Consequences of Erythropoietin Production by Neoplasms

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ABSTRACT

Neoplastic lesions of the kidney and certain other organs are sometimes associated with increased erythropoietin and/or erythrocytosis in man and experimental animals. It seems likely that measurement of erythropoietin, although not specific, could be helpful in detecting renal neoplasms and in following the progress of treated tumors of the kidney and certain other organs. Increasing the sensitivity of the assay of erythropoietin in the exphyoxic mouse, a functional assay, or in an immunologic assay of specific protein concentration might aid in the early detection of yet another hormone marker of neoplasia.

Introduction

A variety of neoplasms has been associated with erythrocytosis secondary to secretion of erythropoietin or erythropoietin-like substances. Excellent reviews by Thorling, Hammond and Winnick and, more recently, Kazal and Erslev summarize evidence that renal tumors (hypernephroma) are the neoplasms most frequently involved with erythrocytosis. The present paper presents an interesting case of this syndrome and reviews evidence that the neoplastic cells themselves may be responsible for production of the erythropoietin material.

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A 58 year old male was admitted to a community hospital via the Emergency Room after collapsing while shopping. He appeared dyspneic and cyanotic. He had had at least one similar episode in 1966 and had been diagnosed as having coronary and peripheral vascular insufficiency. In recent years, he had experienced pain in the thighs and legs after walking a few blocks. In the last few months, he had had aching and fullness about the eyes and decreased and fuzzy vision. Examination revealed red and injected conjunctivae, increased pulse, blood pressure and respirations, a grade I systolic heart murmur, rales at the bases of the lungs, a palpable spleen tip and absent leg pulses in rather plethoric extremities. Laboratory data revealed a hematocrit of 70 percent, a hemoglobin of 23.7 g per dl, WBC 11,600, normal platelets and normal blood gases. Blood volume showed increased red cell mass (5,600 ml) and normal plasma volume (2,400 ml).

At this point the working diagnosis was polythemia vera, ASCVD and peripheral vascular insufficiency. Nine units of blood were removed in two weeks, decreasing his hematocrit to 50. At this time he developed pain and coldness of the legs and a full picture of Larische syndrome. He was transferred to University Hospital where further work-up revealed a left renal mass which at operation proved to be a clear cell carcinoma of the lower pole of the left kidney. The tumor was removed along with the adherent spleen and a dacron graft was placed from aorta to femoral vessels bilaterally. Metastatic disease was noted in the liver. After a prolonged and stormy course which included thrombosis of the remaining right renal
artery, the patient died of renal shut down and a cerebrovascular accident.

In retrospect, an erythropoietin measurement shortly after his admission to the community hospital might have been very helpful in differentiating polycythemia vera from secondary erythrocytosis and speeding therapy along appropriate lines.

**Review of Erythropoietin Producing Renal Tumors**

Review of the literature reveals that in one summary study of 25 patients with hypernephroma and erythrocytosis had elevated erythropoietin levels in serum, urine or tissue extract. The assays were carried out by different investigators, using polycythemic or starved mice, and thus may have been insufficiently sensitive to detect erythropoietin in all cases of erythrocytosis.

Sufrin et al followed 57 patients with renal cancers and found renin was increased in 37 percent while erythropoietin was increased in 63 percent. Chorionic gonadotropin was not increased. Renin elevations were associated with high grade malignancy, increased tumor spread and poor prognosis. Erythropoietin levels were more sensitive but less specific than renin levels in that there was no correlation with tumor stage or type or with hematocrit or hemoglobin. The erythropoietin levels did tend to be higher in patients with increased renin levels. Erythropoietin levels decreased following nephrectomy. Survival was poorer in patients who had increased erythropoietin.

Wilms' tumor of the kidney is frequently associated with an increased erythropoietin level in the blood, although erythrocytosis is relatively rare. In fact, Murphy and his colleagues have suggested that erythropoietin levels might be of prognostic significance. These authors have reported 37 patients with Wilms' tumor and increased erythropoietin as measured by polycythemic mouse assay. Subsequently, they reported four patients who had active metastatic disease with persistent elevations of erythropoietin, while only one of 15 patients without metastatic disease showed an elevation which cleared after several months. No one has reported an elevation of erythropoietin prior to occurrence of obvious Wilms' tumor or metastases, but Murphy had six patients with treated and inactive metastatic disease that showed prolonged elevations of erythropoietin which gradually returned to normal 18 months after nephrectomy.

**Review of Other Neoplasms Associated with Erythropoietin Production**

Several other tumors have been associated with erythrocytosis and erythropoietin production which have little or no relationship to the kidney. Erythropoietin-like material has been isolated from cerebellar hemangioblastoma. This material was an alpha-2-glycoprotein (MW 30,000) which could be neutralized with antierythropoietin and by desialation. Over 50 cerebellar tumors have been associated with erythrocytosis. Removal of the tumor alleviates the erythrocytosis, but it often returns with recurrence of the tumor.

Sixty-four cases of paraneoplastic erythrocytosis in patients with primary liver cell tumors have been described. The erythrocytosis seems to be related to the size of the tumor. In one case where an hamartoma was removed, the erythrocytosis abated. Few of the other liver tumors have been removed successfully.

More than 30 cases of erythrocytosis associated with leiomyomata of the uterus have been observed. Theoretically, extremely large uterine tumors might impinge upon renal blood flow, thus causing relative anoxia and increased erythropoietin production. Recently, however, evidence has been found that an erythropoietin-like substance was secreted directly from a leiomyoma in a 54-year-old woman. There was no evidence of a plasma factor activator as previously suggested.
occur in leiomyomata\textsuperscript{14,15} nor was there evidence of increased erythropoietin substrate in the tumor extract. The directly produced erythropoietin activity could be neutralized with antierythropoietin antibody. Two other cases in the last two years have shown erythropoietin in extracts of the tumor.\textsuperscript{8,16}

There are a few case reports of patients with pheochromocytoma where erythrocytosis has reverted to normal when the tumor was removed\textsuperscript{13} and rare patients with erythrocytosis have been described in association with tumors of the ovary, the lung and the thymus.\textsuperscript{1} In all, 99 of 102 patients have shown alleviation of erythrocytosis after removal of the tumor. Assays of erythropoietin in tumor tissue showed activity in 28 of 44 tumors where it was measured.\textsuperscript{1}

**Benign Lesions Associated with Erythrocytosis**

It is established that erythrocytosis and increase in circulating erythropoietin are associated with benign lesions of the kidney more frequently than with malignant lesions.\textsuperscript{3} Adenomata, cysts and ureteral obstruction leading to hydronephrosis have all been associated with erythrocytosis.\textsuperscript{1,13} The plethora of benign lesions involved with the production of erythrocytosis has suggested that the stimulus for erythropoietin production may be compression of and anoxia of the renal tissues surrounding the lesion. Correction of or removal of the abnormality usually leads to normalization of the erythrocytosis.\textsuperscript{3}

The observations of erythrocytosis in association with various malignant lesions of the kidney has also led to the presumption that erythropoietin production is stimulated by anoxia of adjacent renal tissue. Hammond and Winnick\textsuperscript{1} suggest that in most cases of renal tumors the erythropoietin comes from renal tissue rendered anoxic by the tumor either interfering with blood supply of the renal artery, the renal vein, extra renal pressure, intrarenal pressure or blockage of the ureter. However, they also point out some evidence for erythropoietin production in tumor tissue and metastases.

Hrushesky and Murphy\textsuperscript{2} have described an animal model in rats injected intrarenally with carcinoma cells. The animals developed erythrocytosis and increased erythropoietin levels. Intraperitoneal, central nervous system and intravenous injections produced tumor formation without erythrocytosis or erythropoietin production. These studies indicated intrarenal growth of tumor was a crucial factor in the development of erythrocytosis.

Landon\textsuperscript{5} has theorized that erythropoietin or other hormones might be found in tumor tissues because (1) the tumor might concentrate the hormone by adsorption, (2) the tumor cells might have an endocrine origin, (3) there might be depression or loss of control within the chromosome allowing expression of a normal genome abnormally or (4) there might be an abnormal genome developed in the malignant cell. Little evidence is provided that allows choice of one or the other mechanism.

On the other hand, Kvarstein\textsuperscript{4} presented a case of renal carcinoma in which the hematocrit and hemoglobin returned to normal after the left kidney and carcinoma were removed. A few months later, the hematocrit again increased and another operation demonstrated regrowth of tumor in the left flank. Since there was no kidney tissue remaining there at second operation, it seems most likely the erythropoietin was being elaborated by the tumor.

Sherwood\textsuperscript{10} has presented recent evidence that human renal carcinoma cells grown in tissue culture will produce erythropoietin. Three human renal carcinomas were minced in Hank's balanced salt solution and dissociated by incubation with trypsin six times. Washed cells were seeded in 20 ml culture medium 199 with 10 percent fetal calf serum. The medium was changed weekly, pooled, dialyzed and
Conclusions

observation of an elevated level is not a
elevation of erythropoietin, an isolated
cinoma cell production of erythropoietin
seems
tumors1,8'9'11,13,16 may produce erythro-
erythropoietin would be useful in follow-
tissue culture evidence of renal car-
findings.

With evidence now accumulating that
isolated tumor cells can produce erythro-
and that tumors other than renal
tumors1,8,9,11,13,16 may produce erythro-
without involving the kidney, it
it seems clear that a sensitive assay for
erthropoietin would be useful in follow-
patients with tumors associated with
the kidney and other organs. Elevation of
serum erythropoietin has been helpful in
the progress of Wilms' tumor,
primary liver tumors and rare cases of lung, adrenal, ovarian and thymus tumors. Because of the wide vari-
erythropoietin, an isolated observation of an elevated level is not a
specific finding and must be interpreted
in light of the patient's other clinical
findings.

Conclusions

Erythropoietin activity has been found
in a number of tumor extracts. Recently,
tissue culture evidence of renal car-
cinoma cell production of erythropoietin
has been obtained.

It appears that when neoplasms or,
indeed, benign lesions compress the cir-
culation intrarenally or immediately
extrarenally, the mechanism of erythro-
poietin increase is probably relative
anoxia of the renal tissues responsible
for erythropoietin production. When the
neoplasm is remote from the kidney, such
as a metastasis from a hypernephroma,
a cerebellar hemangioblastoma, a pri-
mary liver cell cancer or a uterine leio-
myoma, it seems most likely the tumor
itself is responsible for the elaboration of erythropoietin.

References

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