Case report

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Colorectal Adenocarcinoma With Dedifferentiated Germ Cell Tumor Metastasis: A Case Report

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1. Abstract

The concept of neoplastic dedifferentiation describes a process in which a population of malignant cells become so undifferentiated pathologically they resemble a more primitive cell line [1]. In this case report, a 42-year-old woman presented with stage IVB colonic adenocarcinoma and markedly elevated beta human chorionic gonadotropin (β-hCG). Due to concern for pregnancy, chemotherapy was delayed, and she underwent multiple rounds of treatment for presumed ectopic and intrauterine pregnancy. Ultimately, through analysis of various pathologic samples from the primary colon mass and supraclavicular lymph nodes, it was suspected her primary colonic adenocarcinoma had dedifferentiated to resemble a germ cell tumor (GCT) capable of secreting β-hCG. During chemotherapy of her colonic adenocarcinoma component, the GCT component proliferated. Throughout treatment of her GCT component, her adenocarcinoma component proliferated. This case represents a diagnostically challenging presentation, adds to the collective knowledge of dedifferentiation of a primary tumor into germ cell morphology, and offers insight to clinicians for chemotherapy selection to target the GCT component.

2. Keywords:
Germ Cell Tumor, Colonic Adenocarcinoma, Dedifferentiation

3. Introduction

In the literature there are few reports of colonic adenocarcinoma with germ cell tumor components [1-4]. This is a rare malignancy demonstrating the concept of “dedifferentiation” in which a population of neoplastic cells become so undifferentiated they display a more primitive morphology[1]. In this case we present a patient with stage IVB colonic adenocarcinoma with dedifferentiation in a portion of the metastasis that resembles a germ cell tumor (GCT). She began treatment with a chemotherapy regimen targeting colonic adenocarcinoma, during which her GCT component proliferated. During treatment of the GCT tumor population, the adenocarcinoma component proliferated. This is a unique case of a diagnostically challenging malignancy with poor prognosis requiring a high index of suspicion for implementation of the most effective chemotherapy regimen to target both cell lines.

4. Case Presentation

The patient is a 42-year-old female who presented with nausea, vomiting and an unintentional weight loss for two months. She was anemic and reported bright red rectal bleeding and melena. Chest, abdominal and pelvic computerized tomography (CT) scan revealed extensive retroperitoneal, pelvic and supraclavicular lymphadenopathy, with a thickened rectosigmoid wall mass suggestive of malignancy. A colonoscopy revealed an obstructive mass in the distal rectum, and biopsy confirmed invasive moderately differentiated colonic adenocarcinoma with classic features(Figure 1A, 1B). A fine needle aspiration (FNA) of an enlarged left supraclavicular node was performed and revealed metastatic adenocarcinoma morphologically different from the previous rectal biopsy; however, the biopsy was scant and in the setting of known primary colorectal cancerthis was thought to be compatible. The patient was officially diagnosed with stage IVB (cT4a, cN2b, cM1b) colorectal adenocarcinoma. During her pre-treatment labs, the patient was found to have an elevated beta human chorionic gonadotropin (β-hCG) level at 910 mIU/mL. A transvaginal ultrasound (TVUS) revealed no evidence of intrauterine or ectopic pregnancy; however, chemotherapy was held due

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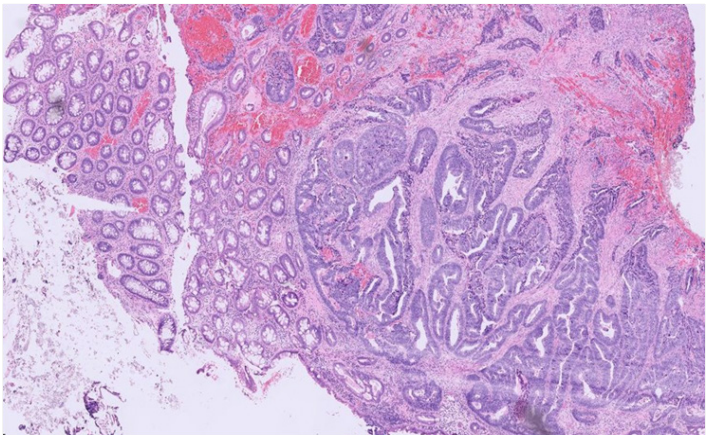
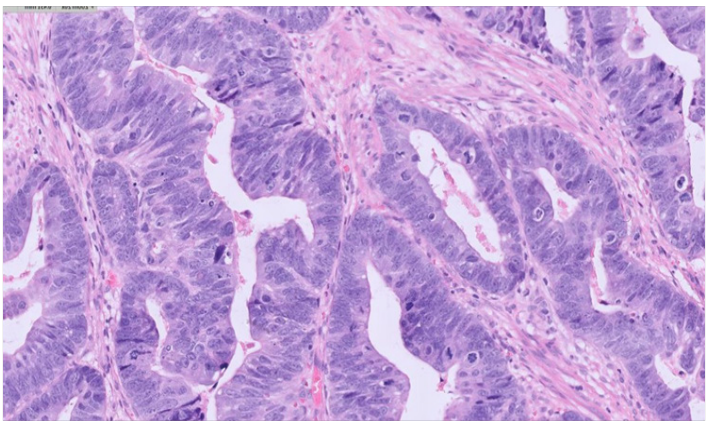
to an upward trend of β-hCG to 1,288 mIU/mL.

Figure 1: Rectal Biopsy. A) Tumor shows morphology typical of colonic adenocarcinoma. Here there is normal colonic epithelium to the left, with a submucosal infiltrate of adenocarcinoma on the right. There is focal cribriform glandular architecture and marked desmoplasia. B) Higher power view of colonic tumor, showing typical morphology (hyperchromatic, pseudostratified nuclei). No immunohistochemical stains were performed, as tumor morphology is classic for colonic adenocarcinoma.

1A

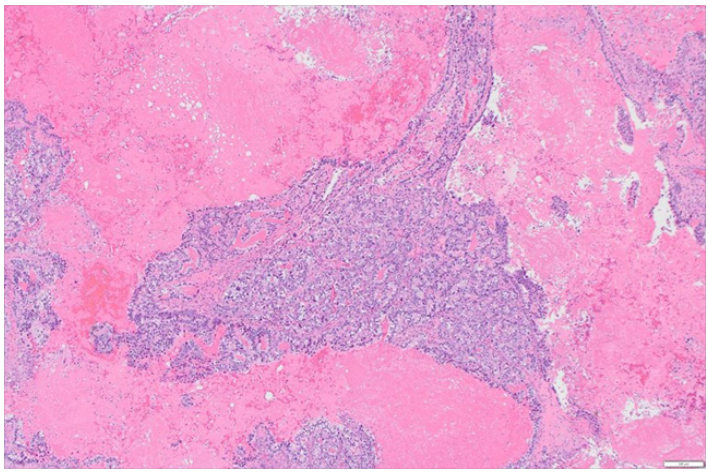


1B

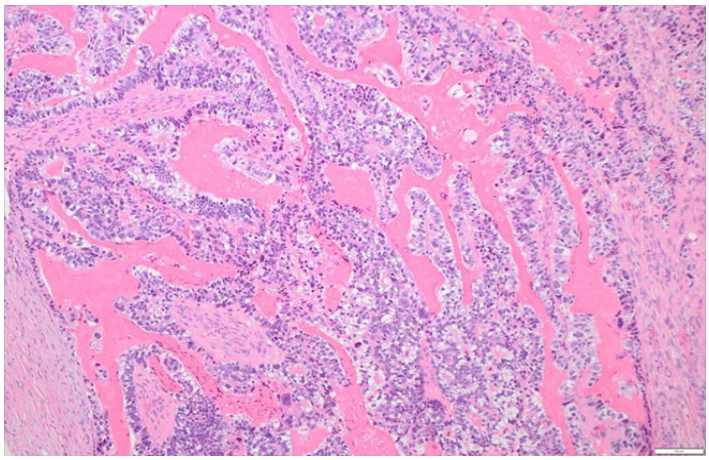


The patient underwent a suction dilation and curettage (D&C) procedure for diagnostic and therapeutic intervention. Surgical pathology revealed no evidence of intrauterine pregnancy. The patient's β-hCG continued to rise to 1,965 mIU/mL after the D&C and a repeat TVUS again revealed no ectopic pregnancy. For further investigation, a β-hCG stain of the supraclavicular lymph node FNA tissue and colonic tissue were performed with negative results. The patient did not want to delay cancer treatment;therefore, she decided to receive a dose of methotrexate for treatmentof a pregnancy of unknown location (PUL). Following methotrexate administration, her β-hCGwas 1,804 mIU/mL on day four and 1,545 mIU/mL on day seven, which is considered an inadequate decrease. Her left supraclavicular lymph node FNA was re-evaluated with additional immunostainsto assess for a second primary tumor. The tissue was negative for chromogranin and synaptophysin, and again stained only for CDX-2 and SATB2. After thorough review, the lymph node was determined to be morphologically different than the rectal specimen; however,there was no definitive evidence of a second primary. At this time, her clinical presentation was thought to be paraneoplastic β-hCG secretion from her colorectal cancer despite a negative stain. She received cycle 1 of leucovorin calcium (folinic acid), fluorouracil, oxaliplatin (FOLFOX) and panitumumab with an initial serum carcinoembryonic antigen test (CEA) measuring 276 ng/ml. Prior to cycle 2 of FOLFOX + pantitumumab, the patient's treatment was halted due to a spike in β-hCG to 3,414 mIU/mL. Her CEA following cycle one of chemotherapy measured 376 ng/ml. Due to the previously scant FNA of the lymph node, an excisional supraclavicular lymph node biopsy was performed which revealed a poorly differentiated malignancy with glandular features, abundant clear cytoplasm with subnuclear vacuoles (Figure 2A, 2B).

2A



2B



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The patient's elevated beta-hCG raised the possibility of a germ cell tumor, and morphologic findings were suggestive of a glandular pattern of yolk sac tumor (Figure 2C).

2C

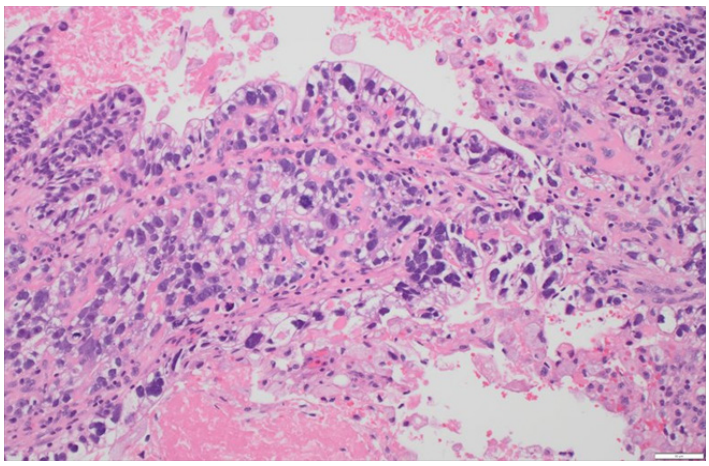
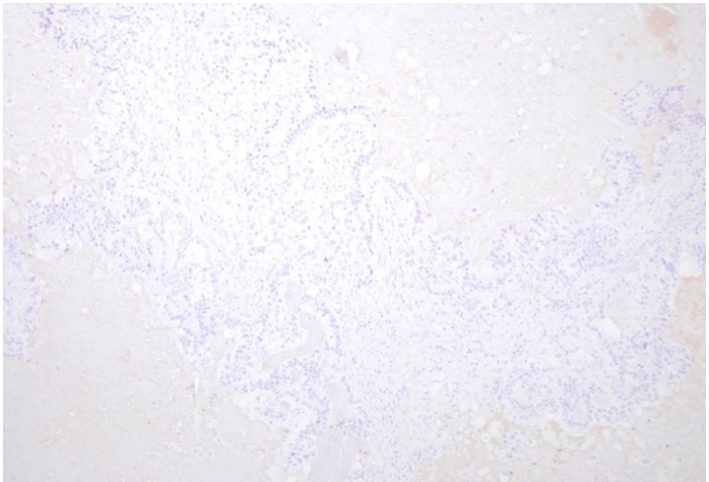


Figure 2: Lymph Node Excisional Biopsy. A) Tumor within left neck level IV lymph nodeshows different morphology. B) Tumor cells have abundant clear cytoplasm with subnuclear vacuoles. C) There are intermixed pleomorphic nuclei, some with prominent nucleoli. In this setting of elevated b-HCG, morphologic findings are suggestive of a glandular pattern of yolk sac tumor.

The tumor showed a non-specific staining pattern, precluding a definitive subclassification. Importantly, it was negative for germ cell / yolk sac tumor markers (SALL4, AFP, PLAP; only very focal glypican 3) (Figure 3A, 3B).While it did stain for CDX-2 and showed weak staining for SATB2, markers of gastrointestinal tumor, it was predominantly negative for CK20, a common marker of colonic adenocarcinoma. As the tumor bore no morphologic similarity to herprior rectal mass, a second primary was favored at this timeIn the setting of an elevated b-HCG,it was thought to be a GCT.

3A



3B

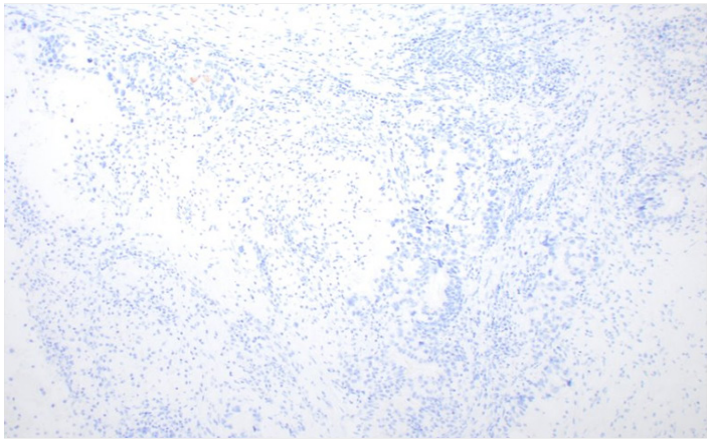


Figure 3: Lymph node excisional biopsy immunostains, A) Negative SALL4 immunostain. B) Negative AFP immunostain

The patient was referred to gynecology oncology and she was scheduled for etoposide and cisplatin chemotherapy for a presumed retroperitoneal mixed germ cell tumor with supraclavicular metastasis. Prior to initiating etoposide/cisplatin (EP) therapy, various cancer tumor markers were obtained which were all elevated including β-hCG 4,372 mIU/mL, alpha fetoprotein (AFP) 821 ng/mL, cancer antigen 19-9 (CA 19-9) 106 U/mL and CEA 65.8 ng/mL. On Cycle 1 day 2 of EP therapy, the patient developed a large bowel obstruction and was admitted for a diverting colostomy. Prior to cycle 2 , her β-hCG fell to 94.4 mIU/mL, however her AFP elevated to 1,875 ng/mL.After cycle 3 , her β-hCG rose to 123 mIU/mL and a follow-up CT scan revealed progression of retroperitoneal and pelvic adenopathy, therefore EP was stopped.During this time, next generation sequencing of both the colon and lymph node biopsies returned, which revealed APC and p53 mutations at the same location, tumor mutation burden low and microsatellite stability. Ultimately, her cancer was thought to be a stage IV colonic adenocarcinoma, in which a portion of the metastasis de-differentiated with primordial regression and secreted β-hCG.

The patient was switched to folinic acid, fluorouracil and irinotecan (FOLFIRI) and panitumumab. After two cycles of FOLFIRI with panitumumab, CEA levels fell from 42.4 ng/mL to 17.8 ng/mL after cycle two. During her third cycle, the patient was admitted for severe back pain, bilateral pulmonary emboli and cauda equina syndrome. A pathologic lumbar spine (L5) fracture raised concerns for a new lytic metastasis. A CT scan revealed progression of disease with new pulmonary, hepatic and spinal metastasis. While admitted, her chemotherapy was held, and she received palliative radiation with 30 Gray in 10 fractions to the retroperitoneal mass and L5 lesion. During admission several tumor markers were repeated which showed her CEA fell to its lowest at 9.8 ng/mL, but a rise in both β-hCG to 223 mIU/mL, CA 19-9 to 175 U/mL and markedly elevated AFP to 9,175 ng/mL. Upon re-evaluation by her oncology team, it was suggested that her de-differentiated component

had become predominant, explaining the lack of response to FOLFIRI + panitumumab regimen. To determine her next plan of care, a fine needle aspiration of a pelvic mass was performed which revealed metastatic adenocarcinoma compatible with the primary colonic malignancy staining SATB2 and CK20 positive. In discussing her next treatment options, she developed a large bowel obstruction and had a poor performance status. Goals of care were discussed and she was ultimately discharged home with hospice care.

5. Discussion

This case is a unique presentation of acolorectal adenocarcinoma in which a portion of the metastasis regressed into germ cell tumor morphology. This concept has been described in the literature beforeand is termed "dedifferentiation", "neometaplasia" or "retrodifferentiation" [1].The terms refer to a process in which a subpopulation of rapidly dividing neoplastic cells lose differentiation of the original tumor and adopt both the morphology and immune profile of a different tumor cell line, often of a germ cell tumor [1]. This concept was first described by Pick in 1926 who proposed that neoplastic cells maintain totipotentiality as they contain the entire genome [2]. Due to the instability in the structure and function of the genome in neoplastic cells, they are able to express a more primitive phenotype [2]. This patient's clinical course began with three identified areas of malignancy: rectosigmoid colon, retroperitoneal lymph nodes and the left supraclavicular lymph node, each representing a unique subset of neoplastic cells. Initially, all three sites were presumed to be the primary or a metastasis of colonic adenocarcinoma as seen in the colonic mass pathology. Notably, the sample of cells from both the colon mass and supraclavicular node did not stain positive for β-hCG. After excluding pregnancy and a cycle of FOLFOX, β-hCGspiked to 3,414 mIU/mL.This likely represented a separate population of cells secreting β-hCGthat were not well targeted by the FOLFOX regimen. When the excisional biopsy of the supraclavicular node bore no resemblance to the primary CRC and had a morphology favoring a germ cell tumor, a second primary tumor was initially entertained and EP therapy was initiated.After 3 cycles of EP, her CT revealed progression of retroperitoneal lymph nodes despite improvement in the b-HCG tumor marker (β-hCG fell to 129mIU/mL from 4372 mIU/mL). This suggests a portion of the tumor was responding to EP therapy while the retroperitoneal metastasis progressed. Interestingly, the first recorded AFP was extremely elevated at this time to 2,901 ng/mL,which continued to rise with each round of chemotherapy thereafter and may be representative of further undifferentiated germ cell tumor.

The patient had a partial response to FOLFIRI therapy, with CEA levels falling to their lowest at 9.8 ng/ml; however, β-hCG and AFP rose again to 223mIU/mL and 9,175 ng/mL respectively and she developed new pulmonary, hepatic and spinal metastasis. At this pointher tumor became predominantly germ cell, making it unresponsive to the FOLFIRI. In summary, with colorectal targeted chemotherapy the dedifferentiated neoplastic GCT-like cells did not respond, evidenced by rising β-hCGor AFP, while with germ cell tumor directed therapy, the colorectal cells did not respond, evidenced by worsening retroperitoneal disease andrising CEA levels. On a diagnostic level, this case was unusually difficult due to the nonspecific immune and histochemical staining seen in the various biopsies, and the rapid evolution of mutation in the patient's neoplastic cells. Even with extremely elevated serumβ-hCG, none of her tissue biopsies stained positive for this marker throughout her treatment. The concept of dedifferentiation helps explain the development of a germ cell tumor morphology from a classic appearing colorectal carcinoma. In this case, dedifferentiation of a primary colorectal tumor is supported by the non-specific immunostaining of the lymph node and the identical mutations noted on next generation sequencing of the colorectal and lymph node biopsies.

Few other case reports detail a similar evolution. Otani et al. describes a female patient with recurrent colorectal carcinoma and a yolk sac component with widespread metastasis [3]. This tumor was positive for β-hCGand displayed characteristic Schiller-Duval bodies in addition to the solid carcinoma-like cells[3]. Genetic sequencing of this patient's original colorectal cancer and the recurrent pelvic tumor exhibited monoclonality, confirming that the yolk sac tumor component arose from the colorectal adenocarcinoma [3]. This conclusion supports the idea of dedifferentiation; the colonic cells became so undifferentiated they pathologically resembled a germ line tumor, in this case, ayolk sac tumor. In a second case described by Kawahara et. al., a male patient developed primary colorectal carcinoma with germ cell tumor components and germ cell tumor metastasis [1]. Within the same surgical specimen resected from the cecum were two distinct populations of neoplastic cells: the colorectal carcinoma demonstrating classic CDX-2 and p53 mutations, a transitional zone of mixed morphology, anda germ cell component demonstrating CDX-2, p53 as well as β-hCGand AFP staining [1]. The authors describe the malignancy as a "combination tumor" demonstrating dedifferentiation of colonic neoplastic cells into a more "primitive phenotype" with GCT characteristics [1]. In a case described by Boyce et. al. a 26-year-old female patient presented with primary colonic adenocarcinoma with multiple hepatic metastasis and profoundly high β-hCG [4]. Like the patient presented in this case, she was initially presumed to have an ectopic pregnancy and received multiple doses of methotrexate after episodes of rectal and vaginal bleeding [4]. When her β-hCG elevated to 101,290 mIU/mL she underwent a CT scan which revealed a colonic mass and hepatic metastasis. Pathology of the colonic mass demonstrated colonic adenocarcinoma cells with choriocarcinoma cells staining positive for β-hCG [4]. Similarly, in a case by Petricek et al., a 29 year-old male presented with colonic adenocarcinoma with hepatic germ cell metastasis, with yolk sack and choriocarcinoma morphology [2]. During autopsy, pathology of the rectal mass demonstrated classic adenocarcinoma elements and undifferentiated areas staining positive for β-hCG and AFP[2].

In all four of these cases, a transition zone was identifiablewithin one pathology specimen; the carcinoma cells became more undifferentiated and stained positive for germ cell components. The identification of

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thetransition zone supports the idea of dedifferentiation as a sequential process occurring due to the genetic instability of the neoplasm. In our case, there was no discernable transition zone identified in any of the surgical specimens. None of the tissue sampled included a germ cell and adenocarcinoma element within the same specimen. Despite the lack of a clear transition zone and a biopsy containing both types of malignancy, this case is interpreted as dedifferentiation due to next generation sequencing showing APC and p53 mutations at the same location in the primary tumor and lymph node metastasis.

As with many germ cell malignancies, these cancers tend to be more aggressive than traditional colonic adenocarcinomas with average survival around 8 months [4]. Of the cases described, only one patient was found to respond well to therapy and was alive at the time of publication [4]. This patient, described by Boyd et. al., was 26 years old at the time of diagnosis and was initially treated with FOLFOX. After further pathologic review of the primary mass and hepatic metastasis revealed choriocarcinoma, she was transitioned to etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine (EMA/CO) to target the germ cell component.She responded rapidly to this regimen and was eventually switched back to FOLFOX with bevacizumab. She had mild progression at one year and therefore transitioned to FOLFIRI with bevacizumab, with good response at the time of publication. Patients treated with prompt initiation of chemotherapy targeting the germ cell component, specifically with EMA/CO in Boyd et. al., rather than targeting the adenocarcinoma component had longer survival [4]. Currently there are no identified genetic drivers of the development of a combination type GCT and adenocarcinoma.

6. Conclusion

This is an interesting case of metastatic colorectal carcinoma with a portion of the metastasis undergoing dedifferentiation into germ cell tumor morphology, secreting b-HCG and AFP with no identifiable transition zone despite multiple biopsies. The tumor cells with germ cell morphology did not respond to colorectal directed therapy and the tumor cells with colorectal morphology did not respond to germ cell tumor directed therapy.

Further investigation needs to be done to investigate a regimen that can treat both classic colorectal morphology and the dedifferentiated metastasis. In addition to exploring treatment regimens, further research into the drivers of dedifferentiation or other factors contributing to the development of a combination GCT and adenocarcinoma malignancy is warranted.

7. Patient Consent Statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial team upon request.

References

1. Kawahara M, Takada A, Tachibana A, Kodama T, Kobayashi H, Takino Y, et al. Germ cell tumor of the colon with an adenocarcinomatous component. International Journal of Clinical Oncology. 2009;14:537-40.
2. Petricek CM. Colonic Adenocarcinoma Metastasizing as a Germ Cell Neoplasm: A Case Report and Review of the Literature. Archives of Pathology & Laboratory Medicine. 2001;125:558-61.
3. Otani T, Kanemura H, Kimura M, Mitani S, Takeda M, Matsuki M, et al. Yolk Sac Tumor in a Recurrence of Colonic Adenocarcinoma With Shared Mutations in APC and TP53 Genes: A Case Report. Int J Surg Pathol. 2022;30:646-51.
4. Boyce J, Tawagi K, Cole JT. Primary colon adenocarcinoma with choriocarcinoma differentiation: a case report and review of the literature. J Med Case Rep. 2020;14:220.