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Undifferentiated (Anaplastic) Thyroid Carcinoma: Exploring the Coexistence of Differentiated and Dedifferentiated Anaplastic Elements—Critical Insights from a Case Series and Review of Literature

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Abstract

Undifferentiated (anaplastic) thyroid carcinoma (ATC) is a rare thyroid malignancy, constituting <2% of all thyroid carcinomas. It is an aggressive tumor, manifesting as a rapidly growing neck mass with compressive symptoms. Given that ATC often arises from dedifferentiation of well-differentiated thyroid carcinoma (WDTC), it is also possible that WDTC and ATC elements coexist, necessitating a clear distinction between WDTC with anaplastic transformation and pure ATC, due to significant differences in prognosis and treatment. Emphasizing the significance of cytological evaluation, particularly with the assistance of fine-needle aspiration, we present three cases that underscore the importance of timely detection for achieving precise diagnoses and guiding subsequent management decisions.

Keywords

- anaplastic
- carcinoma
- cytology
- fine-needle aspiration cytology
- thyroid
- undifferentiated

Introduction

Undifferentiated (anaplastic) thyroid carcinoma (ATC) is a rare malignancy, accounting for <2% of thyroid cancers,[1] typically presenting as a rapidly enlarging neck mass[2] displacing adjacent structures; hence, causing symptoms related to compression of surrounding structures.[3] It is an aggressive tumor derived from thyroid glands' follicular cells. However, ATC cells lack the biological features of original follicular cells, such as iodine uptake and thyroglobulin synthesis.[3] Early diagnosis, often assisted by fine-needle aspiration (FNA), improves patient prognosis. As per the 2021 American Thyroid Association guidelines for management of patients with ATC by Bible et al,[4] its treatment involves surgery (if feasible), radiation therapy, and chemotherapy.[4] In this case series, we will explore three cases of ATC with a particular emphasis on cytopathological evaluation. According to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), in all three of our cases, the final impression was rendered as "TBSRTC Category-VI (Malignant) Undifferentiated (Anaplastic) Carcinoma." Immunostaining, histopathological evaluation, and molecular/cytogenetic analyses were recommended for further management, along with clinicoradiological correlation.

Case Report

Case 1

A 67-year-old woman presented with a 1-month history of anterior neck swelling, cough with expectoration, generalized weakness, and loss of appetite. Additionally, she reported experiencing increasing breathlessness over the past week. During the physical examination, the patient's vital signs were stable. A hard, nontender swelling measuring

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5 × 4 cm was observed in the anterior neck, which moved with deglutition. Computed tomography (CT) scan evaluation of the thorax and neck revealed a predominantly hypodense lesion measuring 4.4 × 4.4 cm in the right thyroid lobe, with specks of calcification. The lesion caused mild luminal compression and left lateral displacement of the trachea. Additionally, cervical lymph node enlargement on the right side of the neck and a few subpleural and centrilobular nodules in bilateral lower lobes, along with bilateral minimal pleural effusion, were also noted. As the patient was already under ventilator support, bedside ultrasonography (USG) and USG-guided FNA cytology (FNAC) of the right thyroid lobe lesion were performed, yielding a hemorrhagic aspirate. On microscopic examination, highly cellular smears revealed several discrete, loosely cohesive, clusters and syncytial groups of large, pleomorphic, and variably shaped neoplastic cells (►**Fig. 1**) ranging from polygonal, epithelioid, oval, and spindle-shaped cells. Such anaplastic cells displayed marked nuclear enlargement, nuclear pleomorphism, multiple prominent macronucleoli, and moderate-to-abundant cytoplasm. Occasional papillary fragments were identified (►**Fig. 2**). Several bizarre and multilobulated cells were seen, along with numerous binucleated and multinucleated giant cells. Numerous mitotic figures were also identified. The background was dirty, comprising cellular debris, marked acute inflammatory cell infiltrate, extensive necrosis, and hemorrhage. The final impression was rendered as "TBSRTC Category-VI (Malignant) Undifferentiated (Anaplastic) Carcinoma." Unfortunately, she died within 4 days, which precluded any possibility of conducting further investigations.

Case 2

A 52-year-old woman presented with a 1-and-a-half-month history of right lobe thyroid swelling, weight loss, hoarseness of voice, and increasing dysphagia over the past 15 days.

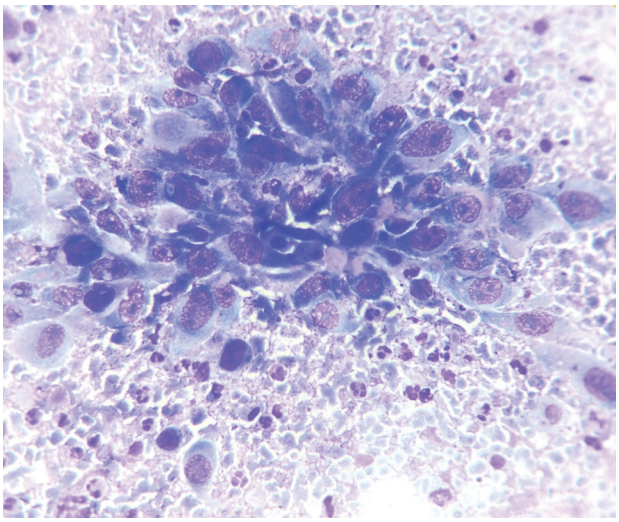

Fig. 1 Undifferentiated (anaplastic) thyroid carcinoma: Moderately cellular smears reveal highly pleomorphic bizarre anaplastic tumor cells displaying marked nuclear atypia, prominent nucleoli, and moderate-to-abundant cytoplasm against a background of tumor diathesis and inflammation comprising chiefly of neutrophils (MGG, ×40).

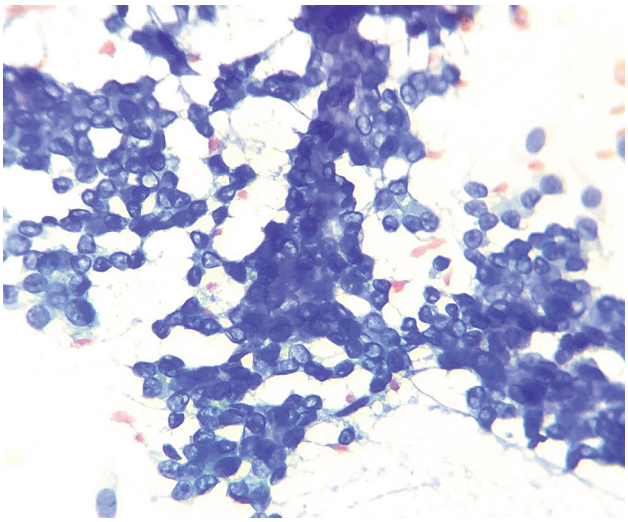

Fig. 2 Undifferentiated (anaplastic) thyroid carcinoma: A papillary fragment lined by neoplastic cells reveals nuclear clearing, nuclear molding, pale powdery chromatin, occasional pseudo-inclusions, and longitudinal grooves. Dedifferentiated anaplastic component was identified elsewhere in the same smear (Papanicolaou, ×40).

From a clinical standpoint, thyroid carcinoma was suspected, leading to further recommendations for radiological and cytological evaluations. On contrast-enhanced CT (CECT) of the neck, a large heterogeneously enhancing lesion measuring 5.7 × 7.6 × 8 cm was observed. This lesion completely replaced the right thyroid lobe, resulting in lateral displacement of the trachea, esophagus, and right jugular vein toward the left. Multiple parenchymal and pleural-based nodules were also noted in bilateral lung fields, with the largest measuring 3.6 × 2.4 cm in the left lobe, likely indicating metastasis, along with mild left pleural effusion. Thus, the imaging findings revealed a neoplastic right thyroid lesion, measuring 5.7 × 7.6 × 8 cm, with signs of local compression and evidence of distant metastasis. FNAC from the right lobe of thyroid swelling yielded a hemorrhagic aspirate. On microscopic examination, moderately cellular smears revealed several discrete, clusters and sheets of bizarre, very large, highly anaplastic cells. Occasional follicular clusters adjacent to severely anaplastic elements were also identified (►**Fig. 3**). Striking neutrophilic cannibalization by tumor cell phagocytosis (cannibalism) was also noted (►**Fig. 4**). Several giant cells with multiple nucleoli were noted, along with many epithelioid, spindle-shaped, squamoid, and bizarre multilobulated cells against a background of necrosis and hemorrhage admixed with chunks of thick colloid and inflammatory cells. Hence, finally, the diagnosis was "TBSRTC Category-VI (Malignant) Undifferentiated (Anaplastic) Carcinoma." Due to its advanced stage, this patient was deemed unfit for surgery and was referred to an advanced oncology center for adjuvant chemoradiation. However, eventually, her condition deteriorated rapidly and only palliative care could be provided. Unfortunately, she died within a week following the referral.

Case 3

A 56-year-old woman presented with a rapidly enlarging anterior neck swelling along with increasing dyspnea and

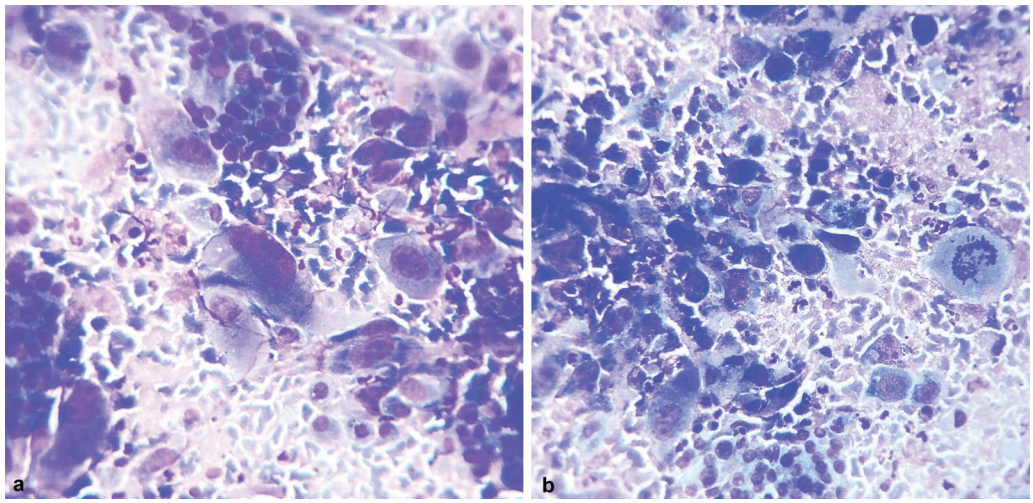

Fig. 3 (**a**) Undifferentiated (anaplastic) thyroid carcinoma: Moderately cellular smears reveal extremely anaplastic cells against a background of tumor diathesis and inflammation with few three-dimensional ball-like clusters of crowded follicular neoplastic cells, indicating possible dedifferentiation from adjacent well-differentiated follicular component (MGG, ×40). (**b**) Undifferentiated (anaplastic) thyroid carcinoma: Moderately cellular smears reveal highly anaplastic tumor cells and a mitotic figure (right) against necrotic and inflammatory background, with few three-dimensional ball-like clusters of follicular neoplastic cells (bottom), indicating possible dedifferentiation from adjacent well-differentiated follicular components (MGG, ×40).

hoarseness of voice over 1 week. On CECT of the neck, a hyperdense mass measuring 4.8 × 4.2 cm had nearly replaced the left thyroid lobe, leading to lateral displacement of the trachea toward the right side. This mass exhibited internal calcification and areas of necrosis. Additionally, several subpleural and centrilobular nodules in bilateral lower lobes, as well as minimal pleural effusion on both sides, were also observed. FNAC from left thyroid swelling yielded a hemorrhagic aspirate. On microscopic examination, moderately cellular smears revealed several isolated and loosely cohesive clusters of markedly anaplastic cells. Several multinucleated giant cells along with an occasional follicular cell cluster were noted against a necrotic and hemorrhagic background. The final diagnosis was "TBSRTC Category-VI (Malignant) Undifferentiated (Anaplastic) Carcinoma." The patient's refusal of further treatment and departure against medical advice, coupled with her being from a low socioeconomic background from a remote village in a neighboring state, resulted in a loss of follow-up. Hence, we were unable to conduct further investigations.

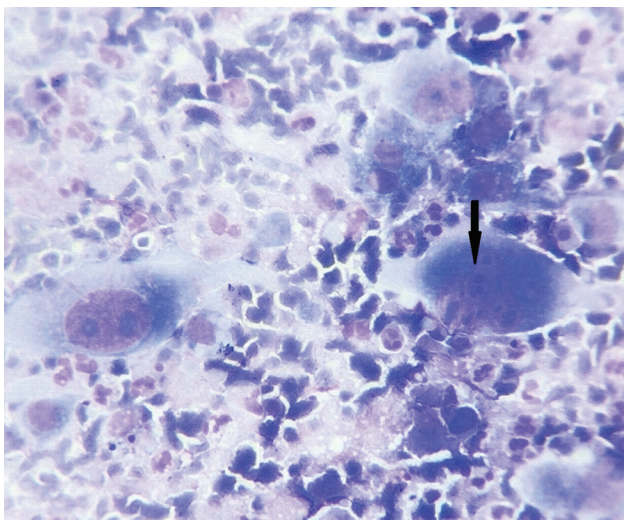

Fig. 4 Neutrophilic cannibalization in undifferentiated (anaplastic) thyroid carcinoma: Extremely bizarre anaplastic tumor cell, with engulfed neutrophil (black arrow), can be identified amid highly anaplastic tumor cells and numerous neutrophils against a background of tumor diathesis (MGG, ×40).

Discussion

ATC is a rare and aggressive form of thyroid cancer. It is characterized clinically by rapidly enlarging tumor mass with an early propensity to invade into adjacent structures. On pathological evaluation, the presence of extremely bizarre undifferentiated (anaplastic) neoplastic cells is a characteristic finding. A study by Chiacchio et al[3] concluded that ATC usually arises from well-differentiated thyroid carcinoma (WDTC) (especially follicular) but can also arise de novo. Additionally, it has the propensity to invade surrounding fat, trachea, muscles, esophagus, and larynx in more than 70% of cases. Diagnosis is confirmed by FNAC, or in doubtful cases, by histology or core biopsy. Radiology defines the local extent and distant metastasis. Management includes surgery, chemotherapy, hyperfractionated radiation, tracheostomy for airway obstruction, and interventional bronchoscopy (Nd: YAG laser and airways stenting, which are preferred in inoperable ATC-induced tracheal obstruction). Gene therapy is under investigation. Despite these efforts, which offer only palliation, ATC remains highly aggressive, with a median survival period of 6 to 8 months. Molinaro et al[1] stated that ATC is characterized by the accumulation of several oncogenic alterations, and an increased number of oncogenic alterations equates to an increased level of dedifferentiation and aggressiveness. Next-generation sequencing analysis has confirmed a major role for *TP53* alterations.

In our series, all patients exhibited common clinical features associated with ATC, including neck swelling, compressive symptoms, and distant metastases to cervical lymph nodes and lungs. Radiological findings provided additional evidence supporting our suspicion of ATC. In nearly all cases, we observed large heterogeneous masses that had replaced substantial portions of thyroid lobes, leading to displacement of adjacent structures. Furthermore, the presence of multiple nodules in lungs indicated the likelihood of metastases from a highly aggressive malignancy. In the multicenter, retrospective cohort study by Jannin et al[5], all patients with ATC diagnosed between 2010 and 2020 were identified from the national database of the French ENDOCAN-TUTHYREF network. Females constituted 61% with a median age of 72 years. Histologically, pure ATC accounted for 62.5%, while synchronously transformed ATC (st-ATC), also known as mixed-ATC, comprised 26.7%. ATC following differentiated thyroid cancer treatment was termed metachronously transformed ATC. Factors independently linked to overall survival included European Cooperative Oncology Group performance status, disease stage, multimodality treatment, st-ATC, and lower neutrophil-to-lymphocyte ratio. Ngo et al[6] concluded that secondary ATCs were comparable to primary ATCs in demographics, clinical features, and survival, except for larger tumor size in primary ATCs. *BRAF* mutations were more common, whereas *RAS* mutations were less common in secondary ATCs, suggesting distinct tumorigenic pathways.

The cytological evaluation in all three cases revealed typical features of undifferentiated (anaplastic) carcinoma. Smears were moderately to highly cellular with a predominance of several discrete, clusters, loosely cohesive groups, and syncytia of highly anaplastic tumor cells (►**Fig. 1**). However, in Case 1, a 67-year-old woman with anterior thyroid swelling and worsening breathlessness underwent FNA thyroid swelling, and cytological evaluation revealed occasional papillary fragments lined with neoplastic cells exhibiting characteristic nuclear features (►**Fig. 2**). In contrast, in Cases 2 and 3, we also noted occasional follicular clusters adjacent to severely anaplastic elements (►**Fig. 3a, b**). These findings hint at the presence of a residual differentiated component along with undifferentiated components within the same tumor. Anaplastic (undifferentiated) neoplastic cells exhibited extreme pleomorphism, with bizarre, irregular shapes and multiple lobulations, suggesting chromosomal instability and genetic abnormalities. The presence of such highly bizarre atypical nuclei is a hallmark of highly active and aggressive tumor cells. As several cells were observed to possess such characteristics, they were referred to as binucleated and multinucleated giant cells, which are common in rapidly dividing tumor cells. The presence of numerous mitotic figures indicated a high rate of cell division within tumor, contributing to its aggressive growth. As already illustrated in ►**Fig. 4**, striking tumor cell cannibalism was observed. While macrophages exclusively phagocytose dead cells, cannibalistic tumor cells can ingest and consume live cells for sustenance. Neutrophilic cannibalism although rare has been reported in anaplastic carcinomas and other high-grade (or poorly differentiated) carcinomas associated with metastasis at presentation,[7] as noted in our case. The key takeaway from this case series is that when background appears highly inflammatory with extensive necrosis, mimicking an abscess, particularly in cytology, it should not rule out the presence of a lethal anaplastic component elsewhere. In such instances, it is prudent to perform extensive resampling from multiple areas to ensure an adequate sample that includes diagnostic anaplastic elements. Thus, cytopathological evaluations of all three cases concluded with a diagnosis of ATC.

In given clinical contexts involving patients with suspected ATC, it is essential to contemplate various notable differential diagnoses based on cytological and radiological findings. Primary among these considerations is poorly differentiated thyroid carcinoma (PDTC), which presents with partial loss of thyroid differentiation and increased nuclear atypia. Immunohistochemistry (IHC) and molecular markers can help differentiate between PDTC and ATC.[8] Medullary thyroid carcinoma (MTC) is another differential diagnosis especially when the spindle component is chiefly present along with amyloid deposits which could be mistaken for chunks of colloid; neuroendocrine appearance could help in correct diagnosis. Papaparaskeva et al[9] retrospectively reviewed 128 thyroid aspirates of MTC and found that spindle-shaped cells were found in 40.1% of them. Finally, IHC, particularly for detecting calcitonin and chromogranin A markers, can aid in differentiation.[10,11] Thyroid lymphoma may show a monotonous population of lymphoid cells with atypical features.[12] Chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), Riedel's thyroiditis,[13] and subacute thyroiditis (De Quervain's thyroiditis) can also present with a thyroid mass and inflammatory changes. A cytological examination can reveal lymphocytes, plasma cells, and occasional Hurthle cells in chronic thyroiditis. Subacute thyroiditis may show multinucleated giant cells. Clinical context and serological markers can help differentiate thyroiditis from carcinoma. Some benign thyroid nodules may appear as heterogeneous masses on imaging, potentially raising suspicion for malignancy. A cytological examination can help distinguish benign nodules from malignancies based on characteristic cytological features and the absence of atypical cells. Podany et al[2] also found that identifying key cytological features by FNA coupled with clinical history aids in diagnosis and helps distinguish it from other mimickers.

Metastatic carcinomas to the thyroid from primary cancers elsewhere in the body can be another differential diagnosis. In the differential diagnosis of ATC cytodiagnosis especially its spindle cell variant; the involvement of thyroid by a sarcomatoid squamous cell carcinoma (SSCC) of larynx by local extension also needs to be considered. Radiology and focal squamous differentiation are helpful in distinction in such cases. Cytological features may resemble those of primary tumor;[14] however, clinical history, radiology, and IHC can aid in identifying the primary site of origin. As in SSCC, imaging reveals a primary laryngeal mass with extension into the thyroid, and histopathology reveals foci of squamous differentiation, such as keratinization or intercellular bridges, amidst spindle cell areas. On IHC, ATC is usually

negative for markers of squamous differentiation (p63, CK5/6), while SSCC is positive for p63, CK5/6, and CK AE1/AE3 confirming squamous differentiation.[15] Hence, it is crucial to distinguish ATC from thyroid malignancies and nonneoplastic thyroid conditions.

If only a few foci of follicular cells or well-differentiated components are identified in a cytological specimen consistent with ATC, the interpretation would be challenging. Therefore, the most accurate diagnostic category shall depend on overall assessment and clinical context. The goal is to provide the most precise and informative diagnosis to guide appropriate patient management for this condition. Possible opinions and considerations may include atypical cells of undetermined significance, differentiated thyroid carcinoma (such as papillary or follicular carcinoma) with anaplastic transformation, sampling issues, and rarely, cases of hybrid lesions where a mixture of differentiated and undifferentiated components is present in the same tumor. This is an unusual scenario but can complicate diagnosis. Indeed, such an observation can raise suspicion of dedifferentiation into ATC. Dedifferentiation refers to transformation of a WDTC, such as papillary or follicular carcinoma, into a more undifferentiated and aggressive form, such as ATC. This process may occur in some patients with preexisting WDTC and is associated with poorer prognosis. Coexistence of well-differentiated follicular cells alongside highly pleomorphic and undifferentiated cells

Table 1 Management strategy based on the presence of differentiated component in ATC

S. no.	Management plan	ATC de novo	ATC arising on the background of WDTC
1	Surgical resection	Often not feasible due to extensive local invasion and distant metastases at the time of diagnosis	Often feasible, especially if the transformation is detected early
		When possible, debulking of the tumor is preferred and complete surgical resection is attempted	The surgery may be more aggressive due to the presence of the more indolent DTC component. A total thyroidectomy and extensive neck dissection needs to be performed
		The primary goal remains palliation, to relieve symptoms caused by local mass effect	The goal is to achieve clear margins and remove both the differentiated and anaplastic components
2	Radiation therapy	EBRT is used to control local disease and alleviate symptoms	Definitive IMRT ± chemotherapy is usually preferred for stage IVA and IVB cancers. Postoperative EBRT is employed to control residual ATC and prevent recurrence
3	Chemotherapy	The objective is primarily palliative, aiming to slow progression and manage symptoms	The focus is more on the anaplastic component due to its aggressive behavior than the differentiated one
		Systemic chemotherapy: due to the aggressive nature and chemotherapy resistance of ATC, regimens may include paclitaxel and carboplatin or doxorubicin	Systemic chemotherapy: similar to ATC de novo, chemotherapy regimens may include paclitaxel, carboplatin, or doxorubicin
		Combination therapy: often used in combination with radiation to enhance local control and systemic effects	Combination therapy: used in conjunction with radiation therapy for a synergistic effect
4	Targeted therapy and experimental treatments	Molecular profiling: genetic profiling may identify specific mutations (e.g., BRAF, PIK3CA, or TP53) that could be targeted with newer therapies	Molecular testing: detailed genetic profiling is crucial, especially to identify mutations in differentiated component that may have therapeutic implications
		Clinical trials: patients are often considered for clinical trials involving novel agents such as immune checkpoint inhibitors, tyrosine kinase inhibitors, or other experimental treatments	Specific inhibitors (e.g., BRAF and MEK inhibitors for BRAF-mutant tumors) can be included in the treatment plan based on the mutation profile
5	Long-term follow-up and monitoring	Needed to arrest further progression	Given the presence of WDTC, long-term surveillance for recurrence or progression of the differentiated component is necessary, alongside monitoring the ATC component

Abbreviations: ATC, undifferentiated (anaplastic) thyroid carcinoma; DTC, differentiated thyroid carcinoma; EBRT, external beam radiation therapy; IMRT, intensity-modulated radiation therapy; WDTC, well-differentiated thyroid carcinoma.

in the same tumor suggest dedifferentiation into ATC. This often represents a more aggressive phenotype, combining features of both differentiated and undifferentiated tumors.[8] The presence of dedifferentiation can considerably impact patient management and treatment decisions, influencing the choice of the therapies and guiding multidisciplinary teams in determining the most appropriate course of action. If features of ATC dominate and presence of follicular cells is limited, focus may still be on the aggressive nature of tumor. In such cases, categorizing lesion as a more aggressive

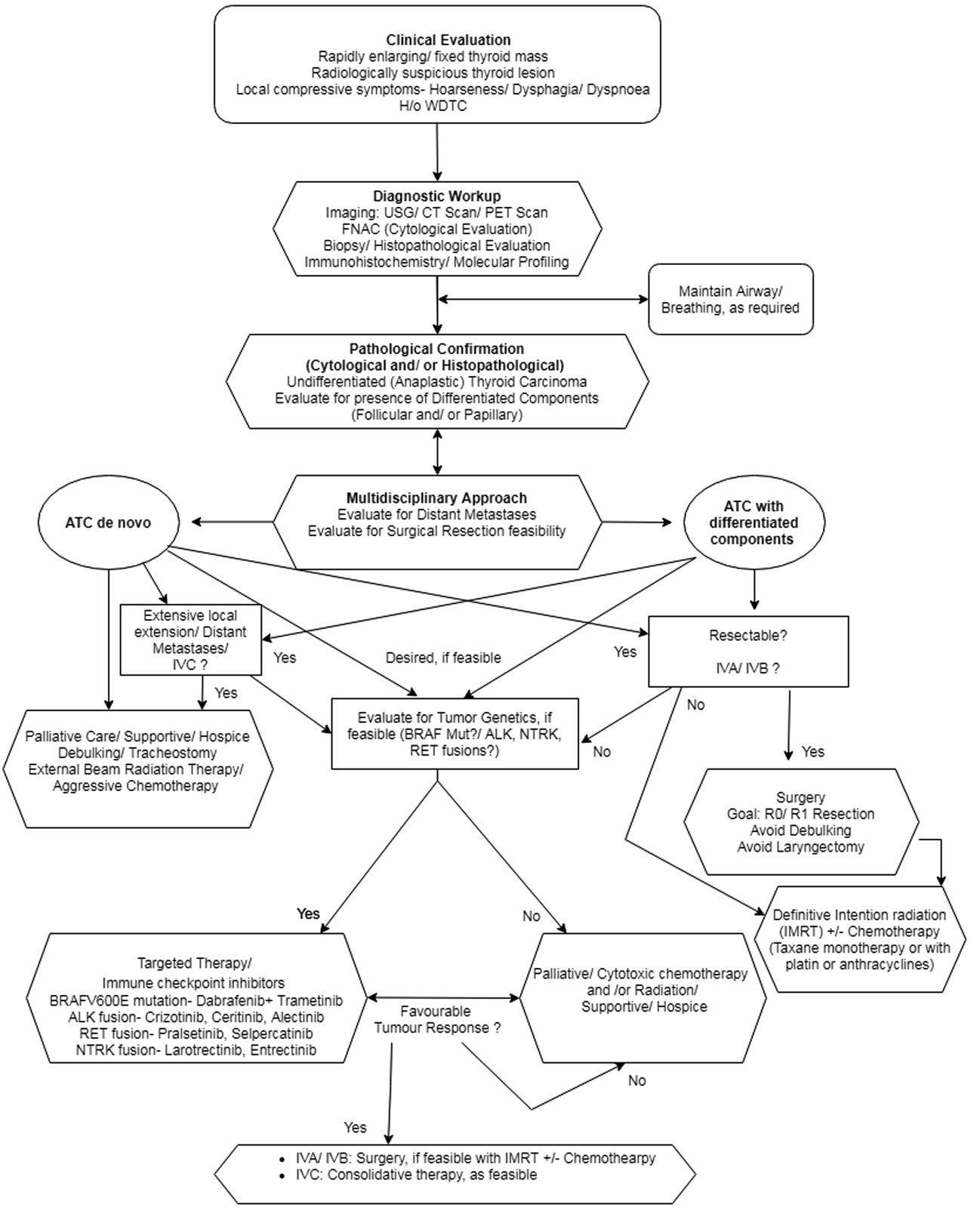

Fig. 5 Flowchart: Management algorithm for undifferentiated (anaplastic) thyroid carcinoma.

malignancy (e.g., TBSRTC Category-VI—Malignant, suggestive of Undifferentiated/Anaplastic Carcinoma) may be appropriate. Conversely, if presence of follicular cells is more notable instead of the more anaplastic bizarre undifferentiated cells and aggressive features are not as predominant on clinical and radiological evaluation, a more cautious approach may be taken. In this situation, categorizing it as an indeterminate lesion (e.g., TBSRTC Category-III—Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS)) could be more suitable to highlight uncertainty and the need for further evaluation. A study done by Ho et al[16] suggested that nodules classified as AUS/FLUS cytology have higher malignancy rates (26.6–37.8%) than previously thought. This challenges traditional beliefs about the cancer risk in Bethesda Category-III nodules, prompting repeat FNA or observation.

Further management of a patient with suspected ATC or an indeterminate thyroid lesion with features suggestive of ATC and a few foci of follicular cells depend on overall assessment, diagnostic findings, and clinical context. If the patient has a history of any WDTC, there is a possibility that dedifferentiation might have occurred. In such cases, sequential cytological and histopathological assessments to track the progression of dedifferentiation will be very helpful. But if a patient is presenting with rapid thyroid enlargement or compressive symptoms, it is likely due to the aggressive behavior of ATC compared with WDTC and can be indicative of dedifferentiation; however, to confirm the diagnosis and categorize tumor accurately, a cytopathological evaluation followed by histopathological examination of tissue becomes essential. While cytology provides an initial and valuable diagnosis, histopathological evaluation is indispensable for the detection of vascular invasion, extrathyroidal extension, and other high-risk features critical for staging and prognostication, which might not be evident on cytology. It also confirms the presence and extent of anaplastic transformation and identifies any residual differentiated components more accurately; thus, ensuring complete surgical resection of anaplastic and differentiated components. Detailed histopathological findings guide the precise targeting of radiation, focusing on areas with incomplete resection or high-risk features and supports initiation/adjustment of chemotherapy and experimental/molecular therapy (BRAF/MEK inhibitors) tailored to the identified mutations, based on tumor's characteristics.[4] The latter is typically done through a surgical biopsy or excisional biopsy of thyroid lesion.

IHC and molecular testing can provide additional information on tumor's characteristics, including its origin, genetic mutations, and expression of specific markers. IHC is a valuable tool in identifying markers specific to WDTC and those associated with ATC. While both ATC de novo and ATC arising from WDTC involve aggressive treatment approaches, the presence of a differentiated component in the latter allows for additional therapeutic options and more extensive surgical interventions. Molecular profiling and targeted therapies play a crucial role in both scenarios. Nevertheless, the treatment for ATC arising from WDTC can be more tailored due to underlying differentiated components. Cytotoxic chemotherapy may be started as a "bridge" while awaiting genomic information or while awaiting targeted therapy.[4] The overall strategy is multimodal, aiming to manage both aggressive anaplastic carcinoma and any residual well-differentiated disease. We have summarized a detailed management strategy for ATC de novo and ATC arising on the background of WDTC in ►**Table 1**.

Given the complexity of such cases, effective communication between cytopathologists and clinicians, along with additional investigations, is necessary to arrive at an accurate diagnosis. As per the 2021 American Thyroid Association guidelines for the management of patients with ATC by Bible et al,[4] we have incorporated a detailed management algorithm (►**Fig. 5**).

Conclusion

In conclusion, these cases have brought to light the intricate diagnostic challenges and aggressive nature of ATC. Integration of clinical, radiological, and cytological findings is paramount for early detection and timely intervention. Ongoing advancements in histopathology, molecular analysis, and genetics hold promise for the development of more efficacious treatment approaches for this formidable malignancy. A worldwide research endeavor is imperative to investigate prognostic significance and treatment implications when a coexistent differentiated component is present within this lethal malignancy. Furthermore, additional research is warranted to enable prediction and assessment of dedifferentiation, thus enabling early intervention to halt the progression to ATC.

Statement

Statement of manuscript approval by all authors, meeting authorship requirements, and representing honest work:

We affirm that all the authors meet the required criteria for authorship, and that this research represents a genuine honest research work undertaken at the Department of Pathology, Shri Balaji Institute of Medical Science, Raipur, India. All authors have meticulously reviewed and approved the final manuscript, committing to be accountable for the work's accuracy and integrity.

Authors' Contribution

A.D. conceptualized, designed, and drafted the initial manuscript, conducted the literature search, and meticulously reviewed patient information, providing diagnostic expertise and photographs. A.S.T. and P.C.A. reviewed and edited the manuscript for important intellectual content. A.M.(W.) performed procedures, gathered clinical and radiological details, and assisted in manuscript preparation. A.S. participated in patient care, synthesized clinical details, and conducted literature searches. All authors have reviewed and approved the final manuscript, committing to be accountable for the work's accuracy and integrity.

Declaration of the Patient Consent

Written informed consent was obtained from all the patients and/or guardians.

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Conflict of Interest
None declared.

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