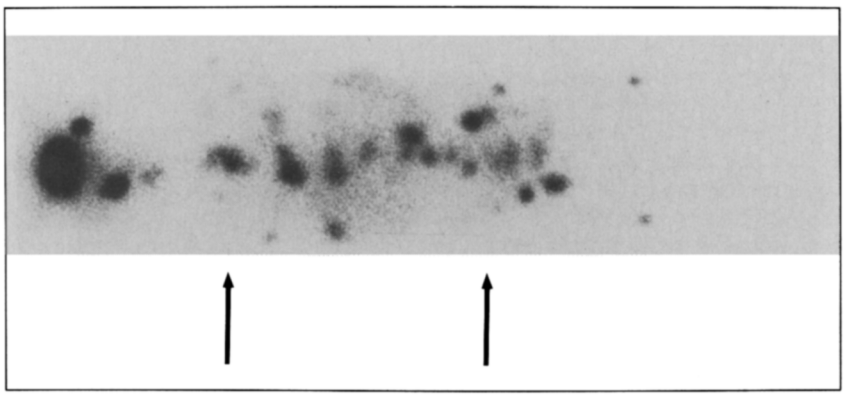

*Figure 1. Total body image obtained two days after the intravenous administration of 98 mCi of I-131-metaiodobenzylguanidine. **Arrows** indicate the location of the right shoulder and right iliac crest. Each of the focal areas of uptake represents a metastatic deposit. Multiple lesions are seen in the skull, including the very large area superiorly with intense uptake, the thoracic and lumbar spine, ribs, pelvis, and femurs, indicating extensive disease.*

nontender and the results of pulmonary examination were unremarkable. These findings were attributed to venous insufficiency. The patient has not kept subsequent appointments and serial phlebotomies have not been performed as planned.

## COMMENTS

The association of polycythemia and pheochromocytoma is rare. Of 130 patients with benign and malignant pheochromocytomas evaluated at this institution since the introduction of I-131-metaiodobenzylguanidine in 1980, for whom hematologic data are available, only six patients have had hematocrits greater than 50; all, however, except for the patient described herein, have had hematocrits less than 55. This includes a 25-year-old man whose polycythemia was discovered eight years prior to the diagnosis of pheochromocytoma. His hematocrit at age 8 was 73 and has been controlled for the past 13 years by periodic phlebotomy. As with the previous patient, results of pulmonary function, blood gases, hemoglobin electrophoresis, and oxygen dissociation studies were all normal. Erythropoietin levels were not, however, measured.

The observed increases in hematocrit may be more commonly due to reduction in plasma volume [12] and less frequently to expansion of red cell mass. Pheochromocytoma has been found in association with von Hippel-Landau disease [13], in which case the cerebellar hemangioblastomas that may occur appear to secrete an erythropoietin-like substance. Erythropoietin-like activity has been extracted from the pheochromocytomas of patients with polycythemia [14], and resolution of the polycythemia occurs when the tumor is totally removed [12,14,15]. The syndrome differs from polycythemia vera by the lack of splenomegaly, or increases in leukocyte or platelet counts, and, as in this case, by the demonstration of excessive and inappropriate circulating erythropoietin immunoactivity. Other causes of polycythemia with elevated erythropoietin activity, such as chronic hypoxia and hemoglobinopathies, are not present.

In patients with pheochromocytoma, anemia occurs much more commonly than polycythemia. We observed 18 patients with pheochromocytoma in whom at least one hematocrit determination was less than 35. There are multiple causes, including prior chemotherapy and probable tumor-induced iron reutilization effects, but the most common cause appears to be extensive phlebotomy during evaluation.

**TABLE II Levels of Plasma and Urinary Catecholamines and Derivatives***

| | 1980 | 1982 | 1984 | 1986 |
|---|---|---|---|---|
| Plasma | | | | |
| Norepinephrine (<500 pg/ml) | 25,314 | 28,920 | 16,758 | 5,594 |
| Epinephrine (<100 pg/ml) | 618 | 406 | 269 | 261 |
| Urine | | | | |
| Norepinephrine (<110 μg/24 hr) | 2,956 | 2,467 | 1,570 | — |
| Epinephrine (<30 μg/24 hr) | 102 | 230 | 4 | — |
| Normetanephrine (<165 μg/24 hr) | 1,628 | 1,937 | 467 | — |
| Metanephrine (<85 μg/24 hr) | 782 | 22 | 6 | — |
| Vanillylmandelic acid (<7 mg/24 hr) | 96 | 92 | 22 | — |

* Normal values are listed in parentheses.

The low leukocyte count in our patient and the decline in circulating platelets were likely due to prior chemotherapy and to the effects of high doses of I-131-metaiodobenzylguanidine upon the bone marrow. Despite this patient's large tumor burden and massive catecholamine production, his blood pressure is controlled and he continues to work. To our knowledge, however, this is the first demonstration of excessive erythropoietin immunoactivity in the circulation of a patient with pheochromocytoma and polycythemia. The levels of erythropoietin immunoreactivity, most likely secreted by the tumors, were moderately elevated and, given the elevated hematocrit and the normal oxygen delivery, strikingly inappropriate and autonomous. Complications from the polycythemia can occur [16] and, thus, the polycythemia of pheochromocytoma may require prophylactic measures to prevent untoward events.

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