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BRIEF REPORT:

Cardiac Metastasis and Hypertrophic Osteoarthropathy in Recurrent Infantile Fibrosarcoma

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Abstract

Cardiac metastasis and hypertrophic osteoarthropathy are both quite rare. We describe a patient presenting with hypertrophic osteoarthropathy as the first symptom of recurrent infantile fibrosarcoma (IF). During surgical resection of lung metastasis, the patient suffered sudden cardiac arrest. Autopsy demonstrated a metastatic lesion in the intraventricular septum of the heart, which is previously undescribed in the literature. This case demonstrates that IF can be aggressive despite its more typical benign course.

Keywords

cardiac metastasis; hypertrophic osteoarthropathy; infantile fibrosarcoma

INTRODUCTION

Infantile fibrosarcoma (IF) is a rare soft tissue sarcoma accounting for 10% of nonrhabdomyosarcoma soft tissue sarcomas in children [1]. Although histologically identical to “adult” fibrosarcoma, IF typically has a less aggressive course and can be cured by surgery alone with an event free survival (EFS) of 80–92% and overall survival (OS) of 89–95% [1,2]. Lesions are most commonly found on an extremity (61–71%), then trunk (19–29%) [1], and are also seen in the abdomen. Local recurrence rates are as high as 50% [1]. Cytogenetic abnormalities in IF include trisomies 8, 11, and 20 and the t(12;15) translocation corresponding to the ETV6 (TEL)-NTRK3 gene fusion product [3,4]. Tumors with this translocation (also found in secretory breast cancer and mammary analogue secretory carcinoma) [5,6] may be more chemosensitive, making neoadjuvant chemotherapy an option for large unresectable lesions [1,2,7–10]. IF is metastatic in less than 10% at diagnosis (26% for primary axial lesions) and can be seen in the lungs and bones with case

reports of central nervous system (CNS), ocular, and renal metastasis [9], but not to the heart.

Hypertrophic osteoarthropathy (HOA) is characterized by clubbing of digits, periosteal new long bone formation, polyarthritis, and can be seen with intra thoracic malignancies. Although prevalent in adult oncology patients, HOA is rare in pediatric oncology [11]. Symptoms of HOA are what led our patient to seek evaluation at the time of disease recurrence.

CASE

A previously healthy 21 month old female presented with a local 3.5 cm × 4 cm left sided upper abdominal wall mass which was surgically excised with negative margins. Histology and demonstration of t(12;15) translocation confirmed IF. Given low metastatic potential, the patient did not receive systemic treatment and had routine imaging for monitoring. A surveillance CT scan 14 months after diagnosis revealed three pulmonary nodules, all less than 1 cm in diameter. Biopsy confirmed IF, and fluorescence in situ hybridization (FISH) revealed the t(12;15) consistent with the original diagnosis.

Treatment was initiated with vincristine (2 mg/m²/cycle), doxorubicin (75 mg/m²/cycle), cyclophosphamide (1,200 mg/m²/cycle), MESNA (720 mg/m²/cycle), and dexrazoxane (750 mg/m²—cycle 3 only) for three cycles during which she had progressive disease. Therapy was switched to ifosfamide (9,000 mg/m²/cycle) and etoposide (500 mg/m²/cycle) with MESNA (5,400 mg/m²/cycle) for four cycles with stable disease. Two right sided nodules, demonstrating active tumor, were resected with negative margins followed by two cycles of vincristine (2 mg/m²/cycle), cyclophosphamide (1,200 mg/m²/cycle), topotecan (5 mg/m²/cycle), and MESNA (1,250 mg/m²/cycle) with no radiographic change in the remaining nodule, which was subsequently resected with negative margins. No additional chemotherapy was administered.

Routine restaging scans showed continued remission until 7 years from her diagnosis when she presented with bilateral lower extremity pain preventing ambulation, a cough, and fever. Chest X-ray and CT scan demonstrated a 7.6 cm right upper lobe lesion (Fig. 1). Plain films of the lower extremities (Fig. 1) and bone scan showed diffuse periosteal reaction consistent with HOA. MRI revealed a right distal femur lesion (Fig. 1), which biopsy proved to be IF.

This extensive metastatic disease was treated with vincristine (1.5 mg/m²/cycle), irinotecan (250 mg/m²/cycle), and temozolamide (750 mg/m²/cycle, PO). Nonsteroidal anti inflammatory drugs were started for her HOA and symptoms resolved promptly. A routine echocardiogram performed prior to chemotherapy demonstrated normal structure and function.

Despite three cycles of chemotherapy, the patient had progressive disease including a pathologic fracture in her right femur and a new lesion in the right middle lobe. She was taken to the operating room (OR) for open reduction, internal fixation, and stabilization of the femur fracture for symptomatic relief. A few weeks later, she was taken to the OR for surgical resection of her lung lesion to alleviate symptoms given her overall previously

excellent performance status. During this procedure, the patient suffered sudden cardiac arrest and died. Autopsy revealed a previously unrecognized 1 cm × 0.6 cm × 0.5 cm white, indurated, well-circumscribed mass in the posterior intraventricular septum of the heart (Fig. 2), and the presumed cause of death was an arrhythmia related to this lesion.

DISCUSSION

This case is notable both as the first report of intracardiac metastasis in IF and the presentation with HOA, with less than 40 cases reported in children with cancer, none with IF. Additionally, this case demonstrates the aggressive nature of our patient's multiply recurrent metastatic disease, despite its classification as a low risk soft tissue sarcoma.

The incidence of cardiac metastasis ranges from 2% to 18% [12], most commonly from lymphoma, leukemia, melanoma, and lung, breast, and esophageal carcinoma [13]. Cardiac metastases of sarcoma are exceedingly rare, with case reports in osteosarcoma and Ewing's Sarcoma [14,15]. The majority of patients with cardiac metastasis are asymptomatic from the lesion but symptoms can include shortness of breath or tamponade from pericardial involvement or arrhythmia from infiltration of the conduction system [12]. An electrocardiogram (EKG) may detect changes in voltage or rhythm and echocardiogram may be used to detect the metastatic lesion.

Primary HOA is extremely rare with an autosomal dominant inheritance pattern. Secondary HOA is seen with various conditions—including bacterial endocarditis, congenital heart disease, cystic fibrosis, idiopathic pulmonary fibrosis, and primary intrathoracic malignancies. HOA is thought to be a paraneoplastic process and vascular endothelial growth factor, platelet derived growth factor, and prostaglandin E2 have all been hypothesized to play a role in the pathogenesis [16]. Approximately 92% of adult HOA cases occur in the setting of malignancy, compared to 12% of pediatric HOA [17,18]. In pediatric cancer, HOA has been reported in nasopharyngeal carcinoma, Hodgkin's Lymphoma, osteosarcoma, thymic carcinoma, rhabdomyosarcoma, periosteal sarcoma, and pleural mesothelioma [17]. This is the first reported case of HOA with IF. A diagnosis of HOA should alert the treating physician to the presence of an underlying, typically intrathoracic, malignancy as well as raise suspicion for recurrent disease.

Most notable about this case is that despite the low metastatic potential of IF and the suggestion that IF with t(12;15)/ETV6-NTRK3 translocations is chemosensitive, this patient had a very atypical course. Surgical resection alone can be adequate for treatment of localized IF. 5-year OS has been found to correlate with Intergroup Rhabdomyosarcoma Study (IRS) clinical group classification, with Group I (complete resection with negative margins) having 100% survival and Group II (microscopically incomplete resection or regional lymph node involvement) having an OS of 76% and a 10-year survival rate of 90% for all patients [2]. Even with positive margins, several reports have shown that IF can regress spontaneously [9,19]. Furthermore, this patient had the characteristic t(12;15) translocation thought to correlate with chemosensitivity, with response rates approximating 75% [2]. Our patient had a complete surgical resection at diagnosis with negative margins and an extremely low risk for metastasis given the underlying disease—providing an overall

excellent long-term prognosis. Despite this, her course was characterized by multiple chemotherapy-refractory recurrences. Reasons for the aggressive nature of our patient's IF are unclear. In a similarly aggressive case of IF, an 11-month-old male was found to have complex cytogenetics and an unbalanced translocation in addition to the t(12;15) [4]. Additional chromosomal aberrations have also been found in IF with unclear implications [20]. It is possible that our patient had additional unrecognized cytogenetic abnormalities or a slightly different fusion product contributing to the unusual behavior of her IF.

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Fig. 1. Radiographic findings. **A:** CT scan of the chest at the time of second relapse showing the 7.6 cm pulmonary mass with a necrotic center. **B:** Plain radiograph of the patient's forearm showing periosteal new bone formation characteristic of hypertrophic osteoarthropathy. **C:** MRI of the femur showing metastatic lesion.

Fig. 2.
Post mortem examination of the heart shows a metastatic nodule in the intraventricular septum (arrow).