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Case Report

Primary Leiomyosarcoma of the Hand in a Patient with Neurofibromatosis Type 1

Vishal Shwetal Desai[1*], Rafael Kakazu[1],
Alvin H. Crawford[1], Amy Sheil[2], and Joel I. Sorger[1]

[1] University of CincinnatiDepartment of Orthopaedic Surgery, OH, USA

[2] Cincinnati Childrens Hospital Medical Center, Department of Pathology, OH, USA

Abstract

Indroduction: NF1 is an autosomal dominant disorder that reduces the effectiveness of the neurofibromin tumor suppressor, resulting in an increased risk for benign and malignant soft tissue tumors. Leiomyosarcoma, a type of soft tissue sarcoma, has been infrequently observed in NF1 patients. This study adds to the limited number of leiomyosarcomas reported in NF1 patients. This particular malignancy presented in a highly unusual location. To our knowledge, this is the first report of an NFI patient who developed a primary leiomyosarcoma of the hand.

Case Presentation: We report an NF1 patient who presented with a 4-month history of pain and swelling of his right fifth finger. Initial imaging revealed a soft tissue mass measuring 3.1x2.9x3.5 cm with destruction of the fifth proximal phalanx. A radical ray excision was carried out to the distal two-thirds of the metacarpal. Pathology review yielded a diagnosis of leiomyosarcoma. Imaging studies including MRI performed at 6 weeks and 18 months post-operatively were normal. The patient has reported constant, subclinical dull pain to the right hand since the resection.

Conclusion: While the final diagnosis of the mass was not anticipated, we encourage a high degree of suspicion for malignancy in any patient with NF1 presenting with a mass following skeletal maturity regardless of its location.

Keywords: Leiomyosarcoma; Neurofibromatosis Type 1; Hand; Resection

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***Correspondence to:** Vishal S. Desai, University of Cincinnati, Department of Orthopaedic Surgery, Cincinnati OH, USA

E-mail: desaivh@mail.uc.edu

Introduction

Neurofibromatosis Type 1 (NF1) is an autosomal dominant disorder that results in an increased risk for benign and malignant soft tissue tumors. The defect involves the neurofibromin-1 protein, a tumor suppressor found on chromosome 17 [1]. NF1 is one of the most common genetic disorders and presents with significant variability but most often, patients present with café-au-lait macules and peripheral nerve sheath tumors, known as neurofibromas [1]. The majority of such neurofibromas are benign neoplasms of Schwann cell origin with a variety of morphologies and unpredictable growth patterns [2]. Other conditions associated with NF1 include iris hamartomas, optic gliomas, osseus lesions, and vasculopathy [3]. Patients are also at an increased risk of developing malignancies, such as malignancy peripheral nerve sheath tumors (MPNST) melanoma, leukemia, rhabdomyosarcoma, pheochromocytoma, carcinoma, astrocytic brain tumors, and pancreatic endocrine tumors [2]. Orthopaedic diagnoses of NF1 can be challenging to manage and most commonly include scoliosis, congenital tibial dysplasia (CTD) (formerly congenital pseudarthrosis of the tibia), and soft tissue tumors. As such, a multi-disciplined approach is often utilized in the care of NF1 patients [2, 4].

Leiomyosarcomas are malignant lesions that arise from smooth muscle. Although they often arise in smooth muscle tissue of the stomach, small intestine, and uterus, leiomyosarcomas have also less commonly been reported in the extremities [5, 6]. Less than 1% of leiomyosarcomas occur in the hand and wrist [5]. They typically present as a painless mobile mass and warrant careful consideration due to their generic presentation and potential, albeit rare, for metastasis [7, 8]. We report an NF1 patient who presented with CTD in childhood and subsequently developed a primary leiomyosarcoma of the hand. He was most recently seen in the orthopedic transition clinic where patients who were treated for pediatric orthopedic disorders by the senior author are seen for long term follow-up into adulthood. To our knowledge, this is the first report of an NFI patient who developed a primary leiomyosarcoma of the hand.

Case Presentation

This 35-year old male with NF1 presented with a 4-month history of pain and swelling of his right fifth finger. He initially presented to the senior author 35 years ago for treatment of CTD. He denies a history of recent trauma. However, thinking he had a fracture, he buddy-taped the finger and watched it. Due to persisting symptoms, he presented to the emergency department. On exam, the finger appeared twice the usual size; the skin overlying the affected digit was intact. Routine blood tests were normal. Radiographs of his right hand revealed near complete destruction of the proximal phalanx of the fifth digit (Figure 1). An MRI revealed a soft tissue mass measuring 3.1x2.9x3.5 cm and destruction of the fifth proximal phalanx. No other involvement of the hand was noted. Chest radiograph and chest CT were normal. A PET scan revealed increased uptake with a concerning SUV (Standardized uptake value) of 8 within the proximal phalanx of the right fifth digit, corresponding to the bone-replacing mass (Figure 2). {The increased SUV reflects an accumulation of radiolabel tracer and can be a useful marker for increased metabolic activity such as in malignancy. Although the use of baseline SUV measurements have been shown to be often times invalid, the presence of a nodule with a greater uptake value than adjacent tissue (as was the case in this patient) may be reason for concern [9]}. An incisional biopsy of the mass was performed. Fluorescent in situ hybridization (FISH) studies for the EWS RNA Binding Protein 1 (EWSR1) gene showed no evidence of gene rearrangement; however, 45% of cells had 3 copies of the gene and 13% of the cells had 4 copies. Histological characteristics and immunochemistry supported a malignant neoplasm; however, a specific diagnosis could not be made based on this initial, small biopsy. Resection of the digit with further

pathologic review was recommended. A radical ray excision was carried out to the distal two-thirds of the metacarpal (Figure 3). The decision was made by the operating physician not to radiate the margins following thorough review of the specimen indicating extremely wide margins.

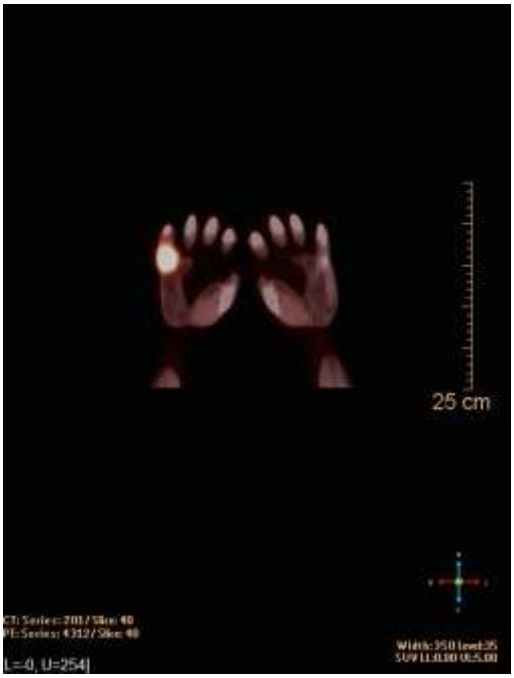

Figure 1 (left) Initial radiograph. Radiograph of the right hand shows complete destruction of the proximal phalanx of the fifth digit.

Figure 2 (right) Initial PET scan. Standardized Uptake Value of 8 corresponds to a potentially malignant mass replacing the bone.

The resected finger was then grossly examined, confirming replacement of the proximal phalanx by a solid, firm, gray-white mass. Histological examination with diffuse positivity of tumor cells for immunohistochemical muscle markers revealed high-grade leiomyosarcoma with osteoclastic giant cells. Extensive destruction of cortical and trabecular bone was seen with scant residual cortex engulfed by tumor (Figure 4A). Spindled neoplastic cells were generally arranged in sweeping fascicles, focally associated with abundant intervening collagen (Figure 4B). In other regions, the neoplasm showed increased cellularity with cells arranged in nests to short fascicles. The neoplastic cells exhibited oval to elongated plump nuclei, vesicular nuclei, conspicuous nucleoli, and moderate to abundant amounts of amphophilic to eosinophilic cytoplasm. Occasional tumor cells displayed large pleomorphic nuclei. Numerous multinucleated osteoclastic giant cells were distributed throughout the neoplasm (Figure 4C). Mitotic activity was brisk and atypical mitotic figures were noted. The lesion extended through the middle interphalangeal joint space and the cortex of the middle phalanx. The bone and soft tissue margins were negative for tumor. By immunohistochemistry, the malignant cells showed strong, diffuse positivity for desmin, while osteoclastic giant cells were negative (Figure 4D). The malignant cells also displayed scant patchy positivity for smooth muscle actin (SMA) (Figure 4E). CD68 and CD163 immunostains highlighted histiocytes; CD68 immunostain also decorated the osteoclastic giant cells (Figure 4F). The malignant cells were negative for CK8, S-100, and muscle specific actin (MSA). Recut H&E-stained slides were sent to a second pathologist, who confirmed a diagnosis of leiomyosarcoma, high grade, with osteoclastic giant cells. Imaging studies including MRI performed at 6 weeks post-operatively were normal. A repeated chest CT

revealed no changes from the previous exam. Imaging studies at 18 months showed no evidence of residual tumor (Figure 5). The patient has reported constant, subclinical dull pain to the right hand since the resection.

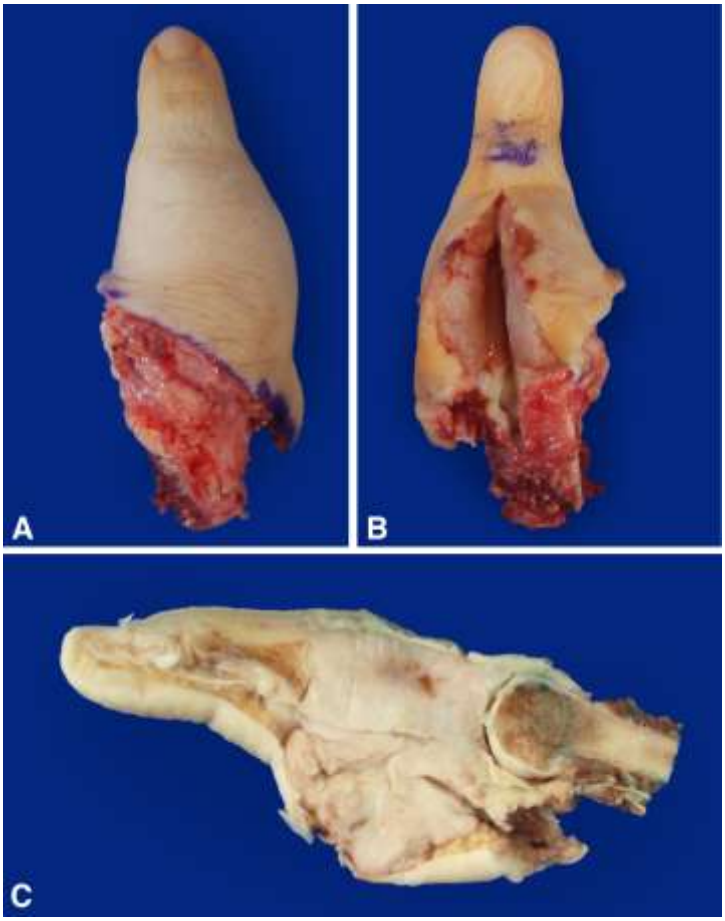

Figure 3 Excised digit. A radical ray excision was carried out to the distal third of the metacarpal.

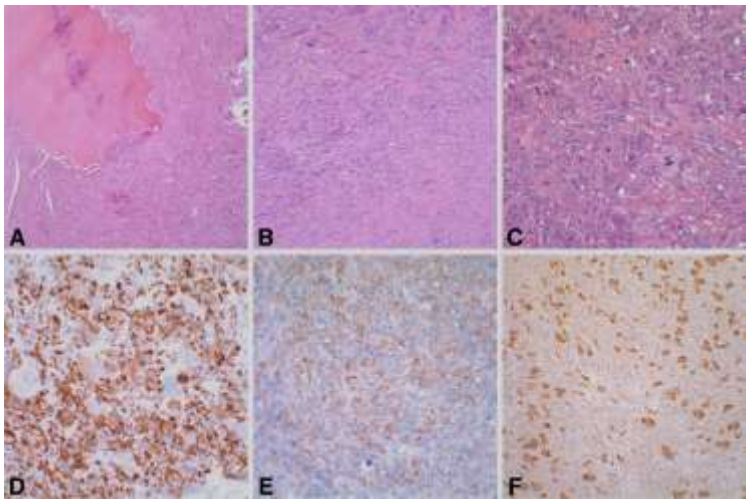

Figure 4A-F Histopathology of resected digit. A. Extensive destruction of cortical and trabecular bone with scant residual cortex engulfed by tumor. B. Focally, the neoplastic cells were spindled, arranged in sweeping fascicles associated with abundant intervening collagen. C. Numerous multinucleated osteoclastic giant cells

were distributed throughout the neoplasm. D. The neoplastic cells showed strong, diffuse positivity for desmin, while osteoclastic giant cells were negative. E. The malignant cells also displayed scant patchy positivity for smooth muscle actin (SMA). F. CD68 and CD163 immunostains highlighted histiocytes; CD68 immunostain also decorated the osteoclastic giant cells

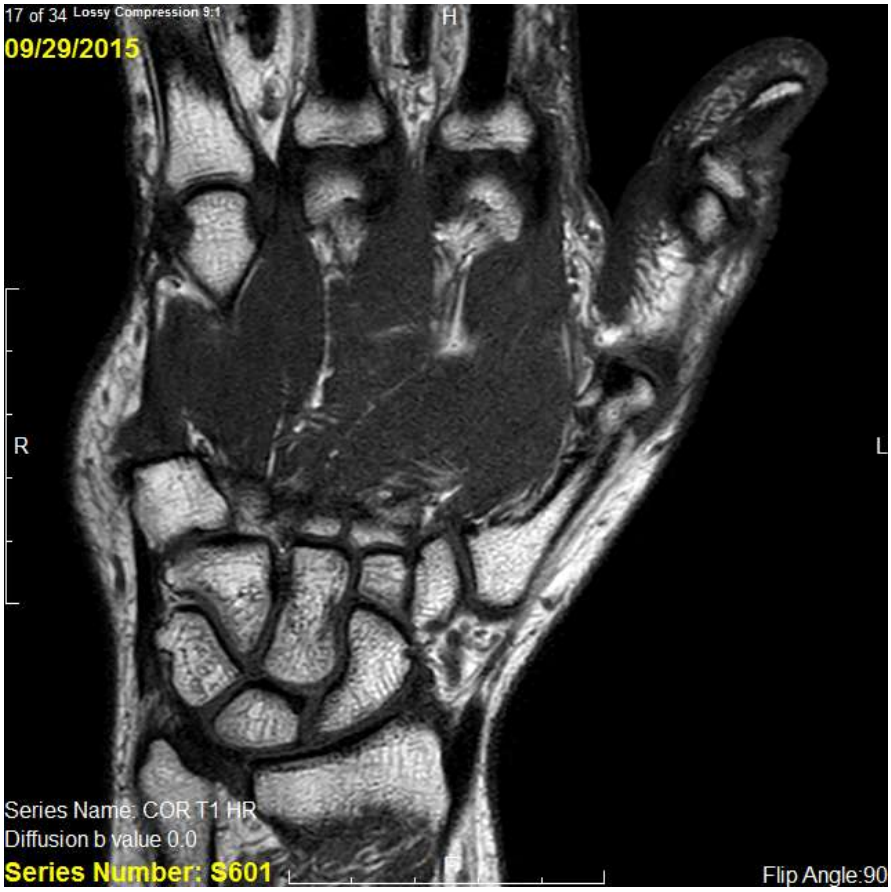

Figure 5 18 month post operative MRI. MRI showed no evidence of residual tumor.

Discussion

NF1 is an autosomal dominant disorder that reduces the effectiveness of the neurofibromin tumor suppressor, resulting in an increased risk for benign and malignant soft tissue tumors. Patients with NF1 are predisposed to developing malignant tumors originating from the nervous system and while soft tissue sarcomas have been observed in adults with NF1, they occur infrequently [1, 10]. Leiomyosarcomas arise from smooth muscle and represent 10-20% of all diagnosed sarcomas [11]. They can present in the extremities and most commonly occur in the lower extremity, predominantly the thigh [5]. Rarely, leiomyosarcomas have been reported in the hand and wrist. A review from Brenton et al suggested that of the limited number of leiomyosarcomas diagnosed in the upper extremities, only .7% of those involved the wrist or hand [5].

Leiomyosarcomas in the NF1 population have been described in the literature. Patients with NF1 more commonly develop neurofibromas (which can progress to MPNST) although tumors unrelated to the nervous system rarely do coexist with neurofibromatosis [10]. A systematic review by

Afşar et al. described patients with NF1 developing rare tumors. Their literature review yielded 75 articles and resulted in the following comorbid tumors in 84 NF1 patients: 43 patients with somatostatinoma, 26 patients with osteosarcoma, and 15 patients with leiomyosarcoma [10]. Jhas et al described the development of an intracranial leiosmyosarcoma in a pediatric NF1 patient, however, were unable to definitively determine if the tumor arose *de novo* or in association with the underlying NF1 diagnosis [12]. And finally, Kluger et al presented a pelvic leiomyosarcoma in an NF1 patient and also suggested the possibility that the mass may have been related to the patient's history of NF1 [13]. While it is difficult to conclude that a causative relationship exists between NF1 and leiomyosarcomas, the recent literature as well as our own experience warrant a high degree of caution with any masses in an NF1 patient, particularly those prone to being dismissed as benign.

Leiomyosarcomas are often unresponsive to chemotherapy and radiation; thus, wide margin surgical removal has proven to be the most accepted treatment method [7]. Because leiomyosarcoma of the hand is a rare finding, reports of treatment recommendations are sparse. Patients 1 and 2 reported by Brenton et al presented with masses on the dorsolateral surface of the right wrist and on the dorsal aspect of the first web-space of the right hand, respectively [5]. Both patients underwent wide, local excisions to remove the mass followed by radiation therapy on the forearm and hand. No local relapse or metastasis was seen on follow up clinical examinations or radiographs in either patient up to three years post operatively. DeHart et al. presented a 61-year-old male had a reddish nodule on the ulnar aspect of his left palm. Biopsy resulted in diagnosis of low grade leiomyosarcoma. The patient underwent wide excision with wide margin and was given a split thickness skin graft to covering the resulting defect. After the wound healed, radiation therapy was administered. At 2 year follow up, there was no evidence of recurrence of the disease and function of the hand was satisfactory [6].

In our case, the decision to omit radiation therapy of the margins after the resection was made by the operating physician due to the specific location of the lesion, the size of the post operative margins, and in order to prevent future stiffness of the hand.

Conclusion

This study adds to the limited number of cases of leiomyosarcomas that have been reported in NF1 patients. This tumor presented in a highly unusual location. A literature review revealed few cases of leiomyosarcoma of the hand, in accordance with its rarity. After a comprehensive search of the NCBI database, not a single prior study was found describing the presence of a primary leiomyosarcoma of the hand or wrist in a patient with NF1. Furthermore, no studies were found to suggest that there is a correlative relationship between CTD and leiomyosarcoma. While the final diagnosis of the mass was not anticipated, we encourage a high degree of suspicion for malignancy in any patient with NF1 presenting with a mass following skeletal maturity regardless of its location.

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