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CASE REPORT

Case Report

Elevated Serum Beta Human Chorionic Gonadotropin in a Woman With Osteosarcoma

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Abstract Human chorionic gonadotropin is a glycoprotein hormone normally synthesized by placental syncytiotrophoblast cells. It also is secreted by gestational trophoblastic tumors, gonadal tumors, and even various nongonadal tumors, including bone and soft tissue sarcomas, as a paraneoplastic syndrome. The literature contains one case report of beta human chorionic gonadotropin production from a primary bone sarcoma occurring in a male patient. We report a woman of childbearing age who presented with a distal femur lytic lesion, clinical symptoms suggestive of pregnancy, and elevated serum beta human chorionic gonadotropin. Although the clinical diagnosis of a sarcoma was never in doubt, we present this case to emphasize a need to exclude pregnancy in women of childbearing age to avoid delay in biopsy and subsequent management. Positive immunohistochemical staining of the biopsy specimen established the tumor cells as the source of beta human chorionic gonadotropin.

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Each author certifies that his or her institution has approved or waived approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

The paraneoplastic production of hormones plays an important role in the diagnosis and treatment of associated tumors. Human chorionic gonadotropin (hCG) is a glycoprotein synthesized in normal pregnant women 4 to 7 days after implantation until term by the syncytiotrophoblast cells of the placenta [7]. The hCG molecule is made up of two distinct subunits. The alpha subunit is not a specific marker for hCG because it is common to glycoprotein hormones, including thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone [6, 13, 14]. The beta subunit (βhCG) confers biologic activity and has 80% homology with luteinizing hormone; an additional 24-amino acid carboxyterminal peptide differentiates the two molecules and makes the beta subunit a reliable marker for hCG [6, 14]. As a paraneoplastic syndrome, βhCG is secreted by gestational trophoblastic tumors, gonadal tumors, and nongonadal tumors as well [1, 4–6, 11, 12].

The literature contains three reported cases with documented βhCG expression in osteosarcoma cells [5, 6, 13]. In addition, two reports describe the detection of βhCG in the serum of patients with osteosarcoma [2, 3]. One case of βhCG production from a pelvic chondrosarcoma has been reported in a male [8]. We report a case of osteosarcoma of the femur in a woman of childbearing age associated with elevated serum βhCG and symptoms suggestive of pregnancy, which led to a delay in operative biopsy.

Case Report

A 37-year-old woman presented to our institution because of left knee swelling and pain of 6 months' duration. Twenty years earlier, she had been treated for a left distal

femur fracture with open reduction internal fixation and autogenous iliac crest bone grafting. Her obstetric history revealed four full-term normal vaginal deliveries, one spontaneous abortion, and two terminations of pregnancy. Her social history revealed tobacco use for 27 years, daily alcohol consumption, and a history of cocaine and marijuana use. Physical examination showed left knee swelling, tenderness over the distal femur medially, and a flexion contracture. Radiographs revealed a large radiolucent lesion in the distal femur metaphysis with permeative borders and areas of sclerosis (Fig. 1). She was admitted for open biopsy. However, preoperative laboratory evaluation revealed an elevated serum βhCG of 254 mIU/mL for which a gynecology consultation was obtained. The patient admitted to having vaginal bleeding with passage of blood clots and abdominal cramping since the previous day. On pelvic examination, the cervix was closed but the uterus could not be adequately palpated because of obesity. A missed abortion and an early ectopic pregnancy were considered by the gynecology service who also recommended a repeat serum βhCG determination after 48 hours. Open biopsy was deferred and she was discharged. Despite attempts to contact the patient, she was lost to followup.

Seven months later, she was admitted to an outside institution for amenorrhea of 6 weeks' duration along with persistent left knee pain and swelling. A pelvic ultrasound revealed no intrauterine gestation. She underwent a laparoscopy and uterine dilation and curettage. The latter procedure revealed abundant clots with small fragments of inactive endometrial tissue and moderate inflammation. She then was transferred to our institution for additional management of her gynecologic and orthopaedic issues.

On transfer, physical examination revealed a large mass in the left knee with areas of skin necrosis and several tumor nodules. Her serum βhCG on admission was 2177 mIU/mL and a repeat pelvic ultrasound confirmed the absence of intrauterine gestation. Repeat radiographs revealed progressive destruction of her distal femur. Magnetic resonance images showed a large necrotic soft tissue mass invading all compartments of the thigh and the neurovascular structures (Fig. 2). A chest radiograph revealed multiple lung nodules, whereas a whole-body bone scan revealed no other skeletal lesions. We performed a core-needle biopsy of the soft tissue mass using a Tru-Cut™ needle (Baxter International Inc, Deerfield, IL), a special 14-gauge needle that allows recovery of slivers of tissue through a small skin stab. This showed a high-grade osteosarcoma (Fig. 3); the tumor cells had focal positivity on immunohistochemical staining for βhCG (Fig. 4). Because of the extensive soft tissue mass with ulcerating skin nodules and neurovascular infiltration, an above-knee amputation was performed. Her incision healed uneventfully and she

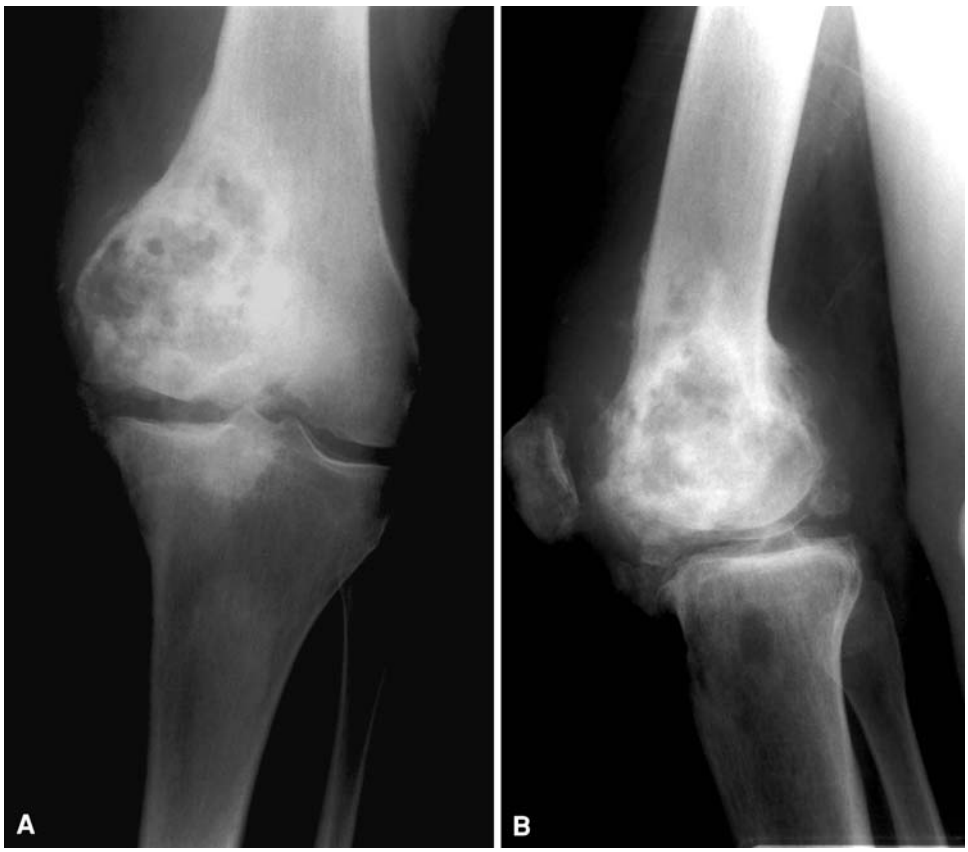

Fig. 1A–B (**A**) Anteroposterior and (**B**) lateral radiographs of the initial tumor show a large radiolucent lesion in the distal femoral metaphysis with permeative borders and areas of sclerosis.

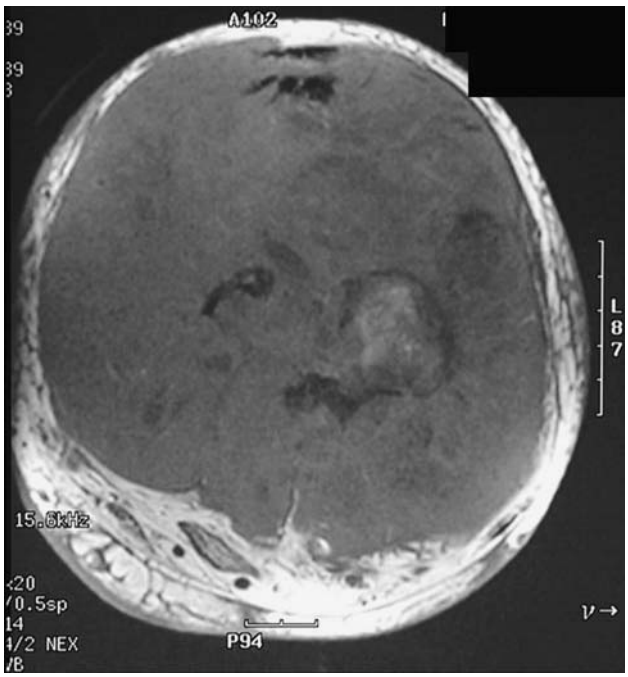

Fig. 2 An axial T1-weighted MR image through the distal femur shows a large soft tissue mass affecting all compartments of the thigh. The neurovascular structures cannot be identified because of the massive tumor.

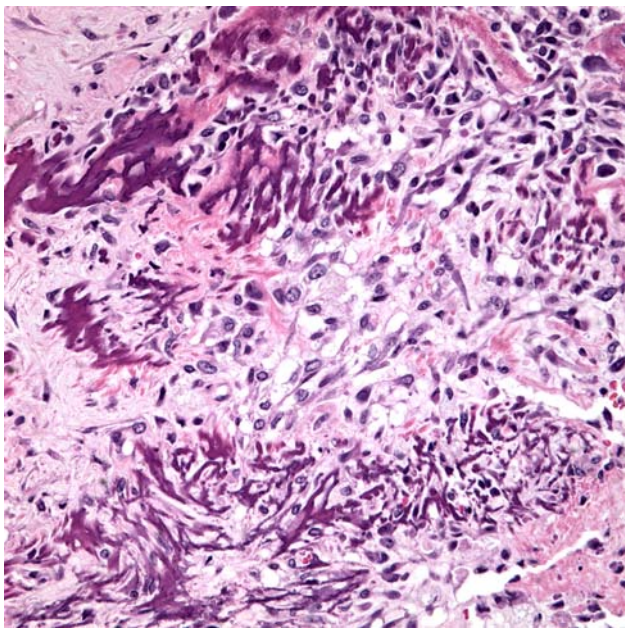

Fig. 3 A photomicrograph of the biopsy specimen shows spindle-shaped tumor cells and a dense, pink osteoid matrix (Stain, hematoxylin and eosin; original magnification, ×100).

was discharged stable after a discussion with the oncology service for palliative chemotherapy. However, the patient did not return for chemotherapy and subsequently died of her disease.

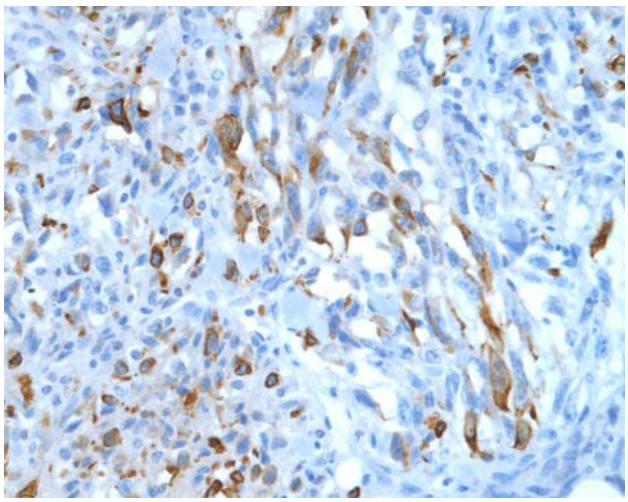

Fig. 4 A photomicrograph shows the biopsy specimen with immunohistochemical staining for βhCG (Stain, anti-βhCG, PAP method; original magnification, ×100). Brown pigmentation in the cytoplasm confirms the expression of βhCG by the tumor cells.

Discussion

In 1977, Mack et al. [8] described a 26-year-old man who had an undifferentiated malignant acetabular neoplasm. A urine pregnancy test was performed twice because a germ-cell tumor was considered; the test was returned positive. Only on autopsy was the diagnosis of a chondrosarcoma definitively established; using an indirect immunoperoxidase reaction, hCG expression by the tumor was observed.

The literature contains three reports of βhCG production by osteosarcomas in females of reproductive age [5, 6, 13]. Kalra et al. [5] reported a 22-year-old woman with a distal femur osteosarcoma that was treated surgically. She refused chemotherapy, and 14 months later, she returned with leg pain and amenorrhea of 4 months' duration. Her serum βhCG level was 5000 mIU/mL. Pelvic examination revealed a normal-sized uterus with no adnexal masses. She was treated with a hip disarticulation and uterine dilation and curettage in one visit. Ordonez et al. [13] reported a 26-year-old woman with a high-grade osteosarcoma of the fibula. Serum βhCG was markedly elevated at 20,460 IU/L. A pelvic ultrasound revealed no intrauterine or adnexal pregnancy and a uterine dilation and curettage showed no conceptual products. A third case, reported by Leidinger et al. [6], involved an 18-year-old woman presenting with arm pain. She had been treated 2 years previously for a proximal humerus osteosarcoma. Her serum βhCG level was markedly elevated at 717 mIU/mL; pregnancy was excluded by ultrasound. A forequarter amputation was performed. In all three cases, immunohistochemistry of the resected tumor was positive for

βhCG. Except for the case of Mack et al. [8], a double-antibody radioimmunoassay with an antibody specifically targeted for βhCG was used; this test is sensitive for detecting 1.0 ng/mL or 5 mIU hCG per mL serum and avoids cross-reactivity with other glycoproteins, like luteinizing hormone or carcinoembyonic antigen [15].

Our case illustrates a situation in which the elevated serum βhCG in a woman of reproductive age with clinical symptoms suggestive of pregnancy led to a delay in operative biopsy of a suspected sarcoma. In our institution, women of reproductive age are screened with urine βhCG tests before surgery or chemotherapy. Currently, the hospital uses a screening test (Sure-Vue® STAT; Fisher HealthCare, Houston, TX) based on a combination monoclonal and polyclonal antibody reagent that selectively detects elevated hCG levels. This is considered a sensitive screening test such that positive tests and/or clinical signs compatible with pregnancy would indicate a quantitative serum βhCG determination. Our patient's serum βhCG was elevated at 254 mIU/mL; however, because she presented with concurrent symptoms of amenorrhea, vaginal bleeding, and abdominal cramping, the other considerations were a missed abortion and an ectopic pregnancy. A decision was made to repeat the serum βhCG determination after 48 hours, which is expected to double in a normally progressing pregnancy [14]. If the βhCG levels did not increase at the expected levels, then additional workup with a pelvic ultrasound, uterine dilation and curettage, or laparoscopy would be directed at delineating an ectopic pregnancy, missed abortion, or a gestational trophoblastic tumor. The patient, however, was lost to followup, and in hindsight, the patient's discharge could have been deferred and/or pelvic ultrasound could have been performed early to exclude the other differentials and expedite biopsy of the lesion.

The importance of βhCG expression in osteosarcoma cells is unknown. Leidinger et al. [6] suggested it may be a sign of tumor dedifferentiation based on the presence of further dedifferentiation in a local recurrence with abundant βhCG expression compared with sparse expression in the original tumor. However, Kalra et al. [5] reported the undifferentiated portion of their osteosarcoma specimen stained negatively for hCG. In the chondrosarcoma specimen from the patient of Mack et al. [8], positive staining for hCG occurred only in the areas of cartilaginous differentiation and was negative in the undifferentiated areas. Some authors suggest βhCG production may indicate recurrent disease [5, 6]. In one case of recurrent osteosarcoma with a high serum βhCG level, an analysis of the patient's frozen plasma taken from the time of initial diagnosis showed normal serum βhCG levels; archival specimens of the original tumor stained sparsely for βhCG [6]. Still, other studies report detectable levels of βhCG in the serum of patients with known osteosarcoma using routine assays [2, 3]. Currently, there is no established role for βhCG in osteosarcoma management. Nonetheless, an awareness of its possible expression in bone sarcomas is important so the clinician can act decisively when a positive pregnancy test is found in a woman with suspected sarcoma, especially if there are clinical findings suggestive of an active pregnancy. This seemingly obscure information is useful not only to orthopaedic oncologists but also to general orthopaedic practitioners who perform biopsies of musculoskeletal tumors [9, 10]. A viable intrauterine pregnancy should be ruled out early, and an early missed abortion or ectopic pregnancy should be diagnosed expediently, so as not to delay the operative biopsy required for definitive diagnosis of a suspected bone sarcoma and ultimately its treatment.

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