Synovial Sarcoma of the Hypopharynx in a Filipino Female: A Case Report

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ABSTRACT

Synovial sarcoma of the hypopharynx is an uncommon malignancy, with less than 100 cases reported in available journals. We report a case of a 22-year-old female presenting with dysphagia and enlarging hypopharyngeal mass, clinically diagnosed as hypopharyngeal malignancy, right, at least stage III. Histopathologic examination including immunohistochemistry study with TLE1 and *SS18* Fluorescence In Situ Hybridization (FISH) confirm the diagnosis of synovial sarcoma. This is the first reported case of synovial sarcoma of the hypopharynx in the Philippines confirmed by *SS18* FISH. Due to the size of the mass, chemoradiotherapy followed by surgery is the current plan of management for this patient.

Keywords: sarcoma, synovial, case report, hypopharynx

INTRODUCTION

Synovial sarcoma is a tumor of uncertain differentiation, described as a monomorphic blue spindle cell sarcoma with variable epithelial differentiation, characterized by a specific *SS18-SSX1/2/4* fusion gene mutation.[1] Majority of cases (70%) are found in the soft tissues of both extremities. These are rare when found in the head and neck (7%), particularly the hypopharynx, with less than 100 cases reported in the English literature.[2] The first case was reported in 1954, which was a 21-year-old male presenting with dysphagia that eventually expired post laryngoscopy.[3] Patients usually present with dysphagia, dyspnea, and an enlarging neck mass. Historically, diagnosis was made on histomorphologic features alone. However, due to the discovery of immunohistochemical and molecular studies, confirmation of diagnosis is now made by using FISH to demonstrate *SS18* rearrangements that is positive 90% of the time.[4] In the Philippines, only one similar case was previously reported in 1991, which was in a 29-year-old female treated surgically.[5] No molecular studies done at that time. Complete surgical resection is usually the cornerstone of treatment.[6] These tumors are also observed in pediatric patients.[6,7] However, tumor debulking with chemotherapy and radiotherapy is recommended for large tumors. In this paper, we present a 22-year-old female with enlarging hypopharyngeal mass and progressive dysphagia.

CASE PRESENTATION

This is a case of a 22-year-old female presenting with 3-month history of enlarging hypopharyngeal mass, accompanied by progressive dysphagia, odynophagia, and weight loss. Past medical, family, and psychosocial histories

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of the patient are generally unremarkable. The patient initially sought consults at multiple provincial hospitals wherein she was given unrecalled medications and advised for imaging studies and referral to a specialist. However, she was lost to follow-up due to financial constraints. One week prior to consult, patient started experiencing progressive dyspnea and hoarseness due to the mass effects of the tumor. An episode of hematemesis of around 200 cc made the patient seek consult at the Emergency Room of our institution. The patient arrived tachypneic and hypoxemic, hence emergency tracheostomy was done (Figure 1). Patient went into cardiac arrest, but was eventually revived and stabilized. Initial CT scan revealed a 7.2 x 5.6 x 3.4 cm (CC x W x AP) heterogeneously-enhancing mass in the region of the hypopharynx, more on the right, spanning the levels of C3 to C7, highly suggesting a neoplastic process. The mass completely obstructs the oropharyngeal and supraglottic lumen at the levels of C3 to C4. Anteriorly and inferiorly, it compresses the laryngeal structures with poor plane of differentiation along the posterior surfaces and there is suspicious involvement of the right aspect of epiglottis. It also abuts the base of the tongue. The mass is also in close proximity and cannot be clearly delineated from the adjacent right tonsillar pillar and right prevertebral muscle. Superiorly, it abuts the medial aspect of the bilateral thyroid lobes with no gross infiltration. There is ill-definition of the cervical esophagus from the mass. Clinical assessment was hypopharyngeal malignancy, right, at least stage III (T3N0M0). Endoscopic biopsy was done on the tumor and the specimen was sent for histopathologic examination.

Afterwards, plans for possible surgery were discussed. However, because of the size of the tumor and its close relation to the nearby structures, a decision to start systemic neoadjuvant chemotherapy to at least shrink the tumor before operation was made. On subsequent admissions, patient was scheduled for AIM protocol Doxorubicin (25 mg/m^2), MESNA (1800 mg/m^2), Ifosfamide (3000 mg/m^2) by Medical oncology. Tentative plan is to maximize upfront systemic chemotherapy, followed by concurrent chemoradiotherapy and the palliative radiotherapy alone, depending on the response of the tumor. Currently, the patient is still ongoing systemic chemotherapy (4th cycle).

GROSS AND MICROSCOPIC FINDINGS

Grossly, the specimen labeled as "mass from R base of tongue" consists of an irregularly-shaped, dark brown to tan grey, firm tissue measuring 3.4 cm x 3.0 cm x 2.5 cm. Cut sections show dull, homogenous, tan-brown cut surfaces. Representative sections are then taken.

On microscopy, low power magnification shows that the tumor is hypercellular and arranged in dense sheets or fascicles with occasional herringbone architecture (Figure 2). On higher power magnification, the tumor is made up of blue spindle shaped cells with scant to moderate amount of cytoplasm, ovoid hyperchromatic nuclei with granular chromatin and inconspicuous nucleoli (Figure 3). No areas of necrosis seen and the mitotic count is 5 mitoses per 10 high power fields.

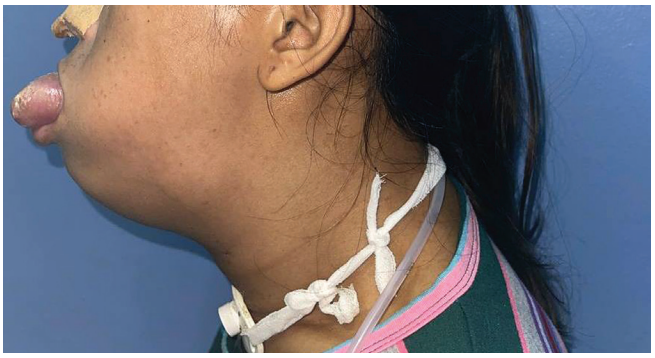

Figure 1. External examination of the hypopharyngeal mass post tracheostomy. The mass occupies the hypopharynx and extends to the oral area, hence pushing the tongue out.

Initial immunohistochemistry studies with EMA (Epithelial Membrane Antigen) showed very focal positive staining in tumor cells, while SMA (Smooth Muscle Antigen), Pancytokeratin, CD34, S-100 and Desmin were all negative. TLE1 (Transducin-like enhancer of split 1) was requested and showed strong, diffuse, nuclear staining in tumor cells (Figure 4), compatible with synovial sarcoma. FISH was done to detect *SS18* rearrangements showing 87% of nuclei with break apart signals (Figure 5). Hence, the case is positive for *SS18* translocation, confirming the diagnosis.

DISCUSSION

Synovial sarcoma is a tumor of uncertain differentiation, usually described as spindle cell tumor showing variable epithelial differentiation with a characteristic *SS18::SSX1/2/4* fusion gene.[1] The term is a misnomer because it does not arise from the joint synovium but rather is believed to be from the mesodermal cells that differentiate into synovium-like tissues.[5] Thus, it is virtually reported in various anatomic sites and should be considered as a differential for any spindle cell lesion.

Clinical diagnosis of synovial sarcoma of the hypopharynx is difficult due to its low frequency, variable nonspecific symptoms, and that the manifestations appear once the tumor is large enough to create mass effects on adjacent structures.[2] The age of presentation is also variable and encompasses all ages from the pediatric[7] to the geriatric age group[4].

Historically, the histopathologic diagnosis used to be dependent on morphology alone. There are two forms of synovial sarcoma. The biphasic type has epithelial and sarcomatous components of varying proportions, hence it contains epithelial cells arranged in solid nests, cords,

or glands and spindle shaped cells arranged in dense cellular sheets. The monophasic type contains only either an epithelial or spindle cell component but it comprises majority of synovial sarcoma cases.[1] Immunohistochemically, synovial sarcoma usually shows positivity for cytokeratin in epithelial and sarcomatous areas, though patchy in the latter component. Other markers that may be positive include cytokeratin 7 and 19[8], desmoplakin ZO-1, claudin-1 and occludin[9]. Epithelial membrane antigen is usually positive, while S-100 can be focal.[8] Staining with Transducin-like enhancer of split 1 (TLE1) antibodies is usually diffusely positive. TLE1 is a transcriptional repressor that can form a complex with the *SS18::SSX* fusion gene formed during the translocation that occurs in synovial sarcoma. This complex, together with activating transcription factor 2 (ATF2), binds to a promoter early growth response 1 (EGR1) causing transcriptional dysregulation and oncogenesis.[10] In a meta-analysis done in 2020, TLE1 immunohistochemical staining showed a mean sensitivity and specificity for synovial sarcoma of 94% and 81%, respectively.[11] However, it is not exclusive to synovial sarcoma and is also seen in peripheral nerve sheath tumors and variably expressed in some nonneoplastic tissues

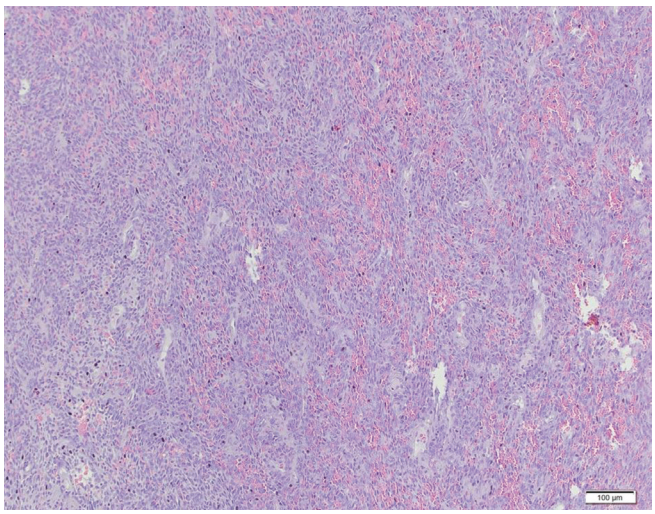

Figure 2. Low power magnification shows that the tumor cells are arranged in dense cellular sheets *(Stain: Hematoxylin and Eosin, Magnification: 100x).*

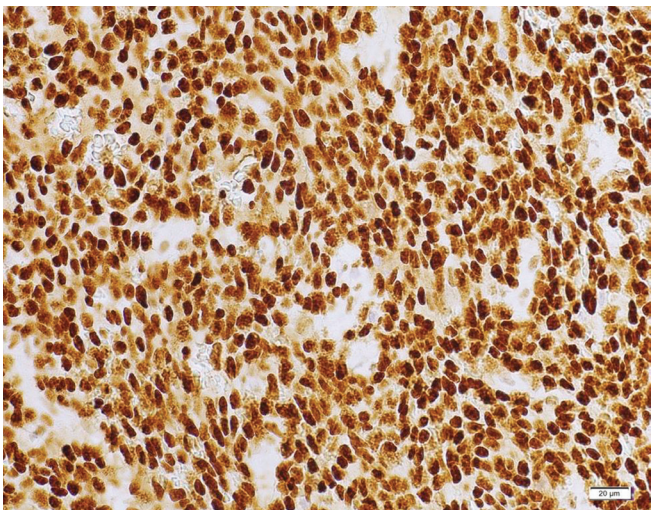

Figure 4. Immunohistochemistry study with TLE1 *(Transducin-like enhancer of split 1)* showed strong, diffuse, nuclear staining in tumor cells *(Stain: TLE1, Magnification: 400x).*

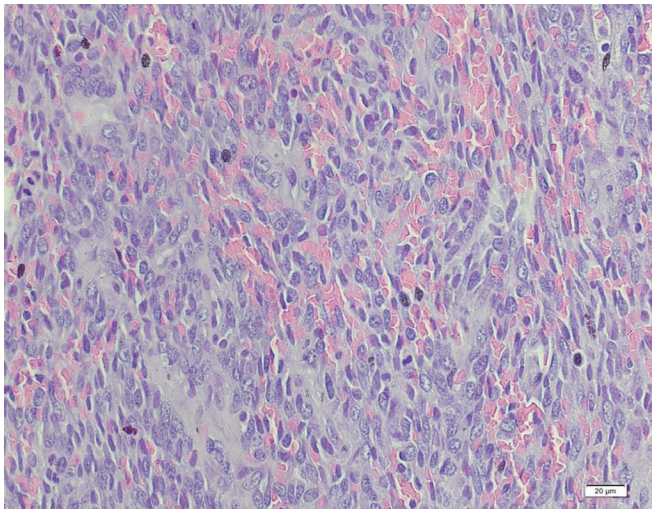

Figure 3. Higher power magnification shows that the tumor is composed of spindle cells with scant to moderate cytoplasm, ovoid to spindle shaped nucleoli with granular chromatin and inconspicuous nucleoli *(Stain: Hematoxylin and Eosin, Magnification: 400x).*

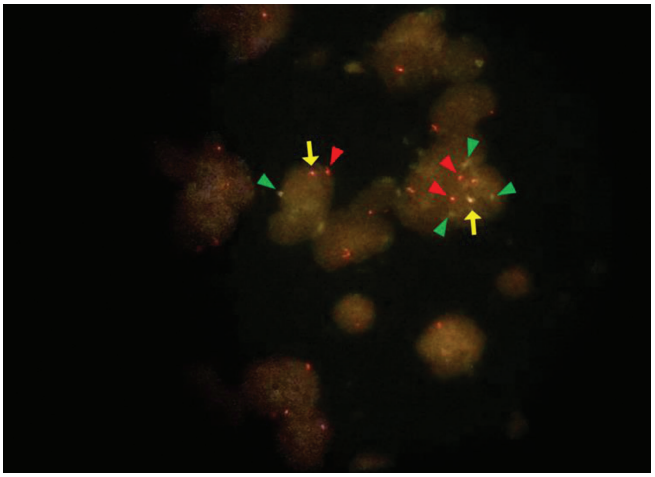

Figure 5. FISH showing nuclei with the normal fused signals *(yellow arrows)* with the break apart signals *(red and green arrowheads)* confirming SS18 rearrangement.

including basal keratinocytes, adipocytes, perineural cells, endothelial and mesothelial cells.[12] A study done by Terry et al. showed that only molecularly confirmed synovial sarcomas (97% of cases tested positive) demonstrated intense (2+ to 3+), diffuse, nuclear staining for TLE1. Hemangiopericytomas (40%), schwannomas (31%), solitary fibrous tumor (27%), and fibroxanthoma (25%) came next but demonstrated only moderate staining (1+ to 2+), while the 40 other tested mesenchymal tumors showed less than 20% positivity and very weak staining (0 to 1+).[13]

The advent of molecular studies brought about greater understanding of the tumor oncogenesis of synovial sarcoma. Since the initial description of a t(X;18)(p11.2;q11.2) chromosomal translocation in synovial sarcoma cases[14], several studies have followed and were published showing the high prevalence of this translocation in this kind of tumor and that it is seen almost exclusively in all synovial sarcoma cases and not in other tumors[15]. This translocation creates fusion products of the *SS18* gene with other genes, particularly *SSX1, SSX2* and *SSX4*, which can be detected by FISH. Some assays make use of break-apart probes, which was the one utilized in this case. Break apart probes target the two ends of a specific gene sequence. Therefore, if the gene sequence is intact, the two probes should be in close proximity with each other and will fluoresce as a single fusion signal. However, if translocation occurred, one of the probes will be in another location, hence a break apart signal is observed. Break apart probes are nonspecific because they can only detect that a translocation took place but not the type of fusion product that was made. Thus, molecular studies may supplement histomorphologic and immunohistochemical studies in the diagnosis of synovial sarcoma.

Management of synovial sarcoma, as with other malignancies, is tailored to each individual case, but the cornerstone treatment still remains to be surgery with negative margins.[16] Since synovial sarcoma is often found in extremities, historically, patients were treated with amputation. Luckily, advances in surgical techniques helped develop limb-salvaging procedures in the present times. Neoadjuvant chemoradiotherapy may be done for larger tumors (>5 cm) or for tumors that are in close proximity to major neurovascular structure or vital organ. Intensity-modulated radiation therapy (IMRT) and anthracycline-based chemotherapy with the addition of ifosfamide are usually the preferred regimen for synovial sarcoma cases. Prognosis greatly varies, and worse outcomes are observed in patients with older age, larger tumor size and those with neurovascular or osseous invasion. Late recurrence is also observed, hence longer follow-up schedules are usually recommended.

CONCLUSION

In summary, this is the first reported case of synovial sarcoma in the hypopharynx in the Philippines that was confirmed by *SS18* FISH. This case report demonstrates the importance of molecular testing in these rare sarcomas which do not present with a straightforward clinical and histopathologic presentation. We also emphasized the significance of knowing the immunohistochemical pattern for these cases, especially in centers who do not have advanced molecular testing capabilities. For this case, the patient is currently still undergoing chemoradiotherapy, while awaiting plans for surgery.

Informed Consent

Consent from the patient was secured prior to the reporting of this case.

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Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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