Open Access Library Journal
2024, Volume 11, e11371
ISSN Online: 2333-9721
ISSN Print: 2333-9705

A Rare Case of Infantile Fibrosarcoma (IFS) Resistance to Treatment Misdiagnosed with Plexiform Neurofibroma

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How to cite this paper: Şeyhibrahim, H., Chawshly, E.A., Hallak, M.H., Fraij, R.A. and Aksoy, B.A. (2024) A Rare Case of Infantile Fibrosarcoma (IFS) Resistance to Treatment Misdiagnosed with Plexiform Neurofibroma. *Open Access Library Journal*, **11**: e11371.
http://doi.org/10.4236/oalib.1111371

Received: February 28, 2024
Accepted: April 15, 2024
Published: April 18, 2024

Abstract

Fibrosarcoma (FS) is a rare, highly aggressive tumor that results from pathological changes in spindle-shaped fibroblasts that divide at an extremely rapid rate. Typically, it manifests as a painless mass usually in the upper and lower extremities, with varying symptoms based on its location and size. Diagnosis of spindle-shaped FS tumor is nearly often one of exceptions due to it is rarity and variability. As a consequence, misdiagnosis of similar tumor types is prevalent and often leading to an inappropriate therapeutic approach resulting in an overall poor prognosis when the correct diagnosis is known. We report a unique case of a 6-year-old boy who presented with a growing mass in his left arm that was initially diagnosed and treated as a plexiform neurofibroma; however, upon further examination, it was discovered to be an infantile fibrosarcoma (IFS) that had spread to the nearby lung, and showing poor response to chemotherapy or radiotherapy. By presenting the case, we aim to draw clinician's attention to the prevalence of IFS in pediatrics as well as its diagnosis and treatment, given that misdiagnosis is particularly common in underdeveloped countries that lack the resources and expertise to conduct appropriate investigations.

Subject Areas

Pediatric Hematology and Oncology

Keywords

Fibrosarcoma (FS), Infantile Fibrosarcoma (IFS), Undifferentiated Sarcoma (UDS), Soft Tissue Sarcomas (STS), Plexiform Fibrosarcoma, Misdiagnosis

1. Introduction

Fibrosarcoma (FS) is a rare tumor that predominantly originates from soft tissue tendons and fascia, and it can also arise as a primary or secondary tumor in bone. It is characterized by fibroblast cells with altered collagen synthesis [1]. According to the World Health Organization, it is classified as undifferentiated sarcoma (UDS) of soft tissues that account for 2% to 6% of all pediatric STS [2].

Two types of fibrosarcoma can be distinguished: infantile/congenital fibrosarcoma and adult-type fibrosarcoma (IFS). IFS is an infrequent malignant tumor accounting for 5% - 10% of STS diagnosed in infants less than one year old [3], it usually presents as a painless, aggressive growing mass with rare distant metastasis especially in the lungs [4]. Prognosis is good with long term survival rate [5] in compare to adult-type fibrosarcoma [6] [7]. Surgery is the mainstay of management FS with limitations in chemotherapy and radiotherapy [5].

With the variation in mesenchymal differentiation of FS, diagnosis and prognosis are usually complicated with other types of STS. Another contributing factor is the nature of these tumors, with some showing early progression, recurrence, and mortality while others show frequent recurrence and late onset [8]. With this diversity, rapid detection represents a diagnostic challenge [9], especially in hospitals with limited resources in developing countries [10].

We reported a case of a 6-year-old boy who was referred to our hospital with a growing mass in his left arm, after further investigation, the mass was confirmed as infantile fibrosarcoma (IFS).

2. Case Presentation

We present a case of a 6-years-old boy presenting to the pediatrics out-patient department with a mass in the left arm, that was noticed nine months ago at 2 - 3 cm in diameter in a gradually growing manner, at first, a biopsy was taken from the mass and was diagnosed as plexiform neurofibroma thus Selumatinib was started in another hospital, despite the therapy the mass continued to grow and was referred to our hospital for further evaluation. The patient was born in normal vaginal labor without any complications. Medical and family history is unremarkable, except for a drop in the left arm at 1 year of age, the exact reason for this drooping was not clear. Medical examination, imaging, and laboratory tests were repeated, and based on the results, the diagnosis was confirmed as infantile fibrosarcoma (IFS) with metastases to the left lung. Medical intervention suggested extracting the tumor by amputation of the entire arm, but the decision was rejected due to the family's desire to continue radiotherapy and chemotherapy.

On physical examination, he had a solid soft tissue mass in the left upper arm with dimensions: upper diameter 61 cm, middle diameter 70 cm (**Figure 1**) with edema of the distal limb along with necrotic areas.

Magnetic Resonance Imaging (MRI) (**Figure 2**) of left upper arm with contrast revealed a large soft-tissue mass containing cystic and solid areas within

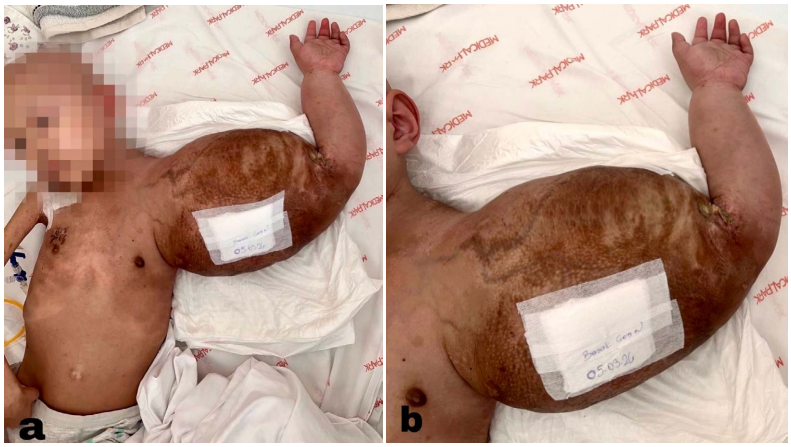

Figure 1. (a) Left upper arm mass diameter 61 cm, middle diameter 70 cm; (b) ulceration in noticed and edemain distal limb.

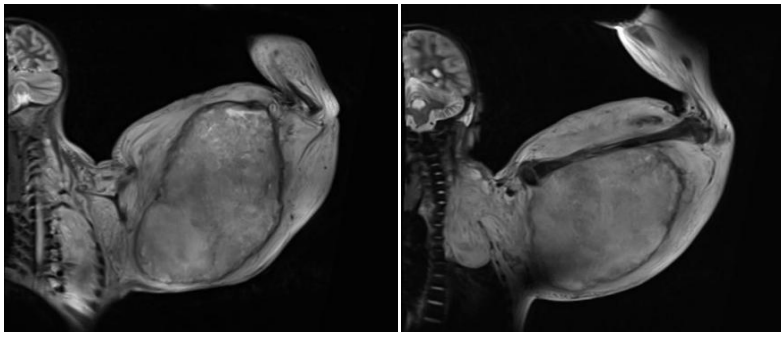

Figure 2. Hypotenuse T1A hypertens T2A MRI image show mass starting from the left shoulder extended to the elbow. abnomarl mass extanded to the lung. Thinning of the bone was noted in the humerus adjacent to the mass, especially in the middle and distal parts.

lobulated contours starting from the shoulder area to the lower half of the thorax and up to the elbow, with a long axis of 341 mm and a width of 224 mm.

Thorax CT (**Figure 3**) revealed 8 cm metastatic mass extending from the left shoulder to the left hemithorax, causing atelectatic changes in the left lungs lingular and lower lobe segments, enlarged heart and presence of a central venous catheter in the superior vena cava.

Laboratory data was as follows: Hb 9.6 gr/dL, Hct 30.1%, WBC 5140/mm^3, Plt 112,800 mm^3, PT 21.9 seconds, aPTT 38.3 seconds. Serum electrolytes, urinalysis, AST and ALT were within normal limits. Biopsy of the mass reported malignant mesenchymal tumors with predominant cellular spindle morphology, areas of necrosis, and myxoid changes indicative of fibrosarcoma. Macroscopic was interpreted as slippery, shiny, cream colored soft tissue pieces, measuring 10x9x4 cm. Immunohistochemical finding showing positive for PAN NTRK1 leans towards the diagnosis of spindle cell infantile fibrosarcoma (IFS) in his upper left arm.

The patient was started on Larotrectinib, a TRK inhibitor. The patient received radiotherapy to the primary area. Due to the gradual progression of the

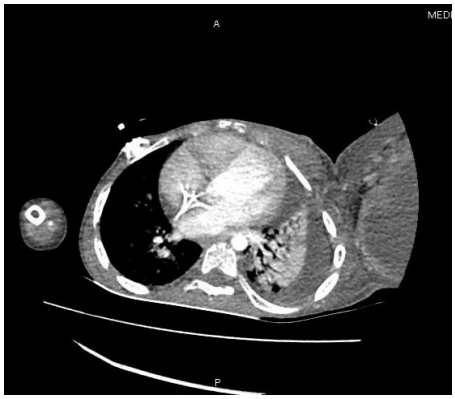

Figure 3. Thorax CT shows a mass extending from left lower cervial region to the left arm in the upper half of the chest. Diffuse ground glass appearances were observed in ventilated lung areas.

patient's mass, the patient's imaging was repeated and evaluated at the pediatric tumor council. Even though the patient's tumor mass infiltrated the left hemithorax through the left neurovascular bundle, extended to the spinal canal and compressed at 3 different levels, and was a very widespread and infiltrative involvement, it was recommended that the patient receive treatment with the addition of high dose ifosfamide + etoposide ± carboplatin (ICE). It was noticed that the patient did only partially benefit from chemotherapy and radiotherapy. However, an amputation plan was not possible due to the extension of the tumor. Thus, the tumor council decided to continue chemo-therapy. The bevacizumab therapy was also added to chemotherapy cycles in order to decrease vascularization of the tumor.

3. Discussion

Infantile fibrosarcoma (IFS) is a rare malignant tumor of early childhood with a very low incidence of five per million infants and represents approximately 10% of all pediatric soft tissue sarcomas [11]. According to WHO, IFS is a subtype of undifferentiated sarcoma (UDS) of soft tissue. IFS presentation usually occurs at birth and is less common after the age of 2 years [12]. Chung and Enzinger [13] found 41 scenarios in which the tumor appeared during the first year of life and 20 cases in which the tumor was present at birth. In comparison to adults, the nature of the tumor in newborns is more favorable prognosis with a five-year survival rate after treatment of 83% to 94%, and the likelihood of developing metastatic spread is fairly limited to 58.3% among cases [6] [7].

Morphologically, fibrosarcoma consists of spindle fibroblasts with uncontrolled proliferation and a variable amount of stromal collagen within the fibrosarcoma, which may mimic fibromatosis in some tumors [1].

Clinically, fibrosarcoma often presents as a painless, soft tissue mass in the upper and lower extremities mainly. Other sites include the trunk, head, and neck [14]. Due to mass-causing injury to nearby neurovascular systems or or-

gans, the patient may experience verities of symptoms depending on the mass size and location, symptoms such as edema, numbness, weakness, pain, or organ dysfunction may be present and in advanced metastatic disease, constitutional symptoms may occur [15]. The primary etiology of infantile fibrosarcoma (IFS) is still unclear, however various gene fusions owing to translocation and trisomies have been identified [16].

Appropriate early diagnosis is essential, considering FS is a rabid and aggressively growing tumor. MRI and CT scans were found to be useful diagnosing tumors in the leg, trunk, head and neck [15] [17], Core needle biopsy is warranted to rule out similar etiologies such as lipomas, lymphomas, leiomyomas, neuromas, or other malignant lesions, including primary or metastatic carcinoma, melanoma, or lymphoma, in addition to STS [1] [15].

Other modern diagnostic techniques such as immunohistochemistry, electron microscopy, and molecular methods reveal to be useful in differentiating FS from other spindle cell tumors [18].

Currently, the main treatment in most cases is surgery with wide local excision of the mass, is advanced stages amputation of entire limb is preferable. Radiotherapy and chemotherapy have been shown to be useful in reducing tumor bulk, especially in metastatic, relapsing, and un-respectable tumors [19] [20].

Multidrug resistance has been observed in FS. Anthracyclines are the first-line treatment chemotherapy in patients with advanced stage of FS, doxorubicin is the most widely applied drug [5].

In the presented case, the mass was initially identified as a plexiform neuro-fibroma and was treated with selumetinib for approximately 7 months without any notable response to the growing mass. Subsequently, the patient was referred to our hospital where biopsies and imaging were repeated and the patient was confirmed to have spindle IFS. Treatment resistance may be greatly influenced by advanced patient age and delayed diagnosis. Alhough, some advanced cancers may show some response, the number of poor/non-responders cases among fibrosarcoma patients is generally very high [5].

Due to their rarity, delay or misdiagnosis is common for STS in general [21] with more complications in limited facilities that lack sufficient resources and expertise to detect uncommon cases [22] along with insufficient follow-up and lack of proper communication between the patient and doctors, especially in developing countries, all of these factors ultimately lead to inaccurate diagnosis and delay proper treatment [1] [10]. Hence, the main focus with regard to this patient is to ensure adequate counseling and continuous follow-up even after completing the course of treatment as recurrence of IFS is possible [6]. We aim to draw the attention of the medical community to the possibility of misdiagnosis among STS patients, especially in devolved countries and under qualified health institutions to avoid such conditions in the future [22].

4. Conclusion

Infantile fibrosarcoma stands out as one of the rarest and most aggressive STS.

Highlighting its pathogenesis, progression, and prognosis and emphasizing the early detection of rapidly growing tumors as it significantly influences the overall outcome. Treatment for FS primarily relies on surgical removal as it plays a more significant role than chemotherapy. In the absence of appropriate expertise or resources, misdiagnosis in incapacitated hospitals is common, especially for tumors with confusing morphology such as STS. This may lead to serious consequences such as metastasis or disease recurrence, causing major problems for patients. Regular follow-up after treatment with history, physical examination and chest imaging is very important.

Conflicts of Interest

The authors declare no conflicts of interest.

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