Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2, 717-724
2025
Publisher: Learning Gate
DOI: 10.55214/25768484.v9i2.4580

Bilateral axillary lymph node metastasis after radioactive ablation in recurrent papillary thyroid carcinoma: A case report

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Abstract: Papillary thyroid carcinoma (PTC) is associated with indolent growth and a good prognosis. PTC has a tendency to metastasize into nearby lymph nodes, and 10% of PTC cases may present with metastatic disease. Axillary lymph node metastasis (ALNM) is an ineffably scarce event in thyroid carcinoma, and it may indicate a poor prognosis, with only a few cases reported in the literature. A 44-year-old woman with a previous history of total thyroidectomy, left radical neck dissection, and radioactive iodine (RAI) ablation was clinically presented with a recurrent thyroid mass, cervical lymphadenopathy, extensive skin involvement, and bilateral axillary lymph nodes from metastatic papillary thyroid carcinoma. Imaging scans revealed metastasis to the lungs and cervical bone. She was managed by completion total thyroidectomy, wide excision for the suprasternal nodules, completion left neck dissection, type 3 modified radical right neck dissection, bilateral central compartment clearance, and standard bilateral axillary dissection. ALNM is associated with aggressive histopathology, extensive locoregional disease, and distant metastasis. ALNM in thyroid cancer is uncommon since there is no direct connection between the neck and axilla; thus, ALNM is a culmination of an uncommon pattern. Risk factors contributing to ALNM include skin involvement, bulky cervical lymph nodes, previous surgery, and radiation. Complete surgical resection is the main therapy to achieve the effectiveness of adjuvant therapy.

Keywords: *Axillary lymph node metastasis, papillary thyroid carcinoma, radioactive iodine.*

1. Introduction

Thyroid cancer has become the most common malignancy in head and neck, occupy the 10th position worldwide and the incidence is still arising. Approximately 586,202 thyroid cancer has been diagnosed worldwide in 2022 and 13,000 of them were from Indonesia [1, 2]. Well, differentiated thyroid carcinoma (DTC) such as papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) is the most common malignant neoplasm of the thyroid gland, found in around 90% of all thyroid cancer with indolent growth feature and good prognosis with 10-year survival rate 98% despite any neck lymph nodes involvement [2-4].

PTC has ability to invade adjacent structures such as lymphatics and about 10% patients may present with metastatic disease and 8%-28% of patients with PTC have recurrence which affect their prognosis. Based on a study conducted by Voutilainen in 2001, the prognosis for PTC with cervical lymph nodes recurrence at over 45 years of age was the same as in the general population, in the advanced age the prognosis was worsened [4, 5]. PTC tends to metastasize to regional lymph nodes with incidence may be present 30%-80% and frequently relapsed after the prior surgery. Factors associated in the recurrence of well DTC in the early stage are the presence of distant metastasis while in the advanced stage are distant metastasis, male, total thyroidectomy with limited neck dissection,

History: Received: 7 December 2024; Revised: 24 January 2025; Accepted: 27 January 2025; Published: 4 February 2025
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and high level of serum thyroglobulin [6, 7]. Meanwhile, other studies stated that risk factor contributing for recurrence in PTC are younger age, large tumor size, lymph nodes metastasis, incomplete resection, high risk stratification according to ATA, and frequent accumulated radioactive iodine (^{131}I) therapeutic dose [8]. Ablation with ^{131}I is used to eliminate residual thyroid cancer and this procedure has little or none effect on tissue outside the thyroid glands. Nevertheless, in some patients receiving larger dose resulting in dry mouth to potentially developing other cancer in the future [3].

Thyroid cancer that metastasizes outside the neck area is very rare and prone to be more aggressive with poor outcomes [3]. When ALNM present may indicate a poor prognosis when combined with multi-organ metastasis since they are usually associated with aggressive histopathology, extensive locoregional disease, and distant metastatic disease. ALNM in thyroid cancer are uncommon since the neck and axilla lymphatic systems hardly ever communicate with one another directly [9, 10].

Although the incidence of DTC is increasing gradually, distant metastatic spread in PTC is rare, around 1%-2%. However, despite this marked increase in incidence, the mortality rate remains a constant low level. But the paradox of this phenomenon might appear as the recurrence rate is affected up to 30% of patients and occurred up to 35 years after treatment. For this, DTC patients remain on lifelong oncologic follow-up after treatment [8]. PTC with spread to the axillary lymph nodes is rare even more, it can be associated with cervical bulky lymph node disease and/or skin involvement which alter lymphatic drainage [13, 14]. There are only a few cases of axillary lymph node metastasis from papillary thyroid carcinoma that has been reported and it has been considered as a late manifestation after multiple metastasis to distant organ and lymph nodes or in recurrent papillary thyroid carcinoma and associated with poor prognosis [15]. Herein, we briefly present a case of recurrent thyroid carcinoma with cervical lymph nodes metastasis along with skin infiltration and ALNM.

2. Case Report

We report a case of axillary lymphadenopathy in a 44-year-old Javanese woman who presented to Head and Neck Surgery Division at Dr. Soetomo Surabaya General Hospital with a recurrent PTC. No previous radiological exposure in the neck area or familial history of malignancies. She had a history of total thyroidectomy and left radical neck dissection 3 years ago, which were followed by one dose of radioactive iodine at interval of 6 months. 131I whole body scanning showed radioactive iodine captured by the remaining thyroid tissue and no pathological radioactive iodine capture was seen in other parts of the body. Shortly after the ablation, the patient complained of palpable mass in her neck, chest, and armpits that she felt gradually became larger. The patient also had hoarseness and decreased vocal register in which happened after the surgery. The patient received thyroxine suppression therapy postoperatively.

On clinical examination, there was a recurrent mass at the left neck, palpable cervical lymph nodes, multiple of skin nodules at the upper mediastinum, and bilateral axillary mass (Figure 1). No visible or palpable mass in her breasts. Furthermore, fine needle aspiration cytopathology (FNAC) of the subcutaneous nodules and bilateral axilla found cytopathology suggestive of metastatic PTC.

Edelweiss Applied Science and Technology
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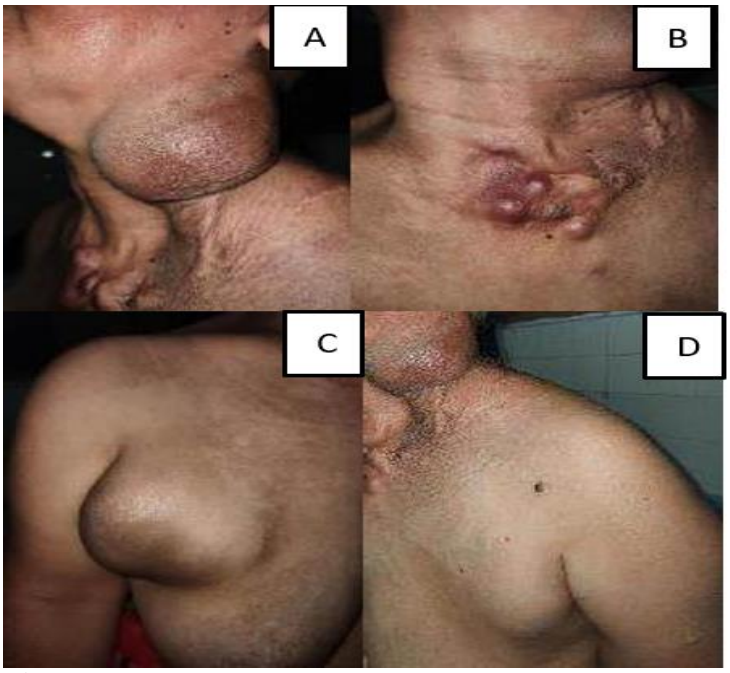

Figure 1.
Residual masses after RAI; (A) conglomerated left lymph node (B) subcutaneous skin nodules at the upper mediastinum and right cervical lymph node (C) left axillary lymph node (D) right axillary lymph node.

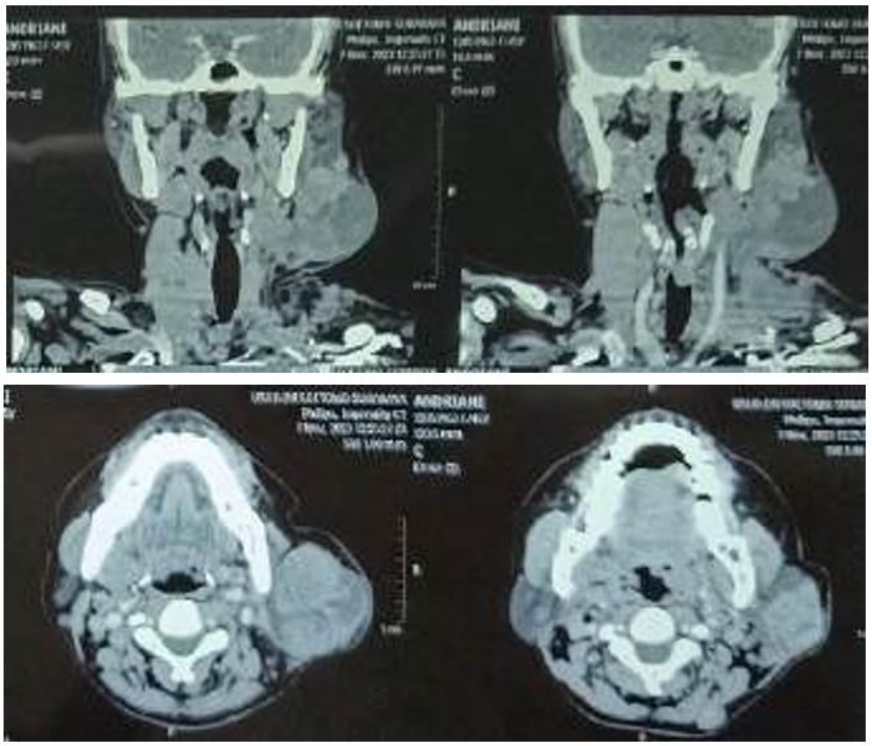

Figure 2.
Head and neck CT scan revealed solid mass in left thyroid lobe and conglomerated lymph nodes di both neck area.

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Contrast enhancement CT scan showed a residual mass in the left thyroid lobe 2.2 x 4.5 x 1.9 cm in size and no mass was found in the right thyroid lobe. A visible mass of 1.2 cm in diameter in the right supraclavicular lymph node was found along with conglomerated left lymph node in the left upper to midjugular 4.5 x 2.9 x 6.4 cm in size. Multiple subcutaneous nodules in the suprasternal region and multiple nodules in both lungs. Lytic lesions on the left lateral aspect of the body and pedicle of the 6th cervical vertebra suggestive of metastasis.

To exclude metastasis from breast cancer, we performed breast ultrasound which revealed multiple oval solid masses in right breast with circumscribed border, parallel to skin, hypoechoic texture measuring 0.5 cm in diameters at 12. 00 o'clock. These lesions were classified benign solid lesions in BI-RADS C2. As preoperative voice assessment for patient undergoing thyroid surgery and confirmed by the existence of voice alteration, we conducted direct laryngoscopy that showed paresis in the left vocal fold adductor and no airway obstruction was found. Thyroid function profile showed TSH 94.3 and FT4 0.62 which might indicate lack of suppressive effect from foregoing Euthyrox. According to the 8th AJCC, the patient was diagnosed with papillary ca thyroid rT3bN1bM1 with suprasternal skin infiltration post total thyroidectomy and left radical neck dissection and post RAI.

She was managed by wide excision on the upper mediastinum mass, completion total thyroidectomy, completion left neck dissection, type 3 modified radical right neck dissection, and bilateral axillary dissection with preservation of the long thoracic nerves and thoracodorsal nerves as shown below (Figure 3).

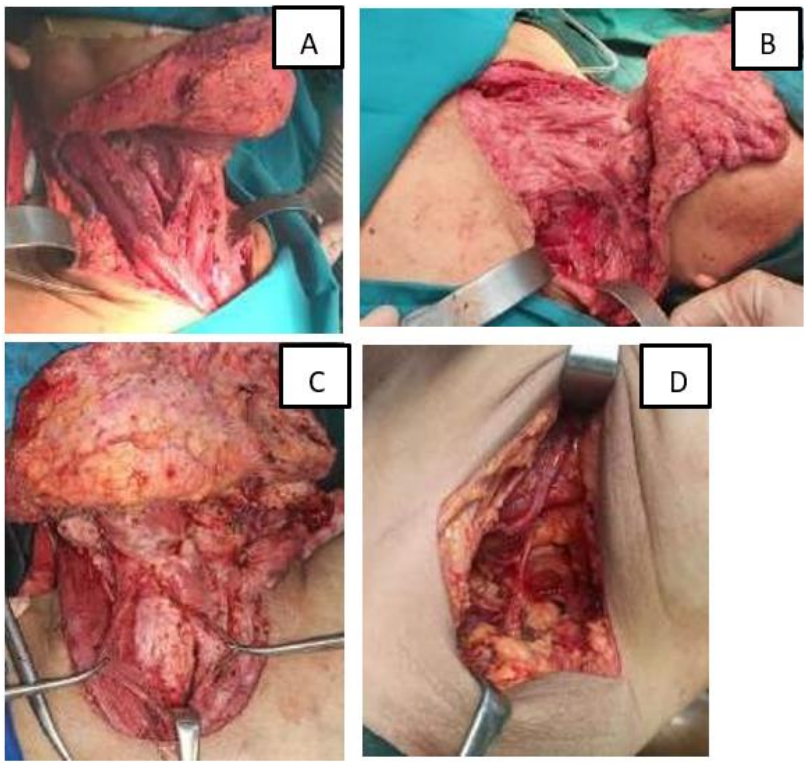

Figure 3.
Intraoperative showed; (A) left type 3 mRND (B) completion left neck dissection (C) bilateral central compartment clearance (D) axillary dissection.

During the surgery, we found some suspicious lymph nodes in both paratracheal, in which subsequently bilateral central compartment clearance was proceeded. Conversely, due to massive cervical neck lymph node and upper mediastinum subcutaneous nodules, all the adjacent structures

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superiorly by the hyoid bone and inferiorly by the level of the innominate artery was obliterated. Pathology reports revealed there was metastasis from papillary thyroid carcinoma from 7 of 24 in right cervical lymph node, 3 of 10 in left cervical lymph node, 10 of 17 right axillary lymph node, and 15 of 26 left axillary lymph node. Postoperative therapy was given IV fluids, antibiotics, levothyroxine as hormone suppression and oral calcium supplementation. The patient underwent external beam radiotherapy for locoregional distant metastasis and regular follow-up including annually neck ultrasound, maintenance of TSH level at <0.1 mU/L in accordance with ATA stratification risk with suppressive dose of levothyroxine. Due to some limitations in our institution, thyroglobulin examination could not be performed. Presently, that patient has some suspicious lymphadenopathy that appear at 9th months after the previous surgery. Neck ultrasound has been conducted and revealed multiple lymph nodes enlargement in left supraclavicular 0.7 cm in size, right infraclavicular 1.4 cm in size, and left infraclavicular matting 2.4 in size.

Nevertheless, FNA cytology of these lymph nodes showed absence of malignancy, hypocellular fibroblast smear. This patient is carefully observed to evaluate the presence of structural and TSH serum changes.

3. Discussions

PTC is the most common type of well- differentiated thyroid carcinoma with tendency to metastasize to regional lymph nodes, including central neck lateral neck (levels II-V), central neck (level VI), and upper mediastinal (level VII). PTC rarely metastasizes through hematogenous spread. ALNM is considered as distant lymph node involvement that implies hematogenous spread and dictates poor prognosis [11]. In cases with recurrent disease process, the time range from initial diagnosis to the development of axillary lymph node metastasis is 5-41 years it was in line with our case whom the patient had been diagnosed first time in three years prior [10].

A review of literature from Singh et al has found 31 cases of histopathology proven thyroid carcinoma with ALNM and most patients are recurrence disease, suggesting that well-differentiated thyroid has the ability to transform into poorly differentiated carcinoma during its course. ALNM from thyroid carcinoma is scarce since commonly associated with breast cancer, lymphoma, melanoma, lung cancer, and digestive tract malignancy. Since Mizukami et al. first reported ALNM in thyroid cancer in 1993, there is a few cases or literature has been reported, especially in Indonesia. The increasing number of incidence in Indonesia is also linear with the mortality rate during the past two decades [9, 12].

Our patient's clinical presentation is ALNM associated with primary recurrent thyroid cancer and other metastasis disease in lungs and cervical bone, with skin involvement. This becomes pivotal feature since skin is involved. Lymphatic drainage of tumor in the skin follows similar patterns to melanoma. There is such a complex relationship between lymph node drainage from axial tumors [13]. demonstrated patients with breast cancer and contralateral axillary lymph nodes involvement, 77% of them had skin involvement and it has been postulated through lymphoscintigraphy that in breast cancer patients have about 20%-30% of lymphatic drainage outside the axilla, so the skin could be the sign of lymphatic drainage [9, 11, 14].

In 1932, Rouvière reported that there is a link between the cervical and axillary lymphatics as the reason for the occurrence of ALNM. The physiologic direction flow in cervical lymphatic drainage is centripetal to the jugulo-subclavian junction. The retrograde spread of the tumor into the axilla may occur because of blockage of the cervical lymphatic vessels due to metastasized lymph nodes, radiotherapy, or surgery in the neck region. This pathway makes mediastinal lymph node metastasis may occurs in PTC but still ALNM is odd and rarely happening [5, 10, 15, 16].

Caso R, et al also pointed that ineffable burden of disease in the cervical lymph nodes ultimately culminate in alteration of lymphatic drainage. Bulky masses, accompanied by previous surgery in neck area, scarring, or radiation have been proposed to obstruct the lymphatic flow in the jugulo-subclavian

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confluence. Regarding PTC with lymphatic spread to the axilla is remarkably infringing the nature of the common metastasis site and only a handful of case reports in the literature exist. Henceforth, hematogenous spread is very unlikely considering the feature of classic type of PTC [11, 12]. As in our patient, there was a history of previous total thyroidectomy along with radical neck dissection 3 years before, this is in accordance with all the risk factors that justify the emergence of ALNM. The clinical presentation of the current recurrence has enormous masses that conglomerated and bulky, this indicates that the current tumor is more aggressive. Nevertheless, Singh et al concur that a vast cervical node metastasis or previous neck dissection could obviously alter lymphatic flow as a respond to lymphatic blockage or fibrosis from previous surgery [9].

Adequate surgery is paramount as the first line treatment that affecting the patient outcome, while RAI treatment, TSH suppression, and other treatments each play adjunctive roles. Removing of all normal thyroid tissue is an important element of initial surgery to clear the tumor burden and optimize the use of adjuvant therapies such as RAI or novel systemic therapies (3). Most scholars believe that surgery combined with adjuvant therapy is the most effective treatment for ALNM in thyroid malignancy since it may improve the quality of life and impede recurrences. Some authors have recommended the external beam radiotherapy for the axillary region, while others have chosen targeted therapy and chemotherapy as alternatives for advanced diseases [5, 12, 16].

As in our patient with ALNM with large primary tumor, metastasis to the regional lymph nodes, and distant metastasis to the lungs and cervical bone, we performed completion total thyroidectomy, comprehensive neck dissection, and standard axillary dissection followed by external beam radiation. This radiation may control treated metastasis, avoid local complications, and delay systemic therapy. Post operative radiotherapy reduced recurrence in DTC without toxicity and safe treatment to locoregional control in well-DTC with high-risk features. According to the National Comprehensive Cancer Network (NCCN), if the disease persists even after RAI treatment, external radiation is one of the therapeutic options to be considered [17].

Major goal for recurrence patient is to be free of disease in long-term follow-up. patients with a higher risk of recurrence are monitored more aggressively because it is believed that early detection of recurrent disease offers the best opportunity for effective treatment. Patient with PTC with lymph node metastasis, age >45 years, distant metastasis, and large tumor size has poor overall survival [3], therefore a routine follow- up planning must be set for this patient regardless any therapeutic strategies given.

A second goal of long-term follow-up is to monitor thyroxine suppression or replacement therapy to avoid under therapy or overly aggressive therapy. Re-evaluation of patient status and continuing follow-up are required as the overall approach to treatment of distant metastatic thyroid cancer [14,18]. Close monitoring of postoperative serum Tg with stimulated or no stimulated TSH is necessary to evaluate therapeutical response and to estimate recurrence risk [3, 18]. This patient is included into indeterminate response since biochemical and structural findings that cannot be classified. There is about 0%-4% of ATA high risk patient with indeterminate response, the vast majority of this category may come up as disease-free during the period of follow-up but up to 20% of these patients will have evidence of progressive disease and may entail additional therapy [3].

The recurrence after RAI treatment for DTC has become one of the risk of second primary malignancy. Although the number of this incidence is small. A meta-analysis study showed that the recurrence risk of second malignancies was increased 1.19 for thyroid cancer patients who not treated with RAI. There is no direct evidence of risk of secondary malignancies after single administration of 30- 100 mCi compared to the patients with risk of second primary thyroid cancer patients who have not been treated with ^{131}I. ATA strongly recommends RAI as the therapy for pulmonary micro metastasis and in our case, the patient received radiotherapy to the locoregional operative bed. The use of radiation after surgery must be case-tailored, considering the risk factors such as disease extent, histology, residual disease, and many more. A study by revealed the outcome of postoperative radiotherapy in DTC with aggressive features and its effect of locoregional control was satisfying, with

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5-year locoregional recurrence free survival was 86% [3].

4. Conclusion

ALNM from papillary thyroid cancer is very rare and associated with poor prognosis, such as recurrence or remote metastasis, more attention needs to be paid in treatment and follow-up. A retrograde mechanism in jugulo-subclavia junction to the axilla resulting from bulky tumor that shatter the natural lymphatic drainage flow due to the blockage could elucidate this disease. Risk factors contributing in axillary metastasis include skin involvement, bulky cervical lymph nodes, previous surgery including previous neck dissection, fibrosis, and radiation.

There is only small magnitude of literature that reports ALNM because of its rarity. Long term follow-up is essential in this patient with unusual metastasis involving the ALNM, cervical bone, and lungs. Biochemical and structural changes after the main therapy are the important factor to evaluate the clinical management.

Complete surgical resection of all gross locoregional tissues remains as the most vital to achieve effectiveness of RAI and postoperative radiotherapy gives effective treatment to improve locoregional control.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

Acknowledgement:

The author would like to express the gratitude for Nina Irawati, MD as the supervisor attending in this report and the director of Dr. Soetomo General Hospital, Surabaya for providing the opportunity to conduct this study.

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