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CASE REPORT

Persistent Elevation of β-hCG Levels in a Patient with Primary Malignant Giant Cell Tumor of Bone: a Case Report and Literature Review

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SUMMARY

Background: **Beta-human chorionic gonadotropin (β-hCG) is commonly used in pregnancy detection and as a tumor marker for reproductive system cancers.**
Methods: **We report a case of a 51-year-old female with primary malignant giant cell tumor of bone (MGCTB) who developed persistently elevated serum β-hCG levels. Considering the possibility of detection interference, we evaluated pre-analytical factors, laboratory quality control, instrumentation, and personnel-related issues, and performed polyethylene glycol precipitation testing to exclude endogenous interference.**
Results: **No interfering factors affecting the β-hCG results were identified, and the measured β-hCG levels were confirmed to be accurate and reliable. The patient was diagnosed with MGCTB, a rare mesenchymal tumor. Eight months after undergoing tumor resection and chemotherapy, she developed pulmonary metastases. During hospitalization, progressive increases in C-reactive protein, D-dimer, and β-hCG levels were observed. We conducted a literature review on mesenchymal tumors with aberrant β-hCG expression, which indicated that elevated β-hCG levels may be associated with poor prognosis.**
Conclusions: **This case suggests that MGCTB may be an unrecognized source of ectopic β-hCG secretion. Clinicians should consider this possibility in similar contexts to avoid misdiagnosis and unnecessary interventions.**
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KEYWORDS

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INTRODUCTION

Beta human chorionic gonadotropin (β-hCG) is a critical biomarker for the diagnosis and monitoring of pregnancy and also functions as a tumor marker in several malignancies, including gestational trophoblastic disease, testicular cancer, and ovarian cancer [1]. Nonetheless, elevated β-hCG levels could also be observed in non-malignant conditions, such as pituitary secretion of β-hCG or interference from heterophilic antibodies [2]. We report a case of persistently elevated β-hCG levels in a patient with primary malignant giant cell tumor of bone (MGCTB).

CASE PRESENTATION

A 51-year-old female patient was admitted to our hospital with complaints of chest tightness, dyspnea, and productive cough with white sputum. Her past medical history was significant for primary MGCTB. On January 29, 2024, she underwent surgical resection of a right tibial lesion, tibial bone grafting, internal fixation with a right tibial plate, and right iliac bone harvesting for grafting purposes. Postoperative histopathology revealed a spindle cell neoplasm of the right tibia. Based on immunohistochemical findings, a diagnosis of primary MGCTB was considered. Immunohistochemical staining showed SAM+, Desmin-, Caldesmon-, CD34-, STAT6-, Ki-67 at 70%, S-100-, SOX10-, WT1-, CAM5.2+, p53 mutant type, H3.3G34W+, H3K27 me3+, weak SATB2+, and Calponin+.

On February 28, 2024, she underwent further surgery including tumor resection of the right tibia, 3D-printed tibial reconstruction, and medial gastrocnemius flap transfer. Pathological consultation reported a malignant mesenchymal tumor of the tibia, again supporting the diagnosis of primary MGCTB based on immunohistochemical results: diffuse H3.3G34W+, scattered weak SATB2+, Ki-67 approximately 60%, SAM+, Desmin-, Caldesmon-, H3K27me3+, S-100-, Calponin+, partial p53+, CD34-, STAT6-, CAM5.2+, WT1-, and SOX10-. She subsequently received four cycles of adriamycin and cisplatin chemotherapy starting on April 13, 2024, with the final cycle administered on July 25, 2024. In September of the same year, follow-up chest CT at Hangzhou Third People's Hospital revealed bilateral pulmonary metastases, indicating disease progression. Upon readmission to our hospital on February 27, 2025, laboratory tests showed an elevated C-reactive protein (CRP) level of 121.57 mg/L, suggestive of infection. Pulmonary angiography demonstrated superior vena cava syndrome and pulmonary embolism, which explained the elevated D-dimer (D-D) level (4.40 mg/L). Tumor markers, including carcinoembryonic antigen, alpha-fetoprotein, cancer antigen 153, and cancer antigen 724, were within normal limits. Unexpectedly, serum β-hCG was markedly elevated at 694.43 mIU/mL (reference range for nonpregnant adults < 5 mIU/mL). Subsequently, the doctor conducted a follow-up blood test to reassess the patient's condition. Upon retrospective review, we observed an increase in CRP to 163.60 mg/L and D-D to 13.50 mg/L compared to previous tests. Concurrently, an additional measurement of β-hCG was performed, revealing an elevated level of 1,586.48 mIU/mL. The patient then received denosumab as antitumor therapy. One week after treatment, repeat testing showed further increases in CRP and D-D, measuring 212.41 mg/L and 22.37 mg/L, respectively. β-hCG was also reassessed, with a result of 1,975.11 mIU/mL. All three markers demonstrated a progressive rise (Table 1).

DISCUSSION

Primary malignant giant cell tumor (MGCT) is a rare and highly aggressive neoplasm that typically arises in bone or soft tissue. It may develop from the malignant transformation of a benign giant cell tumor or originate as a primary malignant lesion. Histologically, MGCT is characterized by marked cellular atypia, active mitotic figures, and locally destructive growth. Unlike the typically slow-growing and well-demarcated primary benign giant cell tumor, MGCT demonstrates a higher likelihood of local recurrence and distant metastasis. We report a case of primary MGCTB that showed disease progression with pulmonary metastasis eight months after surgical resection and adjuvant chemotherapy. During hospitalization at our institution, persistent and unusual elevation of serum β-hCG levels was observed.

Given the absence of clinical or radiological evidence of reproductive system tumors, we conducted a systematic investigation into the potential causes of this unusual finding. The patient's serum sample was clear, showing no hemolysis or lipemia that could interfere with assay performance, and the reaction curve was normal, thereby excluding specimen quality issues. Daily quality control procedures for β-hCG assay in our laboratory confirmed that all controls were within acceptable limits on the day of testing, and no instrument malfunctions were detected. Our laboratory personnel possess extensive immunoassay expertise, ruling out operator-related errors. Furthermore, polyethylene glycol (PEG) precipitation testing was performed by diluting the patient's serum 1:2 with 25% PEG 6000 solution, followed by reassessment of β-hCG, which yielded a recovery rate of 98.23%, effectively excluding endogenous interference. Taken together, these results support the high accuracy and reliability of the elevated β-hCG measurement in this patient.

β-hCG refers to the beta subunit of human chorionic gonadotropin (HCG). HCG is a glycoprotein hormone with a molecular weight of approximately 38,000 Da, composed of two non-covalently linked subunits: alpha (α) and beta (β). The α subunit is identical to that of luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone, whereas the β subunit confers hormone specificity [3,4]. β-hCG has been reported to be produced in gestational trophoblastic diseases as well as in various non-trophoblastic malignancies, including urothelial carcinoma of the bladder and upper urinary tract, gastrointestinal cancers, prostate cancer, and lung cancer [5-8].

This article reports a case of primary MGCTB producing elevated levels of β-hCG. Immunohistochemical detection of muscle-related markers in the pathological specimen confirmed the diagnosis of a mesenchymal tumor. Mesenchymal tissues encompass connective tissue, adipose tissue, muscle, vasculature, bone, and cartilage. Common benign tumors arising from these tissues include lipomas, leiomyomas, and osteomas, while

Table 1. Progressive increases were observed in the patient's CRP, D-dimer, and β-hCG levels.

Date	CRP (mg/L)	D-D (mg/L)	β-hCG (mIU/mL)
2025-02-27	121.57	4.40	694.43
2025-03-06	163.60	13.50	1,586.48
2025-03-12	212.41	22.37	1,975.11

CRP C-reactive protein, D-D D-dimer, β-hCG Beta human chorionic gonadotropin.

malignant counterparts include various sarcomas, such as liposarcomas and leiomyosarcomas.

There have been several case reports of mesenchymal tumors aberrantly expressing β-hCG, with osteosarcoma being the most frequently documented. Mack et al. described a case of pelvic chondrosarcoma with β-hCG levels reaching 5,250 mIU/mL, marking the first reported sarcoma with significantly elevated β-hCG; immunoperoxidase staining demonstrated β-hCG positivity in the cytoplasm of chondrocytes [9]. Kalra et al. reported a 22-year-old female osteogenic sarcoma patient with serum β-hCG levels as high as 5,000 mIU/mL; she subsequently underwent right hip disarticulation and uterine dilation and curettage. Immunohistochemistry of the tumor showed strong β-hCG positivity. After chemotherapy, serum HCG levels declined to 500 mIU/mL, but the patient ultimately succumbed to the disease within weeks [10]. Meredith et al. presented a case of a 22-year-old female with small intestinal leiomyosarcoma who exhibited nausea and vomiting, and whose serum β-hCG was elevated; immunoperoxidase staining localized β-hCG expression to the leiomyosarcoma cells [11]. Ordonez et al. reported elevated β-hCG and positive immunohistochemical staining in a 26-year-old female patient with fibular osteosarcoma. They also examined 10 additional osteosarcoma cases, identifying one more with β-hCG positivity, suggesting β-hCG may serve as a marker for recurrence in rare cases such as osteosarcoma [12]. Seidl et al. described a 51-year-old male patient with leiomyosarcoma of the spermatic cord who exhibited elevated serum β-hCG levels. Immunohistochemical analysis confirmed β-hCG expression by the tumor. Four months after the initial surgery, the patient developed pulmonary metastases, accompanied by a persistent increase in serum β-hCG [13]. Mansi et al. reported a 57-year-old male presenting with progressive abdominal pain and weight loss for one month. A palpable mass extending from the xiphoid process to the pelvis was noted. Urine β-hCG was positive (19.71 mIU/mL), but testicular ultrasound was normal. Abdominal CT revealed a 30 x 21 x 13 cm retroperitoneal mass, and histopathology confirmed leiomyosarcoma. Following chemotherapy, serum β-hCG normalized (< 0.2 mIU/mL) [14]. Inoue et al. reported a case of a full-term neonate with a 2 cm mass on the right dorsal back, which enlarged to 8 cm by 3 months. Imaging studies found no distant metastases. The patient had markedly elevated serum β-hCG (17,528 mIU/mL), with strong immunohistochemical positivity confirming nonrhabdomyosarcoma soft tissue sarcoma. Post tumor resection, residual lesions rapidly recurred with β-hCG rising to 6,018 mIU/mL. Radiotherapy and chemotherapy reduced β-hCG to below 10 mIU/mL for two months, but normalization was not achieved. After four chemotherapy cycles, tumor regrowth and β-hCG elevation (1,553 mIU/mL) occurred. Palliative chemotherapy including cisplatin and irinotecan monotherapy over nine cycles was administered; tumor size increased to 15 cm and β-hCG peaked at 42,236 mIU/mL. The patient died at 22 months of age [15]. Masrouha et al. retrospectively analyzed 37 histopathological slides from 32 osteosarcoma patients, finding β-hCG positivity in five cases, predominantly in tumors with poor histological response to neoadjuvant chemotherapy [16]. Stevens et al. reported a 45-year-old female with synovial sarcoma of the hip presenting with four months of persistent buttock pain. Initial β-hCG was 75.19 mIU/mL, with negative pelvic X-ray and ultrasound for fracture or pregnancy. β-hCG later increased to 180.34 - 193.68 mIU/mL. Misdiagnosis as gynecological malignancy or ectopic pregnancy delayed diagnosis by three months, and the tumor became unresectable [17]. Kugasia et al. described a 49-year-old female with a solitary fibrous tumor of the pleura, a rare mesenchymal tumor. Due to an unexplained elevation of β-hCG, immunohistochemical staining for β-hCG was performed on the tumor specimen, which confirmed that the solitary fibrous tumor was the source of the elevated β-hCG [18]. Oshrine et al. reported a β-hCG-secreting osteosarcoma in a 14-year-old female adolescent; immunohistochemistry of the primary tumor biopsy was β-hCG positive. Her serum β-hCG remained within normal limits during six months post-treatment [19]. Lee et al. performed β-hCG immunohistochemistry on 49 osteosarcoma tissue samples, with 28 (57%) showing positive expression [20]. Carol et al. described a 20-year-old female with an aggressive scapular osteoblastoma who exhibited elevated preoperative serum β-hCG, initially suspected of pregnancy, which delayed surgery. Post-tumor resection, β-hCG immunostaining was positive, and serum β-hCG normalized, confirming paraneoplastic β-hCG secretion [21]. Alan et al. reported a 55-year-old female with a soft tissue sarcoma who was found to have elevated β-hCG on the day of tumor resection; immuno-

histochemistry confirmed the sarcoma as the source of β-hCG [22].

In summary, although previous studies have explored the prognostic significance of β-hCG in mesenchymal tumors, definitive conclusions remain elusive. Given the potential adverse prognostic implications of β-hCG elevation, we conducted close monitoring of this patient to assess clinical outcomes. In cases of unusual, particularly persistent, β-hCG elevation, clinicians should consider the possibility of malignant tumors, including mesenchymal tumors, after excluding pregnancy and other reproductive system disorders.

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Declaration of Interest:

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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