

**Case Report**

Axillary Lymph Node Metastasis in Medullary Thyroid Cancer: Atypical Lymphatic Spread or Expression of a Systemic Disease?

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Citation: Traini E, Daloiso G, Carnassale G, Lanzafame A, Mattia A, et al. (2023) Axillary Lymph Node Metastasis in Medullary Thyroid Cancer: Atypical Lymphatic Spread or Expression of a Systemic Disease? Ann Case Report 8: 1545. DOI: 10.29011/2574-7754.101545

Received: 05 December 2023; **Accepted:** 11 December 2023; **Published:** 13 December 2023

Abstract

Medullary thyroid cancer (MTC) is a rare tumor which usually spreads to cervical lymph nodes. Axillary lymph nodes (ALN) involvement is exceptional. We describe the eighth case of ALN metastasis from MTC ever reported and discuss its unusual presentation that suggests the coexistence of undetectable visceral localization. A patient underwent total thyroidectomy with the unexpected finding of MTC when he was 69 years old. For persistent disease, he, afterward, underwent VI level lymphadenectomy, right cervical neck dissection and left cervical lymph node sampling. After 7-years he developed recurrence requiring VI level compartment revision surgery. After that calcitonin levels remained detectable but without any evident relapse at imaging till 2021 when serum calcitonin suddenly and highly increased and 18F- DOPA PET showed a left axillary relapse. A retrograde flow from lymphatics in the neck to the ipsilateral axilla was suggested as possible explanation of atypical spread of ALN. Another explanation is a regular spread of cells from visceral localization in the thorax. In the present case axillary metastases were found in the opposite side of both the primary tumor and the cervical lymph-node metastases. In addition, just after the ALN involvement, the disease showed a more aggressive progression. The high rate of visceral localization reported in patients with ALN metastases from thyroid cancer, together with the evidence, in the present case, of opposite side involvement of lymph-nodes metastases support the idea of an unrecognized visceral spread and a more aggressive behavior of the disease.

Keywords: Medullary Thyroid Cancer; Axillary Metastasis; Retrograde Lymphatic Drainage; Visceral Spread

Introduction

Medullary thyroid cancer is a rare tumor that approximately represents 3-5% of all thyroid cancers [1]. MTC prognosis is

good if it is confined into the gland, but considerably declines if associated with distant metastases, with a 10-years survival rate of 40% [2]. Lymph node involvement is a very common finding. During the initial staging the reported incidence of lymph node metastases is 71% - 80% in the neck and 36% in the mediastinum [3-5]. Distant visceral metastases typically occur in the lungs,

bones, liver, and brain [6]. Calcitonin is a specific marker used in the follow-up [7]. In this scenario, ALN involvement from MTC is a very rare encounter, and the present case is the eighth one ever reported. The peculiarity of the present case is the contra-laterality of the ALN metastases respect to the side of both the primary tumor and the lymph node involved in the neck. This evidence has never reported before.

Case Presentation

In February 2007 the patient, 69 years old man, underwent total thyroidectomy for preoperative diagnosis of multinodular goiter. Histology reported the unexpected finding of 1cm MTC in the right thyroid lobe. Into the sample also one lymph node positive for MTC metastasis, incidentally removed, was found. At the first follow-up control after surgery the patient showed high serum calcitonin level (140 pg/mL) suggestive for persistent disease due to inadequate primary clearance of the central compartment. Before planning the revision surgery, 18-F-DOPA PET was done with no evidence of hyperactive foci in the body. Neck ultrasonography instead showed a solid hypoechoic nodule in the right side of the central compartment (VI level) and a suspicious lymph-node at the IV level in the right cervical compartment. Fine needle aspiration biopsy of both the lymph nodes was performed and cytology revealed lymph node metastases with immunocytochemistry positive for calcitonin. In July 2007 the patient underwent right lateral and central neck dissection. Moreover, a left III-IV levels selective neck dissection was achieved for frozen section.

Histology confirmed the right cervical lymph node metastases and VI level metastases. The left lateral cervical lymph nodes had not pathological features. The patient continued the follow-up with serum calcitonin level and neck ultrasound check every year. In 2014, during the follow-up, he showed a new calcitonin increase (108 pg/mL). 18-F-DOPA PET confirmed the presence of right paratracheal lymph node hyperactivity. A VI level revision lymphadenectomy was performed and histology confirmed the MTC lymph node recurrence. The patient continued the follow-up with the evidence of a slow but continuous increase of serum calcitonin levels from 2017 to 2021 with no evidence of detectable recurrence at imaging both in the neck and the body. In 2021 the patient showed a sudden and huge increase of serum calcitonin level (1119 pg/dL) with 18-F-DOPA PET positive for a left axillary metabolic hyper-activity with no other metastases evidence in the body (Figure 1). A left radical axillary lymphadenectomy was carried out. Histology confirmed ALN metastases from MTC into two out of twenty-one lymph nodes excised. After a first dramatic drop, in February 2022 the patient showed a new serum calcitonin level rise (73,8 pg/mL), confirmed by the exams of September 2022 (245,8 pg/mL). In December 2022 18-F-DOPA PET showed a posterior and right to the trachea hyper-activity area, at the D2-vertebra level, compatible with a neck lymph node recurrence (Figure 2). After a multidisciplinary discussion including surgeons, radiologists, and oncologists, in consideration of the elder age of the patient, his co-morbidities, and his will, the patient neither started any chemotherapy nor underwent any kind of surgery.

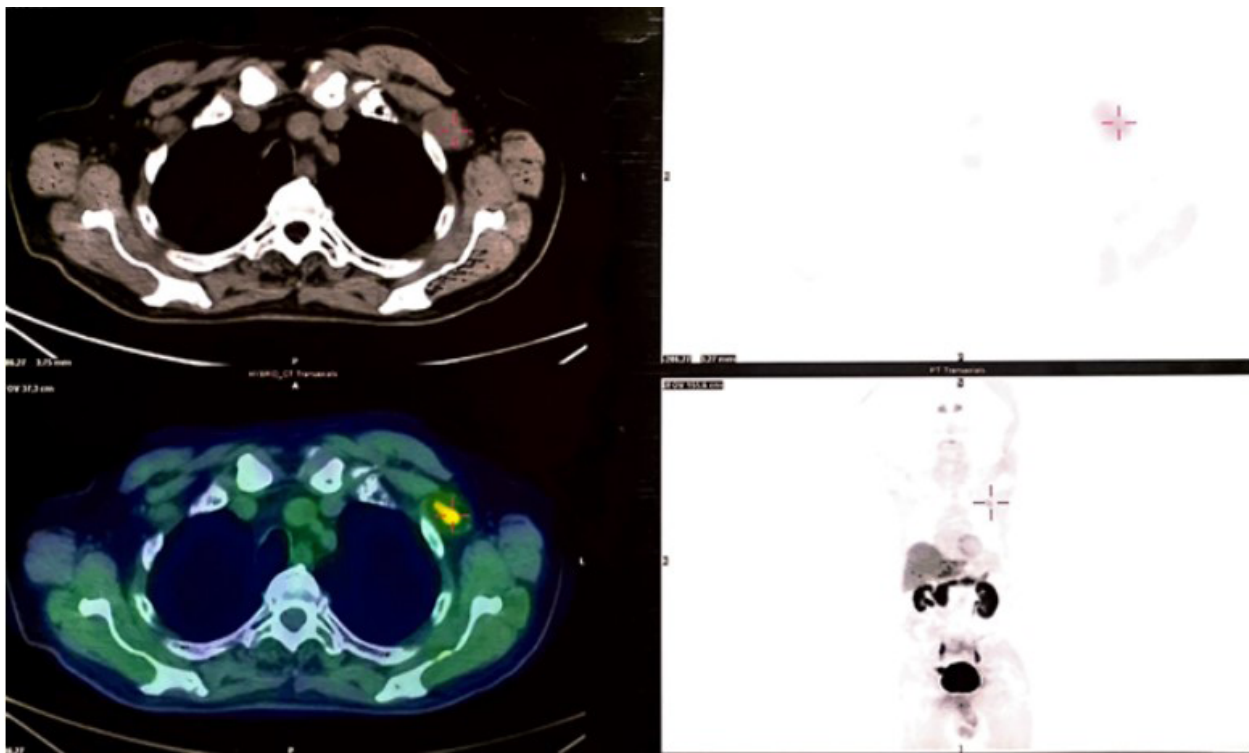


Figure 1: 18-F-DOPA PET showing the presence of a hyperactivity into the left axilla.

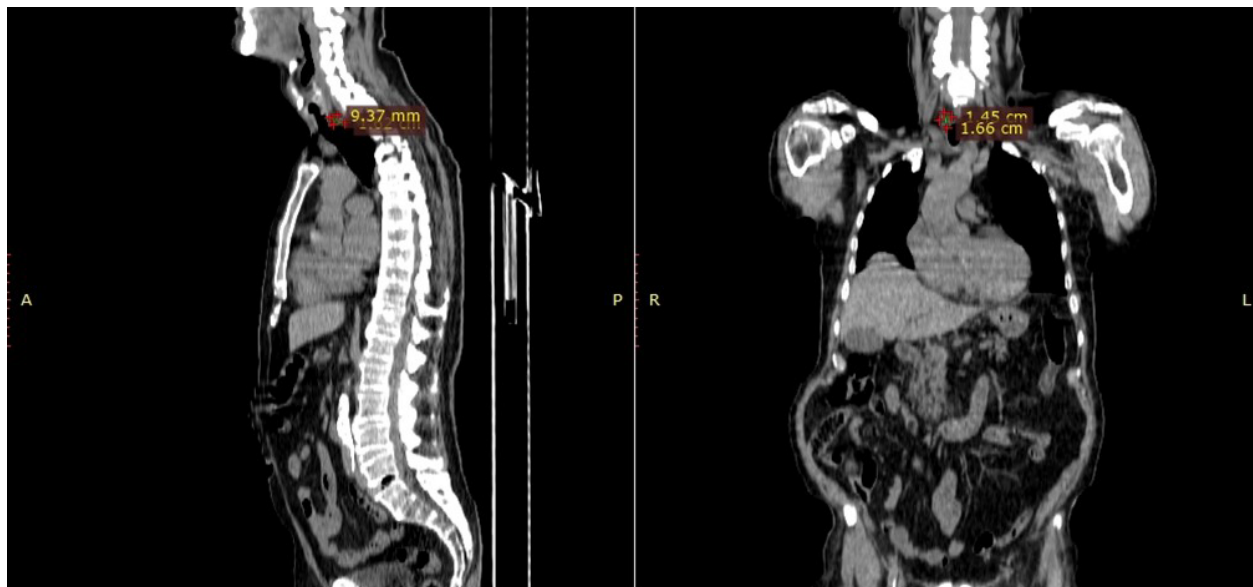


Figure 2: 18-F-DOPA PET showing the presence of recurrence after 10 months from axillary lymph-node dissection.

Discussion

Lymph node involvement in MTC is a very common finding. The incidence of cervical lymph node metastases at the initial staging has been reported in 71-80% of cases. Furthermore, lymphatic spread to mediastinum is described in 36% of cases. ALN involvement is not typical. It is a rare encounter even if considering all histological types of thyroid cancer. In literature we found out only 33 cases of ALN metastases from thyroid carcinoma. One half of them were from papillary thyroid carcinoma [8-10]. If we consider only ALN metastases from MTC, only 7 cases but ours have been previously reported [8-15].

Rouvière first described the communication between cervical and axillary lymphatics in 1932. The transverse cervical artery lymph nodes or the transverse cervical chain is connected to the apical lymph nodes of the axilla. They follow the transverse cervical artery through its lateral and upper course and the lymph flows in the opposite way of the blood ending into the thoracic duct in the left side and into the jugulo-subclavian junction in the right side. Moreover, Rouvière reported the cervical lymphatic communication with the mediastinal lymph nodes and the centripetal flow to the jugulo-subclavian junction. In such a way it was explained why mediastinal lymph nodes can be a site of thyroid metastasis [16].

A retrograde flow which goes from lymphatics of the neck to the lymph nodes of the ipsilateral axilla was suggested as possible explanation of ALN compartment involvement. Ozdemir et al.

[17] hypothesized that the blockage of the lymphatic centripetal flow around the lymphatic terminus in the jugulo-subclavian confluence may predispose to the abnormal spread of metastatic cells to the ipsilateral axillary lymph nodes. According to Odzemir the centripetal flow can be altered by the involvement of sentinel nodes around the lymphatic terminus by the carcinoma, or from the fibrosis of the subclavian junction caused by radiation therapy or surgical manipulation. When the jugulo-subclavian junction is blocked by any of these causes a retrograde flow occurs along the transverse cervical lymph nodes in the supraclavicular region that, at the end, leads to axillary lymph nodes metastases. This was supported by the studies of Kowalski et al. who found ALN metastasis during the autopsy in 2-9% of patients who died of other head and neck malignancy [18].

In our case, the patient, underwent a kind of surgical dissection, which theoretically could compromise the natural ways of lymphatic flow at the jugulo-subclavian junction (level IV) even if the left selective dissection was not such deep and inferior as the jugulo-subclavian junction is. Therefore, in our patient to hypothesize a jugulo subclavian flow obstruction and then a reverse flow to the ALNs is difficult. Moreover, noteworthy, in the present case both the primary tumor and the lateral neck lymph nodes metastases were found only at the contralateral side with respect to the axillary metastases. This means that a skip lesion should have started from the VI level, bypassed all lateral cervical lymph-nodes, and ended into the ALNs in a patient in whom there is no certainty of a reverse flow lymphatic drainage.

The finding of all lymph nodes metastases ipsilateral to the tumor but the axillary ones is evidence never been reported before.

In addition, the clinical behavior of the disease changed after the development of ALN metastases becoming more aggressive. Indeed, before ALN metastases the patient had a long period with only detectable level of calcitonin but no evidence of hyperactivity at 18-F-DOPA PET, on the contrary, less than one year after ALN metastases PET-TC showed new recurrence. Therefore, MTC ALN metastases might represent a clinical mark of an acquired new trend of the disease.

Lastly, another possible explanation of ALN involvement is a regular spread of cells from visceral localization in the thorax such as from lung and breast reached from the thyroid by hematogenous way. As a matter of fact, in literature 15 out of 34 patients who developed ALN metastasis due to thyroid malignancy had or had had visceral metastases (lung or breast) at ALN metastasis presentation [8-10,15].

In the present case no evidence of visceral metastases had ever shown at PET-TC but it can't be excluded, due to the limited resolution of imaging. Unfortunately, in our case, the usefulness of serum calcitonin in clarifying the coexistence of visceral undetectable foci after axillary clearance is limited because of the early recurrence in the neck.

Conclusion

ALN metastasis from MTC is an exceptional but possible event. It should be considered in patients with a history of MTC in case of increasing serum level of biomarkers when ultrasonography in the neck is negative. Metastases into the ALNs may be explained by hematological spread in the lung or breast from primary tumor and secondary involvement of regional lymph nodes as well as by the reverse lymphatic flow at the basis of the neck due to previous neck surgery or irradiation. In the present case, the opposite side involvement of lymph node metastases between the neck and the axilla makes the reverse flow hypothesis unlikely. The high visceral metastases rate described in previous reports as well as the faster progression of the disease acquired in the present case after the ALN involvement, suggest, in our opinion, to consider ALN as a clinical mark of a more aggressive disease and a possible reason to start systemic therapy.

Ethical statement: Not applicable

Support/Funding: None.

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

Patient Protections: The authors declare that they have obtained written informed consent from the patient reported in this article

for publication of the information about him that appears within this case report.

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