

PD-L1-positive Anaplastic Transformation in a BRAF V600E Expressing Papillary Thyroid Carcinoma with Cutaneous Metastasis: An Unusual Case Report

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ABSTRACT

Cutaneous metastasis in thyroid carcinoma is extremely rare (<1%) and usually accompanies follicular and papillary thyroid carcinoma (PTC). Less than 20 cases of anaplastic thyroid carcinoma with cutaneous metastasis have been described so far. We present a case of a 53-year-old male who presented with a longstanding thyroid swelling with a history of rapid increase for 2 months associated with bilateral cervical lymphadenopathy. Fine needle aspiration cytology revealed a variable picture from both lobes of the thyroid with PTC in the left lobe and anaplastic carcinoma in the right lobe. Total thyroidectomy with bilateral modified radical neck dissection was performed which supported the cytology findings. BRAF V600E and PD-L1 expression were analyzed using immunohistochemistry. Postoperatively, the patient received radioactive iodine ablation therapy, but developed cutaneous metastasis in the neck and thoracic region, which on fine needle aspiration cytology revealed metastatic anaplastic thyroid carcinoma. The patient did not respond to the therapy and succumbed to the disease within a month after surgery. Cutaneous metastasis may develop in thyroid carcinoma, which must be differentiated from skin adnexal malignancies due to different management strategies. BRAF V600E and PD-L1 expression in primary thyroid tumors can identify the possible cases who may benefit from immunotherapy, which can lead to an improved overall survival.

Keywords: Anaplastic transformation, Cutaneous metastasis, Papillary, Thyroid.

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INTRODUCTION

Cutaneous metastasis is a rare manifestation of visceral malignancies, the most common primary being breast cancers, and may mimic skin adnexal cancers.^{1,2} Thyroid carcinoma with cutaneous metastasis usually occurs in association with diffuse diseases and typically is associated with a poor prognosis.¹ Cutaneous metastasis from anaplastic thyroid carcinomas is even rarer with only a handful of cases reported so far.³ Most commonly, cutaneous metastasis from a thyroid carcinoma develops in the scalp region.^{1,4} We present an interesting case of anaplastic transformation in PTC associated with cutaneous metastasis in the thoracic region. We present the following case in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/gs-20-845>).

CASE PRESENTATION

A 53-year-old male presented with a thyroid swelling which progressively increased in size for 12 years followed by a rapid increase for the last 1 month and was associated with weight loss. The patient also complained of compressive symptoms like dysphagia and hoarseness of voice for the last 15 days. The complete blood count revealed anemia. Biochemically, the patient was euthyroid. On physical examination, there was a firm-to-hard nodular swelling on the anterior aspect of the neck that moved with deglutition and was associated with bilateral cervical lymphadenopathy.

Contrast-enhanced computed tomography (CECT) revealed a heterogeneously enlarging soft tissue mass with coarse calcifications and cystic changes, measuring 5.2 × 4 × 4.2 cm, in the left lobe of the thyroid. Multiple enlarged lymph nodes were noted bilaterally at levels II through V with necrotic changes. Contrast-

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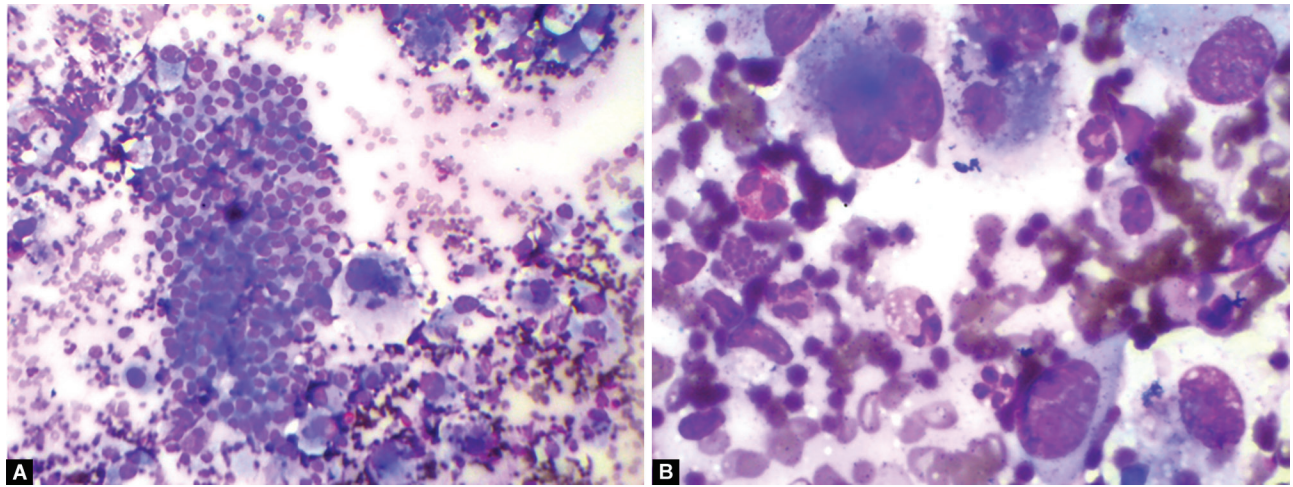
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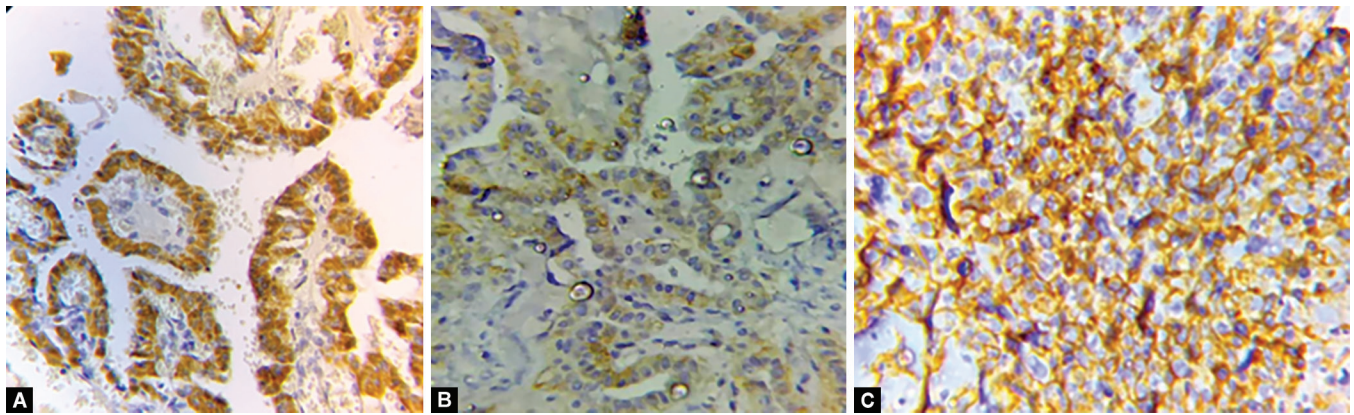
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enhanced computed tomography of the chest also showed multiple nodular lesions of variable sizes in both lung fields, suggesting metastasis. With these findings, the clinical diagnosis of a primary thyroid malignancy with systemic metastasis was considered and fine needle aspiration (FNA) was advised for confirmation and typing.

Fine needle aspiration was performed on both the lobes of the thyroid swelling along with the cervical lymph nodes, which displayed a variable cytomorphological picture. Fine needle aspiration smears from the left lobe of the thyroid displayed small clusters of atypical cells with classical features of PTC characterized by the presence of oval overlapping nuclei with dispersed chromatin, inconspicuous nucleoli, and a moderate amount of cytoplasm. Nuclear grooving and frequent intranuclear inclusions are also seen. Along with these clusters, there was a second population of cells with markedly pleomorphic hyperchromatic



Figs 1A and B: Anaplastic transformation in a papillary thyroid carcinoma with cutaneous metastasis. (A) Cytology smears composed of two types of atypical cell population, i.e., sheets of cells with oval elongated overlapping nuclei with grooving and anaplastic cells with marked pleomorphism; (B) Cutaneous metastatic site displaying scattered anaplastic cells with bizarre markedly pleomorphic nuclei



Figs 2A to C: (A) Displaying BRAF V600E cytoplasmic positivity in tumor cells; (B) Incomplete membranous PD-L1 positivity in tumor cells in papillary thyroid carcinoma component; (C) Diffuse strong complete membranous positivity in the anaplastic component

nuclei, irregular nuclear membrane, and prominent nuclei. Fine needle aspiration smears from the right lobe were composed entirely of cells with the above-mentioned undifferentiated morphology, in a background of tumor diathesis along with many atypical mitotic figures. Hence, the diagnosis of anaplastic transformation in PTC with cervical lymph node metastasis was considered (Fig. 1).

The patient underwent total thyroidectomy with central compartment and bilateral modified radical neck dissections (MRNDs). Histopathological evaluation supported the cytomorphological features of anaplastic transformation in PTC. However, the anaplastic component was predominantly composed of spindle-shaped cells arranged in haphazard and intersecting fascicles. Bilateral cervical lymph nodes were also involved. The tumor was extending beyond the nodal capsule and was seen infiltrating the overlying dermis. The tumor cells in the papillary carcinoma component diffusely expressed BRAF V600E on immunohistochemical analysis. PD-L1 expression was also analyzed and it was seen that the marker was diffusely expressed in an anaplastic component with focal patch expression in the papillary component (Fig. 2).

The patient was further treated with RAIA for the metastatic disease. Three weeks after discharge from the ward, he presented

again with two subcutaneous nodules over the neck and upper chest, confirmed as metastatic deposits on fine needle aspiration cytology that entirely had an anaplastic morphology. He received 150 mCi of RAIA but succumbed to the disease within a month.

DISCUSSION

Cutaneous metastases are a rare finding in visceral malignancies, with a reported total incidence of 5.3%.¹ Breast cancer is the most common primary malignancy to develop cutaneous metastasis with the chest being the commonest site.⁵ Distant metastases occur in 4–15% of all differentiated thyroid cancer patients, most commonly to the lungs and bones.⁶ Cutaneous metastasis in thyroid carcinoma is extremely rare (<1% cases) and usually accompanies disseminated metastatic disease.⁷ Few studies have documented a prevalence of 0.06–0.82% of skin metastasis in PTC.^{4,8} There had been conflicting results from various studies, some documenting PTC as the most common thyroid malignancy with cutaneous metastasis while others suggest follicular thyroid carcinoma.^{1,4,9,10} The present case report is about an elderly male who developed anaplastic transformation in a PTC followed by cutaneous metastasis. Papillary and follicular thyroid carcinomas show a higher propensity for cutaneous metastasis than anaplastic thyroid carcinoma.^{1,4,9}

To the best of our knowledge, only 11 cases of anaplastic thyroid carcinoma with cutaneous metastasis have been reported since 1965.³ Presentation is usually as an asymptomatic erythematous nodule, but itching, pain, or ulceration can occasionally occur.¹

Our case developed subcutaneous nodules in the neck as well as chest three weeks after the surgery. Fine needle aspiration track seeding^{6,10,11} or implantation of exfoliated tumor cells during surgery¹² could be the possible explanation for the neck nodule; however, the chest nodule represented the true cutaneous metastasis. The majority of metastatic skin lesions from thyroid carcinoma are known to involve the scalp (approximately 2/3 of cases) and the remainder generally involves the head and neck regions.¹⁰ Although the mechanism of spread to the skin is not established, it is proposed that tumor cells may get trapped in the abundant network of dermal vessels, especially in the upper body, which provides a suitable environment for the formation of a tumor deposit.¹

It can be sometimes diagnostically challenging to differentiate between primary cutaneous adnexal carcinomas and metastatic visceral tumors to the skin on the histological ground alone. This distinction is, however, very important based on the fact that the presence of cutaneous metastases usually indicates a poor prognosis due to disseminated disease, possibly requiring extensive chemotherapy or radiotherapy, on the other hand, whereas primary cutaneous adnexal carcinomas can be generally managed by complete excision.² In this scenario, the use of immunohistochemical markers like CK7, CK20, TTF-1, and thyroglobulin can be very helpful. Treatment options for cutaneous metastasis include excision of skin lesions when feasible and external beam radiation therapy/symptomatic therapy for extensive metastases or hypervascular lesion.¹

BRAF V600E is the most common mutation observed in PTC, and BRAF V600E has received special attention since this protein kinase may contribute to cell proliferation, growth, and division. The majority of studies done so far claim it to be associated with poor prognostic factors and a higher risk of recurrence.¹³ PD-L1 is an immune checkpoint protein that when expressed on tumor cells acts as an adaptive immune resistance mechanism to attenuate the host antitumor immune response.¹⁴ Angell et al. for the first time documented a significant positive association between BRAF V600E and PD-L1 expression.¹⁵ BRAF V600E may achieve more aggressive behavior when accompanied by disruption of endogenous host immune surveillance and promotion of tumor immune escape.¹⁵ The present case also showed BRAFV600E and PD-L1 expression in tumor cells both in the papillary and anaplastic components which could possibly explain the aggression such that the patient died within a month of undergoing total thyroidectomy with bilateral MRNDs. The patient was resistant to radioactive iodine therapy both due to the presence of anaplastic component as well as BRAF mutation. Cancer immunotherapy has emerged over the past few decades as a transformative approach to treating a wide variety of cancers. Hence, patients resistant to conventional thyroid cancer therapies and expressing PD-L1 can be the potential targets for immunotherapy that could provide the overall survival benefit.¹⁴

CONCLUSION

To conclude, we describe a very unusual case of anaplastic transformation in PTC with thoracic cutaneous metastasis which was associated with a dismal prognosis. Cutaneous

metastases might pose a diagnostic challenge to practitioners through nonspecific clinical presentations and may require immunohistochemical analysis for proper identification. Analysis of BRAF V600E and PD-L1 expression status in these tumors may help in selecting suitable candidates for immunotherapy which may improve the overall outcome of the disease.

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