

# A Case of a 22-year-Old Man with Primary Synovial Sarcoma of the Parapharyngeal Space with an *AR* Somatic Mutation: A Clinicopathologic Study and Literature Review

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## Case Report

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# Abstract

**Background:** Synovial sarcoma (SS) is a rare and aggressive entity that occurs predominantly in young adults. SS can arise in almost any part of the body, especially in the extremities. The incidence of SS in the parapharyngeal space is, however, quite low.

**Case presentation:** Herein, we describe a case of a biphasic SS in the parapharyngeal space. A 22-year-old man presented with a pharyngeal foreign body sensation and underwent excision of the mass with a clear margin. Pathological examinations of the tumour specimen revealed a 1.7×1.5×1.2 cm spherical, well-circumscribed mass arising from the left side of the postpharyngeal wall. Histological examination showed a biphasic pattern of epithelioid and spindle cells, including glandular differentiation.

**Immunophenotype:** Immunohistochemically, the tumour cells were positive for vimentin, and the spindle cells were positive for bcl-2; in contrast, the epithelioid tumour cells were positive for cytokeratin (CK) and epithelial membrane antigen (EMA) and weakly positive for CD99. The tumour cells were scattered positive for SMA. Thyroid transcription factor 1 (TTF-1), thyroglobulin (TG), p63, WT-1 and S100 were negative, and the proliferative index (Ki-67) was found in approximately 70% of the tumour cells. Then, the presence of the *SYT-SSX* gene fusion was demonstrated by fluorescence in situ hybridization (FISH). In addition, androgen receptor (AR) gene somatic mutations were detected by next-generation sequencing (NGS).

Two months postoperatively, the patient had neither developed a recurrence nor received adjuvant radiotherapy and chemotherapy.

**Conclusions:** Accurate diagnosis depends on morphological and immunohistochemical examination and a proper molecular analysis, and novel technologies can detect a wide variety of genetic alterations. The prognosis is relatively good in patients who undergo surgical resection with a clean margin.

## Background

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 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. 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 Presentation

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 2.2×1.7×1.2 cm smooth surface mass arising from the left parapharyngeal space with abnormal enhancement (Fig. 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 two 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 comprised of spindle-shaped cells and epithelial cells. Its architectural formation is characteristic of epithelial differentiation, including a well-differentiated glandular cavity. Immunohistochemically, staining for vimentin was positive in the spindle and epithelial tumour cells, staining for bcl-2 was positive in the spindle tumour cells, and staining for cytokeratin (CK) and epithelial membrane antigen (EMA) were both positive in the epithelioid tumour cells. However, immunohistochemically, staining for CD99 was only weakly positive in the epithelioid tumour cells. The proliferative index (Ki-67) was found in approximately 70% of the tumour cells. Staining for SMA was positive in some of the individual spindle-shaped and epithelial cells. The tumor cells were negative for thyroid transcription factor 1 (TTF-1), thyroglobulin (TG), p63, WT-1 and S100 (Fig. 2).

We performed the molecular genetic examination by FISH and NGS. The presence of an *SYT-SSX* gene fusion was demonstrated from the paraffin blocks by FISH.

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.

## Treatment And Outcome

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

## Discussion And Conclusions

Approximately 70–80% of neoplasms in the parapharyngeal space reported in the literature are benign, which means that sarcoma in this location is rare[4]. Synovial sarcoma 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[5], which means that pathological examination is extremely important and necessary.

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 synovial sarcomas. The origin of synovial sarcoma has nothing to do with the synovium[6]. Previous studies showed that myoblast-specific expression of *SS18-SSX2* induced synovial sarcoma in mice, indicating that myogenesis might be one of the cells-of-origin of synovial sarcoma[7].

Immunohistological staining is significant in the differential diagnosis of SS from other tumours. The literature states that spindle cells are positive for CD99, bcl-2 and CK, and EMA is diffusely positive in the glandular part[8]. 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 synovial sarcoma, and ninety percent of SS appears to carry this specific translocation[9].

Analysing the clinicopathology of 34 cases of synovial sarcoma with *SYT-SSX* fusion in the head and neck, Owosho AA *et al.*[10] 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 synovial sarcoma has similar survival rates to sarcomas that arise in the limbs[11].

Generally, survival rates of head and neck tumours are associated with the tumour location, their size, and their extension[12]. There is no significant correlation of disease specific survival (DSS) with tumour site, surgical margin, tumour size (< 5 cm vs. >5 cm) or histopathologic subtype[10]. No significant correlation with overall survival of tumours > 5 cm has been noted[13], but Mallen-St *et al.*[14] and Wushou *et al.*[15] have concluded that the overall survival rate is shorter for patients with a tumour size > 5 cm; among 15 patients with synovial sarcoma, the tumour size in those with recurrent cases was less than 5 cm[16]. In conclusion, head and neck synovial sarcoma is relatively rare, and clinicopathological research data are limited.

No previous studies have recommended biomarkers to monitor tumour recurrence. Synovial sarcoma-specific miRNAs may be possible biomarkers[16]. Haldar *et al.*[7] showed that increased expression of miR-214 is associated with a poor prognosis in synovial sarcoma. Uotani *et al.*[17] 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.

Synovial sarcoma 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, next-generation sequencing 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 tumor DNA (the *SS18-SYT* 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 next-generation sequencing is currently routine clinical practice[18,19], but no AR gene mutation has been found in synovial sarcomas 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[20,21,22] and soft tissue tumours [23,24] in recent years. The androgen receptor gene is located on the X chromosome and it contains a segment of polymorphic CAG tandem repeats in exon 1, and it is an ideal tool to study the clonality of female sarcoma[25], adenomas of the salivary gland[26], and malignant fibrous histiocytoma[27]. Its product is a steroid hormone nuclear receptor, and it is a target in prostate cancer treatment by androgen deprivation. Prostate cancer frequently evolves into resistant androgen-independent prostate cancer after it develops mutations in *AR*[20]. Mutations in the *AR* gene are reported in 1% of primary prostate cancers and in approximately 60% of metastatic prostate cancers [21]. The incidence may increase with tumour progression due to the influence of various treatment methods[28,29].

Furthermore, the localization of point mutations in *AR* might be influenced by the type of treatment given for prostatic cancer[21]. AR F877 L, F876 L and T878A mutations confer resistance to enzalutamide treatment and have been reported in primary and metastatic prostate cancer[30,31]. In the presence of *AR* point mutations in prostate cancer, a potential new approach to treatment has been developed.

Our patient did not have a history of androgen inhibitors or radioactive exposure, and the mutation position is novel. *AR* has been shown to play an important role in prostate cancer, and its role in soft tissue tumours has been evaluated. In vestibular schwannomas, AR is deregulated by a hormonal effect or a change in the tumour microenvironment[23]. AR is key to the CDK11 signalling pathway in osteosarcoma, and patients with high AR expression respond well to preoperative chemotherapy but have a worse 5-year survival[24]. Under certain conditions, AR may serve as a novel therapeutic target in prostate cancer and in some sarcomas.

In summary, we describe a case of a 22-year-old with primary synovial sarcoma 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 by 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. Further study of AR in SS is warranted.

## Abbreviations

PPSS: Primary Parapharyngeal space Synovial sarcoma; SS: synovial sarcoma; NGS: Next-generation sequencing;

CT: Computed tomography; TG: Thyroglobulin; TTF-1: thyroid transcription factor 1; CK: cytokeratin; EMA: epithelial membrane antigen; FISH: fluorescence in situ hybridization; AR: androgen receptor; MRI: magnetic resonance imaging.

# Declarations

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## Informed consent statement

Informed consent was obtained from the patient.

## Written informed consent

Patient has provided informed consent for publication of the case.

## Conflict-of-interest statement

The authors declare that there is no conflict of interest related to this report.

## Authors' contributions

Conceptualization: Ying Guo. Supervision;Ying Guo and and Jin Zhu;He Jiang participated in drafting the manuscript and conducted critical reviews. Ge Ma provide clinic imagings on patient.Zunzhen Nie, Hongzhang Chen and Qingguo Yan carried out the histopathological evaluation and reviewed.Haiyan Nan did immunohistochemical test.

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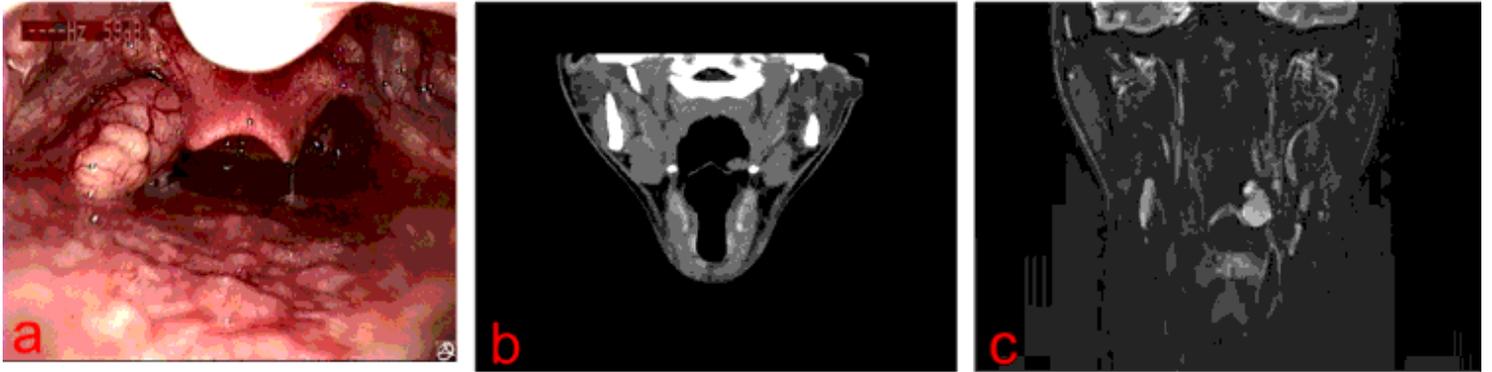
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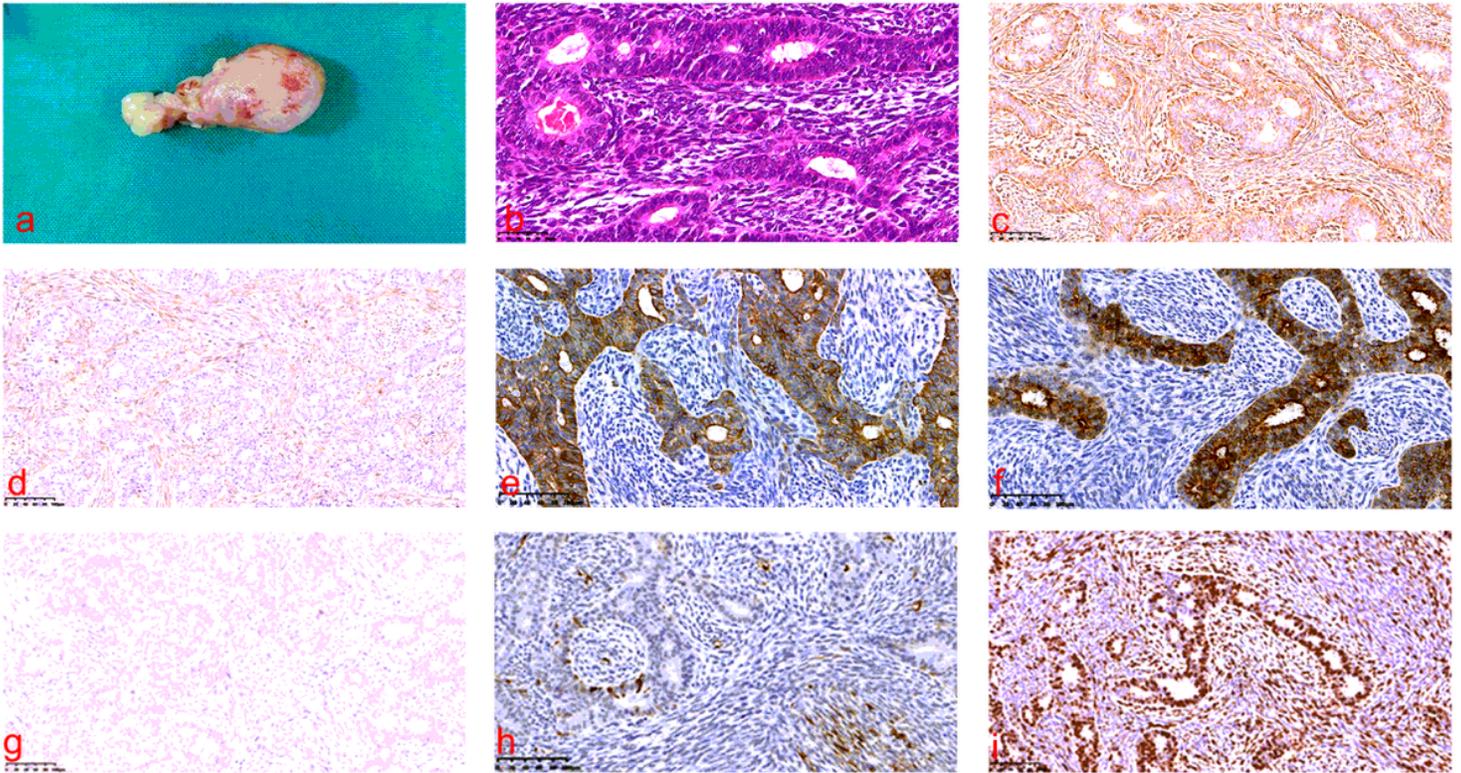
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## Figures



**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 2.2×1.7×1.2 cm smooth surface mass arising from the left parapharyngeal space.



**Figure 2**

a Gross image of the case. b Histological features revealed a biphasic pattern comprised of spindle-shaped cells and glandular spaces (H&E, 40×). Immunohistochemically, staining for vimentin (c) was positive in the spindle and epithelial tumour cells, bcl-2 (d) was positive in the spindle tumour cells, and staining for CK (e) and EMA (f) was positive in the epithelioid tumour cells. However, immunohistochemically, staining for CD99 (g) was weakly positive in the epithelioid tumour cells, and staining for SMA(h) was individually positive in some spindle-shape and epithelial cells; The proliferative index (Ki-67) (i) was found in approximately 70% of tumour cells.

## Supplementary Files

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