CASE REPORT

 β hCG-secreting osteosarcoma

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SUMMARY

A 35-year-old woman presented to our institution with tender, right knee swelling. Radiological and pathological work-up revealed metastatic osteosarcoma. Prior to the initiation of chemotherapy, she underwent a routine urine pregnancy test and was surprised with a positive result. Serum beta human chorionic gonadotropin (β hCG) levels were also consistently positive and rising. No gestational sac was seen at transvaginal ultrasound. The paraneoplastic ectopic secretion of β hCG has been well described in gestational trophoblastic and gonadal tumours but has very rarely been associated with other tumour types. This patient's β hCG level was reflective of osteosarcoma activity and normalised with response to chemotherapy. The prognostic implications of β hCG expression in more diverse tumours is unclear; however, where raised, it can be used to monitor disease activity.

BACKGROUND

Human chorionic gonadotropin (hCG) is a glycoprotein hormone produced predominately by syncytiotrophoblast cells of the placenta, but can also be produced by the pituitary and non-trophoblastic malignancies.¹ Paraneoplastic ectopic secretion of β hCG has been well described in the setting of gestational trophoblastic and gonadal tumours, for which β hCG measurement is central to diagnosis and therapeutic monitoring. It has also been reported in the setting of other solid tumour types including breast, lung, pancreatic, colorectal and bladder cancers^{2–5} and has been associated with poor prognosis.^{6,7} However, secretion of β hCG by osteosarcomas has rarely been described.^{8,9}

We report on the case of an osteosarcoma of the tibia in a young woman of childbearing age in whom rising β hCG levels initially thought to represent pregnancy were ultimately attributed to ectopic tumour production. The initial positive pregnancy result and the rising β hCG levels delayed immediate chemotherapy initiation and resulted in additional emotional strain for the patient at an already difficult time.

This case highlights the need for serial daily β hCG levels for at least 48 hours and imaging to definitively exclude pregnancy in a patient undergoing work-up for malignancy, to prevent delays in essential treatment initiation. Additionally, when an unusual pattern of serial β hCG levels is observed, ectopic tumour secretion, however rare, should be considered. In this case, despite negative immunohistochemical staining on the patient's tumour biopsy, the serum β hCG levels were reflective of disease activity and treatment response.

Furthermore, it highlights the potential utility of β hCG as a marker in therapeutic monitoring for β hCG-secreting osteosarcomas.

CASE PRESENTATION

A previously healthy 35-year-old woman presented to our institution with right knee pain of 3 weeks duration. Physical examination demonstrated right knee swelling with associated tenderness over the distal tibia posteriorly and a flexion contracture. Medical history was otherwise unremarkable.

INVESTIGATIONS

Plain film radiograph (figure 1) of right knee identified an irregular predominately lucent lesion with surrounding sclerosis within the anterolateral aspect of the right tibial plateau with cortical erosion anteriorly representing a pathological fracture. MRI knee (figure 2A,B) delineated an aggressive ill-defined mixed lytic sclerotic bone lesion in the proximal metaphysis and epiphysis of the right tibia immediately beneath the lateral tibial plateau extending to adjacent soft tissues. Systemic CT staging (figure 3) demonstrated multiple (more than 40) bilateral pulmonary and renal nodules, and an intermuscular right buttock metastasis suggestive of extensive metastatic disease. A CT-guided bone biopsy from the proximal right tibia and adjacent muscle was consistent with a high-grade osteogenic sarcoma with infiltration of skeletal muscle (figure 4A–C). A plan was made to begin multi-agent chemotherapy with

Figure 1 Plain radiograph of the right knee demonstrates an ill-defined, predominantly sclerotic lesion centred on the lateral tibial condyle (red arrow).

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Figure 2 MRI of the right knee. (A) Coronal T1-weighted image of the right knee demonstrates an aggressive appearing, irregular, hypointense lesion at the site of radiographic abnormality. There is cortical destruction at the lateral aspect of the joint surface. (B) On STIR imaging, the lesion demonstrates hyperintense signal, and this sequence best demonstrates the tumorous involvement of the adjacent soft tissue in the region of the proximal tibiofibular joint (red arrow).

alternating cycles of high-dose methotrexate and doxorubicin/cisplatin. A prechemotherapy urinary pregnancy test was positive, and a confirmatory serum β hCG level was found to be elevated at 1008 IU/L (miu/mL).

There was clinical concern that the patient was pregnant; however, she indicated that this was unlikely. A transvaginal ultrasound failed to demonstrate the presence of a gestational sac. Subsequent serial β hCG levels were consistently raised but the rate of doubling expected in the setting of viable pregnancy was not observed.

There was an additional concern from the clinical biochemistry department of potential cross-reactivity of the β hCG assay. To outrule false-positive results, additional testing was undertaken including sample dilution and assay using an alternative method at another facility.

Ultimately elevated β hCG levels were attributed to ectopic hormone production by the tumour. Subsequent immunohistochemistry for β hCG was performed on the patient's tumour biopsy but no staining was observed. Immunostains for HPL and PLAP were also negative. No trophoblast cells were identified on review.

TREATMENT

Immediately prior to commencement of chemotherapy, our patient's serum β hCG was 1214 IU/L (reference range 0.0–5.0 IU/L). After the first cycle of chemotherapy, the level fell rapidly to 175.2 IU/L and the serum β hCG had normalised by the time she attended for the third cycle of chemotherapy (figure 5).

Figure 3 Systemic CT staging scan. Coronal contrast-enhanced CT demonstrates a soft tissue mass with internal calcification centred on the right gluteal region (red arrow), compatible with an osteosarcoma metastases.

OUTCOME AND FOLLOW-UP

Repeat imaging after four cycles of treatment showed a partial response to chemotherapy with improvement at all sites of soft-tissue disease and some further calcification of distant metastases. Post cycle 6, the patient relocated to another country where she continued with chemotherapy; however, serum β hCG levels were not monitored. She proceeded to limb-sparing resection of the primary tibial tumour following the completion of cycle 10 of chemotherapy. The pathological specimen resected at the time of her surgery showed no viable tumour and so repeat immunohistochemistry for β hCG could not be performed. The patient is currently on a break from chemotherapy.

DISCUSSION

Ectopic secretion of β hCG in osteosarcoma is extremely rare with few reported cases in the literature. The clinical significance of raised β hCG levels in these cases is unclear, particularly given that positivity for serum β hCG is usually an incidental finding prompted by a positive pregnancy test performed prior to radiological investigations; consequently, the higher proportion of these cases identified in women versus men may be artefactual. This is further compounded by the infrequent synchronous positive immunohistochemical staining for β hCG in tumour samples which may reflect the limitations of tumour sampling and/or

Figure 4 High-grade osteogenic osteosarcoma with medullary and cortical involvement and extension into the surrounding soft tissue. Histological section shows stromal cells of tumour producing thin trabeculae of osteoid matrix not connected by cartilage. Immunostains for human chorionic gonadotropin, HPL and PLAP were negative. No trophoblasts were identified. (A) H&E 100x; (B) H&E 200x; (C) skeletal muscle invasion, H&E 40x.

Figure 5 Graph of beta human chorionic gonadotropin (β hCG) levels with arrows denoting first day of chemotherapy cycles.

tumour heterogeneity.^{8–10} Additionally, reported serum levels vary significantly from 48 to 20 460 IU/L.^{5 8}

In general, β hCG-secreting tumours have been shown to have a poor prognosis.^{1 6 7 11} Their high proliferation rate results in a more aggressive tumour type with increased propensity for metastases and high rates of recurrence.^{1 12} In vitro experimental data from animal studies suggest that hCG may play a role in angiogenesis, metastasis and immunogenicity of malignant neoplasms.^{1 13} This may be due to the structural similarities between β hCG and platelet-derived growth factor-B and transforming growth factor-beta as well as the ability of hCG to promote cell growth, invasion and malignancy through blocking apoptosis.¹ The extensive metastatic pattern evidenced by imaging in our case in the setting of markedly raised β hCG levels may lend some support to this hypothesis.

Prognosis in metastatic osteosarcoma is poor with an overall 5-year survival of <20%.^{14 15} The osteoblastic subtype of tumour, presence of extrapulmonary metastases and failure to achieve complete remission are poor prognostic features.¹⁴ From the few reported cases pertaining specifically to β hCG-secreting osteosarcomas, there is conflicting evidence as to whether tumorous β hCG production is indeed associated with a worse prognosis. Some studies have concluded that β hCG-secreting tumours are associated with the development of metastases, a suboptimal response to chemotherapy and/or tumour recurrence.¹⁶ Others have failed to detect any statistically significant differences in the development of metastases or in other clinical prognostic parameters.¹⁷

While the value of β hCG for prognostication purposes is thus uncertain, its value as a potential tumour marker is clearly evidenced. Previous studies have shown the value of β hCG as an indicator for tumour recurrence or as a marker for persistent disease in osteosarcoma.^{8 18 19} β hCG expression has been described as a feature of tumour dedifferentiation based on its sparse expression in the patient's primary tumour relative to that seen at a site of disease recurrence.²⁰ In our patient's case, her serum β hCG levels peaked prior to the initiation of chemotherapy and normalised following just two cycles of treatment. This was concordant to subsequent radiological imaging which confirmed a good response.

Patient's perspective

"In the preceding months I had begun to embrace running, I genuinely thought the pain in my knee was due to a running injury. I had no reason to suspect anything else. The symptoms came on over a matter of weeks. Then my world was turned upside down and shaken about. The elevated hcg level was like a curve ball, I never saw it coming! The team were fantastic and arranged the relevant consults and tests. It has been great to see the hcg level normalising. I am happy to say a close eye has been kept on the hcg levels throughout."

Learning points

- ▶ Beta human chorionic gonadotropin (β hCG) levels in a viable pregnancy double every 48 hours, and when this does not occur the possibility of a β hCG-secreting tumour should be considered.
- ▶ Ectopic β hCG production by tumour is rarely seen in osteosarcomas but where elevated, can be used to monitor response to treatment.
- ▶ The primary tumour may or may not show immunohistochemical staining for β hCG, and in these cases metastatic tumour may be considered the source.

Further large-scale studies are required to determine the influence of β hCG on tumour biology in osteosarcoma, the results of which may contribute to the identification of new therapeutic targets, for example, a vaccine against β hCG that may have antineoplastic effects.¹⁷ This is particularly pertinent given the poor prognosis in metastatic osteosarcoma that has seen little advances in treatment in the last few decades.^{15 21}

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