



A case report of paraneoplastic syndrome in β -hCG-secreting duodenal adenocarcinoma

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Abstract: Human chorionic gonadotropin (hCG) is a glycoprotein hormone that is used in clinical practice to detect pregnancy and serves as a sensitive marker for trophoblastic tumors. Other organs besides placental trophoblasts naturally express the hormone at low levels, which can be elevated in nontrophoblastic malignancies. Some studies have suggested that elevated β -hCG levels in nontrophoblastic tumors are a sign of aggressive disease and strongly associated with poor prognosis. We describe a case of a 50-year-old post-menopausal woman with metastatic duodenal adenocarcinoma who presented with a negative pregnancy test that later changed to positive. Biopsy of the primary duodenal mass showed positive immunohistochemical expression of β -hCG. The patient was also found to have multiple brain metastases, which is uncommon in gastrointestinal cancer. This is a rare case of paraneoplastic syndrome in a β -hCG-secreting duodenal adenocarcinoma.

Keywords: Duodenal adenocarcinoma; human chorionic gonadotropin; paraneoplastic syndrome; brain metastasis

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Introduction

Elevations in serum beta-human chorionic gonadotropin (β -hCG) are usually found in pregnancy or pregnancy-related conditions such as gestational trophoblastic tumors. However, β -hCG can also be produced in the stomach, colon, liver, and lung in small amounts (1). Malignancies in these organs can consequently result in increased serum levels of β -hCG, which is typically a sign of aggressive disease and poor prognosis (2). We report a case of a 50-year-old female newly diagnosed with stage IV duodenal adenocarcinoma with metastasis to the lungs, liver, lymph nodes, and left adrenal gland. Her pregnancy test was initially negative but later in her course changed to positive. Workup including pelvic ultrasound was unrevealing, making intrauterine and ectopic pregnancy unlikely. Her elevated β -hCG was consistent with a paraneoplastic syndrome originating from malignancy of the duodenum, which has not been previously reported on review of literature.

Case presentation

A 50-year-old Hispanic female with multiple liver and lung lesions presented with acute abdominal pain and melena. She had recently been admitted to the hospital with early satiety, intermittent emesis, and unintentional weight loss. This prompted imaging that demonstrated numerous masses in her lungs and liver. After her symptoms improved, she was discharged home with plans for outpatient biopsy until her unintended readmission. Initial urine pregnancy screening was notably negative and the patient was reported to be postmenopausal. Esophagogastroduodenoscopy (EGD) showed extrinsic compression of the gastric antrum and a malignant-appearing duodenal stricture that was biopsied. Pathology revealed infiltrating moderately differentiated papillary and villoglandular adenocarcinoma with extensive lymphatic invasion (Figures 1,2). Molecular studies detected a KRAS mutation in codon 12, 13, but no microsatellite instability nor BRAF mutation. Serum CEA was elevated to 122.9 ng/mL (normal value <3 ng/mL).

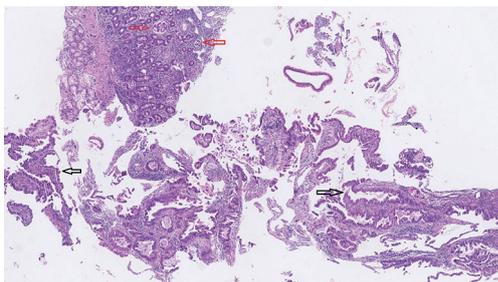


Figure 1 Fragments of duodenal tissue with (H&E staining), demonstrating contain foci of infiltrating moderately differentiated papillary and villoglandular adenocarcinoma (black arrows) with extensive lymphatic invasion (red arrows). High power view (45 \times).

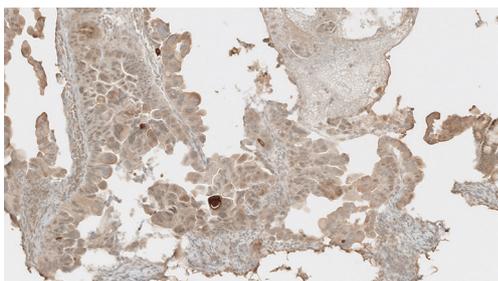


Figure 2 β -hCG immunohistochemistry. Cytoplasmic expression is strong in several cells, indicating presence/production of human chorionic gonadotropin-beta chain in these cells. High power view (160 \times).



Figure 3 β -hCG immunohistochemistry. High power view (80 \times) of the liver core biopsies showing strong cytoplasmic expression of B-hCG, revealed in metastatic foci lesions.

Subsequent biopsy of one of the liver lesions confirmed metastasis from primary duodenal carcinoma (*Figure 3*).

Imaging for cancer staging incidentally revealed bilateral segmental and subsegmental pulmonary emboli and re-demonstrated disseminated disease throughout the lungs, liver, lymph nodes, and left adrenal gland in addition

to the duodenal mass. The patient's symptoms of back pain led to a whole body bone scan that showed focal uptake in the lower cervical spine and left first and second ribs. Magnetic resonance imaging (MRI) of the cervical spine showed enhancement within the right C6 superior articular process as well as possible contrast-enhancing intradural extramedullary nodules suggestive of dural and leptomeningeal metastasis (*Figure 4*). MRI of the brain demonstrated metastasis within the bilateral frontal and parietal lobes with mild edema and restriction diffusion in the right corpus callosum, which was difficult to delineate between an acute ischemic event and leptomeningeal disease on review by neurologists (*Figure 5*). Evaluation for potential stroke etiology, including echocardiogram, monitoring for arrhythmias on telemetry, and serum lab markers (lipid profile and hemoglobin A1c), was negative. Cerebrospinal fluid studies showed elevated protein and indeterminate cytology limited by cell degeneration from a traumatic tap. The patient was discharged with plans for repeat brain imaging and initiation of palliative chemotherapy.

Prior to starting cancer treatment, the patient was again readmitted for hyponatremia (sodium level 125) secondary to SIADH and elevated liver function tests. Urine β -hCG was newly positive despite initial negative result. Serum β -hCG was elevated to 17 IU/L (normal value <5 IU/L). The patient's last menstrual period was about one year ago and she had undergone tubal ligation during her 20s. Pelvic ultrasound was negative for evidence of intrauterine pregnancy or focal mass within the uterus and adnexal regions, with a normal endometrial thickness of 60 mm. Immunohistochemical stainings of both the duodenal and liver biopsies were strongly positive for β -hCG (*Figures 2,3*). The plan was to initiate mFOLFOX6 + avastin inpatient. Unfortunately, the patient developed worsening altered mental status and decreased responsiveness, and ultimately was transitioned to home hospice after extensive discussion with her husband.

Discussion

Duodenal adenocarcinoma is a rare but aggressive malignancy, representing less than 1% of all gastrointestinal cancers. Patients most often present with abdominal pain and other nonspecific symptoms including nausea, vomiting, fatigue, and weight loss. More advanced disease is associated with bowel obstruction, jaundice, and anemia (3). Metastases to the liver, lungs, and bone are

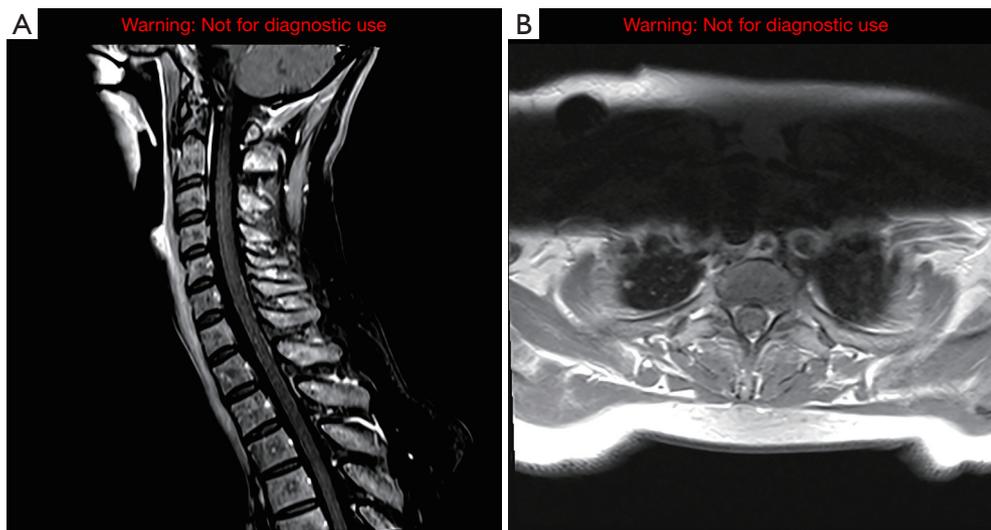


Figure 4 Dural metastases on MRI cervical and thoracic spine imaging. (A) Sagittal view of the cervical and upper thoracic view, showing multiple dural metastatic lesions; (B) axial view of the Th1-Th2 levels, reveals small contrast enhancing intradural extramedullary nodule along with a pulmonary nodule in the right lung lobe.

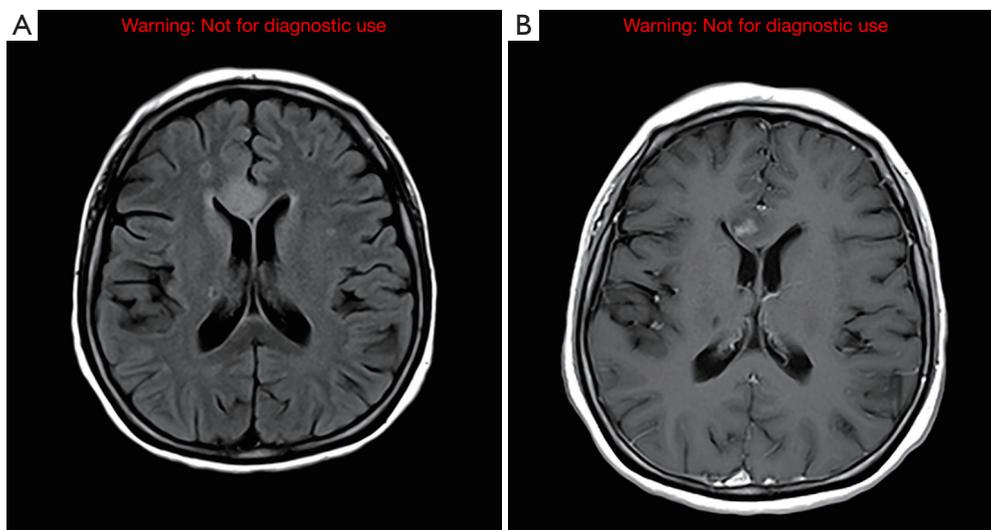


Figure 5 Brain metastases on MRI brain imaging. (A) Axial view of the brain parenchyma with T2 shows a metastatic nodule in the right anterior corpus callosum; (B) T1 view of the same lesion as (A) with contrast

common at presentation, occurring in about 33% of patients. Brain metastasis from small intestine malignancies are uncommon; the largest published case series included only 15 patients with small bowel malignancy metastatic to the brain, including 12 adenocarcinoma and 3 neuroendocrine. Another case series reported a median survival of 10 months in patients with solitary cerebral

metastases from primary intestinal malignancies, although they did not differentiate between tumors of the small intestine, colon and rectum (4). Paraneoplastic syndrome from duodenal adenocarcinoma is also exceedingly rare, and there are no published case reports available for review at the time of publication. Paraneoplastic disorders are a heterogeneous group of disorders caused

Table 1 Characteristics and survival rates associated with hCG positivity in gastrointestinal malignancies

Primary malignancy	Patient N [% male]	Median age (years)	hCG positivity [%]	Survival 5 years (%)	References
Esophagus	76 [96]	62.2	hCG immunoreactivity		Couvelard (7)
			Positive [56]	20	
			Negative	40	
Colorectal	239 [50]	69.5	Serum β -hCG		Lundin (8)
			<2 pmol/L	58.6	
			>2 pmol/L [17]	23.1	
Pancreatic	160 [49]	63.8	Serum β -hCG		Louhimo (9)
			<2 pmol/L	23*	
			>2 pmol/L [60]	1*	
Gastric	150 [75]	56	hCG immunoreactivity		Murhekar (10)
			Positive [18.7]	NA	
			Negative	NA	
Biliary	7 [NA]	78	Serum β -hCG		Alfthan (11)
			Positive [86]	NA	
			Negative	NA	

NA, not available. *, survival 2 years (%).

by substances released by a tumor or produced in reaction to it. These substances are most commonly hormones or other compounds such as antibodies. Paraneoplastic syndromes alone are uncommon, estimated to affect up to 8% of patients with malignancy and are most commonly associated with small cell lung cancer, gynecologic tumors, breast cancer, and hematologic malignancies. Our patient presented with SIADH, but also was suspected to have paraneoplastic β -hCG production.

hCG is a placental hormone secreted by cells from the implanting conceptus that promotes progesterone production by corpus luteal cells, which in turn supports the endometrial lining and therefore maintains pregnancy. In medical practice, the hormone is primarily used for detection and monitoring of pregnancy, but it is also used as a marker for trophoblastic tumors of placental and germ cell origin (2). Similar to other gonadotropins, hCG is a heterodimeric glycoprotein made up of α and β subunits. The α subunit is common to all glycoprotein hormones whereas the β subunit is unique to each hormone and distinguishes the biological activity (5). β -hCG in particular has been shown to promote cell invasion and tumor growth, as well as to suppress immune responses (6). Although hCG is mainly produced by placental syncytiotrophoblast cells,

it is also produced at low levels in other organs. Increased β -hCG serum levels have been shown to occur in various cancers of the GI tract, most commonly in biliary (60%), pancreatic (46%), and gastric cancer (40%), and less frequently in liver (20%) and colorectal cancer (15%) (2) (*Table 1*).

Factors associated with worse outcome in duodenal adenocarcinoma include lymph node metastasis, tumor stage, lymphovascular or perineural invasion, and overall cancer stage, with lymph node positivity as one of the most important predictors of decreased survival (3). Serum tumor markers are not frequently used as prognostic indicators and more often monitored as a sign of treatment response. β -hCG production is linked with aggressive behavior in nontrophoblastic tumors and has been found to be associated with poor prognosis in most studies, although others indicate it is of limited prognostic value (2). One report found colorectal cancer patients with normal β -hCG levels had a median survival of 7.9 years compared with 1 year for patients with elevated serum levels, with a statistically significant difference between survival curves in Dukes' D cancer stage (12). Another study demonstrated 20 colorectal cancer patients with positive β -hCG on both histology and serology had a 5-year survival of 21% versus

62% in the group with no expression in tissue or serum (8). Although β -hCG can be elevated in peri-menopausal stages, our patient initially had a negative pregnancy test that later became positive as her overall clinical condition declined suggestive of increased tumor burden from an aggressive malignancy.

Resection of the primary tumor is the only curative treatment option for duodenal adenocarcinoma; survival benefit has been reported with adjuvant chemotherapy or chemoradiation after curative resection, and with palliative chemotherapy for stage IV disease. Given the similarities between small bowel adenocarcinoma and colorectal cancer, treatment strategies are used interchangeably (3). Current chemotherapy regimens for metastatic stage IV colorectal cancer have shown improved, although modest, survival duration. Given the significant toxicity associated with standard therapy, novel treatment modalities are currently being studied.

Active specific immunotherapy (ASI) has been under investigation with some studies using hCG as a target. Moulton *et al.*, describes a randomized control trial phase II study comprised of 77 patients with metastatic colorectal cancer divided into two vaccine dose groups using a synthetic vaccine targeting the C-terminal peptide of hCG. No significant differences were found in antibody response and survival, however patients who developed anti-hCG antibody levels higher than or equal to the median value exhibited a median survival of 45 weeks compared to 24 weeks for patients who developed levels lower than the median. A different study proposed another vaccine containing a β -hCG mutant designed to eliminate cross-reactivity with luteinizing hormone. Compared to C-terminal β -hCG peptide vaccines, the mutant vaccine resulted in the highest antibody titers, making it a promising therapy in β -hCG-positive cancers (13). Another report by Nand *et al.* describes a recombinant PiPP monoclonal antibody conjugated to exotoxin that was shown to kill almost 90% of cells *in vitro* of β -hCG-expressing lymphoma, T-lymphoblastic leukemia, and lung carcinoma (14). Further studies will need to be performed to determine whether ASI can improve overall outcomes of patients with colorectal cancer.

Conclusions

In conclusion, this is the first case of paraneoplastic β -hCG production from a duodenal adenocarcinoma reported in literature. According to some studies serum β -hCG may be an independent prognostic indicator of more aggressive

disease and adverse outcomes in colorectal cancer. Investigational studies developing therapies targeting β -hCG are currently underway.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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