

Distant Soft-tissue Metastasis of Follicular Thyroid Carcinoma: A Series of Three Cases

RITUPARNA DAS¹, SAYANTAN JANA², BISWANATH PAUL³, ANURIMA NAYAK⁴

ABSTRACT

Follicular Thyroid Carcinoma (FTC) accounts for 25–40% of thyroid cancers and is more common in women. The peak incidence is between 40 and 60 years of age. The extent of invasion and stage at presentation are the main prognostic factors of FTC. Invasive carcinoma often presents with systemic metastases to the lungs, skeleton, and brain, with other less common sites including the breast, muscle, and skin. Soft-tissue metastasis is a rare presentation; only limited data are available in the literature. Here, we report three adult females with soft-tissue metastasis of FTC in the gluteal, facial, and inguinal regions. All cases had a prior diagnosis of FTC and had undergone thyroidectomy. During postoperative evaluation, they presented with soft-tissue swelling. All cases presented six months to one year after successful thyroidectomy. In two cases, metastasis occurred in distant soft-tissue sites such as the thigh and gluteal region, whereas in one case the face (a closer region) was involved. The cases were provisionally diagnosed by Fine Needle Aspiration Cytology (FNAC), followed by tru-cut biopsy and Histopathological Examination (HPE). The diagnosis was confirmed by immunohistochemical staining. As metastasis of FTC to soft-tissue is unusual, postoperative follow-up of all FTC patients is mandatory for early detection and treatment.

Keywords: Fine needle aspiration cytology, Immunohistochemical stain, Post-thyroidectomy follow-up, Prognostic factor, Thyroidectomy, Tru-cut biopsy

INTRODUCTION

FTC is a thyroid malignancy arising from follicular cells in which the diagnostic nuclear features of Papillary Thyroid Carcinoma (PTC) are absent. The lesions are usually encapsulated and show invasive growth [1]. It is more common in women (3:1) and the peak incidence is between 40 and 60 years of age [2]. The prognosis depends largely on the extent of invasion and stage at presentation. Invasive FTC often presents with systemic metastases to the lungs, skeleton, and brain [3]. Other less common sites include the breast, muscle, and skin [4]. Subcutaneous soft-tissue metastasis is relatively rare and difficult to diagnose [3]. Tumours with any vascular (venous) invasion may show evidence of haematogenous metastasis even if only 1–2 vessels are invaded. However, the larger the number of vessels involved, the worse the prognosis [1]. The incidence of distant metastasis of FTC has been reported to be between 11% and 25% [3,5]. Tissue diagnosis is necessary to confirm the diagnosis of metastatic disease [4]. In our case series, three adult females with soft-tissue metastasis of FTC have been reported involving the gluteal region, face, and thigh region.

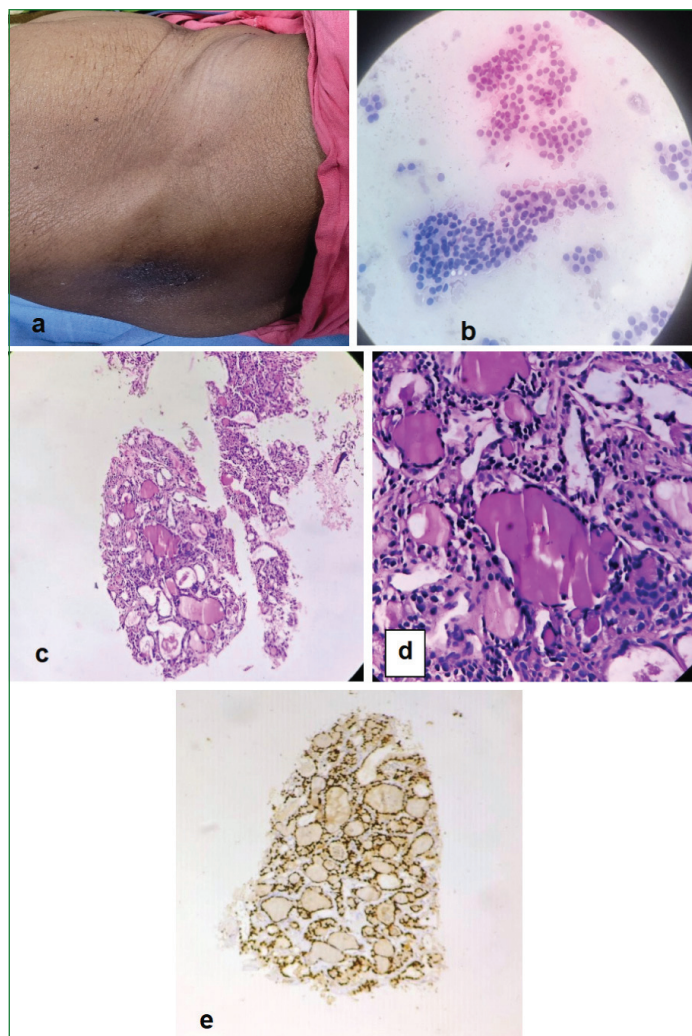
CASE SERIES

Case 1

A 58-year-old female presented to the Otorhinolaryngology Department with a painless neck swelling measuring 6×4 cm and hoarseness of voice for six months, without any lymphadenopathy. She underwent ultrasound (USG) of the neck followed by FNAC from the neck swelling, and thyroid function status along with routine haematological tests were performed. Routine tests were within normal limits except for a mildly raised free T3 level (264 ng/dL). On USG, it was a TI-RADS 4 lesion featuring a hypoechoic, irregularly margined lesion with a peripheral halo in the right thyroid lobe involving the isthmus. On FNAC, it was diagnosed as Bethesda IV, showing predominant microfollicular pattern of thyroid follicular cells in a colloid-free background, raising the possibility

of FTC [Table/Fig-1a]. Subsequently, she underwent USG of the abdomen and Computed Tomography (CT) chest, which showed no lung nodules, abdominal lymphadenopathy, or any metastatic deposits suggesting metastatic thyroid carcinoma. Thereafter, total thyroidectomy was performed, and histopathology diagnosed FTC, featuring a trabecular pattern of arrangement of small to normal-sized thyroid follicles, brisk mitotic activity, and capsulovascular invasion; no further investigations were performed. The FTC did not invade extra thyroidal soft-tissues and was staged as pT3aNxMx.

Seven months after total thyroidectomy, she presented with a tender, progressive swelling in the inguinal region of the right thigh [Table/Fig-1b] and was referred to our surgery department. USG of the inguinal region and FNAC from the swelling were performed. Clinically, it was diagnosed as lymph node swelling, but USG revealed a solid hypoechoic lesion with partially regular margins, exclusively involving adjacent muscular regions and not infiltrating the underlying bone. The lesion was provisionally diagnosed as a neoplastic lesion, possibly a lymph node or a soft-tissue lesion. FNAC showed thyroid follicular cells arranged in microfollicles and sheets with nuclear crowding in a background devoid of colloid. A provisional diagnosis of metastatic deposit was given, followed by core needle biopsy. HPE revealed thyroid follicular cells arranged in follicular patterns of uniform size, lacking nuclear features of PTC [Table/Fig-1c,d]. Follicles were filled with colloid, and fragments of fibrous tissue were also seen. Immunohistochemistry (IHC) confirmed the diagnosis of a metastatic deposit of FTC in the right inguinal soft-tissue, with TTF-1 positivity [Table/Fig-1e]. Finally, it was diagnosed as an FTC metastatic deposit in the inguinal region soft-tissue. As the patient had a prior history of FTC and the recent lesion was TTF-1 positive, no further IHC was performed. Positron Emission Tomography (PET) scan was advised, but the patient could not afford it. Following the diagnosis of metastatic FTC, the patient was referred to the radiation oncology department and treated with radiotherapy followed by wide local excision.



[Table/Fig-1]: a) Swelling in the inguinal region; b) Showing predominant microfollicular pattern of thyroid follicular cells in a colloid free background (Leishman Giemsa stain, 100x magnification); c,d) Showing fragmented tissue having thyroid follicular cells arranged in follicular patterns of uniform size lacking nuclear features of PTC (H&E stain, 100x and 400x magnification); e) IHC showing nuclei of follicular cells stained with TTF-1 in 100x magnification.

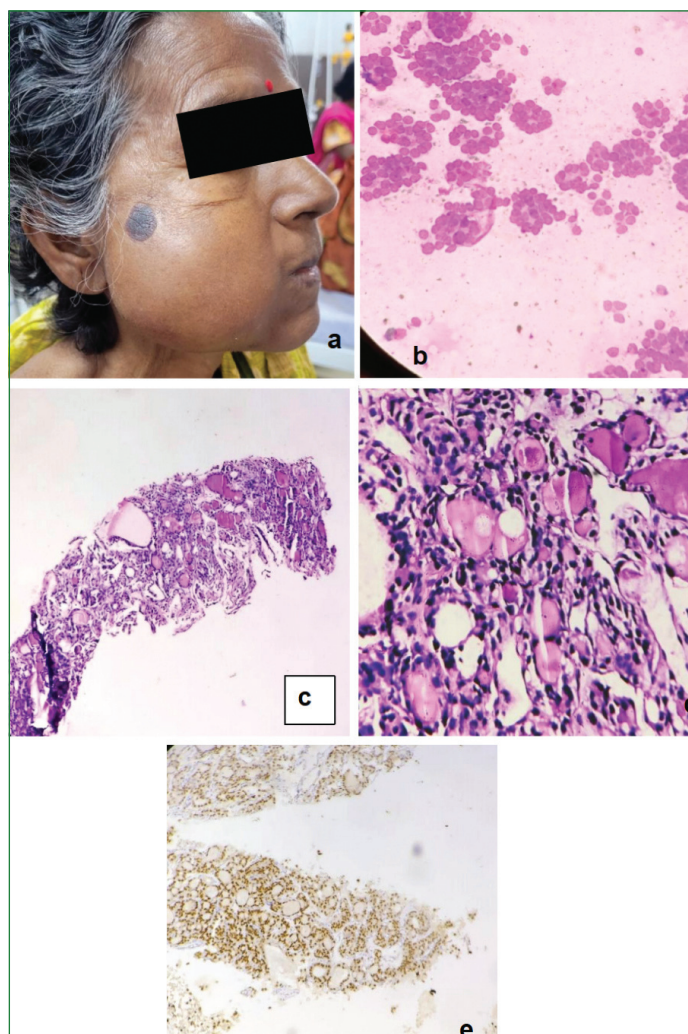
Case 2

A 64-year-old female previously diagnosed with FTC, pT2NxMx, presented to Surgery Department with a painful swelling for eight months measuring 8×4 cm in the right maxillofacial region during postoperative evaluation after thyroidectomy performed at an outside private institution [Table/Fig-2a]. CT scan showed an irregular hypodense mass exclusively in the right maxillofacial soft-tissue, not invading the underlying bone, provisionally diagnosed as a neoplastic lesion arising from soft-tissue. FNAC was performed and the diagnosis of metastatic deposit was given, as the cytological smears showed mononuclear thyroid follicular cells predominantly arranged in a microfollicular pattern with mild nuclear crowding in a clear background without colloid [Table/Fig-2b]. It was later diagnosed as a metastatic deposit of FTC in the right maxillofacial soft-tissue through HPE of core needle biopsy, which featured follicles of uniform size lined by thyroid follicular cells without nuclear features of PTC [Table/Fig-2c,d] and with TTF-1 positivity on IHC [Table/Fig-2e]. Based on the past treatment history, current histopathological and immunohistochemical findings, the diagnosis was FTC metastatic deposit in the right maxillofacial soft-tissue. In the follow-up period, the patient died.

Case 3

A 62-year-old female came to Pathology Department to review two Hematoxylin and Eosin-stained slides along with the corresponding blocks from a core needle biopsy. After careful history taking, we learned that she had been diagnosed with FTC, pT3bNxMx, two years

earlier after total thyroidectomy and had been under postoperative follow-up every three to six months. There had been no abnormalities

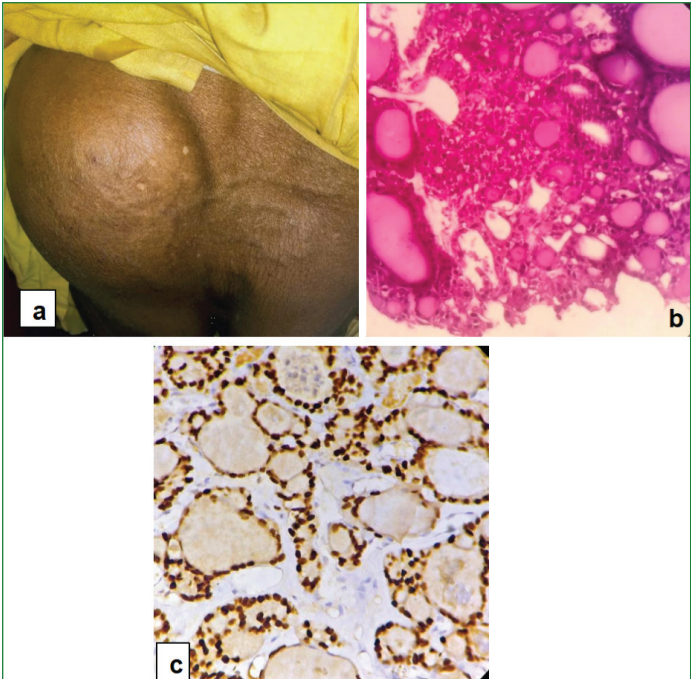


[Table/Fig-2]: a) Right maxillofacial swelling; b) Showing predominant microfollicular pattern of thyroid follicular cells in a colloid free background (Leishman Giemsa stain, 100x magnification); c,d) Showing fragmented tissue having thyroid follicular cells arranged in follicular patterns of uniform size lacking nuclear features of PTC (H&E stain, 100x and 400x magnification); e) IHC showing nuclei of follicular cells stained with TTF-1 in 100x magnification.

except for a gluteal swelling that had occurred seven months earlier; it was tender on palpation and gradually increased in size [Table/Fig-3a]. A private practitioner had clinically diagnosed it as a soft-tissue neoplasm, but USG of the gluteal region showed a solid hypoechoic lesion with irregular margins, and the provisional diagnosis was metastatic deposit in soft-tissue, as FNAC performed during follow-up showed mononuclear thyroid follicular cells predominantly arranged in a microfollicular pattern in a colloid-free background. It was later diagnosed as a metastatic deposit of FTC in subcutaneous soft-tissue on HPE of the core needle biopsy, featuring follicles of uniform size without any nuclear features of PTC, with a fragment of fibrous tissue [Table/Fig-3b].

During review of the two H&E-stained slides and their corresponding blocks, the histopathological diagnosis from the outside laboratory and institution was compatible with ours after considering the previous cytological smears and immunohistochemical examination featuring TTF-1 positivity [Table/Fig-3c]. The final diagnosis, based on the past treatment history and present histopathological and immunohistochemical examination, was a metastatic deposit of FTC in the left buttock. During follow-up, the patient was lost to follow-up.

In this case series, the metastatic sites were predominantly soft-tissue involving the gluteal region, thigh, and face, respectively; in the gluteal region it exclusively involved muscle, whereas the others involved multiple soft-tissue components such as muscle, adipose tissue, and fibrous tissue. All three patients were aged about 58-64



[Table/Fig-3]: a) Swelling in the gluteal region; b) Showing fragmented tissue having thyroid follicular cells arranged in follicular patterns of uniform size lacking nuclear features of PTC (H&E stain, 100x and 400x magnification). c) IHC showing nuclear positivity of TTF-1 in thyroid follicular cells in 400x.

years. One died, one was referred for further radiation therapy, and one was lost to follow-up. Molecular analysis could not be performed due to unavailability. Demographic, clinical, histopathological, immunohistochemical, and follow-up data of the present study are summarised in [Table/Fig-4].

DISCUSSION

The FTC is the second most common differentiated thyroid malignancy. It is difficult to distinguish between thyroid follicular carcinoma and follicular adenoma before thyroidectomy [4]. The diagnosis of FTC requires histological evidence of capsular and/or vascular invasion. FTC is subclassified into three groups: (1) minimally invasive (capsular invasion only); (2) encapsulated

angioinvasive; and (3) widely invasive. Tumours with limited invasion of vessels (<4) have a better prognosis than those with extensive vascular invasion [1].

Widely invasive follicular carcinoma often presents with systemic metastases, and as many as one-half of affected patients succumb to their disease within 10 years [2]. Around 5.4-11% of patients with FTC have distant metastases, which usually carry a poor prognosis [1,3,4]. Distant metastases as an initial presentation are seen in 1-3% of cases and are associated with a poor prognosis (10-year survival rate of 50%). FTC is known to metastasise not only to the lung and bone but also to rare sites (brain, breast, liver, kidney, muscle, and skin) and to unusual soft-tissue sites such as the suprarenal region and pelvis [6]. In this study, the first case had capsular and vascular invasion and presented with distant metastasis on follow-up, while the invasion status of the remaining two cases was unknown because they were diagnosed outside.

Soft-tissues account for more than 40-50% of body weight; however, hematogenous metastases to these areas are uncommon. It has been hypothesised that muscle movement and mechanical destruction of tumour cells, nonoptimal muscle pH, and the muscle's ability to remove tumour-produced lactic acid have been postulated to contribute to the resistance of skeletal muscle metastases [7]. Thus, skeletal muscle metastases are very rare, with an occurrence rate of about 0.86% in the total cancer patient population [8].

Following a thorough literature search, we found the following cases of soft-tissue metastasis from FTC. A brief literature review of previously reported cases is summarised in [Table/Fig-5] [3,8-12]. Regarding soft-tissue metastasis in the gluteal region, Tunio MA et al., first described synchronous metastatic infiltration of the gluteal muscles in a 55-year-old woman as an initial presentation of FTC [9]. Gupta P et al., reported ten female patients diagnosed with metastatic follicular carcinoma of the thyroid; six presented with subcutaneous and soft-tissue swelling and metastasis, while the other cases included metastases to bone, lung, and breast [4]. Sevinc A et al., reported a 58-year-old female with FTC who initially presented with a soft-tissue mass in the right scapular region, which later spread to multiple soft-tissue sites, the orbits, lung, and bone

| Case no. | Age | Sex | Clinical details | Site | HPE | IHC | Impression | Follow-up |
|-------------|-----|--------|--|--------------|---------------------------------------|----------|--|---|
| First case | 58 | Female | Swelling in inguinal region of unilateral thigh and weight loss. | Right thigh | Metastatic Deposit; suggestive of FTC | TTF1 (+) | Follicular carcinoma of thyroid metastasis | Referred to Radiation Oncology Department |
| Second case | 64 | Female | Facial swelling causing cosmetic deformity. | Right cheek | Metastatic Deposit; suggestive of FTC | TTF1 (+) | Follicular carcinoma of thyroid metastasis | Died |
| Third case | 62 | Female | Swelling in gluteal region and weight loss | Left buttock | Metastatic Deposit; suggestive of FTC | TTF1 (+) | Follicular carcinoma of thyroid metastasis | Lost during follow-up |

[Table/Fig-4]: Demographic, clinical, histopathological, immunohistochemical and follow-up data of recent study.

| Name of Author | Age | Gender | No. of cases | Clinical presentation | Site of metastasis | Before or after thyroidectomy | Follow-up | Place of study |
|--------------------------|-----|--------|--------------|---|--|--------------------------------|---|----------------|
| Sevinc A et al., [10] | 58 | Female | 1 | Soft-tissue mass in right scapular region. | Right scapular soft-tissue metastasis | Before thyroidectomy | Patient showed disseminated metastasis but was stable after chemotherapy. | Turkey |
| Basu S et al., [11] | 54 | Female | 1 | Left sided proptosis, epiphora and blurred vision | Left retro-orbital soft-tissue metastasis | Before thyroidectomy | Total thyroidectomy followed by radioiodine therapy | India |
| Tunio MA et al., [9] | 45 | Female | 1 | Right buttock swelling and lethargy | Metastasis to right sided gluteus medius muscle | Before thyroidectomy | Patient lived after palliative radiotherapy and total thyroidectomy | Saudi Arab |
| Olejarski J et al., [12] | 73 | Female | 1 | Right thigh mass. | Soft-tissue metastasis in right proximal, mid femoral region. | Before thyroidectomy | Radiation | USA |
| Xue Y L et al., [8] | 65 | Female | 1 | Right thigh mass | Right thigh and buttock muscle metastasis | Before thyroidectomy | Surgical Excision of thigh mass, Total thyroidectomy & PET/CT Scan | China |
| Wang Y et al., [3] | 62 | Male | 1 | Anterior neck mass | Bilateral anterior neck soft-tissue metastasis on the surface of sterno-cleidomastoid muscle | Four years after thyroidectomy | Surgical excision followed by periodic postoperative Ultrasonography (USG). | China |

[Table/Fig-5]: A brief literature review of previously reported cases [3,8-12].

[10]. Basu S et al., reported a 54-year-old woman presenting with unilateral proptosis resulting from solitary retroorbital soft-tissue metastasis from FTC of the thyroid [11]. The patient underwent total thyroidectomy followed by radioiodine therapy. Olejarski J et al., reported a 73-year-old woman presenting with an enlarging right thigh mass as an initial presentation of metastatic FTC [12]. Xue YL et al., reported large thigh and buttock muscle metastases as the initial manifestation of FTC in a 65-year-old female [8]. Wang Y et al., reported a case of metastatic FTC in a 62-year-old male, invading surrounding striated muscle, adipose tissue, and vessels, with TTF-1 positivity [3]. The specimens of these nodules were further investigated for TERT promoter mutation, and a TERT promoter mutation was detected.

According to the 8th edition of the AJCC for differentiated thyroid cancers, patients aged 55 years or older with distant metastasis are staged as IVB, irrespective of tumour size and nodal status [13]. The cases in the present study also involve patients older than 55 years and demonstrate a poorer prognosis. Current guidelines for the treatment of distant metastases from FTC include surgery, radiotherapy, and Iodine-131 therapy [5].

CONCLUSION(S)

In this case series, the metastatic sites were predominantly soft-tissue involving the gluteal region, thigh, and face, respectively. In the gluteal region, metastasis exclusively involved muscle, whereas the other sites involved multiple soft-tissue components such as muscle, adipose tissue, and fibrous tissue. Metastasis of FTC to soft-tissue is an unusual presentation that can lead to diagnostic difficulties; therefore, postoperative follow-up after thyroidectomy and evaluation for capsular and vascular invasion are mandatory for early detection and treatment.

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