Case Report

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Surgery Section

Delayed Diagnosis of Follicular Thyroid Carcinoma with Skull Base and Lung Metastases in a Long-standing Neck Swelling: A Case Report

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ABSTRACT

Follicular Thyroid Carcinoma (FTC) is a differentiated thyroid cancer characterised by haematogenous metastases and the potential for distant metastases. This case report presents a 35-year-old female patient from rural India with a painless, gradually enlarging anterior neck swelling for the last 16 years. The patient presented with compressive and systemic symptoms, including stridor, hoarseness of voice, heat intolerance, and facial asymmetry. Imaging showed a large retrosternal thyroid mass with pulmonary and sphenoid bone metastases. A preoperative diagnosis of thyroid malignancy was made. The patient underwent total thyroidectomy with Level II, III, and IV neck dissection under general anesthesia, and histopathology identified FTC with distant metastases. The postoperative course was uneventful, and she was referred for Radioactive Iodine (RAI) therapy. This case highlights the importance of recognising and intervening early in cases of long-standing thyroid swellings to prevent complications from delayed diagnosis of malignancy.

Keywords: Endocrine neoplasms, Hyperfunctioning thyroid, Rural healthcare, Tracheal compression, Thyroidectomy

CASE REPORT

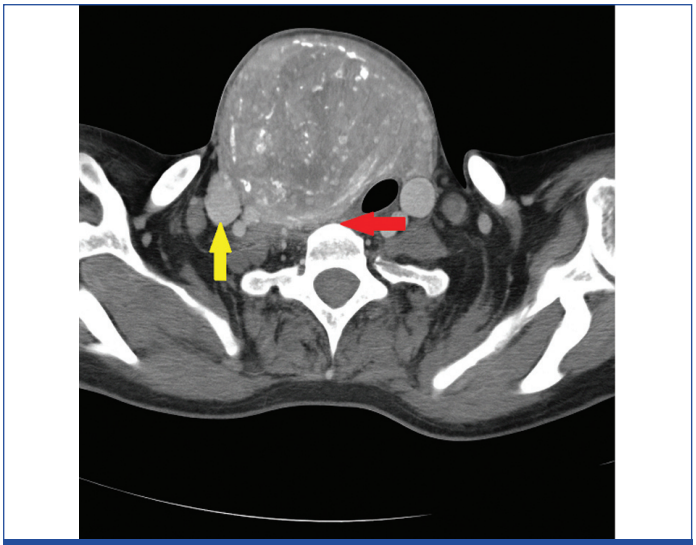
A 35-year-old female from a rural region of India, belonging to a lower socioeconomic background, presented with a painless, progressive swelling over the anterior aspect of the neck for the past 16 years. The swelling began insidiously and gradually increased to a size of 12×10 cm with ill-defined borders, without any associated pain or identifiable aggravating or relieving factors. The swelling had a nodular surface and was firm and nonmobile in consistency [Table/Fig-1]. Over the past eight years, she developed additional symptoms, including occasional headaches, drooping of the left angle of the mouth, inability to close the left upper eyelid, palpitations, dyspnea, stridor, hoarseness of voice, and heat intolerance. She also reported breathlessness on exertion for the past three to four years. There was no significant history of trauma, weight loss, or fever. In addition, facial asymmetry and inability to close the left eyelid added to the psychological distress and functional limitations such as impaired vision and oral competence. She had no significant past medical history apart from hypertension diagnosed one month ago, for which she was taking amlodipine 5 mg once daily. She is not a known case of diabetes mellitus, tuberculosis, bronchial asthma, stroke, ischaemic heart disease, or seizures. There is no relevant family history.

[Table/Fig-1]: The swelling over the anterior aspect of the neck of the patient.

A thyroid scintigraphy revealed a hyperfunctioning thyroid gland with heterogeneous increased tracer uptake, suggestive of toxic multinodular goitre. On general examination, the patient was conscious and oriented. She had pallor, was dehydrated, and had a BMI of 22 kg/m^2. Vitals were stable with a pulse rate of 96 bpm and blood pressure of 100/70 mmHg. On inspection, the neck was abnormally swollen with visible engorged superficial veins. On palpation, the neck swelling was grossly enlarged (approximately 12×10 cm), firm, nodular, nonmobile, with an ill-defined border. The lower border was felt at the sternal notch; the upper border was not palpable. Cervical lymphadenopathy was present. Auscultation over the neck revealed a systolic bruit.

A Contrast Enhanced Computed Tomography (CECT) of the neck showed a large, heterogeneously enhancing solid thyroid lesion in the right lobe with multiple calcific foci and retrosternal extension, indicative of a neoplastic process [Table/Fig-2]. A cranial Computed Tomography (CT) scan showed a dural-based enhancing soft-tissue lesion along the greater wing of the left sphenoid bone. CT thorax showed multiple nodules of soft-tissue density scattered in both lung fields, indicative of pulmonary metastases.

Based on clinical, radiological, and scintigraphic features, a provisional diagnosis of thyroid malignancy was rendered, with differentials of papillary carcinoma, follicular carcinoma, and toxic multinodular goitre. The patient was taken up for total thyroidectomy with Level II, III, and IV neck dissection under general anaesthesia. A Kocher's low collar transverse cervical incision was made and extended bilaterally up to the sternocleidomastoid muscles.



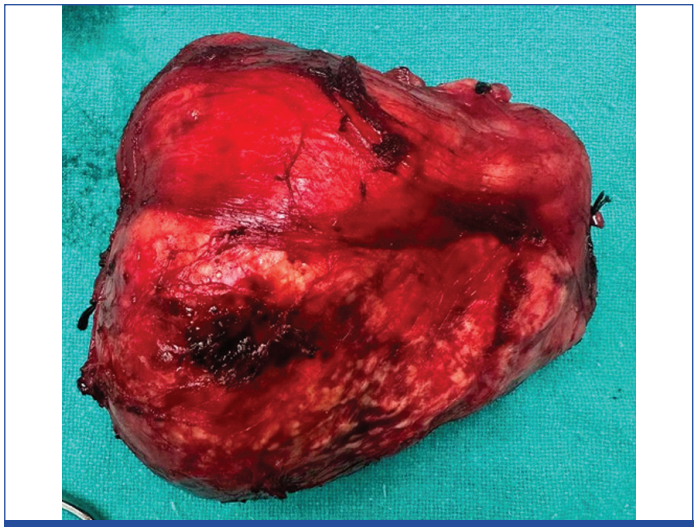
[Table/Fig-2]: CECT scan of neck.
Red coloured arrow pointing swelling showing retrosternal extension; Yellow coloured arrow pointing swelling compressing the right internal carotid artery

Subplatysmal flaps were raised. The right thyroid lobe was enlarged, and the strap muscles on the right were divided for better exposure. The superior, middle, and inferior thyroid pedicles were ligated and divided. The recurrent laryngeal nerve was identified and preserved. The parathyroid glands were identified and preserved. The left lobe appeared normal intraoperatively. A total thyroidectomy was performed along with dissection of Level II, III, and IV cervical lymph nodes. Haemostasis was achieved, a drain was placed, and the incision was closed in layers. The surgical procedure of total thyroidectomy with ipsilateral neck dissection is shown in [Table/Fig-3]. Excised specimen of thyroid after the total thyroidectomy surgery is shown in [Table/Fig-4].

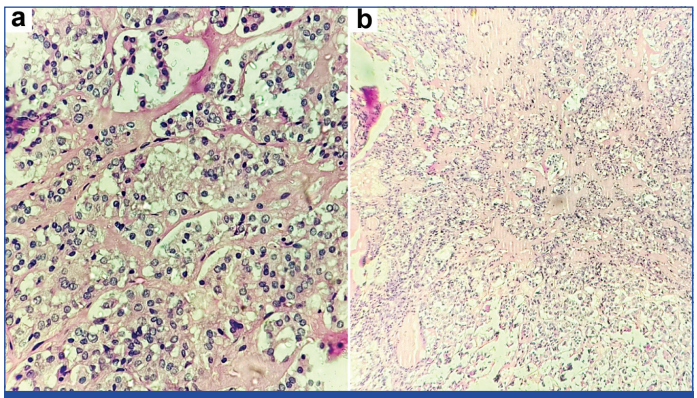
[Table/Fig-3]: Surgical procedure of total thyroidectomy with ipsilateral neck dissection.

On histopathological examination, the excised tumour specimen measuring 9.5×9×6 cm was encapsulated but showed evidence of capsular and minimal vascular invasion with lymphovascular infiltrates, characteristic of malignant follicular neoplasms. Numerous microfollicles and normofollicles were present, lined by uniform cuboidal to columnar cells with hyperchromatic nuclei and eosinophilic cytoplasm. Areas of haemorrhage and fibrosis were noted, with focal calcifications. Lymphovascular invasion was prominent, supporting the diagnosis of a tumour with metastatic potential. Deposits of metastasis were identified in dissected cervical lymph nodes (levels 2a, 3, 4, 5b), findings consistent with follicular origin. There was no evidence of papillary nuclear features or medullary differentiation, which helped to rule out other thyroid malignancies. Histopathological images of the excised specimen are shown in [Table/Fig-5].

The surgical procedure took four hours and 45 minutes and was uneventful. The postoperative course was smooth. The patient



[Table/Fig-4]: Excised specimen of thyroid after the total thyroidectomy surgery
Legend: Excised specimen measuring 6.6×6.2×7.4 cm.



[Table/Fig-5]: Histopathological images of excised specimen of patient.
Legend: Minimally invasive Follicular Thyroid Carcinoma (FTC) showing capsular invasion only with trabecular pattern growth: a) 40x magnification; b) 10x magnification.

was transferred to the Intensive Care Unit (ICU) intubated for close observation after total thyroidectomy with Level II-IV neck dissection under general anaesthesia. She was successfully extubated once haemodynamic stability and satisfactory respiratory status were ensured. Pain was adequately controlled, and there was no immediate evidence of bleeding or airway compromise. Serum calcium levels were tracked closely given the risk of postoperative hypocalcaemia due to possible parathyroid manipulation; calcium was kept within normal parameters, reflecting successful preservation and identification of the parathyroid glands intraoperatively. Voice quality was evaluated after extubation with no evidence of hoarseness or vocal cord paralysis, reflecting integrity of the recurrent laryngeal nerves. The drain was removed after 48 hours due to significantly decreased output and healthy wound healing, with no evidence of infection. Following surgery, the patient was started on levothyroxine replacement therapy and referred to oncology for further assessment and planning for high dose RAI therapy in consideration of distant metastasis to the lungs and sphenoid bone. A modest decline in serum thyroglobulin levels was observed over the next three months, suggesting a partial biochemical response. Clinically, the patient also had mild improvement in exertional dyspnoea and palpitations. However, follow-up imaging at six months showed stable disease in the lungs and sphenoid bone, without formation of any new metastatic lesions. Due to persistent metastatic disease despite partial response, additional RAI therapy cycles were planned. Based on the preserved functional status, stable disease course, and continued RAI avidity, the long-term prognosis remains hopeful, with potential for disease control over several years with ongoing suppressive therapy and surveillance.

DISCUSSION

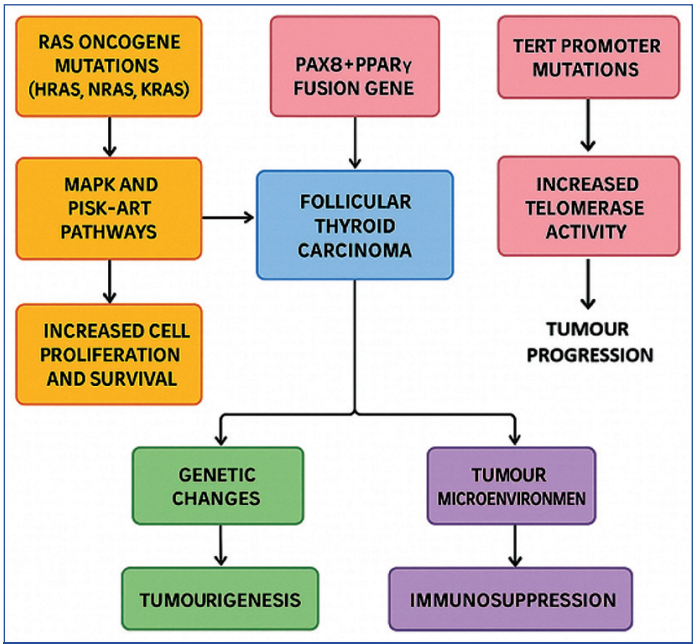
Thyroid swelling is a common clinical manifestation with a wide variety of causes ranging from benign to malignant [1]. The most

common causes of thyroid swelling are colloid goitre, Hashimoto's thyroiditis, subacute thyroiditis, and neoplastic conditions [2,3]. Subacute thyroiditis, which is usually of viral origin, typically presents with a painful, diffusely enlarged thyroid gland, elevated free T4, and extremely low radioiodine uptake [4]. Hashimoto's thyroiditis, also called chronic lymphocytic thyroiditis, shows hypothyroidism, goitre, and thyroid autoantibodies [2,5]. Rapid enlarging thyroid masses require work-up to exclude malignancy or abscesses [5]. Among thyroid malignancies, FTC accounts for approximately 15-20% of cases [6]. FTC usually appears as a single thyroid nodule, with peak incidence in women between 40 and 60 years of age [6,7]. FTC is often more aggressive than papillary thyroid carcinoma with a higher likelihood of vascular invasion and haematogenous metastasis leading to distal metastasis [7]. Diagnosis of FTC is challenging, as Fine Needle Aspiration Cytology (FNAC) cannot reliably distinguish it from benign follicular adenomas; definitive diagnosis requires histological evidence of capsular and vascular invasion [7]. FTC commonly metastasises to the lungs and bones [7]. However, metastasis to the sphenoid bone is exceedingly rare [8]. In such cases, patients may present with symptoms related to parasellar mass effect, such as cranial nerve deficits [8]. Pulmonary metastases may be asymptomatic or with respiratory symptoms, depending on the degree of lung involvement [9]. Toxic Multinodular Goitre (TMNG) is a frequent cause of thyrotoxicosis, especially in older people. It is characterised by an enlarged thyroid gland with multiple autonomously functioning nodules [10]. TMNG potentially mimics FTC, making it difficult to distinguish, especially if FTC has a mult nodular appearance and hyperthyroid symptoms [10]. The diagnostic method for FTC requires clinical evaluation, imaging, and histopathological evaluation [7]. Although fine-needle aspiration biopsy is a helpful initial method, it does not confer a definitive diagnosis of FTC [7]. Surgery and detailed histologic evaluation must be performed to ascertain capsular and vascular invasion, which are defining features of FTC [7]. Differential diagnosis and diagnostic features of thyroid swelling are described in [Table/Fig-6].

Condition	Key features	Diagnostic tools	Distinguishing features
Colloid goitre	Benign, painless diffuse or nodular enlargement, euthyroid state	Ultrasound, thyroid function tests	Absence of autoimmune markers or malignancy; colloid filled follicles on histology
Hashimoto's thyroiditis	Hypothyroidism, goitre, positive Anti Thyroid Peroxidase antibodies (anti-TPO)/ Anti Thyroglobulin antibodies (Anti-Tg) antibodies, firm gland	Thyroid Function Tests (TFTs), anti-thyroid antibodies, ultrasound	Autoimmune aetiology, lymphocytic infiltration on biopsy
Subacute (De Quervain's) thyroiditis	Painful thyroid, viral prodrome, elevated Erythrocyte Sedimentation Rate (ESR), low Radioactive Iodine (RAI) uptake	Thyroid scan, ESR, TFTs	Self-limiting course, painful thyroid, low Radioactive Iodine Uptake (RAIU)
Toxic Multinodular Goitre (TMNG)	Enlarged thyroid with multiple nodules, signs of thyrotoxicosis, often in elderly	TFTs, thyroid scan (patchy uptake), ultrasound	Multiple functioning nodules, absence of capsular/ vascular invasion
Follicular adenoma	Solitary thyroid nodule, benign on histology	FNAC, ultrasound	Cannot be distinguished from FTC cytologically; no capsular/ vascular invasion on histology
Follicular Thyroid Carcinoma (FTC)	Solitary nodule, more common in females aged 40-60, with potential for distant metastases	Ultrasound, FNAC (limited), surgery with histology for definitive diagnosis	Histological proof of capsular and/or vascular invasion; haematogenous spread (lungs, bones)
FTC with pulmonary metastases	Asymptomatic or respiratory symptoms, depending on lung involvement	Chest X-ray, CT thorax, whole-body radioiodine scan	Multiple lung nodules with radioiodine uptake in post-thyroidectomy scans
FTC with sphenoid metastases	Rare; headache, cranial nerve palsies, signs of parasellar mass	Magnetic Resonance Imaging (MRI) brain, CT head, biopsy of lesion if accessible	Unusual metastatic site, diagnosis via neuroimaging and confirmation with histology

[Table/Fig-6]: Differential diagnosis and diagnostic features of thyroid swelling.

The FTC originates from the follicular epithelial cells of the thyroid and is characterised by capsular and vascular invasion. Certain genetic alterations leading to activation of key cellular pathways, such as RAS oncogene mutations (HRAS, NRAS, KRAS), are found in an estimated 40-50% of FTC. RAS oncogene mutations further activate the Mitogen Activated Protein Kinase (MAPK) and PI3K-AKT pathways, increasing cell proliferation and survival. The PAX8-PPARγ fusion gene, caused by a translocation (t(2;3)(q13;p25)), occurs in roughly one-third of FTC, suggesting a role in tumourigenesis by interfering with normal gene transcription. FTC aetiopathogenesis is also influenced by several other genetic changes. Telomerase Reverse Transcriptase (TERT) promoter mutations, which are linked to an aggressive tumour phenotype and poor prognosis, may be related to increased telomerase activity. Increased telomerase activity allows a cell to bypass senescence and continue dividing. The tumour microenvironment in FTC may also become immunosuppressive over time, contributing to tumour progression [Table/Fig-7].



[Table/Fig-7]: Pathogenesis and progression of Follicular Thyroid Carcinoma (FTC).

The delayed diagnosis and treatment in the given case highlight challenges common in such low-resource settings, such as rural India [11]. Patients from rural backgrounds who are socioeconomically disadvantaged often experience diagnostic delays due to limited access to healthcare infrastructure, lack of specialised medical personnel, and poor health-seeking behaviour [11]. Geographic barriers, coupled with economic constraints and low health literacy among people, lead to late stage presentations of thyroid malignancies in resource-limited settings [12]. The patient's 16-year history of a progressively enlarging neck mass without medical evaluation reflects systemic healthcare deficits, including inadequate screening programmes and the absence of community-level awareness regarding early warning signs of malignancy [13]. Moreover, cultural stigma, fear of surgery, and the lack of prioritisation

Case	Patient details	Presentation	Diagnosis method	Surgical intervention	Outcome and clinical insights
Ogawa Y et al., [20]	65-year-old Japanese female	Asymptomatic skull lesion with pulmonary metastasis; later intracranial extension	Histopathology + Immunohistochemistry	Total thyroidectomy	Died due to spontaneous intracerebral haemorrhage; had complex course and diagnostic delay; skull base involvement detected radiologically
Aoyama M et al., [21]	57-year-old Japanese female	Skull + lung metastasis, developed Graves' disease after RAI	Imaging, Histopathology	Thyroidectomy + RAI	Hyperthyroidism post-RAI complicated further treatment; ultimately died from progressive disease
Altinay S et al., [22]	68-year-old Turkish female	Retro-orbital tumour mimic; widespread metastases (lungs, bones, skull base)	PET-CT, IHC (TTF-1, thyroglobulin)	Total thyroidectomy	Occult thyroid primary; emphasised role of FDG-PET and interdisciplinary approach in unusual metastases
Luján-Martínez D et al., [23]	80-year-old Spanish male	Acute neuro symptoms after fall; frontal lobe lesion; incidental thyroid mass	Brain biopsy + Histopathology + Imaging	Total thyroidectomy	Sudden neuro onset led to FTC diagnosis; highlights importance of metastasis workup in elderly
Taywade SK et al., [24]	82-year-old Indian female	Longstanding goitre, parietal scalp mass, pituitary insufficiency from sellar metastasis	Imaging (MRI + PET-CT), Histopathology	Total thyroidectomy	Hypopituitarism required rhTSH for RAI; non-avid metastases posed therapeutic challenge
Present case	35-year-old Indian female (rural, low SES)	Longstanding toxic multinodular goitre, dyspnea, hoarseness, facial palsy, proptosis; metastasis to sphenoid and lungs	CT/MRI, Histopathology	Total thyroidectomy + ipsilateral neck dissection	Good recovery, no complications; early systemic symptoms enabled timely surgery; highlights impact of access to care

[Table/Fig-8]: Comparative analysis of present case and previously published cases [20-24].

of health among women in rural India further contribute to delays in diagnosis [12].

To improve early diagnosis and timely intervention in such cases, strategies suitable for low-resource settings include community-based screening and mobile thyroid clinics, as used in certain rural regions of India, which have resulted in identification of goitrous lesions and malignancies at earlier stages [12,14]. Training of primary healthcare workers in basic thyroid examination techniques and recognition of symptoms can significantly aid early referrals. The use of Point-of-Care Ultrasound (POCUS) by trained, non-specialist providers is emerging as a cost-effective, feasible method to triage neck masses for further evaluation [15]. Integration of a thyroid assessment protocol into national non communicable disease programmes, along with awareness campaigns to promote health education, can address both system- and individual-level barriers [13,14]. Follow-up using telemedicine, subsidisation of imaging tests, and government-sponsored diagnostic programmes can be crucial for ensuring equitable access to diagnosis of thyroid malignancies in rural at-risk populations [12].

Patients with FTC and distant metastases require a multistep, risk-adapted therapeutic approach [16]. The initial treatment approach involves total thyroidectomy, which enables effective RAI ablation and monitoring of thyroglobulin [16]. Patients should receive high-dose RAI until all metastatic uptake resolves, as achievement of an RAI-negative scan correlates with excellent 10-year survival, whereas RAI-refractory disease portends poor outcomes [16,17]. In cases of symptomatic lesions or bone metastases from FTC, resection, stabilisation, and External Beam Radiotherapy (EBRT) offer good symptomatic relief, which synergises with RAI and improves disease control [18]. For FTC with RAI-refractory metastatic disease, systemic therapy with multikinase inhibitors (e.g., sorafenib, lenvatinib) is also useful, and newer targeted agents such as BRAF/MEK inhibitors, REarranged during Transfection (RET) and Neurotrophic Tyrosine Receptor Kinase (NTRK) inhibitors are gaining traction in molecularly selected cases [18]. Prognostic factors that influence the selection and intensity of therapies include age ≥ 55 years, degree of vascular and extrathyroidal invasion, invasive histology, and initial metastasis; these parameters aid risk stratification and guide the need for aggressive intervention [19].

The previously published case by Ogawa Y et al., involving a 65-year-old Japanese woman, is similar to the present case, specifically in terms of the shared diagnosis of FTC with distant metastases [20]. A comparative analysis of the present case and previously published cases is described in [Table/Fig-8] [20-24].

CONCLUSION(S)

This case of a 35-year-old Indian female serves as a reminder of the need for early diagnosis and intervention in chronic thyroid swellings. It also underscores the challenges of rural practice, where healthcare is limited and patients may present with advanced disease. Increased awareness of thyroid conditions that may have an aggressive course is essential, with timely imaging and care from a multidisciplinary team to improve outcomes in FTC-like malignancies with compressive and systemic symptoms.

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