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Case Report
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Management of Bilateral Humeral Pathologic Fracture in Metastatic Anaplastic Hemangiopericytoma and Doege-Potter Syndrome: A Case Report and Review of the Literature

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Abstract

Background: Solitary Fibrous Tumor/Hemangiopericytoma (SFT/HPC) is a rare, aggressive, and highly vascularized fibroblastic neoplasm, derived from the pericytes of Zimmerman. Intracranial anaplastic hemangiopericytoma, a grade III SFT/HPC, has shown high rates of recurrence and metastasis. Metastasis to bone often leads to pathologic fractures, making careful surgical management to optimize patient's quality of life. Bilateral pathologic humeral fracture is an unusual clinical dilemma and has not been previously reported in the setting of metastatic anaplastic hemangiopericytoma. The paraneoplastic syndrome known as Doege-Potter syndrome can additionally complicate management and recognizing this entity is essential. The rarity and complexity of both clinical presentations warrant a review of the topic.

Case Report: We described a 44-year-old man with widely metastatic intracranial anaplastic hemangiopericytoma who presented intractable pain in upper extremities and limitation of daily activities due to bilateral pathologic humeral fracture caused by bone metastasis. In addition, the orthopedic management was complicated by several episodes of hypoglycemia caused by Doege-Potter Syndrome. The patient was surgically managed with bilateral humeral intramedullary nail stabilization and clinically managed with dextrose-containing fluids and prednisone to correct his hypoglycemia.

Conclusion: Despite the patient's extremely guarded prognosis, surgical management resulted in immediate improvement in pain, disability, and quality of life. It is essential for orthopedic surgeons to be aware that rare paraneoplastic such as Doege-Potter syndrome exists. Attention to the patient's preoperative laboratory values, the medical assessment, and the patient's medical history is all important and can help prevent perioperative complications and avoidable morbidity.

Keywords: Anaplastic hemangiopericytoma; Solitary fibrous tumor; Bilateral pathologic humeral fracture; Bone metastasis; Doege-Potter syndrome

Abbreviations

SFT/HPC: Solitary Fibrous Tumor/Hemangiopericytoma; SFT: Solitary Fibrous Tumor; HPC: Hemangiopericytoma; WHO: World Health Organization; IAHPC: Intracranial Anaplastic Hemangiopericytoma; AHPC: Anaplastic Hemangiopericytoma; CNS: Central Nervous System; RT: Radiation Therapy; DPS: Doege-Potter Syndrome; NITCH: Non-Islet Cell Tumor Hypoglycemia; ROM: Range of Motion; IM: Intramedullary; IMN: Intramedullary Nail Fixation; D10W: Dextrose Infusion; IGF-I: Secrete Insulin-Like Growth Factor I; IGF-II: Secrete Insulin-Like Growth Factor II; BID: Two Times A Day; IV: Intravenous

Introduction

Hemangiopericytoma (HPC) is a rare, aggressive, and highly vascularized fibroblastic neoplasm [1,2], derived from the pericytes of Zimmerman [3]. The World Health Organization (WHO) has recently combined HPC and Solitary Fibrous Tumor (SFT) into a single entity (SFT/HPC) [4].

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SFT/HPC most commonly arises within the bone, followed by deep somatic soft-tissues and body cavities, such as the pleura, pelvis, and retroperitoneum [2]. SFT/HPC represents only 0.4% of all primary CNS tumors [1]. While rare, SFT/HPC of the CNS is aggressive and exhibits frequent recurrences and extracranial metastases [5,6] to locations such as bone (20%), lung and pleura (18%), liver (18%), and vertebra (14%) [1]. The WHO has established three grades for CNS SFT/HPC [4]; grade I (previously diagnosed as a solitary fibrous tumor) a high collagenous, low cellularity, spindle cell lesion tumor; grade II (formerly diagnosed as hemangiopericytoma) a more cellular, less collagenous tumor with "staghorn" vasculature; and grade III (termed in the past as anaplastic hemangiopericytoma) defined as having ≥ 5 mitoses per 10 high-power fields [4]. Intracranial Anaplastic Hemangiopericytoma (IAHPC) Grade III HPC/SFT [4] has a median survival of 142 months [6], a progression-free survival of 61 months [3], and a local recurrence ranging from 28.6% to 53.8%, with and without the addition of adjuvant Radiation Therapy (RT) respectively [7]. SFT/HPC has been associated with a rare paraneoplastic syndrome called Doege-Potter Syndrome (DPS), which is a Non-Islet Cell Tumor Hypoglycemia (NITCH) [8]. It has been described mostly in pleural SFT/HPC [9] and is encountered in fewer than 5% of cases [10]. In this case report, we plan to present a patient with an IAHPC who developed extensive widespread metastatic disease involving bone, lung, liver, and intra-abdominal soft tissue. He furthermore demonstrated clinical features suggestive of DPS, further complicating his clinical and surgical management. We highlight the role of palliative orthopedic surgical intervention in the setting of advanced and widespread disease as well as the perioperative management of a metabolic phenomenon consistent with DPS. Given the paucity of literature on the matter and the clinical complexity inherent in caring for these fragile patients, we believe a review of the relevant medical and surgical data associated with this challenging condition is merited.

Case Presentation

A 44-year-old man with a known diagnosis of metastatic AHPC was referred to the orthopedic oncology service for management of bilateral humeral pathologic fractures after fainting and falling due to a hypoglycemic episode. Previously, he had experienced multiple syncopal episodes associated with hypoglycemia, with glucose values ranging between 30 ng/ml and 40 ng/ml that improved after oral intake. He reported no history of diabetes mellitus or the use of hypoglycemic agents. Past medical history was significant for an IAHPC in the right parieto-occipital area, which was treated successfully with gross total resection and adjuvant RT. Despite his initial treatment, he developed progressive metastatic disease over the ensuing 11 years, involving bones, lungs, spine, liver, and intra-abdominal soft tissues. He was treated with numerous chemotherapy regimens (gemcitabine and docetaxel, bevacizumab, pazopanib, and temozolomide); however, his disease proved refractory. He additionally received palliative RT to multiple sites, which partially alleviated his pain. Upon presentation, he was unable to perform even the most basic functions, such as sitting up, holding a light cup, or positioning himself in bed. His examination revealed no active Range of Motion (ROM) of either shoulder owing to severe and unremitting pain, refractory to standard oral narcotic medication. He maintained intact ROM of other joints in the upper and lower extremities but was unable to use his upper extremities in any meaningful way. Radiographs of the right humerus demonstrated an expansile lytic lesion with an associated pathologic fracture involving the proximal shaft and a smaller centrally located lytic lesion in the mid-third of the humeral shaft. Radiographs of the left humerus demonstrated an irregular lytic lesion within the proximal humeral metadiaphysis extending to the level of the surgical neck, with an associated pathologic fracture and early callus formation. Our multi-disciplinary tumor board reviewed the patient's case, and the consensus opinion was that his disease's progressive nature made non-operative healing unlikely. His degree of pain and his clinical course both argued in favor of palliative surgical intervention, despite his poor prognosis. The consensus opinion was to offer the patient staged palliative surgical fixation of his bilateral humeri, as a means of affording pain relief, fracture stability, minimal use of his upper extremities, and improved quality of life. He agreed and subsequently underwent staged Intramedullary Nail fixation (IMN) of both humeri. He tolerated both procedures well and at follow-up, reported substantial pain reduction in both extremities. He no longer required narcotics and tolerated gentle passive ROM. His incisions were healing well. Pre-operatively, the patient met the Whipple's triad (symptoms, signs, or both consistent with hypoglycemia; low plasma glucose concentration at the time of suspected hypoglycemia; and resolution of those symptoms or signs after hypoglycemia is corrected) [11] for which hypoglycemia was investigated (The Endocrine Society Guidelines recommends investigating hypoglycemia in patients who meet Whipple's triad) [12] based on the suspicion of hypoglycemia caused by NITCH secondary to his widely metastatic SFT/HPS. Pertinent tests were within normal limits except for the IGF-II/IGF-I ratio which resulted in 19 (IGF-I 20 ng/ml [n: 52-328]; IGF-II level 380 ng/ml [n: 267-616 ng/ml]) confirming the diagnosis of NITCH secondary to SFT/HPC, therefore, DPS [8]. During hospitalization, hypoglycemia management consisted of dextrose-containing fluids and prednisone dose of 40 mg daily. Intraoperatively, the patient received Dextrose Infusion (D10W). Subsequently, he was titrated off the D10W, and the prednisone dose was decreased to 20 mg BID to avoid nocturnal hypoglycemia. The patient was discharged with the latter treatment and the addition of a glucagon intramuscular syringe to treat severe hypoglycemia. After discharge, the patient tolerated the treatment well with prednisone, reported no further hypoglycemic episodes, and no need for glucagon use.

Discussion

NITCH is known as a paraneoplastic syndrome caused by extra-pancreatic tumors that secrete Insulin-like Growth Factor II (IGF-II). NITCH rarely develops in the context of SFT/HPC and when it does, the clinical condition is known as Doege-Potter syndrome (DPD); [13] first described by physicians Karl W. Doege and Roy P. Potter in 1930. 14 in such cases, the SFT/HPC is most often located within the pleura, followed by the retroperitoneum, abdomen, and pelvis [12]. Only 5% of these tumors are estimated to cause NITCH, highlighting the condition's relative rarity [12]. The current pathophysiology of NITCH is correlated with the "big" IGF-II molecule (pro-IGF-II) and the high-molecular-weight-form IGF-II, which ranges between 10 kDa to 20 kDa peptides while its normal molecular weight is 7.5-kDa peptide [12]. This big IGF-II molecule is formed due to abnormal processing of an IGF-II precursor in tumors with aberrant IGF-II gene transcription and gene expression [12,14]. It exhibits increased permeability across membranes and binds to insulin receptors leading to hypoglycemia [15]. The IGF-II levels are expected to be high in DPS, however low and normal IGF-II levels have also been reported [16]. It is thought that this discrepancy in reporting lies in assay variation of different laboratories to detect

abnormal IGF-II forms [17]. Elevated total IGF-II leads to a greater concentration of free IGF-II causing feedback suppression of Growth Hormone (GH), which causes a decrease in Insulin-Growth Factor I (IGF-I) levels [18]. Initial treatment of the hypoglycemia is achieved by oral glucose and/or IV glucose- or dextrose-containing fluids, as necessary [12]. Once NITCH is identified and a primary tumor is found, the primary management consists of complete surgical resection, which can definitively correct the hypoglycemia. However, when complete tumor resection is not possible, such as in the case of a large tumor burden or widely metastatic disease, medical management is necessary. Strategies that have shown best results are (1) increase caloric intake in addition to IV glucose or dextrose, or partial or total parenteral nutrition (not for long-term strategy), (2) glucocorticoids, and (3) glucagon; the latter mostly as adjunctive therapy in the setting of acute hypoglycemia. Systemic anti-tumor therapy has been reported with limited success [12]. Other treatment options described in the literature include diazoxide [19], octreotide [20], and recombinant growth hormone; [21] but each has limited success rates in the treatment of hypoglycemia caused by NITCH.

SFT/HPC metastasize to bone in ~ 20% of cases, [1] with the humerus representing the second most common site of metastasis after the femur [22,23]. However, bilateral pathologic fractures of the humerus are exceedingly rare, with only a few multiple-myeloma-associated cases reported [24-26]. No cases involving metastatic AHPC have been identified, underscoring the rarity of this case. Most surgeons still consider nonsurgical treatment for humeral shaft fractures the standard of care [27]. However, recognized indications for operative management include (1) unacceptable alignment with bracing, (2) skin condition precluding bracing, (3) high-velocity gunshot injury, (4) open fracture with severe soft tissue injury, (5) vascular injury requiring repair, (6) brachial plexus injury, (7) pathologic fractures, (8) radial nerve injury after manipulation, (9) intra-articular fractures, and (10) a floating elbow [27]. Operative treatment for pathologic fractures of the humerus is generally recognized as superior to non-operative methods [23,29,30]. The decision to intervene depends on factors such as the size of lesion, the degree of bone destruction, the presence of a fracture, the patient's prognosis, and co-morbidities [31]. In the setting of tumor, surgical indications include (1) impending pathologic fracture following exhausted adjuvant management [23], (2) intractable pain [30], (3) lytic destruction of 50% of the cortex (outer or inner layer), [32] (4) pathological fracture that disables [31], (5) bilateral pathologic fracture [27], and (6) fracture risk with Mirels score of ≥ 9.33 indications based on life expectancy varies [23,32,33]; Bickels et al. [30] recognize that while it is impractical to set a rigid time frame, a life expectancy of 6 weeks to 12 weeks is reasonable for relatively simple procedures such as IMN, while a minimum life expectancy of six months is suggested for more complex procedures. However, the authors note that even in cases of shorter life expectancy, providers should take into account a patient's overall medical status, quality of life, and the magnitude of the operation and rehabilitation when considering intervention. When surgery is performed, IM fixation appears to be the preferred approach [34]. IMN involves less soft tissue injury, a lower infection rate, and a theoretically smaller risk of radial nerve injury [35,36]. Given the fragile state many patients are in, there has been some effort to minimize iatrogenic insult and mitigate complications to the extent possible. Toward that end, Younis et al. [35] evaluated the difference between reamed and un-reamed humeral IMN use for pathologic fracture management and have suggested that un-reamed procedures result in less blood loss, fewer systemic complications, and a lower length of hospital stay. Ofluoglu et al. [36] have similarly suggested that un-reamed procedures are associated with fewer pulmonary emboli.

Conclusion

AHPC is a rare but aggressive tumor that can metastasize extensively to the bone resulting in substantial morbidity. In this report, we describe a patient who was experiencing intractable pain and disability stemming from bilateral pathologic humeral fractures. Despite his guarded prognosis, he was surgically treated; undergoing staged bilaterally un-reamed IM nailing which resulted in immediate improvement in pain, disability, and quality of life. It is important for the orthopedic surgeon to recognize that rare paraneoplastic syndromes exist. In the context of SFT/HPC, the DPS results in severe hypoglycemia, which when recognized can be easily and effectively managed medically. Attention to the patient's preoperative laboratory values, the medical assessment, and the patient's medical history are all important; it can help prevent perioperative complications as well as avoidable morbidity.

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