Quiz Case

Cytomorphological diagnosis of rapidly growing, hard, non-tender thyroid lesion

Gaurav Singla, MD¹, Tanisha Singla, MD¹, Sumanta Das, MD¹, Rashmi Arora, MD¹, Swati Singla, MD¹

¹Department of Pathology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.

A 65-year-old male presented with rapidly growing left side thyroid swelling for the past 45 days. He complained of breathlessness and difficulty in eating food for a month. The patient did not have any other significant clinical history. On examination, the swelling measured 8 cm × 6 cm was nontender and hard in consistency. Ultrasound findings suggested a hyperechoic lesion in the left thyroid lobe measuring 8 cm × 5 cm × 4 cm. Fine needle aspiration cytology (FNAC) stained smears show the following findings [Figure 1a-d].

Figure 1: (a) Follicular neoplasm showing presence of repetitive prominent microfollicular pattern in a colloid free background (Giemsa, ×40), (b) medullary carcinoma small cell variant showing singly scattered cells with stippled chromatin in a background of magenta-colored amyloid (Giemsa, ×40), (c) papillary carcinoma showing a cellular smear forming syncytial aggregates and sheets focally with a distinct anatomical border and scanty viscous colloid (depicted by black arrow) also known as chewing gum colloid can be seen (Giemsa, ×10), (d) large, oval, and pale nuclei seen with pale powdered chromatin and presence of intranuclear cytoplasmic inclusion (depicted by black arrow) best appreciated in Papanicolaou (Papanicolaou, ×40).

Q1: What is your interpretation?
   a. Follicular neoplasm
   b. Medullary carcinoma
   c. Papillary carcinoma
   d. Anaplastic carcinoma
Answer: Q1-d. Anaplastic carcinoma

A1 – In follicular neoplasms (FNs), there is a presence of prominent microfollicular pattern in a colloid free background [Figure 2a]. The cell clusters are of uniform size and rosette formation can be appreciated.

In medullary carcinoma (MC), cells show the presence of uniform, stippled (neuroendocrine) nuclear chromatin. There is the presence of amorphous pink/violet background material also known as amyloid [Figure 2b]. Cells may be either plasmacytoid small cell or spindle cell in appearance.[1]

In papillary carcinoma, the cells form syncytial aggregates and sheets with distinct anatomical borders. The colloid appears as scant, viscous, and stringy also known as chewing gum colloid [Figure 2c]. They have a characteristic presence of intranuclear pseudo-inclusions and grooves [Figure 2d]. Psammoma bodies may be seen.

In anaplastic carcinoma, the cells are highly pleomorphic and dispersed in a necrotic background. The cells have coarsely granular clumped chromatin, prominent nucleoli, and occasional intranuclear pseudo-inclusions. Multinucleation, multilobation, and numerous mitotic figures are common.[2] All these morphological characteristics were observed in our FNAC findings. Thus, a diagnosis of anaplastic carcinoma thyroid was given and the patient was advised surgery and histopathology correlation. However, the patient was unwilling for surgery and was lost thereafter.

Q2: Which of the following is true regarding anaplastic carcinoma thyroid?
   a. It shows the presence of amorphous pink/violet material (amyloid) in background
   b. It stains positive for calcitonin
   c. Any of the three major patterns can be seen – squamoid cell, spindle, and giant cell
   d. Nucleus shows the presence of stippled chromatin

Q3: Anaplastic carcinoma stains positive for
   a. PAX8
   b. Calcitonin
   c. Thyroglobulin
   d. None of the above

Q4: Which of the following is not true of anaplastic carcinoma thyroid?
   a. It is the most aggressive variant among thyroid cancers
   b. It is the most common thyroid cancer
   c. It has a poor prognosis
   d. Both a and c are true

Q5: Most of the anaplastic carcinoma thyroid tumors are
   a. Stage I

ANSWERS TO ADDITIONAL QUIZ QUESTIONS

Answers: Q2-c, Q3-a, Q4-b, Q5-d

A2 – On FNAC, any of the three major patterns can be seen – squamoid cell, spindle, and giant cell in anaplastic carcinoma thyroid.[2] Majority of the cases show admixture of these patterns. However, the cell type does not affect the treatment and prognosis of the patient.[2] Rest all other options, i.e., presence of amyloid, calcitonin positivity, and presence of stippled chromatin are seen in MC thyroid.[1]

A3 – Anaplastic thyroid carcinoma (ATC) cells are non-reactive for thyroid transcription factor-1 (TTF-1), calcitonin, thyroglobulin, and RET/PTC oncoprotein. PAX8 (also known as paired box gene 8) has a useful role and is positive in 79% of ATCs and in up to 92% of ATCs showing squamoid features[3] they are also positive for cytokeratin (40–100%), epithelial membrane antigen, and carcinoembryonic antigen. Vimentin positivity is seen in spindle cell component. FNs stain positive for thyroglobulin and TTF-1. Calcitonin is positive in MC thyroid.

A4 – ATC represents the most aggressive extreme of the clinical spectrum of thyroid epithelial neoplasms, being one of the most lethal human tumors. It constitutes <5% of clinically recognized thyroid malignancies, but it accounts for more than half of the deaths for thyroid cancer, with a mortality rate that is over 90% and a mean survival of 6 months after the diagnosis.[3] The most common thyroid cancer is papillary thyroid carcinoma.
A5 – Most of the anaplastic thyroid cancers are Stage IV thyroid tumors because they are very aggressive. The American Joint Committee on Cancer divides anaplastic thyroid cancer into three stages: IVA is characterized by an intrathyroid tumor, IVB primary tumor with eccentric spreading, and IVC with distant metastases.[4]

BRIEF REVIEW OF THE TOPIC

ATC is also known as undifferentiated, dedifferentiated, or sarcomatoid carcinoma. It is an uncommon, aggressive tumor which constitutes 2–5% of all thyroid tumors, but is invariably fatal.[3,5] All the subtypes of thyroid carcinoma can progress to ATC but papillary and follicular carcinoma are the most common types to undergo this transformation.[6] Approximately 25–50% of patients with anaplastic thyroid cancer will have a history of well-differentiated thyroid cancer (papillary or follicular thyroid cancer). About 50% of the cases have a prior multinodular goiter. The incidence of ATC has decreased in recent times. Improved socioeconomic conditions and iodine prophylaxis are suggested as the main reason for the decline, as ATC is more common in iodine-deficient regions.[6] Another factor that may explain the decreased incidence of ATC is that many tumors are now being correctly diagnosed as lymphoma, undifferentiated insular carcinoma, or MC with the increased availability of immunohistochemical studies.[7] It is, therefore, easy to explain the decreased incidence in recent years. ATC is seen in elderly with peak incidence in 6–7th decade and is more common in females (55–77%). Risk factors include history of goiter, iodine deficiency, and radiation.

Anaplastic carcinoma thyroid can be differentiated from insular carcinoma thyroid as cells of insular carcinoma thyroid are arranged in three dimensional clusters in a background of single cells with high n: c ratio. Intranuclear cytoplasmic inclusions, nuclear grooves and microfollicles with dense colloid may be seen in some cases.[8] Also necrosis and mitosis may or may not be present as compared to anaplastic carcinoma where the cells are highly pleomorphic with presence of necrosis and mitosis. The cells of anaplastic carcinoma thyroid are more pleomorphic due to p53 over expression. p53 mutation has been proposed to have a role in the stepwise dedifferentiation of human thyroid carcinomas, from well-differentiated thyroid carcinoma to poorly differentiated thyroid carcinoma to anaplastic carcinoma.[9] Also the cells of insular carcinoma thyroid are thyroglobulin positive as compared to anaplastic carcinoma thyroid where they are negative[10] thus differentiating between the two.

There are two theories of etiopathogenesis of the occurrence of anaplastic thyroid cancer. The first theory suggests that anaplastic thyroid cancer is due to the transformation of a well-differentiated thyroid tumor, while the second theory is de novo (derived first from follicle cells without transformation from well-differentiated thyroid tumors).[3]

Clinical manifestations develop rapidly due to invasion of surrounding local tissues and metastasis into distant organs. Locally, these cancers show rapid anterior neck enlargement accompanied by dysphagia (40%), hoarseness (40%), and stridor (24%). Regional symptoms include enlarged lymph nodes (54%) and neck pain (26%). Systemic symptoms include anorexia, weight loss, and shortness of breath with pulmonary metastasis. Approximately 20–50% of patients already have distant metastases (80% in lung, 6–16% in bone, and 5–13% in brain) by the time it is diagnosed.[11,12]

Various studies have been conducted to understand the genetic and molecular aberrations in anaplastic cell carcinomas. The most common mutation is p53 (55%), followed by RAS (22%), BRAF (26%), b-catenin (38%), and PIK3CA (17%).

Treatment includes surgical resection, with neoadjuvant chemotherapy or external beam radiation X ray Therapy (XRT). New treatment strategies include evaluating the benefits of vascular disrupting agents and tyrosine kinase inhibitors for advanced ATC with driver mutations, which can be targeted.[9]

SUMMARY

Anaplastic carcinoma with poor prognosis is usually observed as Stage IV presentation. The patient can be accurately diagnosed based on adequate clinical history and FNAC findings, thus facilitating an early treatment and prolonging the life of the patient.

COMPETING INTERESTS STATEMENT BY ALL AUTHORS

The authors declare that they have no competing interests.

AUTHORSHIP STATEMENT BY ALL AUTHORS

Each author has participated sufficiently in the work and take public responsibility for appropriate portions of the content of this article. All authors read and approved the final manuscript. Each author acknowledges that this final version was read and approved.

ETHICS STATEMENT BY ALL AUTHORS

As this is case without identifiers, our institution does not require approval from institutional review board (IRB) (or its equivalent).
LIST OF ABBREVIATIONS (In alphabetic order)

ATC - Anaplastic thyroid carcinoma
FN - Follicular neoplasm
FNAC - Fine needle aspiration cytology
MC - Medullary carcinoma.

EDITORIAL/PEER-REVIEW STATEMENT

To ensure the integrity and highest quality of CytoJournal publications, the review process of this manuscript was conducted under a double-blind model (the authors are blinded for reviewers and vice versa) through automatic online system.

REFERENCES

1. Mehdi G, Maheshwari V, Ansari HA, Sadaf L, Khan MA. FNAC diagnosis of medullary carcinoma thyroid: A report of three cases with review of literature. J Cytol 2010;27:66-8.
2. Nagpal R, Kaushal M, Kumar S. Cytological diagnosis of an uncommon high grade malignant thyroid tumour: A case report. J Clin Diagn Res 2017;11:ED03-5.
3. Ragazzi M, Ciarrocchi A, Sancisi V, Gandolfi G, Bisagni A, Piana S. Update on anaplastic thyroid carcinoma: Morphological, molecular, and genetic features of the most aggressive thyroid cancer. Int J Endocrinol 2014;2014:790834.
4. Dwipayana MP, Yogi P, Semadi S, Wirawan S, Widiana K. Diagnosis and management of an anaplastic thyroid cancer: Case report. Biomed Pharmacol J 2017;10:1369-77.
5. Chiacchio S, Lorenzoni A, Boni G, Rubello D, Elisei R, Mariani G. Anaplastic thyroid cancer: Prevalence, diagnosis and treatment. Minerva Endocrinol 2008;33:341-57.
6. Saunders CA, Nayar R. Anaplastic spindle-cell squamous carcinoma arising in association with tall-cell papillary cancer of the thyroid: A potential pitfall. Diagn Cytopathol 1999;21:413-8.
7. Nix PA, Nicolaides A, Coatesworth AP. Thyroid cancer review 3: Management of medullary and undifferentiated thyroid cancer. Int J Clin Pract 2006;60:80-4.
8. Mehta J, Sukheela D. Cytomorphology of insular carcinoma thyroid: A diagnostic dilemma. Med J DY Patil Univ 2016;9:549-50.
9. Lam KY, Lo CY, Chan KW, Wan KY. Insular and anaplastic carcinoma of the thyroid: A 45-year comparative study at a single institution and a review of the significance of p53 and p21. Ann Surg 2000;231:329-38.
10. Khetrapal S, Rana S, Jetley S, Jairajpuri Z. Poorly differentiated carcinoma of thyroid: Case report of an uncommon entity. J Can Res Ther 2018;14:1142-44.
11. Taccaliti A, Silvetti F, Palmonella G, Boscaro M. Anaplastic thyroid carcinoma. Fountiers Endrocinol 2012;3:1-7.
12. Keutgen XM, Sadowski SM, Kebebew E. Management of anaplastic thyroid cancer. Gland Surg 2015;4:44-51.