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Case Report

Ileal signet-ring cell carcinoma with brain metastases: A case report

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ABSTRACT

Background: Signet-ring cell carcinoma (SRCC) is a rare subtype of adenocarcinoma that frequently originates in the stomach. Uncommonly, this tumor can lead to brain metastases; an event rarely reported in the literature.

Case Description: A 76-year-old man with a history of cognitive impairment was diagnosed with two brain space-occupying lesions. A whole-body 18F-FDG PET/computed tomography scan revealed a hypermetabolic lesion in a segment of the ileum corresponding to mural thickening and an ulcerated lesion detected on colonoscopy. A brain biopsy, using an immunohistochemistry protocol, showed signet-ring cells with a pattern that suggested an intestinal origin. The diagnosis of SRCC brain metastases with an ileal origin was made, and a treatment protocol was designed. However, the patient rapidly deteriorated, and passed away shortly afterward.

Conclusion: To the best of our knowledge, this is the first case report of an ileal SRCC with brain metastases.

Keywords: Adenocarcinoma, Brain metastases, Ileum, Signet-ring cell, Small bowel

INTRODUCTION

Signet-ring cell carcinoma (SRCC) is an aggressive and rare type of adenocarcinoma, most frequently found in the stomach.[2,3,5,13,14,17] The characteristics of this carcinoma when located in the digestive tract (poor differentiation,[5] bowel wall thickening with absence of an obstructing intraluminal mass,[17] mucosae ulcerations,[17] and propensity for lymphovascular invasion and peritoneal seeding[4]) make this tumor an aggressive variant that can be easily misdiagnosed as Crohn's Disease.[1,3,5,14,17] This consequently delays an adenocarcinoma diagnosis, leading to metastases, that have in fact, in several cases, been reported as the first identified lesions in the setting of an unknown or recurrent cancer.[2,7] Thus, SRCC often presents at an advanced stage and lends a poor prognosis.[4,5,13] The literature has quoted a 5-year survival rate of 9.1% for those diagnosed with SRCC of the colorectum, though this percentage is largely influenced by tumor stage.[4]

Metastatic sites commonly reported in the literature are the liver, lungs, bones, and lymphatics.[17] Metastasis to the central nervous system is rare, occurring in an estimated 1.6% of cases of the primary SRCC of the colon,[16] and an estimated 1.1% of cases of the primary SRCC of the small bowel, as documented in a case series.[18]

The aim of this article is to present the rare case of a patient with brain metastases in the setting of a primary SRCC of the ileum, as well as to assess, by a search for similar cases in the literature, the particularity of such an occurrence.

CASE DESCRIPTION

Herein, we present the case of a 76-year-old man with no clinical history other than well-controlled arterial hypertension, who came to the emergency department accompanied by his daughter, after a 20-day period of progressive cognitive impairment, characterized by forgetfulness, and decreased attentional capacity. Initial physical and neurological examination was notable for confusion, as the patient was not oriented to time nor space. No other clinical signs were detected.

A computed tomography (CT) brain scan [Figure 1] was performed, showing two brain-occupying lesions; one located in the right frontal lobe, and the second in the left basal ganglia, both with peripheral contrast ring-enhancement, and vasogenic edema, suggesting brain metastases as the most likely diagnosis.

The patient was subsequently admitted and administered IV corticosteroids (Dexamethasone 4 mg/8 h) for symptomatic treatment. As he had no known medical or family history of an oncologic disease, the detection of a possible primary tumor, once the patient was stabilized, became the priority. A whole-body CT and a 18F-FDG PET/CT scan were performed [Figure 2]. The whole-body CT scan showed mural thickening extending 30 mm at the level of distal ileum, close to the ileocecal valve [Figure 2a]. The PET/CT showed a significant pathologic uptake of 18F-FDG, represented by a 10.2 SUV_{max} (Maximum Standardized Uptake Value) at the same site of detected mural thickening [Figures 2b and c]. A diagnostic colonoscopy was performed, revealing an ulcerated and mural-engrossed ileal segment [Figure 3], corresponding to the location of mural thickening and increased 18F-FDG uptake noted in the aforementioned imaging. An incisional biopsy of the borders of the ulcerated lesion was made, though the pathological results were found to be indeterminate.

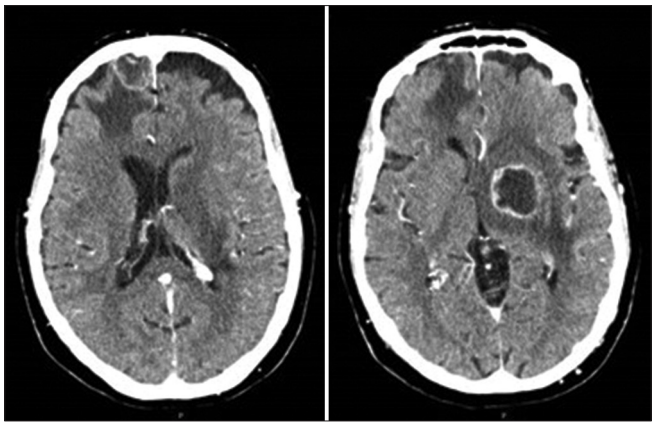

Figure 1: Computed tomography brain scan showing two (right frontal and left basal ganglia) ring contrast-enhancing brain-occupying lesions with associated vasogenic edema.

A brain biopsy was proposed and accepted by the patient and family, and planned for the next few days, after informed consent was signed. However, the patient began presenting with gait instability and a significant neurological decline, with progressive loss of strength in his right leg; thus, the brain biopsy was prioritized and performed the next day.

Surgical management

An open brain biopsy targeting the right frontal lobe lesion was performed under general anesthesia and a burr-hole was made in the bone overlying the lesion. A cruciate opening of the dura was made, exposing a gray tumor-like infiltrated cortex underneath. Macroscopic pathologic material was obtained in all directions. Adequate hemostasis was assured, and soft-tissue closure was completed without difficulty. There were no intraoperative complications and sufficient tissue was obtained for a pathology and immunohistochemistry (IHC) examination.

Pathological findings

Pathological examination showed the presence of an abundant number of signet-ring cells, with large amounts of mucin displacing the nucleus to the cell periphery, as classically described in the literature.[3] These findings are shown in [Figure 4].

The IHC analysis showed a particular pattern (CK7−, CK20+, CEA+, and CDX2+) suggestive of gastrointestinal tract origin [Figure 4].

Given the imaging and pathology findings, a diagnosis of the primary SRCC of the gastrointestinal tract with brain metastases was made, establishing the location of the primary tumor at the distal ileum.

Clinical course and outcome

A therapeutic plan for systemic chemotherapy and holocraneal radiation was proposed and discussed in a multidisciplinary committee. However, the patient's clinical and neurological status rapidly declined, and he had become aphasic, apathetic, and abulic with impairment in motor function and gait, limiting his ability to eat, bathe, or move independently. After discussion with a second multidisciplinary committee, he was transferred to a medium-stay center for palliative care and symptomatic treatment, where he died shortly thereafter. The total time course from the initial diagnosis of brain metastases to his death was 2 months.

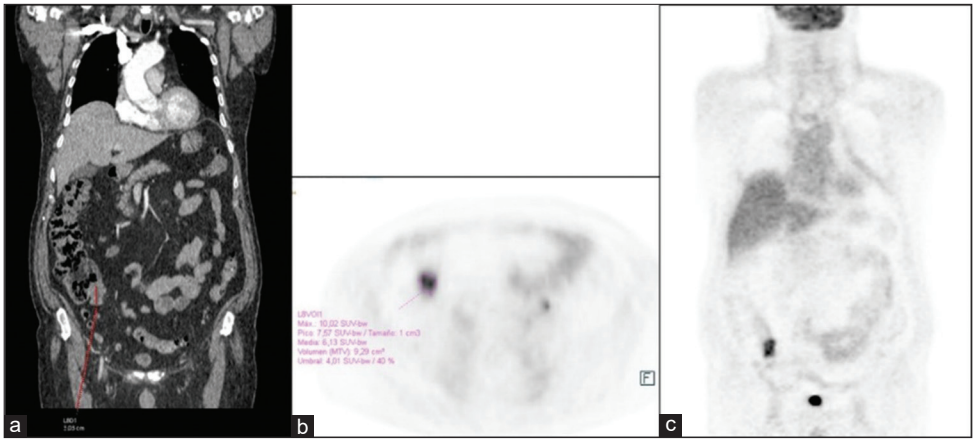

Figure 2: (a) Whole-body computed tomography (CT) scan showing mural thickening at an ileal segment (red line). (b and c) PET-CT scan showing a significant uptake at the same engrossed segment founded in CT scan. (F): Frontal.

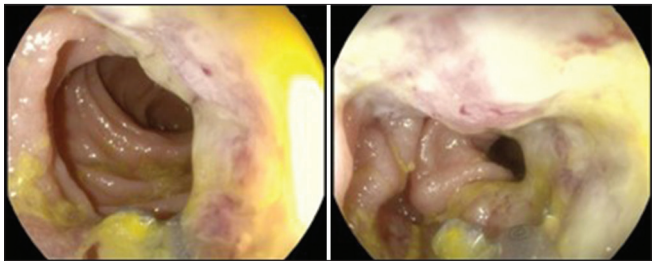

Figure 3: Colonoscopy showing mural thickening and ulcerated lesion in an ileal segment close to the ileocecal valve, corresponding to the findings in imaging.

DISCUSSION

SRCC is a rare variant of adenocarcinoma, most frequently found in the stomach,[2,3,5,13,14,17] and rarely found elsewhere.[3,14,17] This tumor typically occurs in younger patients when compared to other histologic subtypes, with a mean age of 54.3, and a slightly higher rate in males, as described when analyzing a series of patients with SRCC of the colon.[4] Other series have, however, noted a higher mean age (64 years [51–73]), as reported by Wang *et al*.[16] This tumor represents <14% of gastric cancers treated with gastrectomy and 1% of colon cancers treated with colectomy.[17] The characteristics of this carcinoma include a poor differentiation,[5] no specific and evident symptoms even at an advanced stage,[17] and propensity for invasion,[4] making this tumor a malignant variant, which can lead to metastases and often late diagnosis. Very rarely, SRCC arising in the digestive tract can lead to central nervous system metastases.[16] Locations other than the colon leading to brain metastases are even rarer and have not often been reported in the literature (an estimated 0.81%[6] and 1.1%[18] of patients with brain metastasis from gastric and small bowel SRCC, respectively, have been reported in case series). The absence of specific symptoms when such a tumor presents in the digestive tract has led to cases, in which the manifestation of metastasis from SRCC is the first detected expression of an unknown or recurrent tumor.[2,7] At this point, the disease is often at an advanced stage, with a poor prognosis,[5,13,16] as demonstrated in the case in this report.

Table 1 presents data extracted from three case reports, as well as the presented case, with the primary SRCC of the digestive tract with brain metastases.[8,12,15] In the case reported by Kobayashi *et al*.,[8] the patient presented a surveillance of 3 years and 6 months, differing from the typically short surveillance in this disease. This could be explained by the superficial mucosae affectation with no lymphatic dissemination at the time of diagnosis, receiving radical surgical treatment, followed by chemotherapy. As stated by Lee *et al*., this circumstance could confer a favorable prognosis, with a described disease specific survival rate and recurrence-free survival rate of up to 102 and 98.2 months, respectively.[9] The authors of the reported case discuss the possibility of a hematologic dissemination secondary to mucosae venule disruption and cell invasion during surgery, leading to late bone and brain metastases. In addition, the young age of the patient could have contributed to a more favorable prognosis. In contrast to series describing SRCC of the colon, Lee *et al*.[9] described in their series of 176 patients with gastric SRCC, an even younger age of diagnosis of this disease, reporting 71.6% of the patients with this diagnosis to be under 60 years of age. This is congruent with the younger age of the patient reported by Kobayashi *et al*., when compared to the other reported cases.

Two large series have been published, describing one group of patients with SRCC of the colon,[16] and a second group of patients with SRCC of the small bowel,[18] as well as presenting characteristics of tumors, as represented in Table 2 (colon) and Table 3 (small bowel). As seen in these data, both series report the tendency of this tumor to be poorly differentiated, with a small percentage of cases with metastases to the brain,

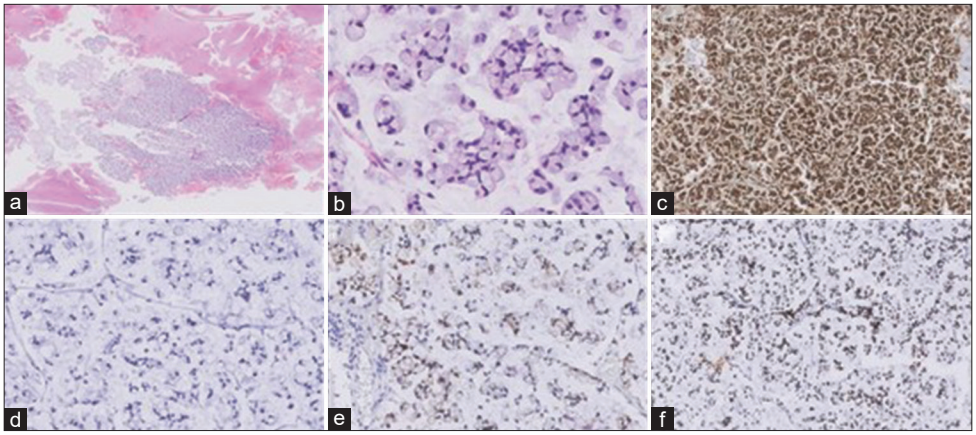

Figure 4: Brain biopsy IHQ analysis. (a) H&E ×4. b. H&E ×20. Signet-ring cells. (c) CEA ×10. (d) CK7 ×20. (e) CK20 ×20. (f) CDX2 ×10

Table 1: Demographic, clinical, tumor, and disease's characteristics of case reports including brain metastases arising from three different SRCC in digestive locations.

Articles	Location	Patient	Characteristics	Neurological symptoms	Place of metastases	Time period since diagnosis to metastases	Time to death since diagnosis
Present case	Ileum	76 y-o Male	Ulceration+ mural engrossment	Confusion+ cognitive impairment	Right frontal lobe+ left basal ganglia	Simultaneously	2 months
Matsuoka *et al*., 2013	Ampullary Duodenum	61 y-o Female	-	Left visual disturbances and left hemiparesis	Right occipital Lobe	2 years	-
Terada *et al*., 2014	Non-ampullary duodenum/ yeyunum	71 y-o Male	Ulceration	-	Multiple (Not specified)	Simultaneously	4 months
Kobayashi *et al*., 2002	Gastric	40 y-o Female	Ulceration+fold convergence	Nausea, vomiting, diminished visual acuity	Multiple (Not specified)	-	3 years and 6 months

"-" when not specified. SRCC: Signet-ring cell carcinoma

Table 2: Characteristics of SRCC of the colon extracted from a series in Wang *et al*., 2020.[16]

Article	Patients' characteristics	Location primary tumor	Tumor grade	Site of metastasis (% of all metastases in each location)	Treatment	3-year overall survival (unique metastasis)
Wang *et al*., 2020	64 (51–73) years 56.03% Male, 43.97% Female	64.89% Proximal Colon 23.94% Distal Colon 11.17% Other	0.71% Well differentiated (I) 3.19% Moderately differentiated (II) 71% Poorly or undifferentiated (III/IV)	20.57% Liver 6.9% Lung 7.27% Bone 1.60% Brain	Surgery 56.74% No surgery/ Unknown 43.26% Chemotherapy 63.30% No Chemotherapy/ Unknown 36.70%	Liver 26.8% (95% CI, 25.8–27.8%) Lung 34.0% (95% CI, 29.9–38.1%) Bone 21.6% (95% CI, 10.8–32.5%) Brain 14.0% (95% CI, 3.6–24.4%)

SRCC: Signet-ring cell carcinoma, CI: Confidence Interval

a poor prognosis, and an overall survival rate reduced in the case of brain metastases (14% in a 3-year period in SRCC of the colon).

When comparing characteristic of primary small bowel SRCC to other adenocarcinomas in this location, poor differentiation, local invasion, lymph node metastases, and

Table 3: Characteristics of small bowel SRCC, extracted from a series in Zhou *et al*., 2021.[18]

Article	Patients' characteristics (Age and Sex)	Location primary tumor	Tumor grade	Site of metastasis (% of all patients with metastases in each location)	Treatment	1-,3-,5-years disease-specific survival (time from diagnosis to death due to SRCC)
Zhou *et al*., 2021	≤40 years 6.2% 40–50 years 16.5% 50–60 years 21.6% 60–70 years 27.3% >70 years 28.4% 52.8% Male, 47.2% Female	47.7% Duodenum 7.4% Jejunum 30.1% Ileum 0.6% Meckel Diverticulum 0.6% Overlapping 13.6% NOS	0%Well differentiated 2.8% moderately differentiated 76.7% Poorly or undifferentiated (III/IV) 20.5% Unknown	0.6% Bone 1.1% Brain 2.8% Liver 1.1% Lung	Surgery 68.2% No surgery 31.8% Radiotherapy 9.1% No Radiotherapy 90.9% Chemotherapy 54.5% No Chemotherapy/ Unknown 45.5%	58.9% (1 year) 21% (3 years) 15.3% (5 years)

SRCC: Signet-ring cell carcinoma

distant metastases were more likely in SRCC. The treatment for this aggressive variant includes surgery and chemotherapy, which, in association with M stage, have been reported to be independent predictors of survival. A minority of patients receive radiotherapy, but this treatment modality has not been associated with increased survival in this histological variant.[18]

As previously mentioned, few cases of brain metastases secondary to SRCC of digestive tract origin have been reported in the literature, with a small percentage of cases of brain metastases documented in series involving SRCC of the colon and small bowel.[16,18] Several cases of leptomeningeal metastasis have been reported, with rapid neurological deterioration.[2,10] Other than colon;[16] gastric,[6,8,9] ampullary,[12] non-ampullary duodenum, and proximal jejunum[15] SRCC with brain metastases have been reported, though noted to be exceedingly rare [Table 1]. However, there have been no reports to this date of intracerebral metastasis arising from SRCC of ileal origin – a very rare location for this tumor. To the best of our knowledge, this is the first case report of such an occurrence.

The patient in this reported case initially presented with neurological symptoms as a manifestation of a previously unknown metastatic lesion. Macroscopic analysis of the intestinal tumor in this case (see "Case Description") revealed characteristics in line with the ones described previously, making this lesion easily misdiagnosed as Chron's Disease.[1,3,5,14,17] In addition, PET imaging revealed increased ileal uptake represented by 10.2 SUV_{max}. These levels are particularly similar to those described previously in ileal SRCC imaging findings (11 SUV_{max}).[14] When analyzing this type of tumor microscopically, negative or unconclusive biopsies from SRCC of the digestive tract have been reported, requiring several colonoscopies and repeat biopsies to achieve a final diagnosis,[1,11] and thus suggesting the need for special attention to biopsy technique (deep-tissue biopsies).[14] This may explain the indeterminate intestinal biopsy in this patient's case. In contrast to the intestinal biopsy findings, microscopic analysis of the metastatic brain lesion showed abundant signet-ring cells [Figure 4b], with a positive CK20 and negative CK7 in IHC analysis. CK20+/CK7− is the most frequent IHC pattern found in adenocarcinoma of the bowel, especially in colorectal cancer (75–94%), and reported in up to 43% of patients with small intestinal adenocarcinoma.[13] These findings, in addition to a positive CDX2, a marker found to be positive in up to 70% of small bowel adenocarcinomas,[13] are highly suggestive of intestinal, specifically small bowel, origin.

Given the combination of clinical, radiologic, and pathological findings, the diagnosis of brain metastases from a primary ileal SRCC was established.

Limitations

The most notable limitation was an inconclusive intestinal biopsy. However, as has been shown, several reports have found intestinal biopsies to be negative or inconclusive more frequently than in other types of tumors.

Given the rapid decline of the patient's clinical course, retrieving repeat biopsies of the intestinal lesion and performing additional diagnostic tests were not possible. However, whole-body CT and PET/CT scans only showed pathological findings at the distal ileum.

Necropsy and post-mortem analysis were not performed.

CONCLUSION

SRCC brain metastases arising from the digestive tract, and particularly from ileal segments, are extremely rare. To the best of our knowledge, this report presents the first case of ileal-origin SRCC brain metastases.

Our analysis of different reported cases, published series and available literature, has offered us valuable information to describe this kind of tumor as an aggressive subtype with a poor prognosis. In addition, this tumor is reported to have histological similarities to Crohn's Disease, allowing for misdiagnosis. Given these findings, in cases where response to adenocarcinoma treatment is inadequate, or in an unclear workup of Crohn's Disease, suspicion for SRCC should be high. Early diagnosis and early treatment may improve the prognosis of this complex histological variant.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of our institution, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Achneck HE, Pradhan SK, Kavic SM, Longo WE. Primary signet-ring cell carcinoma mimicking segmental Crohn's colitis. Dig Liver Dis 2005;37:537-41.
2. Assi R, Hamieh L, Mukherji D, Haydar A, Temraz S, El-Dika I, *et al*. Leptomeningeal metastasis as initial manifestation of signet ring colorectal adenocarcinoma: A case report with review of literature. J Gastrointest Oncol 2015;6:E89-101.
3. Carvalho JR, Tavares J, Goulart I, Santos PM, Vitorino E, Ferreira C, *et al*. SRCC, ileal crohn disease or both?-A case of diagnostic challenge. GE Port J Gastroenterol 2018;25:47-51.
4. Chen JS, Hsieh PS, Chiang JM, Yeh CY, Tsai WS, Tang R, *et al*. Clinical outcome of SRCC and mucinous adenocarcinoma of the colon. Chang Gung Med J 2010;33:51-7.
5. Hammami MB, Aboushaar R, Musmar A, Azhar M. Ileal SRCC masked by Crohn disease. Ochsner J 2020;20:323-5.
6. Huang L, Wang L, Shi Y, Zhao Y, Xu C, Zhang J, *et al*. Brain metastasis from gastric adenocarcinoma: A large comprehensive population-based cohort study on risk factors and prognosis. Front Oncol 2022;12:897681.
7. Jarabin JA, Klivényi P, Tiszlavicz L, Molnár FA, Gion K, Földesi I, *et al*. Late simultaneous carcinomatous meningitis, temporal bone infiltrating macro-metastasis and disseminated multi-organ micro-metastases presenting with mono-symptomatic vertigo-a clinico-pathological case reporT. Ideggyogy Sz 2020;73:354-60.
8. Kobayashi M, Araki K, Matsuura K, Kawai S, Moriki T. Early gastric cancer giving rise to bone and brain metastases--a review of the Japanese literature. Hepatogastroenterology 2002;49:1751-4.
9. Lee D, Son SY, Kim YB, Han SU, Hur H. Neural invasion is a significant contributor to peritoneal recurrence in signet ring cell gastric carcinoma. Ann Surg Oncol 2018;25:1167-75.
10. Lin DM, Park JW, Gattuso P. Metastatic signet-ring cell carcinoma of the bladder in cerebrospinal fluid. Diagn Cytopathol 2017;45:73-6.
11. Lui IO, Kung IT, Lee JM, Boey JH. Primary colorectal SRCC in young patients: Report of 3 cases. Pathology 1985;17:31-5.
12. Matsuoka G, Wanifuchi H, Suzuki S, Honda K, Okada Y. A brain metastasis from ampullary carcinoma: A case report. No Shinkei Geka 2013;41:143-8.
13. Overman MJ, Pozadzides J, Kopetz S, Wen S, Abbruzzese JL, Wolff RA, *et al*. Immunophenotype and molecular characterisation of adenocarcinoma of the small intestine. Br J Cancer 2010;102:144-50.
14. Paparo F, Piccardo A, Clavarezza M, Piccazzo R, Bacigalupo L, Cevasco L, *et al*. Computed tomography enterography and 18F-FDG PET/CT features of primary SRCC of the small bowel in a patient with Crohn's disease. Clin Imaging 2013;37:794-7.
15. Terada T. SRCC of the nonampullary duodenum and proximal jejunum: A case report with an immunohistochemical study. Endoscopy 2014;46:E348.
16. Wang J, Li S, Liu Y, Zhang C, Li H, Lai B. Metastatic patterns and survival outcomes in patients with stage IV colon cancer: A population-based analysis. Cancer Med 2020;9:361-73.
17. Winter MW, Dokmak A, Marnoy Z, Sinagare S, Levy AN. Metastatic gastric signet ring cell carcinoma mimicking Crohn's disease. ACG Case Rep J 2018;5:e36.
18. Zhou YW, Xia RL, Chen YY, Ma XL, Liu JY. Clinical features, treatment, and prognosis of different histological types of primary small bowel adenocarcinoma: A propensity score matching analysis based on the SEER database. Eur J Surg Oncol 2021;47:2108-18.

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