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Secondary Erythrocytosis as Presenting Feature of Central Nervous System Hemangioblastoma: A Case Report and Review of Literature

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Abstract

Secondary erythrocytosis is most commonly a normal physiologic response to hypoxia, but in less frequent circumstances can also present as a paraneoplastic syndrome due to autonomous production of erythropoietin. Paraneoplastic erythropoietin production has been associated with renal cell carcinoma, hepatocellular carcinoma, and uterine leiomyomas. In rare cases, this can also be seen in CNS hemangioblastomas. Here, we report a case of a patient with remote history of resected astrocytoma who presented with symptoms concerning for astrocytoma recurrence. On laboratory evaluation, she was noted to have erythrocytosis. Workup revealed an elevated erythropoietin level suggesting secondary erythrocytosis, but without any apparent contributing etiology with no history of smoking, cardiopulmonary disease, or radiographic evidence of a tumor apart from MRI findings concerning for recurrence of her astrocytoma. Ultimately, surgical pathology of her brain tumor revealed a CNS hemangioblastoma and erythrocytosis resolved with resection of the tumor.

Keywords: Erythrocytosis; Secondary erythrocytosis; Hemangioblastoma; Paraneoplastic

Introduction

Erythrocytosis is defined as an elevation of the hemoglobin level above 16.5 g/dL in men and above 16 g/dL in women and an elevation of the hematocrit level above 49% in men and more than 48% in women [1]. Primary erythrocytosis are caused by acquired or inherited mutations causing functional changes in erythroid progenitors leading to accumulation of red cells. Secondary erythrocytosis can represent a physiologic compensation to tissue hypoxia (appropriate erythrocytosis) or due to erythropoietin-secreting tumors (inappropriate erythrocytosis). We present one such case of secondary erythrocytosis as an uncommon paraneoplastic syndrome (PNS) in a patient with cerebellar hemangioblastoma.

Case Presentation

A 77-year-old female with a past medical history of diabetes mellitus, hypertension and astrocytoma (resected in 1982) presented with vertigo, unsteady gait and double vision. She underwent an MRI of her brain which showed a 3.5 x 4 cm cystic mass within the lower aspect of posterior fossa with an intracystic nodule extending into the foramen magnum, resulting in significant compression of the cervicomedullary spinal cord concerning for recurrence of her previous astrocytoma. She was admitted to the hospital for operative planning. A CBC done while she was hospitalized showed a hemoglobin of 19.7 g/dL and hematocrit of 62%. The last CBC available dated back to 2012 and showed a hemoglobin of 11.5 g/dL and a hematocrit of 33.3%. All other blood work was within normal limits. She denied any history of smoking, obstructive sleep apnea, underlying pulmonary or cardiac conditions. On further investigation she did report a history of aquagenic pruritis but attributed it to her dry skin. She had also noticed conjunctival injection. She denied a history of early satiety, painful digits or abnormal bleeding. There was no palpable splenomegaly. Serial therapeutic phlebotomies were done to target a hemoglobin of less than 45% to optimize the patient prior to surgery.

In the meantime, a workup was ordered for the erythrocytosis including an US of the spleen which did not reveal any splenomegaly. Erythropoietin (EPO) levels were elevated to 20.7 mIU/mL (normal 2.6 – 18.5 mIU/mL) suggesting that this was a secondary process. On review of literature, erythrocytosis was reported in renal cell carcinomas, hepatocellular carcinomas, uterine leiomyomas and CNS hemangioblastomas. A CT of the chest, abdomen and pelvis was done to rule out tumor associated polycythemia due to autonomous production of EPO which was negative for the same. JAK-2, CALR and MPL mutation analysis were negative. She underwent a suboccipital craniectomy for resection of neoplasm, the pathology from which confirmed a hemangioblastoma, WHO grade 1. The erythrocytosis resolved after resection of her tumor. Nine months post-operatively, hemoglobin remained at 13.2 g/dl.

Discussion

This case represents an uncommon presentation of secondary erythrocytosis as a paraneoplastic syndrome in the setting of cerebellar hemangioblastoma. Initial workup of the patient's erythrocytosis included EPO levels, ultrasound of the spleen to rule out splenomegaly, and mutation analysis for JAK-2, CALR, and MPL genes to rule out myeloproliferative neoplasm. However, this workup was revealing only for an elevated EPO level, suggesting secondary erythrocytosis. Given no history of smoking or cardiopulmonary disease, CT chest/abdomen/pelvis was obtained due to suspicion for tumor-associated polycythemia. However, there were no findings of a primary mass or metastatic disease on CT imaging of her chest, abdomen, and pelvis. At this point, we suspected her erythrocytosis could be secondary to a CNS hemangioblastoma, which surgical pathology eventually confirmed. Diagnosis was further established with improvement of erythrocytosis following removal of the tumor.

PNS often represent a sign of malignancy or its relapse. Secondary erythrocytosis as a PNS is rare and has been reported in clear cell renal cancer [3], hepatocellular carcinoma [4], uterine leimyoma [5], germ cell testicular cancer [6]. Another rare cause is cerebellar hemangioblastoma. Hemangioblastomas are uncommon and slow growing tumors of the central nervous system mainly occurring in the posterior fossa and spinal cord. Symptoms are caused by local mass effect or paraneoplastic complications. The characteristic appearance on an MRI is that of an intra-axial cystic mass with an enhancing nodule or a solid intensely enhancing mass with flow voids. Secondary erythrocytosis in cerebellar hemangioblastoma has been reported to occur

in up to 20% of patients [7]. In a case report by Trimble et al., EPO concentrations were measured pre-operatively and postoperatively in the serum as well the cyst fluid drained during excision of a hemangioblastomas [8]. They found that the preoperative and postoperative serum levels of EPO were within the upper limit of normal range but the cyst fluid contained markedly elevated levels of EPO. They also confirmed the presence of EPO mRNA in the tumor by Northern blot analysis. Hemangioblastomas are also associated with Von Hippel Lindau disease with mutations of VHL. Hypoxia-inducible factor 1 alpha (HIF1A) and 2 alpha (HIF2A) are two of the major proteins regulated by VHL. HIF2A is involved in erythropoiesis through its ability to induce transcription of messenger RNA coding for erythropoietin. In patients with VHL disease, loss of the sole functioning VHL allele in somatic tissues causes a situation analogous to hypoxia, despite the presence of normal oxygen tension. A mutation in VHL gene may therefore cause impaired oxygen tension sensing and production of EPO. Erythrocytosis in hemangioblastomas resolves with the excision of tumor, as was seen in our patient.

Conclusion

This case represents a unique case of secondary erythrocytosis in the setting of a CNS hemangioblastoma. Alternative causes of secondary erythrocytosis were considered, however the patient did not have any history of smoking or prolonged hypoxia, and CT of the chest, abdomen, or pelvis did not reveal any evidence of malignancy. Ultimately, surgical pathology from the patient's brain lesion revealed hemangioblastoma, which is a known etiology of paraneoplastic erythropoietin production. This case highlights the importance of performing an adequate workup for erythrocytosis. While this patient did present with neurologic symptoms that mandated brain imaging, in other cases, erythrocytosis may be the only early presenting sign of a malignancy.

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