A Cooperative Approach to Diagnosis of Rare Diseases: Primitive Myxoid Mesenchymal Tumor of Infancy

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Abstract. Primitive Myxoid Mesenchymal Tumor of Infancy (PMMTI) is a recently recognized locally aggressive myofibroblastic tumor. It is a low- to intermediate-grade fibroblastic malignancy with a high local recurrence rate but low metastatic potential and is composed of primitive spindled cells in a myxoid background. We present the eleventh reported case of PMMTI, occurring in the sinonasal tract of a 3-year-old child. This case is novel in both the relatively older age of the child, the location of the tumor, and the role that immunohistochemical stains, and cytogenetic analysis played in differentiating it from similar diagnoses that differ considerably in their chemosensitivity and recurrence rates. Close collaboration between the pathologist and surgeon was crucial as different diagnoses would have led to vastly different treatment strategies for the patient.

Introduction

Undifferentiated pediatric sarcomas are a subset of unclassified soft tissue tumors and comprise approximately 5% of all pediatric sarcomas [1]. Until recently, primitive myxoid mesenchymal tumor of infancy (PMMTI) was categorized as one such undifferentiated tumor. However, special staining and cytogenetic techniques have distinguished it from this group and have resulted in important advances in understanding the disease, affecting its treatment and prognosis. First described by Alaggio et al. in 2006 [2], PMMTI is a locally aggressive tumor that is on the spectrum of myofibroblastic disease. It is notable for its proclivity to recur and, due to its high level of resistance to chemotherapy, must be differentiated from similar diagnoses in order to facilitate treatment. Here we report a 3-year-old child with a PMMTI arising in the paranasal sinus tract. This is the first case report of a child (non-infant) with this disease as well as the first reported paranasal PMMTI.

Case Report

AR was a previously healthy 3-year-old female when she presented to her PCP with a slowly enlarging mass on her hard palate in January of 2012, a biopsy of which showed low-grade myofibroblastic sarcoma. A computed tomography (CT), a magnetic resonance imaging (MRI), a lumbar puncture, a bone scan, and bone marrow biopsy showed no evidence of metastasis. She began treatment with three rounds of vincristine, actinomycin-D, and cyclophosphamide, but the tumor continued to grow and she presented to our clinic for further evaluation and treatment in June of 2012. At that time, imaging showed an expansile destructive mass arising from the left hard palate with extension into the left maxillary sinus, nasal cavity, and oral cavity (Figure 1). Given the failure of medical management, the patient was taken to the operating room for excision of the tumor. A large intraoral component of the tumor was transected from its stalk-like attachment at the palate (Figure 2). A Weber-Ferguson incision was then made through which the maxillary sinus and nasal cavity were exposed. The remainder of the tumor was removed through this incision by direct and endoscopic visualization. Orbital function and facial cosmesis were preserved. The surgical pathology showed primitive myxoid mesenchymal tumor of infancy (PMMTI), as discussed below. The patient was given an obturator for the palatal defect with which she was able to eat and drink normally. At her 3

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month follow-up, her MRI showed no evidence of disease, but within 6 months, her parents noticed a new mass in her palate and swelling of her left cheek which were evaluated and found to be a recurrence of the tumor. She completed further treatment with ifosfamide and doxorubicin in an attempt to control the tumor, but ultimately required an orbital-sparing total maxillectomy to remove the disease in May 2013. She continues to be closely followed by the Oncology and Otolaryngology services, and at present has no evidence of disease recurrence.

**Pathological findings.** Grossly, the mass was found to be tan-pink, partially lobulated, and encapsulated in a thin, translucent capsule. The intraoral component measured 7.0x6.5x1.8 cm and grew from a stalk-like attachment to the palate measuring 4.5x3.5 cm (Figure 2). The maxillary portion of the tumor could not be resected en bloc and was removed in several pieces. Sectioning of the oral mass demonstrated a tan-pink to tan-red cut surface with focal hemorrhage and calcifications. Histologically, the mass was composed of an outer capsule of stratified squamous epithelium. The tumor itself was vaguely nodular, and the stroma was composed of a loose, pale basophilic myxoid matrix with individually dispersed ovoid to stellate and spindled cells (Figure 3). The cells were characterized by a scant, pale eosinophilic cytoplasm with a high nuclear to cytoplasmic ratio and a nucleus containing finely granular chromatin. Occasional lymphocytes and rare mitotic figures (five figures in 10 high-power fields) were seen. Discrete linear lines with a palisading-like effect were also visualized. Focal areas of bone formation and small vessels were scattered across the section. Several interesting findings of note were: (1) areas containing collagen deposition and tumor cells with smaller nuclei resembling more differentiated fibroblasts; (2) portions of the tumor with a higher abundance of tumor cells arranged in interlacing fascicles; and (3) a vaguely circumscribed myxoid nodule with markedly increased cellularity and large, plump spindle cells with occasional mitotic figures.

Immunohistochemistry staining was performed and showed no immunoreactivity of tumor cells with desmin, myogenin, or muscle-specific actin. There was focal smooth muscle actin reactivity with cells found near vascular structures and at the periphery of the tissue sections. Focal staining for S100 protein was also found in more cellular areas containing spindled cells. There was no immunohistochemical evidence of beta-catenin mutation within the tumor cells. In order to further confirm the diagnosis, molecular pathology tests were also performed. Evaluation by reverse-transcription, polymerase chain reaction (RT-PCR) for a mutation in codon 41 or 45 of the Beta-catenin gene (CTNNB1) was negative. RT-PCR for the ETV6/NTRK3 gene fusion and associated t(12;15) translocation was also negative. These mutations are characteristic of desmoid fibromatosis and congenital infantile fibrosarcoma, respectively [3,4].

**Discussion**

PMMTI is a soft tissue neoplasm first described in 2006 by Alaggio et al [2]. It is a focally aggressive mesenchymal tumor that represents the primitive end of the spectrum of fibroblastic-myofibroblastic tumors. Recent studies employing specific immunohistochemical stains and genetic analysis for particular mutations have been able to distinguish PMMTI from other tumors such as congenital infantile fibrosarcoma and undifferentiated sarcomas [2]. This distinction is crucial due to PMMTI’s poor response to chemotherapy and tendency to recur, necessitating a treatment approach different than that of similar tumors.

Since Alaggio’s initial report, only ten cases of PMMTI have been reported in the literature. Of those ten cases, doubt has been cast on the diagnosis of one case as it involved only the dermis, occurred in the setting of a previous histiocytic...
proliferation, and had an immunohistochemistry phenotype not seen in the other reported cases (Table 1) [5]. Prior to its recent description as a distinct entity, most cases of PMMTI were diagnosed as congenital infantile fibrosarcoma (CIFS) [2]. Differentiating between these entities is crucial due to the remarkable difference between the chemosensitivity and clinical course of PMMTI and CIFS.

PMMTI usually occurs during the first year of life and has a long, indolent course complicated by frequent relapses [2,4-6]. Grossly it is characterized by local infiltration and multinodular growth without encapsulation. The tumors reported range in size from 2-15 cm and have a gray to white, homogeneous cut surface with a firm periphery. Microscopically the tumor is composed of primitive mesenchymal cells that vary in shape from round or polygonal to spindled. The tumor cells have bland, uniform nuclei with fine, homogenous chromatin. The nucleoli are inconspicuous and the cytoplasm is pale to eosinophilic. Tumor cells are embedded in a diffuse myxoid background with a delicate vascular network and scattered small cystic spaces. In general, the tumor is characterized by low to moderate cellularity with increasing cellularity at the periphery of nodules and an occasional focal herringbone pattern. The mitotic rate is variable and abnormal mitoses are typically absent. Of note it has been found that recurrent tumors showed increased cytologic atypia. Immunohistochemistry shows diffuse positivity for vimentin and some positivity for CD99 and CD117 but is negative for myoid, lipoblastic, histiocytic and neural markers such as smooth muscle actin, muscle specific actin, cytokeratin, desmin, and S100. This pattern of staining helps to illustrate the primitive nature of PMMTI.

Cytogenetic studies reveal an absence of the t(12;15) ETV6-NTRK3 fusion gene and lack of mutations in the CTNNB1 gene, characteristic of congenital infantile fibrosarcoma and desmoid fibromatosis, respectively [3,4].

The clinical course of PMMTI is usually prolonged with frequent local recurrences but rare metastases [2,4,6]. Of the nine verified cases reported to date, all but two have recurred, there have been no metastases, and only one patient has died of the disease. The gold standard of treatment is radical surgical excision with establishment of negative margins. This may require partial amputations or extensive dissections creating large and morbid defects. The most notable risk factor for local recurrence is excision without negative margins, and recurrences usually occur within months. This tumor is unresponsive to chemotherapy making treatment of primary tumors and recurrences difficult [2,4,6]. To date, radiation therapy has not been implemented as a treatment modality.

PMMTI must be distinguished from a number of similar pathologies in the spectrum of both benign and malignant myofibroblastic diseases (Table 2). The differential includes congenital infantile fibrosarcoma, infantile fibromatosis, fibromyxoid sarcoma, myofibrosarcoma, and dermatofibrosarcoma protuberans. Other diagnoses such as liposarcoma,
lipoblastoma, rhabdomyosarcoma, and malignant peripheral nerve sheath tumor may be entertained with initial microscopic examination, but can easily be ruled out based on immunohistochemical staining [6].

Congenital infantile fibrosarcoma (CIFS) is a subset of fibrosarcomas that presents in children less than 4 years of age and has a uniquely favorable prognosis as compared to adult-onset fibrosarcoma [7]. Depending on the degree of differentiation, CIFS can have a range of pathologic appearances but is most often composed of sheets of solidly packed spindle cells arranged in bundles and fascicles [8]. Its increased mitotic activity with areas of necrosis and hemorrhage as well as a specific t(12;15)(p13;q25) translocation causing an ETV6-NTRK3 gene fusion help distinguish this entity from other diseases [3]. As compared to adult fibrosarcoma, CIFS has a much lower incidence of local recurrence (17-30% as compared to 50-72%), distant metastasis (5-8% as compared to 21-43%), and a 5-year overall survival (85-95% as compared to 56-71%) [7]. From what little is known thus far, CIFS also has significantly better rates of local recurrence than PMMTI, although rates of metastasis and overall survival have yet to be determined. Due to the chemosensitivity of CIFS and chemoresistance of PMMTI, differentiating the two is paramount as the diagnosis determines the proper treatment of chemotherapy versus surgery. This differentiation is possible because of the characteristic ETV6-NTRK3 gene fusion found in CIFS but absent in PMMTI.

Infantile fibromatosis most often involves the upper extremities, head, and neck of children less than one year of age [9]. It has been divided into two subclasses: the less common desmoid type is indistinguishable from the adult form of fibromatosis, and the more common diffuse mesenchymal type is less differentiated and more akin to fibrosarcoma than adult-type desmoid fibromatosis [10]. While distinct from one another, the two types are easily distinguishable from PMMTI due to their pattern of infiltrative fibroblastic proliferation, scattered adipocytes, peripheral lymphocytes, tendency for higher cellularity, and greater mitotic activity. These characteristics are especially notable in the more common diffuse mesenchymal type [11]. Infantile fibromatosis is known to be strongly associated with mutations in the beta-catenin gene (CTNNB1) and stains accordingly on immunohistochemistry [4]. Further staining is positive for proteins such as S100, smooth muscle actin, and epithelial membrane antigen. Due to these differences, cytogenetic analysis of the CTNNB1 gene as well as immuno-

![Figure 3. The tumor has variable histopathologic appearances. Tumor with myxoid background and slightly spindled immature mesenchymal stromal cells with low (A) to moderate (B) cellularity. Tumor with moderate cellularity with bland spindle cells in myxoid stroma with fine collagen fibers in stroma (C). Tumor with increased moderate to high cellularity and tumor cells in close apposition with mildly collagenized stroma (D). (H&E stain, 100x).](image)
histochemical staining play a key role in differentiating infantile fibromatosis from PMMTI.

Fibromyxoid sarcoma is also found in young children although it rarely presents before age two [12]. The tumor consists of bland stellate and spindled fibroblastic cells arranged in a swirling or fascicular pattern. These cells are further divided into separate fibrous and myxoid zones with prominent vasculature, and giant collagen rosettes are characteristic of this disease [12]. None of these histological patterns have been described in relation to PMMTI, nor were they found in this case. A related diagnosis, myofibrosarcoma, typically occurs in the head and neck region but is quite rare in infants [13,14]. It is composed of infiltrative fascicles of spindle cells with pale eosinophilic cytoplasm, fusiform nuclei, and inconspicuous nucleoli embedded in a hyalinized collagen matrix. Immunohistochemistry can easily differentiate between myofibrosarcoma and PMMTI. Myofibrosarcoma is positive for desmin, alpha-smooth muscle actin and muscle specific actin, whereas PMMTI is positive for vimentin but none of the others [2].

Lastly, dermatofibrosarcoma protubersans (DFSP) is an entity which typically presents in adults but has been known to present in the pediatric population as well. The uncommon myxoid variant, the most similar to PMMTI, is composed of bland spindle or stellate shaped fibroblasts in a pronounced myxoid stroma with interspersed vasculature [15]. Although its architecture is similar to PMMTI, DFSP can be differentiated by its relatively lower mitotic activity, presentation in dermal and subcutaneous tissue, characteristic honeycomb trapping of adipose tissue, and positive staining for CD34 [6].

<table>
<thead>
<tr>
<th>Author</th>
<th>Age, Sex</th>
<th>Site</th>
<th>Size (cm)</th>
<th>Treatment</th>
<th>Recurrence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alaggio, 2006</td>
<td>15 d M</td>
<td>Larynx</td>
<td>2.5</td>
<td>Surgery, chemo</td>
<td>Larynx, perilaryngeal soft tissue, salivary gland, skin</td>
<td>AWD, 4 yrs</td>
</tr>
<tr>
<td>Alaggio, 2006</td>
<td>1 m</td>
<td>Thigh</td>
<td>15</td>
<td>Surgery, chemo</td>
<td>Inguinal soft tissue</td>
<td>NED, 4 yrs</td>
</tr>
<tr>
<td>Alaggio, 2006</td>
<td>2 m</td>
<td>Forearm</td>
<td>10</td>
<td>Surgery</td>
<td>None</td>
<td>NED, 1 yr</td>
</tr>
<tr>
<td>Alaggio, 2006</td>
<td>2 m</td>
<td>Paraspinal soft tissue</td>
<td>5.5</td>
<td>Surgery</td>
<td>Unknown</td>
<td>Not available</td>
</tr>
<tr>
<td>Alaggio, Newborn F, 2006</td>
<td>Supracavicular soft tissue</td>
<td>5</td>
<td>Surgery</td>
<td>Supraclavicular soft tissue</td>
<td>AWD, 4 mos</td>
<td></td>
</tr>
<tr>
<td>Alaggio, Newborn F, 2006</td>
<td>Back, chest, neck, abdomen</td>
<td>15</td>
<td>Surgery</td>
<td>Residual disease</td>
<td>DWD, 6 wks</td>
<td></td>
</tr>
<tr>
<td>Mulligan, 2011</td>
<td>8 m F</td>
<td>Thenar eminence</td>
<td>2</td>
<td>Surgery</td>
<td>Thenar eminence</td>
<td>NED, 5 yrs</td>
</tr>
<tr>
<td>Lam, 2011*</td>
<td>3 m</td>
<td>Back</td>
<td>3.5</td>
<td>Surgery</td>
<td>None</td>
<td>NED, 4 yrs</td>
</tr>
<tr>
<td>Gong, 2012</td>
<td>5 m</td>
<td>Anterior neck soft tissue</td>
<td>4.5</td>
<td>Surgery</td>
<td>Neck soft tissue, larynx</td>
<td>AWD, 5 mos</td>
</tr>
<tr>
<td>Gong, 2012</td>
<td>Newborn F</td>
<td>Dorsal lumbar region</td>
<td>6</td>
<td>Surgery</td>
<td>Lumbar spinal canal</td>
<td>Not available</td>
</tr>
<tr>
<td>Present case</td>
<td>3 y F</td>
<td>Hard palate</td>
<td>7</td>
<td>Surgery, chemo</td>
<td>Hard palate and maxillary sinus</td>
<td>NED, 9 mos</td>
</tr>
</tbody>
</table>

*Diagnosis of PMMTI is questionable based on histology and tumor behavior.

d = day, m = month, y = year, M = male, F = female, AWD = alive with disease, NED = no evidence of disease, DWD = dead with disease.
Case Report of Primitive Myxoid Mesenchymal Tumor of Infancy

Conclusion

As immunohistochemical techniques and cytogenetic technology advance, the diagnostic capabilities of the medical community are becoming ever more precise. Such is the case of primitive myxoid mesenchymal tumor of infancy, which until less than a decade ago was classified variably as congenital infantile fibrosarcoma, infantile fibromatosis, or undifferentiated sarcoma [2]. Detection of the ETV6-NTRK3 gene fusion and CTNNB1 gene mutation, however, have made the distinctions between these diagnoses possible. The differentiation of these diseases is crucial, for these diagnoses carry with them significant differences in both treatment and prognosis. For example, PMMTI is highly resistant to chemotherapy and therefore must be excised in its entirety for a cure to be achieved, whereas CIFS is chemosensitive and has much lower recurrence rates.

We report a PMMTI that is the first case of a child over 1 year of age, the first case of a paranasal sinus tumor, and one of the most invasive cases reported to date. Much like those previously described, the tumor was resistant to chemotherapy, rapidly growing, and had a tendency to recur. Although further research is necessary to better define the genetic features and biologic characteristics of PMMTI, this disease serves as a reminder that close collaboration between the pathologist and treating clinician is becoming increasingly important, especially when dealing with complex disease processes whose treatment is guided by the correct histological diagnosis.

Table 2. Reviews the histological and differentiating features between PMMTI and two of the most closely associated diagnoses, congenital infantile fibrosarcoma (CIFS) and infantile fibromatosis (IF). Pictures for CIFS and IF used with permission from www.Webpathology.com, by Dharam Ramnani, MD.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Age</th>
<th>Histology</th>
<th>Characteristic Features</th>
<th>Treatment</th>
<th>Prognosis</th>
<th>Example Specimen</th>
</tr>
</thead>
</table>
| PMMTI              | < 1 yr  | Primitive mesenchymal cells with SMA, desmin, uniform nuclei, myxoid background with delicate vasculature and cystic spaces | Positive: Vimentin, negative: Myoid, cytokeratin, S100        | Surgical resection | 72-90% recurrence 70-91% survival | ![Image](image)
| Congenital< 4 yrs | Sheets of solidly packed spindle cells arranged in fascicles | t(12;15)(p13;q25) causing ETV6-NTRK3 gene fusion  | Chemo-therapy   | 17-30% recurrence     | ![Image](image)
| Infantile fibrosarcoma | Infiltrative fibroblastic proliferation, scattered adipocytes and lymphocytes, high cellularity | Beta-catenin (CTNNB1) gene mutation | Surgical resection | 40-60% recurrence 80-85% survival | ![Image](image)


