Case Report

Diagnostic limitations and considerations in the imaging evaluation of advanced multicentric infantile myofibromatosis

Abhinav Parikh, MDa,b, Colleen Ann Hughes Driscoll, MDb, Helena Crowley, MDb, Teresa York, MDb, Guillaume Dachy, MDb, Jean-Baptiste Demoulin, PhDd, Suma Bhat Hoffman, MD, MSb,*

aDepartment of Pediatrics, New York Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY
bDepartment of Pediatrics, University of Maryland School of Medicine, 110 S. Paca St., 8th Floor Neonatology, Baltimore, MD 21201
bDepartment of Surgery, University of Maryland School of Medicine, Baltimore, MD
de Duve Institute, Brussels, Belgium

ARTICLE INFO

Article history:
Received 19 May 2020
Revised 2 September 2020
Accepted 4 September 2020

Keywords:
Infantile myofibromatosis
Pulmonary hypertension
Bowel obstruction
Soft tissue tumors

ABSTRACT

Infantile myofibromatosis, the most common fibrous tumor of infancy, is classified in 2 forms; as a solitary nodule or as numerous, widely-distributed multicentric lesions with or without visceral involvement. Although benign, multicentric myofibromas are still associated with a high incidence of morbidity and mortality due to the infiltration of critical structures. Herein, we present a case of an infant with aggressive PDGFRB and NOTCH3 mutation-negative myofibromas distributed throughout the vascular, respiratory, and gastrointestinal systems. The extensive disease resulted in pulmonary hypertension, respiratory failure and gastrointestinal obstruction refractory to chemotherapy and unamenable to surgical resection. Despite the presence of numerous highly invasive myofibromas, multiple imaging modalities largely underestimated, or even missed, tumors found at autopsy. This case demonstrates the limitations of radiographic imaging to assess disease burden in multicentric infantile myofibromatosis. The postmortem findings of extensive disease far exceeding what was demonstrated by multiple imaging modalities suggests that pediatricians should have a high index of suspicion for undetected tumors if clinical deterioration is otherwise unexplained.

© 2020 The Authors. Published by Elsevier Inc. on behalf of University of Washington. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)
Introduction

Infantile myofibromatosis (IM) is the most common fibrous tumor of infancy [1,2]. The tumor may present as a solitary nodule or as multicentric lesions involving the skin, soft tissue, muscle, bone, or viscera [3,4]. Multicentric and generalized lesions are associated with high incidence of visceral involvement leading to increased morbidity and mortality [4]. Accurate assessment of tumor burden is paramount for prognosis and direction of care; however, various imaging modalities lack the diagnostic reliability and may underestimate the true extent of disease [5]. Clinicians should have high index of clinical suspicion and maintain a close follow up to prevent complications [6].

Here, we describe a case of IM with significant visceral involvement resulting in mortality associated with superior vena cava (SVC) syndrome, pulmonary hypertension, respiratory failure, and gastrointestinal obstruction. While these histologic findings were identified on autopsy, the proliferation of disease was grossly underestimated on radiographic, ultrasonographic, and magnetic resonance studies, complicating the clinical management.

Case report

Clinical history

A 36-week gestational age female infant with a prenatal history only notable for growth restriction was transferred to a Level 4 neonatal intensive care unit on day of life one for evaluation of inspiratory stridor, a diffuse maculopapular skin rash, and multiple subcutaneous nodules. The nodules varied in size from 0.5 cm to 3 cm, and were either fixed or mobile, with occasional erythema overlying the skin (Fig. 1). An open biopsy of a chest wall lesion confirmed the diagnosis of IM. Right-sided vocal cord paralysis and right-sided tongue weakness were identified during an airway evaluation. Subsequently, the infant clinically deteriorated, developing respiratory failure and pulmonary hypertension requiring intubation. The pulmonary hypertension was minimally responsive to inhaled nitric oxide and milrinone. The infant also became intolerant to enteral feeding with the development of recurrent emesis and an inability to pass a postpyloric feeding tube. She developed abdominal distention concerning for intestinal obstruction, but an obstructing lesion was not identified by radiographic assessment. She also developed SVC syndrome without sonographic evidence of venous thrombosis. This constellation of clinical symptoms led to a suspicion of extensive infiltration of her IM. Given the high risk of mortality, she was started on a chemotherapy protocol that included vinblastine and methotrexate at 39 days of life. Severe respiratory failure precluded surgical exploration of the abdomen to address the intestinal obstruction. Of note, there was no evidence on an intestinal perforation or necrosis which would typically mandate an exploration. She succumbed to cardiopulmonary failure at 2 months of age.

Radiologic findings

Whole-body MRI (Fig. 2) with contrast at day of life 5 revealed a normal brain, multiple subcutaneous and intramuscular le-
sions in the neck, back, and legs, 3 focal liver lesions, and multiple lytic bone lesions in the ribs, sacrum, and humerus. Multiple echocardiograms demonstrated progressive pulmonary hypertension, but were without evidence of intracardiac fibromas. At 2 weeks of life, an upper gastrointestinal contrast study demonstrated normal stomach contour and caliber, as well as normal caliber duodenum, and duodenojejunal junction. Abdominal ultrasound at day of life 26 noted dilated loops of bowel and biliary ductal dilation. Multiplanar, multisequence MRI of the abdomen and pelvis with contrast and cholangiopancreatography at 1 month of life showed re-demonstration of 2 liver lesions, an additional liver lesion, and mild dilation of the common hepatic duct without evidence of intestinal obstruction. At that time, a chest CT scan showed numerous lytic lesions in the thoracic spine and pathologic rib fractures with patchy bilateral pulmonary opacities, likely atelectasis. A lower gastrointestinal contrast study at 41 days of age showed mild narrowing in the distal descending colon and 2 similarly narrowed areas in the mid- to distal transverse colon suggestive of areas with myofibromas; however, there was no significant upstream bowel dilation to suggest high-grade obstruction.

Pathologic/Genetic findings

An excisional biopsy of a subcutaneous nodule of the chest wall revealed a myofibroblastic proliferation with immunohistochemistry positive for smooth muscle actin and negative for S100 and desmin, consistent with IMF. Clinical genetic evaluation was negative for germline mutations in the PDGFRB and NOTCH3 mutations. Postmortem analysis of multiple tumors using previously described methods [7,8] showed no somatic PDGFRB mutations. Gross anatomical findings (Fig. 3) showed hepatomegaly and multiple myofibromas in both lobes (largest 0.6 cm), a patent extrahepatic biliary system without dilatation, 3 tan-grey nodules in the body

---

Fig. 2 – Radiologic imaging. (A) CT chest noting patchy scattered bilateral pulmonary opacities without evidence of myofibromas. (B) MR abdomen showing 3 liver lesions (denoted with arrows) and mild dilation of the bile ducts. (C and D) Additional MR abdomen views showing no further evidence of myofibromas.
and pyloric region of the stomach (the largest measuring 1.6 cm in diameter), and greater than 20 nodules in the small intestine and colon (largest 0.5 cm in diameter) causing near total obstruction at the terminal ileum. There were multiple dilated loops of bowel with irregular thickening of the bowel wall in the proximal small intestine and inter-loop adhesions at multiple points throughout the small and large intestines. There were multiple myofibromas within the right and left ventricles of the heart (largest 0.2 cm in diameter) with right ventricular hypertrophy and healing ischemic lesions. Multiple grey white nodules consistent with myofibromas were observed in all lung lobes, ranging from 0.2 to 0.3 cm in diameter. Lung sections contained multiple parenchymal fibromas with intimal arterial thickening with focal intravascular myofibromas. Sections from the spleen, kidney, adrenal cortex, and ovaries also revealed myofibromas. The remaining organs, including the brain, were unremarkable. Head and neck vessels were unable to be assessed.

**Discussion**

Infantile myofibromatosis is the most common fibrous tumor of infancy with 90% of the cases occurring before 2 years of age [4]. Though the majority of cases present as solitary nodules with a good prognosis, the less common multicentric forms are more concerning as they often have a poor prognosis secondary to multiorgan complications [4,6,9]. To the best of our knowledge, we are the first to describe an aggressive case of mutation-negative IM with widespread myofibromas associated with SVC syndrome, pulmonary hypertension, respiratory failure, and multilevel gastrointestinal obstruction.

A strong clinical concern for heavy visceral tumor burden was not identified by multiple imaging modalities. The MRI appearance of IM lesions can be variable; however, typically they are noted to have hypotensity on T1 imaging and hyperintensity on T2-weighted imaging [10]. In our case, abdominal MRI failed to demonstrate any intraintestinal lesions, despite clinical intestinal obstruction. Upper and lower gastrointestinal contrast studies failed to show the large tumor in the pylorus and underestimated the tumor burden of the remaining gastrointestinal tract. A lack of sensitivity of MRI for detecting GI lesions has previously been described [5,6,10]. It further confirms that a high index of suspicion is warranted in generalized IM with any clinical signs of gastrointestinal distress. Direct visualization by endoscopy, if the patient size allows, may be warranted to confirm the presence of myofibromas in the gastrointestinal tract, especially when considering the potential complications of tumors [11]. Future research should be directed at improved imaging techniques to identify these tumors, as they contribute significantly to mortality risk.

Difficulties assessing tumor burden were not limited to the GI tract, as both lung and cardiac involvement were undetected by echocardiography, conventional radiography, CT and MRI of the chest. Inability to detect cardiac involve-
ment is particularly important as this has been associated with worsened prognosis [2,6]. Knowing the limitations of imaging is extremely helpful in assessing IMF with visceral involvement. Clinical signs of pulmonary hypertension, respiratory failure, or intestinal obstruction in patients with multifocal IM should raise suspicion for aggressive, diffuse disease with a heavy visceral burden. This knowledge may have prompted earlier initiation of chemotherapy, or alternatively, prompted discussions to redirect care toward a palliative strategy. With respect to the multiple lung, liver, and intestinal lesions that were not identified by MRI, we speculate that there may be a critical mass size required for detection of myofibromas on MRI.

In addition, we also noted vascular involvement yet to be clearly described, with clinical evidence of pulmonary hypertension and SVC syndrome along with postmortem evaluation demonstrating involvement of the pulmonary artery intima. Huang et al [6] reported a case of 11-month-old patient with IM and clinical pulmonary hypertension, questioning the potential for vascular involvement of the pulmonary system, which we have confirmed in this case. The refractory nature of the pulmonary hypertension in our patient may be explained by a unique pathophysiology, similar to other cases caused by vascular remodeling, such as pulmonary hypoplasia. In addition to the pulmonary vascular bed, other vasculature may also be involved [12]. We noted clinical SVC syndrome indicating neck vessel involvement however this could not be confirmed on postmortem examination.

IM lesions often regress spontaneously, and a watchful waiting approach is recommended. In more severe cases with local infiltration and/or visceral involvement, more aggressive approaches are warranted such as surgical excision and chemotherapy. Though there has been success noted using chemotherapy to treat the multicentric form of IM [13], this was not the case in this patient. The most common regimen is the combination of methotrexate and either vincristine or cyclophosphamide, [4,14] although tumor suppression is noted only after weeks of therapy. In some cases, chemotherapy with sunitinib has shown to have success in patients with a PDGFRB germline mutation [13]. This case, however, was noted to be negative for the previously reported mutations of interest. This may suggest that an unidentified mutation may be responsible for the extremely aggressive presentation described.

**Conclusion**

We present a case of gene mutation negative, chemotherapy resistant, multicentric IM with involvement in nearly every organ system that was vastly under estimated by imaging. This aggressive variant demonstrates that the disease burden of multicentric IM may be challenging to estimate despite extensive imaging with different modalities. In the setting of multicentric IM, pediatricians should be aware of the limitations of diagnostic imaging and recognize that clinical deterioration, which is otherwise unexplained, may be attributed to infiltrative disease, even if not demonstrated by imaging. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

**Contributors’ statement**

Drs Hoffman, Parikh, and Driscoll conceptualized this report, drafted the initial manuscript, and reviewed and revised the manuscript.

Drs Dachy and Demoulin analyzed the tumors for somatic mutations conceptualized this report and critically reviewed and revised the manuscript.

Drs Crowley, and York conceptualized this report and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**References**

[1] Chung EB, Enzinger FM. Infantile myofibromatosis. Cancer 1981;48:1807–18.
[2] Wiswell TE, Davis J, Cunningham BE, Solenberger R, Thomas PJ. Infantile myofibromatosis: the most common fibrous tumor of infancy. J Pediatr Surg 1988;23:315–18.
[3] Koujok K, Ruiz RE, Hernandez RJ. Myofibromatosis: imaging characteristics. Pediatr Radiol 2005;35:374–80.
[4] Mashiah J, Hadij-Rabia S, Dompmartin A, et al. Infantile myofibromatosis: a series of 28 cases. J Am Acad Dermatol 2014;71:264–70.
[5] Spadola L, Anoshiravani M, Sayegh Y, Jequier S, Hanquetin S. Generalised infantile myofibromatosis with intracranial involvement: imaging findings in a newborn. Pediatr Radiol 2002;32:872–4.
[6] Huang CJ, Lin KI, Jung SM, Wu CT, Wang HS. Infantile myofibromatosis presenting with scalp dermoid cyst. Pediatr Neurol 2005;33:296–9.
[7] Arts FA, Sciut R, Brichard B, et al. PDGFRB gain-of-function mutations in sporadic infantile myofibromatosis. Hum Mol Genet 2017;26:1801–10.
[8] Dachy G, de Krüger RR, Friggas S, et al. Association of PDGFRB mutations with pediatric myofibroma and myofibromatosis. JAMA Dermatol 2019;155(8):946–50.
[9] doi:10.1001/jamadermatol.2019.0114.
[10] Pelluard-Nehme F, Coatleven F, Carles D, Alberti EM, Briex M, Dailly D. Multicentric infantile myofibromatosis: two perinatal cases. Eur J Pediatr 2007;166:997–1001.
[11] Counsell SJ, Devile C, Mercuri E, Allsop JM, Birch R, Muntoni F. Magnetic resonance imaging assessment of infantile myofibromatosis. Clin Radiol 2002;57:67–70.
[12] Alberti LR, Souto Bittencourt PF, Rodrigues Ferreira A, et al. Multicentric infantile myofibromatosis of the small bowel detected by video capsule endoscopy in a child. Endoscopy 2012;44 Suppl 2 UCTN:E258–9.
[13] Matthews MR, Cockrelli CJ. An historic perspective of infantile myofibromatosis. Adv Dermatol 2006;22:279–305.
[14] Mudry P, Slaby O, Neradi J, Soukalova J, Melicharkova K, Rohleder O, et al. Case report: rapid and durable response to PDGF targeted therapy in a child with refractory multiple infantile myofibromatosis and a heterozygous germline mutation of the PDGFRB gene. BMC Cancer 2017;17:119.
[15] Wu SY, McCavit TL, Cederberg K, Galindo RL, Leavey P. Chemotherapy for generalized infantile myofibromatosis with visceral involvement. J Pediatr Hematol Oncol 2015;37:402-5.