Papillary Thyroid Carcinoma with Central Lymph Node Metastases

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Abstract

Lymph nodal involvement in papillary thyroid carcinoma (PTC) is very common. Preoperative neck ultrasonography (USG) allows for the early detection of nonpalpable cervical lymph node metastasis prior to thyroidectomy in patients with FNAB-proven or suspected thyroid cancer. In patients with clinically involved central nodes, therapeutic central compartment (level VI) neck dissection should be performed. Lateral neck dissection performed for macroscopic PTC metastases should be the selective neck dissection of levels IIa, III, IV, and Vb. We present a 38-year-old female patient of unilateral PTC with central and ipsilateral lateral lymph node metastasis who underwent total thyroidectomy and bilateral central and ipsilateral lateral lymph node dissection followed by radioactive iodine ablation (RAI) treatment. Postoperative RAI adjuvant therapy should be considered in ATA intermediate-/high-risk level patients. In PTC patients, no biochemical, clinical, or radiological evidence of tumor during the follow-up after total thyroidectomy and RAI treatment is defined as excellent response to treatment. The rate of recurrence ranges between 1 and 4% in patients with excellent response. In intermediate-risk patients who are subsequently reclassified into excellent response category, non-stimulated thyroglobulin assays and neck USG at 12–24-month intervals are considered to be appropriate in the follow-up.

33.1 Case Presentation

A 38-year-old female patient was referred to our institution for thyroidectomy in January 2016. She has been suffering from a gradually enlarging neck lump for 3 years. She had undergone neck ultrasonography (USG) previously at another institution, and fine needle aspiration biopsy (FNAB) had been performed for a large thyroid nodule located in the left thyroid lobe. The cytologic features of FNAB specimen have been reported as a highly cellular specimen with enlarged, oval, and irregular nucleus and intranuclear grooves. The findings were consistent with papillary thyroid carcinoma (PTC) (Bethesda 6). She had no family history of thyroid cancer or history of radiation to the head and neck. Physical examination revealed a large thyroid nodule sized approximately 4 cm in the left thyroid lobe. Serum thyrotropin (TSH) level was 2.5 mIU/L. The patient was scheduled for surgery. In our institution, routine preoperative

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Fig. 33.1 Ultrasonographic image of enlarged central lymph node with hypoechogenicity, rounded shape, and irregular borders
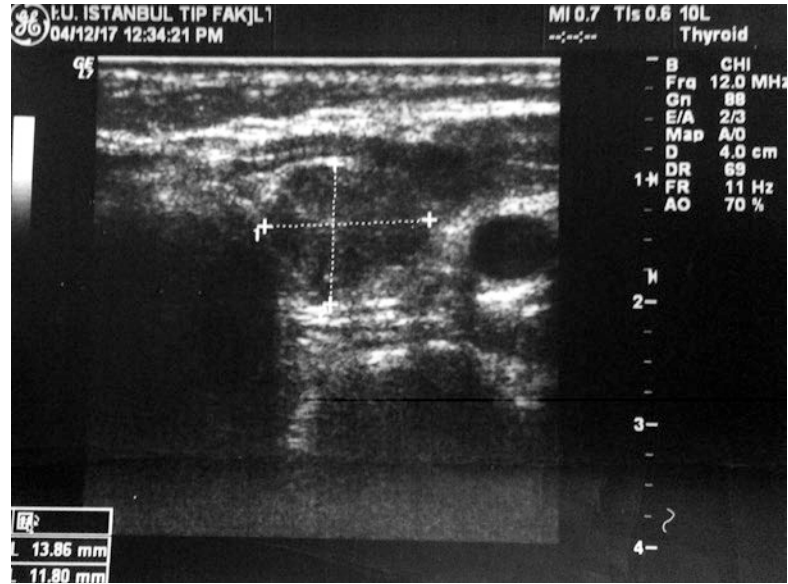
neck USG is performed in patients with a diagnosis of PTC in order to detect central or lateral suspicious lymph nodes, if any, which might have been missed during previous imaging studies. Preoperative neck USG showed a heterogenous, hypoechoic thyroid nodule with ill-defined borders in the left thyroid lobe. The transverse and longitudinal diameters of the nodule were measured as 39 and 20 mm, respectively. There were no nodules detected by USG in the right lobe. Preoperative neck USG also revealed an enlarged and hypoechoic lymph node with a rounded shape and irregular borders located at the inferior border of the left thyroid lobe (central lymph node) and suspicious subcentimetric lymph nodes at level IV at the left lateral compartment. The largest diameter of the central lymph node was measured as 13.9 mm (Fig. 33.1). The size of the largest lymph node at the left lateral compartment was measured as 9 mm. Thyroglobulin (Tg) measurement of fine needle aspiration (FNA-Tg) from the central and lateral lymph nodes was found as 355 ng/mL and 780 ng/mL, respectively. Macroscopic central lymph nodes in the left paratracheal compartment were observed intraoperatively (Fig. 33.2). The patient underwent total thyroidectomy, bilateral central lymph node dissection, and left lateral lymph node dissection with continuous nerve monitoring. Lateral lymph node dissection included levels III and IV. At the left side, macroscopic paratracheal central lymph nodes were found to show dense adherence to the recurrent laryngeal nerve. The postoperative histopathological diagnosis revealed classical variant PTC with a maximum diameter of
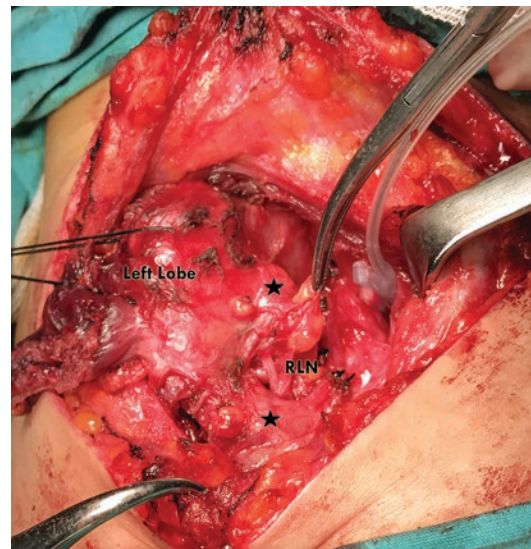

Fig. 33.2 Intraoperative image of macroscopic central lymph nodes (★)

3.8 cm located in the left lobe. The tumor showed microscopic extrathyroidal extension (ETE) and lymphatic invasion. No vascular invasion was recorded. Of 12 lymph nodes dissected from the central compartment, ipsilateral metastasis was found in 5. Of 14 lymph nodes dissected from the left lateral compartment, metastasis was detected in 6. Two of the metastatic lateral lymph nodes showed extranodal extension. Postoperative stimulated Tg (sTg) value was 5.6 ng/mL in the absence of anti-thyroglobulin (Anti-Tg) antibodies. Transient hypoparathyroidism developed postoperatively which was managed by oral calcium and vitamin D supplementation for 2 weeks following surgery. The stage of the PTC was defined as stage I according to the AJCC/UICC TNM system and ATA intermediate risk according to the ATA 2009 Risk Stratification System with Proposed Modifications [1].

33.2   Discussion

33.2.1 Evaluation and Diagnosis

The clinical importance of thyroid nodules, besides local compressive symptoms or thyroid dysfunction, is primarily the possibility of thyroid cancer which occurs in about 5% of thyroid nodules [2]. Thyroid nodules should be evaluated primarily to rule out thyroid malignancy. USG is the most reliable diagnostic modality to detect thyroid nodules, and USG-guided FNAB is the gold standard method to determine the malignant potential of the thyroid nodules [3, 4]. Several ultrasonographic thyroid nodule characteristics have been found to correlate highly with malignancy, including irregular borders, microcalcifications, height greater than width, hypoechogenicity, and increased vascularity [3, 4]. Combination of these suspicious sonographic features, especially of hypoechogenicity, irregular borders, and microcalcifications, is strongly associated with an increased risk for differentiated thyroid cancer [4]. USG-guided FNAB is strongly recommended in nodules ≥1 cm with

highly suspicious findings [1]. Lymph nodal involvement in PTC is very common, and in up to 90% of cases, lymph node micrometastases are observed [5, 6]. In PTC patients with lymph node metastasis, the nodal metastasis predominates in the ipsilateral central and ipsilateral cervicolateral compartments [7, 8]. The extent of initial thyroidectomy should be total or near total thyroidectomy in patients with clinical evidence of metastatic lymph nodes [1]. Preoperative neck USG for cervical lymph nodes is recommended for all patients undergoing thyroidectomy for malignant or suspicious for malignancy cytologic findings [1]. Preoperative neck USG allows for the early detection of nonpalpable cervical lymph node metastasis prior to thyroidectomy in patients with FNAB-proven or suspected thyroid cancer that otherwise might have been missed intraoperatively, thereby minimizing the risk for persistent disease [9, 10]. Preoperative USG can identify suspicious cervical lymphadenopathy, thereby potentially altering the extent of and overall surgical approach in 1/3 of these PTC patients [9, 10]. The sonographic features which are associated with metastatic lymph nodes include hypoechogenicity, rounded appearance, irregular borders, macro- or microcalcifications, loss of the fatty hilus, cystic appearance, and increased size [3]. The sensitivity of USG to detect central compartment metastatic lymph nodes is low prior to primary thyroidectomy when the thyroid gland is in situ. Kouvaraki et al. reported the sensitivity of preoperative USG to detect metastatic lymph nodes in the central and ipsilateral compartments as 52% and 77%, respectively [9]. The authors documented that most false-negative USG results occurred in the central neck compartment, especially in patients whose thyroid gland was still in situ. Confirmation of malignancy in lymph nodes with a suspicious sonographic appearance is achieved by USG-guided FNA for cytology and/or measurement of Tg in the needle washout [3]. Although the cutoff values for the FNA-Tg have not been standardized, preoperative values of >32.04 ng/mL and postoperative values of >0.9 ng/mL are recommended for identifying neck LN metastasis [11]. Several studies reported that tumor size >2 cm,

male sex, age <45 years, lymphatic invasion, ETE, multifocality, BRAF mutation, and the presence of lateral cervical lymph node metastasis were significant predictive factors for central lymph node metastasis in PTC [12–17].

33.2.2 Management

In patients with clinically involved central nodes, therapeutic central compartment (level VI) neck dissection should be performed [1]. At a minimum, central compartment neck dissection should include the prelaryngeal, pretracheal, and at least one paratracheal lymph node basin [18]. The presence of ipsilateral central or lateral cervical lymph node metastasis is a strong predictor of contralateral central lymph node metastasis in PTC [19, 20]. Skip metastasis to the lateral neck sparing the central compartment is uncommon but may be found up to 21.8% of the patients with upper pole tumors [21]. In patients who present with clinically evident disease involving cervical lymph nodes, the standard of care is to perform a therapeutic neck dissection, which entails the systematic removal of the lymph nodes in the central compartment [1]. Lateral neck dissection performed for macroscopic PTC metastases should be the selective neck dissection of levels IIa, III, IV, and Vb [1]. However, the patients with image-based, isolated lateral level IV involvement and no macroscopic extranodal extension might be potential candidates for limited levels III–IV dissection [22].

Because the AJCC/TNM risk of mortality staging system does not adequately predict the risk of recurrence in PTC, ATA thyroid cancer guidelines proposed a postoperative risk stratification system that classified patients as having low, intermediate, or high risk of recurrence according to clinicopathological and imaging findings [1]. Our patient was classified as intermediate risk due to the presence of microscopic ETE and >5 pathologic N1 with all involved lymph nodes <3 cm in the largest dimension. Of the patients who are classified as intermediate risk, approximately 60% have been reported to show excellent response to total thyroidectomy

and RAI ablation treatment [1]. However, 20–30% of such patients may have persistent disease or develop locoregional or distant metastasis. Large tumor size (>4 cm), macroscopic lymph node in more than five nodes or metastatic nodes larger than >3 cm, extranodal invasion, gross extrathyroidal invasion, vascular invasion, and detection of certain molecular markers, such as BRAF, TERT, or TP53 mutations, were found to be associated with increased risk of recurrence in PTC [1]. Recently, the percentage of positive lymph nodes among the total number of nodes removed (lymph node ratio(LNR)) has been used to predict the risk of recurrence in PTC. A LNR >0.3 in the central, lateral, or both compartments has been reported to present a strong prognostic factor for recurrence [23]. In PTC patients, postoperative disease status can be determined by means of serum Tg levels, neck USG, and diagnostic whole-body scan (WBS) [1]. Postoperative Tg is expected to reach its nadir by 3–4 weeks after surgery. Postoperative sTg level <1–2 ng/mL (in the absence of Anti-Tg antibodies) and no evidence of disease by radiological evaluation are strong predictors of remission [1]. Low postoperative serum Tg (<1 ng/mL) levels in low-risk patients confirm the classification of such patients as being low risk and might alter the decision of RAI ablation therapy [1]. Postoperative RAI adjuvant therapy should be considered in ATA intermediate-/high-risk level patients. In intermediate-risk level PTC patients, thyroid hormone treatment at suppressive doses is recommended for TSH suppression to 0.1–0.5 mU/L. In patients who underwent total thyroidectomy and RAI treatment, the criteria for disease-free status include all of the following findings: (1) no clinical evidence of tumor, (2) no imaging evidence of tumor (WBS or neck US), and (3) serum Tg levels <0.2 ng/mL under TSH suppressive therapy or sTg <1 ng/mL following stimulation. The follow-up of the intermediate-risk level PTC patients includes serum Tg assay and neck USG at 6–12-month intervals following surgery and RAI ablation therapy. In intermediate-risk PTC patients who have clinical features associated with increased risk of

recurrent or persistent disease, diagnostic WBS 6–12 months after RAI treatment is recommended [1]. Routine diagnostic WBS 6–12 months after RAI treatment is not recommended in intermediate-risk patients without high-risk factors and undetectable levels of serum Tg (in the absence of Anti-Tg antibodies) on thyroid hormone and negative US [1]. The adjustment of risk stratification in PTC patients during the course of further follow-up is important to provide an individualized therapeutic approach. After thyroidectomy and RAI treatment, biochemical and radiological findings during the first 2 years can be used to determine the individual response to initial treatment and reclassify the patients (dynamic risk assessment) [1]. The response to initial treatment is defined as excellent, biochemical incomplete, structural incomplete, and indeterminate response according to the serum Tg and/or Anti-Tg levels and radiological or clinical evidence of recurrent or persistent disease [1]. Excellent response to treatment is defined as no biochemical, clinical, or radiological evidence of tumor. The patients with negative or nonspecific imaging findings but abnormal Tg and Anti-Tg levels are reclassified as biochemical incomplete or indeterminate response. The patients with structural and functional evidence of tumor despite appropriate initial treatment are redefined as structural incomplete response. The rate of recurrence ranges between 1 and 4% in patients with excellent response, whereas it is 20% in patients with biochemical incomplete or indeterminate response. In patients with structural incomplete response, disease-specific death rate might be as high as 11%. Appropriate reclassification of intermediate-risk patients into the excellent response category with its very low risk of recurrence should lead to reevaluation of intensity of diagnostic surveillance procedures and treatment [1]). In intermediate-risk patients who are subsequently reclassified into excellent response category, the recommended TSH goal is 0.5–2 mU/L. Non-stimulated Tg assays and neck US at 12–24-month intervals are considered to be appropriate in the follow-up of such patients [1].

33.3 Follow-Up and Outcome

The patient received 150 mCi adjuvant radioactive iodine (RAI) therapy. There were no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment WBS. After RAI therapy, the patient received thyroxine therapy to maintain TSH levels between 0.1 and 0.5 mU/L. Measurement of serum Tg values on thyroxine therapy and neck USG was performed at 6-month intervals during the first year after RAI treatment. The diagnostic WBS with thyroid hormone withdrawal which was done 12 months after RAI showed no uptake in the neck and distant sites. The sTg level at the time of diagnostic WBS was found 0.04 ng/mL. Further follow-up of the patient was planned as Tg measurement at 6-month intervals and neck USG annually.

33.3.1 The Future

Future research related to the identification of gene mutations which are associated with aggressive tumor behavior and the impact of such mutations on the clinical course of the disease would guide the therapeutic decision-making in PTC patients.

What Can We Learn from This Case?
- Cervical lymph nodes should be evaluated by preoperative neck USG in all patients undergoing thyroidectomy for malignant or suspicious for malignancy cytologic findings.
- Preoperative neck USG allows for the detection of nonpalpable cervical lymph node metastasis prior to thyroidectomy. When the thyroid gland is in situ, the sensitivity of USG to detect central compartment metastatic lymph nodes is lower compared to lateral metastatic lymph nodes.
- In patients with clinically involved central nodes, therapeutic central compartment (level VI) neck dissection should

be performed. At a minimum, central compartment neck dissection should include the prelaryngeal, pretracheal, and at least one paratracheal lymph node basin.

- The presence of ipsilateral central or lateral cervical lymph node metastasis is a strong predictor of contralateral central lymph node metastasis in PTC. In patients who present with clinically evident disease involving cervical lymph nodes, the standard of care is to perform a therapeutic neck dissection, which entails the systematic removal of the lymph nodes in the central compartment.

- The PTC patients with more than five metastatic lymph nodes with all involved lymph nodes <3 cm in the largest dimension are defined as ATA intermediate risk. Postoperative RAI adjuvant treatment should be considered in ATA intermediate-risk patients.

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