

Hemangioblastoma of the Gastrointestinal Tract: A First Case

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Abstract

We present the first documented case of hemangioblastoma located in the left colon. A 75-year-old woman undergoing adjuvant chemotherapy for breast cancer experienced rectal bleeding. Colonoscopy revealed a roundish mass covered with normal mucosa in the sigmoid colon. Endoscopic ultrasound showed an isoechoic lesion originating from the third layer of the intestinal wall; underlying layers were normal. Endoscopic ultrasound features were not suggestive of either cancer or malignant stromal tumor. Left hemicolectomy was subsequently performed due to repeated episodes of lower gastrointestinal bleeding. Grossly, a circumscribed submucosal yellowish nodule (13 mm) was observed, which was not attached to any peripheral nerve. Histologically, the lesion was composed of large, atypical cells traversed by a network of blood vessels. Immunohistochemically, the cells showed positivity for inhibin and NSE and weak positivity for S-100. A diagnosis of hemangioblastoma was made. This case highlights that hemangioblastoma of the gastrointestinal tract can also occur.

Keywords

hemangioblastoma, Von Hippel–Lindau disease, colon cancer

Introduction

Hemangioblastomas are rare benign vascular tumors of the central nervous system (CNS) and are composed of endothelial cells, pericytes, mast cells, and stromal cells. They account for 2.5% of all intracranial tumors and 8% to 12% of all posterior fossa tumors.^{1–3} In about 80% of patients the tumor is a sporadic, single lesion of the brainstem, upper cervical spinal cord, or cerebellum.⁴ The highest incidence is in young adults, with a slight male predominance. Approximately 20% of patients with intracranial hemangioblastomas have Von Hippel–Lindau disease.⁵ Hemangioblastomas have also been reported outside the CNS, for example, in peripheral nerves,^{6,7} liver,^{8,9} lung,¹⁰ pancreas,¹ retroperitoneum,¹⁰ kidney,^{3,11–13} pancreas,¹¹ urinary bladder,¹¹ soft tissues of the ankle and popliteal fossa,^{13,14} and nasal skin.¹⁵ We present the first documented case of hemangioblastoma located in the left colon.

Case Report

In May 2009, a 75-year-old woman undergoing adjuvant chemotherapy for breast cancer (pT2, pN2a M0) at our

institute experienced rectal bleeding, which led to significant anemia (Hb = 7.8 g/dL). Colonoscopy was performed, revealing a roundish mass covered with normal mucosa in the sigmoid colon (Figure 1A); the remaining gastrointestinal tract was normal. Biopsy of the lesion revealed normal histology. The bleeding was treated by endoscopic instillation of adrenaline. Endoscopic ultrasound (EUS) was performed using a 12-MHz miniprobe, revealing an isoechoic lesion of 14 mm × 11 mm with homogeneous echotexture originating from the third layer of the intestinal wall (submucosa; Figure 1B); the underlying layers were normal. As EUS imaging was not strongly suggestive of either colon cancer or a malignant gastrointestinal stromal tumor, close monitoring was recommended.

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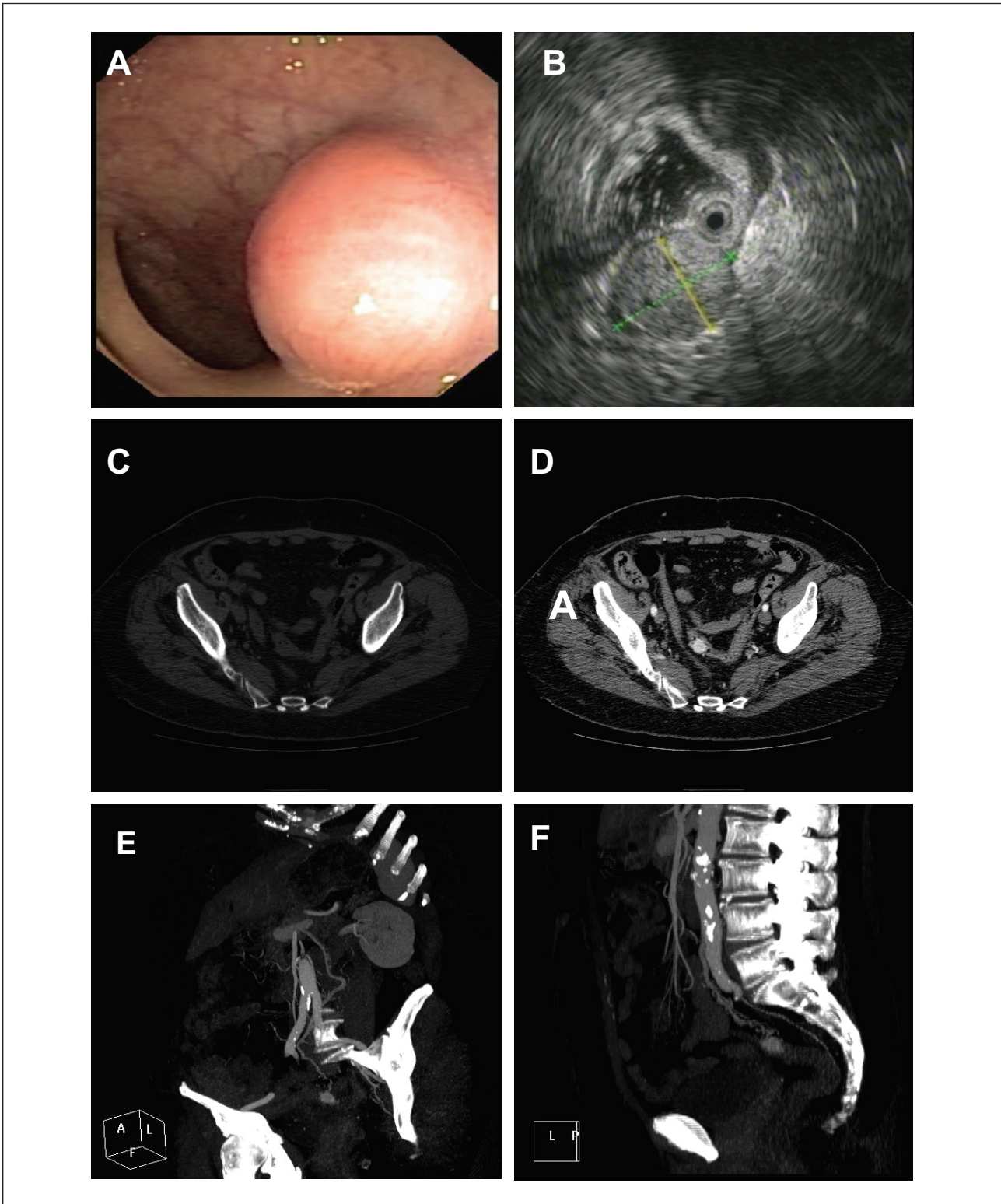


Figure 1. A) Colonoscopy showing a roundish mass covered with normal mucosa in the sigmoid colon. B) Endoscopic ultrasound showing an isoechoic lesion. C) CT scan without contrast showing hypodense lesion. D) After contrast infusion, the lesion appeared hyperdense. E) Vascularization of the inferior mesenteric artery. F) Outflow from the superior mesenteric artery.

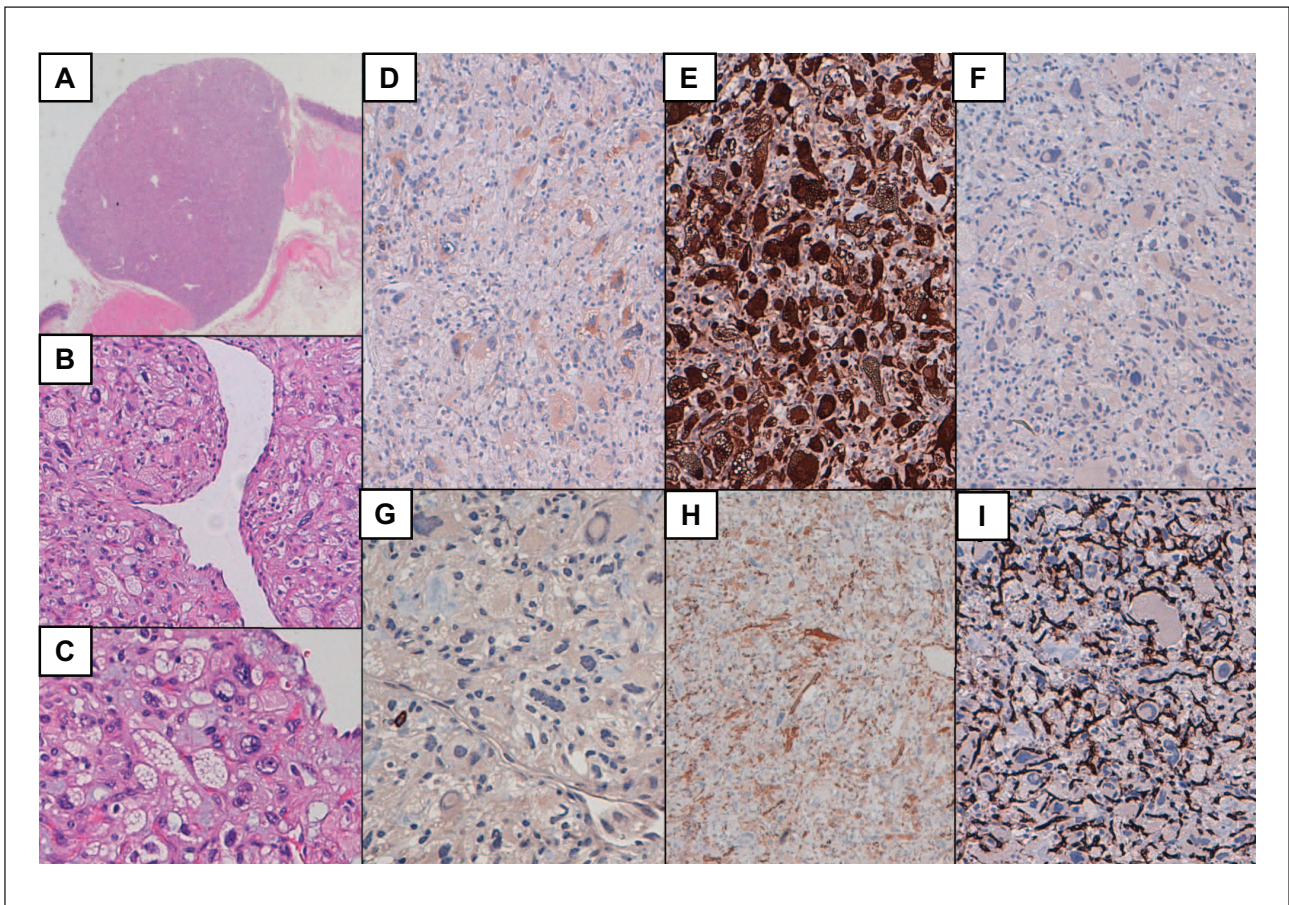


Figure 2. A-C) Microscopic features of the lesion. D) Neoplastic cells strongly positive for inhibin. E) Neoplastic cells strongly positive for neuron-specific enolase. F) Neoplastic cells negative for pan-cytokeratin. G) Neoplastic cells negative for c-kit. H) Neoplastic cells negative for muscle-specific actin. I) Immunostaining for CD34 highlighted an abundance of non neoplastic vessels.

At the 6-month follow-up, both endoscopy and EUS imaging was unchanged. A computed tomography (CT) scan performed without contrast revealed a hypodense lesion (Figure 1C); after contrast infusion the lesion appeared hyperdense (Figure 1D). Vascularization of the inferior mesenteric artery was visible (Figure 1E), as was the outflow from the superior mesenteric artery (Figure 1F). Following repeated episodes of lower gastrointestinal bleeding, the patient underwent left hemicolectomy in October 2010.

Macroscopic Features

The tumor (13 mm × 11 mm) was localized in the submucosal layer of the large bowel and was well demarcated from the surrounding fibroadipose tissue. The cut section of the tumor was solid and yellow, with no evidence of necrosis or hemorrhage. The lesion was not associated with any visible nerves.

Microscopic Features

The tumor consisted of sheets of variously sized polygonal, epithelioid cells with eosinophilic cytoplasm and irregular, pleomorphic nuclei (Figure 2A and B). There was a sub-population of tumor cells with bizarre nuclei and microvacuolated cytoplasm, indicating the presence of lipids. A very prominent branching thin-walled vascular network was present. A number of vessels were ectatic, showing a hemangiopericytomatous pattern (Figure 2C). Mitotic figures were rare. There was no evidence of necrosis.

Immunohistochemical Findings

Slides for immunohistochemical staining were prepared from formalin-fixed, paraffin-embedded tissue. Staining was carried out using Bond-Max automated immunostainer with heat-induced antigen retrieval and a polymer-based immunohistochemical detection system. The

neoplastic cells were strongly and diffusely positive for α -inhibin (Figure 2D) and neuron-specific enolase (Figure 2E). Positivity for S100 protein was weak and multifocal. The tumor was negative for pan-cytokeratin (Figure 2F), c-kit (Figure 2G), DOG1, HMB45, muscle-specific actin (Figure 2H), desmin, chromogranin, and synaptophysin. Immunostaining for CD34 highlighted an abundance of nonneoplastic vessels (Figure 2I). A diagnosis of intestinal hemangioblastoma was made. On the basis of the histological findings, it was decided not administer adjuvant chemotherapy or radiotherapy. Almost 3 years have passed since surgery and the patient is disease-free and in good clinical condition.

Discussion

As far as we know, ours is the first reported case of hemangioblastoma of the gastrointestinal tract. CT and EUS imaging did not facilitate diagnosis, which ultimately was based on the presence of typical morphology and immunophenotype. The recognition of hemangioblastoma depends, to a large extent, on awareness of the existence of such tumors. However, its occurrence in extraneural sites is so rare that such a hypothesis may not even be included in the differential diagnosis, which takes into account lipogenic tumors, melanoma, metastatic clear cell carcinoma, gastrointestinal stromal tumor, capillary hemangioma, and paraganglioma. Large, multivacuolated cells of hemangioblastoma are similar to lipogenic cells.

Well-differentiated liposarcoma is normally paucivascular, in contrast to the hemangioblastoma of our patient, which was not surrounded by areas of adipose tissue. Multivacuolated cells with centrally located vesicular nuclei and a rich capillary network are typical of hibernoma, but hibernoma cells do not show the pronounced nuclear atypia of our case. However, the strong positivity for α -inhibin¹⁶ helped in formulating the differential diagnosis. We also took the possibility of melanoma into consideration as an in situ melanoma had been removed from the patient's leg in October 2007, but this was rejected as tumor dimensions remained unchanged for almost 2 years and mitoses were rare in the biopsy specimen. Furthermore, HMB45 was completely negative. From a morphological point of view, differential diagnosis of hemangioblastoma includes metastatic carcinoma, in particular renal clear cell carcinoma and adrenocortical carcinoma. Taking into account the patient's breast cancer history, it was also necessary to rule out metastatic lobular carcinoma of the breast. The absence of pancytokeratin, cytokeratin 7, and HMB45 and the expression of S-100 and α -inhibin excluded the hypothesis of carcinoma. In view of the anatomical location of the lesion, we also included gastrointestinal stromal tumor in the differential diagnosis, but

immunohistochemistry for DOG1 and c-kit was completely negative. Like CNS hemangioblastomas, our patient's tumor was characterized by prominent vascular proliferation, but the presence of peculiar stromal cells led to the exclusion of hemangioma or hemangiopericytoma. The lesion also had a very prominent network of thin-walled branching blood vessels similar to that of paraganglioma but lacked its typical nested architecture.

Given the rarity of this tumor and the patient's history of breast cancer and melanoma, genetic counseling was also performed because hemangioblastoma sporadically occurs in association with Von Hippel–Lindau disease. The patient's professional activity had not exposed her to specific occupational carcinogens. The genealogical tree did not reveal a family history or any other clinical manifestation of the syndrome. Molecular genetic analysis, a more specific instrument to confirm or exclude Von Hippel–Lindau disease, was offered to the patient, but was refused.

Cerebral hemangioblastomas frequently exhibit overexpression of erythropoietin, which manifests as an increase in hemoglobin and of hematocrit values. This was not seen in our patient because of the numerous episodes of rectal bleeding. Furthermore, hemangioblastomas are benign but our case showed a marked nuclear atypia, which is unusual for this tumor. It was thus decided to monitor the patient closely with an annual CT scan and biannual clinical follow-up with full blood counts. Colonoscopy was performed 1 year after surgery and will be repeated at 3 and 5 years. Given the small dimensions of the tumor and the negative resection margins, it was decided not to administer chemotherapy or adjuvant radiotherapy.

The identification of hemangioblastoma depends, to a large extent, on both the clinical manifestation of the disease and radiological images. Surgery is performed and diagnosis is confirmed by histological examination. Because of its rarity, hemangioblastoma was not included in the differential diagnosis of our patient by either the clinicians (oncologist and gastroenterologist) or radiologist involved. Immunohistochemical results (coexpression of α -inhibin, NSE, and S100), together with salient histological features (vacuolated epithelioid cells associated with a prominent vascular component), are other elements required for a correct diagnosis.

In conclusion, our experience shows that hemangioblastoma can also occur in the gastrointestinal tract, indicating that such a hypothesis should be taken into consideration in the differential diagnosis of similar clinical cases.

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Declaration of Conflicting Interests

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