

## Case report

# Widespread choriocarcinoma metastases from de-differentiated gastro-esophageal junction primary adenocarcinoma: A case report with literature review

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## ABSTRACT

**Background:** Non-gestational choriocarcinomas represent a small subset of germ cell tumors. The majority of non-gestational choriocarcinomas arise from the gynecologic tract. In rare cases, they can originate from other sites, and very few such cases have been reported in peer-reviewed literature. We add to this small collection with an interesting case of non-gestational choriocarcinoma arising from a primary gastrointestinal adenocarcinoma.

**Case Presentation:** A 62-year-old female presented to the emergency department with ocular hemorrhage. Originally thought to have melanoma, full-body computed tomography (CT) revealed widespread metastases including a 3 cm hemorrhagic brain mass, hepatic metastases, and a mass at the gastro-esophageal (GE) junction. Pathology of the intracranial mass revealed a malignant neoplasm consistent with choriocarcinoma. Recent dilation and curettage (D&C) were negative for malignancy. Esophagogastroduodenoscopy (EGD) biopsy of the GE junction mass showed poorly differentiated adenocarcinoma, likely the primary lesion, while the liver biopsy matched the  $\beta$ -hCG staining pattern as seen in the brain.

**Conclusions:** Choriocarcinomas can rarely originate outside of the female reproductive tract (non-gestational, primary choriocarcinomas). In the infrequent cases where a gestational origin is clinically unlikely, the differential diagnosis includes a non-gestational primary choriocarcinoma and choriocarcinomatous differentiation in another primary malignancy. Careful correlation with imaging and clinico-pathologic studies is paramount to determining their origin and guiding further clinical treatment.

## 1. Introduction

Choriocarcinoma is characterized by an abnormal proliferation of trophoblastic cells. Choriocarcinoma represents a small subset of gestational trophoblastic neoplasia that originates in villous cells, one of the two lines of trophoblastic differentiation (Benirschke et al., 2006). Common signs and symptoms of a choriocarcinoma include pelvic pain or pressure, abnormal uterine bleeding, and elevated serum  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG), but may also have symptoms specific to the location of metastatic disease. Choriocarcinoma is highly aggressive with a well-known tendency to metastasize early via hematogenous spread. Common sites of metastasis include the brain, mediastinum, lung, stomach, pancreas, cervix, and ureter (Benirschke et al.,

2006). As choriocarcinoma invades blood vessels, lesions develop extensive necrosis and parenchymal hemorrhage.

Gestational choriocarcinomas are of fetal trophoblastic origin that can develop in association with abortion, ectopic pregnancy, or an intrauterine pregnancy of any gestational age. In contrast, non-gestational primary choriocarcinomas are exceedingly rare and arise from germ cells in the ovary, with an incidence of 1 in 369,000,000 (Yadav et al., 2015).

Some choriocarcinomas are not considered primary malignancies, but rather have de-differentiated from another primary carcinoma. When this occurs, the most common primary site of carcinoma is the upper gastrointestinal tract (Imai et al., 1994; Shastri et al., 2011).

The process by which gastrointestinal adenocarcinomas de-

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**Table 1**  
Previous cases of gastric/esophageal adenocarcinoma de-differentiated to choriocarcinoma.

Study Author, Year	Location of GI Adenocarcinoma	β-hCG Elevation?	Was it Surgically Excised?	Chemotherapy Regimen	Survival
Wasan et al. (1994)	Esophageal	Yes	No	Carboplatin, Etoposide, Bleomycin	Deceased at 19 months
McKechnie and Fechner (1971)	Esophageal	Yes	No	Chlorambucil, Methotrexate, Doctinomycin	Deceased at 2 months
Satake et al. (2011)	Gastric	Yes	Yes	TS-1 (titanium silicate) and CDDP (Cisplatin)	Alive at 8 months
Fujiyoshi et al. (2012)	Gastric	Yes	Yes	Not reported	Deceased, unknown longevity
Nakao et al. (1998)	Gastric	Yes	Yes	Cisplatin, 5-FU	Deceased at 6 months

differentiate to choriocarcinoma is not well understood. The most popular theory suggests that the adenocarcinoma de-differentiates at the cellular level to that of the embryonal ectoderm, acquiring the primary components of trophoblastic tissue (Imai et al., 1994; Shastri et al., 2011). In this new cell line, de-differentiation proceeds to choriocarcinoma, which classically invades vasculature, resulting in widespread metastases.

Because choriocarcinoma arising from de-differentiated adenocarcinoma is such a rarely diagnosed entity, it is important to document cases and their clinical outcomes for future research and future insights into improved patient care. In this report, we add to the limited collection of confirmed cases of de-differentiated choriocarcinoma [Table 1], including a description of the radiographic workup and pathological assessments.

## 2. Case presentation

A 62-year-old woman presented to the emergency department with a chief complaint of sero-sanguinous drainage from her right eye. She reported a 4-month history of nausea and vomiting, progressive dysphagia, right upper quadrant abdominal pain, constipation, visual changes, and a 50-lb weight loss. She was seen in the outpatient setting by an ophthalmologist and was suspected to have melanoma based on clinical presentation. Brain CT showed a 2.9x3.2x3.0-cm hemorrhagic mass in the left temporo-parietal region with surrounding moderate vasogenic edema with mass effect on the left lateral ventricle [Fig. 1A]. This was better characterized by subsequent MRI [Fig. 1C], showing its hemorrhagic nature as well as multiple other sub-centimeter cerebral metastases. Within the right posterior orbital globe, there was a heterogeneous mass measuring 0.6x1.3x0.6-cm, the likely source of her ocular hemorrhage. Abdominal CT showed multiple liver metastases [Fig. 1B]. While pelvic ultrasound demonstrated two masses in the wall of the uterus, measuring 7.6 × 4.7 × 5.8-cm and 3.5 × 2.9 × 2.6-cm, respectively, these were radiographically consistent with uterine fibroids. The uterus did not show significant hypermetabolism on PET/CT [Fig. 1D], and a recent outpatient D&C revealed benign polyps.

A chest CT showed a mass in the GE junction involving the distal esophagus and the proximal stomach [Fig. 1E]. There were also several pulmonary metastases and enlarged right hilar lymph nodes.

A craniotomy was performed to relieve intracranial pressure from the mass. Microscopic examination showed a pleomorphic malignant neoplasm with extensive hemorrhage [Fig. 2A, B]. The tumor was negative for melanoma markers and positive for cytokeratin and the preliminary diagnosis was a poorly differentiated metastatic carcinoma. On further characterization, the tumor cells were found to be positive for β-hCG, supporting the diagnosis of choriocarcinoma. This prompted further laboratory investigations that revealed a serum β-hCG of 250,188 mIU/mL and a subsequent working clinical diagnosis of non-gestational choriocarcinoma.

The patient underwent esophagogastroduodenoscopy (EGD) with biopsy of the GE junction mass revealing poorly differentiated adenocarcinoma [Fig. 2D, E]. Percutaneous liver biopsy showed poorly differentiated carcinoma and β-hCG staining cells, histologically similar to the brain pathology [Fig. 2F, G, H]. With this new information and review of reported cases, the diagnosis became GI primary adenocarcinoma with de-differentiated choriocarcinoma metastases in at least two of the multiple metastatic sites.

The patient was treated with the FOLFOX [FOL = Leucovorin Calcium (Folinic Acid), F = Fluorouracil, OX = Oxaliplatin] chemotherapy regimen as it is a recommended first-line regimen for the treatment of advanced adenocarcinoma of the esophagus and GE junction<sup>10</sup>. FOLFOX therapy was decided upon by our multidisciplinary tumor board. One month after the initiation of therapy, the patient's serum β-hCG levels decreased to 140,884 mIU/mL. Unfortunately, the patient's status worsened with transaminitis, multi-organ failure, and sepsis. Imaging showed drastic progression of the liver lesions. The

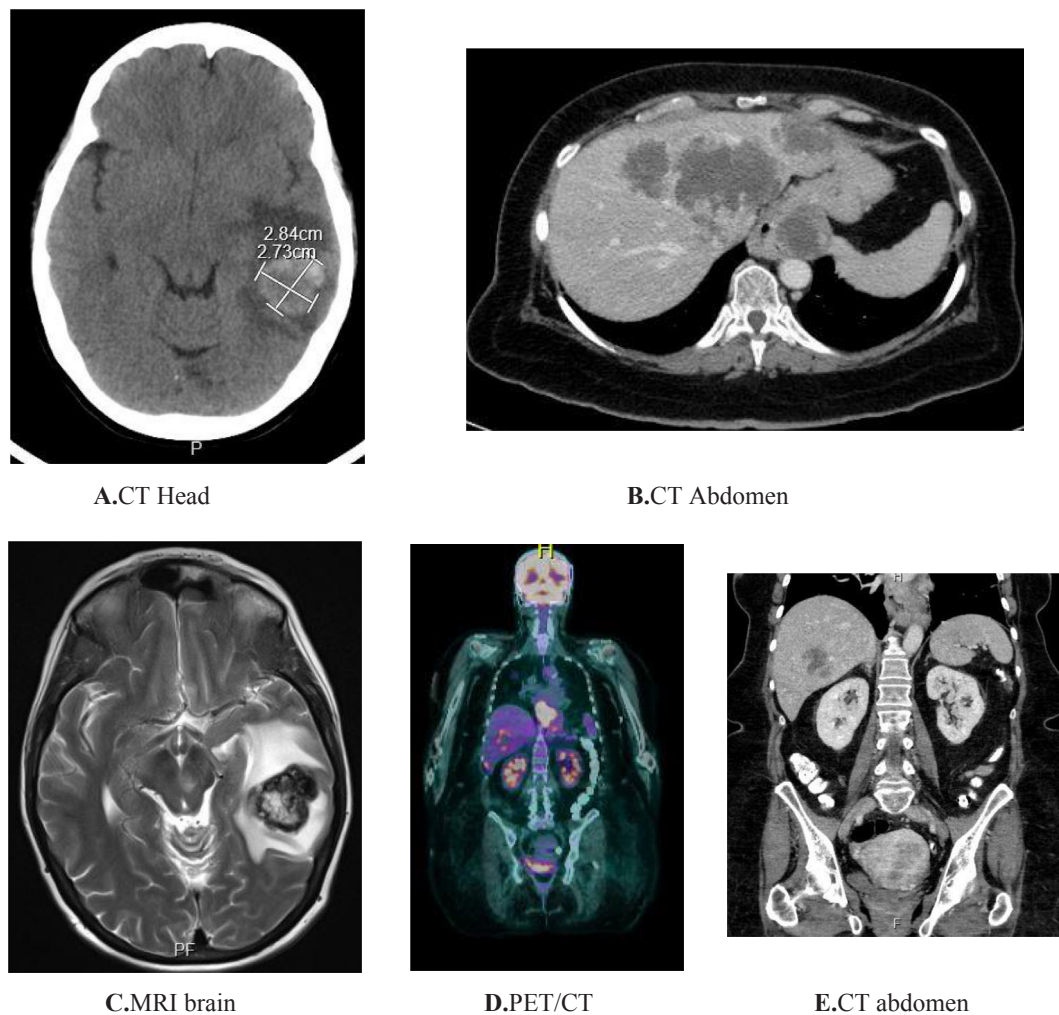


Fig. 1. Patient imaging.

patient discontinued treatment, entered hospice, and died 1.5 months following initiation of treatment.

### 3. Discussion

This case highlights the potential of divergent differentiation in high-grade, poorly differentiated malignancies and the importance of establishing the correct site of origin in cases of non-gestational choriocarcinoma. The pathologist's role in detecting these divergent histologies can be critical in directing appropriate treatment plans. Had this extensive radiographic and pathologic assessment not been performed sequentially as outlined above, the assumption could have otherwise been that of a primary gynecologic choriocarcinoma.

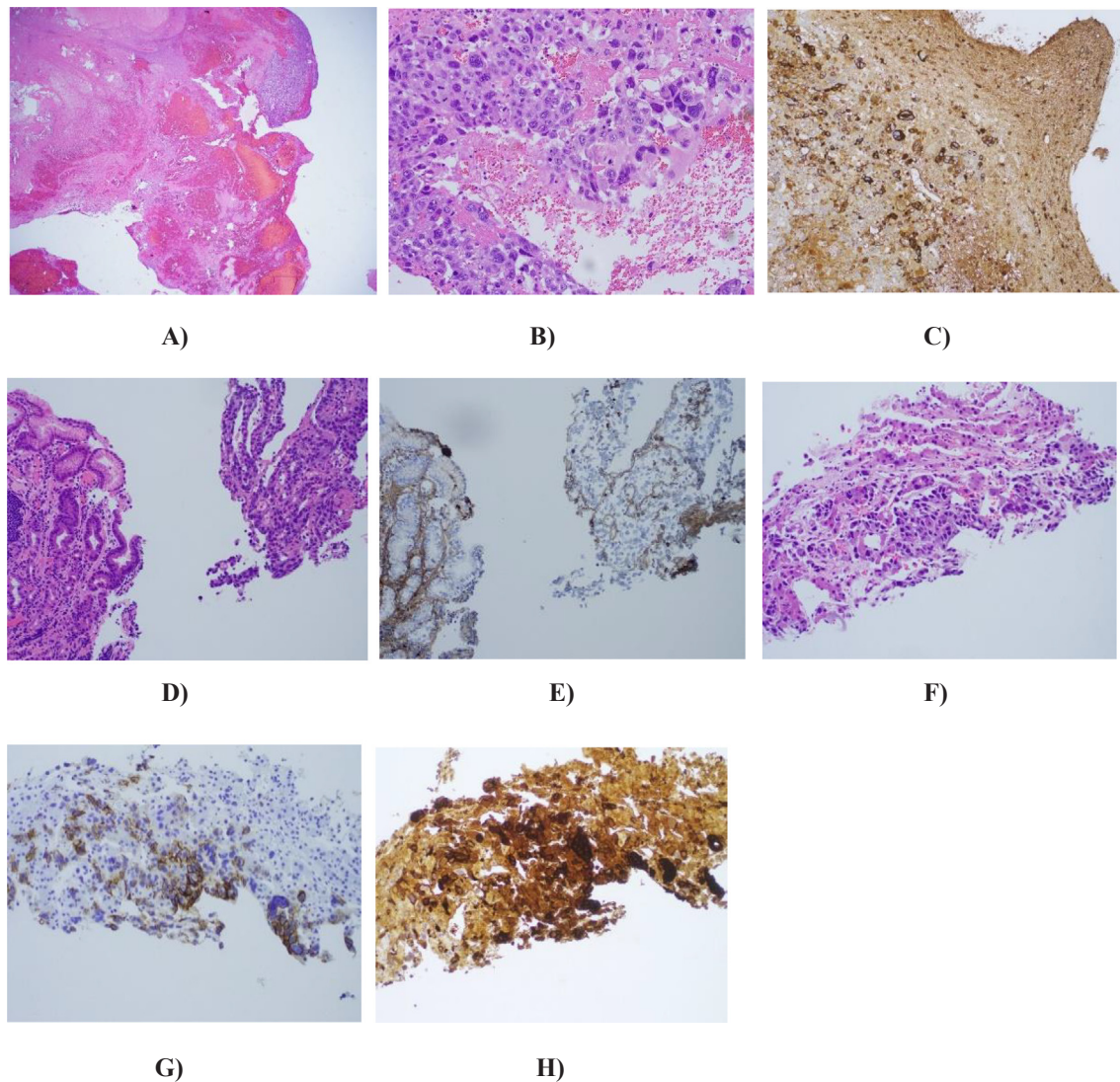
A limited number of similar cases have been reported that outline the diagnostic evaluation and treatment of a de-differentiated esophageal or gastric adenocarcinoma with choriocarcinoma elements [Table 1]. One such report treated with chemotherapy generally used for choriocarcinoma involved a 44-year-old male patient with a 9-cm fungating adenocarcinoma in the lower third of the esophagus, an elevated serum  $\beta$ -hCG and metastases to the lungs, stomach, small intestine, liver, pancreas, spleen, kidneys, brain, and prostate. The primary esophageal lesion was treated with radiation therapy, followed by chlorambucil, methotrexate, and dactinomycin. The lesion initially decreased in size, but after 2 months of treatment the disease progressed and the patient died 62 days after diagnosis (McKechnie and Fechner, 1971). Autopsy findings of the esophageal mass showed well-differentiated adenocarcinoma with coexisting areas of

choriocarcinoma. Biopsy of all other metastatic lesions were consistent with choriocarcinoma.

In another case where a choriocarcinoma chemotherapy regimen was used, a 49-year-old male presented with Barrett's esophagitis and a 20-cm polypoid esophageal mass. The endoscopic biopsy was consistent with poorly differentiated adenocarcinoma and de-differentiated choriocarcinoma. The patient received a carboplatin, etoposide, and bleomycin regimen. The  $\beta$ -hCG normalized and he achieved complete remission within 6 months. However, 10 months later, he relapsed with cerebral metastases and died within 3 months, despite salvage cranial radiation therapy (Wasan et al., 1994).

While there is no consensus on optimal treatment for widespread metastatic choriocarcinoma de-differentiated from another primary malignancy, a thorough diagnostic workup is important. The most effective frontline therapy for gastrointestinal adenocarcinomas is a FOLFOX regimen (Al Batran et al., 2008), whereas primary choriocarcinomas are treated with high-dose methotrexate regimens (Yadav et al., 2015). While we are unable to determine how she would have responded to a methotrexate regimen, literature review [Table 1] provided in this report would suggest that survival is poor regardless of treatment rendered.

Given the extreme rarity of these cases and inability to conduct clinical trials, there is no established chemotherapy protocol for the treatment of choriocarcinoma arising in GI adenocarcinoma. Given the origin from GI adenocarcinoma and the subsequent de-differentiation to choriocarcinoma, decisions about the specific cytotoxic regimen offered is difficult and exposes a significant research gap for these



**Fig. 2.** Pathology: (A) Low power view of brain mass with extensive hemorrhage and necrosis. (B) High power view of the brain tumor cells with extreme pleomorphism, primitive phenotype with frequent multinucleated cells (recapitulating the syncytiotrophoblast). (C) Brain tumor cells are positive for  $\beta$ -hCG and negative for S100. (D) Biopsy demonstrating normal cardia/lower esophageal mucosa on the left with a poorly differentiated adenocarcinoma on the right upper corner. (E) A  $\beta$ -hCG stain on this GI tissue was negative in the malignant cells. (F) Liver biopsy demonstrates a poorly differentiated malignancy, positive for MOC 31 (G) and  $\beta$ -hCG (H) consistent with metastatic choriocarcinoma.

patients. In addition, molecular differences between gestational choriocarcinoma and choriocarcinoma arising in an adenocarcinoma are unknown. Perhaps future genomic assessments using Next Generation Sequencing (NGS) could aid in diagnosis as well as our understanding of the origins of these cancers, and possible targets for therapy.

#### Patient consent

This study was deemed exempt by our AdventHealth Institutional Review Board.

#### Financial disclaimer

None.

#### Author contributions

All authors were substantially involved in the acquisition of case report data, contributing to drafting of the manuscript, and critically revising the manuscript for important intellectual content.

#### Declaration of Competing Interest

The authors declare that there are no conflicts of interest associated with this manuscript.

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