Judi Clinical Journal | 2026;2(1):49-53
Journal home page: https://judijournal.com

Case Report

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Anaplastic Thyroid Carcinoma and Toxic Multinodular Goiter: A Case Report and Literature Review

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***Received**: May 11, 2026* ***Revised**: Jun 01, 2026* ***Accepted**: Jun 07, 2026* ***First Published**: Jun 20, 2026*

Introduction: Anaplastic thyroid carcinoma (ATC) is a rare thyroid malignancy, comprising approximately 2% of all thyroid cancers, yet accounting for the majority of thyroid cancer-related deaths. ATC is characterized by aggressive behavior and rapid local invasion, leading to life-threatening complications such as airway compromise, dysphagia, and vascular encasement. Longstanding thyroid conditions such as multinodular goiter (MNG) may predispose to malignant transformation into ATC. We report a case of ATC arising in a patient with a decade-long history of toxic MNG, underscoring the potential for severe complications even in seemingly stable thyroid disease.

Case presentation: A 68-year-old female with a 10-year history of toxic MNG presented with neck swelling, dyspnea, and dysphagia. Laboratory findings showed suppressed thyroid-stimulating hormone and elevated free T4. Ultrasonography revealed nodules with macrocalcifications. A total thyroidectomy was performed, and histopathological examination revealed ATC originating from one of the MNG nodules. Postoperatively, she received adjuvant chemoradiotherapy with carboplatin and doxorubicin. Initial imaging showed no metastasis, but after 10 months, a supraclavicular lymph node and posterior lung nodules indicated disease progression. She developed pneumonia during treatment, leading to its discontinuation. Despite restarting therapy, her condition worsened, and she passed away eight months later.

Literature review: A literature review identified six reported cases of ATC arising from MNG published between 2001 and 2020. The duration of MNG before malignant transformation varied from years to decades.

Conclusion: Longstanding MNG may progress to malignancy over time. Early diagnosis and appropriate management of MNGs are critical to minimizing the risk of malignant transformation.

Keywords: Anaplastic thyroid carcinoma, Multinodular goiter, Macrocalcification, Total thyroidectomy, Chemotherapy

How to cite this article: Salih AM, Ali ReM, Ali RaM, Ahmed AH, Hassan SH, Nasralla HA, et al. Anaplastic Thyroid Carcinoma and Toxic Multinodular Goiter: A Case Report and Literature Review. Judi Clin. J. 2026;2(1):49-53. https://doi.org/10.70955/JCJ.2026.07

1. Introduction

Thyroid malignancy is the most common endocrine cancer, representing 2.1% of cases. Papillary thyroid carcinoma accounts for the majority at 80%, followed by follicular thyroid carcinoma (10%), medullary thyroid carcinoma (4%), oncocytic cell carcinoma (3%), and anaplastic thyroid carcinoma (ATC) (2%) [1]. Anaplastic thyroid carcinoma is among the most aggressive and deadly solid tumors in humans, with an incidence rate of 1–2 cases per million [2]. It has the worst prognosis among thyroid cancers, with an average survival period of 3–9 months and a 3-year overall survival rate of just 10% [3]. Clinically, ATC presents with rapid onset of compressive symptoms, including dyspnea, dysphagia, and hoarseness, and frequently progresses to local invasion and distant metastasis, posing significant life-threatening complications [4]. Pre-existing thyroid conditions, such as longstanding multinodular goiter (MNG) or well-differentiated thyroid malignancies, may act as risk factors for anaplastic transformation [5]. Multinodular goiter, currently classified in the WHO 2022 classification as thyroid follicular nodular disease, is an enlargement of the thyroid gland distinguished by the presence of discrete palpable nodules. It is more prevalent in mountainous areas, including Southeast Asia, Latin America, and Central Africa. Among thyroid cancers, papillary thyroid carcinoma is most frequently associated with MNG, followed by follicular carcinoma and anaplastic carcinoma [3]. The prevalence of thyroid malignancy in thyrotoxic conditions, particularly toxic MNG, remains a subject of debate. Reported rates of thyroid cancer in MNG range from 3% to 35%, whereas cases of ATC arising from long-standing toxic MNG are exceedingly rare [3,4,6,7]. Here, we present a case of ATC occurring in a patient with a 10-year history of toxic

MNG. The report was prepared in accordance with the CaReL guidelines, and all references were assessed for eligibility and relevance [8,9].

2. Case presentation

2.1 Patient information

A 68-year-old female patient presented with anterior neck swelling for 10 years. She reported symptoms of dyspnea and dysphagia. She had a medical history of diabetes mellitus, hypertension, and anemia, but no history of prior surgeries.

2.2 Clinical findings

During the physical examination, the patient's vital signs were stable. A large anterior neck swelling was observed on physical examination, with a firm consistency upon palpation.

2.3 Diagnostic approach

Routine thyroid function tests revealed a thyroid-stimulating hormone level of <0.005 mIU/mL (reference range: 0.4 to 4.0 mIU/mL), free T4 of 27.04 pmol/L (reference range: 9.0 to 23.0 pmol/L), and a serum calcium level of 9.04 mg/dL (reference range: 8.5 to 10.5 mg/dL). A neck ultrasound showed a significantly enlarged thyroid gland with heterogeneous echotexture containing multiple well-defined nodules of varying sizes. The largest nodule in the right lobe measured 37 × 31 × 30 mm and was categorized as TI-RADS 3 (TR3), while the largest nodule in the left lobe measured 59 × 40 × 38 mm (TR3). Macrocalcifications were noted within some nodules. These findings were consistent with MNG and mild retrosternal extension on the left side.

2.4 Therapeutic intervention

The patient underwent a total thyroidectomy under general anesthesia, with the procedure lasting 90 minutes. A drain was placed, and the excised tissue was sent for histopathological examination. The surgery was completed without complications. The surgical specimen was fixed in 10% neutral-buffered formalin at room temperature for 24 hours, embedded in paraffin, and sectioned at 5 µm thickness. Histological examination was performed using hematoxylin and eosin (H&E) staining (Bio Optica Co.), applied for 1–2 minutes at room temperature, and evaluated under a light microscope (Leica Microsystems GmbH). Microscopic examination demonstrated a heterogeneous tumor arising within an MNG. Low-power evaluation revealed residual benign thyroid follicles adjacent to extensive malignant epithelial proliferation arranged in nests, accompanied by areas of necrosis. Higher-magnification examination showed malignant squamous cells with prominent intercellular bridges and extracellular keratin formation, intermixed with malignant spindle-cell proliferation. Additional sections demonstrated a clear transition between benign thyroid tissue and the malignant component, with numerous mitotic figures indicating a highly proliferative neoplasm. Collectively, these histopathological findings were consistent with ATC arising from one of the nodules within the longstanding MNG (Fig. 1).

2.5 Follow-up

The patient's vital signs remained stable following surgery, and levothyroxine 100 µg daily was initiated as replacement therapy. At the six-week follow-up, neck ultrasonography demonstrated a complex cystic nodule in the right thyroid lobe operative bed, along with small solid hypoechoic, hypovascular nodules in the left operative bed. The bilateral lateral cervical lymph nodes were largely unremarkable, except for two nodes in the right level III region; one exhibited features suggestive of malignancy and was subsequently confirmed on histopathological examination as an ATC-positive lymph node. The patient subsequently initiated weekly chemoradiotherapy with carboplatin (40 mg) and doxorubicin (60 mg). At the three-month follow-up, neck ultrasound demonstrated a well-defined hypoechoic, mildly vascular nodule measuring 22 × 19 × 18 mm in the right thyroid bed. At eight months, the patient developed pneumonia during chemotherapy, likely secondary to treatment-related immunosuppression, necessitating temporary interruption of therapy. Contrast-enhanced computed tomography (CT) of the chest and abdomen showed no evidence of distant metastasis at that time. However, subsequent CT imaging revealed an enlarged right supraclavicular lymph node or recurrent mass compared with prior studies, suggesting possible disease progression. In addition, two suspicious nodules were identified in the posterior segments of both lower lobes of the lungs. During this period, the patient's clinical condition deteriorated significantly, with evidence of rapid disease progression. Chemotherapy was later resumed in an attempt to control the advancing disease; however, despite reinitiation of treatment, the patient died eight months later.

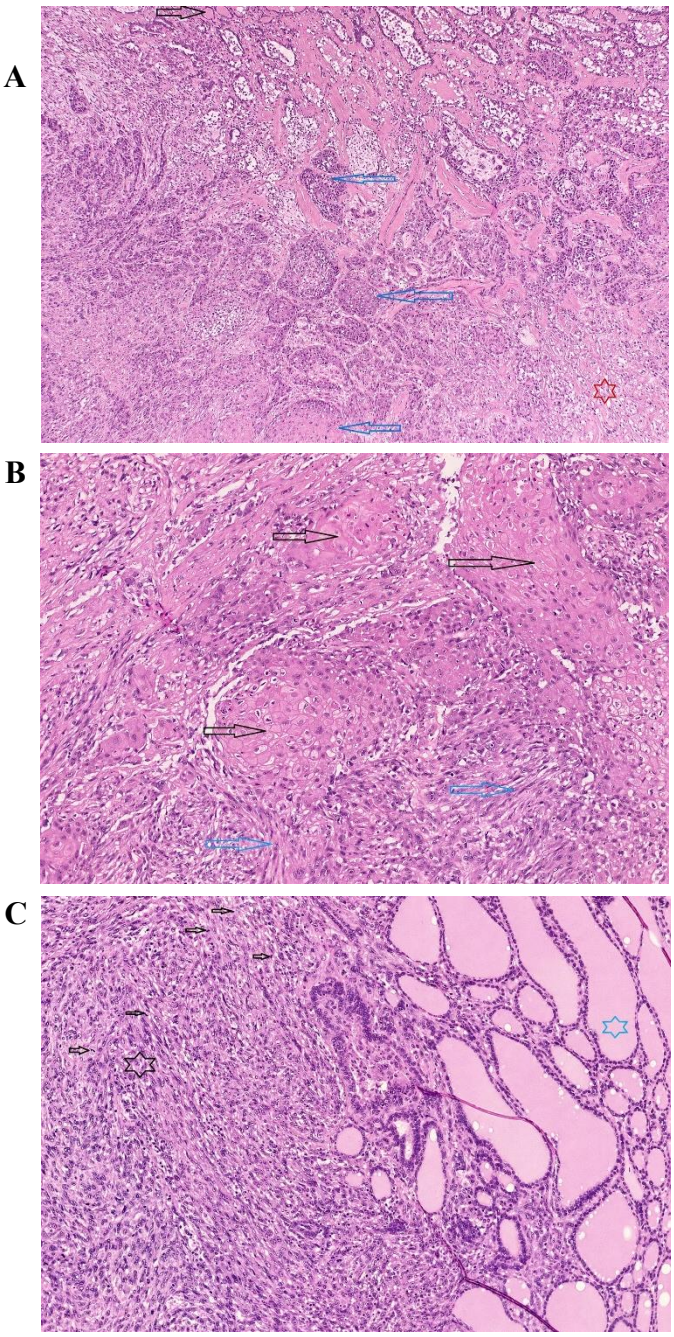

Figure 1. Histopathological analysis images: **A**) Low-magnification view (4x) showing benign thyroid follicles (dark arrow) in the upper left corner, with numerous nests of malignant squamous cells (blue arrows) and an area of necrosis (red star) in the lower right corner. Hematoxylin and eosin stain. **B**) High-magnification view (40x) of another tumor area, displaying nests of malignant squamous cells (dark arrows) with clear intercellular bridges and extracellular keratin formation, intermixed with malignant spindle cell proliferation (blue arrows). Hematoxylin and eosin stain. **C**) Another area of the tumor, showing the interface between benign thyroid tissue on the left (blue star) and malignant spindle cell proliferation on the right (dark star), with numerous mitotic figures present (black arrows). Hematoxylin and eosin stain.

3. Discussion

Anaplastic thyroid carcinoma is most commonly diagnosed between the ages of 55 and 65, with peak incidence occurring in the sixth and seventh decades of life. Anaplastic thyroid carcinoma is more common in women, although the degree of female predominance varies among studies, with reported female-to-male ratios ranging from approximately 1.2:1 to 3.1:1 [5]. ATC carries one of the highest mortality rates among solid malignancies, with a median survival of approximately 3–5 months after diagnosis. One-year and 10-year survival rates are estimated at 10–20% and less than 5%, respectively, although the validity of some long-term survival reports has been questioned. ATC accounts for up to 14–50% of annual thyroid cancer–related mortality. Recent advances in understanding its genetic and molecular pathogenesis have opened new avenues for the development of targeted therapies [2].

A notable feature of the present case is the prolonged 10-year history of MNG before the diagnosis of ATC. This clinical course differs from the typical presentation of ATC, which is characterized by the rapid enlargement of a neck mass over weeks to months, often accompanied by compressive symptoms such as dysphagia, dyspnea, and hoarseness. McIver et al. reported that rapidly progressive neck swelling is the predominant presenting feature in the vast majority of patients with ATC, reflecting the highly aggressive nature of the disease [10]. However, accumulating evidence suggests that ATC may arise through dedifferentiation of pre-existing benign thyroid lesions or well-differentiated thyroid carcinomas, a process that can occur over many years before the onset of the aggressive anaplastic phase [5]. Consistent with this hypothesis, several case reports have documented the development of ATC in patients with longstanding MNG, with disease durations ranging from several years to decades before malignant transformation became clinically evident (Table 1) [3,4,7,11-13]. The relatively indolent course observed in the present patient likely reflects the prolonged presence of MNG, with subsequent anaplastic transformation occurring within one of the pre-existing nodules rather than the de novo development of ATC. This observation highlights an important diagnostic consideration: although most MNGs follow a benign course and ultrasound risk stratification may suggest a low risk of malignancy, longstanding nodular thyroid disease may rarely harbor or develop highly aggressive malignancies. Therefore, new or worsening compressive symptoms, accelerated growth, or other concerning clinical changes in patients with chronic MNG should prompt careful reassessment, even when previous imaging findings appear relatively reassuring.

Thyroid carcinogenesis models have demonstrated that the progression from well-differentiated thyroid cancer to ATC is often linked to the loss of the p53 tumor suppressor gene. Additionally, many ATCs occur in elderly individuals with long-standing goiter or a history of thyroid malignancy, supporting the idea of anaplastic transformation. It is also well-established that the incidence of ATC is higher in regions endemic for goiter and among patients with inadequately treated papillary or follicular thyroid cancer [5]. Around 15–50% of patients presenting with ATC have extensive local invasion and distant metastasis at the time of diagnosis, with the lungs and pleura being the most common metastatic sites (up to 90% of metastatic cases) [11]. In the present case, although ATC developed from a longstanding MNG, no metastasis was observed either at the time of diagnosis or during the initial follow-up.

The time frame for MNG to progress to ATC can vary greatly. Villa et al. described a case with a goiter persisting for 50 years, marking the most prolonged reported duration. In contrast, Capraru et al. noted the onset of ATC after only six years of goiter [7,14]. The patient in this report had been diagnosed with MNG for 10 years. The progression of a decade-long MNG into ATC emphasizes the need for careful monitoring and timely intervention of MNGs. The diagnosis of ATC is typically established through clinical examination and fine-needle aspiration biopsy (FNAB). The FNAB plays a crucial role in confirming the diagnosis, demonstrating an accuracy rate of 90% [5]. The FNAB is widely recognized as a key component in the assessment of thyroid nodules, particularly in MNGs with suspicious imaging features. Maatouk et al. and Marcelino et al. have shown that FNAB is instrumental in identifying cytological abnormalities indicative of malignancy, allowing for timely intervention [4,11]. By contrast, in this case, the diagnosis of ATC was made only after total thyroidectomy. Moreover, no molecular or genetic analyses were conducted, limiting our understanding of the mechanisms underlying the progression from MNG to ATC. Molecular studies, such as the detection of p53 mutations or thyroglobulin gene alterations, have been shown to play a pivotal role in identifying the malignant potential of thyroid lesions [3,13].

The role of surgery in managing ATC remains controversial and is largely determined by the extent of the disease at diagnosis. Unfortunately, most patients present with a disease that has progressed beyond the scope of effective surgical resection. It is widely recognized that surgery alone is unlikely to significantly influence the disease's progression [5]. In the case reported by Camargo et al., the patient underwent a total thyroidectomy followed by postoperative radioiodine therapy [12]. In the present case, total thyroidectomy was initially performed because of the patient's longstanding toxic multinodular goiter, substantial thyroid enlargement, and compressive symptoms, including dyspnea and dysphagia. The diagnosis of ATC was established postoperatively through histopathological examination. Following surgery, the patient underwent adjuvant weekly chemoradiotherapy with carboplatin (40 mg) and doxorubicin (60 mg). Therefore, surgical resection not only provided definitive treatment for the symptomatic goiter but also facilitated subsequent oncologic management by reducing local tumor burden and enabling adjuvant therapy. While surgery alone is unlikely to significantly alter the overall prognosis of ATC, it may improve local disease control and form an essential component of multidisciplinary care in appropriately selected patients.

The development of pneumonia during treatment represented a significant clinical event in this case. Although the exact etiology could not be definitively established, several factors may have contributed. Chemotherapy with carboplatin and doxorubicin is associated with immunosuppression, which can increase susceptibility to respiratory infections [15]. Furthermore, the patient presented with dysphagia at diagnosis, raising the possibility of aspiration-related pneumonia [16]. The resulting interruption of chemoradiotherapy may have adversely affected disease control, as ATC is characterized by rapid progression and limited therapeutic windows. The interval without treatment may have contributed to tumor progression. This case highlights the importance of promptly identifying and managing treatment-related complications to minimize interruptions and maintain therapeutic continuity whenever possible.

Table 1. Review of the anaplastic thyroid carcinoma cases associated with MNG

Authors, year [Reference]	Age/ Sex	History	Clinical Presentation	TSH	Imaging	Met	Diagnostic method	Treatment	Follow-up
Shahi et al., 2020 [3]	54y/ M	Anterior neck swelling for 20 years	Pain, gradual swelling, dysphagia, shortness of breath, fever, loss of appetite	N/A	Multinodular goiter, multilocular cystic and solid mass, trachea shift	No	FNA, Cytology, US, CECT, Histo	Total thyroidectomy with neck dissection, IMRT radiation therapy	No progression for 12 weeks
Marcelino et al., 2014 [4]	70y/ M	A recent growth of a toxic MNG	Initial complaints of the growth of a goiter; later, dyspnea, hoarseness, and dysphagia	<0.001 mU/l	Showed two nodules (51 mm and 38 mm in diameter)	No	US, CT, TS, FNAB, Bronchoscopy	Methimazole, β-blockers, radiotherapy (70 Gy in 30 sessions). Tracheostomy, PEG tube	No symptom relief; refused surgery; the patient died from tracheal compression
Villa et al., 2004 [7]	76y/ F	Large, euthyroid multinodular goiter, Wegener's Granulomatosis	Weight loss, hoarseness, shortness of breath, and rapid goiter growth	<0.005 mU/L	Showed a large thyroid mass with coarse calcification extending into the mediastinum. The iodine-131 scan showed low uptake in the thyroid lobes	No	CT, FNA	Propranolol for thyrotoxic symptoms, high-dose oral dexamethasone, and urgent radiotherapy (30 Gy over 10 fractions)	Died after four weeks
Maatouk et al., 2009 [11]	90y/ M	Over 45 years of multinodular goiter (MNG) with thyrotoxicosis, multiple radioiodine (I-131) treatments	Dyspnea, dysphagia, neck swelling, unintentional weight loss	N/A	Showed large MNG with retrosternal extension and calcifications	No	CT, FNA, Histo	The patient refused management and was discharged	Died 2 days later; no autopsy was performed
Camargo et al., 2001[12]	53y/ F	Congenital deafness and a large multinodular goiter (150 g) present since childhood	Weight loss, hoarseness of voice, shortness of breath, rapid enlargement of goiter, noticed over 6 months.	2.8 mU/mL	Showed a large thyroid mass with retrosternal extension	Lung	Histo, genetic analysis	Total thyroidectomy, Radioiodine therapy	Died after one week due to severe hemoptysis
Yoon et al., 2020 [13]	46y/ F	LT4 therapy since age 14	Compressive symptoms	0.205 µIU/mL	6 cm hypoechoic nodule with calcification (right lobe) and 0.9 cm calcification (left lobe)	Lung, bone	FNA, CT, US, Histo, Molecular genetics	Total thyroidectomy, Lenvatinib 20 mg/day	Died in 14 months post-surgery

Abbreviations. M: *male,* ***F:*** *female,* ***y:*** *year,* ***LT4:*** *levothyroxine,* ***RT:*** *radiotherapy,* ***MNG:*** *multinodular goiter,* ***N/A:*** *not available,* ***FNA:*** *fine-needle aspiration,* ***CT:*** *computed tomography,* ***US:*** *ultrasound,* ***CECT:*** *contrast-enhanced computed tomography,* ***Histo:*** *histopathology,* ***FNAB:*** *fine-needle aspiration biopsy,* ***PEG:*** *percutaneous endoscopic gastrostomy,* ***IMRT:*** *Intensity-Modulated Radiation Therapy,* ***Met:*** *Metastasis*

This report has several limitations. First, fine-needle aspiration cytology was not performed preoperatively despite the presence of thyroid nodules, limiting the opportunity for preoperative cytological assessment. Second, preoperative cross-sectional imaging, including computed tomography, and laryngoscopic evaluation were not obtained despite the presence of compressive symptoms, which restricted the assessment of possible tracheal, esophageal, or laryngeal involvement before surgery. Third, no molecular or genetic analyses, such as evaluation of TP53 or other thyroid cancer–related mutations, were conducted, limiting insights into the mechanisms underlying the transformation from MNG to anaplastic thyroid carcinoma. Finally, as a single case report, the findings have limited generalizability and do not allow conclusions regarding causality or the incidence of malignant transformation in patients with longstanding MNG.

Conclusion

Longstanding MNG may progress to malignancy over time. Early diagnosis and appropriate management are critical to minimizing the risk of malignant transformation.

Declarations

Conflicts of interest: The authors have no conflicts of interest to disclose.

Ethical approval: Ethical approval was not required for this case report, in accordance with our institution's policies.

Consent for participation: Not applicable.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and the accompanying images following the initial diagnosis.

Funding: The present study received no financial support.

Acknowledgments: None to be declared.

Authors' contributions: AMS, ReMA: Major contributors to the conception of the study, as well as the literature search for related studies, and critical revision. RaMA, HAN, AHA, SHH, SAN, AAQ, HAA: Literature review, drafting the first and last versions of the manuscript, and processing of the tables and figures. All authors have read and approved the final version of the manuscript.

Use of AI: During the preparation of this work, the authors used ChatGPT (version 4.0) to enhance the clarity, coherence, and overall linguistic quality of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Data availability statement: Not applicable.

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