Original Article

Retroperitoneal Soft Tissue Sarcoma with Ectopic Beta-human chorionic gonadotropin (ß-hCG) production mimicking a Nonseminomatous Germ Cell Tumor in a 33-year-old male: A Case Report

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ABSTRACT

Background: Beta-human chorionic gonadotropin (ß-hCG) is produced by the placenta syncytiotrophoblasts and some nonseminomatous germ cell tumors (GCT). In this paper, we report a rare case of retroperitoneal soft tissue sarcoma in a young male with elevated serum ß-hCG, which presents a diagnostic dilemma for clinicians.
Case Discussion: A 33-year-old male presented with a 4-year history of right lower quadrant abdominal mass. A computed tomography (CT) scan revealed bilateral iliopsoas masses with enhancing ileocolic lymph nodes. Tumor markers showed a 131x elevated ß-hCG. Based on these findings, the patient was diagnosed with extragonadal GCT and referred to medical oncology for chemotherapy. He has no history of cryptorchidism; testicular physical examination and ultrasound were unremarkable. CT scan-guided biopsy of the mass was pursued, which revealed a high-grade sarcoma. After work-up, the patient already had liver metastasis and subsequently underwent palliative chemotherapy. There was an improvement in symptoms during chemotherapy with decreasing ß-hCG trends. However, the patient contracted a coronavirus disease 2019 infection, which delayed his treatment. On follow-up, he presented with progressive disease, and ß-hCG was also further elevated at >1,361 mIU/mL.
Conclusion: Young adult male patients presenting with a retroperitoneal mass and elevated serum ß-hCG should also be differentially diagnosed with soft tissue sarcomas. This will help avoid delays in the initiation of treatment, as these have different management and prognosis.

Keywords: Beta-hCG, soft tissue sarcoma, retroperitoneal mass

INTRODUCTION

The placenta's syncytiotrophoblasts and some germ cell tumors produce beta-human chorionic gonadotropin (ß-hCG). However, it can also be secreted ectopically by some epithelial tumors, such as bladder, colorectal, and lung cancers, and is associated with a poor prognosis.[1] Interestingly, only a few cases report sarcomas to be secreting ß-hCG, and even in sarcomas, most of them are found in leiomyosarcomas and osteosarcomas.[2] We report a rare case of ß-hCG-secreting soft tissue sarcoma, which presented as a diagnostic dilemma among clinicians.
In a young male presenting with a retroperitoneal tumor, one of the differential diagnoses would be germ cell tumors (GCT). Tumor markers, including alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), and ß-hCG, play a valuable role in diagnosing, treating, and following

GCTs. Elevated levels of these markers can often help identify the histological type of the tumor.[3] The markedly elevated ß-hCG level in the patient's blood tests led medical oncologists to suspect an extragonadal germ cell tumor. GCT predominantly arises from the testis, but a subset may be extragonadal. 5 to 10% of these arise in nongonadal sites, especially in the mediastinum and retroperitoneum. The initial hypothesis on the tumorigenesis of GCT is that these tumors represent metastasis from an occult gonadal primary.[4] However, the patient's history and physical examination do not align with a typical presentation of extragonadal GCT. Therefore, medical oncologists sought a definitive diagnosis through histological examination.

METHODS

A 33-year-old male presented with a tumor located in the lower right region of his abdomen. The patient initially had right lower quadrant abdominal pain in 2018, which gradually increased in intensity over time. In January 2022, the patient noticed a mass in the exact location, about 5 inches in diameter. He then consulted a gastroenterologist, and a whole abdominal CT scan revealed a mass in the right iliopsoas muscle measuring 13.35 x 12.48 x 13.46 cm and another mass in the left iliopsoas measuring 3.78 x 3.21 x 2.77 cm. There were also enhancing nodes in the ileocolic region. The patient was then referred to surgical oncology for further management. The differential diagnoses at this time were extragonadal soft tissue tumor, gastrointestinal stromal tumor, or soft tissue sarcomas. Tumor markers were requested, and they showed an elevated ß-hCG at 350.91 mIU/ml, normal CEA of 1.220 ng/ml, and normal AFP at 1.920 ng/ml. The markedly elevated ß-hCG level and a retroperitoneal mass in a young adult male suggested an extragonadal germ cell tumor. Based on these findings, doctors referred the patient to medical oncology for chemotherapy. He has no comorbidities, no cryptorchidism history, and unremarkable family history. On physical examination, he has a performance status of Eastern Cooperative Oncology Group (ECOG) 1, with a palpable mass in the right hemiabdomen measuring approximately 17 x 16 cm, fixed, solid, and non-tender on palpation. The testicular examination and scrotal ultrasound requested were unremarkable.

CT scan-guided biopsy of the right iliopsoas mass revealed a spindle cell neoplasm with the following immunohistochemical staining results:

25% of the cells were partially positive for cytokeratin, while vimentin showed diffuse strong positivity. The tests were negative for smooth muscle actin (SMA), Desmin, S100, and CD-45. The pathologist identified the tumor as unusual due to its expression of both vimentin and cytokeratin and, therefore, recommended a repeat biopsy. The patient was referred back to surgical oncology for surgery. However, it was deemed unresectable at that time. The patient's complex diagnosis and treatment plan were presented at a multidisciplinary team (MDT) conference. To obtain a larger tissue sample and expedite treatment, the team decided to perform an open tumor biopsy. Chemotherapy for the spindle cell neoplasm would begin while awaiting the final pathology report. The patient's serum ß-hCG level increased to 468.54 mIU/ml. In September 2022, he underwent a cranial, chest, and repeat whole abdominal CT scan. This scan revealed an increase in the size of the large, hypodense, heterogeneously enhancing lobulated masses in the right and left iliopsoas muscles. The right mass now measured 17.8 x 16.7 x 21.5 cm, and the left mass measured 4.4 x 4.7 x 4.1 cm. Recent fairly-defined hypodense masses are seen in segments 8 and 7 of the liver, measuring 3.1 x 2.5 x 3.5 cm and 1.8 x 1.4 x 1.7 cm, respectively, suspicious for metastasis (Figure 1). The cranial and chest CT scans were unremarkable.

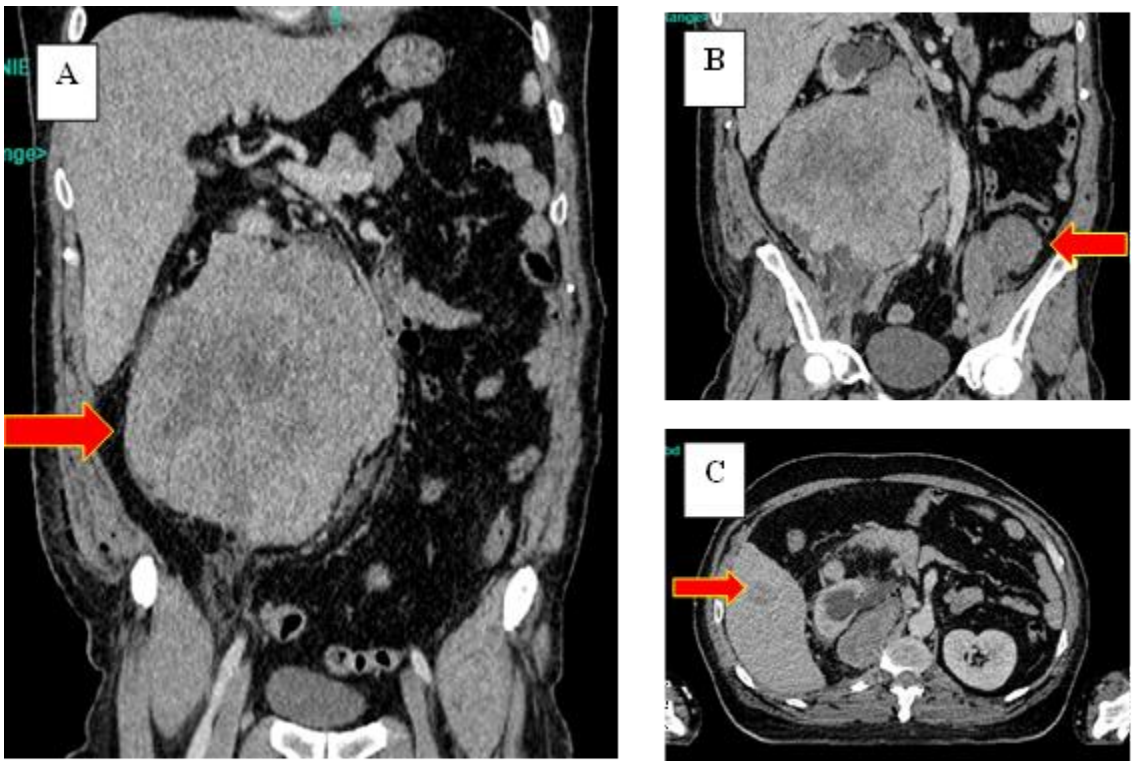

FIGURE 1 CT scan of the patient showing the patient's tumor. (A) Right iliopsoas muscle mass. (B) Left iliopsoas muscle mass. (C) Hypodense mass in the liver is suggestive of metastasis.

The final histopathology report of the repeat biopsy of the iliopsoas mass revealed atypical spindle-shaped cells interlacing fascicles with areas in a storiform pattern. Cells showed nuclear pleomorphism and hyperchromatism, giving the impression of high-grade sarcoma. Consider undifferentiated pleomorphic sarcoma (Figure 2).

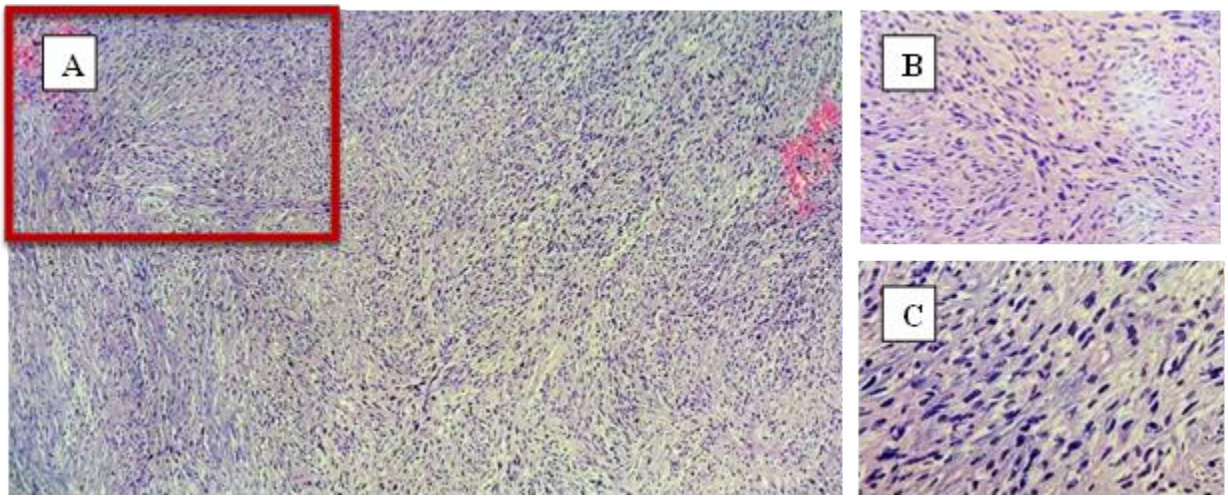

FIGURE 2 The patient's histopathology report shows (A) atypical spindle cells in interlacing fascicles with areas in a storiform pattern and cells showing (B and C) nuclear pleomorphism and hyperchromatism.

The patient was given palliative chemotherapy composed of ifosfamide at 1,500 mg/m2 on days 1-4 and doxorubicin at 25 mg/m2 on days 1-3. MESNA was given with ifosfamide to reduce the risk of hemorrhagic cystitis. ß-hCG was monitored on each cycle and was noted with a decreasing trend, with the lowest ß-hCG of 181.39 mIU/mL (Figure 3), with improvement of symptoms as manifested by a decrease in abdominal pain and feeling of fullness. The medical oncologists planned a repeat imaging study after the third cycle of chemotherapy.

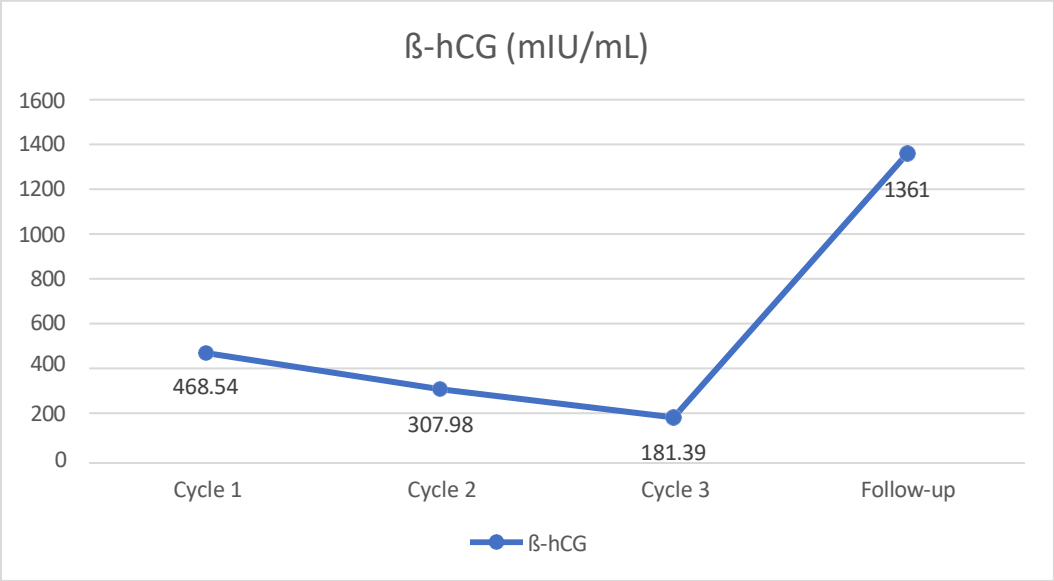

FIGURE 3 ß-hCG trend of the patient during chemotherapy and upon follow-up.

However, after three cycles of chemotherapy, the patient contracted a coronavirus disease 2019 (COVID-19) infection, which resulted in the delay of his treatment. Two months later, he was now presenting with severe abdominal pain, with elevated ß-hCG to >1,361 mIU/mL (Figure 3). Whole abdomen ultrasound showed massive ascites, with an increase in the size of the right iliopsoas mass to 25.9 x15.8 x 9.5 cm, with marked kidney compression by the mass. The patient also suffered acute kidney injury secondary to the mass effect. Due to his poor performance status and elevated creatinine, he was ineligible for chemotherapy. The patient received supportive care, including paracentesis, for fluid drainage. He was also referred to palliative care for pain management and psychosocial support. Ultimately, he chose to return home and discontinued further follow-up appointments.

CASE DISCUSSION

Soft tissue sarcomas are a heterogeneous collection of rare, solid tumors of mesenchymal origin. Each subtype is categorized depending on clinical imaging, histopathologic morphology, special stains, and evaluation of translocations. These tumors so rarely secrete ß-hCG that medical oncologists do not routinely check for this marker in patients with them. However, if they do secrete ß-hCG, they are associated with poorer outcomes, and some authors have published ß-hCG as a marker of soft tissue tumor response.[2] They can occur at almost any anatomical site and

account for 1% of all malignant tumors in adults and 15% of all malignant tumors in children. The incidence varies in different countries and regions, with a crude incidence of 2.91 per 100,000 population in China and a 1.05% overall cancer incidence.[5] It has a poor prognosis with a 5-year disease-specific survival rate of 50-70%.[6] In the Philippines, there is no published data regarding ß-hCG-secreting sarcomas.

ß-hCG is a quaternary structure with a "cysteine knot" in its X-ray crystallography. It is structurally similar to transforming growth factor beta (TGFß), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and bone morphogenic proteins. This finding aligns with observations linking high serum hCG levels with tumor neovascularization. Studies also show that hCG can counteract the cell death effects of TGFß, thereby promoting tumor growth. These findings suggest that ß-hCG might play a role in resistance to VEGF inhibition.[7]

The first case reported on ß-hCG-secreting sarcomas is that of Meredith et al., where a 22-year-old female diagnosed with primary leiomyosarcoma presented with nausea and vomiting that could easily be associated with hyperemesis gravidarum in a pregnant female.[8] She showed high levels of serum ß-hCG, which were eventually localized to the leiomyosarcoma cells using the immunoperoxidase staining technique. This led to the thought that ß-hCG may be used as a tumor marker in some sarcoma patients.[8] Another case report in 2002 was in a 57-year-old man presenting with a one-month history of abdominal pain and a palpable abdominal mass in the xiphisternum down to the pelvis. This case is similar to our patient's case. The examination included a testicular exam and ultrasound, which were both normal. A CT scan revealed a retroperitoneal mass measuring 30 x 21 x 13 cm. Serum ß-hCG levels were serially measured and increased to 19.71-22.71 mIU/mL. Histopathology showed leiomyosarcoma. After chemotherapy, the level of serum ß-hCG decreased to <0.2 mIU/mL.[9]

Below are the cases found in the literature of elevated serum ß-hCG in soft tissue sarcomas using keywords "Beta-hCG" and "sarcoma" on PubMed and Google Scholar. The most common soft tissue sarcomas associated with ectopic ß-hCG production was leiomyosarcoma. Similar to our case, there have been two reported cases of retroperitoneal tumors in males with elevated serum ß-hCG that were initially suspected to have germ cell tumors, which presented a diagnostic dilemma as well. Treatment varied from surgery to chemotherapy and radiotherapy. Four of the cases found in the literature died from the disease.

In the case of a young male patient (like our 33-year-old example) presenting with a retroperitoneal mass and elevated ß-hCG, the initial impression typically leans towards germ cell tumors. This is because nonseminomatous germ cell tumors, particularly choriocarcinomas, are known to be associated with elevated ß-hCG levels.[16] In cancers of unknown primary, it is essential to identify favorable features as they often have a higher response to locoregional or systemic therapy, such as that of GCT.[17] Given the unresectable nature of the lesion and established knowledge of high chemosensitivity in nonseminomatous GCTs[18] initiating chemotherapy might seem like a straightforward course of action. However, the patient's medical history – lacking cryptorchidism and showing a normal testicular ultrasound – argued against this approach. Therefore, we opted to proceed with a biopsy of the retroperitoneal mass for a more definitive diagnosis.

The initial biopsy then only involved spindle cell neoplasm. Indeed, the mass was not an extragonadal germ cell tumor. The unusual presentation of the case led to a delay in the treatment initiation, and eventually, the patient's lesion became unresectable and metastasized before we were able to initiate treatment.

TABLE 1 Cases of soft tissue sarcomas in the literature presenting with elevated serum ß-hCG.

No.	First Author	Age	Sex	Diagnosis	Baseline ß-hCG	Post-treatment ß-hCG	Management	Outcome
1	Krishnan V[10]	33	F	Uterine leiomyosarcoma	49.7 U/L	0.7 U/L	Surgery	Alive
2	Inoue N[11]	3 mos	M	Back nonrhabdomyosarcoma soft tissue sarcoma	17,528 mU/ml	3.4 mU/ml	Surgery and Chemotherapy	Died after 19 months
3	Tsakos E[12]	54	F	Uterine leiomyosarcoma	383.3 IU/L	2.2 IU/L	Surgery and Chemotherapy	Died after six months
4	Froehner M[13]	65	M	Retroperitoneal pleomorphic leiomyosarcoma	48 U/l	0.5 U/l	Chemotherapy	Died after two months
5	Stevens E[14]	45	F	Synovial sarcoma of the hip			Unavailable	
6	Mansi I[9]	57	M	Retroperitoneal leiomyosarcoma	22.71 mIU/mL	<0.2 mIU/mL	Chemotherapy	Alive
7	Seidl C[15]	51	M	Spermatic cord pleomorphic leiomyosarcoma	35 IU/l	<0.15 IU/l	Surgery	Unknown
8	Meredith R[8]	22	F	Small bowel leiomyosarcoma	2900 mIU/ml	7,550 mIU/ml	Surgery	Died after six weeks
9	Blank A[2]	55	F	Posterior thigh unclassified pleomorphic sarcoma	1122 IU/L	Negative	Surgery and Radiotherapy	Alive
10	Index Case	33	M	Retroperitoneal undifferentiated pleomorphic sarcoma	468.54 mIU/mL	181.39 mIU/mL	Chemotherapy	Alive

CONCLUSION

Young adult male patients presenting with a retroperitoneal mass and elevated serum ß-hCG should include the differential diagnosis of soft tissue sarcomas as well, in addition to the more common extragonadal germ cell tumors. Clinicians should be aware that these cases exist to avoid delays in initiating treatment as they have different management and prognosis. In the case presented, the serum ß-hCG levels seem to coincide with the improvement and worsening of the patient's symptoms, suggesting that this could be used not only as a marker of tumor response but also of relapse and poor prognosis. This report recommends further investigation into the characteristics of these patients. It also suggests exploring the usefulness of ß-hCG as a marker for predicting prognosis and tumor response.

DATA AVAILABILITY STATEMENTS

The authors will make the raw data underpinning this article's conclusions accessible upon request without unnecessary restriction. To protect ethical considerations and participant privacy, the

authors cannot publicly share the data. However, they can make it available upon reasonable request with approval from the institutional ethics committee.

ETHICS STATEMENT

Informed consent was secured from the patient and his identity was kept confidential. The paper did not include any data that could identify the patient, such as address and patient initials pertaining to his name.

AUTHORS CONTRIBUTION

OGB, investigation, methodology, writing original draft, review, and editing; CNM, supervision, review and editing

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The authors declare no conflicts of interest related to commercial or financial relationships.

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DECLARATION OF USE OF GENERATIVE ARTIFICIAL INTELLIGENCE

No generative AI technologies were used in the writing of this manuscript.

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