

## Undifferentiated (Anaplastic) Carcinoma of The Thyroid with Abundant Mucin Production: A Rare Presentation Causing Diagnostic Difficulty

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### ABSTRACT

Most pathologists are unaware that thyroid gland also produces mucin; often associated with typical thyroid carcinoma rather than primary mucinous neoplasm. We report an unusual case of anaplastic carcinoma of thyroid presenting with abundant extracellular mucin. A 65 year old lady presented with painless, neck swelling since 7-8 months. Thyroid function tests were within normal limits. Imaging suggested neoplastic aetiology of thyroid. Cytology revealed abundant extracellular mucin with occasional large atypical cells. Hence, metastasis followed by primary mucinous thyroid carcinoma was considered. After excluding secondary neoplasms, total thyroidectomy with lymphadenectomy was performed. Histopathology revealed an infiltrative tumour with abundant mucin & necrosis amidst fibrotic bands. Tumour cells were arranged in sheets, with features of anaplasia. Focus of papillary thyroid carcinoma also identified. Mucicarmin and Alcian blue special stains were positive. Immunohistochemistry results of positive cytokeratin and negative TTF1, thyroglobulin and calcitonin confirmed our results.

**Keywords:** Anaplastic carcinoma, Extracellular mucin, Mucinous carcinoma, Papillary carcinoma, Thyroid neoplasm

### Introduction

The presence of mucin in endocrine neoplasms is rare, unlike, non-endocrine epithelial tumours. Most pathologists are unaware that the thyroid gland can also produce mucin. Such rarity, often associated with typical thyroid carcinoma rather than primary mucinous neoplasm.<sup>[1-3]</sup> Generally, these tumours produce variable amounts of intracellular or extracellular mucin admixed with areas of typical thyroid carcinoma.<sup>[2-7]</sup> The aim of this article is to describe the cytopathology and corresponding histopathology of an unusual anaplastic carcinoma of thyroid presenting with abundant extracellular mucin and discuss the potential pitfalls related to this phenomenon with review of literature.

### Case Report

We report a 65 year old lady with right sided neck swelling since 7-8 months. The painless swelling was insidious in onset and gradually progressed to current size. On examination, the huge swelling measured 20 x 15 x 10cms, did not move with deglutition and protrusion of the tongue.

Patient's thyroid function tests were within normal limits. Ultra-sonography of neck revealed a large, well defined, heterogeneously enhancing lesion measuring 4.9x6.9x6.7 cms, with hyperechoic and hypoechoic areas and mild internal vascularity within in the right lobe of thyroid. Computed Topography of neck confirmed the neoplastic aetiology arising from the thyroid. Fine needle

aspiration cytology of the thyroid lesion revealed abundant extracellular mucin amidst which occasional large atypical cells were seen. [Figs 1-2] Hence, metastasis from mucinous tumours was considered as our first differential diagnosis; followed by primary mucinous carcinoma of the thyroid. Even after thorough evaluation of the patient, none of her other organs revealed any evidence of tumour. Considering the possibility of primary thyroid neoplasm, total thyroidectomy with nodal dissection was performed.

We received a total thyroidectomy specimen with nodal mass measuring 15x10x7cms. The infiltrative tumour measured 6x5x4cms with thin rim of normal thyroid parenchyma at the periphery. The cut surface was white, soft, and fleshy along with large areas of necrosis. The nodular lymph nodal mass measured 8x8x6cms with greyish white cut surface; few areas were soft and gelatinous with focal haemorrhagic areas. [Fig 3] Extensive histopathological examination revealed an infiltrative tumour with predominant areas of necrosis and cholesterol clefts amidst broad fibrotic bands. [Fig 4] The tumour cells were arranged in sheets, having spindle and polygonal cell morphology with marked pleomorphic, bizarre, hyperchromatic nuclei, prominent nucleoli and atypical mitoses. Occasional scattered tumour giant cells were also noted. [Figs 5-6] Focal area of typical papillary thyroid carcinoma was identified. The nodal mass had similar morphology of tumour cells as well.

The striking nature of abundant extracellular mucin was positive for Mucicarmin and Alcian blue special stains.

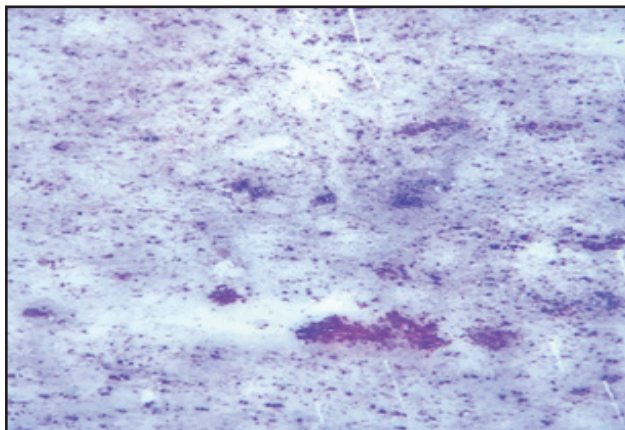
The immunohistochemical examination results of positive cytokeratin and negative Thyroid Transcription Factor-1 (TTF1), thyroglobulin and calcitonin confirmed our results. [Fig 7] Hence, the diagnosis of Undifferentiated

(Anaplastic) Carcinoma with abundant extracellular mucin and regional lymph nodal metastasis was offered in this case.

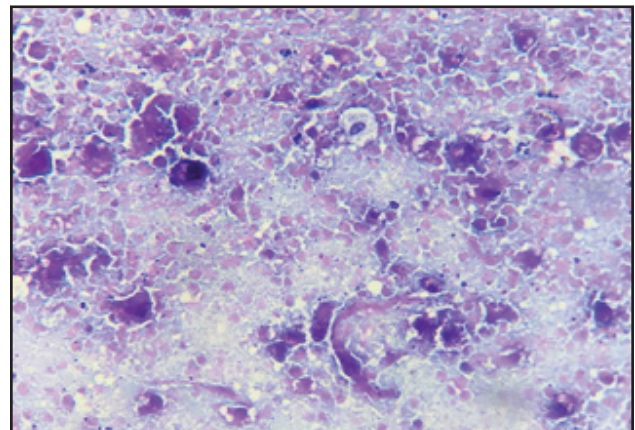
**Table-1: Criteria for differential diagnosis in primary and secondary mucinous thyroid carcinoma.**

ENTITY	HISTOLOGY	Thy*	TTF-1†	CK‡	CEA§	Cal
Primary Mucinous thyroid carcinoma	Mucus pool with transition of solid and glandular areas seen.	+	+	+	-	-
Associated with other typical thyroid carcinoma	<i>MEDULLARY CARCINOMA VARIANT</i> -mucus pool with spindle cells and interstitial amyloid seen.	-	+	+	+	+
	<i>ANAPLASTIC CARCINOMA</i> - mucus pool with pleomorphic, bizarre spindle cells and giant cells seen.	-	Rare	+	<10%	-
Secondary Mucinous thyroid carcinoma	Large mucus pool with small clusters of epithelial cells seen.	-	-	+	Variable	-

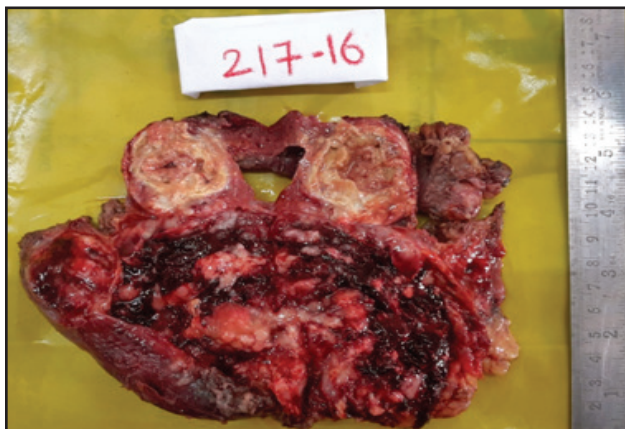
\*.Thyroglobulin, †Thyroid Transcription Factor-1, ‡ Cytokeratin, §Carcinoembryonic Antigen, ||Calcitonin.



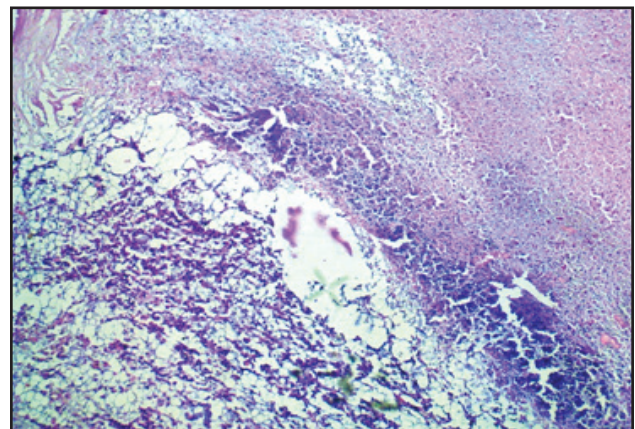
**Fig. 1: GIEMSA (10x) - Abundant extracellular mucin with occasional large atypical cells seen on cytology smears.**



**Fig. 2: GIEMSA (40x) - Few large atypical cells with spindle cytoplasm and macrophages seen in mucinous & necrotic background.**



**Fig. 3: Total thyroidectomy specimen with nodal mass shows an infiltrative tumour with thin peripheral rim of normal thyroid parenchyma. Cut surface is white & fleshy along with areas of necrosis & haemorrhages.**



**Fig. 4: H & E (10x) - Infiltrative tumour with abundant extracellular mucin & areas of necrosis.**

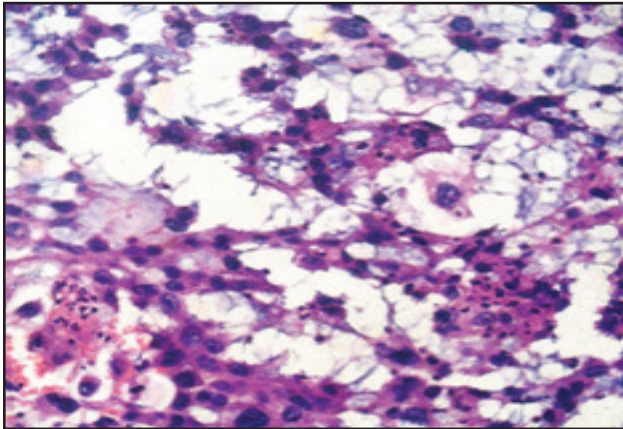


Fig. 5: H & E (40x) - Tumour cells scattered amidst extracellular mucin.

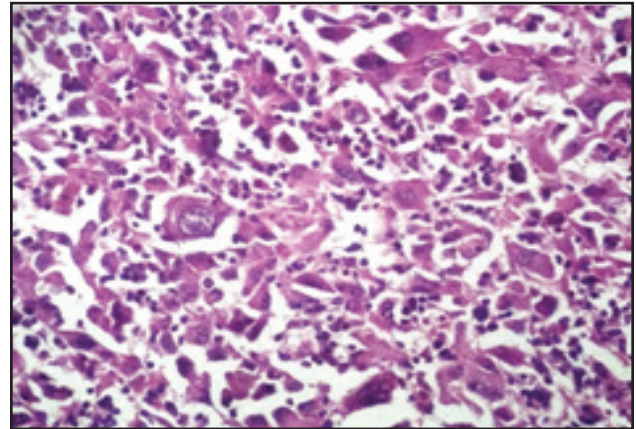


Fig. 6: H & E (40x) - Tumour cells are spindly & polygonal with marked pleomorphic, bizarre, hyperchromatic nuclei & prominent nucleoli.

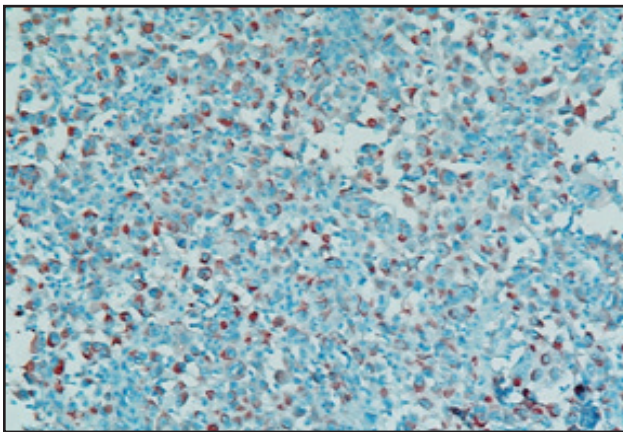


Fig. 7: IHC (40x) - Cytokeratin AE1/AE3 shows strong cytoplasmic positivity in tumour cells.

## Discussion

Mucin, a high molecular weight glycoprotein, is secreted by the epithelium. The embryological origin of the thyroid from endodermal cells of the second and third pharyngeal pouch, supports the mucin association in various tumours of the thyroid.<sup>[1,3]</sup> Mucosubstances detected in several thyroid tumours can be intracellular or extracellular in nature. In 1871, Mueller reported the occurrence of mucin in a thyroid tumour first in the German literature; followed by, Diaz-Perez et al. in 1976 described it in the English literature. Thereafter, mucin production was found in a wide variety of thyroid lesions including follicular neoplasm, papillary carcinoma, anaplastic and medullary carcinoma.<sup>[2,4-7]</sup>

The possible pathogenesis of the mucin in a thyroid neoplasm enumerated as follows:<sup>[8]</sup>

1. Protein-degradation of thyroglobulin implying that mucin is produced by thyroid follicular cells

2. Origin from the ultimobranchial gland
3. solid cell nests
4. Intrathyroidal embryonal nests of salivary gland
5. Thyroglossal duct cyst

When thyroid epithelial cells undergo neoplastic transformation, the mucin gene production may be activated in rare cases. This leads to the paradoxical combination of endocrine and exocrine mucin secretion. Recent discovery of the MUC1 mucin gene, transcripts, and protein in follicular adenoma and papillary carcinoma also confirms this view.<sup>[9]</sup> Such change may influence the invasive and metastatic properties of neoplastic cells by changing cancer cell growth regulation, immune recognition and cell adhesion. Such mucin deposition consists of uniformly sulphated acid mucin, which are stained with Mucicarmine and Alcian blue at pH 2.5 but not with Periodic acid-Schiff, with or without diastase treatment.

The most salient features of our case were mitotically active pleomorphic spindle cells with large areas of necrosis amidst abundant extracellular as well as focal intracellular mucin, surrounded by residual focus of papillary thyroid carcinoma. Mucin producing thyroid tumours documented so far are signet ring follicular adenoma, mucoepidermoid carcinoma, sclerosing mucoepidermoid carcinoma with eosinophilia, papillary carcinoma, undifferentiated (anaplastic) carcinoma, medullary carcinoma and primary mucinous carcinoma.<sup>[1,3,5,8]</sup> Out of these, the main differential diagnosis considered in our case were metastasis from mucinous carcinomas of other regions, primary mucinous carcinoma, medullary carcinoma (spindle cell variant) and undifferentiated (anaplastic) carcinoma. Absence of mucus pool with transition to solid and glandular areas, nests of epithelial cells, amyloid deposits on histology

along with radiological evidence of negative primaries elsewhere narrowed down our differentials. Furthermore characteristic IHC staining confirmed our results. [Table-1]

Literature so far have found focal extracellular and intracellular mucin expression significantly higher in medullary carcinomas (42% to 50%) and papillary carcinoma (57.5%) than in follicular (35%) and anaplastic variants (21%).<sup>[5]</sup> However, treatment and clinical prognosis are similar to those of typical thyroid carcinoma counterpart.

### Conclusion

To our knowledge, abundant extracellular mucin associated with undifferentiated (anaplastic) carcinoma is barely reported till date. Mucinous change is one of the several histological changes occurring in thyroid neoplasms. Recognition of such entity would help the reporting pathologists to avoid misdiagnosis of this variant.

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