Molecular and Clinicopathological Findings in a Tonsillar Synovial Sarcoma. A Case Study and Review of the Literature

U. Vogel · M. Wehrmann · W. Eichhorn ·
B. Bültmann · M. Stiegler · W. Wagner

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Abstract Synovial sarcoma (SS), 3–5% of which occurs in the head and neck region, has generally been regarded as high grade sarcoma. Recent analysis of clinical, morphological, and molecular characteristics of SS, however, identified low and high risk group of patients, resulting in important implications for the treatment of patients diagnosed with SS. We describe the case of a 31-year-old male who presented with biphasic SS with poorly differentiated areas (clinical stage IIA) in a palatine tonsil, an extremely rare site of SS. Molecular analyses revealed typical t(X;18) translocation of the SYT gene and a SYT/SSX1 fusion type. The tumor was surgically resected with free margins. Adjuvant radiotherapy or chemotherapy was not considered indicated. To date, the patient has remained free of tumor for 4 years after surgery. Literature review reveals that primary tonsillar HNSS has previously been documented only in three patients. In all of these patients the tumor was histologically biphasic; however only one published case and the case presented here showed areas of poor differentiation. We discuss the relevance of the presented findings with regard to prognostic and therapeutic considerations in SS in the head and neck region.

Keywords Synovial sarcoma · Tonsil · Tonsillar

Introduction

Synovial sarcoma (SS) is defined as mesenchymal spindle cell tumor that exhibits variable epithelial differentiation, including gland formation, and specific chromosomal translocation [1]. It may occur at any site in the body, however only 3–5% of SS arise in the head and neck region [1–3]. We describe the clinical, pathological, and molecular pathological findings in a biphasic, focal poorly differentiated SS in the left palatine tonsil (T-PDSS), a rare site of this tumor [3–5]. We also discuss the relevance of our findings with regard to prognostic and therapeutic considerations in SS, particularly in the head and neck region (HNSS).

Case Report, Methods and Results

A previously healthy 31-year-old male presented with a 3-months history of left-sided sore throat, accompanied by increasing dysphagia. Pre-operative computed tomography (CT) disclosed a $4.2 \times 2.3 \times 2.6$ cm encapsulated tumor in the left palatine tonsil. No signs of tumor necrosis or calcification, nor suspicious regional lymph nodes were seen on CT. The patient underwent transoral surgical resection. Intra-operative evaluation of frozen sections revealed an encapsulated malignant mesenchymal tumor covered by small remnants of pre-existing normal tonsillar tissue (Fig. 1a). Post-operative histological and immunohistological investigation showed biphasic SS with large areas of spindle cells that were positive for vimentin, CD99, bcl2, and calponin (all Dako, Hamburg, Germany) intermingled with glandular structures positive for cytokeratin (AE1/3), EMA, CD99 and bcl2 (all Dako, Hamburg, Germany) (Fig. 1a–c). Thirty percentage of the

U. Vogel · M. Wehrmann · W. Eichhorn · B. Bültmann
Institute of Pathology, University of Tübingen,
Liebermeisterstr.8, 72076 Tübingen, Germany

M. Stiegler · W. Wagner (✉)
Department of Otolaryngology, Head and Neck Surgery,
University of Tübingen, Elfriede-Aulhorn-Str.5, 72076
Tübingen, Germany
e-mail: w.wagner@med.uni-tuebingen.de

Fig. 1 Histological and immunohistological characterization of the T-SS **a** Biphasic encapsulated SS with a rare cytokeratin-positive epithelial component (*arrowheads*) covered by remnants of normal tonsillar tissue with cytokeratin-positive epithelial cells (*asterisk*) in tonsillar crypts. (AE1/AE3 immunostaining, original magnification $\times 30$) **b** Spindle cell component of the T-SS with several mitoses

(*arrowheads*) (H&E, original magnification: $\times 200$) **c** Well-differentiated areas of T-SS with AE1/AE3-positive glandular structures intermingled with spindle cells (original magnification: $\times 200$) **d** Poorly differentiated part of the T-SS with high ki-67 proliferative activity of tumor cells (Mib-1, immunostaining, original magnification: $\times 200$)

tumor was poorly differentiated (PDSS), containing a mixture of epithelioid and spindle cells that were unreactive for cytokeratin, CD34, actin, and desmin (all Dako). The mitotic index in PDSS was $>18/10$ high power fields, and the proliferative activity as demonstrated by ki67 staining (Mib1, Dako) was up to 50% (Fig. 1b, d). Four days later, wide primary ($2.1 \times 1.9 \times 1.6$ cm) reexcision of the tumor base was performed together with right-sided tonsillectomy and bilateral cervical lymphadenectomy. Histological investigation revealed no residual tumor and no lymph node metastases. Fluorescence in situ hybridization (FISH) using dual colour break apart rearrangement probe (Abbott Molecular, Abbott Park, IL, USA) demonstrated rearrangement of the SYT gene on chromosome 18q11.2 indicative of t(X;18) translocation (Fig. 2a). In order to determine SYT-SSX fusion-type we performed RT-PCR assays using primer sets specific for detection of SYT-SSX consensus, SYT-SSX1, and SYT-SSX2 fusion gene transcripts as described previously [6]. In brief, total RNA was extracted from deparaffinized synovial sarcoma tissue of the patient after proteinase K digestion phenol/chloroform [7]. A reverse transcription of the isolated RNA was performed using the primer SYT-FP

5'-AGACCAACACAGCCTGGACCAC-3' at 42°C for 1 h. The resulting cDNA was amplified by PCR using the forward primer SYT-FP and the reverse primers SYT-SSX consensus 5'-TCCTCTGCTGGCTTCTTG-3', SYT-SSX1 5'-ACACTCCCTTCGAATCATTTTCG-3', and SYT-SSX2 5'-GCACTTCCTCCGAATCATTTTC-3', generating PCR amplicons of 87 bp (SYT-SSX consensus), 110 bp (SYT-SSX1), and 110 bp (SYT-SSX2), respectively. Amplification was performed with 35-cycles each consisting of denaturation at 94°C for 30 s, annealing at 52°C for 30 s, and extension at 72°C for 45 s using a GeneAmp PCR System 9600 (PerkinElmer, Boston, MA). A control without template was performed to exclude contamination. As control for successful extraction of nucleic acids, primer sequences were chosen from the sequence of the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene and subjected to RT-PCR (data not shown). Amplification products of all RT-PCR reactions were analysed by electrophoresis on a 2% agarose gel followed by staining with ethidium bromide (Fig. 2b). SYT-SSX consensus (Fig. 2b, lane 2) and SYT-SSX1 (Fig. 2b, lane 3) but not SYT-SSX2 fusion gene transcripts (Fig. 2b, lane 4) could be detected in the tumor material of the patient. Specificity of the

Fig. 2 Molecular-pathological characterization of the T-SS **a** Rearrangement of the SYT gene on chromosome 18q11.2 indicative of t(X, 18) translocation (fluorescence in situ hybridization, original magnification $\times 1000$) **b** Detection of SYT-SSX1 fusion gene

positive PCR products of the SYT-SSX consensus and SYT-SSX1 fusion gene transcripts were additionally confirmed by automatic DNA sequencing (data not shown).

On the basis of these histological, immunohistological and molecular pathological findings the tumor was classified as biphasic tonsillar synovial sarcoma (T-PDSS), with poorly differentiated areas (high grade), typical t(X;18) translocation and SYTSSX1 fusion type at clinical stage IIA (TNM classification: pT1a, GIII, pN0, pR0, Mx). Due to the adequate local excision and absence of lymphogenous or hematogenous spread, the interdisciplinary tumor conference of the local Comprehensive Cancer Center did not recommend adjuvant radiotherapy or chemotherapy. To date, the patient has remained free of tumor for 4 years after surgery.

Discussion

The most common site for HNSS is the hypopharynx, but other sites (masticator space, sinonasal cavity, pharynx, parapharyngeal space, tongue, and trachea) have also been described [1–5, 8–10]. Primary tonsillar HNSS has been previously documented only in three other patients [3–5]. In all of these patients the tumors were histologically biphasic, but only one showed areas of poor differentiation as in our case. One tumor occurred in a 25-year-old patient [3] and measured 5×3 cm. This patient only underwent surgery. The second patient (age and tumor size not reported) received additional post-operative radio- and chemotherapy [4]. During the reported follow-up times of 38 months and 10 years, respectively, no local or systemic recurrence occurred. The third tumor (tumor size not reported) was found in a 19-year-old man and displayed poor differentiation in a small portion [5]. No adjuvant therapy was administered. Eighteen months after primary

transcripts in the synovial sarcoma of the patient by RT-PCR using SYT-SSX consensus specific (lane 2; 87 bp), SYTSSX1 specific (lane 3; 110 bp), and SYT-SSX2 specific primer (lane 4). M = size marker

surgery a cervical lymph node metastasis measuring 7 cm was removed. Histologically, the mass was mainly composed of poorly differentiated SS. After 2 years and 10 months of follow-up examinations, no recurrence or metastasis could be revealed even without any adjuvant therapy [5]. Our patient with T-PDSS has shown no signs of local or systemic recurrence 4 years after surgery.

Review of these four cases of tonsillar SS underlines the clinical dilemma concerning assessment of prognosis and treatment of SS in general and HNSS in particular. With regard to prognosis, multivariate analysis of clinicopathological parameters associated with SS in different topographical locations identified a low-risk group (patient age <25 years, tumor size <5 cm, and well differentiated mono- or biphasic SS) and a high-risk group (patient age ≥ 25 years, tumor size ≥ 5 cm and a histological diagnosis of PDSS) [11–13]. According to these prognostic criteria, most HNSS, including two of the reported T-SS, belong to the low-risk category. With regard to age, HNSS patients are typically young men (mean age 26.4 years, range 10–63 years) or young women (mean age 21.8 years, range 7–49 years). Imaging studies [2, 3] have shown that most HNSS present with localized disease (mean tumor size: 4.2 cm, range 2–9 cm) [2, 3]. Early detection of the tumor at a favourable stage can be explained by early appearance of symptoms such as soar throat, hoarseness or dysphagia. Histological investigation of the small number of reported cases mostly revealed well-differentiated mono- or biphasic tumors. Poorly differentiated tumors have rarely been described [5, 12].

Immunohistochemically the SS presented here displayed the characteristic pattern with strong positivity for cyto-keratin (AE1/AE3), EMA, CD99 and bcl2 in the glandular structures and strong reactivity for vimentin, CD99, bcl2 and scarce positivity for calponin in the spindle cell component. Cytokeratin subtypes like cytokeratin 7 and

cytokeratin 19 which are positive in most cases of SS, were not studied in the presented case. SS is characterized cytogenetically by the translocation t(X;18) (p11.2;q11.2) in more than 95% of cases [1, 14]. This translocation fuses the SYT gene from chromosome 18 with one of three closely related genes, SSX1, SSX2 or SSX4, which are located on the X chromosome. Whether different fusion types influence the outcome of the disease is still controversial. Older studies showed a reduction in metastasis-free survival in SS carrying the SYT-SSX1 fusion type as compared to those associated with the SYT-SSX2 fusion type [1, 14, 15]. Recent studies, however, could not prove that the SYT-SSX fusion type is of prognostic value in SS in terms of disease-specific survival and metastatic-free survival [16–18]. RT-PCR of the T-PDSS of our patient revealed a SYT-SSX1 fusion type, which typically occurs in biphasic SS [15]. Ishiki et al. also found the SYT-SSX1 fusion type in their case of T-PDSS [5]. No information about SYT-SSX fusion transcript in other HNSS and PDSS is available from the literature.

The optimal approach to treatment in SS in general and HNSS in particular remains to be determined [19]. The standard treatment for localized disease is surgery with adequate wide excision. Radiotherapy seems to have an established role in improving local control after inadequate surgical resection [19]. The role of post-operative chemotherapy remains unclear [19]. Recent studies of SS without metastases at presentation disclosed that chemotherapy did not significantly influence the rate of local recurrence, metastasis or tumor-related death, even in PDSS [13]. The differences in metastasis-free survival among the various SYT-SSX fusion types could not be attributed to adjuvant chemotherapy [14, 20]. These findings support the post-operative watch-and-wait strategy, which was followed in our patient with T-PDSS.

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