Extragonadal germ cell tumor, a report of two cases presenting in the gastrointestinal tract

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Abstract
Germ cell tumors are a heterogeneous group of tumors that can present primarily as gonadal tumors in either a localized or metastatic pattern. Rarely these tumors can initially present at extra-gonadal locations, including the gastrointestinal tract. We report two young male patients who presented with nonspecific gastrointestinal symptoms caused by a mass lesion involving the duodenum. Pathologically, both were confirmed to be germ cell tumors; an unfamiliar initial presentation of germ cell tumors. In both cases, evidence of pre-existing gonadal tumor in the form of a testicular mass and a burned-out tumor with microlithiasis, in the first and second cases, respectively was detected following the confirmed diagnosis of extra-gonadal germ cell tumor. Each patient’s clinical course and outcome emphasizes the importance of a high index of suspicion, timely diagnosis, and appropriate management.

Keywords
Extra-gonadal germ cell tumors, duodenum, metastasis, pathology, radiology

Introduction
Germ cell tumors are a histologically heterogeneous group of tumors with a common origin in primitive germ cells that can show features reminiscent of the primordial germ cell including differentiation into embryonic structures. Although they most commonly arise in the gonads, that is, testes and ovaries, they can sometimes arise elsewhere with no evidence of primary gonadal tumor and therefore called extra-gonadal germ cell tumors (EGCT).

The annual incidence of EGCT ranges from 1.27 to 3.3 per million in different studies. EGCT comprised between 5.5% and 15.2% of all germ cell tumors in males. These can be diagnosed at any age, but are mostly seen in 15–35 year old males. They arise anywhere along midline structures presumably along the migration path of germ cells during development. The most common locations include the mediastinum, retroperitoneum, pineal gland and suprasellar region, and presacral area. Their diagnosis in other organs such as the bladder, prostate, liver, and gastrointestinal tract (GIT) is usually limited to case reports and series. Within the GIT, EGCT has been reported in different sites including the esophagus, stomach, duodenum, cecum, colon, and rectum. Their clinical presentation

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varies depending on location but intestinal obstruction and/or gastrointestinal bleeding were the most common. Diagnosis in a timely fashion is important to prevent complications as well as to administer suitable chemotherapy that would be less effective if given later in the course of the disease. This cannot be achieved unless the treating physician has a high index of suspicion of this uncommon encounter. In this paper we aim to report two cases of gastrointestinal involvement by EGCT. In addition, review of available literature will also be presented.

**Case reports**

**Case-1**

A 28-year-old male patient presented with a history that started in October 2018 with fatigability after performing minor physical activity and vomiting. Initial investigation revealed anemia. An upper gastrointestinal endoscopy (EGD) demonstrated an ulcerating mass obstructing more than 50% of the duodenal lumen, however, biopsy showed granulation tissue with no evidence of malignancy. Further investigation by CT scan demonstrated a large mass lesion posterior to the second part of the duodenum which is displaced anteriorly (Figure 1(a) and (b)), compressing and stretching the inferior vena cava (IVC). The differential diagnosis included a duodenal tumor versus a pseudopapillary pancreatic tumor. An attempt at endoscopic ultrasound (EUS) failed as the stomach was full of solid food despite prolonged fasting, so the procedure was cancelled with recommendation for transabdominal biopsy.

The first ultrasound guided biopsy revealed no malignancy and the second transabdominal biopsy demonstrated spindle cells, suggesting the diagnosis of gastrointestinal stromal tumor (GIST). In December 2018, PET-CT scan confirmed the presence of heterogeneously and peripherally mildly hypermetabolic large mass in the retro-duodenal area, posterior to the second part of the duodenum, displacing the surrounding viscera with no evidence of invasion, compatible with the known GIST tumor. No other hypermetabolic metastatic lesions could be detected.

In July 2019, the patient had constant vomiting, mild abdominal pain, and dehydration, for which he was treated conservatively. A CT-scan revealed progression in the size of the retro-duodenal mass (Figure 1(c)). In October 2019, his anemia worsened so the suspicious of bleeding prompted gastroduodenal artery embolization.

![Figure 1](image-url). **Figure 1.** Case-1: (a) axial abdomen CT scan with contrast (venous phase) on 7th October 2018, shows a large retro-duodenal mass displacing the second part of the duodenum anteriorly and compressing the IVC, (b) sagittal CT scan with contrast shows large retroperitoneal mass invading the duodenum that appears displaced anteriorly, (c) CT scan with contrast on the 24th June 2019 shows progression in size of the retroperitoneal mass with more invasion of the duodenum, (d) low power magnification of the bowel wall with ulceration, with underlying immature cartilage consistent with the teratomatous component of the germ cell tumor (H&E, ×20), (e) squamous epithelium and glandular component are other components of teratoma (H&E, ×20), and (f) cartilaginous component is seen in other foci (H&E, ×20).
In January 2020, the patient presented with diffuse abdominal pain and vomiting, so the plan was to go for surgery. Intraoperative finding showed a huge exophytic mass arising from the duodenum adherent to the IVC and aorta. The retroperitoneal mass along with the duodenum were resected. Microscopic examination showed a non-germinomatous malignant mixed germ cell tumor. The tumor was composed of choriocarcinoma (50%), and mature cystic teratoma (50%), showing ulceration of the overlying mucosal lining (Figure 1(d)), with squamous and glandular epithelium (Figure 1(e)), and cartilage (Figure 1(f)) as the main components of the teratoma. The choriocarcinoma component was positive for SALL4, GATA-3, P63, with focal staining for B-HCG. Additionally, alpha feto-protein, Glypican-3, CD30, and C-Kit immunostains were negative, ruling out yolk-sac, embryonal carcinoma, and germinoma. There was no evidence of GIST tumor.

Subsequently, a testicular US showed a right testicular mass. Serum markers were ordered. Lactate dehydrogenase (LDH) was elevated (419 U/L), B-hCG was minimally elevated (28.45 mIU/mL), and alpha fetoprotein was normal (2.62 ng/mL).

Initially, the patient refused chemotherapy. In May 2020, a marked elevated in serum markers was reported, including LDH (3375 U/L), B-hCG (78,777 mIU/mL), but not in alpha fetoprotein (2.83 ng/mL). Eventually, the patient agreed to receive chemotherapy and was started on BEP (Bleomycin, etoposide, and cis-platinum) regimen. The patient, however, developed refractory anemia. He succumbed to his disease on the 19th August 2020, 22 months following his initial presentation.

Case-2

In December 2015, a 24-year-old male patient presented to another hospital with history of recurrent vomiting, right abdominal pain, and weight loss. An abdominal CT scan revealed a 6 cm right upper retroperitoneal and abdominal mass (Figure 2(a)). Esophagogastroduodenoscopy (EDG) revealed a fungating ulcerating mass in the second part of the duodenum. Pathological examination of a tru-cut biopsy from the abdominal mass and a biopsy from the duodenal mass was reported as an undifferentiated anaplastic pancreatic cancer and an adenocarcinoma, respectively, so a...
many physicians have not been formally trained to do so.17 Examination and imaging are not routinely ordered and microlithiasis detected by US. However, genital physical clinical clue is the presence of a testicular mass and/or young patients in this particular age group. An important plausible unless there is a high index of suspicion among diagnosis of EGCTs based on symptoms alone is not proper diagnosis. Gonadal examination should be performed in all patients with EGCTs, for which an evidence specimen. So is the second case, in which microlithiasis was noted later on, suggesting a burned-out testicular GCT.

Another important issue raised by the both patients is that EGCTs can frequently be missed on pathological examinations. The first patient was initially diagnosed as GIST, for which he received Gleevec for 6 months. Review of the original biopsies, once the diagnosis was rendered on the resection specimen, did not reveal the presence of any microscopic hint of a germ cell tumor. The issue with the second patient, however, is different. The presence of atypical glandular proliferation encouraged the diagnosis of pancreatic carcinoma, an unusual diagnosis in this young age group, for which Whipple resection was planned. Re-evaluation of the biopsy prompted the reviewing pathologist to include pan-germ cell tumor markers in the evaluation of the case, as adencarcinoma of pancreas and duodenum are quite uncommon in this age group.

GCTs were once the leading cause of cancer death among young men. This changed in the mid 1970s after the introduction of cisplatin-based chemotherapy.18,19 The outcome of metastatic and EGCTs is worse than non-metastatic testicular GCTs. The closest parallel to our patients would be retroperitoneal non-seminomatous EGCTs which, in a multicenter study, had 5-year overall survival and progression free survival rates of 62% and 45%, respectively.19

Conclusion
In conclusion, we present two cases of young adult male patients, both of whom presented with duodenal EGCT, with an initial erroneous pathological diagnosis, for which the actual and planned treatment plan was affected. Although the first patient succumbed to his disease, the second patient is still alive with no evidence of tumor. Therefore, timely diagnosis is crucial for administrating the proper treatment. A high index of suspicion by the treating physician and the pathologist should help in reaching the proper diagnosis. Gonadal examination should be performed in all patients with EGCTs, for which an evidence of a mass or burned-out tumor can be unmasked.

Author contributions
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Discussion
We are presenting two cases of young adult male patients, who were diagnosed with abdominal germ cell tumor. Both patients were in their 20s, which is consistent with the usual demographic of GCTs.7 Both had non-seminomatous germ cell tumors involving the duodenum at their initial presentation, with non-specific GI symptoms including vomiting, epigastric pain, in addition to fatigue and anemia, all secondary to mass effect and invasion of the duodenal wall, with associated ulceration and blood loss. At such, the clinical diagnosis of EGCTs based on symptoms alone is not plausible unless there is a high index of suspicion among young patients in this particular age group. An important clinical clue is the presence of a testicular mass and/or microlithiasis detected by US. However, genital physical examination and imaging are not routinely ordered and many physicians have not been formally trained to do so.17

In the first patient, the testicular tumor was only noticed after histopathological diagnosis was made on the resected Whipple procedure was planned. In February 2016, the patient presented to our center. Review of his original pathological slides revealed a germ cell tumor with large areas of necrosis, as well as focal granulomatous reaction (Figure 2(b)). The tumor cells were diffusely strongly positive for SALL4 (Figure 2(c)), OCT 3/4, and CD30, with focal positivity for pan CK AE1/E3. Scattered groups of tumor cells were positive for Glypican3. The tumor cells were negative for alpha-fetoprotein. So, an embryonal carcinoma was confirmed. Other components in the original tumor, however, could not be excluded due to the limited size of the biopsy.

Accordingly, serum markers were requested. His serum level of LDH was 261 U/L, beta-HCG 10.4 mIU/mL and alpha fetoprotein (AFP) <2 ng/mL. Testicular ultrasound showed multiple small calcific foci that could represent microlithiasis (Figure 2(d)). His treatment plan was initially four cycles of BEP (Bleomycin, etoposide, and cisplatinum) chemotherapy protocol starting in March 2016 but was changed in June to etoposide and cisplatin as he developed pulmonary side effects secondary to bleomycin. He had excellent response to chemotherapy with regression of the tumor noted in April (Figure 2(e)) and June 2016 (Figure 2(f)). In August 2016, he underwent surgery for resection of the residual tumor along with retroperitoneal lymph node dissection. Microscopically, there was no residual tumor in any lymph node. His serum markers were all within normal limits. The patient was due to CT scan follow-up imaging on March 2021, but failed to come to Jordan due to the current COVID-19 pandemic. However, he was last seen in a follow up visit in December 2019 with no evidence of recurrence or new metastasis on CT scan and normal tumor markers. The patient is alive 52 months following his initial presentation.
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**Ethical approval**

Ethical approval for this study was waived from the King Hussein Cancer Center Institutional Review Board.

**Informed consent**

The request for Informed consent was waived by the IRB since non-identifiable data was obtained.

**Trial registration**

Not applicable because of the nature of the manuscript.

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