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Case Report

Diagnostic difficulties in congenital tumor with positive antibodies for skeletal muscle. Lipofibromatosis case report

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Abstract

Introduction: Congenital soft tissue tumors are uncommon; proper diagnosis calls for histopathological experience and ancillary techniques based upon immunohistochemial, cytogenetic, and molecular biology. Following excision, intermediately aggressive soft tumors tend to local recurrence, which significantly impacts prognosis; some cases occur close to malignity; subsequently, diagnostic implications are enormous for the patient.

Case report: A 26-day old neonate with a posterior left thigh mass entered hospital. Initial biopsy analysis could not rule out either striated muscle origin or malignancy; resection and classification of surgical piece followed. Pursuant to resection, using immunohistochemistry panel, tumor analysis and classification took place.

Conclusion: Soft tumor diagnosis is a complex process, even more so for newborns. Infrequent occurrence requires that examiners have ample histopathological experience in the handling of ancillary techniques. Furthermore, as in lipofibromatosis, determining the presence of trapped vs. malignant tissue hinders proper classification, which, in turn, has profound implications for the patient. We include a standard diagnostic algorithm based on clinical and histological characteristics for this type of congenital lesions.

Keywords: Congenital Tumor; Fibroblastic/ Myofibroblastic Tumor; Lipofibromatosis; Pediatric Pathology.

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Introduction

Soft tissue tumor categorization covers mostly benign tumors: lipomas, fibro histiocytic tumors and fibromas; however, a significant number of malignant sarcomas also fall into this group: i.e., lipofibromatosis, a rare class of frequently recurring soft tissue tumors characterized by involvement of the distal extremities, can appear within intermediate–locally aggressive tumors. Lipofibromatosis etiology remains unknown; incidence prevails in the pediatric population, from birth to second decade of life; specifically, half of diagnosed cases belong to first year of life and 20% are congenital; frequency doubles in males [1]. Clinical presentation is a painless, poorly demarcated, and slow-growing mass that can affect skeletal muscle. Histologically, tumor shows abundant mature adipose tissue, admixed with a spindle cell component. Proper diagnosis requires histopathological experience and expertise in immunohistochemical, cytogenetic and molecular biology. This article describes the diagnostically challenging case of a pediatric patient, with a congenital tumor complicated by the presence of muscle tissue within the tumor itself, as well as adipose and fibroconnective tissues, defined neither as tumorous or healthy.

Case report

Clinical data

A 26-day-old neonate, born during cesarean section brought on by macrosomia, undergoing 10-day treatment for congenital syphilis entered hospital, following identification of a 3 x 2 cm solid, immobile, painless mass located on posterior left thigh. Further study revealed a mass solid in appearance, with heterogeneous echogenicity, blood flow present on color Doppler and apparent cleavage plane abutting the femur. Subsequent magnetic resonance contrast revealed a 52 x 35 x 30 mm, 29 cc, septate mass with well-defined contours, heterogeneous signal intensity, hypointense in T1 and hyperintense in T2, extending into soft tissues, with no infiltration of the femur. Consequently, differential diagnosis suggested lymphatic and / or venous malformation. Given low certainty, pediatric surgery service performed soft tissue biopsy (muscles, tendon, fascia and bursa). The use of cefazolin as a procedural prophylactic ensured adequate post-anesthetic recovery; patient discharge included care-giver information and recommendations on warning signs; pediatric check-up took place at one week, followed by visit to pediatric surgery section once biopsy results became available.

Perinatal history included a 32-year-old, G2P1 mother; cesarean section at gestation week 40; birth weight of 3500gr, and APGAR scores were 8 and 9 at 5 minutes and 10 minutes, respectively. Biopsy revealed abnormalities: difficult to classify spindle cell and myxoid tumor; consequently, complete lesion resection took place.

Patient underwent procedure at age 45 days; complete surgical excision rendered a 54 x 33 x 32 mm oval mass, smooth surface, solid consistency, adhered to muscle planes and proximal periosteum. Patient had satisfactory postoperative recovery, with surgical wound in good condition, no signs of infection, normal oral intake, hemodynamic stability, no signs of respiratory distress or low output. After 3-day hospital stay, Pediatric Care authorized discharge.

Pathology

Pathology lab received three cylinders of off-white, rubbery tissue; histological report described fusocellular and myxoid proliferation with no major anaplasia or necrosis, with up to 4 mitosis per 10 high power fields (phh3) and ki67 between 10 and 20; AML and CD10 expressed focal reactivity; results were negative for β-Catenin, S100, SOX10, ALK, Olig2, AE1-AE3, CD34, ERG-1 and CD99. Interpreting the presence of striated muscle fibers proved difficult, as they were either part of the tumor or were trapped muscle fibers; in any event, they exhibited focal reactivity for desmin, myo D1 and myogenin; there was no loss of INI-1% (Figure 1).

Physician and lab analysts set forth several differential diagnoses: childhood fibrosarcoma, myofibromatosis, lipoblastoma, rabdomyoma and even rabdomyosarcoma; further discussion by medical board concluded that possibly malignant tumor originated in the striated muscle; therefore, discussion followed on the necessity for resection and classification of surgical piece.

Consequently, Pathology Lab received a 5.2 x 2.9 x 1.5 cm surgical specimen consisting of a mass of soft tissue, neither oriented nor repaired, ovoid in shape, generally light yellow in color with occasional grayish areas,rubbery in consistency; external surface was smooth with apparent pseudocapsula present (Figure 2a); cut surface, light yellow and homogeneous in shape. Microscopically, tumor featured abundant adipose tissue with spindle fibroblastic component that involved fat septa and trapped skeletal muscle. Fibroblastic element had fascicular growth and exhibited minimum mitotic activity; there was no myxoid component and no cytological atypia. Mature adipocytes accounted for all fatty tissue; skeletal muscle was mature, with no atypia. Tumor showed no signs of necrosis, immature spindle cell aggregates or mitotic figures; peripherally, a faint pseudocapsuleenclosed it and there was no apparent invasion. Immunohistochemistry results revealed partial reactivity for CD34, S100 and SMA. There was no positivity for CD31, EMA, CD99, Bcl2, CK, TFE-3, TLE-1, β-Catenin; Ki 67 was 10% immunoreactive with positivity for PHH3, Desmin, Myogenin and MyoD1; conclusive classification was for trapped benign muscle (Figure 2b-2e).

Discussion

Congenital tumors occur very infrequently; incidence is 7.2 per 100,000 in live newborns [2]. Estimated incidence of soft tissue tumors is close to 3000 cases per 1 million population for benign tumors, predominantly vascular origin; and nearly 50 cases per 1 million population for sarcomas. The latter represents less than 1% of all malignant tumors in the human body [1]. Pediatric soft tissue sarcomas account for approximately 10% of all malignancies in children, thus representing a very important chapter of pediatric oncology [3] with high mortality [4]. In order of occurrence, the most common tumors in newborns are teratomas, soft tissue tumors, neuroblastomas, leukemia and brain tumors [4].

Benign and malignant soft tissue tumors in the childhood are perplexing; its final diagnosis requires histopathological experience and knowledge of ancillary techniques in immunohistochemical testing, cytogenetics and molecular biology [5].

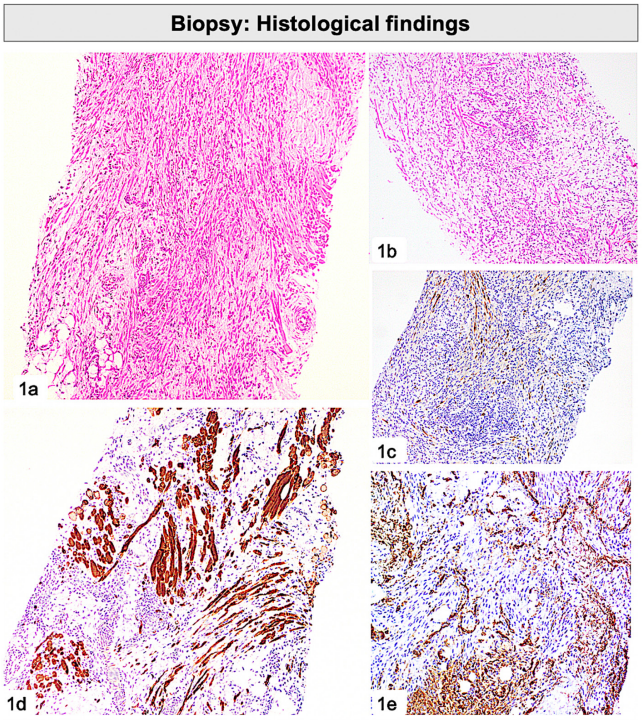

Figure 1: Panel biopsy: 1a-cylinder with fusocellular proliferation what includes striated muscle fibers, adipose and fibroblastic tissue. It was not possible to know if striated muscle fibers are trapped or are a main component of the lesion. Major anaplasia or necrosis was not observed (H&E 10x); 1b- myxoid component was seen in the same cylinder and again the muscular component was disturbing (H&E 10x); 1c and 1d- immunohistochemistry for Myogenin and Desmin respectively, highlighted the muscle fibers (10x); 1e- CD34 showed the vascular component (10x).

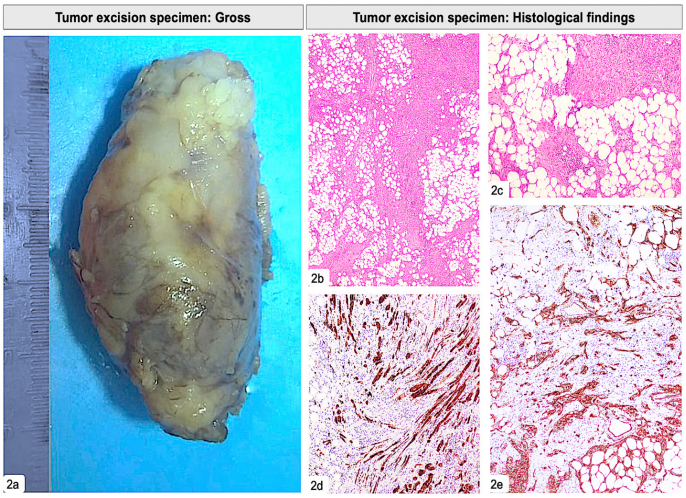

Figure 2: 2a-surgical specimen, a mass of soft tissue, ovoid in shape, light yellow in color with grayish areas,rubbery in consistency. It measured 5.2 x 2.9 x 1.5 cm. The external surface was smooth. Panel complete resection: 2b- panoramic microphotograph exhibits abundant adipose tissue with a spindle fibroblastic component that mainly involved the fat septa and trapped skeletal muscle (H&E 14x); 2c- The fibroblastic element had fascicular growth and exhibited minimum mitotic activity, and no cytological atypia. Fat tissue and skeletal muscle were mature, also without atypia (H&E 10x); 2d - immunohistochemistry for Myogenin highlighted the muscle fibers (10x); 2e- CD34 showed the vascular component (10x).

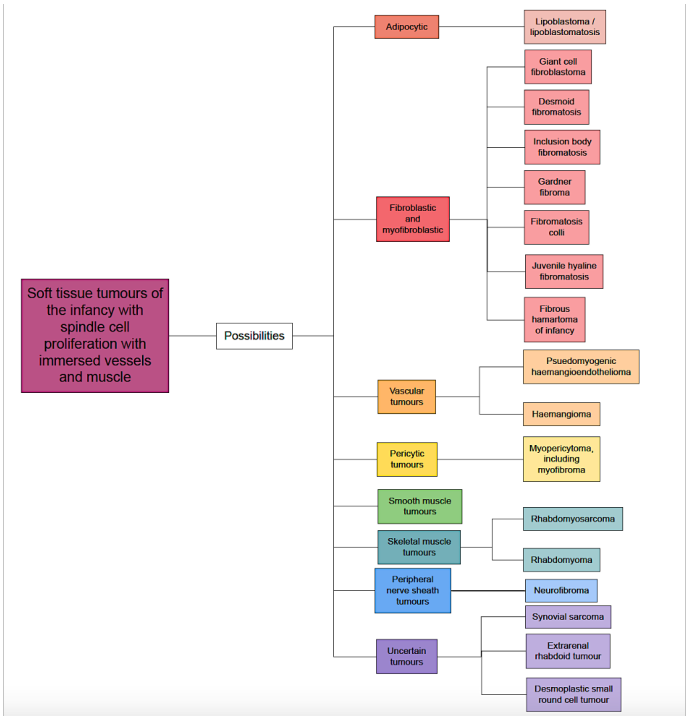

Figure 3: Algorithm: according to OMS classification, for soft tissue tumors of the infancy with spindle cell proliferation with immersed vessels and muscle, taking into account age (congenital), localization, histological appearance, histological components and the immunohistochemical panel.

Following excision, intermediately aggressive soft tumors tend to be locally recurrent, a fact which significantly impacts prognosis. Among soft tissue mesenchymal tumors occurring in first year of life, 12% were found in first week of perinatal period [6], with head and neck area (60%) cited as principal location [4]. Neurogenic tumors are the most frequent among congenital tumors in contrast with the group between 8 days and 12 months, in which vascular, fibroblastic-myofibroblastic and fibrohistiocytic tumors are predominant [6].

Pediatric fibroblastic and myofibroblastic tumors are a relatively common group of softtissue proliferations. Clinically the spectrum of behavior is wide, and includes the following categories: benign (ie, myositis ossificans, myofibroma, fibromatosis colli), intermediate–locally aggressive (ie, lipofibromatosis, desmoid fibromatosis, giant cells fibroblastoma), intermediaterarely metastasizing (ie, inflammatory myofibroblastic tumors, infantile fibrosarcoma,myofibroblastic sarcoma), and malignant (ie, low-grade fibromyxoidsarcoma) [1,7].

Lipofibromatosis is a rare, yet frequently recurring pediatric tumor [1], whose preferred location in the subcutis [1,10] or deep soft tissues of the distal portion of neonates´ and infants´ extremities [8-10];additionally, cases exist of tumor location in the trunk and head and neck regions [1,10].

Clinical features at moment of tumor presentation include patient age ranging from newborn to 14 years, median age is 1 year [11]. Approximately 20% of the lesions are congenital [1]; frequency rate is double in males. Slow-growing tumor mass is painless, and poorly demarcated, and tends to affect skeletal muscle [1]. Recurrence rate is high, up to 72% [11]. Recurrence has been linked to congenital character, male sex, acral location, incomplete excision, and mitotic activity [11]. On the other hand, the lesion has no metastatic potential [1,11]. It could present soon after birth [3], like the present tumor.

Gross measurement of most tumors is between 1 and 7 cm, and color ranges from white to yellow, based on adipose component; consistency varies from firm to rubbery or gritty with characteristically ill-defined margins [1,8].

Histologically, the tumor shows abundant mature adipose tissue admixed with a spindlecell component, often concentrated in septal and perimysial locations [8], arranged in short fascicles [1]; the adipose tissue lobes are seen crossed by fibroblasts and myofibroblasts, similar to desmoid tumors [12]. The fatty component usually makes up more than 50% of tumor total [8], and spindle cell are reserved for septal regions. Spindle cells show bland and uniform elongated nuclei. Another important tumor feature is lack of circumscription; in immature patients, there is an expectation of greater myxoid change.

There are no accounts of lipoblasts, or of nuclear pleomorphism in the fibroblastic component being present, nor of a high mitotic rate. Necrosis is absent. Crucial to accurate diagnosis is recognition of normal tissue entrapment, ie: skeletal muscle, nerves, blood vessels, skin adnexa [8]. Because it is clinically and histologically delineated, with difficult-to-discern margins, assessment of macroscopic and microscopic infiltration is challenging. Surgical difficulties for complete resection, especially in certain areas, could be related to recurrence. This characteristic could also have an impact on the interpretation of the histological components, as in the present patient, in whose tumor the muscle was considered as a component and as trapped tissue and its complex differentiation required deferring the definitive diagnosis until procuring both the complete mass and a new immunohistochemical panel.

Due to average patient age as well as taking into account the aforementioned roster of components, achieving differential diagnosis can often be a complex task.

The immunohistochemical profile of lipofibromatosis lacked specificity: spindle cells show CD99 positivity. SMA, CD34, Bcl2, S-100, and EMA may be positive, usually focally. These cells are negative for desmin and keratins; desmin negativity in spindle cells contrasts with immunoreactivity exhibited by rhabdomyoma and lipoblastoma [13]. Adipocytes as expected, show S100 and Bcl-2 positivity.

No recurrent genetic alteration has been described in the literature, such findings could prove useful for diagnosis, subclassification, prognosis or predicting familial recurrence [8]. Activation of the PI3K/AKT/mTOR pathway might be involved in the etiology of lipofibromatosis [1]. Ibraheemi put forth an interesting theory derived from his series of two out of three recurrent cases, and of four cases in total, in which FN1-EGF fusion occurred. Due to the fact that in some cases calcifications are present, the theory states that lipofibromatosis and calcifying aponeurotic fibroma are specters of the same disease [9].

Through immunohistochemistry, lipoblastoma is recognized for PLAG1 expression of, and its FISH-verified rearrangement indicates 8q11-q13 alterations, either translocation, inversion, insertion, or ring chromosome. On the other hand, juvenile hyaline fibromatosis affects chromosome 4 (4q21.21); this translates into an altered relation between laminin and collagen IV and, perhaps, failures in collagen IV degradation. In contrast, fibrous hamartoma of infancy has only recently been considered neoplastic rather than just a hamartoma, due to recurrent EGFR exon 20 insertion/ duplication mutations. Its location is chromosome 7. As was mentioned above, lipofibromatosis can present fusions between some ligands or tyrosine kinase receptors that activate the PI3K/AKT/mTOR pathway; this important intracellular signaling pathway of the cell cycle is hyperactive in many tumors, which reduces apoptosis and allows for proliferation. Alterations do not belong to one gene or one alteration that, therefore, explain the lesion. For diagnosis, however, the FN1-EGF fusion could be useful. Its usefulness is still limited based on its novelty and to the fact that it is not universal for all histologically diagnosed Lipofibromatosis.

Although the discussion is interesting for pathogenesis, the confirmation of any of these molecular alterations has yet to have prognostic implications.

In our patient, many options in the biopsy were available; primary differential diagnosis was rhabdomyosarcoma. During first analysis, spindle cell and myxoid component were more conspicuous, and immunohistochemistry profile was nonspecific; hence surgical specimen classification was necessary. In second analysis, we ruled out rhabdomyosarcoma because muscle was organized and mature, with no mitotic activity, atypia, or necrosis.

When working towards definitive differential diagnosis, it is important to not rule out fibrous hamartoma of infancy, in which an expected mix of soft tissues (fibroblastic, mesenchymal, and mature adipose) cover a myxoid stroma. Although we encountered some of these indicative factors in our patient; our diagnosis, we concluded rested on the preeminence of fibroblast; furthermore, we recognized that the trapped skeletal muscle and adipose tissue were not tumor components. In addition, fibrous hamartoma of infancy is usually smaller, more central than axial, and more superficial than deep. Differentiation with other fibrous tumors required epidemiological and clinical data, to rule out for example fibromatosis coli and conventional fibromatoses. Other differential diagnoses are included in Figure 3, which is a useful diagnostic algorithm.

The goal for treatment is complete surgical excision. Unlike other tumors, lipofibromatosis has no histological characteristics that allow for predicting recurrence or infiltration potential. By definition, it lacks necrosis, mitosis or cellular atypia. Its very nature makes it advisable to avoid disfiguring surgeries, since, as is known, some partially excised patients survive with controlled lesions; therefore, it is important to keep in mind the benefit of conservative procedures when the possibility of impaired function or morbidity may be high.

Declaration of conflicting interests: No author has any potential or actual interests relevant to the topics discussed in this manuscript.

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