Infantile myofibromatosis: multiple firm nodules in a premature newborn

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Abstract

Infantile myofibromatosis is a rare myofibroblastic proliferative disorder characterized by firm, skin-colored to red-purple cutaneous and subcutaneous nodules; these are the most prevalent fibrous tumors observed in infancy. A premature male infant presented at birth with multiple subcutaneous firm skin-colored nodules measuring about 1-2cm each. Full body MRI and excisional biopsy of the right chest nodule confirmed the diagnosis. We review the case of infantile myofibromatosis and discuss its highly heterogeneous presentation and clinical course, as well as histopathology, genetic testing, and approaches to management.

Keywords: infantile myofibromatosis, IMF, myofibroma, myofibromatosis

Introduction

Infantile myofibromatosis (IMF) is a rare myofibroblastic proliferative disorder characterized by firm, skin-colored to red-purple cutaneous and subcutaneous nodules. Though rare, they are the most common fibrous tumor of infancy with a predilection to male infants, although the disorder can present later in childhood or occasionally in adults. Three forms of IMF have been delineated: 1) solitary myofibroma; 2) multicentric or multiple myofibromatosis; and 3) generalized myofibromatosis, which includes both multicentric lesions and visceral involvement [1]. Although the prognosis of solitary IMF is generally excellent with a self-limiting benign course, multicentric IMF can lead to infiltration of the viscera and generalized IMF, which is associated with high morbidity and mortality and for which there is a lack of effective therapeutic approaches. Timely accurate diagnosis and thorough monitoring is therefore of the utmost importance for IMF, especially given its variable presentation. Herein, we describe the case of a premature newborn male presenting with multiple enlarging firm lesions at birth.

Case Synopsis

A male infant, born via cesarean section due to maternal pre-eclampsia at 34 weeks' gestational age, presented at birth with multiple subcutaneous firm skin-colored nodules measuring about 1-2cm each. Palpable nodules were found on the right inferolateral posterior chest wall, left posterior upper arm, anterior right thigh, and posterior left calf. Two additional nodules presented on the occipital scalp (**Figure 1A**, **B**). A plain chest radiograph revealed an opacity in the right upper lobe region. Subsequent full body MRI at age 24 days demonstrated hyperintense signal of the nodules on STIR (short tau

inversion recovery sequence with suppression of signal from fat) images and hypointense signal on T1-weighted images, with heterogeneous opacity noted within the pulmonary tissue of the right upper lobe. No other intra-thoracic or intra-abdominal abnormalities were noted. Laboratory studies were unremarkable. Physical examinations were age-appropriate for growth and development, with no lymphadenopathy or hepatosplenomegaly. Parents had denied family history of similar lesions.

An excisional biopsy was obtained from the right chest wall nodule (which was adherent to the muscle layer) at age 25 days and was submitted for histopathological examination.

Overall findings were consistent with a diagnosis of infantile myofibromatosis (IMF). The excisional mass biopsy from the right chest wall revealed intersecting bundles of bland spindled cells with focal areas forming myoid nodules with chondromyxoid changes surrounded by hemangiopericytoma-like vasculature, that was also focally located at the periphery of the lesion. Skeletal muscle was observed at the periphery and entrapped within the nodule (**Figure 1C**). Desmin staining highlighted skeletal muscle but was

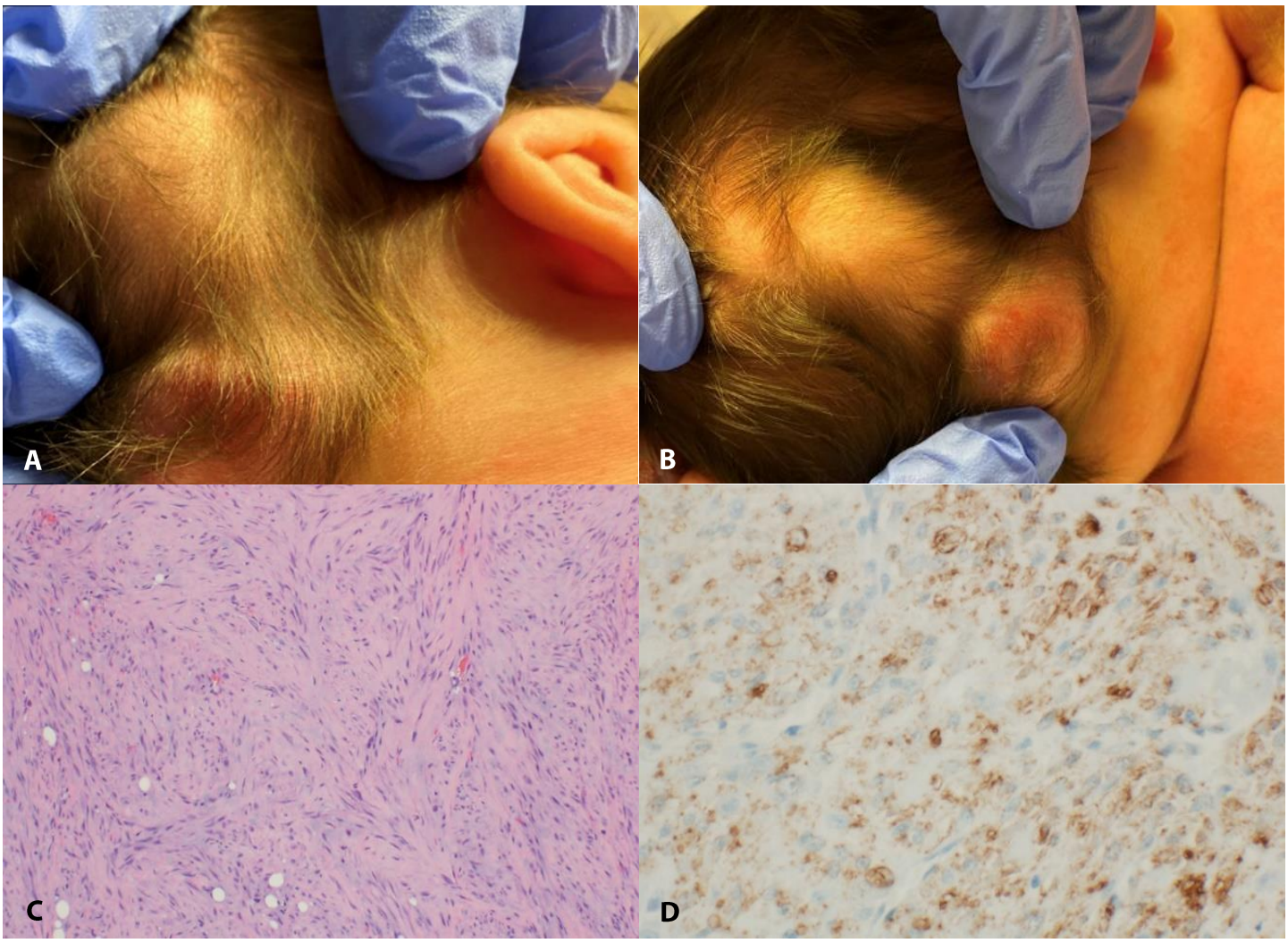

Figure 1. ***A, B).*** *Two firm non-mobile subcutaneous nodules on the occipital scalp of a male infant presenting with infantile myofibromatosis.* ***C).*** *H&E of right chest wall subcutaneous nodule, excisional biopsy from 25 day old male infant. Intervening cellular area of myoid nodule with chondromyxoid matrix, showing bland elongated spindled cells and associated delicate branching vasculature indicative of myofibroma, 20x.* ***D).*** *SMA (smooth muscle actin): Immunohistochemical stain for SMA showing patchy positivity in spindled lesional cells of biopsied right chest wall subcutaneous nodule, consistent with diagnosis of infantile myofibromatosis, 40x.*

negative in lesional cells. Immunohistochemical staining was positive for smooth muscle actin (SMA), demonstrating patchy positivity in lesional cells (**Figure 1D**). Genetic studies were negative for the gain-of-function *PDGFRB (platelet-derived growth factor receptor beta)* gene mutation located on chromosome 5q31-q32 associated with a constitutively active PDGFRB kinase present in the familial (autosomal dominant) form of IMF [2].

The patient presented two days after the right chest nodule excisional biopsy with poor oral intake, irritability, and seizure-like activity. A brain MRI revealed widespread diffusion restriction in the cerebral white matter compatible with viral encephalitis, but no intracranial masses. No causative organism was identified and he was discharged home after a period of observation in the neonatal intensive care unit. Chest radiograph and CT angiogram findings during this hospitalization confirmed the presence of a pulmonary mass within the right upper lobe, homogeneous in appearance and isodense to skeletal muscle, without associated abnormal or anomalous vasculature. Owing to the absence of a *PDGFRB* gene mutation, IMF therapy with imatinib (which has been shown to demonstrate a marked treatment response and sustained remission of lesions in *PDGFRB*-mutated IMF) was not pursued [2]. Chemotherapy with vinblastine and methotrexate was deferred in favor of expectant management.

Chest radiographs at 55 days of age showed a decrease in size of the right upper lobe mass, but revealed subtle asymmetric lucency in the anterior right ninth rib, indicating a possible osseous lesion without pathologic fracture. Although the other lesions remained stable, the parents reported continued growth of the occipital scalp nodules, one of which showed signs of pressure injury with erythema and thinning of the skin. A surgical excision of both occipital nodules was therefore performed at 69 days of age. The pathology report was consistent with the previous specimen and lacked cytologic atypia, confirming IMF. As nodules had not interfered with normal movement and development, no additional therapies or surgical procedures were undertaken and remaining nodules were monitored by physical examination and imaging over the next few months. Follow-up brain MRI also demonstrated resolution of the diffusion restriction findings observed during the previous hospitalization. One newly presenting left neck mass at 6 months of age was initially favored to be an enlarged posterior cervical lymph node, but was later perceived to be more consistent with myofibroma. Nodules were generally observed to stabilize or decrease in size, with no visceral involvement. Available procedure details, exams, and imaging findings throughout the patient's clinical course are summarized in **Table 1.**

Case Discussion

Although a majority of IMF patients present with solitary cutaneous or subcutaneous nodules involving the head or neck soon after birth, the clinical appearance of IMF is often non-specific and variable. Initial presentations of intramuscular or intraosseous growths have been reported, as well as atrophic or pedunculated lesions that may be mistaken for hemangioma or rhabdomyosarcoma [3]. Prompt biopsy is therefore necessary for accurate diagnosis.

On histopathology, myofibromatosis shares some features of other benign hemagiopericytoma-like tumors, with oval cells surrounding blood vessels branching in a staghorn pattern. Concentric perivascular growth is indicative of myopericytoma and a variant of myopericytoma called glomangiopericytoma contains cells resembling glomus cells [4]. However, the biphasic growth characterized by alternation between oval cells with scant cytoplasm, followed by spindle-shaped cells with eosinophilic cytoplasm in the dermis and subcutaneuous tissue, are particular to myofibromatosis [4]. Significant cytologic atypia is not usually seen [1]. Immunohistochemical staining is typically positive for SMA and may also be positive for muscle-specific actin in most cases, while less commonly positive for desmin [5].

The solitary form of IMF is characterized by a single skin nodule [6] and is the most common form, accounting for 50-80% of cases with some reported

in adults [7]. The cutaneous lesions which commonly involve the head or neck, trunk, or limbs are asymptomatic, but discomfort related to compression and ulceration may occur, as was observed for the scalp nodules in this patient. Their clinical appearance can vary from subcutaneous nodules without any skin changes to red-to-purple nodules resembling hemangioma; rarely sclerodermoid-like changes may be observed [1]. The prognosis of solitary IMF is excellent, with an often benign course [7]. Most lesions can be monitored or surgically excised and recurrence is exceedingly rare [1].

The multicentric form frequently presents with cutaneous and subcutaneous lesions on the head [8], neck, bones, trunk, or muscles. Multicentric IMF without visceral involvement or metastasis additionally tends to have a promising prognosis with a benign course and can benefit from surgical excision and close monitoring. Like solitary IMF, spontaneous regression may occur in up to two years [5] and is thought to relate to modulation of angiogenic processes [1]. Many cases of the multicentric form are congenital with autosomal dominant inheritance, owing to mutations in *PDGFRB*. The *NOTCH3* gene located on chromosome 19p13.12, which is involved in cellular differentiation, has also been implicated in a familial form of IMF, suggesting rare instances of genetic heterogeneity [1].

About 15-20% of multicentric IMF cases can become the generalized form [8], defined by multicentric lesions and visceral involvement, which most commonly involves the larynx, lungs, gastrointestinal tract, kidney, and ovaries or testes. Infiltration into the subcutaneous tissue, bones, heart, and central nervous system has also been observed [1,9]. This type is associated with a poor prognosis, with high morbidity and up to 76% mortality [5]. However, cases of spontaneous regression for generalized IMF have also been reported in the literature [1], consistent with our observations for this patient. Although involvement of the lung parenchyma of the right upper lobe was initially seen on imaging, no further intra-thoracic or intra-abdominal abnormalities were noted during the patient's clinical course, and the right upper lobe lesion eventually decreased in size and regressed without incident. Therefore, close clinical monitoring may be recommended in the absence of acute life-threatening complications.

Extensive surgical excision or chemotherapy have been beneficial for multicentric IMF, but explicit guidelines for approaches to treating generalized IMF with multi-organ infiltration are lacking. Low-intensity chemotherapy with vincristine, vinblastine, methotrexate, interferon alpha, and anti-angiogenic therapies have been effective in some cases [1]. Since the gain-of-function *PDGFRB* gene mutations are also more frequent in the generalized form of IMF, possible therapeutic avenues may include the development of targeted therapies in conjunction with imatinib. When gene mutations are identified, expanded family counseling and advising is warranted [1,10,11].

Conclusion

Prompt diagnosis including genetic testing and adequate monitoring are recommended, especially given the variable presentation and tendency for lesions to self-resolve. These studies aid in determination of prognosis and are essential in guiding the therapy and follow-up of IMF.

Potential conflicts of interest

The authors declare no relevant conflicts of interest.

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Table 1: *Infantile myofibromatosis patient clinical course: procedures, exams, and imaging findings over time.*

Patient age (days)	Exam or procedure	Notes and findings
20	Physical exam	**Multiple firm 1-2cm non-mobile subcutaneous nodules:** R superior occipital scalp R inferior occipital scalp R chest wall L posterior proximal humerus R anterior thigh L posterior calf
24	Full body MRI	**Confirmed multiple subcutaneous lesions:** R chest wall: 1.5x0.8x1.5cm L upper thoracic paraspinal: 1.9x1.8x1.3cm L posterior proximal humerus: 1.2x1.7x1.3cm R deep inguinal: 1.8x1.5x1.7cm R anterior thigh: 1.8x2.4x2.7cm L posterior calf: 2.2x2.0x2.9cm All lesions demonstrate predominantly hyperintense signal on STIR images and hypointense signal on T1-weighted images. Heterogeneous opacity of R upper lobe pulmonary tissue. Occipital scalp outside field-of-view. No definite intra-abdominal signal abnormality
25	Excisional biopsy: R chest wall	**Firm well-circumscribed 1.5cm diameter mass adherent to R chest wall, excised.** Pathology revealed intersecting bundles of bland spindled cells with focal areas forming myoid nodules with chondromyxoid changes surrounded by hemangiopericytoma-like vasculature, focally located at the periphery of the lesion. Skeletal muscle was observed at the periphery and entrapped within the lesion. Desmin staining highlighted skeletal muscle but was negative in lesional cells. Immunohistochemical staining positive for smooth muscle actin (SMA), demonstrating patchy positivity in lesional cells. Consistent with diagnosis of infantile myofibromatosis (IMF). Genetic testing negative for PDGFRB mutation, preventing imatinib therapy
27	Neonatal intensive care unit (NICU) hospitalization (5 days)	Admission to NICU with poor oral intake, irritability, and seizure-like activity on EEG. Widespread diffusion restriction in the cerebral white matter compatible with viral encephalitis on MRI. No causative organism identified. Continued R upper lobe opacity on chest x-ray (CXR)
34	Physical exam	**Multiple firm 1-2cm non-mobile subcutaneous nodules:** R superior occipital scalp R inferior occipital scalp: overlying erythema and thinning of skin (not ulcerated) R chest wall: excised at age 25 days L posterior proximal humerus R anterior thigh L posterior calf
55	CXR	Decreased R upper lobe lesion size. Possible osseous R anterior 9th rib lesion without pathologic fracture
55	Physical exam	**Multiple firm non-mobile subcutaneous nodules:** R superior occipital scalp: 2.5x3cm R inferior occipital scalp: 2.5x2.5cm, erythema R chest wall: excised at age 25 days L posterior proximal humerus: 3.75x2cm R anterior thigh: 3x4cm L posterior calf: 5x5cm
62	Physical exam	**Multiple firm non-mobile subcutaneous nodules:** R superior occipital scalp: 2x3cm (decrease) R inferior occipital scalp: 3x3cm (increase), erythema R chest wall: excised at age 25 days

		L posterior proximal humerus: 3x3cm (increase) R anterior thigh: 3x3.5cm (decrease) L posterior calf: 4x4cm (decrease)
69	Surgical resection: R occipital scalp	**Surgical resection of subcutaneous nodules:** R superior occipital scalp: 4x2x1.5cm R inferior occipital scalp: 3x2x1.5cm, erythema Pathology revealed multinodular spindled cell proliferation with short chondromyxoid-like fascicles and whorls of myofibroblasts without cytologic atypia. Bundles of hyalinized collagen were also seen. Consistent with diagnosis of infantile myofibromatosis
76	Physical exam	**Multiple firm non-mobile subcutaneous nodules:** R superior occipital scalp: excised at age 69 days R inferior occipital scalp: excised at age 69 days R chest wall: excised at age 25 days, regrowing, 1.5 cm L posterior proximal humerus: 2.5x2cm (decrease) R anterior thigh: 3.5x3.5cm (increase) L posterior calf: 4x4cm (no change)
87	Physical exam	**Multiple firm non-mobile subcutaneous nodules:** R superior occipital scalp: excised at age 69 days R inferior occipital scalp: excised at age 69 days R chest wall: excised at age 25 days, regrowing, 2 x 2cm (increase) L posterior proximal humerus: 2.5 x 2.5cm (increase) R anterior thigh: 3x3cm (decrease) L posterior calf: 3.5x3.5cm (decrease)
101	Brain MRI	Patchy diffusion restriction in cerebral white matter (compatible with viral encephalitis) from day 27 resolved. No new diffusion restriction identified
125	Physical Exam	Multiple firm non-mobile subcutaneous nodules, stable or decreasing in size
153	Full body MRI	**Stability in size of lesions on MRI:** R chest wall: 0.9x1.5x1.9cm, less well-defined R upper lobe: 1.2x1.8x1.8cm, more well-defined R lower rib signal: 1.3x1.1cm axial plane, extending 2.5cm along rib L upper thoracic paraspinal: 1.2x1.9x1.6cm L posterior proximal humerus: 1.7x1.7x1.6cm R deep inguinal: 1.5x2.4x1.3cm R anterior thigh: 1.9x2.2x2.4cm L posterior calf: 1.4x2.0x3.1cm L lower cervical lymph node enlarged: 1.0 x 0.8 x 1.0cm R inguinal lymph node enlarged: 1.1 x 0.8 x 0.5cm. Intra-abdominal region unremarkable
202	Physical exam	**Four palpable firm non-mobile subcutaneous nodules:** R chest wall L posterior proximal humerus R anterior thigh L posterior calf New L neck nodule, pea-sized, firm, non-mobile
216	Physical exam	**Four palpable firm non-mobile subcutaneous nodules, all decreasing in size:** R chest wall L posterior proximal humerus R anterior thigh New L neck nodule, 1-2cm, firm, non-mobile
221	Full body MRI	**Stability or decrease in size of lesions on MRI:** R chest wall: not apparent R upper lobe: 1.7x1.0x2.0cm L upper thoracic paraspinal: 1.3x1.1x0.9cm, not well-defined L posterior proximal humerus: 1.6x1.5x1.8 cm R deep inguinal: 1.7x1.1x0.9cm, not well-defined R anterior thigh: 1.6x2.6x2.1cm

		L posterior calf: 1.6x2.1x2.3cm L neck mass enlargement: 1.3x1.6x1.5cm Intra-abdominal region unremarkable
244	Physical exam	**Four palpable firm non-mobile subcutaneous nodules, all decreasing in size:** R chest wall L posterior proximal humerus R anterior thigh New L neck nodule, 1-2cm, firm, non-mobile, growing in size and tender on palpation. More consistent with new myofibromatosis nodule than lymph node
272	Physical exam	**Four palpable firm non-mobile subcutaneous nodules, all decreasing in size:** R chest wall L posterior proximal humerus R anterior thigh New L neck nodule, 1-2cm, firm, non-mobile, stable
314	Full body MRI	**Stability or decrease in size of lesions on MRI:** R chest wall: 5mm R upper lobe: 1.1x1.6x1.6 cm L upper thoracic paraspinal: not apparent L posterior proximal humerus: 1.6x1.2x1.4cm R deep inguinal: not apparent R anterior thigh: 1.7x1.4x2.0cm L posterior calf: 1.5x1.3x1.8 cm L neck mass: 0.8x1.2x1.5 cm Intra-abdominal region unremarkable
314	Physical exam	**Four palpable firm non-mobile subcutaneous nodules, all decreasing in size:** R chest wall L posterior proximal humerus R anterior thigh New L neck nodule, 1-2cm, firm, non-mobile, stable

L, left; R, right.