



Gastric Signet Ring Cell Adenocarcinoma With Metastasis to the Testicles and Leptomeninges

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ABSTRACT

Gastric signet ring cell adenocarcinoma (SRCA) is an aggressive malignancy primarily diagnosed in advanced stages. Metastasis to other organ systems is uncommon, however, associated with poor prognosis. We present a young patient with persistent pain in the testicle. Histopathologic examination of the resected testicle revealed metastatic signet ring adenocarcinoma prompting follow-up endoscopy with biopsy confirming gastric SRCA. After 10 months of systemic chemotherapy, the patient developed worsening headaches, and cerebrospinal fluid cytology confirmed leptomeningeal metastasis. This case underscores the rare manifestation of SRCA and the importance of vigilance for atypical presentations to ensure timely diagnosis and management.

KEYWORDS: signet; ring; adenocarcinoma; testicle; leptomeninges; metastasis

INTRODUCTION

Signet ring cell adenocarcinoma (SRCA) is a subtype of gastric adenocarcinoma with an increasing incidence in the younger population associated with poor prognosis.¹ Although peritoneal carcinomatosis is frequently involved in advanced cases, gastric SRCA rarely metastasizes to other organ systems. In this article, we present a rare case of a young patient initially with localization of gastric SRCA in the testicle and eventually to the leptomeninges.

CASE REPORT

The patient was a 38-year-old man with significant medical history of unprovoked deep vein thrombosis (DVT) on rivaroxaban, alcohol use 3 times per week for 10 years, and tobacco use for 22 pack-years who presented with right lower extremity swelling concerning for recurrent DVT along with right groin pain radiating to his right testicle. He was hemodynamically stable and afebrile. Physical examination demonstrated right lower extremity edema and slight tenderness of the right testicle. Occult malignancy was suspected, given recurrent unprovoked DVTs; thus, computed tomography (CT) was obtained showing diffuse gastric wall thickening, multiple lymphadenopathy, and nodularity and stranding densities along the peritoneal surfaces (Figure 1). Scrotal ultrasound demonstrated a hypoechoic mass in the right testicle (Figure 2). The patient underwent an orchiectomy of the right testicle with pathological evaluation showing SRCA infiltrating both the testicle parenchyma and spermatic cord with angiolymphatic invasion (Figure 3). Immunohistochemical evaluation was positive for cytokeratin (CK)-7, CK20, CK AE1/AE3, and caudal-type homeobox transcription factor 2 and negative for *Helicobacter pylori*. The findings from CT and pathology raised suspicion of a primary lesion in the stomach; thus, an esophagogastroduodenoscopy was performed visualizing diffuse ulceration, thickening, and friability of the lower esophagus and stomach (Figure 4). Endoscopic ultrasound demonstrated irregular, hypoechoic lymph nodes of the perigastric and porta hepatis regions as well as a noncircumferential, poorly circumscribed, hypoechoic mass at the gastroesophageal junction (Figure 5). Biopsies of a gastric fundus ulceration and the gastroesophageal junction mass and fine needle aspiration of the gastrohepatic ligament and porta hepatis lymph nodes revealed invasive adenocarcinoma with signet ring features (Figure 6).

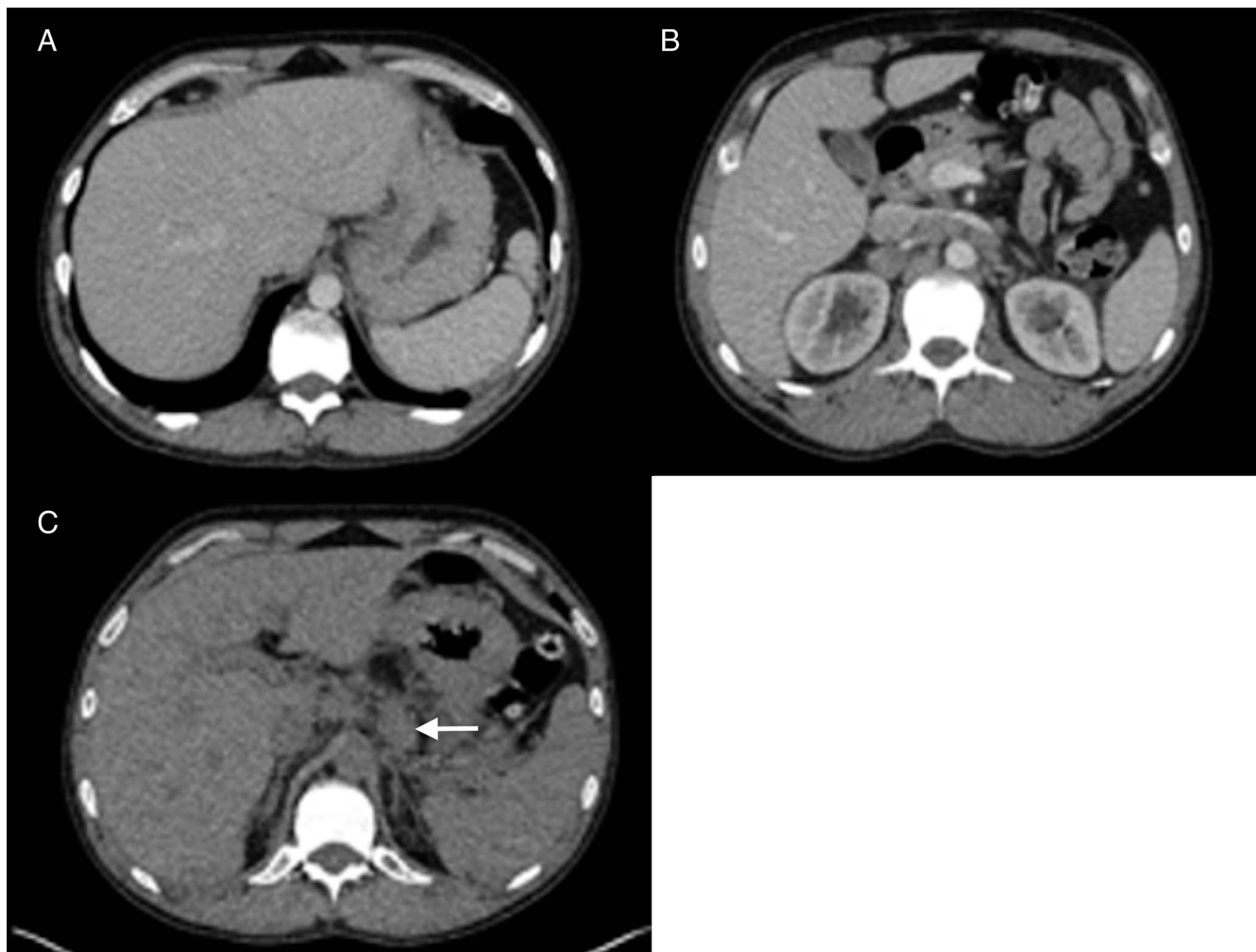


Figure 1. Abdominal computed tomography scan. (A) Significant thickening of the gastric fundus measuring up to 27 mm. (B) Extensive retroperitoneal lymphadenopathy in the para-aortic and aortocaval regions. (C) Enlargement of the gastrohepatic lymph node (white arrow) measuring 24.5×29.6 mm.

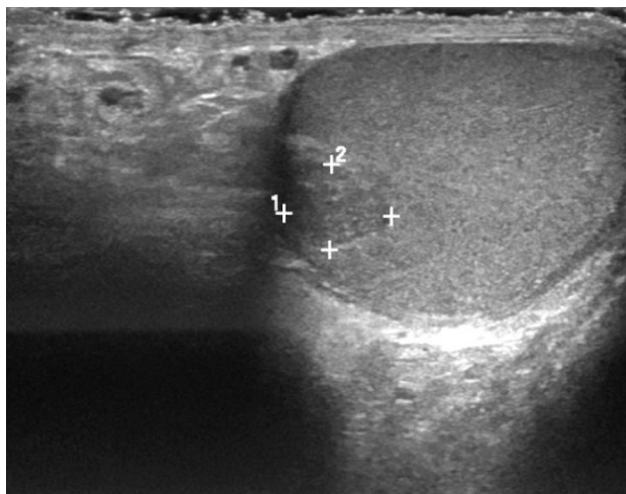


Figure 2. Ultrasound of the right scrotum demonstrating a $0.9 \times 0.7 \times 0.8$ -cm marginated hypoechoic area (white crosses) in the upper pole of the right testicle.

The patient underwent a chemotherapy regimen consisting of oxaliplatin and 5-fluorouracil for 7 months and then a course of capecitabine for 3 months. A follow-up CT was evident for new peritoneal implants consistent with peritoneal carcinomatosis. He then presented with acute worsening headache. Physical examination was unremarkable for focal neurological deficits. His pain was controlled with intravenous dexamethasone. Magnetic resonance imaging of the brain and lumbar spine showed enhancement of the posterior cerebral sulci and right cauda equina nerve root, respectively, suggestive of leptomeningeal metastasis (LM). The cytology of the cerebrospinal fluid obtained through lumbar puncture showed SRCA and confirmed LM. Intrathecal therapy was not pursued, given his mental deterioration. The patient was transferred to hospice care where he died after 2 months.

DISCUSSION

Gastric adenocarcinoma represents the fifth leading cause of mortality related to cancer in the world, with more than 960,000

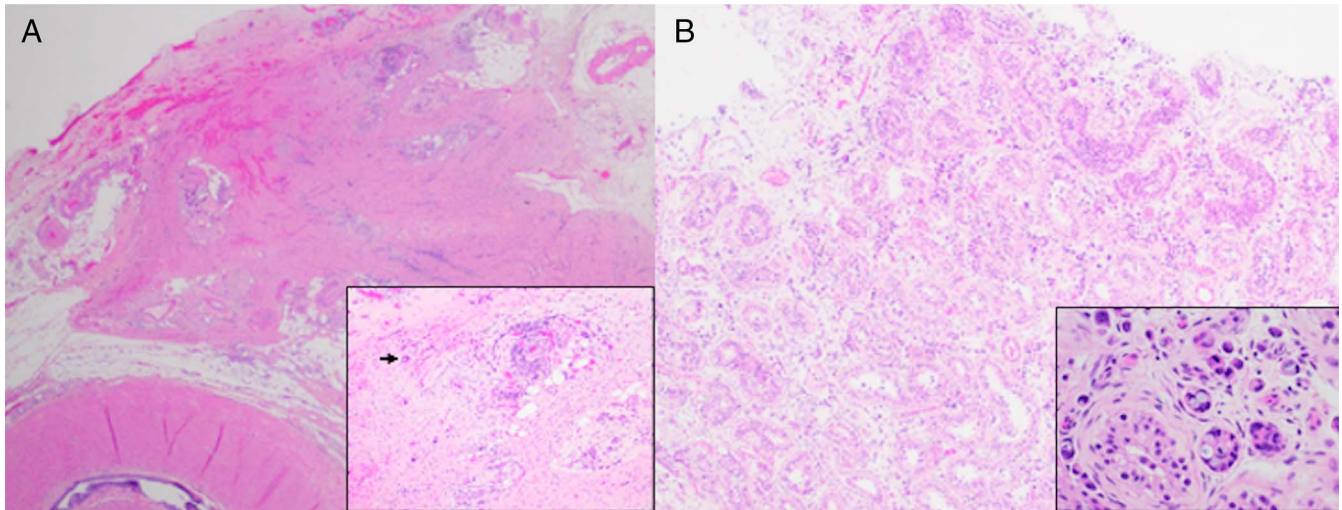


Figure 3. Histology of spermatic cord and testicle (hematoxylin and eosin [H&E]). (A) Spermatic cord margin with invasive adenocarcinoma (2× objective, 20× magnification); inset shows signet ring adenocarcinoma cell (black arrow) on high power magnification (100×). (B) Signet ring cell adenocarcinoma infiltrating the testicular parenchyma (4× objective, 40× magnification); inset shows signet ring cell adenocarcinoma on high power magnification (400×).

new cases estimated in 2022 though is relatively uncommon in North America.² SRCA is a diffuse subtype that comprises a significant proportion of all gastric malignancies reported up to 37%.^{1,3} According to the World Health Organization classification, it is a poorly cohesive carcinoma composed of predominantly signet ring-appearing cells morphologically derived from accumulation of intracellular mucin pushing the nucleus to the periphery of the cell.⁴ If SRCA is detected early and removed with endoscopic resection or gastrectomy, prognosis has been shown to be favorable compared with other undifferentiated gastric malignancies without signet ring features.^{5,6} However, SRCA is an indolent disease typically found at an advanced stage with poor prognosis on presentation of common symptoms including weight loss, abdominal pain, nausea, and anorexia.⁷ Metastasis to lymph nodes and the

peritoneum has been frequently reported as manifestations of the advanced stage.^{8,9}

Inflammatory drivers, typically related to *H. pylori* infection or toxigenic exposure, are suspected to contribute to the pathogenesis of SRCA.⁴ Immunohistochemical evaluation in our patient was not evident for *H. pylori*, although smoking and alcohol abuse were also considered as potential risk factors. The initial finding of diffuse malignant lymphadenopathy with progression to peritoneal carcinomatosis in our patient aligned with the literature. However, there have been only a handful of studies describing dissemination of SRCA of gastric origin to the testicle and leptomeninges individually.¹⁰⁻¹³ There has not been documentation of metastasis of gastric SRCA to both regions in a single patient.

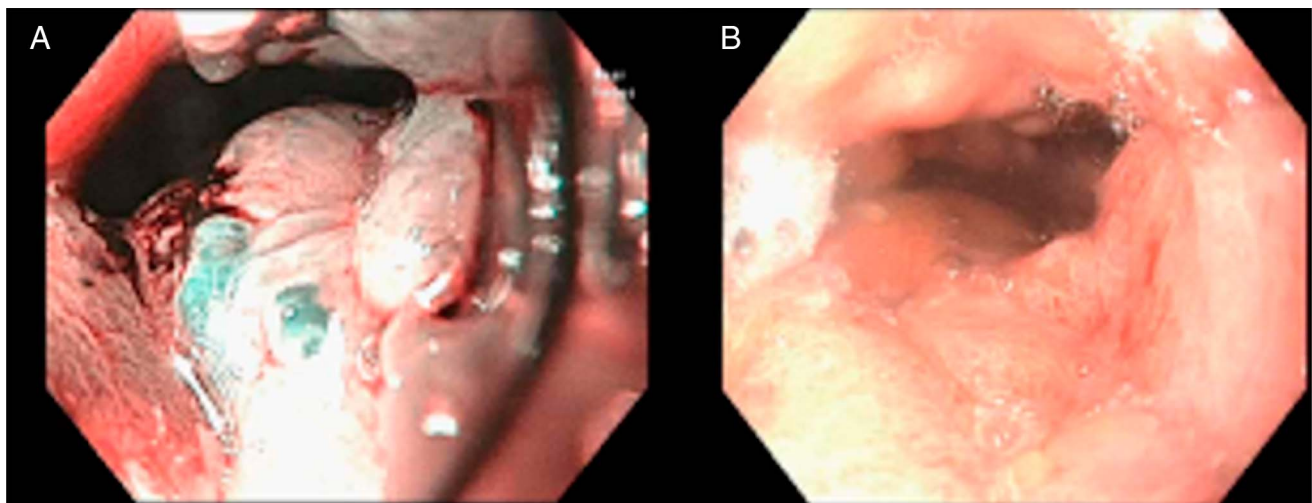


Figure 4. Esophagogastroduodenoscopy visualizing (A) congestion and friability of the gastroesophageal junction and (B) congested, erythematous thickening and increased vascular pattern of the gastric body.

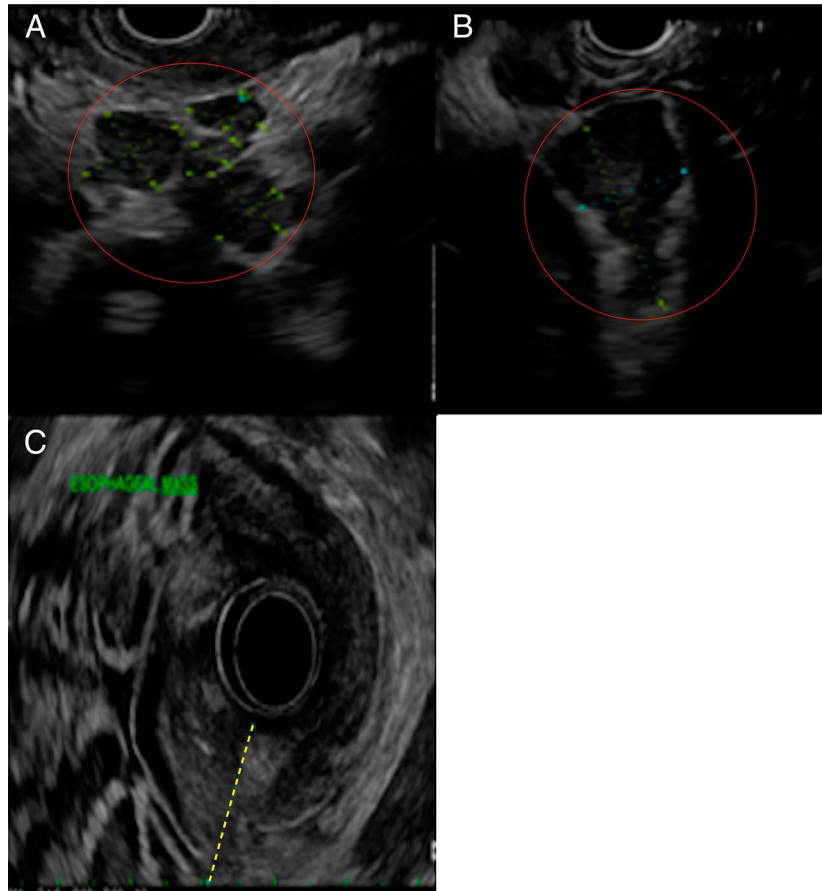


Figure 5. Endoscopic ultrasound with findings of lymphadenopathy (red circle) in the (A) perigastric region largest measuring 13×14 mm, (B) porta hepatis region measuring 31.9×15.6 mm, and a (C) noncircumferential, hypoechoic and heterogenous esophageal mass with maximum thickness of 24 mm (dashed yellow line).

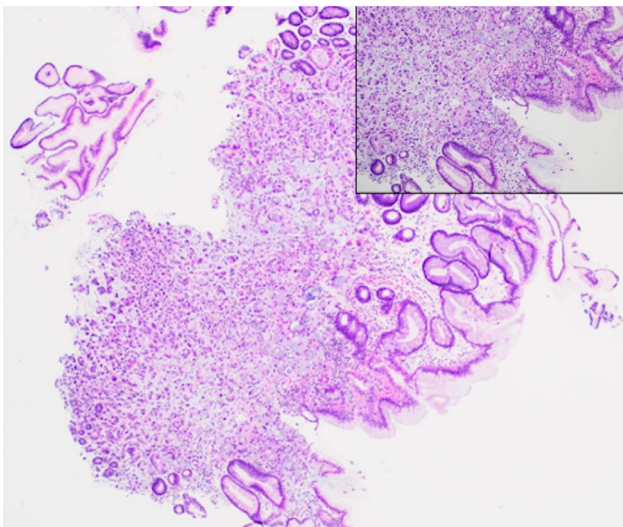


Figure 6. Gastric biopsy (hematoxylin and eosin [H&E]) showing invasive signet ring cell adenocarcinoma (4 \times objective, 40 \times magnification); inset shows signet ring cell adenocarcinoma on high power magnification (100 \times).

Orchialgia, as seen in our patient's presentation, and painless hemiscrotal swelling or sensation of heaviness are infrequent presenting symptoms relative to the common gastrointestinal upset seen in SRCA.^{11,12} This mimics a primary testicular neoplasm; thus, the differential should include germ cell and sex cord tumors in addition to secondary neoplasms.¹⁴ Scrotal ultrasound was evident for a testicular mass in our patient. The histopathological examination showed SRCA with a positive CK profile (CK7, CK20, and CK AE1/AE3) strongly suggesting origination from the upper gastrointestinal tract.¹⁵ Esophagogastroduodenoscopy with biopsies of the gastric and gastroesophageal ulcerations confirmed primary SRCA. Endoscopic ultrasound further demonstrated diffuse regional lymph node involvement.

Testicular metastasis is rarely documented because of the protective blood-testes barrier and lower temperature in the testicles.¹⁶ However, retrograde lymphatic drainage can occur because of the intersection of the gastric and testicular lymphatic channels at the para-aortic lymph node station as exhibited by retroperitoneal lymphadenopathy in the initial CT scan of our patient. Transperitoneal seeding is another

possible pathway in our patient, given metastatic implantation of the peritoneum.¹⁷

LM is defined as the spread of cancer to the cerebrospinal fluid, which is found in about 5%–8% of patients with cancer and 0.06%–0.24% specifically in gastric cancer.¹⁸ Headache followed by nausea and vomiting are frequent presenting symptoms in patients with gastric leptomeningeal carcinomatosis.¹⁹ SRCA on cytology confirmed LM in our patient.

Perineural invasion has emerged as a possible mechanism of LM in primary gastrointestinal cancer and may have been a mechanism of metastasis in this case, given cauda equina nerve root involvement.²⁰ Intrathecal methotrexate, radiotherapy, and systemic chemotherapy have been attempted as treatment with limited and variable survival duration ranging from 1 to 10 months.¹⁹ Unfortunately, the declining performance status of our patient limited his prognosis, and thus, supportive care remained our mainstay treatment plan.

In this report, we present a young patient afflicted with gastric SRCA with the rare complication of testicular and LM. Secondary testicular malignancy such as gastric SRCA should be considered in the differential diagnosis of persistent inguinal and testicular pain. New neurological symptoms in the setting of gastric SRCA should trigger clinical suspicion for possible metastasis to the leptomeninges.

DISCLOSURES

Author contributions: All persons listed have met all 4 criteria for authorship per ICMJE guidelines including providing substantial contribution to the intellectual content of the case report, critically reviewing each draft, approving the final version of the report, and holding accountability for accuracy and integrity of the work. H. Shariff is the article guarantor.

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REFERENCES

- Benesch MGK, Mathieson A. Epidemiology of signet ring cell adenocarcinomas. *Cancers*. 2020;12(6):1544.
- Ferlay J, Ervik M, Lam F, et al. *Global Cancer Observatory: Cancer Today*. International Agency for Research on Cancer: Lyon, France (<https://gco.iarc.who.int/media/globocan/factsheets/cancers/7-stomach-fact-sheet.pdf>). (2024). Accessed March 28, 2024.
- Bamboato ZM, Tang LH, Vinuela E, et al. Stage-stratified prognosis of signet ring cell histology in patients undergoing curative resection for gastric adenocarcinoma. *Ann Surg Oncol*. 2014;21(5):1678–85.
- Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76(2):182–8.
- Otsuji E, Yamaguchi T, Sawai K, Takahashi T. Characterization of signet ring cell carcinoma of the stomach. *J Surg Oncol*. 1998;67(4):216–20.
- Ha TK, An JY, Youn HK, Noh JH, Sohn TS, Kim S. Indication for endoscopic mucosal resection in early signet ring cell gastric cancer. *Ann Surg Oncol*. 2008;15(2):508–13.
- Wanebo HJ, Kennedy BJ, Chmiel J, Steele G, Winchester D, Osteen R. Cancer of the stomach: A patient care study by the American College of Surgeons. *Ann Surg*. 1993;218(5):583–92.
- Kim JP, Kim SC, Yang HK. Prognostic significance of signet ring cell carcinoma of the stomach. *Surg Oncol*. 1994;3(4):221–7.
- Honoré C, Goéré D, Messenger M, et al. Risk factors of peritoneal recurrence in eso-gastric signet ring cell adenocarcinoma: Results of a multicentre retrospective study. *Eur J Surg Oncol*. 2013;39(3):235–41.
- Moldovan TR, Căinap C, Fekete Z, et al. Signet ring cell gastric carcinoma with breast and leptomeningeal metastases: A case report. *Med Pharm Rep*. 2022;95(1):88–91.
- Li B, Cai H, Kang ZC, Wu H, Hou JG, Ma LY. Testicular metastasis from gastric carcinoma: A case report. *World J Gastroenterol*. 2015;21(21):6764–8.
- Schaefer IM, Sauer U, Liwocha M, Schorn H, Loertz H, Füzesi L. Occult gastric signet ring cell carcinoma presenting as spermatic cord and testicular metastases: “Krukenberg tumor” in a male patient. *Pathol Res Pract*. 2010;206(7):519–21.
- Lee JL, Kang YK, Kim TW, et al. Leptomeningeal carcinomatosis in gastric cancer. *J Neurooncol*. 2004;66(1-2):167–74.
- Albers P, Albrecht W, Algaba F, et al. EAU guidelines on testicular cancer: 2011 update. *Eur Urol*. 2011;60(2):304–19.
- Terada T. An immunohistochemical study of primary signet-ring cell carcinoma of the stomach and colorectum: I. Cytokeratin profile in 42 cases. *Int J Clin Exp Pathol*. 2013;6(4):703–10.
- Wang G. Metastatic carcinoma to the testis—a mini review. *J Rare Dis Res Treat*. 2019;4(2):16–22.
- Young JJ, Pahwa A, Patel M, et al. Ligaments and lymphatic pathways in gastric adenocarcinoma. *RadioGraphics*. 2019;39(3):668–89.
- Rogers LR. Neurologic complications of cancer, 2nd ed. *Neuro Oncol*. 2009;11(1):96–7.
- Oh SY, Lee SJ, Lee J, et al. Gastric leptomeningeal carcinomatosis: Multi-center retrospective analysis of 54 cases. *World J Gastroenterol*. 2009;15(40):5086–90.
- Kokkoris CP. Leptomeningeal carcinomatosis: How does cancer reach the pia-arachnoid? *Cancer*. 1983;51(1):154–60.

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