Non-Islet Cell Tumor Hypoglycemia in Metastatic High-Grade Undifferentiated Mesenchymal Sarcoma: Complete Resolution after Palliative Above-Knee Amputation

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ABSTRACT

Background: Non-islet cell tumor hypoglycemia (NICTH) is a rare paraneoplastic syndrome that is mainly caused by the excessive production of incompletely processed insulin-like growth factor-2 (big IGF-2) by non-pancreatic tumors; it is most frequently linked to large mesenchymal neoplasms, even though it is very rare in cases of metastatic high-grade undifferentiated mesenchymal sarcoma. Diagnosis is especially difficult in areas with limited resources because there are no specialized IGF-2 assays available.

Case Presentation: A 66-year-old woman was diagnosed with high-grade undifferentiated mesenchymal sarcoma of the distal left femur, with pulmonary metastases. She declined the initially offered palliative above-knee amputation and was treated with anthracycline-based chemotherapy and pazopanib. Repeat radiologic imaging of the primary site after 6 courses of chemotherapy showed a partial response. However, she developed recurrent episodes of fasting hypoglycemia, with associated symptoms such as sweating, confusion, and weakness, and a single episode of loss of consciousness. Biochemical evaluation confirmed hypoglycemia and identified no other potential causes, supporting a probable diagnosis of NICTH. There was associated intractable pain that was not controlled with analgesics. An above-knee amputation was performed as a palliative procedure. The hypoglycemia resolved completely within 48 hours of the operation.

Conclusion: NICTH should be considered in patients with large mesenchymal sarcomas accompanied by recurrent fasting hypoglycemia, and it is proven that palliative tumor resection can completely eradicate paraneoplastic hypoglycemia even in the presence of residual metastatic disease; this therefore highlights the importance of multidisciplinary care and of early surgical intervention, especially in resource-limited settings.

Keywords: NICTH (non-islet cell tumor hypoglycemia); High-Grade Undifferentiated Mesenchymal Sarcoma, Insulin-like growth factor-2; paraneoplastic hypoglycemia; palliative above-knee amputation.

INTRODUCTION

Non-islet cell tumor hypoglycemia (NICTH) is a rare and potentially fatal paraneoplastic syndrome caused by non-pancreatic tumors that secrete incompletely processed insulin-like growth factor-2 (big IGF-2) [(1)]. The excess IGF-2 acts like insulin, increasing glucose uptake in the body's tissues and suppressing glucose production in the liver, resulting in repeated episodes of fasting hypoglycemia and low levels of insulin and C-peptide [(2)]. NICTH is associated with a variety of large mesenchymal and epithelial tumors, particularly solitary fibrous tumors and hepatocellular carcinoma, and, less commonly, high-grade sarcomas [(1, 3)]. Because the condition is rare and its symptoms are non-specific, diagnosis is generally made only after a delay [(4)]. In regions where resources are limited, the inability to obtain specialized IGF-2 testing means that diagnosis must rely on clinical features, typical biochemical findings, the exclusion of other possible causes, and the patient's response to treatment aimed at the tumor [(1, 4)].

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Case Presentation

A Nigerian woman aged 66 years came in with a painful swelling in the lower part of her left thigh which had been growing over a period of 11 months. The swelling had developed slowly and had increased in size steadily, causing severe pain, making it difficult for her to walk, and leading to a gradual loss of function in the affected limb. She said that there had been no prior injury, no fever, and no other general symptoms.

On examination, her Eastern Cooperative Oncology Group (ECOG) performance status was 2; a large, firm, irregular and tender mass was found in the distal part of the left thigh and spread to the knee. (Figure 1a). The skin above the mass was stretched, with noticeable superficial veins, but neither ulceration nor bleeding was present. Movement of the knee was greatly limited by pain and the size of the tumor, and the distal neurovascular status was normal.

Baseline laboratory investigations were normal except for anemia. Plain radiographs (Figure 1b) demonstrated an aggressive lytic lesion of the distal femur with cortical destruction and an associated soft tissue mass. Magnetic resonance imaging (MRI) revealed a large heterogeneous tumor arising from the distal one-third of the femur, with medullary involvement, and extra-osseous soft tissue extension (Figure 1c). Computed tomography (CT) of the chest demonstrated a right pleural-based lesion at the level of the 10^{th} rib (Figure 2a), and computed tomography (CT) of the abdomino-pelvic demonstrated a hypodense hepatic lesion, left inguinal, pelvic, and paraaortic lymphadenopathy (Figure 2b).

Core needle biopsy showed features of a poorly differentiated, high-grade malignant mesenchymal neoplasm. Despite extensive immunohistochemical evaluation, no specific lineage of differentiation was identified, and the tumor was classified as a high-grade undifferentiated mesenchymal sarcoma (Figure 3).

The case was reviewed at the institutional multidisciplinary tumor board, comprising orthopedic surgeons, radiation oncologists, medical oncologists, radiologists, and pathologists. Given the extensive local disease, pulmonary metastases, and severe pain, palliative above-knee amputation was recommended as the preferred initial treatment. However, after detailed counseling, the patient declined surgery due to concerns about permanent disability and the psychological impact of limb loss. Consequently, she began anthracycline-based chemotherapy combined with pazopanib for tumor cytoreduction and symptom control.

She completed six cycles of systemic therapy with satisfactory tolerance; a repeat MRI of the primary site demonstrated a partial radiological response with reduction in tumor volume, although extensive residual disease remained (Figure 4a). Despite this response, she continued to experience severe intractable pain requiring escalating opioid analgesia. The patient also developed recurrent episodes of dizziness, diaphoresis, generalized weakness, palpitations, confusion, and an episode of loss of consciousness, predominantly in the early morning. Although initially attributed to reduced oral intake, repeated bedside glucose measurements obtained during symptomatic episodes confirmed hypoglycemia; Even though nutritional support was provided, the number of hypoglycemic episodes grew. When biochemical tests were carried out during spontaneous hypoglycemia, the fasting plasma glucose level was found to be in the range of 37–67 mg/dL, with both serum insulin and C-peptide being suppressed, thyroid function was normal, the HbA1c was low (4.4%), morning cortisol was normal (15.67 µg/dL), liver and kidney function were within normal limits, growth hormone was low (0.7 ng/mL), IGF-1 was markedly reduced (16 ng/mL), and β-hydroxybutyrate could not be detected. All possible causes of spontaneous hypoglycemia—including insulinoma, adrenal insufficiency, severe hepatic dysfunction, renal failure, sepsis, and medication-induced hypoglycemia—were thoroughly ruled out by means of clinical assessment and laboratory tests. Cranial CT (Figure 4b) was also normal.

A diagnosis of NICTH was considered likely because of the presence of a large, high-grade mesenchymal sarcoma, the suppression of insulin and C-peptide during hypoglycemia, and since other possible causes had been ruled out [(7)]. The patient had to receive repeated doses of intravenous dextrose and eat frequent high-carbohydrate meals, but the episodes of hypoglycemia continued and in fact became more frequent.

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Meanwhile, the patient's quality of life declined due to severe tumor-related pain, despite maximal analgesic therapy.

After further multidisciplinary discussions and repeated counseling on risks and benefits, the patient agreed to a palliative above-knee amputation.

The procedure was carried out using spinal anesthesia and no complications occurred.

The tissue sections examined confirmed the earlier diagnosis of high-grade undifferentiated mesenchymal sarcoma, together with extensive tumor necrosis and negative surgical margins.

There were no complications during the period of recovery after surgery. The episodes of hypoglycemia stopped altogether within 48 hours of the amputation and, thereafter, her fasting blood glucose levels stayed normal without the need for any additional intravenous dextrose. There was a marked improvement in pain control, which enabled a large decrease in the amount of opioids being used. She is now having follow-up appointments with both oncology and rehabilitation services.

The fact that hypoglycemia is completely resolved following the removal of the primary tumor is strong evidence in support of the diagnosis of NICTH caused by a high-grade mesenchymal sarcoma.

Figure 1 displays the Picture, X-ray, and MRI of the left femur at the time of presentation, revealing a large destructive sarcoma in the distal femur with extensive invasion into the soft tissues.

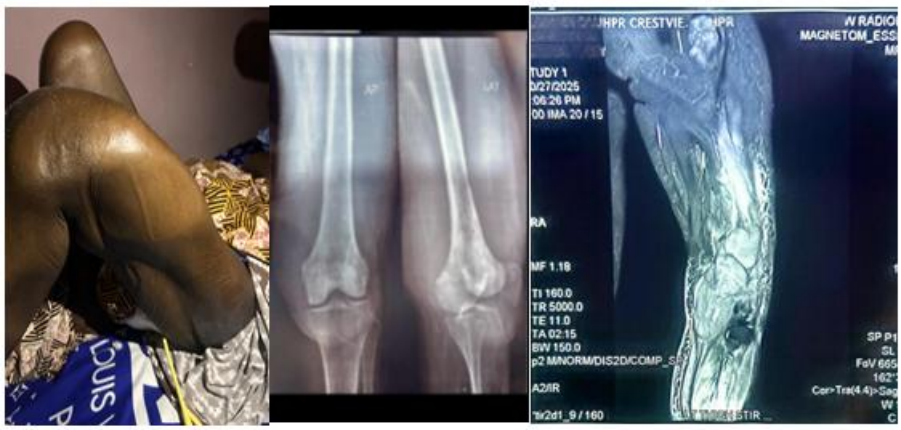

Figure (2a. b) Computed tomography (CT) of the chest demonstrated a right pleural-based lesion, and computed tomography (CT) of the abdomino-pelvic demonstrated a hypodense hepatic lesion, left inguinal, pelvic, and paraaortic lymphadenopathy.

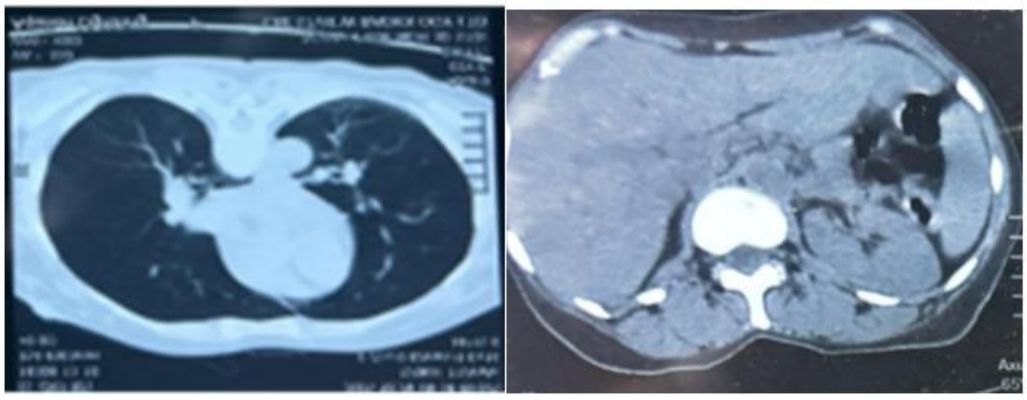

Figure 3. Low-power hematoxylin and eosin (H&E) photomicrograph of the resected distal femoral tumor demonstrating a highly cellular high-grade undifferentiated mesenchymal (spindle cell) sarcoma. The tumor is composed of densely packed spindle cells with extensive areas of coagulative tumor necrosis (right side), consistent with a high-grade malignant mesenchymal neoplasm.

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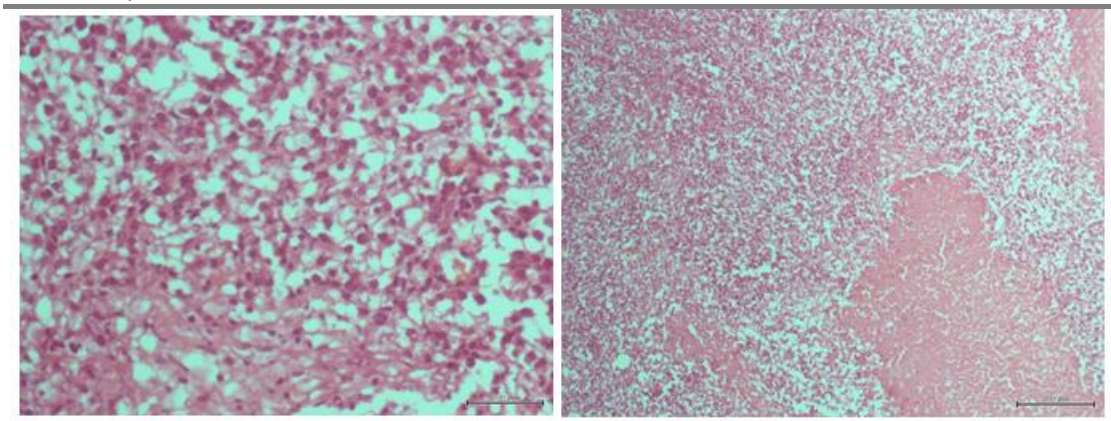


Figure 4a, b: After six cycles of chemotherapy based on anthracyclines and with the use of pazopanib, an MRI shows a partial radiological response. And cranial CT

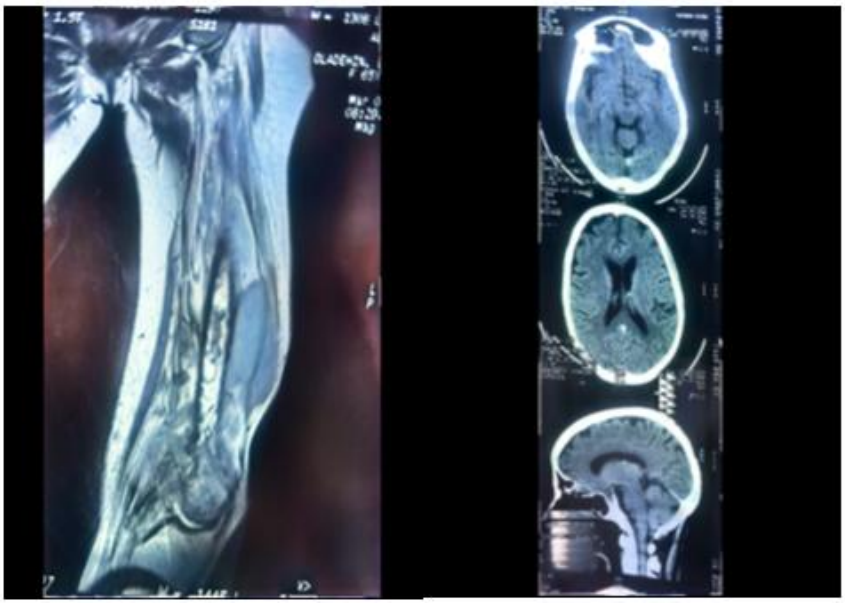
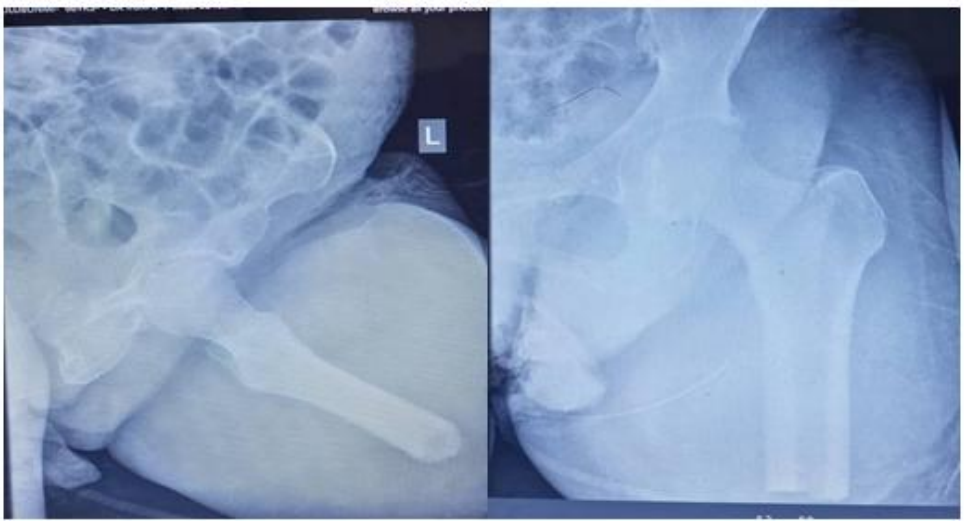


Figure 5: X-ray post-above knee amputation



DISCUSSION

Non-islet cell tumor hypoglycemia (NICTH) is a rare paraneoplastic syndrome that most commonly results from excessive release of incompletely processed insulin-like growth factor-2 (big IGF-2) by non-pancreatic tumors [(1)]. While solitary fibrous tumors are still the neoplasm most typically linked with NICTH (Doege–

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Potter syndrome), the condition has also been observed in patients with hepatocellular carcinoma, gastrointestinal stromal tumors, leiomyosarcoma, fibrosarcoma, malignant peripheral nerve sheath tumors, and undifferentiated pleomorphic sarcoma [2, 3, 10, 11]. However, there are very few reports of cases involving metastatic high-grade undifferentiated mesenchymal sarcoma in our environment.

A high degree of suspicion is needed when diagnosing NICTH, especially in patients with advanced cancer who have a recurrence of fasting hypoglycemia [1]. In our patient, spontaneous hypoglycemia was associated with suppressed insulin and C-peptide levels, low IGF-1 and growth hormone, undetectable β-hydroxybutyrate, and the exclusion of other possible causes of hypoglycemia. Although a serum big IGF-2 measurement was not available, the combination of clinical and biochemical findings strongly supported a probable diagnosis of NICTH, in agreement with current guidelines for resource-limited settings [4].

Our case exhibits several features noted in earlier studies, including occurrence in an older adult, a large, high-grade mesenchymal tumor, recurrent fasting hypoglycemia, suppressed insulin and C-peptide levels, and biochemical evidence of hypoinsulinemic hypoglycemia [1, 2]. These features have been consistently reported in previously published cases of NICTH and confirm the syndrome's typical clinical phenotype [12].

This case also highlights several important distinguishing features. First, the patient initially refused the recommended palliative amputation, allowing observation of the metabolic course during systemic treatment. Although there was a partial radiological response to anthracycline-based chemotherapy combined with pazopanib, hypoglycemia persisted and worsened over time. This indicates that a reduction in tumor size on radiographs does not always correspond to a decrease in endocrine activity, especially when a large volume of viable tumor remains.

Second, despite pulmonary metastases present during treatment, hypoglycemia was rapidly and completely resolved after removal of the primary tumor. This pattern has also been reported in separate cases of NICTH, supporting the idea that the primary tumor is usually the main source of hypoglycemia-inducing factors, not the metastatic deposits [5, 6]. Our case provides additional evidence that metabolic remission can be achieved by removing the primary tumor or substantially reducing its size, even in the presence of metastatic disease [7].

Compared with earlier published cases, the present report is noteworthy for documenting the sequence of systemic therapy, a partial radiological response, ongoing hypoglycemia, and subsequent complete metabolic resolution after a palliative above-knee amputation. Because few reports have clearly shown this temporal relationship in metastatic high-grade undifferentiated mesenchymal sarcoma, this case represents a valuable addition to the literature.

The report also highlights the diagnostic challenges in low-resource settings. Although measurement of big IGF-2 remains the biochemical gold standard for confirming NICTH [2], such tests are not available in many institutions. As a result, doctors must rely on a thorough clinical assessment, appropriate biochemical testing during hypoglycemia, the exclusion of other possible causes, and close correlation of the patient's response to treatment directed at the tumor. This practical approach to diagnosis aligns with published recommendations when specialized endocrine testing is not accessible.

The main drawback of this report is that it does not include a measurement of serum big IGF-2 or Western blot analysis. That said, the typical biochemical profile, the exclusion of other possible diagnoses, and the close temporal relationship between the tumor surgery and the sustained normalization of blood glucose levels provide strong evidence for a probable diagnosis of NICTH. Although the report consists of only a single case, the findings cannot be applied to other cases; however, since NICTH is very rare in metastatic high-grade undifferentiated mesenchymal sarcoma, a thorough record of the case is still of clinical value.

In summary, this case contributes to the small body of literature on sarcoma-associated NICTH. It highlights the need to consider paraneoplastic hypoglycemia in patients with large mesenchymal tumors who have recurrent fasting hypoglycemia. It also indicates that successful reduction of the primary tumor burden may restore normal glucose homeostasis, even when metastatic disease remains, underscoring the value of multidisciplinary management and individualized surgical decision-making.

CONCLUSIONS

Non-islet cell tumor hypoglycemia (NICTH) is a rare, potentially life-threatening endocrine paraneoplastic syndrome that must be considered in any patient presenting with recurrent fasting hypoglycemia and a large mesenchymal tumor [9]. This case illustrates the diagnostic challenges associated with NICTH in resource-limited settings, where specialized IGF-2 testing is unavailable. The diagnosis was established through a thorough clinical evaluation, typical biochemical findings, exclusion of other causes of hypoglycemia, and complete resolution of symptoms after surgical resection of the primary tumor.

A striking aspect of this case was that recurrent hypoglycemia persisted despite a partial radiologic response to anthracycline-based chemotherapy combined with pazopanib. This indicates that a reduction in tumor size on imaging does not necessarily mean that the paraneoplastic endocrine activity has been resolved. After a palliative above-knee amputation, blood glucose levels normalized immediately. They remained normal, even though pulmonary metastases persisted, showing that the primary tumor plays the main role in producing the hypoglycemia-inducing factors.

This case underscores the importance of collaboration among orthopedic surgeons, medical oncologists, radiation oncologists, endocrinologists, pathologists, radiologists, and anesthesiologists at an early stage when managing patients with advanced sarcoma accompanied by paraneoplastic hypoglycemia; early identification and definitive surgical treatment may prevent recurrent neuroglycopenic injury, reduce hospitalizations, enhance quality of life, and enable better supportive oncological care.

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