Case Report:
Cytological Diagnosis of Rare Synchronous Primary Malignancies

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Abstract: Introduction: Synchronous tumours are rare. The defining criteria is the occurrence of more than one tumour simultaneously or within a span of six months, having different histology and involving different organs. Similarly, distinction of a metastatic lesion from the primary tumour is imperative and has diagnostic and prognostic implications. Here we report of rare occurrence of polymorphous low-grade adenocarcinoma (PLGA) of minor salivary gland and diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) in a 70-year-old female diagnosed at fine needle aspiration cytology (FNAC). Case report: A 70-year female presented with swelling over the right side of the cheek and left lobe of thyroid for 3 months. Cheek swelling was 4 x 4 cm, well defined, firm and with smooth external surface. Thyroid swelling left sided 3 x 3 cm, solitary and firm to hard. FNAC from the cheek swelling showed papillae, acini, nuclear crowding, overlapping, fine chromatin, nuclear clearing, nuclear grooving and basement membrane material favouring a diagnosis of low-grade epithelial malignancy possible PLGA. Thyroid FNAC smears showed typical features of papillary thyroid carcinoma (PTC) along with areas of extensive squamous metaplasia. Diagnosis of both the cases were confirmed at histopathology. Conclusions: Synchronous malignant tumours of head and neck region is rare. Both PLGA and DSVPTC show common features like papillae formation, nuclear features and squamous metaplastic cytoplasm. Accurate diagnosis of these lesions is challenging at cytology. Cytopathologist should be aware of this novel entity to avoid misdiagnosis and plan proper management. Key Words: Synchronous, Minor salivary gland tumours, Cytomorphology, Multiple primary malignancies.

Introduction:
Multiple primary cancers (MPC) are defined as the occurrence of multiple malignancies that develop from different tissues with distinct morphologies. MPC can be either synchronous or metachronous. [1] Synchronous primary malignancy is defined as two or more neoplasms identified simultaneously or up to six months after the initial diagnosis in the same patient. Metachronous primary malignancy is defined as a second primary lesion identified six months after the detection of the first cancer and located not more than 3 cm from the anastomosis.[2] Patients with cancers in the head and region are at increased risk of developing synchronous primary cancers,[3] The overall prevalence of multiple primary malignancies is between 0.73% and 17%. About 3-5% of MPM are secondary, only 0.5% are triple tumours, whilst quadruple tumours occur in 0.3% cases. The possibility of developing a second metachronous cancer 5 years after undergoing treatment of the initial head and neck cancer is approximately 22%.[4] Multiple primaries are seen in about 9.7% of head and neck cancer patients including metachronous and synchronous malignancy of which 46.9% presents as synchronous.[3] The outcome of patients with head and neck cancers are influenced by several factors, one among it being the development of second malignancy which further worsens the prognosis of these patients. Therefore, early recognition and detection of these tumours is essential.[5] A pre-operative diagnosis is particularly important as surgery or radiation/ chemoradiation can be offered simultaneously as indicated, therefore reducing the associated morbidity and cost of multiple treatments.[6] Data regarding the occurrence and the outcome of MPC from the Indian subcontinent are limited.[7] Herein we report a rare case of synchronous malignancies arising in minor salivary gland and thyroid and review the cytology of these lesions.

Case Report
A 70-year female presented with swelling over the right side of the cheek (shown in Fig. 1). The swelling was noticed by the patient three months back. The lesion was initially small, a size of a pea and had since grown gradually to the present size.
of 4 x 4 cm. There was no history of pain at the site of swelling. On local examination, the swelling was well defined, easily mobile, firm and with smooth external surface. Skin above the swelling was normal. There was no evidence of any lymphadenopathy in the cervical, submandibular or submental region. The patient did not have any history of diabetes mellitus, hypertension, renal, cardiovascular disease or malignancy in the past. Her family history was unremarkable. At ultrasound a diagnosis of soft tissue sarcoma was suggested.

FNAC was done by standard technique using 22-gauge needle with syringe attached to it. The ethanol fixed smears were stained with haematoxylin and eosin and pap stain while the air-dried smears were stained with Giemsa stain. FNAC smears were cellular. Smears showed tumour cells arranged predominantly in papillary pattern that is clusters of tumour cells clinging to endothelial strands, (Fig. 2 a) sheets clusters and occasional acinar formation (shown in Fig. 2 b). The individual cells were uniform round with evidence of nuclear crowding, overlapping, fine chromatin, and nuclear grooving (shown in Fig. 2 c). Background showed basement membrane material (shown in Fig. 2 d). An FNAC diagnosis of low-grade epithelial malignancy of salivary gland origin, suggesting a possibility of PLGA was made. She was scheduled for excision coming week but she came back three days later with the complaint of swelling in the thyroid region which she had noticed a day before (shown in Fig. 3). There was no history of pain in the swelling. There was no history of fever, alteration in the weight, palpitation or tremors in the hands.

Laboratory studies revealed that she was euthyroid, her antithyroglobulin antibody and antithyroid peroxidase antibody were normal. On local examination, the swelling was diffuse involving both lobes of thyroid. It was 5.5 x 4.5 cm in size and firm to hard in consistency. The swelling moved with deglutition but not with the protrusion of the tongue. Provisional clinical diagnosis of thyroiditis was made. At ultrasonography the thyroid was diffusely enlarged with heterogeneous echotexture. Multiple areas of microcalcification were noted. Possibility of malignancy was suggested at ultrasonography.

FNAC of thyroid was done by standard technique using 22-gauge needle. Non aspiration technique was used initially. When material was found to be less, repeat FNAC by aspiration technique was performed.

Smears were fixed, air dried and stained with haematoxylin and eosin and pap stain and Giemsa stain respectively. FNAC smears from thyroid swelling showed moderate cellularity. Smears showed tumour cells arranged in sheets with anatomical bordering. The tumour cells showed crowding and overlapping. The nuclei demonstrated pale chromatin with irregular nuclear membranes, frequent intranuclear pseudo-inclusions and nuclear grooving. There was extensive squamous metaplasia amongst the tumour cells (shown in Fig. 3 b & c).

In view of the overlapping cytomorphological features of the thyroid lesion with that of the cheek lesion, there was a diagnostic dilemma where in following possibilities were considered
1. Two primaries occurring synchronously, one being low grade epithelial malignancy of salivary gland origin in the cheek and the other being papillary thyroid carcinoma in the thyroid gland.
2. Metastasis of papillary thyroid carcinoma to the cheek
3. Metastasis of low-grade epithelial malignancy of salivary gland origin to the thyroid

Following this, the FNAC smears of both the lesions were revisited, literature reviewed and a cautious diagnosis of Synchronous malignancies of Polymorphous low-grade adenocarcinoma of minor salivary gland and papillary carcinoma of thyroid gland with extensive squamous metaplasia was rendered. Histopathological evaluation for further management was suggested. Patient and patient’s relatives were briefed about the diagnosis, management plan and future complications if any.

A multidisciplinary team comprising of ENT and Head and neck surgeon, onco surgeon and a general surgeon operated on the case. The surgery decided upon was wide local excision of the minor salivary gland tumour and total thyroidectomy with radical neck dissection. At surgery the minor salivary gland tumour was excised uneventfully. However, during total thyroidectomy, the operating team felt difficulty in removing the thyroid as the tumour was felt adherent to the surrounding structures. The formalin fixed specimen of both the tumours were received in the histopathology department. The grossing was done as per the standard protocol after inking the surgical margins.

**Gross Specimen of minor salivary gland tumour**: The specimen was 4.5 x 3.5 x 2.5 cm with smooth external surface. The cut surface showed a tumour measuring 4 x 4 cm, which had irregular margins, was homogenous grey white and firm in consistency (shown in Fig. 4). No evidence of necrosis was noted. FNAC site haemorrhage was observed.

**Gross Specimen of thyroid tumour**: The total thyroidectomy specimen measure 6 x 6 x 5.5 cm. External surface was smooth with intact capsule. Cut surface was uniform grey white with friable amidst hard areas (shown in Fig. 5). Areas of cystic change and necrosis were noted. Neck dissection specimen revealed 12 lymph nodes, all very negative for malignancy. Representative bits from both the tumours were given. Processing was done by routine procedure, paraffin embedding and cutting the slide were prepared and stained with haematoxylin and eosin stain.

**Histopathology of cheek tumour**: Sections studied shows stratified squamous epithelium with hyperplasia, focal ulceration covered with exudates. Subepithelial tissue showed a poorly circumscribed, unencapsulated infiltrating tumour showing a variegated appearance. Tumour cells were arranged predominantly in solid sheets, cribriform, papillary, tubules, tubulopapillary, focal trabecular and cystic papillary pattern. The tubules were round to elongated at places forming complex tubulo glandular architecture (shown in Fig. 6. a & b). At places streaming of narrow tubules was noted. The cribriform as well as other areas showed extensive extracellular mucin. Individual tumour cells were uniform with moderate pale eosinophilic cytoplasm with round to oval nuclei showing vesicular chromatin and occasional nuclear grooving (shown in Fig. 6 c & d). Clear cells, mucinous, oncocytic and squamous differentiation was noted. Perineural invasion and extension into surrounding salivary gland tissue was noted.

**Fig. 1**: Swelling over the right side of the cheek
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Fig. 2. a: FNAC smears showing papillae (Inset shows endothelial traversing) [H & E, X 100] Fig. 2. b: FNAC smears showing acini formation (Inset shows normal acini) [H & E, X 100] Fig. 2. c: FNAC smears showing mild nucleomegaly, nuclear crowding and overlapping. [H & E, X 400] Fig. 2. d: FNAC smears showing basement membrane material and hyaline globules (Inset shows cyst macrophages) [Giemsa, X 100]

Fig. 3. a: Swelling in the thyroid region. Fig. 3. b: FNAC smears showing papillae (Inset shows intranuclear cytoplasmic inclusions) [Giemsa, X 100] Fig. 3. c: FNAC smears showing metaplastic cytoplasm (Inset shows chewing gum colloid) [Giemsa, X 100]

Fig. 4: Cut surface of salivary gland tumour showing solid, homogenous, grey whit tumour with irregular margins.

Fig. 5: Cut surface of thyroid lobe showing an irregular, grey white homogenous tumour.

Fig. 6. a: Section showing cribriform pattern. Mucin. (Inset shows cyst macrophages) [H & E, X 100] Fig. 6. b: Section shows complex tubulopapillary pattern (Inset shows tubule pattern) [H & E, X 100] Fig. 6. c: Section shows solid pattern (Inset shows clear cells) [H & E, X 100] Fig. 6. d: Section shows nuclear clearing and grooving [H & E, X 100]

Fig. 7. a: Section shows papillae, squamous metaplasia and sclerosis (Inset shows high power view of squamous metaplasia) [H & E, X 40] Fig. 7. b: Section shows nuclear grooving and nuclear clearing (Inset shows eosinophils) [H & E, X 400]

Histopathology of thyroid tumour: Sections showed extensive areas of sclerosis with islands of tumour cells embedded within it were noted. Tumour cells were arranged in papillary pattern with classical nuclear features of papillary thyroid carcinoma. Extensive squamous metaplasia of cytoplasm and psammoma bodies and infiltration into surrounding skeletal muscle was noted (shown in Fig. 7 a & b).

Final diagnosis of Polymorphous low-grade adenocarcinoma of minor salivary gland and sclerosing variant of papillary thyroid carcinoma, rare synchronous malignancies was made. Written informed consent was taken from the patient for publishing the study, using the case data and images for the same.

Discussion

Literature reveals an incidence of multiple primary malignancies (MPM), no specific site, as ranging from 0.3 to 17%. [8] In head and neck region, the incidence of MPM has been reported as to range from 1.3% to 9.7%. In a large series of 4184 cancers of head and neck region, synchronous primary malignancies (SPM) were reported in 56 (1.33%) cases. [3] Metachronous malignancies are more common than synchronous malignancies. Similarly, MPM have been reported to occur at higher frequency in head and neck region [9] These figures represent the western population, data on incidence of MPM from developing countries is scarce.

Preoperative diagnosis of SPM has profound influence on the management and overall survival. Preoperative diagnosis would pave way for a multidisciplinary and patient specific approach. Informed participation from patient is important to avoid unforeseen complications. The present study provides a
data point to the role of FNAC in diagnosis of MPM in a single patient.

In the present case report, overlapping cytomorphonuclear features of polymorphous low-grade adenocarcinoma (PLGA) and diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) and simultaneous presence of both the tumours made the diagnosis challenging at FNAC. In addition, rarity of PLGA and diffuse sclerosing variant of PTC and scarcity of data on the FNAC findings of both the lesions made the diagnosis even more thought-provoking.

Minor salivary gland tumours are rare and account for 15 to 20% of all salivary gland neoplasms, of which malignant tumours contribute to 66% of the cases. [10] The trouble of accessing the intraoral tumours of minor salivary gland origin has led to minimal research and very few studies in this arena of FNAC. [11-15] Sensitivity and specificity of FNAC in MSGL range from 71.4% to 92.59%. However, specificity (97.8% and 100%) and diagnostic accuracy in the literature (87.7% and 100%) is high. [11] PLGA is the second most common and exclusive tumour of minor salivary gland. In a study by Subrata et al, out of 42 cases of minor salivary gland neoplasm examined, only two were of PLGA. Though palate is the most common site of PLGA, it has been reported to occur in the tongue, lip [16] buccal mucosa, retromolar region and tonsil. [17] Architectural diversity and cytomorphological uniformity are the defining feature of this low-grade malignancy. Blad appearance of nuclei has traditionally led to high false negative diagnosis at FNAC, even in locally aggressive tumours. In a retrospective analysis of 42 cases of intra and extra oral MSGL, Subrata et al reported two false negative cases, both being PLGA which were misdiagnosed as pleomorphic adenoma (PA) on cytology. Similar interpretation error was reported by Gupta N et al in which, one case of PLGA it was falsely diagnosed as PA on cytology. In a study by Gibbons et al, two cases of PLGA were initially misconstrued as adenoid cystic carcinoma (ADCC). [14] In a study involving two cases of primary PLGA of parotid gland and three metastatic PLGA, accurate preoperative FNAC diagnosis was possible in only one primary case and two metastatic tumours which had an initial histopathology confirmed PLGA of salivary gland. [18] PLGA need to be differentiated from plethora of benign and malignant tumours of salivary gland origin (pleomorphic adenoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, basal cell adenoma and epithelial myoepithelial carcinoma) on cytology. Pleomorphic adenoma is common in minor salivary gland. Nevertheless, absence of plasmacytoid cells and chondromyxoid fibillary stroma aids to rule out pleomorphic adenoma. Presence of uniform nuclei and hyaline globules as were seen in the present study, brings adenoid cystic carcinoma in the differential diagnosis of PLGA. However, hyperchromatic nuclei, nuclear moulding, cribriform arrangement and cup shaped structures made by tumour cells are distinctive of ADCC. Basal cell adenoma is rare in minor salivary gland. Epithelial myoepithelial carcinoma shows a characteristic dual population of small cuboidal cells in sheets representing epithelial cells and loose clusters of cells with pale vacuolated cytoplasm or bare nuclei indicating myoepithelial cells. Hyaline globules and basement membrane material noted in PLGA can be seen in pleomorphic adenoma, basal cell adenoma, ADCC and epithelial myoepithelial carcinoma. Reliance on stromal globules usually results in erroneous diagnosis. Careful attention to the nuclear details along with clinical and radiological data aids in accurate diagnosis.[18] Presence of tumour cells with rounded to short spindled cells, cellular palisading around the myxoid stromal tumour formation and tumour cells clinging to the endothelial strands (papillary tumour fragments), liner cell groups and basement membrane material are useful clue to the diagnosis of PLGA at FNAC. [14]

At histopathology, PLGA reproduces the features seen at cytology. The nuclei in PLGA are pale, with washed out appearance akin to PTC. Therefore, in the present study, a possibility of metastatic deposits from thyroid to check or vice versa was also considered. However, the presence of concentric arrangement of tubules and cords of tumour cells reminiscent of a targetoid appearance, perineural invasion and infiltration into the surrounding normal salivary tissue supports the diagnosis of PLGA. Though clinic radiologic correlation accompanied by morphologic and immunohistochemistry is fairly diagnostic, immunoreactivity for cytokeratin, EMA and S100, over expression of BCL2 and negative staining for GFAP is noted in PLGA. [14]

DSVPTC is a rare variant (0.1% and 6% of all PTC) and is characterized by presence of extrathyroidal extension, high rate of lymph node metastasis (70 to 93%), high lymph node disease burden and pulmonary metastasis (13%). [20] This makes the preoperative diagnosis imperative for planning aggressive treatment to ensure good survival. Ultrasound findings of this rare variant though characteristic, are sometimes misleading, leading to delay in treatment. At histopathology, DSVPTC shows focal tumour nests amidst the sclerotic stromal, patchy but moderately dense lymphocytic infiltrate, multiple psammoma bodies and extensive squamous metaplasia. Clinical, radiological and cytological features singly or in combination often points towards the diagnosis of Hashimoto’s thyroiditis. Chen CC et al and Bongiovanni M have reported the challenges in preoperative diagnosing DSVPTC. [21,22] The importance of aspiration from multiple sites to obtain representative tumour cells cannot be overemphasized. The difficulties in diagnosis of DSVPTC has been illustrated in various case series published so far. [20-23] In a study by Fujimoto [23] involving 14 cases of DSVPTC, four cases were misinterpreted as Hashimoto’ thyroiditis. In the present case, diagnosis of PTC was not problematic as nuclear features of tumour cells were quite characteristic. Presence of extensive squamous metaplasia in tumour cells prompted us to consider DSVPTC at cytology, which was later confirmed on histopathology.

It is rare for DSVPTC to occur in older population, as in the present study. In a study by et al, of case series involving 30 DSVPTC, the predominant age group affected was the younger population. Aggressive surgical intervention in the form of total thyroidectomy with radical central and bilateral neck dissection followed by radio iodine treatment and regular follow-up is recommended for DSVPTC. Hence accurate preoperative diagnosis and proper communication with the clinician is the key to best outcome.

Conclusion:
Synchronous malignant tumours of head and neck region is rare. Both PLGA and SV of PTC show common features like papillae formation, nuclear features and squamous metaplastic cytoplasm. Accurate diagnosis of these lesions is challenging at cytology. Cytopathologist should be aware of this novel entity to avoid misdiagnosis and plan proper management.

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Statement of Ethics
The case report follows the guidelines for human studies and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.
Informed written consent for publishing the study and using the images was taken from the patient.

References:


