



Axillary Lymph Node Metastasis from Thyroid Malignancy: Unusual Presentation with Ominous Implications

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Authors' contributions

This work was carried out in collaboration between all authors. Author NOM designed the study, and wrote the final draft of the manuscript. Authors PJC, ZRR, NJK and Sinnakirouchenan managed the literature searches and critically reviewed the manuscript. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Lymph node metastases to cervical group of nodes occur frequently in well-differentiated thyroid carcinoma. Metastasis to axillary lymph nodes however, is exceptional, leading to diagnostic and management dilemma. While presenting a case of thyroid malignancy with axillary lymph node metastasis, the literature is reviewed for similar cases to analyze their clinico-pathological features, investigations, management and outcome. Fifteen cases have been reported so far. Majority of these patients were female (male: female ratio 6:9) and their mean age was 54.5 years. Axillary lymph node metastases occurred concurrently or as recurrent disease after initial treatment of primary disease in about equal number of these patients. The predominant histological type was papillary carcinoma and 83.3% of these were poorly differentiated. Visceral metastases to lungs and bones were often seen. Despite treating these patients with thyroidectomy, lymph node clearance and adjuvant therapy, 40% of them died; some within one year and among the 60% who were alive, 30% still had active disease.

Conclusion: Axillary lymph node metastasis from thyroid cancer, even though rare should be considered in the differential diagnosis in patients presenting with axillary mass and thyroid malignancy. Based on the limited number of cases reported in the

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literature it appears that it is generally a manifestation of the aggressive nature of this tumor with overall poor outcome.

Keywords: Axillary metastasis; thyroid malignancy; thyroidectomy; lymph node dissection.

1. INTRODUCTION

Well-differentiated thyroid cancer is generally considered as an indolent neoplasm associated with low mortality. Metastases to regional lymph nodes in the neck are often encountered [1,2]. However, some of these tumors (10 to 25%) are aggressive in nature and may present with distant metastasis to lung and bone and spread to extra-cervical group of lymph nodes, including those in the mediastinum [2,3]. The involvement of axillary lymph nodes however is extremely rare presenting with diagnostic and management challenge. We present here a case of thyroid malignancy manifesting with axillary lymph node metastases. From review of literature, 15 similar cases were found, which have been analyzed with regards to their presentation, pathology, management and outcome [4-16].

2. CASE REPORT

A 76 year old male patient was referred to us for management of bilateral cervical and left axillary lymph node enlargement. Seven years ago, he had undergone total thyroidectomy with central node clearance in another hospital, which was reported as well differentiated papillary carcinoma with lymph node metastases. A year later he developed cervical lymphadenopathy for which he received four ablative doses of radioiodine (the response was only modest if any) before he was referred to us. However the number and size of his lymph nodes gradually increased and so did his serum levels of thyroglobulin (Tg). His voice became hoarse. Examination revealed multiple bilateral cervical lymphadenopathy (Fig. 1). The nodes were hard and few of them fixed, size ranging from 1 to 3 cms. He also had enlarged nodes in his left axilla with similar characteristics (Fig. 2). Laryngoscopy showed the left vocal cord fixed in paramedian position. Serum Tg level was 8814 ug/L (0-35). CT scan disclosed bilateral cervical lymphadenopathy at level II, III & IV, along with enlarged mediastinal and left axillary lymph nodes (Fig. 3). Fine needle aspiration cytology (FNAC) carried out on the cervical and axillary lymph nodes, confirmed metastatic papillary carcinoma of thyroid. The radioactive iodine whole body scan revealed no other metastases and was not picked by the enlarged lymph nodes. However CT scan of lung revealed 2 lesions suggestive of metastasis in right lung. The patient underwent bilateral functional neck dissection and axillary lymph node clearance. Histology confirmed metastatic papillary carcinoma of both the cervical and axillary lymph nodes. The nodes in the neck were twelve on right side and nine on left side with significant matting of nodes. There was extracapsular extension of the nodes on both sides and with complete replacement of the node by the tumour in most of them (Fig. 4 and Fig. 5). The axillary nodes were six in number showing similar features of matting and extracapsular involvement. In the postoperative period the serum Tg levels dropped from 8814 to 444 ug/L. In view of the persistent high level of Tg even though markedly reduced, it appeared that the patient had residual disease probably in mediastinal nodes and lung metastasis. He then received Sorafenib (tyrosine protein kinase inhibitor) 400 mg bid and suppressive dose of Thyroxine 150 ugm.



Fig. 1. Bilateral cervical lymphadenopathy seen



Fig. 2. Large left axillary lymphadenopathy seen



Fig. 3. CT scans revealing bilateral cervical and left side axillary nodal metastasis

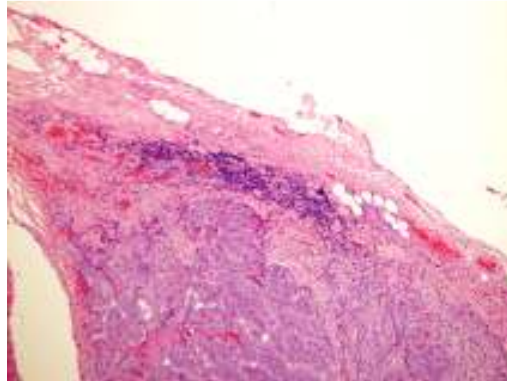


Fig. 4. H & E stain slide at 10 magnifications showing the lymph node is totally replaced by neoplastic process arranged in papillary structures

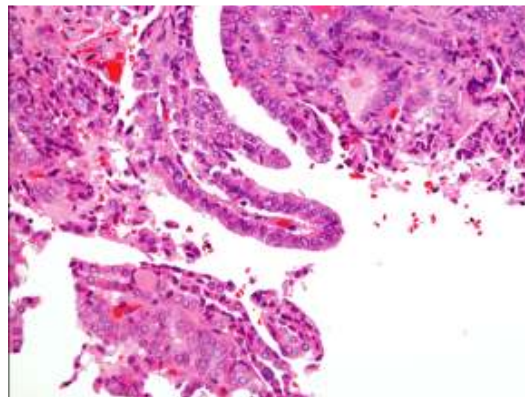


Fig. 5. H & E stain slide at 20 magnifications showing a papillary structure lined by columnar cells with enlarged overlapping optically clear nuclei showing longitudinal grooves

2. DISCUSSION

Lymph node metastases, particularly to the cervical group, are often seen in patients with thyroid malignancy, particularly in papillary thyroid cancer (PTC) [1-3,17]. In patients with PTC who have undergone prophylactic neck dissection, micro-metastases have been found in up to 90% of the cases [17]. Lymph nodal metastases have been associated with an increase in recurrence rate and may impact negatively on survival as well [2,18]. The lymphatic drainage pattern of the thyroid gland is uniform and consistent, allowing the pattern of metastatic spread to be relatively predictable. Overall the probability of nodal metastasis in PTC has been reported in the range of 30-90% with an average of 60% [18,19].

The initial nodal spread from PTC, almost always occurs in the central compartment of the ipsilateral neck, in the paratracheal and pretracheal lymph nodes, and in level VI [20]. In the absence of central disease, cases of macroscopic skip metastasis to lateral compartment of the neck are exceedingly uncommon [20]. However, microscopic skipping of central compartment nodes has been reported to occur in 19.7% of the cases [21]. Spread of PTC to nodes in submental and submandibular nodes (level 1) is so rare that they are not included in routine lymph nodal dissection [20]. However for tumors originating from the upper thyroid pole, the first nodal basin is not invariably the central compartment (as for primaries arising from the inferior thyroid pole) but often the upper part of the ipsilateral lateral compartment. Lymph node dissection of the first basin may differ depending on the location of the primary tumor. Involvement of the contralateral lateral compartment is seen in PTC with extensive central compartment involvement [20]. The involvement of axillary lymph nodes in thyroid malignancy is however exceptional [4-16].

2.1 Axillary Lymph Node Metastases

2.1.1 Pathogenesis of spread

The communication between cervical and axillary lymphatics has been described in the past [22]; however the physiological flow is generally centripetal to the jugulo-subclavian junction [5,7,8]. The cervical lymphatics are also in communication with mediastinal lymph nodes and consequently mediastinal lymph nodes are sometimes involved in thyroid malignancy [8,15]. Metastases to axillary lymph nodes are however exceedingly rare due to the centripetal flow. This centripetal flow can however be altered under certain circumstances; namely blockage of lymphatic flow [23,24] due to involvement by carcinoma of sentinel nodes around the lymphatic terminus in the jugulosubclavian confluence. The retrograde spread that follows occurs along the transverse cervical lymph node in the supra-clavicular region. Their retrograde pathway of lymphatic drainage can ultimately lead to axillary lymph node metastases. This 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 [23,24]. Even though the predominant cause for altered lymphatic flow is the blockage of it by metastasis, this could also be the outcome of alteration in lymphatics caused by fibrosis at the subclavian junction following surgical manipulation or radiotherapy. Some are also of the view, that in a small number of patients, axillary nodes could be involved due to haematogenous spread from thyroid malignancy [9,23].

2.1.2 Manifestation

The axillary metastases either present concurrently along with thyroid lesion and cervical lymph node metastases, or years later as a mass in the axilla, after the initial management of thyroid tumor and cervical lymph nodal metastases [4-16]. A significant number of these patients could have concurrent visceral metastasis, predominately to lung, and often to bone and liver [4,8,11,13]. In patients where the axillary node mass is the predominant presentation, evaluation of the neck for thyroid malignancy should be carried out after ruling out initially the possibility of metastases from the more common primary tumors like breast malignancy.

2.1.3 Risk factors for nodal metastasis

Factors that increase the probability of patients having lymphatic metastasis include; age, gender, size of the primary tumors and oncogene expression [12,25]. PTC in pediatric age group has a clinical incidence of lymph node metastases of 80% and in patients above 60 years these are reported to be higher than in midlife. Histological features that seem to predict lymph node metastases are vascular invasion and extra-capsular involvement [1,2].

Several oncogenes assessed histologically in PTC, including p53 and BRAF have been associated with poor prognosis and higher probability of lymph node spread [26]. In one of the reports in patient with axillary lymph node metastases, the positive cell rates of proliferating cell nuclear antigen and Ki-67 were higher in recurrent lymph nodes than in primary tumor itself, suggesting increased cell proliferation in the recurrent lymph nodes [10].

2.1.4 Risk factors for visceral metastasis

Visceral metastasis to bone, lung, liver, brain and skin have been observed in 9% of patients in one of the large series of 972 patients with PTC [28]. A correlation has been observed between the number of lymph nodes and distant metastasis, with more than 20 lymph nodes having a specificity of 90.8% and a negative predictive value of 92.7%. However the sensitivity and positive predictive value were low (27.6 and 22.9%) [28]. On multivariate logistic regression, 1-5,6-10, and 11-20 involved lymph nodes denoted a moderate risk of lung metastasis (odds ratio (OR), 9.9,10.6 and 13.8; $P \leq 0.004$), whereas more than 20 involved nodes indicated a high risk of lung metastasis[OR, 25.0; $P < 0.001$]. Mediastinal lymph nodes carried a moderate risk of lung metastasis (OR,7.5; $P = 0.001$) [28].

2.1.5 Management

The primary modality of treatment of PTC with lymph node metastasis remains surgical and comprises of thyroidectomy and lymph node clearance. Total thyroidectomy is indicated in patients <15 years or >45 years, with radiation history, known distant metastasis, bilateral nodularity, extrathyroidal extension, tumour > 4 cms in diameter, cervical lymph nodes with metastasis and aggressive variant (tall cell variant etc). Lymph node clearance is carried out if lymph nodes are palpable or are biopsy positive and would involve clearance of the central neck dissection (level V1) or lateral neck dissection (level 11, level 111, level 1V, including level 1 and Va if clinically involved. Importantly, the use of lymphoscintigraphy during surgery in thyroid cancer has not been found to be useful is assisting the surgeon to determine the sentinel node or ambiguous drainage and hence has been abandoned.

In the postoperative period, investigations are carried out to rule out potential metastasis along the lines discussed below. Following the total or near total thyroidectomy the patient undergoes radioiodine remnant ablation and subsequent hormone therapy.

2.1.6 Investigation work up during follow up

The follow up of patients with PTC following initial thyroidectomy and central compartment node clearance is based on regular clinical evaluation, including palpation of the thyroid bed and careful clinical examination of the regional lymph nodes, usually limited to the cervical area. Investigations such as neck sonography, serum thyroglobulin level (Tg) estimation and diagnostic ¹³¹I- whole body scan (dWBS) are useful in evaluation for recurrence or metastasis [5,8-10,29]. When dWBS is negative inspite of raised levels of Tg, the possibility of visceral and non cervical lymph node metastases including those in the mediastinum and axilla is likely. The detection of metastases in them could be facilitated by investigations that include CT scan, MRI (cerebral/neck/thorax) and bone scintigraphy [4-10]. Exceptionally they have been detected by other investigations. One such reported case, the diagnosis was made after discovery of micro-calcification of axillary mass, while undergoing a screening mammography, [14]. The biopsy of the axillary node confirmed it to be metastasis from thyroid cancer. When the possibility of axillary metastases is likely and the above investigation fails to locate the metastases, ¹⁸F-FDG-PET/CT and ¹³¹I SPECT/CT scans have been found to be useful diagnostic tools, as reiterated in recent reports [30,31]. The sensitivity, specificity and diagnostic accuracy is 65, 55 and 59% for WBS, whereas in ¹⁸F-FDG PET/CT scan it is reported to be 61,98 and 86% respectively[30]. SPECT/CT scan was also found to be superior to WBS and PET/CT scan in patients who have received a single challenge of radio-iodine therapy whereas PET/CT scan was superior to WBS (p=0.005) and SPECT/CT (p=0.013) in patients who received multiple challenges[30]. For organ-based analysis, dWBS was found to be the best detector for lymph node metastasis (72.4%) while PET/CT scan was superior to dWBS for detecting metastases of bone (85.7% vs. 71.4%) and lung (94% vs. 62.7%) [31]. When positive for metastases, it could negatively influence the outcome in such patients. The diagnosis is however finally established by FNAC or trucut biopsy.

2.1.7 Management of patients with raised Tg levels and negative dWBS

There is a general agreement that the most reliable parameter for the detection of tumour recurrence is raised Tg levels [32,33]. Elevated Tg levels, post thyroidectomy and radioiodine remnant ablation, suggest persistence or recurrence of viable tumour tissue [33]. In the last few years questions have been raised as to the value of dWBS compared with ¹³¹I post therapy whole body scan (t WBS) [33-35]. tWBS has been reported to detect new lesions in upto 50% of patients [34,35]. Hence a negative dWBS does not definitely exclude the presence of ¹³¹I avid lesions [33,34]. Empiric radioactive iodine therapy (100-200 mci) might be considered in patients with elevated Tg levels of 10ng /ml or higher after T4 withdrawal, or a level of 5 ng/ml or higher after TSH stimulation, or rising serum Tg levels when imaging (dWBS) has failed to reveal a potential tumour source [36]. If tWBS is negative, no further RAI therapy should be administered (recommendation rating C). If persistent non resectable disease is localized after an empiric dose of RAI and there is objective evidence of significant tumour eradication, then RAI therapy should be repeated until the tumour has been eradicated or tumour no longer responds to treatment [36]. If an empiric dose (100-200 mCi) of RAI fails to localize the persistent disease, than ¹⁸F-FDG-PET/CT scanning should be considered, especially in patients with estimated serum Tg levels >10-20ng/ml or in those with aggressive histologic variant, in order to localize metastatic

lesions that may require treatment or continued close observation [36]. In patients who are Tg positive, tWBS negative and have disease that is incurable with surgery and is structurally evident or visualized on ¹⁸F-DG- PET CT scan, the options of management include thyroid hormone suppression therapy, external beam radiotherapy, chemotherapy, radiofrequency ablation, chemoembolization or monitoring without additional therapy if stable. (recommendation rating C) [36].

3. LITERATURE REVIEW

Review of medline database of articles in English language on axillary metastases from thyroid cancer, revealed a total of 15 cases and include the largest number of cases reported so far [4-16]. Most of the reports in the past, including some recent ones, have reported a maximum of 9 cases.

3.1 Analysis of Results of Literature Review

The male female ratio was 6:9 and the mean age of the patient was 54 years (range 21 to 66) (Table 1). The commonest thyroid cancer among these, 11(73.3%) was papillary carcinoma. The other histological type that were reported, included one each case of follicular, medullary, sclerosing mucoepidermoid carcinoma with eosinophilia, mucoepidermoid carcinoma, mucin producing adenocarcinoma [11-13,16]. Among the 11 cases where the differentiation details of the tumor were mentioned, in 9 cases (81.8%) the tumors were either poorly differentiated or had variant with poor outcome like the tall cell variant. In 8 (53.3%) of these patients, the axillary lymph nodes manifestation was concurrent with the thyroid malignancy and cervical metastasis. In the rest, the axillary lymph node metastases occurred following the initial management of the thyroid malignancy and cervical node metastasis. The recurrent disease in the axilla occurred in these patients as early as 7 months or as late as 41 years following the initial surgery, with a mean period of 11.7 years (Table 1). In 9 (60%) of these cases the patients also had visceral metastasis, the commonest organ of spread being lung and the bone [4,8,11,13] with an exceptional case of metastasis in the breast [7]. The primary management strategy in these patients was thyroidectomy followed by functional block dissection of cervical nodes and axillary nodes clearance. The adjuvant therapy comprised of radioactive iodine therapy and suppressive dose of thyroxine. Some of the patients in addition received external beam radiotherapy to the neck and in those with visceral metastasis received chemotherapy (Table1). Among the 10 patients where the outcome was reported, 4(40%) of these patients died some within one year, 3(30%) were alive with disease and 3(30%) were alive being disease free (Table 1). Off late treatment with thyrosine kinase inhibitor has been tried for patients with differentiated thyroid cancer [37]. This has been shown to be useful in patients with progressive radioactive iodine- resistant differentiated thyroid cancer where management options have been limited. Their effectiveness has been reported in patients with widely metastatic progressive differentiated thyroid cancer with most patients achieving stable disease or partial response despite having progressive disease at baseline. The most noticeable response was reported in lung in contrast with minimal changes in nodal metastasis and progressive disease in pleural and non-irradiated bone metastasis suggesting a tissue specific response [37].

Table 1. Literature review results-axillary lymph nodes metastases from thyroid malignancy

Year	Author	Age yrs	Sex	Histology	Differentiation	Appearance of axillary lymph node	Adjuvant therapy	Metastases	outcome
2012	Present case	71	M	Pap.	Well differentiated	Recurrent 7yrs later	RAI Thy Sup	Lung	ALD 8 months
2012	Chiofalo et al.	65	M	Foll.	Hurthle cell Signet cell	concurrent	RAI	Multiple Bone/ liver	ALD 1 yr
2011	Krisnamurthy et al.	64	F	Pap.	Tall cell variant	Recurrent- 6 years	Thy Sup	None	Dis FR 6 months
2009	Kepenecki	63	F	Pap	Well Differentiated	concurrent		none	NA
2009	Angeles-Angeles	58	F	Pap.	insular	Recurrent-17 years		Breast	NA
2007	Nakayama	21	M	Pap.	Partial poorly	Concurrent		Lung	ALD
2006	Ers et al.	62	F	Pap.	NA	Recurrent- 5 years	RAI Thy Sup	none	Dis Fr 10 years
2004	Koike et al.	51	M	Pap.	Partially poor	Recurrent- 5 years		Multiple	Death 8 months
2004	Shehadeh et al.	38	F	SMECE	NA	Concurrent	RAI EBRT Chemotherapy	Lung	NA
2003	Lal	65	M	Pap.	poorly	Recurrence-41 years	NA	Multiple	Death
2003	Lal	59	M	MTC	poorly	concurrent	NA	Multiple	ALD
2003	Lal	45	M	Pap.	poorly	concurrent	NA	Multiple	Death
2002	Minagawa et al.	52	M	MEC	NA	concurrent	chemotherapy	Lung vertebra	Death
1998	Chen et al.	66	F	Pap.	Well differentiated	concurrent	Tomoxifen (oestrogen receptor positive)	None	NA
1996	Ueda et al.	45	F	Pap.	NA	Recurrent- 7 years	None	None	NA
1993	Mizukami et al.	58	M	MAC	poorly	Recurrent- 7 months	RAI	None	Dis Fr

4. CONCLUSION

Axillary lymph node metastases from thyroid cancer are very rare. However it should be considered in the differential diagnosis of axillary masses in the presence of thyroid malignancy. During the follow up in patients with thyroid malignancy, persistent raised serum thyroglobulin level with negative radioactive iodine scan would warrant careful examination for metastasis at other sites including in the axillary nodes. Various diagnostic tools including FDP- PET/CT scan may be useful in doing so. Axillary node metastasis may occur concurrently or manifest as recurrent disease. It however appears that it has an ominous outcome as unfortunately majority of them have other visceral metastasis and two third of them would have succumbed to the disease or are alive with active disease.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Would like to declare that there are no competing interests in writing this article.

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