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Case Report

Medullary Carcinoma of the Thyroid With Axillary Metastasis: A Case Report

Murat Ozdemir[1], Ozer Makay[1], Ilgin Simsir[2], Yeşim Ertan[3], Gokhan Icoz[1], Füsun Saygili[3], Mahir Akyildiz[1]

[1]*Ege University Hospital, Department of General Surgery, Division Endocrine Surgery, Bornova, Izmir, Turkey*

[2]*Ege University Hospital, Department of Internal Medicine, Bornova, Izmir, Turkey*

[3]*Ege University Hospital, Department of Pathology, Bornova, Izmir, Turkey*

We report a case of axillary lymph node metastasis as a consequence of medullary thyroid carcinoma (MTC) in a 42-year-old man. On January 2009, the patient was referred to us for the management of right cervical lymph node enlargement. Total thyroidectomy was performed with right-sided functional neck dissection. Postoperative histopathology revealed MTC in the right lobe of the thyroid, with extrathyroidal extension and right-sided neck metastases. Multiple left cervical, mediastinal, and right axillary lymphadenopathies were detected at the third year follow-up exam. Left-sided functional neck dissection, axillary lymph node dissection, and mediastinal lymph node dissection were performed, and the pathologic outcomes revealed as the metastatic dissemination of MTC. After a disease-free term for 1 year, multiple metastatic lesions were detected in the patient.

Key words: Medullary thyroid cancer – Lymph node metastasis – Axillary involvement

Medullary thyroid cancer (MTC) is a rare tumor originating from the parafollicular C cells of the thyroid gland. MTC accounts for approximately 3% to 5% of all thyroid cancers.[1] The frequently used prognostic markers in the follow-up period of MTC patients are serum calcitonin and carcinoembryonic antigen (CEA) levels. Calcitonin hormone is a specific and sensitive biomarker for parafollicular C-cell disorders. The CEA produced by neoplastic C cells is generally considered a marker of dedifferentiation and is associated with worse prognosis for MTC.[2,3] MTC may occur sporadically or may be inherited. Hereditary forms of this cancer account for 25% of all cases

Corresponding author: Murat Ozdemir, Ege Universitesi Tip Fak, Hastanesi, Genel Cerrahi AD 35100, Bornova, Izmir, Turkey. Tel.: +90 232 3905050; Fax: +90 232 3398838; E-mail: muratozdemir.md@gmail.com

and include familial MTC and multiple endocrine neoplasia syndromes (MEN 2A, MEN 2B). Seventy-five percent of cases are sporadic.[4] The overall prognosis of MTC is affirmative, with a 10-year overall survival rate of approximately 95% for patients with tumors confined to the thyroid gland. However, for patients with distant metastasis at presentation, the 10-year overall survival rate is estimated to be only 40%.[5] For metastatic cases, lymph node involvement is very common throughout the clinical course. During initial staging, the incidence of pathologically proven cervical lymph node metastasis has been reported as 71% to 80%[6–8]; the corresponding value for mediastinal involvement is 36%.[6,8] Whereas, distant metastases have been reported in 20% of MTC patients.[9] Considering the spectrum of MTC, axillary lymph node metastasis (LNM) is rare, and there are reports of isolated cases.[10–12]

Case Report

A 42-year-old man was referred to us in January 2009 for management of right cervical lymph node enlargement. Examination revealed a fixed nodule (2 cm) in his right thyroid lobe. He also had multiple right cervical lymphadenopathies and right supraclavicular lymphadenopathies. The nodes were solid and few of them were fixed; size ranged from 1 to 4 cm. Examination findings were confirmed with ultrasonography (US) and computerized tomography (CT) scan. Laryngoscopy showed that both vocal cords were mobile. Serum calcitonin level was >2000 pg/mL (normal range: 0–18 pg/mL). Past medical and family history was negative for thyroid disease or other endocrinopathies. Fine needle aspiration cytology (FNAC) was carried out on the cervical node and reported positive for MTC. He underwent a total thyroidectomy with right-sided functional neck dissection. He had only temporary hypocalcemia in the postoperative period. Postoperative histopathology revealed MTC in the right lobe of the thyroid, with extrathyroid extension and right-sided neck metastases with 10 of 16 nodes positive for tumor. The thyroid tumor measured 1.5 and 0.8 cm in diameter. Metastatic lymph nodes were reported, including a major one with a diameter of 3.7 cm. He was investigated in terms of multiple endocrine neoplasia. Genotype screening did not reveal mutations associated with familial forms of MTC. He was considered as sporadic MTC. Postoperative calcitonin level was found to be <2.6 pg/mL.

In February 2012, he presented with high calcitonin levels (82.2 pg/mL). US and CT examinations of the neck revealed reactive lymph nodes. Thorax CT and endoscopic US examinations showed multiple metastatic lymphadenopathies (LAPs) in the paratracheal area adjacent to the esophagus. US of right axilla revealed multiple metastatic LAPs. Endosonographic FNAC was carried out on the paraesophageal node and reported positive for MTC. In light of these findings, the patient was discussed in our institutional multidisciplinary weekly meeting and the decision to operate was made.

In March 2012, the patient underwent left-sided functional neck dissection, axillary lymph node dissection, and mediastinal lymph node dissection. Postoperative histopathology revealed metastatic dissemination of MTC in 6 of 26 axillary lymph nodes. All 4 retroesophageal nodes and 6 of 11 mediastinal nodes were metastatic (Fig. 1). Immunohistochemically, the tumor cells were reactive with calcitonin and chromogranin A (Figs. 2 and 3). Eighteen lymph nodes dissected from left-sided neck dissection were reactive. Follow-up was maintained, and on thorax CT dated July 2013, multiple, small, metastatic lesions in the lung, mediastinal lymph node metastases, thoracic vertebral metastases, recurrence suspect at cervical surgery site, and metastatic LAP suspect adjacent to right upper internal jugular vein and beneath left sternocleidomastoid muscle were identified. As a result, we planned to start the patient on sorafenib following 2 cycles of anthracycline-based chemotherapy.

Discussion

During initial staging for MTC, the incidence of pathologically proven cervical lymph node metastases has been reported to be 71% to 80%[6–8]; the corresponding value for mediastinal involvement is 36%.[6,8] Axillary LNM as part of the disease spectrum of MTC is rare, with only isolated reports.[10–12] Rouviere described the communication between cervical and axillary lymphatics in 1932.[13] That physiologic flow is centripetal to the jugulosubclavian junction. The cervical lymphatics are also in communication with mediastinal lymph nodes, and consequently, mediastinal lymph nodes are occasionally involved in thyroid malignancy.[14,15] Metastases to axillary lymph nodes are, however, immensely rare owing to the centripetal flow. This centripetal flow can however be altered under

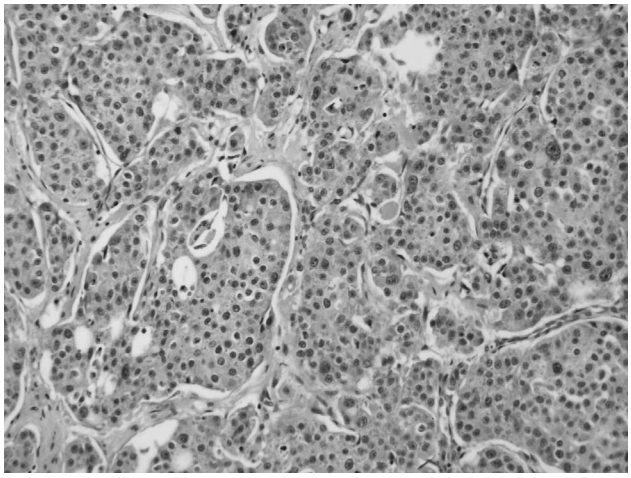

Fig. 1 Histologic appearance of lymph node metastasis of medullary carcinoma composed of nests of tumor cells separated by fibrous stroma (H&E, original magnification ×200).

certain circumstances; namely, blockage of lymphatic flow resulting from involvement by carcinoma of sentinel nodes around the lymphatic terminus in the jugulo-subclavian confluence. The retrograde spread that follows occurs along the transverse cervical lymph node in the supraclavicular region. This retrograde pathway of lymphatic drainage can finally lead to axillary lymph node metastases. This finding is supported by the observation that axillary node metastases are found at autopsy in 2% to 9% of patients who have died of other head and neck cancer.[16,17] Even though the predominant cause for altered lymphatic flow is the blockage of it by metastasis, this could also be the result of alteration

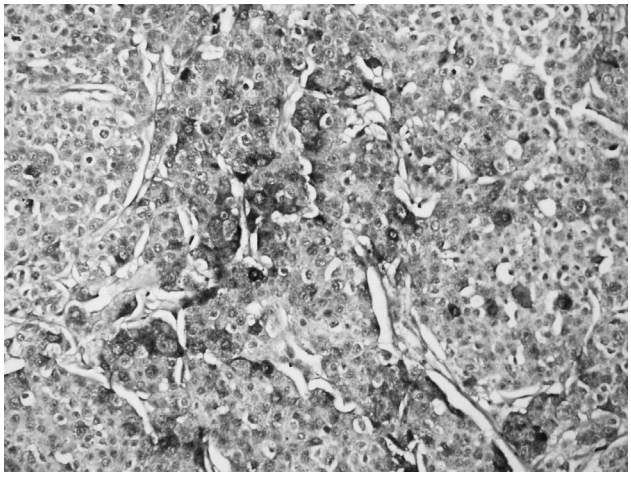

Fig. 2 Immunoreactivity of calcitonin in the tumor cells (Calcitonin, original magnification ×200).

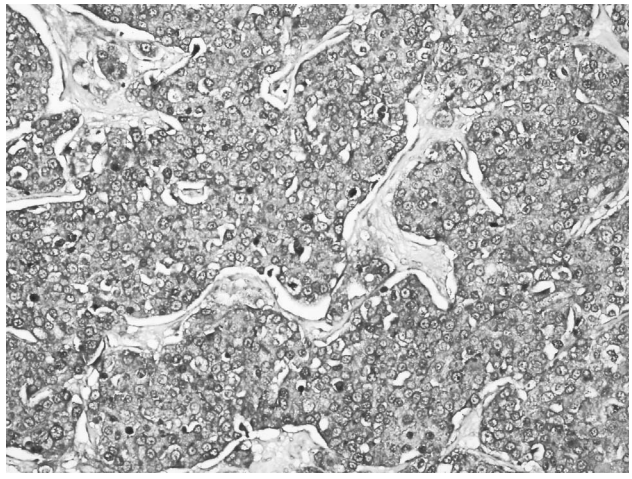

Fig. 3 Immunoreactivity of chromogranin A in the tumor cells (Chromogranin, original magnification ×200).

in lymphatics caused by fibrosis at the subclavian junction, as a result of surgical manipulation or even as a consequence of radiotherapy. Also a few studies show that axillary nodes could be involved owing to hematogenous spread from thyroid malignancy.[17,18]

In the literature, there are scarce case reports that demonstrate a relation between thyroid malignancy and axillary lymph node. In a review study, Machado *et al*[19] addressed 17 patients, including their own case. Among them, 12 had papillary thyroid cancer, and MTC was reported in only 1 case. In our literature search, 2 additional cases were found that were consistent with axillary metastasis of MTC.[10,12] It is obvious that metastasis of MTC to axillary lymph nodes is a very rare event. Nevertheless, there are cases with distant organ metastasis together with axillary metastasis, reported in the literature. Usually, axillary lymph node metastasis is concurrent with distant organ metastasis. Thus, axillary lymph node metastasis can be an indicator of systemic disease and poor prognosis.[10,12–19] In our case, axillary lymph node was previously not associated with distant organ metastasis. However, during a follow-up period of over 1 year, distant organ metastases were found (*i.e.*, lung and bone metastases). Surgical resection is the mainstay of treatment; however, once MTC becomes unresectable, neither radiotherapy nor systemic chemotherapeutic regimens have proved effective in prolonging survival. We decided to start the patient on 2 cycles of anthracycline-based chemotherapy and sorafenib, after distant organ metastasis was found. Sorafenib is a multi-kinase inhibitor with potent activity against Raf and receptor tyrosine

kinase. Studies of sorafenib have demonstrated that the drug has promising potential benefits in metastatic MTC.[10,20] Additionally, the US Food and Drug Administration (FDA) approved cabonzantinib and vandetanib for the treatment of symptomatic or progressive MTC in patients with unresectable locally advanced or metastatic disease. These therapeutics can be safely used in the treatment of metastatic MTC.[21]

In the light of our experience, we can recommend that lymph nodes be followed up with respect to metastasis in patients who undergo aggressive cervical surgery secondary to thyroid malignancy. Moreover, it should be kept in mind that metastasis to axillary lymph nodes can be indicative of systemic dissemination and distant organ metastasis in medullary cancer patients.

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