

Unusual Pediatric Sigmoid Perivascular Epithelioid Cell Tumor with Regional Lymph Node Metastasis Treated Using Gemcitabine and Docetaxel: A Case Report and Literature Review

Hsiu-Chung Cheng

Kaohsiung Medical University and Hospital

Chia-Yu Kuo

Kaohsiung Medical University and Hospital

Ching-Wen Huang

Kaohsiung Medical University and Hospital

Hsiang-Hung Shih

Kaohsiung Medical University and Hospital

Chih-Hung Lin

Kaohsiung Medical University and Hospital

Jaw Yuan Wang (✉ cy614112@ms14.hinet.net)

Kaohsiung Medical University <https://orcid.org/0000-0002-7705-2621>

Case report

Keywords: perivascular epithelioid cell tumor (PEComa), gastrointestinal PEComa, pediatric sigmoid PEComa

Posted Date: August 14th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-58121/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background Perivascular epithelioid cell tumor (PEComa) is an extremely rare neoplasm with distinctive morphology and specific expression of immunohistochemical markers. The lesion is typically diagnosed in middle-aged women, and few pediatric cases have been reported. However, standardized treatment for the tumor type remains unestablished. Herein, we report a case of a pediatric patient with gastrointestinal PEComa of the sigmoid colon with regional lymph node metastasis. The patient was successfully treated with complete tumor resection and gemcitabine/docetaxel combination chemotherapy without local or distant recurrence after 12 months postsurgery.

Case presentation A 17-year-old female adolescent presented with gastrointestinal PEComa of the sigmoid colon with regional lymph node metastasis. She was treated with surgical resection of the tumor and cytotoxic chemotherapy with gemcitabine (900 mg/m²) and docetaxel (100 mg/m²) every 3 weeks. There was no recurrence of hematochezia stool, and complete response was achieved, with a progression-free survival of 12 months.

Conclusion Surgical resection with adjuvant conventional cytotoxic chemotherapy can be considered as the first-line treatment for early-stage gastrointestinal PEComa.

Introduction

Perivascular epithelioid cell tumors (PEComas) are extremely rare neoplasms of mesenchymal origin, featuring distinctive morphology, immunohistochemistry, and ultrastructure[1, 2]. Angiomyolipomas, lymphangioliomyomatosis, and clear-cell sugar tumors are some examples of PEComas[1, 2]. PEComas–not otherwise specified (PEComas NOS) are clear-cell tumors of other anatomic locations, those that do not qualify for the predominant assemblage of the PEComa family, such as the aforementioned tumor types[3]. PEComas NOS are typically diagnosed in women aged 38.9–56 years and are focused on the uterus and gastrointestinal (GI) tract, with the uterine corpus lesions accounting for 41% of the reported cases[1, 4-8]. Immunohistochemically, PEComas NOS typically exhibit positive melanocytic and myogenic markers, such as human melanoma black 45 (HMB45), melanoma antigen recognized by T cells (melan-A), and smooth muscle actin, and negative expressions of protein S100, cytokeratin, and desmin[9-11]. However, the histogenesis and corresponding normal cellular counterpart of PEComa remain unknown[1, 3], and a standardized treatment strategy remains unestablished[2]. Because of their unpredictable histopathological manifestation, patients with aggressive PEComas have poor prognosis and do not respond well to chemotherapy[5, 12, 13]. The mammalian target of rapamycin (mTOR) inhibitor treatment remains controversial in patients lacking the tuberous sclerosis complex (TSC) gene mutation[5, 9]. To date, radical surgical resection is an effective treatment for primary tumor and local recurrence prevention[2]. Herein, we report the case of an adolescent female patient with an unusual PEComa. The patient had regional lymph node metastasis presenting as a large bleeding rectosigmoid tumor, which was successfully treated with complete resection and gemcitabine/docetaxel chemotherapy. No local or distant recurrence was observed even after 12 months postsurgery.

Case Report

A 17-year-old female adolescent visited our emergency room with painless hematochezia stool for 2 days. The patient also had symptoms of dizziness and fainting, but did not have fever, other gastrointestinal symptoms or signs, trauma history, or recent weight loss. The laboratory findings were as follows: hemoglobin level, 6.0 g/dL; white blood cell count, 8720 cells/mm³; and platelet count, 384,000 cells/mm³. The stool culture and laboratory test results were within the reference range, as were the tumor markers. Blood transfusion was performed for severe anemia. Tranexamic acid was also administered for massive bloody stool. Ultrasonography revealed a suspicious 2.9-cm ovoid mass in the pelvis region.

Further abdominal computed tomography (CT) revealed a large pedunculated polypoid lesion measuring 3.5 × 3.1 × 2.8 cm³, with heterogenous enhancement in the rectosigmoid colon and metastatic lymphadenopathy of approximately 0.6 cm in the paracolic region (Figure 1A–D). Colonofiberscopy indicated a large submucosal tumor with ulcerations and a large stalk at 10 cm from the anus. For the rectosigmoid colon tumor, the patient received robotic-assisted low anterior resection, with an uneventful postoperative course. Pathological report (Figure 2A) revealed a perivascular PEComa of the rectosigmoid colon with regional metastatic lymph nodes, and classification was pT1N1. The circumferential resection and surgical resection margins were free of tumor cells. Immunohistochemical staining of the tumor cells revealed strong diffuse positivity for HMB-45 (Figure 2B) and negative expressions for melan-A, cytokeratin (AE1/AE3), paired-box gene 8 (PAX8), discovered on GIST-1 (DOG-1), and synaptophysin.

Six cycles of cytotoxic chemotherapy with a combination of gemcitabine at 900 mg/m² and docetaxel at 100 mg/m² every 3 weeks were completed. A repeat abdominal CT scan 6 months after surgical resection revealed no local recurrence or distant metastasis. Colonofiberscopy results performed 1 year after surgery were unremarkable. The patient's clinical condition remained stable after complete resection and treatment with gemcitabine/docetaxel without local or distant recurrence at the 12-month follow-up.

Discussion

Studies on treatments and outcomes specific to PEComa are limited to institutional series and anecdotal case reports. A PubMed search (accessed in July, 2020) revealed 62 cases of gastrointestinal PEComa NOS in the literature; the colon was the most commonly affected part in the abdominal cavity, followed by the mesentery, rectum, stomach, duodenum, ileum, cecum, and other locations[3]. The GI tract is the subfrequent location, preceded only by gynecological tract[8]. In addition, polypoid tumors centered in the mucosa and submucosa principally occur in the cecum and rectum[14]. Folpe et al.[11, 15] indicated that GI PEComas have a conspicuous female tendency, along with an incidence peak in the fourth or fifth decade of life[3]. However, some GI PEComas have previously been reported in children[14, 16-18]. The first pediatric case of metastatic PEComa of the colon was recorded in 2008[17]. An 11-year-old prepubertal Caucasian boy received resection of a 5.5-cm-long sigmoid colon. At the 5-month follow-up,

the results of repeat CT were unremarkable and the boy was asymptomatic[17]. In 2009, another report similar to our case was published. A girl aged 15 years with rectal PEComa and lymph node involvement was successfully treated with surgical resection and adjuvant chemotherapy (doxorubicin, ifosfamide, and mesna) without recurrence at 9 months postsurgery. Regardless of the affected age group, prognostic pathologic markers of the GI PEComas are few because of the rare nature of the neoplasm[14].

Differentiating GI PEComa from GI stromal tumor (GIST) or other sarcoma is challenging because PEComa generally presents a biphasic GIST-compatible morphology[12]. PEComa's clinical manifestation is variable and with little discrimination, including abdominal pain, rectal bleeding, or asymptomatic[3, 18]. Hematochezia stool was observed in our patient, whereas intermittent rectal bleeding was observed in several pediatric patients[14, 16, 19]. Imaging studies assist in identifying the lesion to a certain degree[20, 21]. Arteriovenous hypervascularity may be observed in contrast-enhanced CT, but most areas are seen as homogeneous and well-demarcated masses with clear boundaries in plain CT[21]. Endoscopy can facilitate the detection of a polypoid tumor or fungating mass with irregular ulceration, and tumors are generally observed as a rich vascularization with a hyaline wall or even necrosis[4, 22].

Immunohistochemical discernment of melanocytic differentiation is the most effective approach to differentiating GI PEComa from other tumors, such as GIST, angiomyolipoma, paraganglioma, malignant melanoma, and alveolar soft part sarcoma[2]. Although the precursor or normal counterpart of PEComa remains undefined[12], HMB-45 continues to be the most sensitive and frequent melanocytic marker in 92%–100% of reports[1, 2, 23]. Other potential melanocytic markers are melan-A, smooth muscle actin, and microphthalmia transcription factor, which were indicated in 23%–88%, 59%–93%, and 50%–92% of reports, respectively, as well as desmin and caldesmon[1, 2, 8, 10, 14, 23]. PEComa has negative expression for chromogranin A, synaptophysin and protein S100, which can divergent from paraganglioma[2]. Diagnosis of GIST can be precluded if either perivascular concentric proliferation or representative granular cytoplasm is present[3] and <50% of GISTs are strongly CD117 positive and completely lack expressions of melanocytic markers, especially HMB-45[12].

Folpe et al.[11] established a series of criteria to distinguish the pathological behavior of aggressive PEComa, namely high-risk features such as a size of ≥ 5 cm, a mitotic rate of ≥ 1 cells/ high power field (HPF), an infiltrative growth pattern, high nuclear grade and cellularity, necrosis, and vascular invasion. Another study proposed that a tumor size of ≥ 5 cm and a mitotic rate of ≥ 1 cells/ HPF are crucially associated with prognosis and recurrence[1, 5, 20, 24]. Tumors with ≥ 2 high-risk characteristics are categorized as malignant PEComa, and 81.6% of such lesions may relapse within 23 months[2, 23]. In our patient, pedunculated polypoid lesion in the sigmoid colon was approximately $3.5 \times 3.1 \times 2.8$ cm³, with no evidence of necrosis. The tumor was well limited in the submucosa, with no further infiltration.

Surgical resection is the preferred treatment for primary tumor GI PEComas, especially in the benign and chemoradioresistant groups[3, 4, 7, 14]. It is also adopted to manage local recurrence after initial therapy, enabling long-term control of metastatic foci[12, 25]. Most tumors are eradicated at the size of 4–6 cm

when excision is performed [12, 18]. Cheng et al.[24] successfully treated patients with recurrent PEComas of the sigmoid colon with pancreatic metastasis by surgical resection alone. In 2018, a patient with rectum PEComa with recurrent liver metastases was cured through surgery. However, 37.1% of patients treated with surgical resection without adjuvant therapy can develop distant metastases after 6 months[26]. All of the pediatric patients[14, 16-18] were treated with surgery as an initial management strategy. However, the preferred adjuvant therapy, including doxorubicin, paclitaxel, gemcitabine, and oxaliplatin alone or in combinations, is a matter of contention[5, 9, 13, 14, 27, 28]. For benign PEComa, no standardized regimen has been provided to avoid recurrence after surgery[3, 4]. Clinical outcomes in the published literature are varied. Ryan et al. reported the case of a patient aged 15 years with rectum PEComa and lymph node involvement. The patient was successfully treated with surgical resection and adjuvant chemotherapy with a combination of doxorubicin, ifosfamide, and mesna, with no recurrence at 9 months postsurgery.[14] In 2010, another report described a patient aged 7 years with ascending colon PEComa who was treated with adjuvant IFN- α 2b immunotherapy after resection, with a good prognosis[27]. Bleeker et al.[4] demonstrated that conventional cytotoxic chemotherapy is not effective in malignant PEComas and emphasized the superiority of mammalian target of rapamycin (mTOR) inhibitor therapy. The mTOR pathway regulates cell growth and is associated with the inactivation of tuberous sclerosis complex 1 (*TSC1*) and *TSC2* genes[1, 12]. Characterization of *TSC1* and *TSC2*, along with their downstream products[2, 13], could help develop targeted therapeutic agents, such as sirolimus or tacrolimus. However, contrary results were observed when a female patient aged 58 years with metastatic PEComa was treated with a combination of topotecan, temsirolimus (mTOR inhibitor), and bortezomib[28]. Moreover, a male patient aged 23 years with colon PEComa demonstrated resistance to mTOR inhibitor therapy but maintained stable prognosis when treated with a combination of doxorubicin and ifosfamide for 9 months[13]. In accordance with the published literature and our institutional experience, we suggest surgical resection with adjuvant conventional cytotoxic chemotherapy as the first-line treatment for early-stage GI PEComas. For tumors manifesting ≥ 2 aggressive pathological behaviors[5, 11], the *TSC* gene should be identified to evaluate the need for mTOR inhibitor therapy.

Metastases may not be observed in some patients even up to 10 years after tumor resection. Thus, such patients especially with tumors measuring >8 cm require monitoring for several years after surgical treatment[2, 12]. Freeman et al. documented the longest follow-up of 180 months in a patient with PEComa of the sigmoid colon measuring 6 cm who was successfully treated with radical excision[29]. Pisharody et al. suggested that physical examination and CT scans must be performed every 6 months and endoscopy should be conducted every year after surgery to monitor local recurrence and distant metastasis.[3, 17]

Conclusion

Studies on PEComas are few and demonstrate high heterogeneity. Therefore, a comparative study to determine the optimal treatment is challenging. This study suggests surgical resection with adjuvant conventional cytotoxic chemotherapy as a treatment option for early-stage GI PEComas. However, well-

documented clinical trials should be performed to accumulate immunohistochemical evidence and suggest empirical therapy. The findings can be extrapolated to practice procedures.

Abbreviations

DOG-1: discovered on GIST-1;

GI tract: gastrointestinal tract;

GIST: gastrointestinal stromal tumor;

HMB45: human melanoma black 45;

HPF: high power field;

Melan-A (MART-1): melanoma antigen recognized by T cells;

mTOR: mammalian target of rapamycin;

PEComa: perivascular epithelioid cell tumor;

PEComas NOS: PEComas–not otherwise specified;

PAX8: paired-box gene 8;

TSC: tuberous sclerosis complex;

Declarations

Ethics approval and consent to participate:

As this study is a case report, ethics approval was not necessary after consulting the Institutional Review Board of Kaohsiung Medical University Hospital

Consent for publication:

Written informed consent was obtained from the patient and the parents for publication of the case report and the accompanying images.

Availability of data and material:

The datasets supporting this manuscript are included within the article. All raw data can be acquired from the corresponding author.

Competing interests:

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

Collection and assembly of patient data: Hsiu-Chung Cheng, Chia-Yu Kuo, Ching-Wen Huang, Hsiang-Hung Shih;

Collection and interpretation of pathological data: Chih-Hung Lin;

Literature Review: Hsiu-Chung Cheng, Chia-Yu Kuo;

Revision and Correction: Jaw-Yuan Wang;

Manuscript writing and final approval of manuscript: All authors.

Acknowledgments

This work was supported by grants through funding from the Ministry of Science and Technology (MOST 109-2314-B-037-035, MOST 109-2314-B-037-040, MOST 109-2314-B-037-046-MY3) and the Ministry of Health and Welfare (MOHW107-TDU-B-212-123006, MOHW107-TDU-B-212-114026B, MOHW108-TDU-B-212-133006, MOHW109-TDU-B-212-134026, MOHW109-TDU-B-212-114006) and funded by from the health and welfare surcharge of on tobacco products, and the Kaohsiung Medical University Hospital (KMUH108-8R34, KMUH108-8R35, KMUH108-8M33, KMUH108-8M35, KMUH108-8M36, KMUH-DK109005~3, KMUHS10903) and KMU Center for Cancer Research (KMU-TC108A04) as well as and a KMU Cohort Research Center Grant (KMU-TC108B07), Kaohsiung Medical University. In addition, this study was supported by the Grant of Taiwan Precision Medicine Initiative, Academia Sinica, Taiwan, R.O.C.

Authors' Information

School of Medicine, College of Medicine, Kaohsiung Medical University, Taiwan

Hsiu-Chung Cheng, Jaw-Yuan Wang

Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan

Chia-Yu Kuo, Jaw-Yuan Wang

Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan

Ching-Wen Huang, Jaw-Yuan Wang

Department of Surgery, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Taiwan

Ching-Wen Huang

**Division of General Pediatrics, Department of Pediatrics, Kaohsiung Medical University Hospital,
Kaohsiung Medical University, Taiwan**

Hsiang-Hung Shih

Department of Pathology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan

Chih-Hung Lin

Graduate Institute of Clinical Medicine, Kaohsiung Medical University, Taiwan

Jaw-Yuan Wang

Center for Cancer Research, Kaohsiung Medical University, Kaohsiung, Taiwan

Jaw-Yuan Wang

References

1. Utpatel K, Calvisi DF, Kohler G, Kuhnel T, Niesel A, Verloh N, Vogelhuber M, Neu R, Hosten N, Schildhaus HU et al. Complexity of PEComas : Diagnostic approach, molecular background, clinical management. *Pathologie*. 2020; 41(Suppl 1):9-19.
2. Sobiborowicz A, Czarnecka AM, Szumera-Ciećkiewicz A, Rutkowski P, Świtaj T. Diagnosis and treatment of malignant PEComa tumours. *Oncology in Clinical Practice*. 2020; 16:22-33.
3. Chen Z, Han S, Wu J, Xiong M, Huang Y, Chen J, Yuan Y, Peng J, Song W. A systematic review: perivascular epithelioid cell tumor of gastrointestinal tract. *Medicine (Baltimore)*. 2016; 95(28):e3890.
4. Zizzo M, Ugoletti L, Tumiati D, Castro Ruiz C, Bonacini S, Panebianco M, Sereni G, Manenti A, Lococo F, Carlinfante G et al. Primary pancreatic perivascular epithelioid cell tumor (PEComa): A surgical enigma. A systematic review of the literature. *Pancreatology*. 2018; 18(3):238-245.
5. Bleeker JS, Quevedo JF, Folpe AL. "Malignant" perivascular epithelioid cell neoplasm: risk stratification and treatment strategies. *Sarcoma*. 2012; 2012:541626.
6. D'Andrea D, Hanspeter E, D'Elia C, Martini T, Pycha A. Malignant Perivascular Epithelioid Cell Neoplasm (PEComa) of the Pelvis: A Case Report. *Urol Case Rep*. 2016; 6:36-38.
7. Armah HB, Parwani AV. Malignant perivascular epithelioid cell tumor (PEComa) of the uterus with late renal and pulmonary metastases: a case report with review of the literature. *Diagn Pathol*. 2007; 2:45.

8. Kanazawa A, Fujii S, Godai TI, Ishibe A, Oshima T, Fukushima T, Ota M, Yukawa N, Rino Y, Imada T et al. Perivascular epithelioid cell tumor of the rectum: report of a case and review of the literature. *World J Surg Oncol*. 2014; 12:12.
9. Starbuck KD, Drake RD, Budd GT, Rose PG. Treatment of Advanced Malignant Uterine Perivascular Epithelioid Cell Tumor with mTOR Inhibitors: Single-institution Experience and Review of the Literature. *Anticancer Res*. 2016; 36(11):6161-6164.
10. Bennett JA, Braga AC, Pinto A, Van de Vijver K, Cornejo K, Pesci A, Zhang L, Morales-Oyarvide V, Kiyokawa T, Zannoni GF et al. Uterine PEComas: A Morphologic, Immunohistochemical, and Molecular Analysis of 32 Tumors. *Am J Surg Pathol*. 2018; 42(10):1370-1383.
11. Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL, Weiss SW. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. *Am J Surg Pathol*. 2005; 29(12):1558-1575.
12. Lin KH, Chang NJ, Liou LR, Su MS, Tsao MJ, Huang ML. Successful management of perivascular epithelioid cell tumor of the rectum with recurrent liver metastases: A case report. *Medicine (Baltimore)*. 2018; 97(31):e11679.
13. Scheppach W, Reissmann N, Sprinz T, Schippers E, Schoettker B, Mueller JG. PEComa of the colon resistant to sirolimus but responsive to doxorubicin/ifosfamide. *World J Gastroenterol*. 2013; 19(10):1657-1660.
14. Ryan P, Nguyen VH, Gholoum S, Carpineta L, Abish S, Ahmed NN, Laberge JM, Riddell RH. Polypoid PEComa in the rectum of a 15-year-old girl: case report and review of PEComa in the gastrointestinal tract. *Am J Surg Pathol*. 2009; 33(3):475-482.
15. Folpe AL, Kwiatkowski DJ. Perivascular epithelioid cell neoplasms: pathology and pathogenesis. *Hum Pathol*. 2010; 41(1):1-15.
16. Baek JH, Chung MG, Jung DH, Oh JH. Perivascular epithelioid cell tumor (PEComa) in the transverse colon of an adolescent: a case report. *Tumori*. 2007; 93(1):106-108.
17. Pisharody U, Craver RD, Brown RF, Gardner R, Schmidt-Sommerfeld E. Metastatic perivascular epithelioid cell tumor of the colon in a child. *J Pediatr Gastroenterol Nutr*. 2008; 46(5):598-601.
18. Gross E, Vernea F, Weintraub M, Koplewitz BZ. Perivascular epithelioid cell tumor of the ascending colon mesentery in a child: case report and review of the literature. *J Pediatr Surg*. 2010; 45(4):830-833.
19. Hornick JL, Fletcher CD. PEComa: what do we know so far? *Histopathology*. 2006; 48(1):75-82.
20. Doyle LA, Hornick JL. Mesenchymal Tumors of the Gastrointestinal Tract Other than GIST. *Surg Pathol Clin*. 2013; 6(3):425-473.
21. Okamoto K, Okada Y, Ohno K, Yagi T, Tsukamoto M, Akahane T, Shimada R, Hayama T, Tsuchiya T, Nozawa K et al. A rare case of perivascular epithelioid cell tumor (PEComa) of the greater omentum. *World J Surg Oncol*. 2018; 16(1):113.
22. Pan CC, Jong YJ, Chai CY, Huang SH, Chen YJ. Comparative genomic hybridization study of perivascular epithelioid cell tumor: molecular genetic evidence of perivascular epithelioid cell tumor

- as a distinctive neoplasm. *Hum Pathol.* 2006; 37(5):606-612.
23. Martignoni G, Pea M, Reghellin D, Zamboni G, Bonetti F. PEComas: the past, the present and the future. *Virchows Arch.* 2008; 452(2):119-132.
 24. Cheng J, Deng M, Gao J, Tao K. A recurrent perivascular epithelioid cell tumor of sigmoid colon with pancreatic metastasis: an extremely rare case report and review of the literature. *Int J Colorectal Dis.* 2016; 31(6):1237-1240.
 25. Rutkowski PL, Mullen JT. Management of the "Other" retroperitoneal sarcomas. *J Surg Oncol.* 2018; 117(1):79-86.
 26. Tynski Z, Chiang W, Barrett A. An Inguinal Perivascular Epithelioid Cell Tumor Metastatic to the Orbit. *Case Rep Pathol.* 2018; 2018:5749421.
 27. Park SJ, Han DK, Baek HJ, Chung SY, Nam JH, Kook H, Hwang TJ. Perivascular epithelioid cell tumor (PEComa) of the ascending colon: the implication of IFN-alpha2b treatment. *Korean J Pediatr.* 2010; 53(11):975-978.
 28. Subbiah V, Trent JC, Kurzrock R. Resistance to mammalian target of rapamycin inhibitor therapy in perivascular epithelioid cell tumors. *J Clin Oncol.* 2010; 28(24):e415.
 29. Freeman HJ, Webber DL. Perivascular epithelioid cell neoplasm of the colon. *World J Gastrointest Oncol.* 2010; 2(4):205-208.

Figures

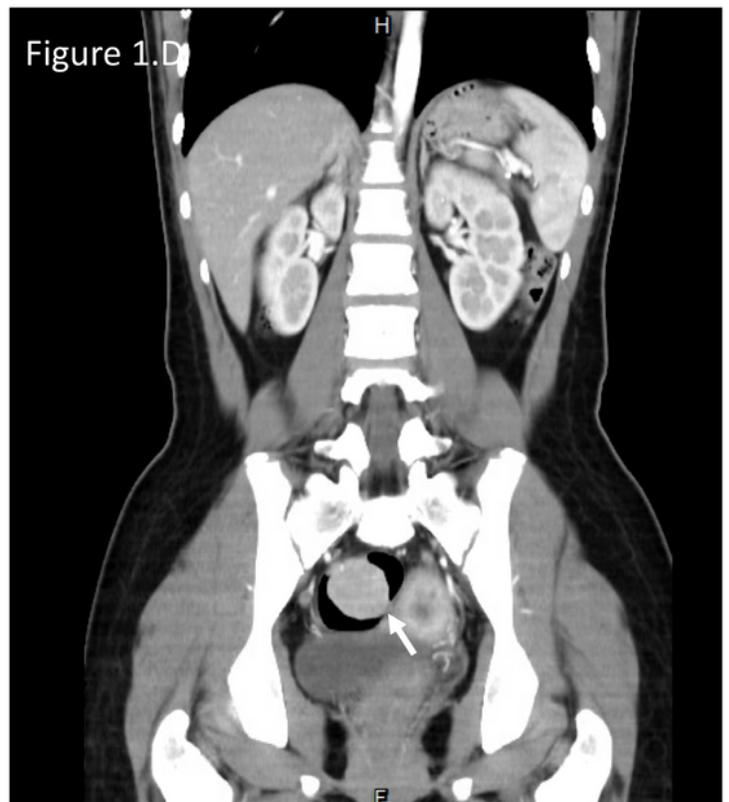
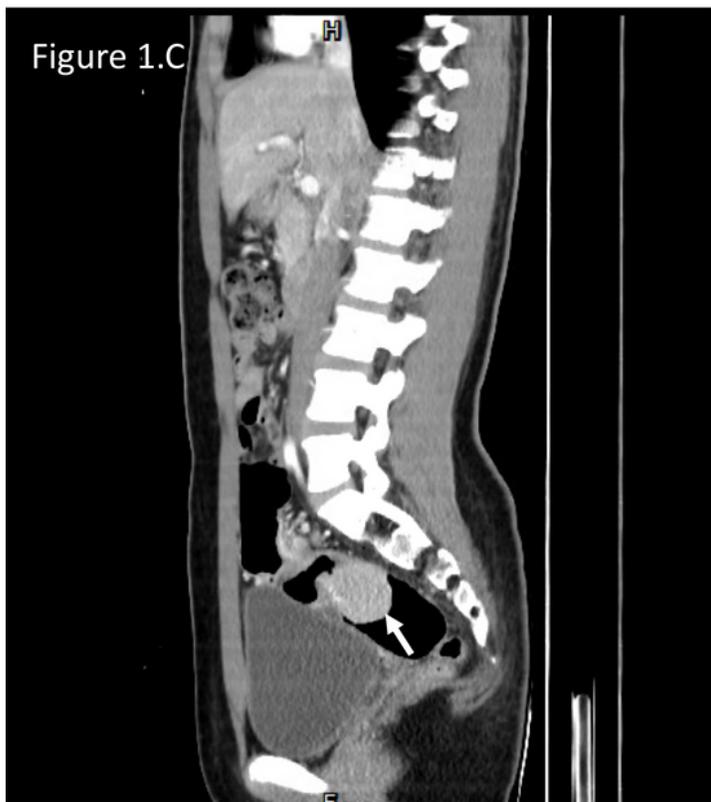


Figure 1

Abdomen computed tomography scan of the primary tumor in the sigmoid colon: (A) plain view, (B) arterial phase, (C) sagittal view, and (D) coronal view.

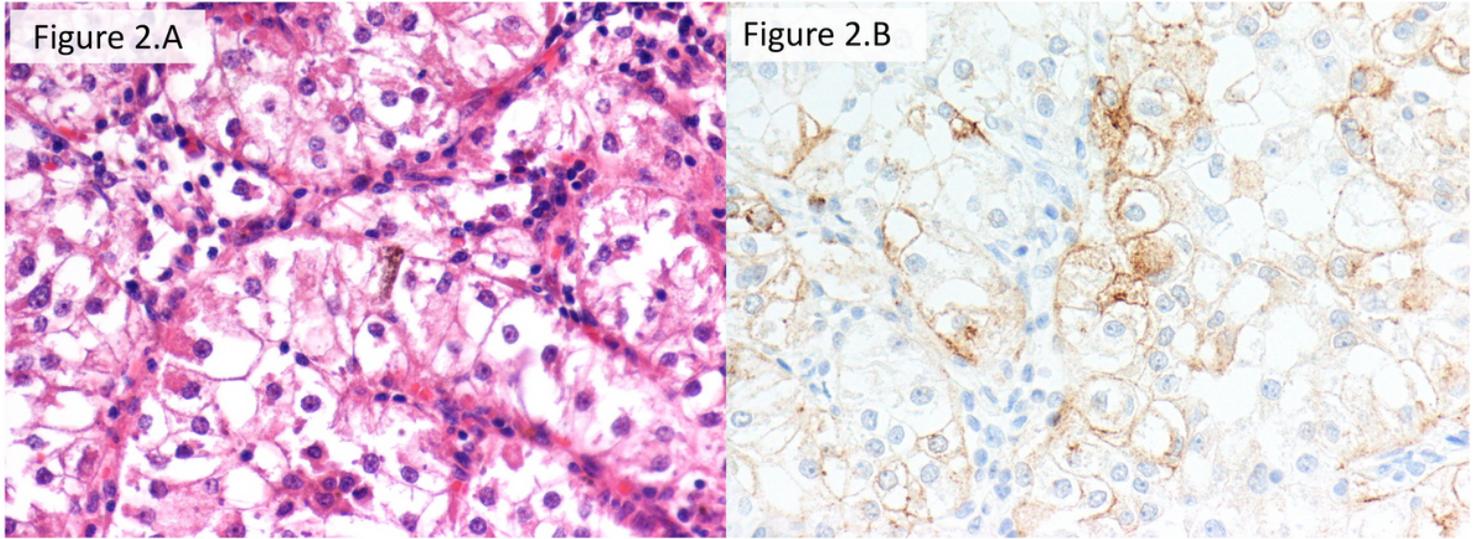


Figure 2

Histologic section of the primary tumor in the sigmoid colon: (A) HE \times 400 and (B) HMB-45(+). Sections of the polypoid lesion show nests and sheets of plump round to polygonal cells with a clear cytoplasm. Large vessels with perivascular growth can be seen. Cytoplasmic pigmentation can also be observed.