RESEARCH PAPER

Sarcoma Ex Pleomorphic Adenoma of the Submandibular Gland: An Unusual Molecular Profile

Dr. Yengkhom Daniel Singh[1]*, Dr. Madan K[2], Dr. Malathi M[3]
[1]Senior Resident, Oncopathology Department, Yenepoya Medical College, Mangalore, ORCID ID - 0000-0001-7644-7894
[2]Associate Professor, Oncopathology Department, Yenepoya Medical College, Mangalore, ORCID ID - 0000-0001-8052-6034
[3]Professor & Head, Oncopathology Department, Yenepoya Medical College, Mangalore
***Author for Correspondence:**
Dr Yengkhom Daniel Singh

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ABSTRACT
Introduction: Pleomorphic adenoma (PA) is the most common tumour of the submandibular gland. PA can rarely show malignant transformation as carcinoma, carcinosarcoma, or pure sarcomas. Pure sarcomatous transformation arising in recurrent pleomorphic adenoma is extremely rare, with only a handful of cases reported in the parotid gland. ***Materials and Methods:*** A 45-year-old female came with complaints of recurrent left cervical swelling. She initially presented with swelling in the left submandibular region in 2021 & 2023. Excision of the submandibular gland was of a pleomorphic adenoma with extensive chondroid differentiation. She had multiple recurrences (2024 and 2025) in the left cervical region. Now, she underwent a left cervical neck dissection. ***Result:*** Histopathology revealed an ill-circumscribed nodular neoplasm composed of lobules of cartilage with variably cellular chondrocytes, focally increased cellularity, moderate anisonucleosis, and sparse mitosis. Osseous differentiation and focal tumour necrosis were present. Immunohistochemistry for CK, p63, SOX10, IDH1, and p53 was performed. After thoroughly analysing the history, a comprehensive diagnosis of Sarcoma Ex Pleomorphic Adenoma (SAExPA) was made. Subsequently, Next-Generation Sequencing (NGS) analysis was performed. ***Conclusion:*** Pure sarcomas arising in a recurrent PA of the submandibular gland are unheard of. SAExPA should be distinguished from Carcinoma Ex Pleomorphic Adenoma (CAExPA) due to its dismal prognosis. Given the lack of existing literature, our report may well be the first case of a pure sarcomatous transformation in the submandibular gland.

Keywords: Pleomorphic adenoma, Sarcoma ex pleomorphic adenoma, TP53 mutation, Submandibular gland.

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INTRODUCTION

Pleomorphic adenoma (PA) is a benign neoplasm of the salivary gland comprising epithelial (ductal) and myoepithelial cells within a chondromyxoid or fibrous stroma. PA is the most common salivary gland tumour, which occurs most commonly in the parotid gland, followed by the submandibular gland, minor salivary glands, and the sublingual gland. In the submandibular gland, it is the most common tumour, comprising 36% of all tumours. [1] PAs have the potential to recur and/or progress into malignancy. Because these are biphasic tumours, pleomorphic adenomas can progress with time and inherently transform into malignant tumours in the form of carcinoma, such as Carcinoma Ex Pleomorphic Adenoma (CAExPA); carcinosarcoma – Carcinosarcoma Ex Pleomorphic Adenoma (CSExPA); or a sarcoma, Sarcoma Ex Pleomorphic Adenoma (SAExPA). Usually, the malignant component is either epithelial or myoepithelial, although it can occasionally become a sarcoma or a poorly differentiated neoplasm. Malignant transformation in the form of pure sarcomas arising in recurrent pleomorphic adenoma is extremely rare, with only a handful of reported cases arising in the parotid gland. [2]

CASE REPORT

We report here a case of a 45-year-old lady who came to the OPD with a medical history of recurrent pleomorphic adenoma.

She first presented 4 years back with swelling and pain in the left submandibular region along with left cervical lymphadenopathy, which was medically managed. 2 years ago, she presented for a second time with similar complaints and a gradual increase in the size of the

**Author for Correspondence: Dr Yengkhom Daniel Singh*

swelling. FNAC was reported as a pleomorphic adenoma, and the biopsy revealed only cartilaginous tissue. Therefore, she underwent a wide local excision of the submandibular gland with left level I and II lymph node dissection. The histopathological (HPE) picture was a pleomorphic adenoma with extensive chondroid differentiation. A year ago, she came back with recurrence in the left cervical region. FNAC and HPE were of a recurrent pleomorphic adenoma with extensive chondroid and focal osseous differentiation.

Now, she came with the complaints of a recurrent left cervical swelling. CECT (Figure 1A) detected multiple necrotic nodular masses in the level Ia and bilateral level Ib cervical regions, some with coarse calcifications. These nodules were seen infiltrating the left sternocleidomastoid muscle. Medially, the nodal mass abutted the left internal jugular vein, which caused significant luminal narrowing. CECT features were highly suggestive of metastases. She finally underwent an excision of the left cervical nodular neck masses.

RESULT

Gross examination showed multiple nodular tissue masses, ranging in size from 7x7x3.5 cm to 0.7x0.4x0.1 cm. The cut surface (Figure 1B) of the masses was nodular, firm, pale white, gelatinous, and glistening with gritty foci of calcification. The specimens were thoroughly examined and extensively sampled, with multiple sections from heterogeneous areas and the surrounding soft tissue.

Microscopic examination revealed an unencapsulated, ill-circumscribed nodular neoplasm composed of centrally localised lobules of cartilage, with many showing chondrocytes of variable cellularity and mild anisonucleosis, and a few binucleate forms were seen. The periphery of the tumour was composed of cellular, spindled to ovoid cells in sheets and fascicles. These cells exhibited moderate anisonucleosis with sparse mitoses (Figure 1C). Foci of osseous metaplasia, wide areas of hyalinisation, and occasional tumour necrosis were observed (Figure 1D). Surrounding areas show fibrocollagenous and skeletal muscle tissues with proliferating blood vessels. No ductal epithelial cells or lymphoid tissue were seen. Suspicion of a sarcomatous transformation in a pre-existing recurrent pleomorphic adenoma was highly favourable.

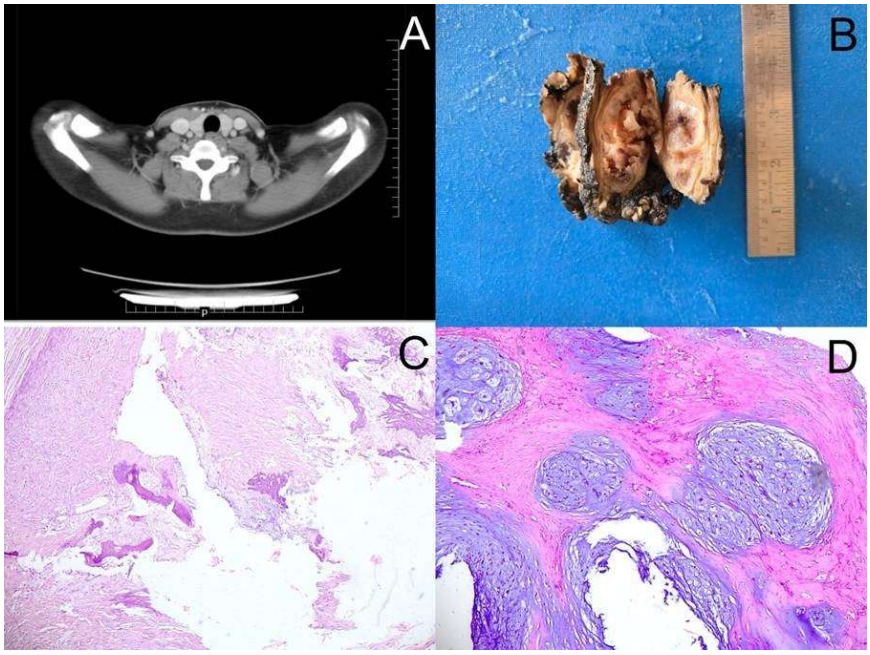

Figure 1: A) A CECT venous phase image showing nodal masses in the cervical region with coarse calcification. **B)** Macroscopic image of the cut surface of the largest nodular mass. **C)** Microphotograph (H&E stain; 200x) showing fibrocollagenous areas with osseous metaplasia. **D)** Microphotograph (H&E stain; 200x) showing lobules of cartilage with atypical chondrocytes.

A panel of immunohistochemistry markers were considered for confirmation, which consisted of PanCK (AE1/AE3), p63, SOX10, S100, IDH1, and p53. Among these, S100 was positive in the chondroid areas. PanCK (AE1/AE3), p63, SOX10 and IDH1 were all negative. IHC for p53 was inconclusive.

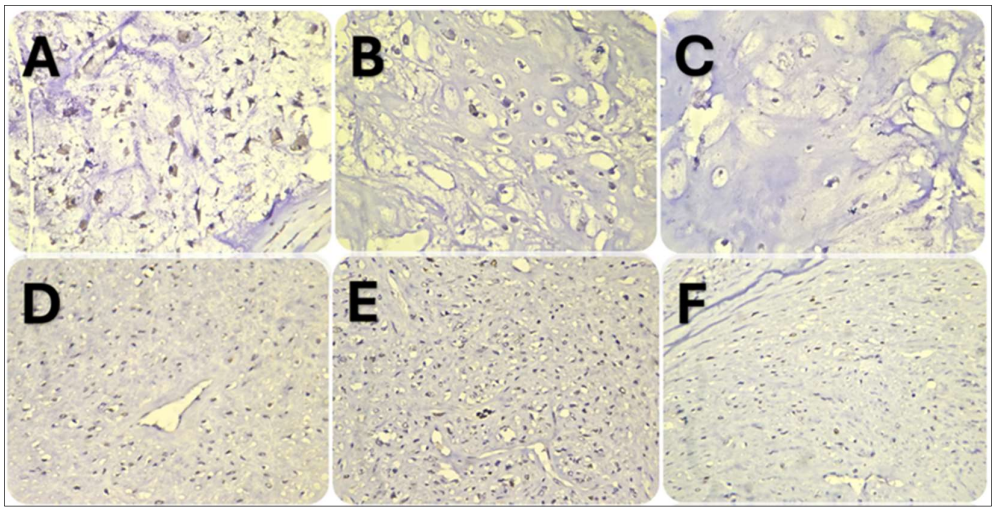

Figure 2: Microphotographs of IHC: **A)** S100 (Beta-Ep32); 400x: Positive in the chondroid areas. **B)** IDH1 R132H(Hmab-1); 400x: Negative. **C)** p53 (BP-53-12); 400x: Inconclusive. **D)** PanCK (AE1/AE3); 400x: Negative. **E)** p63(4A4); 400x: Negative. **F)** SOX10(EP268); 400x: Negative.

Molecular analysis:
Molecular analysis was performed on the Next Generation Sequencing (NGS) platform (Illumina, Inc., San Diego, California) using a lab-developed multi-gene panel covering 109 key soft tissue sarcoma genes. Various genomic alterations, such as SNVs, InDels, and gene fusions. An FFPE tissue block with 40% tumour content was used as the starting material. Nucleic acid extraction and subsequent library preparation were performed using a custom hybrid-capture kit. The QC-passed libraries were sequenced to a minimum depth of 250X on the sequencing platform. The variants were annotated using our in-house annotation pipeline, and genomic alterations are prioritised, classified, and reported in accordance with AMP/ASCO/CAP guidelines.

The NGS analysis revealed a Tier II pathogenic variant in the *TP53* gene, i.e., p.Gln38ArgfsTer2, with a Variant Allele Frequency (VAF) of 12.1%. NGS was negative for *PLAG1, HMGA2, IDH1/IDH2,* or other alterations. The final integrated diagnosis was Sarcoma Ex Pleomorphic Adenoma (SAExPA), with *a TP53* mutation. However, no actionable alterations were detected.

DISCUSSION
Pleomorphic adenoma (PA):
PA is the commonest benign salivary gland tumour. PAs tend to recur locally if incompletely excised. Overall, the recurrence rate has been estimated at 20% to 45% with enucleation, 3% to 5% with superficial parotidectomy, and 0.4% to 2% with total parotidectomy. [3] Under rare circumstances, PAs can also potentially metastasise to the lymph nodes, lungs, and bones.

Carcinoma Ex Pleomorphic Adenoma (CAExPA):
CAExPA comprises ~3.6% of all salivary gland tumours and ~11.6% of the malignant salivary gland tumours. [4] Approximately 5-15% of all PAs eventually transform into CAExPA. [5] There are three theories of its histogenesis, wherein they seem to either arise from *(i) pluripotential/uncommitted mesenchymal cells, (ii) poorly differentiated carcinomas, or (iii) myoepithelial cells with the potential of multidirectional differentiation.* [6]

Carcinosarcoma Ex Pleomorphic Adenoma (CSExPA):
CSExPA is an extremely rare salivary gland neoplasm comprising 0.04-0.16% of all salivary tumors and about 0.1% of the malignant tumours. The diagnosis of CAExPA or CSExPA depends on the composition of the malignant epithelial and sarcomatous components. The most common sarcomatous component reported in CSExPA is chondrosarcoma. Other sarcomatous components can be fibrosarcoma, leiomyosarcoma, and liposarcoma. [7] Rarely, osteosarcoma, rhabdomyosarcoma, and myxofibrosarcoma have been reported in CSExPA. [8, 9, 10] The malignant epithelial component commonly is a poorly differentiated adenocarcinoma, an undifferentiated carcinoma, or a squamous cell carcinoma. [9] Other epithelial malignancies reported are salivary duct carcinomas. [11,12] Rarer carcinomas include adenoid cystic carcinoma, clear cell carcinoma, sarcomatoid carcinoma, and large cell neuroendocrine carcinoma. [12,13,14] At times, myoepithelial carcinoma has been reported to occur in CSExPA. [15] Certain useful immunohistochemical markers are used to demonstrate the malignant epithelial or sarcomatous components, shown in Table 1.

Table 1: Useful IHC markers to differentiate the carcinoma/sarcoma component in CSExPA.

Component	Carcinoma/Sarcoma type	IHC markers
Epithelial / Myoepithelial	Salivary duct carcinoma	CK7, EMA, HER2, AR, p53
	Myoepithelial carcinoma	Calponin, p63, p40, SMMHC, SOX10, PLAG1
	Mucoepidermoid carcinoma	CK7, CK5/6, p63
	Adenoid cystic carcinoma	CK7, S100, SMA, p63, Calponin, CD117, SOX10
	Clear cell carcinoma	CK7, HMWCK, AE1/AE3, p63, EMA
Myoepithelial	Chondrosarcoma	Vimentin, S100
	Fibrosarcoma	Vimentin, PTAH
	Leiomyosarcoma	Vimentin, SMA, MSA, Desmin, h-caldesmon
	Liposarcoma	Vimentin, S100, MDM2, CDK4, CD34, HMGA2
	Osteosarcoma	Vimentin, SATB2, KPNA2
	Rhabdomyosarcoma	Vimentin, Desmin, Myogenin, MyoD1
	Myxofibrosarcoma	Vimentin, SMA, MSA, CD34

Sarcoma Ex Pleomorphic Adenoma (SAExPA):
SAExPA can be defined as a sarcomatous transformation of a pre-existing PA. Pure sarcomas of the salivary gland are exceptionally rare, with only a few case reports arising in the parotid gland.

Molecular alterations in PA, CAExPA, and CSExPA:
The *PLAG1* (Ch 8q12) and *HMGA2* (Ch 12q14-15) fusions, either of which have been found in ~70% of PAs, may be helpful in the diagnosis of CAExPA or CSExPA. However, only 36.4% of CAExPA harbour *PLAG1* fusions, the most common being *CTNNB1::PLAG1*.[16] *PLAG1* rearrangements, especially *CTTNNB1::PLAG1*, have been reported in ~20-70% of CSExPA cases. *HMGA2* rearrangements are much rarer, and no specific fusion partner has been identified. Some recognised fusion partners of the *PLAG1* and *HMGA2* genes, along with their associated salivary tumours, are shown in Table 2.

Table 2: Common mutations and their fusion partners found in PA and CAExPA.

Primary Gene	Common fusion partners	Tumours found in
PLAG1 ∗ fusions	*LIFR::PLAG1*	PA, CAExPA
	CTNNB1::PLAG1	PA
	CHCHD7::PLAG1	PA
	FGFR1::PLAG1	PA, CAExPA
	ND4::PLAG1	CAExPA
	NFIB::PLAG1	PA
	TGFBR3::PLAG1	CAExPA
HMGA2 ∗ fusions	*HMGA2::WIF1*	PA, CAExPA
	HMGA2::NFIB	PA
	HMGA2::TMTC2	PA (metastasising)
PA = Pleomorphic adenoma, CAExPA = Carcinoma ex pleomorphic adenoma		

***TP53* mutations:**
Loss-of-function mutations in the *TP53* gene are among the most frequent genetic alterations across human cancers. *TP53* mutations have also been found in salivary gland sarcomas, particularly carcinosarcomas. They contribute to the sarcomatous progression of the tumour, with mutations often involving exons 5 to 8 of chromosome 17p.13.1. [17] The *TP53* mutations in malignant salivary gland tumours are generally associated with solid histology, advanced stage, lymph node/distant metastasis, a more aggressive clinical course and poorer 5-year overall survival. [18]

Treatment and prognosis:
The prognosis of SAExPA of the submandibular gland is not well understood owing to the paucity of case reports. However, in a systematic review of parotid gland sarcomas, multivariate analysis identified surgery as the only parameter associated with long-term survival. Prognosis depended on the size and extent of the tumour, lymph node involvement, and its histological type. Additionally, the role of RT in parotid gland sarcomas has not been analysed in detail. There are no systematic reviews or meta-analyses at present. [19]

Wang J et al., in a systematic review & meta-analysis, concluded that post-operative radiation therapy offers favourable long-term efficacy & safety in locally advanced salivary gland carcinomas. [20]

With a similar intent, our patient received 66 Gy (2.2 Gy/fraction) RT over 6 weeks postoperatively and is currently on follow-up with no evidence of recurrence.

CONCLUSION
SAExPA should be distinguished from CAExPA due to its dismal prognosis. SAExPA is a fatal, extremely

aggressive malignancy with a high potential for local recurrence and distant metastasis. Median survival reported at 10 months after diagnosis is 63%. Most CAExPA metastasise to the lungs, with an occasional case study reporting abdominal metastases. Pure sarcomas arising in recurrent PA of the submandibular gland are unheard of. Primary sarcomas of the salivary gland are associated with high rates of recurrence, metastasis & frequently mortality. Given the lack of existing literature, our report may be the first case of pure sarcomatous transformation of a recurrent PA of the submandibular gland. However, deep-diving into its genetic and molecular landscape is essential for understanding its natural evolution and identifying new therapeutic targets.

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