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REVEALING THE UNANTICIPATED: AN UNCOMMON CASE OF COLORECTAL ADENOCARCINOMA TRANSITIONING TO CHORIOCARCINOMA - A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Choriocarcinomas are uncommon tumors, with non-gestational types occurring in both males and females. Primary choriocarcinoma of the colon is extremely rare. It presents significant diagnostic and therapeutic challenges due to its aggressive nature and poor prognosis, with no cure available, and a mean survival of 8 months. This case report describes a 48-year-old woman who presented with abdominal pain and an ovarian mass, initially suspected to be ovarian cancer. Further workup showed a primary tumor in the colon, with extension to the ovary and liver metastasis. The pathology findings confirmed the presence of colorectal adenocarcinoma with choriocarcinomatous differentiation, as indicated by immunohistochemistry. The patient initially responded to the cisplatin/etoposide regimen; however, she relapsed shortly after. The patient received additional treatments with pembrolizumab, paclitaxel, and olaparib, which resulted in partial remission. Despite challenges during treatment, such as suspected uveitis related to immune-checkpoint inhibitors and potential interference of antibodies with beta-human chorionic gonadotropin (β-hCG) testing, the patient maintained a good performance status for over 1.5 years after being diagnosed. The case emphasizes the difficulties in treating choriocarcinomas, primarily because of their aggressiveness and the absence of standardized therapy. Our goal with this case is to draw multidisciplinary attention to this rare condition. Further studies are necessary to comprehend its clinical characteristics, prognosis factors, molecular markers, and treatment approaches. Such studies may be crucial in establishing targeted and personalized therapy.

KEYWORDS

Colorectal cancer, adenocarcinoma, non-gestational choriocarcinoma, PD-L1

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LEARNING POINTS

- Primary choriocarcinoma of the colon is rare and often misdiagnosed due to its atypical presentation, complicating timely and accurate diagnosis.
- The aggressive nature of this tumor and lack of standardized therapy necessitates a multidisciplinary approach and personalized treatment plans, especially following relapse.
- Molecular profiling guided the use of immunotherapy, which showed potential but also presented challenges, highlighting the need for further research in treating this rare malignancy.

INTRODUCTION

There are two forms of choriocarcinoma: gestational and non-gestational. The most common presentation is gestational type[1,2]. Non-gestational choriocarcinomas are extremely rare and can develop in females and males in the gonads or midline structures with pluripotent germ cells. They are rarely found outside of the gonads. Their diagnostic complexity, aggressive nature, and lack of established treatment make the prognosis extremely poor, with an average survival of only 8 months[3]. Very few cases of primary choriocarcinoma of the colon are reported in the literature, and due to the rarity and aggressive nature of the disease, timely diagnosis and selecting an effective treatment are a significant challenge for clinicians[3,4].

CASE DESCRIPTION

A 48-year-old gravida 2, para 2, white woman presented with a 3-month history of abdominal pain, bloating, early satiety, and constipation that were steadily worsening. She also reported having copious foul-smelling discharge, for which she received treatment with doxycycline and metronidazole, which resulted in resolution of these symptoms. The pain worsened, for which she presented to an urgent care visit, where an ultrasound revealed a complex right ovarian mass measuring 6 x 6 cm. Her serum human chorionic gonadotropin (hCG) was also elevated at 48 mIU/ml (reference range 1-5 mIU/ml). The patient followed up with gynecology 48 hours after the initial hCG test. A quantitative β-hCG was repeated and showed a rise to 15,000 mIU/ml. A transvaginal ultrasound showed an 8 cm solid mass with multiple segments. Furthermore, carcinoembryonic antigen (CEA) and cancer antigen (CA)-125 were also mildly elevated. The patient underwent exploratory laparotomy due to a suspected malignant ovarian mass. A large tumor was found, which turned out to be located within the lumen of the colon and right ovary. Resection of the sigmoid colon, rectum, uterus, and cervix with upper vagina via radical hysterectomy and bilateral ureteral dissection was performed due to partial ureteral obstruction with end colostomy. Intraoperative margins were all negative. Tumor markers decreased rapidly in the first 72 hours post-surgery, with hCG dropping to 4,000 mIU/ml and CEA also decreasing. The pathology specimen showed colorectal adenocarcinoma with differentiation into choriocarcinoma. Immunohistochemistry (IHC) showed ER-negative, PAX8 negative, CK7 negative, CDX2 positive, CK20 positive, and beta- human chorionic gonadotropin (β-hCG) positive. In addition, computed tomography (CT) scan of the abdomen and pelvis showed multiple lesions of the liver, which are concerning for metastatic disease *(Fig. 1)*. Diagnosis of T4b, N0, M1 - adenocarcinoma of the colon with differentiation of colorectal cancer into choriocarcinoma with liver metastases was established.

The patient was started on systemic chemotherapy with cisplatin/etoposide. Furthermore, a request for PD-L1 IHC analysis was also sent. The patient achieved negative β-hCG after cycle 2 of chemotherapy, CEA decreased to 1.5 (initial value 34) and there was a decrease in the size of the liver lesion compared with the initial CT scan. A positron emission tomography (PET)/CT was done as a follow-up after cycle 4 of initial chemotherapy that showed increased radiotracer uptake within the right side of the labia and within a soft tissue density seen within the region of the pouch of Douglas that was concerning for residual neoplasm. She

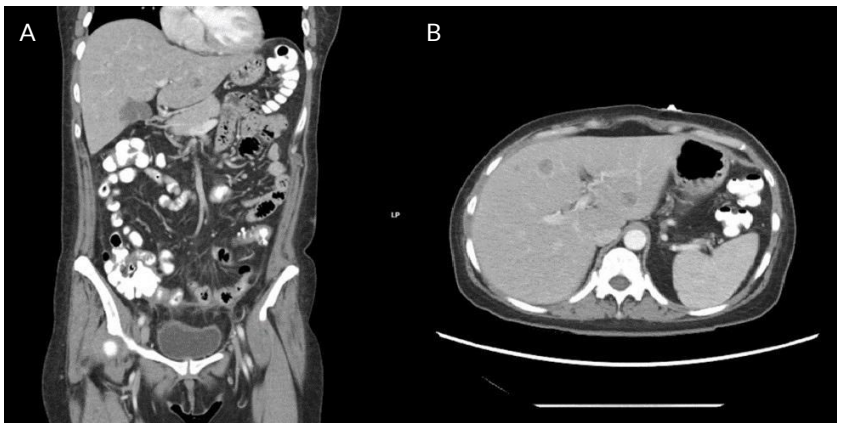

Figure 1. Computed tomography scan of the chest, abdomen, and pelvis at diagnosis confirming metastatic disease to the Liver. A) Coronal plane showing metastatic lesion in the left hepatic lobe and B) Axial plane showing metastatic lesion in the right and left hepatic lobe.

was offered to start chemotherapy with FOLFOX (folinic acid, fluorouracil, oxaliplatin), which she accepted. However, per patient preferences, this would be started after the planned colostomy reversal with flexible sigmoidoscopy and diverting loop ileostomy. The patient underwent surgery and was discharged home with no apparent complications.

Upon recovery, a CT of the chest, abdomen, and pelvis done as part of her follow-up showed a new hypodensity within the left hepatic lobe measuring approximately 2.2 x 2 cm concerning for progressive disease. Additionally, her β-hCG had risen to 11 mIU/ml.

Due to the complexity of the case in the setting of relapse after 2 months of the initial response to upfront chemotherapy, a multidisciplinary meeting was held to discuss the possibility of using other combinations. Molecular profiling showed rectal adenocarcinoma with 8% PD-L1 positive and choriocarcinoma with 50% PD-L1 positive. It was agreed to start treatment with pembrolizumab, paclitaxel, and olaparib.

The patient received 9 cycles of pembrolizumab, paclitaxel, and olaparib, achieving negative β-hCG and CEA after the first cycle. During this regimen, she developed mild peripheral neuropathy that was treated with gabapentin. In addition, pembrolizumab was held on cycles 5 and 6 due to suspected Immune checkpoint inhibitor (ICI) uveitis adverse effects, for which she received treatment initially with ophthalmic steroids, and ophthalmologic evaluation was requested. Per gynecologic oncology evaluation, molecular profiling testing showed Kirsten rat sarcoma viral oncogene homolog (KRAS) and neuroblastoma rat sarcoma oncogene (NRAS) mutated. PD-L1 30%. Tumor mutational burden (TMB) 5 mut/mb, Microsatellite instability (MSI) stable. The pathogenic variant showed a positive adenomatous polyposis coli (APC), ODICER1, and TP53. A second opinion from a specialized cancer center was recommended. She was continued on etoposide 25 mg for 21 days for metronomic therapy. Ophthalmology evaluation ruled out uveitis, and pembrolizumab was resumed. A follow-up PET/CT was performed at cycle 9 of therapy and showed a subtle increased radiotracer uptake within a mesenteric lymph node that was not seen priorly, increased radiotracer uptake within a left cervical chain lymph node, and a left hepatic lobe lesion that shows increased radiotracer uptake concerning progressive metastatic disease.

Since the patient responded well to prior platinum-based chemotherapy during her initial treatment, carboplatin was added to her regimen, which included carboplatin, paclitaxel, and pembrolizumab. Plans were to add olaparib in the future. This last one was added on cycle 3 of this line of therapy. The patient has received 8 cycles, and β-hCG over the last month has trended up, with the highest value being 64 mIU/ml; a heterophile antibody test was drawn and sent to an outside laboratory for analysis that resulted as "not detected." In addition, the urine β-hCG test was negative despite positive serum β-hCG. A new CT of the chest, abdomen, and pelvis was performed *(Fig. 2)* that reported the persistence of the lesion seen in the left hepatic lobe, which has decreased in size compared to the CT 12 months ago. The suspicion of a heterophile antibody remains, for which further discussion is ongoing to see if there is a better, more extensive test to investigate this.

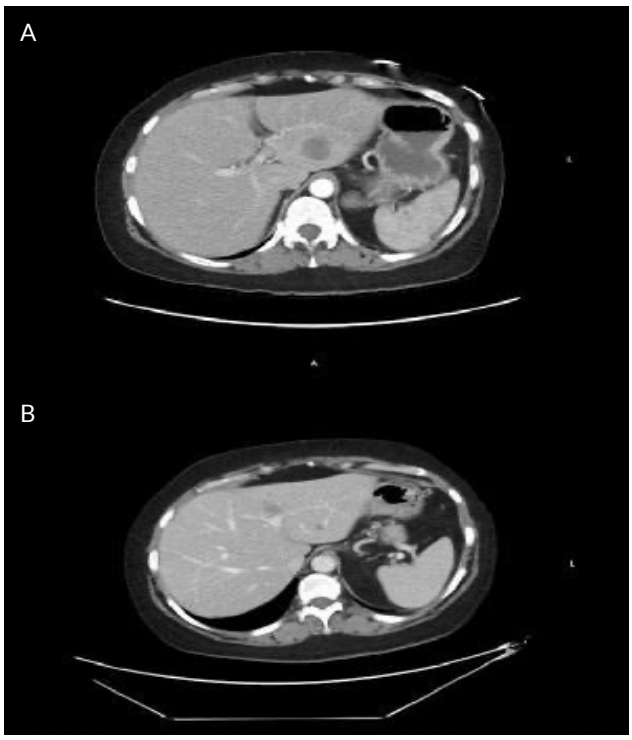

Figure 2. Computed tomography scan of the chest, abdomen, and pelvis. It compares the left hepatic lobe lesion before (A) and after (B) treatment adding carboplatin to the regimen.

Furthermore, paclitaxel and carboplatin were put on hold due to recent persistent neutropenia and thrombocytopenia. Since the patient has not developed any new metastatic lesions, she continues at this time on pembrolizumab during this chemo break. The patient has continued to have a good performance status since the diagnosis 20 months ago and during treatment. Further options are still under consideration based on the potential for disease progression.

DISCUSSION

Per our literature review, the average age of presentation is 50 years; there are 31 reported cases, most of which have been predominantly biphasic tumors composed of adenocarcinoma and choriocarcinoma from the sigmoid or ascending colon. Additionally, they express an early hematogenous metastatic spread. The most common sites of metastasis are the liver and lungs[3,5]. Consequently, patients with these tumors have an increased risk of bleeding and often die of hepatic complications or respiratory failure[6].

In our case, the initial clinical suspicion was likely ovarian cancer due to two ultrasounds showing similar findings. However, the pathology report showed colorectal adenocarcinoma with differentiation into choriocarcinoma, which changed the treatment approach. The reported tissue pattern aligns with the theory suggesting that these cancers might originate from a primary adenocarcinoma that has

undergone retrodifferentiation or trophoblastic metaplasia, leading to a transformation into increasingly primitive cell types[5]. Additionally, the patient had a CT scan of the chest, abdomen, and pelvis when the pathology report became available that showed multiple lesions of the liver concerning for metastatic disease. All these characteristics highlight the diagnostic complexity and aggressive nature of the tumor.

It is essential to understand that despite being called "choriocarcinoma," it is not a trophoblastic tumor or a germ cell tumor. This makes it challenging for the clinician to select treatment and combination options. For our patient, due to the complexity of the case in the setting of relapse, a multidisciplinary meeting was held to discuss the possibility of using other combinations, such as ipilimumab and nivolumab, together. However, the patient did not have mismatch repair deficiency or MSI. Furthermore, of the 31 cases reported, none has shown to be curative using EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine), B-EP (bleomycin, etoposide phosphate, and cisplatin), FOLFOX, FOLFIRI (leucovorin calcium or folinic acid, fluorouracil, irinotecan hydrochloride) plus bevacizumab.

CONCLUSION

There are no established guidelines for this rare malignancy, so further and robust studies need to be conducted to understand its progression, offer better guidance for clinicians, and improve patient treatment options. Currently, additional unconventional options are under consideration for our patient based on the potential for disease progression.

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