Primary Monophasic Synovial Sarcoma of the Tonsil: Immunohistochemical and Molecular Study of a Case and Review of the Literature

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Abstract Synovial sarcoma (SS) arises primarily in the lower extremities with a predilection for sites in proximity to large joints, such as the knee. It rarely occurs in the head and neck region, and the tonsil is an unusual site for the tumor, with only eight previously published cases in this anatomical site. We present a case of a primary monophasic SS arising in the right tonsil in a 63-year-old male. His medical history was noncontributory. Immunohistochemistry showed that cytokeratin OSCAR, EMA, Bcl-2, vimentin, PGP 9.5, and TLE1 were diffusely positive. A molecular analysis using RT-PCR indicated that the patient was positive for the *SYT/SSX1* fusion transcript. A diagnosis of monophasic synovial sarcoma of the tonsil was made.

Keywords Synovial sarcoma · Tonsil · TLE1 · *SYT/SSX1*

Introduction

Synovial sarcoma (SS) is a rare high-grade soft tissue tumor of unknown histogenesis that primarily arises from the deep soft tissues of the extremities, and it accounts for

6–10 % of all soft tissue tumors [1, 2]. Only 3–5 % arise in the head and neck region, and SS arising in the tonsil is a rare finding, with only eight well-documented cases reported in the English language literature [1–6]. We describe the histopathological findings of a primary synovial sarcoma of the palatine tonsil arising in a 63-year-old male, with immunohistochemical expression of TLE1 and molecular detection of the *SYT-SSX1* fusion gene transcript using reverse transcription-polymerase chain reaction (RT-PCR).

Case Report

A 63-year-old man presented with a 3-month history of progressive dysphagia and a growing tumor in the right side of the oropharynx. The remainder of his medical history was non-contributory. A physical examination revealed right tonsillar hypertrophy and a lobulated tonsillar surface. There were no cervical lymphadenomegalies. A right tonsillectomy was performed with the patient under general anesthesia.

Grossly, the right tonsil measured $5.7 \times 4 \times 3$ cm with a smooth lobulated surface and firm consistency. The cut surface of the tonsil was solid, homogeneous, and white-tan, without necrosis or hemorrhage (Fig. 1). The specimen was fixed in 10 % buffered formalin and embedded in paraffin. Histologic 4- μ m sections were stained by hematoxylin and eosin. Immunohistochemistry was performed using the standard streptavidin-biotin complex method. The antibodies and methodology used in this study are summarized in Table 1.

A histopathological examination showed a monophasic synovial sarcoma. The tumor was composed of closely packed spindle cells with scant pale cytoplasm forming

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Fig. 1 **a** Gross appearance of the *right* tonsil, illustrating the solid, homogeneous surface. **b, c** Whole mount of the *right* tonsil. In the *lower* aspects of the images, the residual tonsil is identified, and the

synovial sarcoma is shown in the *upper part* (**b** H & E; **c** Masson's Trichrome). **d–f** Synovial sarcoma primarily composed of closely packed short uniform spindle cells (H & E)

Table 1 Immunohistochemistry

Antibody	Clone	Source	Pretreatment	Dilution
TLE1	M-101	Santa Cruz Biotech	Trilogy	1:100
EMA	E-29	DAKO	Trilogy	1:150
OSCAR	Phenopat	ACD	Trilogy	1:40
Bcl-2	124	Bio SB	Evision-flex	1:15
Vimentin	9	BIOGENEX	Declere	1:2,000
CD99	HO36.1.1	BIOGENEX	Trilogy	1:75
	CD99/B5	Bio SB	Trilogy	1:25
PGP 9.5	Polyclonal	NEOMARKERS	Declere	1:600

Antibodies, clones, source antigen retrieval and dilutions

variably arranged fascicles (Fig. 1). The spindle cells were immunoreactive for OSCAR, EMA, Bcl-2, vimentin, CD99, and PGP 9.5, and showed a strong nuclear expression of TLE1. Focally, few glandular-like formations were present that reacted positively to cytokeratin OSCAR and EMA (Fig. 2). The RT-PCR analysis was performed at Quest Diagnostics Nichols Institute (San Juan Capistrano, CA, USA). RNA was extracted from paraffin-embedded tissue and purified after DNase treatment. The quality was determined using agarose gel electrophoresis. RNA was reversed transcribed to cDNA and amplified by PCR using

a fluorescence reporter probe method for multiplex analysis to detect primary fusion transcripts of the following tumors: synovial sarcoma (SYT/SSX1; SYT/SSX2), Ewing's sarcoma (EWS/FLI1; EWS/ERG), rhabdomyosarcoma (FKHR/PAX3; FKHR/PAX7), and desmoplastic small round cell tumor (EWS/WT1). The molecular analysis indicated that the patient was positive for the *SYT/SSX1* fusion transcript.

On the basis of the histological, immunohistochemistry, and molecular pathological findings, a diagnosis of monophasic synovial sarcoma of the right tonsil was rendered. The surgical margin was free of tumor. Our patient did not receive therapy and was alive and well 1 year after surgery. However, he was lost to follow up.

Discussion

Synovial sarcoma is an aggressive malignant soft tissue tumor arising predominantly in the lower extremities; only approximately 3–5 % of all cases occur in the head and neck region, and the hypopharynx is the most common site. However, other sites (masticator space, sinonasal cavity, pharynx, parapharyngeal space, tongue, and trachea) may also give rise to SS [1–5, 7, 8]. This tumor is most prevalent in adolescents and young adults aged 15–40 years, but it has

Fig. 2 Immunohistochemical staining showing positivity to EMA (a), Bcl-2 (b), vimentin (c), cytokeratin OSCAR (d), PGP 9.5 (e), and TLE-1 (f). In panels a and d, focal gland-like structures are highlighted

Table 2 Summary of cases reported of synovial sarcoma in the tonsil

Author	Side	Age	Gender	Type	Clinical	Molecular studies
Shmookler [5]	Right	35	Male	Biphasic	–	–
Shmookler [5]	–	34	Male	Biphasic	Hemoptysis, respiratory stridor	–
Engelhardt [4]	Right	25	Male	Biphasic	Discomfort	–
Ishiki [2]	Right	19	Male	Biphasic	Pain during swallowing, cervical metastasis	<i>SYT-SSX1</i> fusion gene
Vogel [1]	Left	31	Male	Biphasic	Dysphagia	<i>SYT-SSX1</i> fusion gene
Rangheard [3]	Left	21	Male	Biphasic	Dysphagia dyspnea	–
Khademi [6]	Right	23	Male	Monophasic	Sore throat, ear pain, headache	–
Khademi [6]	Right	26	Male	Biphasic	Throat discomfort, fullness and bleeding	–
Present case	Right	63	Male	Monophasic	Progressive dysphagia	<i>SYT/SSX1</i> fusion transcript

been described at practically all ages [1, 2, 7–9]. In general, males and females are almost equally affected [10, 11].

To the best of our knowledge, primary SS of the tonsil has been previously documented in only eight patients in the English language (Table 2) [1–6]. All of these patients were young males with an age range of 19–35 years. Clinically, the symptoms were related to the respiratory and digestive tracts, with dysphagia and dyspnea. Histologically, all but one were biphasic SS (the other was a monophasic SS), and only two were tested for the SYT-SSX fusion gene transcript.

Microscopically, SS may be classified into four types: biphasic type, monophasic fibrous type, monophasic epithelial type, and poorly differentiated type [12, 13]. The diagnosis requires additional immunohistochemical and occasionally cytogenetic examination. By immunohistochemistry, both the epithelial and spindle cell elements of SS show positive immunostaining for vimentin, various

cytokeratins, and epithelial membrane antigen (EMA). Synovial sarcoma may also stain for Bcl-2 and CD99. In up to 21 % of tumors, the S-100 protein may be focally expressed [14]. No immunoreactivity has been described for actin (HHF-35), myoglobin, CD34, or desmin [15].

The tumor cells in our case showed strong, diffuse, positive nuclear staining for the TLE1 antibody, which is a highly sensitive marker of synovial sarcoma [16]. TLE1 (transducin-like enhancer of split 1)/E (sp1) homolog, *Drosophila* corepressor *groucho* is one of four members of the TLE gene family associated with embryogenesis, hematopoiesis, and neuronal and epithelial differentiation [16–18]. TLE1 is a transcriptional corepressor that binds to a number of transcription factors and plays an important role in the WNT/b-catenin signaling pathway, which is known to be associated with synovial sarcomas [19]. Positive nuclear expression of TLE1 occurs in more than 90 % of synovial sarcoma cases, typically in more than

50 % of the cells [16, 18]. According to the study by Terry et al. [20], other tumors commonly mistaken for synovial sarcoma show lower levels of positive staining for TLE1, such as schwannomas, Ewing sarcomas, MPNST, and malignant fibrous histiocytoma. Therefore, TLE1 should be used in the context of a panel of antibodies, including keratins, EMA, Bcl-2, and CD34 [16, 18].

At least 95 % of all SS bear a unique chromosomal translocation, which results in a fusion of the SYT gene on chromosome 18 with either the SSX1 gene or SSX2 gene or, more rarely, the SSX4 gene on the X chromosome. Because these gene fusions are highly specific, their detection with molecular genetics allows the pathologist to render a correct diagnosis. For application in formalin-fixed and paraffin-embedded tissue the two molecular biologic methods currently available are conventional and variations of reverse transcription-polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH). Ten Heuvel et al. [21] showed that RT-PCR had a higher sensitivity than FISH (94 vs 82 %) and a specificity and positive predictive value of 100 % and a negative predictive value of 80 and 75 % respectively. Another study conducted by Amary et al. [22] concluded that the employment of a combination of molecular approaches is a powerful aid to diagnosing synovial sarcoma giving at least 96 % sensitivity and 100 % specificity but results must be interpreted in the light of other modalities such as clinical findings and immunohistochemical data. Thorson et al. [23] using RT-multiplex PCR for SYT-SSX transcripts, showed 77 % sensitivity and 100 % specificity in synovial sarcoma.

In our case, molecular analysis using a multiplex fluorescence reverse transcriptase-polymerase chain reaction (RT-PCR) assay was used for the identification of the primary fusion transcript types in formalin-fixed, paraffin-embedded tissues. The tumor tested positive for the SYT/SSX1 fusion transcript, which is usually associated with the t (X;18)(p11;q11) translocation.

In summary, we reported a case of a primary synovial sarcoma of the tonsil with immunohistochemical studies and identification of the SYT/SSX1 fusion transcript. Synovial sarcoma is a rare malignant soft tissue tumor that rarely involves the tonsil; nevertheless, it should be considered in the differential diagnosis of tumors in this location.

Conflict of interest None.

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