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A Rare Case of Pediatric Pharyngeal Sarcoma

Bahar Abbassi, MS; Adam Singleton, MD; Anas Eid, MD; Sandeep Samant, MD, FACS; Jon Ver Halen, MD, FACS*

***Jon Ver Halen, MD, FACS**

Division of Plastic, Reconstructive and Hand Surgery, Baptist Cancer Center, Memphis TN

Email: jpverhalen@gmail.com

Abstract

Pharyngeal sarcomas in the pediatric population are extremely rare. The current presentation is a young man with biopsy-proven undifferentiated pleomorphic sarcoma (UPS), in the setting of previous chemoradiotherapy and bone marrow transplant for acute lymphoblastic leukemia. The case was treated with wide surgical excision, and the patient is disease free at one year followup. A review of the literature provides a discussion of the risk factors, prognostic indicators, and methods of diagnosis and treatment for UPS of the head and neck.

Keywords

Pharyngeal sarcoma; Pediatrics; Biopsy

Introduction

Malignant fibrous histiocytoma (MFH) is the previous name forwhat is currently designated by the World Health Organization (WHO) as undifferentiated pleomorphic sarcoma (UPS).[1] While there were 5 subtypes of MFH (storiform-pleomorphic, inflammatory, myxoid, giant cell, and angiomatoid), there are only 3 subtypes of UPS (undifferentiated high-grade pleomorphic sarcoma, UPS with giant cells, and UPS with prominent inflammation). These 3 subtypes have been proven to be of fibrohistiocytic origin. In contrast, the myxoid subtype, now reclassified as myxofibrosarcoma, has been shown to be of myofibroblastic origin due to positive staining for smooth muscle or muscle-specific actin.[2]The cellular lineage of the angiomatoid fibrous histiocytoma is still uncertain.

Before the new WHO classification in 2002, MFH was the most common sarcoma diagnosed in adults accounting for 40% of all soft tissue sarcomas (STS).[3] Now, MFH is an outdated term and only a synonym for undifferentiated high-grade pleomorphic sarcoma. Thus, it has a much lower incidence of diagnosis and only accounts for 5% of adult STS.[2]Historically, 3-10% of UPS occur in the head and neck region, and UPS accounts for only 0.5% of all head and neck cancers.[4,5] However, the incidence of UPS in the head and neck is increasing, and is now being reported as the most prevalent location of UPS.[6]More specifically, UPS is most commonly encountered in the sinonasal tract and craniofacial bones[5,7]Less frequent locations include the salivary glands, temporal bone, scalp, oral cavity, thyroid, and pharynx.

UPS can develop de novo or secondary to tissue radiation or trauma, and secondary UPS tends to be more aggressive in nature.

Primary risk factors for developing secondary UPS include exposure to ionizing radiation, chemotherapy (particularly anthracyclines and alkylating agents), genetic mutations of tumor suppressor genes, and immuno suppression.[8]Additionally, chronic inflammatory states secondary to disease or trauma are causative factors in development of UPS.[7,9]While UPS is the most common radiation-induced sarcoma[5], there are limited reports of it as a secondary cancer after treatment for acute lymphoblastic leukemia(ALL).[8]Histologically, the tumor is characterized by a storiform-pleomorphic pattern without an identifiable cellular line of differentiation. Although not fully elucidated, it appears to be of fibroblastic or primitive mesenchymal origin.[10]Compared to other STS, head and neck UPS has a more favorable prognosis with an average 5-year overall survival rate of 40-48%.[4,5,11] A thorough literature review found 13 previously reported cases of pharyngeal MFH since 1974 with only one case occurring in the pediatric population (Table 1).[4,12-21]

In this article, we present the case of a child previously treated for ALL with chemotherapy, whole-body radiotherapy, bone marrow transplant (BMT) and allogeneic stem cell transplant (SCT) who developed a posterior pharyngeal wall UPS with giant cells 10 years after treatment. The imaging and pathologic features are examined. We review other reported pharyngeal UPS/MFH cases and discuss the diagnosis, treatment and prognosis of UPS.

Case Report

A 14 year-old male received a diagnosis of ALL in 2003 at the age of 3. He was treated under the St. Jude Children's Research Hospital Total XV protocol. Remission was not achieved with chemotherapy alone. He consequentlyunderwent12 Gy of whole body radiation, and an additional 4 Gy of testicular radiation in preparation for haploidentical allogeneic bone marrow transplant and subsequent allogeneic SCT in 2004. His course was complicated by mixed chimerism after the bone marrow transplant and a severe EBV respiratory infection that required a 9-week medically induced coma. He recovered and remained healthy until 2014 when he presented to an outside emergency department for evaluation of a persistent cough. He was discharged after no abnormalities were found on physical examination or chest x-ray. During his follow-up appointment with an outside physician, cervical lymphadenopathy was noted and a CT scan of head and neck was ordered. Two days before the scan, he presented to our emergency department with complaint of a sore throat. It started 2 weeks prior but had progressively worsened over the last 3 days. Additional symptoms included new-onset snoring, fatigue, hypersomnolence, hypernasal speech, odynophagia, dysphagia, and drooling. Physical examination found an afebrile, frail patient with stertorous breathing, tachycardia, tachypnea, and cervical lymphadenopathy. A CT scan revealed a pharyngeal mass extending into the retropharyngeal space (Figure 1). The decision was made to take the patient urgently to the operating room for a tracheostomy and biopsy of the mass. Pathologyanalysis revealed a spindle cell neoplasm with numerous giant cells and rare mitotic figures. Abnormal laboratory findings included elevated LDH (513) and uric acid levels (5.5). No distant metastases were identified.

Surgical extirpation was arranged. Intraoperatively, the tumor was found to extend from the nasopharynx to the esophageal introitus. A paramedianmandibulotomy with mandibular swing was

required for a near-total pharyngectomy. A right prevertebral fascia specimen was also obtained intraoperatively. The pharyngeal specimen was a firm pink-tan 6.0 x 5.5 x 4.0 cm mass. The margins of both the tumor and prevertebral fascia were positive for mitotically active neoplastic cells. The preliminary diagnosis was a fibrohistiocytic lesion with osteoclast-like giant cells of uncertain malignant potential (Figure 2). Immunohistochemical analysis showed a diffusely strong cytoplasmic response to vimentin and a moderate Ki-67 (40-50%) proliferative rate. The tumor stained focally for smooth muscle actin, muscle specific actin, desmin, lysozyme, p53, CD68, and CD163. The osteoclast-like giant cells stained positive for CD68 but not CD163. There was no immuno reactivity demonstrated for S-100, ALK p80, ALK-1, CD34, myogenin, myo-D1, cytokeratin AE1-AE3, and PAS with and without diastase. Mitotic figures were rare. The final pathologic diagnosis was undifferentiated pleomorphic sarcoma with giant cells. The defect was reconstructed with a radial forearm free flap, and the donor site defect was reconstructed with an integra dermal regeneration template and split-thickness skin graft.

Discussion

An inherent limitation in reviewing literature on MFH/UPS stems from the 2002 WHO classification change along with the slow adoption of the new diagnostic term UPS. Furthermore, before the advent of immunohistochemistry in the 1990s, any diagnosis of MFH was uncertain. In fact, studies have since shown that the majority of tumors previously misclassified as MFH were identified as having a specific cellular lineage upon immunohistochemical analysis.[22,23] Therefore, the authors stress the importance of using the term UPS so future conclusions about UPS will be based on a homogenous group of tumors. For the cases reviewed, none were referred to as UPS, even those reported after 2002.

The average rate of sarcoma development following radiation therapy is 0.03-0.3%.[24] Latency between radiation and development of a UPS averages between 12.0 to 12.3 years.[4,25] This is similar to reported latency values for all radiation-induced sarcomas[26] and is consistent with the 10 year latency period in the case presented. The clinical presentation of UPS depends on the size and location of the tumor. As in the case presented, airway obstruction, stertor, dysphagia, odynophagia, and drooling are the most prominent symptoms for pharyngeal UPS. The most common symptom regardless of location is a rapidly enlarging mass, and a painful mass portends a more aggressive tumor.[27] In one case series, 15% of patients with head and neck UPS had regional lymph node involvement upon diagnosis.[11] Regional or distant metastatic disease at time of diagnosis is unusual.

UPS is considered a diagnosis of exclusion. While the work up may consist of radiographic imaging, endoscopy, or fine needle aspiration, the diagnosis of UPS is only confirmed with immunohistochemistry of a tumor specimen.[2] Electron microscopy can also be used as a confirmatory test in certain cases but is not commonly utilized. The immunohistochemical hallmark of the tumor is strong diffuse cytoplasmic immuno reactivity to vimentin with an inconsistent pattern of focal staining for a variety of other markers (myoglobin, S-100, smooth muscle actin, AE1/AE3, CD31, CD34, ALK).[3,28] In the past, histiocytic markers (CD68, α_1-antitrypsin, α_1-antichymotrypsin and factor XIII) were used, but these markers are not specific enough for diagnosis.[29]

Wide local excision with at least 3-centimeter margins is the treatment of choice for UPS. Numerous studies have shown that obtaining negative margins is the most important prognostic factor for local disease control,[11,20,31,32] and a more radical surgery has been shown to provide better survival

outcomes.[11,33] Thus, resection of UPS should be as extensive as the anatomy allows while attempting to preserve functionality. Since sarcomas tend to spread hematogenously and the occult regional metastasis rate of UPS is low, a neck dissection is only warranted if there is clinical or radiographic evidence of lymph node involvement.

As our case illustrates, obtaining negative margins is more difficult with UPS of the head and neck particularly when secondary to radiation exposure. This is reflected in the decreased overall survival for secondary UPS and for UPS of the head and neck when compared to primary UPS and UPS of the trunk and extremities.[11,34] Other significant prognostic factors include UPS subtype, age, sex, tumor size, tumor depth, and regional or distant metastatic disease.[31,32] The giant cell subtype has the worst prognosis, and the high-grade and inflammatory UPS subtypes have similar prognoses. More aggressive behavior has been associated with increased age, male sex, high-grade, and tumor size >5 cm.[5,31] The 5-year overall survival rate of UPS of the head and neck has been reported between 18-75% with an average of 40-48%.[4,5,11,34,35] When arising secondary to radiation, 5-year overall survival rates decrease to 5.9-36%.[4,25,34] If the primary tumor is < 5 cm, 5-year overall survival rates approach 67% compared to 38% in tumors>5 cm.[5] However, one study showed that no patients with UPS > 5 cm were relapse free at 5 years, and thus, it is recommended to offer adjuvant radiation and/or chemotherapy to these patients.[32]

Local recurrence is the most common treatment failure. Previous studies have shown that 20-57% of patients with UPS of the head and neck develop recurrent disease.[11,32] If recurrent local disease is isolated, resection should be attempted. In one study, a larger number of resections was found to be correlated with better patient outcomes.[20] Another study demonstrated that 65% of patients treated with resection as part of salvage therapy were disease free at a median follow-up of 56 months.[32] Overall, the rate of developing metastatic disease after resection of the primary tumor is low but has been reported as high as 31-35%.[19] The most common locations of metastases are the lungs (90%), lymph nodes (12%), and bone (8%).[7,19] In these cases, prognosis is poor and treatment options are limited to radiation and chemotherapy. While radiation has shown some non-significant trends toward local disease control, no survival benefit has yet been shown with chemotherapy. As in our case, radiation is typically offered to patients with positive surgical margins. Our patient is currently receiving adjuvant radiation and chemotherapy. We suspect a poor prognosis considering the positive tumor margins with extension to the prevertebral fascia.

The clinical data on our patient and the 13 previously reported patients are shown in Table 1. There were 10 males and 1 female with an average age of 46 years old (range 13-79). Of the 7 patients with reported outcomes, there were 5 that underwent surgical resection of their tumor. Eighty percent of these patients (4/5) were disease free at an average follow-up of 51 months (range 12-120); one of these patients received adjuvant radiation. The individual patient that did not survive underwent adjuvant chemoradiotherapy and died of his disease 15 months after the initial surgery. There was limited clinical and pathologic information reported for most of these patients, so for many, the diagnosis of what is now termed UPS cannot be scrutinized. Thus, the possibility exists that these masses were actually differing tumors such as leiomyosarcomas, osteosarcomas or undifferentiated carcinomas It is our purpose to illustrate this limitation and advocate for the uniform reporting of UPS by specific tissues involved and with evidence of immunohistochemical diagnosis. This will allow for more accurate comparisons of outcomes as more cases are reported.

One critical difference in our case is the patient received a low-dose of whole body radiation instead of local field radiation. Therefore, his tumor does not meet the criteria set forth by Cahan[36] and Arlen[37] to be categorized asa radiation-induced sarcoma. These criteria include1) treatment with therapeutic irradiation at least three years prior to development of sarcoma, 2) sarcoma arising within the field of previous therapeutic irradiation, and 3) differing histology between the sarcoma and the primary tumor. Our patient also received chemotherapyand BMT/SCT. Both of which have been associated with an increased risk of developing a secondary neoplasm, most likely due to the induction of an immuno compromised state.[38,39]Additionally, EBV has been suggested as playing a causative role in the development of mesenchymal tumors,[40] and our patient had a severe EBV-related complication during his ALL treatment. It is probable that our patient has an unidentified genetic predisposition to cancer given his development of ALL at the age of 3. However, there was no family history of genetic mutations or development of cancer. The eventual outcome is unknown, but the patient is currently doing well 2 months after resection. His pharyngeal reconstruction with a radial forearm flap was successful, and he is currently tolerating a regular diet and has normal speech. Little has been written on pharyngeal reconstruction in the pediatric population. It seems reasonable to assume that pediatric pharyngeal reconstruction would not radically differ from that in adults. A few specific differences that do exist include 1) patients tend to be free of preoperative radiation (and are thus not salvage pharyngolaryngectomies); 2) reconstruction needs to be highly durable and functional, since life expectancy should be longer for the pediatric population; and 3) the reconstruction needs to be able to grow and develop with the patient. Thus far, our technique has fulfilled all of these requirements.

Conclusion

Undifferentiated pleomorphic sarcoma is a rare tumor with an overall declining incidence. However, reported occurrence in the head and neck region continues to increase. Diagnosis requires immunohistochemical staining of a tissue specimen. Improved outcomes are directly related to early detection and adequate surgical resection. Adjuvant therapies include radiation and non-standardized chemotherapeutic regimens. To complement the new WHO classification, reporting of these tumors should be done with descriptions of the immunohistochemical findings and specific anatomic locations.

Figures

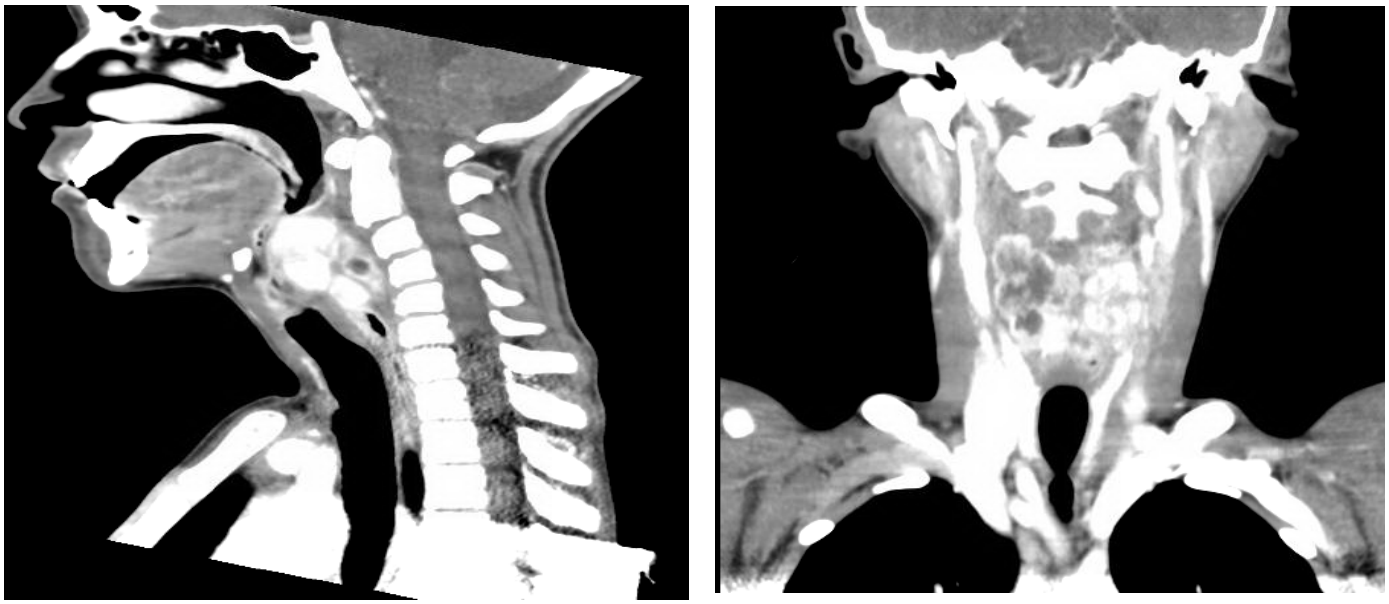

Figure 1: Sagittal and Coronal CT scans of pharyngeal mass

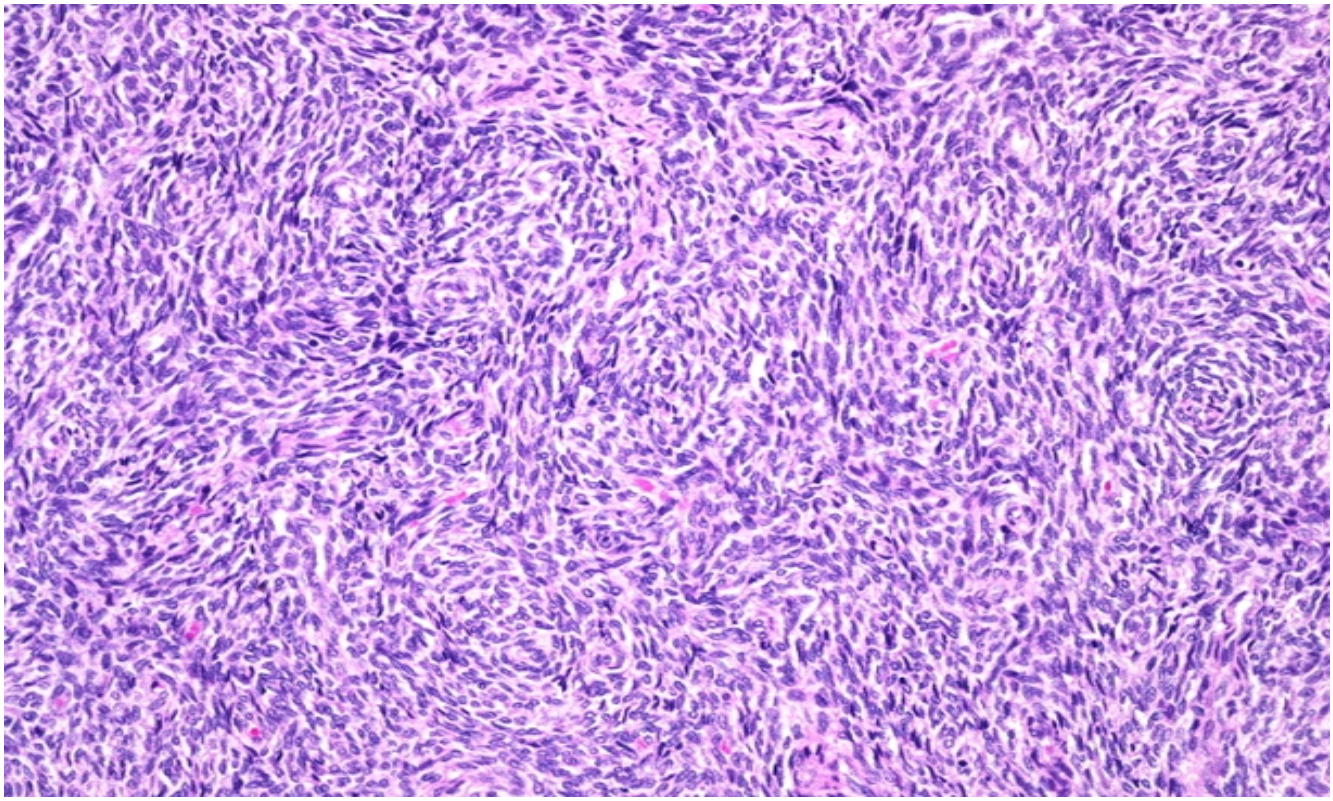

Figure 2: Pathology slide of excision specimen (H&E stain, 40X magnification)

Table

Table 1: Case reports of pharyngeal UPS

Patient	Age/Sex	Type	Location	Radiation History	Treatment	Microscopic Margins	Outcome
1	14/M	2°	Oropharynx and Hypopharynx	Yes	S + CRT	+	
2[12]	36/M	1°	Nasopharynx	No	S + CRT[a]	NR	DOD, 15 months
3[13]	13/F	?	Nasopharynx	?	S	NR	?
4[14]	54/M	1°	Oropharynx	No	S	-	-
5[4]	67/M	2°	Nasopharynx	Yes	P	+	DOD, 1 month
6[4]	53/M	2°	Nasopharynx	Yes	P	+	DOD, 53 months
7[4]	44/M	1°	Nasopharynx	No	S + RT	-	DF, 120 months
8[15]	46/M	NR	Nasopharynx	NR	NR	NR	NR
9[16]	29/M	NR	Hypopharynx	NR	S	-	DF, 48 months
10[17]	70/M	?	Hypopharynx	?	S	?	DF, 24 months
11[18]	?	?	Oropharynx and Hypopharynx	?	S	?	DF, 12 months
12[19]	79/M	NR	Oropharynx and Hypopharynx	NR	NR	NR	NR
13[20]	NR	NR	Hypopharynx	NR	NR	NR	NR
14[21]	?	2°	Nasopharynx	Yes	?	?	?

1° = primary, 2°= secondary, NR = not reported, S = surgery, RT = radiotherapy, CRT= chemoradiotherapy, P = palliative, DOD = died of disease, DF = disease free

[a] External ethmoidectomy approach; 6000 rads; vincristine + cyclophosphamide + dacarbazine with no response then changed to methotrexate + leucovorin with partial response

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Authors Information: Bahar Abbassi, MS[1]; Adam Singleton, MD[1]; Anas Eid, MD[2]; Sandeep Samant, MD, FACS[2]; Jon Ver Halen, MD, FACS[3*]

[1]Department of Otolaryngology-Head and Neck Surgery, University of Tennessee, Memphis, TN
[2]Department of Plastic, Reconstructive and Hand Surgery, Baptist Cancer Center and Baptist Medical Group, Memphis, TN
[3]Department of Surgery, Division of Plastic Surgery, Baylor Scott & White Healthcare, Texas A&M Health Science Center – School of Medicine, Temple TX

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