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CASE REPORT AND REVIEW OF THE LITERATURE

PURE YOLK SAC TUMOUR ARISING IN THE STOMACH: CASE PRESENTATION AND REVIEW OF THE LITERATURE

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Abstract

Introduction. Yolk sac tumours (YSTs) are rare malignant germ cell neoplasms. Primary involvement of the gastrointestinal tract is exceedingly uncommon, with only a limited number of gastric cases described, either as pure YSTs or in mixed forms.
Case presentation. We report a case of a 65-year-old female patient with YST. The diagnosis was established histologically and immunohistochemically after gastric resections. Gross examination revealed an ulcerative lesion measuring 6×5×2 cm, located along the lesser curvature of the stomach. Histologically, the neoplasm exhibited heterogeneous architectural patterns, including reticular, glandular, and solid growth. Numerous glomeruloid structures resembling Schiller–Duval bodies were identified.

Résumé

Tumeur pure du sac vitellin se développant dans l'estomac: présentation de cas et revue de la littérature

Introduction. Les tumeurs du sac vitellin (TSV) sont des néoplasies germinales malignes rares. L'atteinte primitive du tube digestif est extrêmement rare, et seuls quelques cas gastriques ont été décrits, qu'il s'agisse de TSV pures ou de formes mixtes.
Présentation du cas. Nous rapportons le cas d'une patiente de 65 ans atteinte d'une TSV. Le diagnostic a été établi par histologie et immunohistochimie après résection gastrique. L'examen macroscopique a révélé une lésion ulcérée de 6×5×2 cm, située sur la petite courbure de l'estomac. Histologiquement, la néoplasie présentait une architecture hétérogène, avec des aspects réticulaires, glandulaires et solides.

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Immunohistochemical analysis demonstrated diffuse positivity for alpha-fetoprotein (AFP) and Glipican in areas showing clear embryonal differentiation. Postoperatively, the serum alpha-fetoprotein (AFP) level was measured and showed elevation at 174 ng/mL. One month after surgery, a restaging contrast-enhanced computed tomography scan showed metastases in abdominal lymph nodes, liver and bone metastases. Laboratory investigations revealed markedly elevated AFP levels (2138.0 ng/mL). Systemic therapy was initiated within two weeks. At the initiation of chemotherapy, AFP levels were reassessed as a marker of tumour aggressiveness and showed a marked increase to 10,838.7 ng/mL. The clinical course was rapidly progressive, and the patient died in 5 months from initial diagnosis.

Conclusions. AFP represents a key prognostic biomarker in YSTs. AFP levels exceeding 1000 ng/mL have been associated with aggressive tumour behaviour, rapid disease progression, and shorter overall survival.

Keywords: yolk sac tumour, gastrointestinal, stomach, alpha-fetoprotein.

List of abbreviations:
YST – yolk sac tumour
AFP – alpha-fetoprotein
CT – computed tomography
AJCC – American Joint Committee on Cancer
CEA – carcinoembryonic antigen
CA 19-9 – carbohydrate antigen 19-9
SUV max – maximum standardized uptake value
PD-L1 – programmed death-ligand 1
PD-1 – programmed cell death 1
HER2 – human epidermal growth factor receptor 2
CPS – Combined Positive Score

De nombreuses structures gloméruloïdes, évoquant des corps de Schiller-Duval, ont été identifiées. L'analyse immunohistochimique a démontré une positivité diffuse pour l'alpha-fœtoprotéine (AFP) et le glipicane dans des zones présentant une différenciation embryonnaire marquée. En postopératoire, le taux sérique d'alpha-fœtoprotéine (AFP) a été mesuré et s'est révélé élevé à 174 ng/mL. Un mois après l'intervention, une tomodensitométrie (TDM) de restadification avec injection de produit de contraste a mis en évidence des métastases ganglionnaires abdominales, hépatiques et osseuses. Les analyses biologiques ont révélé une élévation marquée du taux d'AFP (2138,0 ng/mL). Un traitement systémique a été instauré dans les deux semaines suivantes. Au début de la chimiothérapie, le taux d'AFP a été réévalué comme marqueur d'agressivité tumorale et a montré une augmentation importante à 10 838,7 ng/mL. L'évolution clinique a été rapidement progressive et le patient est décédé 5 mois après le diagnostic initial.

Conclusions. L'AFP représente un biomarqueur pronostique clé dans les tumeurs du sac vitellin. Des taux d'AFP supérieurs à 1000 ng/mL ont été associés à un comportement tumoral agressif, une progression rapide de la maladie et une survie globale plus courte.

Mots-clés: tumeur du sac vitellin, gastro-intestinal, estomac, alpha-fœtoprotéine

Introduction

Yolk sac tumours (YSTs) are rare malignant germ cell neoplasms that were initially described in the gonads. Approximately 5% of cases arise in extragonadal sites, most commonly along midline structures such as the mediastinum, retroperitoneum, pineal gland, and sacrococcygeal region[1,2]. YSTs have also been reported as a heterologous component of carcinomas in several organs, including the lung, stomach, large intestine, gallbladder, pancreas, and urinary bladder[3]. Primary involvement of the gastrointestinal tract is exceedingly uncommon, with only a limited number of gastric cases described, either as pure YSTs or in mixed forms[4].

The histogenesis of gastric YST remains unclear. Proposed mechanisms include aberrant migration of primordial germ cells during embryogenesis or differentiation from multipotent neoplastic protoepithelial cells of the gastric mucosa[5,6]. Overall, gastric YSTs are exceptionally rare, with only 21 cases reported in the English-language literature to date.

Because of their rarity and lack of distinctive clinical manifestations, gastric YSTs are frequently misdiagnosed as conventional gastric adenocarcinoma. Moreover, the prognosis of gastric YST is generally poor, and optimal management strategies beyond surgical resection are not clearly established yet[7].

Case presentation

We present the case of a 65-year-old female patient, complaining of epigastric pain, nausea,

vomiting, and unintentional weight loss of 10 kg over a 3-month period. Fibrogastroscopy revealed an ulcerative tumour along the lesser curvature in the subcardial region, with an irregular surface and elevated, uneven margins. Two biopsies were obtained and histologically the lesion was classified as a poorly differentiated gastric adenocarcinoma.

Contrast-enhanced computed tomography (CT) of the abdomen and pelvis revealed irregular, asymmetric thickening of the gastric wall along the lesser curvature, with a maximum thickness of up to 20 mm, demonstrating marked and heterogeneous contrast enhancement. An intraluminal filling defect was identified within the portal vein at its confluence with the left gastric vein, measuring approximately 9 × 10 mm in the coronal plane and resulting in significant luminal narrowing, findings consistent with portal vein thrombosis. The liver parenchyma showed no radiological evidence of focal lesions suspicious for metastatic disease, and the spleen was unremarkable. The uterus and ovaries were absent, consistent with prior surgical intervention. Both kidneys demonstrated preserved parenchymal thickness and unobstructed collecting systems; however, a well-circumscribed, heterogeneous, round lesion measuring 10×9 mm was observed in the lower pole of the right kidney, with imaging features consistent with an angiomyolipoma. No free intraperitoneal fluid was detected. Multiple enlarged right paracardial lymph nodes were noted, with a maximal short-axis diameter of up to 20 mm. No evidence of osseous metastatic disease was identified within the examined skeletal structures.

The patient was subsequently admitted for surgical management. A total gastrectomy with omentectomy and reconstruction by anterior esophagojejunostomy using a Braun omega loop was performed. The definitive diagnosis was established based on postoperative histopathological examination. Gross examination revealed an ulcerative lesion measuring 6×5×2 cm, located along the lesser curvature of the stomach. Histologically, the neoplasm exhibited heterogeneous architectural patterns, including reticular, glandular, and solid growth (Figure 1A). Numerous glomeruloid structures resembling Schiller–Duval bodies were identified (Figure 1C and D). In addition, certain areas demonstrated a broad, festooned architecture lined by atypical stratified epithelial cells with enlarged, hyperchromatic nuclei, a high nucleocytoplasmic ratio, and abundant vacuolated cytoplasm containing multiple hyaline globules (Figure 1B). Lymphovascular

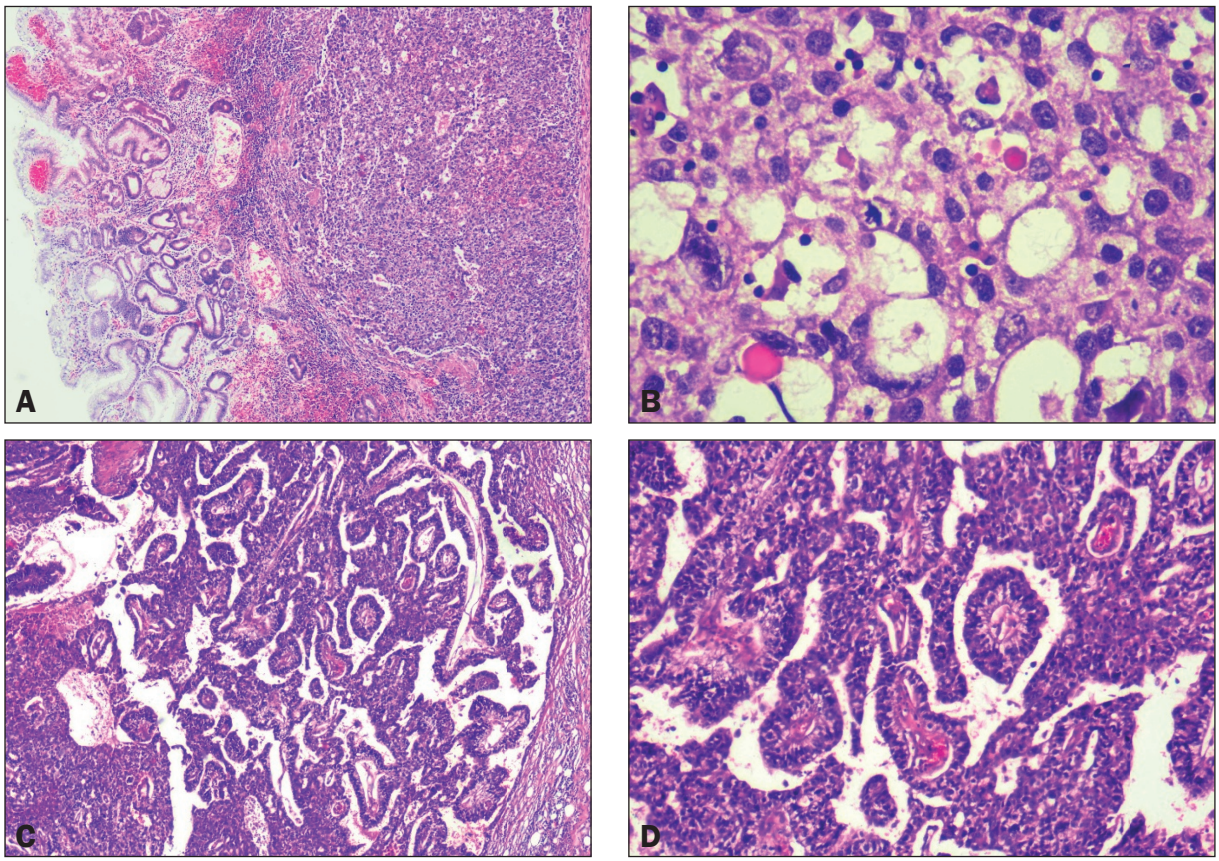


Figure 1. A) Stomach with infiltration of low-grade YSTs, HEx4. B) Alpha-fetoprotein globules in a poorly differentiated area HE x40. C) Schiller-Duval body area HEx4. D) Schiller-Duval body HE x20. (*continuare în pagina următoare*)

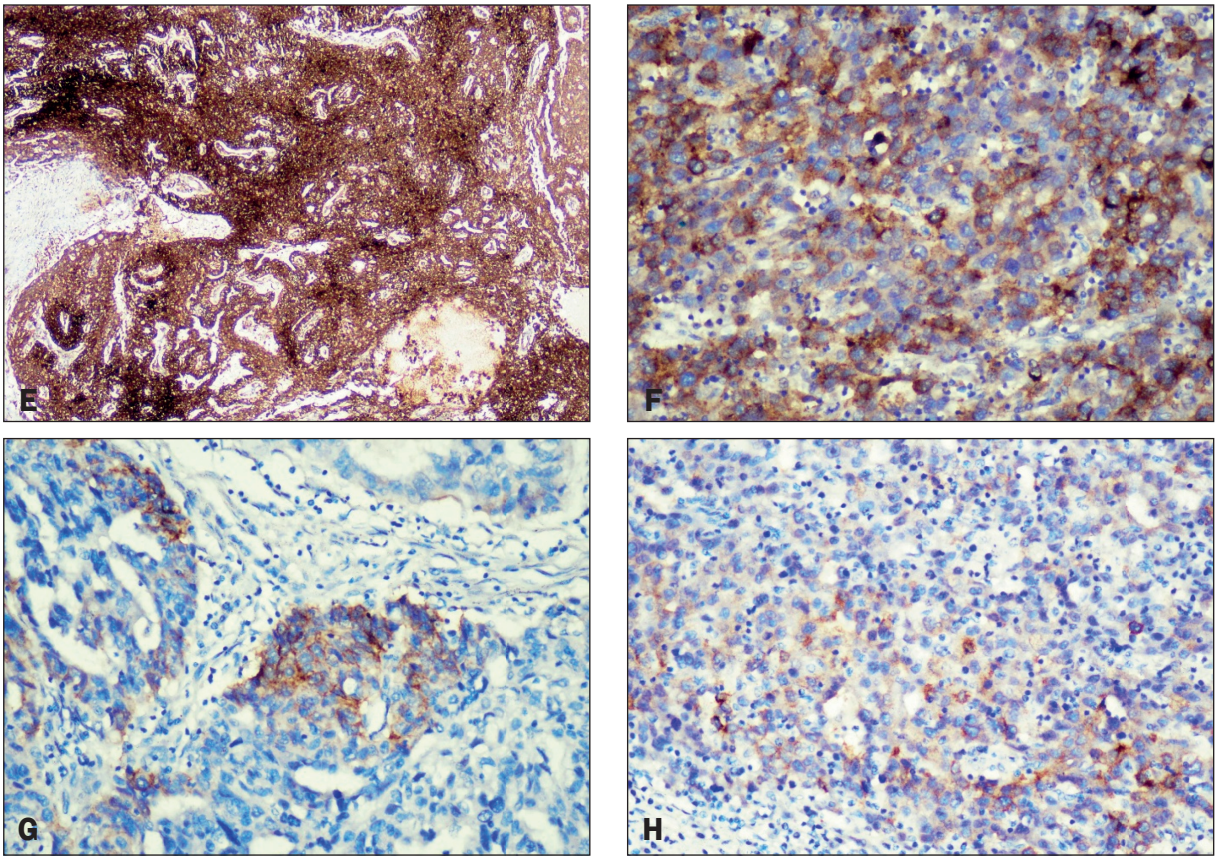


Figure 1. (*continuare*) E) Diffuse positive expression of AFP, IHH x4. F) Diffuse positive cytoplasmic expression of Glipican, IHH x20. G) Focal positivity of CD117, IHH x20 H). Focal positivity of Synaptophysin, IHH x20.

invasion was present. The tumour infiltrated the full thickness of the gastric wall and extended to involve the visceral peritoneum. Surgical resection margins were free of tumour; however, metastatic involvement was identified in 18 regional lymph nodes.

Immunohistochemical analysis demonstrated diffuse positivity for alpha-fetoprotein (AFP) and Glipican (Figure 1E and F) in areas showing clear embryonal differentiation. CD117 and synaptophysin showed focal positivity (Figure 1G and H), whereas cytokeratin 7 (CK7) and GATA3 were negative. The combined morphological and immunohistochemical features were consistent with a diagnosis of YST. According to the American Joint Committee on Cancer (AJCC) staging system (eighth edition), the pathological stage was pT4a pN3 pM0.

Postoperatively, the serum alpha-fetoprotein (AFP) level was measured and showed elevation at 174 ng/mL (reference range: 0–9 ng/mL), whereas serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels remained within normal limits.

One month after surgery, the patient was admitted to the oncology department for further evaluation. A restaging contrast-enhanced CT scan of the head, chest, abdomen, and pelvis revealed metastatic abdominal lymphadenopathy. The liver was enlarged with heterogeneous parenchymal density and contained an ill-defined hypodense lesion in segment VIII measuring 63×59 mm, suggestive for metastatic disease. Bone window imaging demonstrated a suspicious osteosclerotic lesion consistent with possible bone metastasis. Subsequent ^18F-FDG PET/CT confirmed multiple hepatic metastases involving segments I, V, VI, VII, and VIII, with a maximum standardized uptake value (SUV max) of 5.02. Based on these findings, the disease was staged as cT4N3M1.

Laboratory investigations revealed markedly elevated AFP levels (2138.0 ng/mL), while CEA and CA 19-9 levels were within normal limits (0.02 ng/mL and 8.13 U/mL, respectively). As part of the diagnostic workup, programmed death-ligand 1 (PD-L1) and human epidermal growth factor receptor 2 (HER2) expression were assessed. PD-L1 immunohistochemistry demonstrated no expression in viable tumor cells or adjacent mononuclear inflammatory cells, corresponding to a Combined Positive Score (CPS) of 0. HER2 status was also negative (score 0).

Systemic therapy was initiated within two weeks, consisting of Etoposide and Cisplatin administered in a 5-day regimen. At the initiation of chemotherapy, AFP levels were reassessed as a marker of tumour

Table 1. Summary of all reported cases of pure or combined gastric YSTs with emphasis on age at presentation, histology, serum AFP levels and survival.

N	*Authors (year)*	*Age (years)/ Sex*	*Histology*	*AFP ng/ml*	*Survival*
1.	Garcia et al. 1985[16]	65/M	YST, CC, AC	NM	Autopsy case
2.	Motoyama et al. 1985[17]	72/F	YST, AC	NM	Alive (3 yr)
3.	Zámecník et al. 1993[18]	88/M	YST	NM	Died (4 weeks)
4.	Suzuki et al. 1999[19]	56/M	YST, AC	NM	Died (6 mo)
5.	Puglisi et al. 1999[9]	61/M	YST, AC	1050 post surgery	Died (1 mo)
6.	Wang et al. 2000[8]	36/M	YST, AC	38,20	Died (6 mo)
7.	Napaki 2004[20]	38/F	YST, AC	NM	Alive (32 mo)
8.	Kanai et al. 2005[21]	87/M	YST	↑AFP	Died (7 mo)
9.	Singh et al. 2007[22]	67/M	YST, AC	4178	Died (2 mo)
10.	Tahara et al. 2008[23]	74/M	YST	523	Died (6 days)
11.	Kim et al. 2009[10]	61/M	YST	50	Alive (3 mo)
12.	Magni et al. 2010[7]	62/M	YST	0,4 ng/ml post surgery 50 ng/ml upon progression	Died (1 yr)
13.	Satake et al. 2011[3]	74/M	YST, CC, AC	↑AFP	Alive (8 mo)
14.	Bihari et al. 2013[12]	50/M	YST, AC	2291	NM
15.	Yalaza et al. 2017[24]	68/F	YST, AC	50	Died (8 mo)
16.	Lakshmanan et al. 2017[25]	75/M	YST, AC, CC	65	Alive (30 mo)
17.	Qureshi et al. 2018[26]	52/M	YST, AC	normal	Alive (16 mo)
18.	Mandelia et al. 2018[27]	3/M	YST	21	Alive (5 mo)
19.	Ibrahim et al. 2019[28]	86/F	YST	NM	NM
20.	Umeda et al. 2021[29]	77/M	YST, AC	normal	Alive (7 yr)
21.	Taslim S et al. 2023[30]	73/M	YST, AC	NM	Alive (18 mo)
22.	Present case 2026	65 /F	YST	2138	Died (5 mo)

Legend: YST – yolk sac tumour; AC – adenocarcinoma; CC – choriocarcinoma; NM- not measured; mo – months; yr – years.

aggressiveness and showed a marked increase to 10,838.7 ng/mL. Due to grade 1 hepatic insufficiency, hepatoprotective therapy was initiated, including Ademetionine (Transmetil®) at a dose of 2 tablets daily and ursodeoxycholic acid (Ursufalk®) 1 tablet daily. The patient completed two cycles of chemotherapy. The clinical course was rapidly progressive, and the patient died shortly thereafter. The overall survival from diagnosis was 5 months.

Discussion

YSTs are malignant germ cell tumours that most commonly arise in the gonads. Extragonadal YSTs account for approximately 5–20% of cases, depending on the reported series, and typically develop along the midline, including the mediastinum, retroperitoneum, sacrococcygeal region, and skull base[32]. Compared with their gonadal counterparts, extragonadal nonseminomatous germ cell tumours are generally associated with a less favorable prognosis[1,4].

Gastric YST is an exceedingly rare neoplasm. To date, only 21 cases have been reported in the global literature, as summarized in Table 1. The disease predominantly affects older men, with the age at diagnosis reported to range between 60 and 75 years, which is consistent with the age of our patient (65 years). Only two cases have been described in younger individuals, aged 36 and 38 years. Overall, there is a marked male predominance, with a reported male-to-female ratio of approximately 4:1.

The pathogenesis of gastric YSTs remains unclear. One proposed hypothesis suggests that gastric YSTs may arise through retro-differentiation of adenocarcinoma, as most reported gastric YSTs are associated with an adenocarcinomatous component[8,9]. This hypothesis is supported by genotyping analyses demonstrating identical patterns of *p53* mutations in both

the adenocarcinomatous and yolk sac components[9]. Another hypothesis proposes that, like other germ cell tumours, gastric YSTs may originate from primordial germ cells that aberrantly migrate during embryonic development. Alternatively, they may arise from tumour stem cells present within a somatic gastric tumour[6].

In 14 of the reported cases, YST has been identified as part of a mixed tumour, most commonly in association with adenocarcinoma, choriocarcinoma, or embryonal carcinoma, whereas pure YST has been reported less frequently.

In the present case, the histopathological examination revealed a pure yolk sac tumour, which was immunohistochemically confirmed by the expression of AFP and CD117. We also evaluated the expression of HER2 and PD-L1 to explore potential therapeutic options; however, both markers were negative.

Clinical symptoms are often nonspecific and may include epigastric pain, hematemesis, anorexia, abdominal fullness, and weight loss[10]. Our patient presented with abdominal pain and vomiting. Notably, in the present case an asymptomatic partial occlusion of the portal vein was identified, a finding that has not been described in previously reported cases. This presentation may be explained by mechanisms similar to those observed in other intra-abdominal malignancies, in which venous thrombosis involving vessels of the extremities, abdomen, or pelvis occurs as part of a paraneoplastic syndrome[11].

As shown in Table 1, metastatic spread in gastric YST most commonly involves the lymph nodes and the liver, findings that were also observed in our patient. At initial staging, extensive lymph node involvement (18/18 lymph nodes positive for metastases) and portal vein thrombosis were identified, indicating highly aggressive tumour biology. Within one month after radical surgical treatment, rapid disease progression occurred, with the development of hepatic and bone metastases. This clinical course is consistent with the poor outcomes reported in the literature.

AFP represents a key prognostic biomarker in YSTs. AFP levels exceeding 1000 ng/mL have been associated with aggressive tumour behavior, rapid disease progression, and shorter overall survival[9,12,22,31]. Among reported cases of gastric YST, the median overall survival of patients with AFP levels above 1000 ng/mL was approximately 3 months, compared with about 10 months in patients with only mild elevation (around 50 ng/mL)[8,10,24,25]. The longest survival reported is 7 years in a patient with normal AFP serum levels.[29] In our patient, AFP levels increased dramatically from 2,138 ng/mL to 10,838.7 ng/mL within less than two weeks, clearly reflecting the aggressive nature of the disease and correlating with radiological evidence of rapid progression.

The prognosis of gastric YSTs is generally poor, and the optimal therapeutic strategy beyond surgical treatment remains uncertain. Many patients present with widespread metastatic disease at the time of diagnosis, most commonly involving the retroperitoneum, lungs, liver, and bones[12,13]. In previously reported cases, overall survival has ranged from one to seven months. An exception was a 72-year-old patient without distant metastases at the time of diagnosis who survived for an additional three years. Overall, most patients with gastric YST die within one year of diagnosis, largely because the disease is frequently already disseminated at presentation[14]. The poor prognosis of gastric adenocarcinomas containing YST components, which often metastasize to lymph nodes, lungs, or liver, further highlights the diagnostic importance of elevated AFP levels, particularly when gonadal tumours and hepatocellular carcinoma have been excluded[12].

Adjuvant chemotherapy agents, such as cisplatin, vinblastine, bleomycin and etoposide, have not been shown to improve long-term survival of patients with gastric YSTs[14]. Despite the presence of germ cell components, they seem to have poor responses to chemotherapy. At present, there is no large-scale clinical research about YSTs-related targeted therapy. A recent study showed that the programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway could be a novel therapeutic target in testicular germ cell tumours[15]. As in previously reported cases, platinum-based chemotherapy (cisplatin plus etoposide) was the most applied regimen and was also used in our patient. Nevertheless, treatment response remains limited, particularly in the presence of hepatic metastases and underlying liver dysfunction, as observed in this case. Overall survival in patients with liver metastases rarely exceeds six months; our patient achieved an overall survival of five months, which is fully comparable with published data.

Conclusions

The presented case confirms that gastric YST is an exceptionally aggressive malignancy with a poor prognosis, particularly in advanced-stage disease and in the presence of rapidly increasing AFP levels. Despite radical surgical intervention and systemic chemotherapy, survival remains limited. Accumulation of additional clinical cases and further molecular analyses are essential to improve understanding of the biological behaviour of this rare tumour and to optimize future therapeutic strategies.

Authors' contributions

S.N.G. provided original draft preparation, review & editing, diagnosis, conceptualization, IHH analysis. N.E.

provided conceptualization, methodology, draft text; N.T.I. provided conceptualization, methodology, IHH testing of PDL1, HER2; translation; G.A.K. provided draft text, clinical investigation, translation.

Compliance with Ethics Requirements

"The authors declare no conflict of interest regarding this article".

"The authors declare that all the procedures of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient regarding the conducted studies, scientific research, and future publications. "

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