


A case of a 22-year-old man with primary synovial sarcoma of the parapharyngeal space with an AR somatic mutation: A case report and review of the literature

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Abstract

This case report describes a 22-year-old man with a pharyngeal foreign body sensation arising from the left side of the postpharyngeal wall. Histological examination showed a biphasic pattern of epithelioid and spindle cells including glandular differentiation. The tumour was positive for vimentin and SS18-SSX, and the spindle cells were positive for bcl-2; in contrast, the epithelioid tumour cells were positive for pan-cytokeratin, epithelial membrane antigen and CD99. There was no INI-1 loss in tumour cells. Then, the presence of the *SYT-SSX* gene fusion was demonstrated by fluorescence in situ hybridization. In addition, androgen receptor gene somatic mutations were detected by next-generation sequencing. However, 6 months postoperatively, the patient had neither developed a recurrence nor received adjuvant radiotherapy and chemotherapy. Accurate diagnosis depends on morphological and immunohistochemical examination and a proper molecular analysis, and novel technologies can detect a wide variety of genetic alterations. Although androgen receptor somatic mutations cannot provide additional treatment at present, surgical resection with a clean margin and follow-up is an appropriate approach.

Keywords

Synovial sarcoma, pharyngeal, biphasic, AR mutation, fluorescence in situ hybridization, next-generation sequencing

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Introduction

Synovial sarcoma (SS) is a rare soft tissue tumour that predominantly occurs in young adults. SS can arise in almost any part of the body. SS of the head and neck accounts for less than 10% of all SS cases.¹ SS constitutes the third most common malignant soft tissue tumour in teenagers and young adults.² The 5- and 10-year disease-specific survival rates are 83% and 75% in children and adolescents, respectively.³ To date, only a few cases have been reported in the literature. Very few reports of primary parapharyngeal synovial sarcoma (PPSS) have been published, and most of these reports have been diagnosed by histological examination, immunohistochemical examination and fluorescence in situ hybridization (FISH). In this study, we describe a case of PPSS diagnosed based on histology, immunohistochemistry and molecular pathology. In particular, we discovered a novel somatic gene mutation.

Case report

A 22-year-old man presented with a pharyngeal foreign body sensation. Electronic laryngoscopy revealed a white bulge near the left parapharyngeal wall. Enhanced computed tomography (CT) showed a space-occupying lesion on the left side of the posterior hypopharyngeal wall, and magnetic resonance imaging (MRI) images of the head and neck showed a

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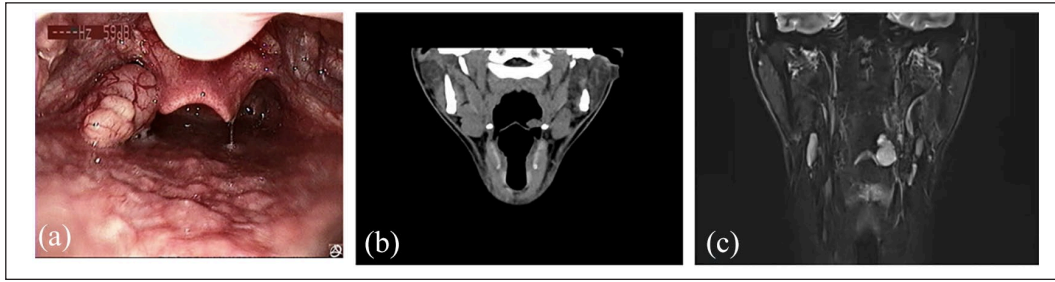


Figure 1. (a) Electronic laryngoscopy revealed a white bulge near the left parapharyngeal region. (b) CT scan showing a space-occupying lesion on the left side of the posterior hypopharyngeal wall. (c) MRI images of the head and neck showed a $2.2 \times 1.7 \times 1.2 \text{ cm}^3$ smooth surface mass arising from the left parapharyngeal space.

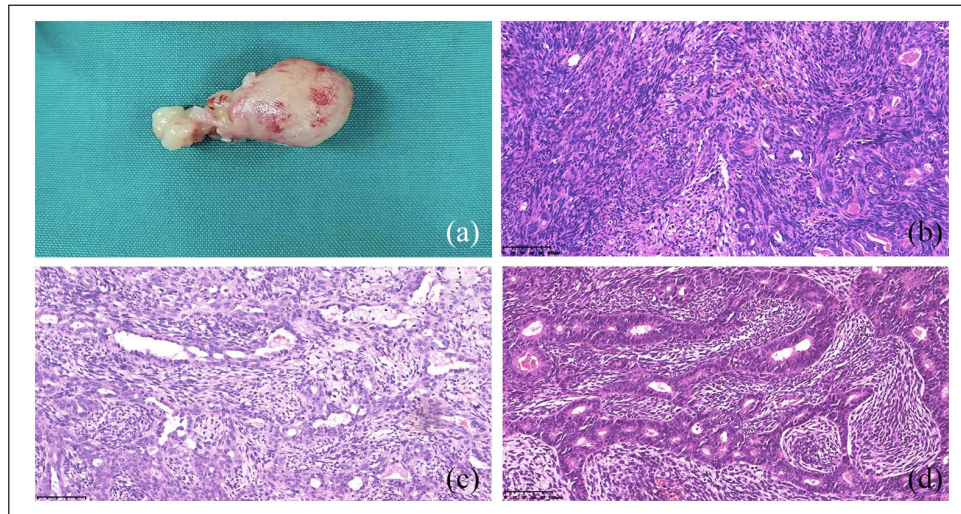


Figure 2. (a) Gross image revealed a grey-white solid mass, swelled at one end. (b) Histological features revealed a biphasic pattern comprising spindle-shaped cells and glandular spaces (H&E, $20\times$).

$2.2 \times 1.7 \times 1.2 \text{ cm}^3$ smooth surface mass arising from the left parapharyngeal space with abnormal enhancement (Figure 1).

The patient was admitted to the Department of Otolaryngology and underwent mass surgical excision of the tumour with a clear margin. He has been followed up for 6 months and has remained free of recurrences and metastases based on radiological and clinical examinations.

After surgical resection of the tumour, pathological examinations of the tumour specimen revealed a grey-white solid mass. Histologically, the tumour presented a biphasic subtype comprising spindle-shaped cells and epithelial cells. Its architectural formation is characteristic of epithelial differentiation, including a well-differentiated glandular cavity (Figure 2). Immunohistochemically, staining for vimentin, INI-1 and SS18-SSX was positive in the spindle and epithelial tumour cells, staining for bcl-2 was positive in the spindle tumour cells and staining for pan-cytokeratin (pan-CK), epithelial membrane antigen (EMA) and CD99 was positive in the epithelioid tumour cells. The proliferative index (Ki-67) was found in approximately 70% of the tumour cells. Staining for smooth muscle actin (SMA) was positive in some of the

individual spindle-shaped and epithelial cells. The tumour cells were negative for thyroid transcription factor 1 (TTF-1), thyroglobulin (TG), p63, WT-1 and S100 (Figure 3).

We performed the molecular genetic examination by FISH and next-generation sequencing (NGS). The presence of an *SYT-SSX* gene fusion was demonstrated from the paraffin blocks by FISH (Figure 4).

We detected (from the paraffin blocks, formalin-fixed) an *AR* somatic mutation by NGS. The adenine (A) in Position 179 was replaced by thymine (T) in the cDNA, resulting in the protein having the glutamine in Position 60 being replaced by leucine (Table 1).

The patient underwent surgical excision of the tumour with a clean margin and was followed up for 6 months. He remained free of recurrences or metastases on radiological and clinical examinations.

Discussion and conclusion

SS of the head and neck is rare, accounting for less than 0.1% of head and neck tumours.¹ Approximately, 70%–80%

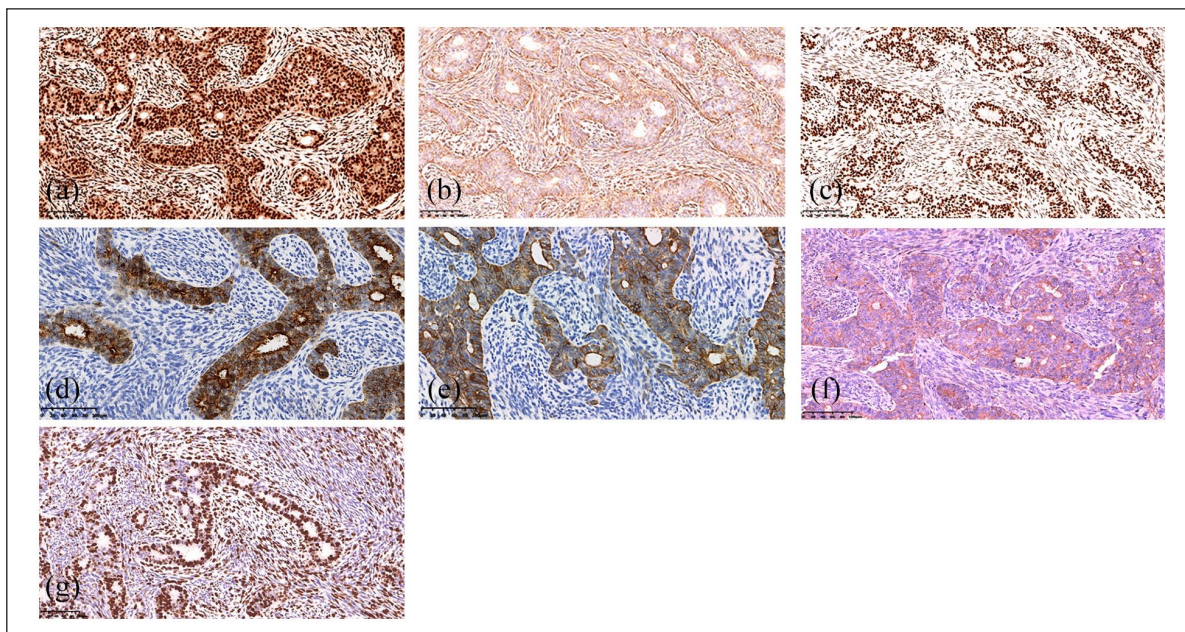


Figure 3. Immunohistochemically, staining for (a) SS18-SSX and (b) vimentin was positive in the spindle and epithelial tumour cells, (c) INI-1 was expressed in the tumour cells, and staining for (d) pan-CK and (e) EMA was positive in the epithelioid tumour cells. However, immunohistochemically, staining for (f) CD99 was positive in the epithelioid tumour cells; (g) the proliferative index (Ki-67) was found in approximately 70% of tumour cells (IHC, 20 \times).

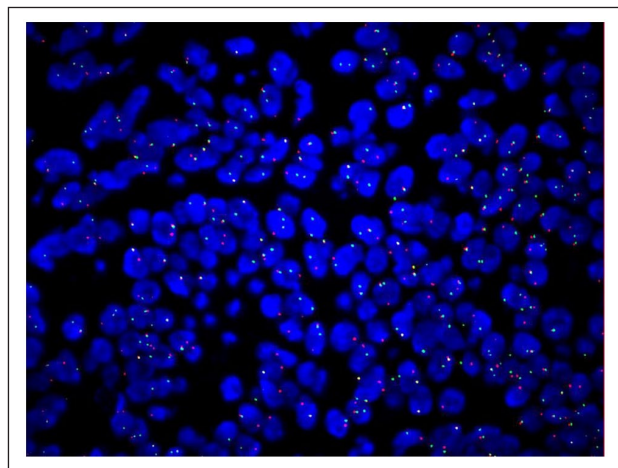


Figure 4. The SS18 gene disruption is proved by FISH. In normal cells, the two signals are close and overlap of these shows yellow signals. The separation of the abnormal cell signals shows one separate green signal and one separate red signal.

of neoplasms in the parapharyngeal space reported in the literature are benign.⁴ The lower limb accounts for the majority of SS cases,⁵ and SSs in parapharyngeal space were less than 100 cases which were reported by searching articles with keywords ‘synovial sarcoma’ and ‘parapharyngeal’ in PubMed. A few studies have shown a predominance for male⁶ monophasic subtype.⁷ The initial presentation of most patients is a foreign body sensation in the pharynx, and bleeding and cystic change were detected in large mass.⁸ In

Table I. NGS analysis.

Gene/biomarker	Alteration
AR	Somatic mutation p.Q60L(c.179A>T)
MSI	MSS
NTRK1/2/3	No mutation
ALK	No mutation

this study, we describe a biphasic SS of a 22-year-old man in the parapharyngeal space.

SS occurring in the head and neck usually lacks unique clinical symptoms and specific imaging modalities; therefore, it is difficult to distinguish between benign and malignant tumours based on imaging examinations and clinical findings, which means that pathological examination is extremely important and necessary.⁹

Histopathologically, SS is usually divided into two subtypes, namely biphasic and monophasic patterns. A biphasic morphology (mesenchymal and epithelial components) is observed in 25% of SSs. The origin of SS has nothing to do with the synovium.¹⁰ Previous studies showed that myoblast-specific expression of SS18-SSX2-induced SS in mice indicating that myogenesis might be one of the cells-of-origin of SS.¹¹

Immunohistochemically staining is helpful in the differential diagnosis of SS from other tumours. The literature states that spindle cells are positive for CD99, bcl-2 and pan-CK, and EMA is diffusely positive in the glandular part,⁸ and a novel SS18-SSX fusion-specific antibody is highly sensitive and specific for SS.¹² The results of immunohistochemical

staining in our study were basically consistent with the prior reports except for the weak positivity of CD99 in the epithelial cells. Currently, the presence of an *SYT-SSX* fusion is the gold standard for the diagnosis of SS, and 90% of SS appears to carry this specific translocation.¹³

Biphasic SS needs to be differentiated from metastatic cancer, malignant peripheral nerve sheath tumour (MPNST) with glandular differentiation. Our patient is relatively young, and clinical examination did not find tumours in other parts of the body. MPNST with glandular differentiation is rarely seen in MPNST. To our knowledge, only a few similar cases have been previously described in the literature.^{14,15} In addition, histologically malignant glandular structures lined by columnar cells with goblet cells and the spindle cells were positive for S100. In our case, the tumour cells were negative for S100 and positive for SS18-SSX.

Analysing the clinicopathology of 34 cases of SS with *SYT-SSX* fusion in the head and neck, Owosho et al.¹⁶ found that the most prevalent location of head and neck SS was in the parapharyngeal space, and it was more common in males than in females. Head and neck SS has similar survival rates to sarcomas that arise in the limbs.¹⁷

Generally, survival rates of head and neck tumours are associated with the tumour location, their size and their extension.⁶ There is no significant correlation of disease-specific survival (DSS) with tumour site, surgical margin, tumour size (<5 cm versus >5 cm) or histopathologic subtype.¹⁶ No significant correlation with overall survival of tumours >5 cm has been noted,¹⁸ but Mallen-St Clair et al.¹⁹ and Wushou and Miao⁷ have concluded that the overall survival rate is shorter for patients with a tumour size >5 cm; among 15 patients with SS, the tumour size in those with recurrent cases was less than 5 cm.²⁰ In conclusion, head and neck SS is relatively rare, and clinicopathological research data are limited.

No previous studies have recommended biomarkers to monitor tumour recurrence. SS-specific miRNAs may be possible biomarkers.²⁰ Haldar et al.¹¹ showed that increased expression of miR-214 is associated with a poor prognosis in SS. Uotani et al.²¹ reported that serum miR-92b-3p levels were significantly higher in SS patients than in healthy individuals; thus, miRNA expression levels may represent a novel approach for monitoring SS.

SS is a rare soft tissue tumour that contains a unique *SYT-SSX* fusion, but not all SSs are associated with this fusion. Very few targeted treatments of sarcomas are currently in routine use; however, NGS is becoming the foundation of personalized oncology. We confirmed the diagnosis of this case with FISH, and we employed an additional panel covering 688 cancer-associated genes to analyse the tumour DNA (the *SS18-SSX* fusion gene was excluded), which resulted in identification of neither recurrent mutation genes nor targeted therapy-associated genes. *AR* somatic mutations were detected. The discovery of potential driver mutations and clinical monitoring of SS through the use of NGS is

currently routine clinical practice,^{22,23} but no *AR* gene mutation has been found in SSs previously.

To the best of our knowledge, this first in-principle study provides new insight into the genomic landscape within SS. Glutamine encoding codon 60 of exon 1 of the *AR* gene was replaced with leucine in our case. To date, *AR* mutations have shown no clear clinical significance in SS. Genetic alterations of *AR* have been found in prostate cancer^{24–26} and some soft tissue tumours.^{27,28} Moreover, the incidence may increase with tumour progression due to the influence of various treatment methods.²⁹ Our patient did not have a history of androgen inhibitors or radioactive exposure, and the mutation position is novel.

Conclusion

In summary, we describe a case of a 22-year-old man with primary SS of the parapharyngeal space, and an accurate diagnosis was obtained based on a morphologic, immunohistochemical and FISH analysis. This report revealed a previously unreported *AR* somatic mutation existing in PPSS using NGS. Each case of parapharyngeal space SS should be published because it is very important to understand new aspects of this rare cancer, such as *AR* somatic mutations, which may be targets for the development of future therapy and diagnostic tests. Maybe, further study of *AR* in SS is warranted.

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Author contributions

Y.G. contributed in conceptualization; Y.G. and J.Z. involved in supervision; H.J. participated in drafting the article and conducted critical reviews; G.M. provided clinic imagings on patient; Z.N., H.C. and Q.Y. carried out the histopathological evaluation and reviewed the article; H.N. performed the immunohistochemical test.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval to report this case was obtained from 'Xi'an Daxing Hospital'.

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Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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