Chapter 9
Papillary Thyroid Cancer with Central Neck Lymph Node Metastases

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Abbreviations

TSH	Thyroid-stimulating hormone concentration
micro-PTC	Micropapillary thyroid cancer
RAI	Radioactive iodine

Case Presentation

A previously healthy 30-year-old female was seen by her family physician for a general medical exam. As part of this evaluation, she underwent measurement of thyroid-stimulating hormone (TSH) concentration and a neck ultrasound. It was not clear why the ultrasound was ordered, as the patient was not aware of any abnormality in her thyroid exam. The patient had no compressive symptoms (i.e., no hoarseness, dysphagia, nor dyspnea). There was no family history of thyroid cancer, nor thyroid disorders. The patient had no significant history of head and neck radiation exposure.

Diagnosis/Assessment

For the case presented, the baseline TSH level was normal (2.49 mIU/L) and a neck ultrasound showed a left-sided solid, 1.0 cm hypoechoic thyroid nodule with smooth margins and no microcalcifications, and there were no other thyroid nodules and no enlarged/suspicious lymph nodes. Ultrasound-guided fine-needle aspiration

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biopsy of the thyroid nodule was positive for papillary thyroid cancer. She underwent total thyroidectomy, and the intraoperative detection of an enlarged a paratracheal lymph node prompted therapeutic left pretracheal and left paratracheal nodal dissection as part of the same procedure. The final surgical pathology showed multifocal micropapillary thyroid cancer (micro-PTC, follicular variant), with two foci, measuring in maximal diameter, 0.9 cm (in the left lobe) and 0.2 cm (in the right lobe), respectively. There was no extrathyroidal extension of the primary tumor, with no lymphatic, vascular, nor capsular invasion. The resection margins were clear. There was evidence of chronic lymphocytic thyroiditis. Upon examination of the eight resected central neck lymph nodes, two of them were positive for PTC, measuring 8 mm and 3 mm, respectively, in maximal diameter, with no evidence of any extranodal extension.

The clinicopathologic stage of disease in this case was interpreted as follows:

T1aN1aMx (Stage I) per the AJCC/TNM VII system [1, 2]
Low risk (for thyroid cancer-related mortality) by the MACIS system (score 3.37) [3]
American Thyroid Association (ATA) intermediate risk of recurrence [4]

Postoperatively, the patient started taking levothyroxine and recovered uneventfully, with normal calcium and parathyroid hormone levels and no problems with her voice. Approximately 11 weeks following surgery, while on levothyroxine therapy (TSH 7.24 mIU/L with a normal free thyroxine concentration), the thyroglobulin was measured to be <0.9 ng/dl, but thyroglobulin antibodies were present at a level of 97 IU/L (thyroglobulin antibody reference range <39 IU/L and the assay detection limit 20 IU/L). Given the presence of thyroglobulin antibodies, the thyroglobulin measurement was considered unreliable, due to potential assay interference [5]. A postoperative ultrasound of the neck 12 weeks after surgery was negative. Her levothyroxine dose was increased, with the intention of suppressing the TSH concentration (<0.1 mIU/L). The patient's endocrinologist recommended radioactive iodine (RAI) adjuvant treatment, given the presence of nodal metastases associated with increased risk of disease recurrence; another reason why RAI was recommended was to facilitate disease follow-up. However, the patient indicated that she did not want to take RAI, unless there was proof that it could reduce the risk of dying from thyroid cancer or distant metastatic recurrence, specifically in her situation. She strongly disliked the idea of taking any form of "radiation," unless it was clear that it could prevent death or distant metastases (which were her primary concerns). She was then referred an endocrinologist at a tertiary care center for further counseling.

Literature Review

Classification of Lymph Node Disease

Randolph et al. of the ATA Surgical Affairs Committee have reviewed the literature on prognostic significance of nodal metastases of papillary thyroid carcinoma and have proposed a categorization system for nodal disease [6]. Pathologic N1

(pN1) is any metastatic papillary thyroid cancer detected on the pathologic specimen of any resected lymph nodes [6]. Clinically apparent nodal disease, referred to as clinical N1, (cN1) is defined as metastatic lymph nodes identified on either physical examination, diagnostic imaging studies, or intraoperative inspection by the surgeon, and the absence of such features is clinical N0 (cN0) [6]. The presence of one or more metastatic lymph nodes that are visible on preoperative physical examination, ultrasound, or during surgery (the latter according to surgical and pathologic reports) has been independently associated with increased risk of recurrence of disease in a multivariable analysis, including data from 545 patients [7]. However, in the central neck, the accuracy of intraoperative surgical inspection is only about 60 % [8], with larger affected nodes being more readily clinically detected [9]. Moreover, the significance of subclinical, low-volume nodal disease in the central neck is not clear.

Regardless of how cN1 disease is detected, resection of such affected nodes and relevant nodal compartments is termed "therapeutic neck dissection" [6]. In contrast, "prophylactic neck dissection" is defined as nodal dissection in the absence of any evidence of cN1 disease prior the procedure [6]. Randolph et al. divided nodal disease into two categories: lower-risk N1 disease and higher-risk N1 disease [6]. Lower-risk N1 disease has been defined by the presence of the following criteria: (a) clinical N0; (b) low-volume nodal disease, specifically micrometastatic nodes (i.e., largest node <0.2 cm in diameter) or small nodal metastases (0.2 to <1.0 cm in diameter); and (c) ≤5 small lymph node metastases (i.e., each measuring <1.0 cm in diameter) [6]. Higher-risk N1 disease has been defined by the presence of the following criteria: (a) clinically detectable lymph node metastases (cN1), (b) metastatic lymph node(s) >3 cm, and (c) >5 metastatic lymph nodes [6]. Randolph et al. have also reported that gross extranodal extension, increasing number of metastatic lymph nodes with microscopic extranodal extension, or the combination of microscopic extranodal extension and metastatic lymph nodes >1 cm is also predictive of a higher risk of disease recurrence [6]. However, the predictive performance of the ATA metastatic lymph node classification system from Randolph et al. [6] has not yet been independently validated. It is important to note that according to the TNM/AJCC VII system, pathologic N1 disease is categorized as follows: N1a (metastases to the pretracheal, paratracheal, and/or prelaryngeal or Delphian lymph nodes, which are in the central neck) and N1b (metastases to unilateral, bilateral, or contralateral cervical or superior mediastinal nodes) (i.e., including the lateral neck or mediastinum) [1, 2]. The location of nodal disease has been reported to be associated with the size of involved nodes in papillary thyroid cancer, particularly for bulky enlarged nodes. For example, Chow et al. reported that 13 % of N1a and 56 % of N1b papillary thyroid cancer patients had involved nodes >2 cm in diameter ($p<0.001$) [10]. Ito et al. suggested that for papillary thyroid cancer patients whose nodal disease is detected on preoperative imaging, the cause-specific survival of patients with N1b level nodal involvement is not significantly different from that of those with N1a nodal involvement [11]. However, in this study [11], the disease-free survival was adversely affected in papillary thyroid cancer patients with N1b level nodal involvement who had pathologic evidence of aggressive nodal disease, including the lymph nodes measuring >3 cm in diameter, extranodal extension, or ≥5 or more

involved nodes [11]. Furthermore, the presence of two or more such adverse features in N1b disease was associated with reduced cause-specific survival [11]. Age also appears to be an important prognostic variable in N1 disease. For example, Verberg et al. reported that in differentiated thyroid cancer, patients aged ≥45 years who have lateral neck lymph node metastases have a reduced long-term life expectancy, but life expectancy is not significantly impacted in younger patients with similar disease features [12]. Furthermore, Hughes et al. have reported that in differentiated thyroid cancer patients with N1 disease, the recurrence rate was 8 % in those <45 years of age, as compared with 31 % in those ≥45 years of age [13]. In this study, all disease recurrences were successfully treated in the N1 patients aged <45 years, but only about a third of those aged ≥45 years of age [13]. In conclusion, the size and number, location of metastatic lymph nodes, the presence of extranodal extension, and patient age are relevant considerations in risk stratification of N1 disease.

Epidemiology of N1 Disease in Patients with Micro-PTC

Lymph node metastases are evident at the time of diagnosis in approximately 12–64 % of cases of micro-PTC [14–26]. If nodal metastases are present in this situation, the ipsilateral paratracheal compartments, followed by the pretracheal compartments, are the levels most frequently affected [20]. Lateral neck nodal metastases may be present in about 3–7 % of individuals with micro-PTC [15, 20, 24, 27, 28]. The presence of primary tumor extrathyroidal extension [14, 19, 29] and tumor multifocality [19, 29, 30] are risk factors for the presence of lymph node metastases with micro-PTC. In summary, N1 disease is not uncommon in patients with micro-PTC, and if it is present, it is most frequent in the central neck.

Prognosis of N1 Disease in Patients with Micro-PTC

The overall risk of disease recurrence of persistence in patients with papillary thyroid microcarcinoma and positive lymph nodes (without distant metastases at presentation) has been reported to range between 3.0 and 22 % [15–17, 19]. The risk of dying of thyroid cancer and developing distant metastatic recurrence in this context are important considerations. In a recent retrospective review of micro-PTCs, Mercante et al. reported that in a subgroup of 27 patients with T1aN1a disease, none of the patients died of disease nor developed distant metastases (follow-up about 8 years) [19]. Similarly, Kim et al. found that in a subgroup of 168 individuals with micro-PTC with no evidence of macroscopic extrathyroidal extension nor distant metastases at initial presentation, no patient died of thyroid cancer nor developed distant metastatic disease (mean follow-up about 5 years) [15]. In a retrospective review of micro-PTC cases from a hospital in Hong Kong, Chow et al. [22] reported

that in a subgroup of 48 patients with micro-PTC and various degrees of severity of lymph node disease without distant metastases, 2 % died due to thyroid cancer (1/50) and 4.0 % (two patients) developed distant metastatic recurrence (mean follow-up about 8 years) [22]. In a retrospective chart review of patients with differentiated thyroid carcinoma ≤1 cm in diameter treated in the years 1962–1995 in France, Baudin et al. reported that in node-positive micro-PTC patients without distant metastases at primary presentation, none of the patients died from thyroid cancer (0/113), and only 1 % developed distant metastatic recurrence (1/113) (mean follow-up of about 7 years) [21]. Also, in a retrospective review of micro-PTC cases at the Mayo Clinic, Hay et al. studied that the outcomes of a subgroup of 273 patients had positive lymph nodes at diagnosis [17]. Hay et al. indicated that no female with initial disease confined to the neck ultimately died of disease or developed distant metastases, but one male with extensive bulky lateral neck disease at presentation developed bone metastases and died of the disease, approximately 30 years after presentation (mean study follow-up 17 years) [17]. In summary, in papillary thyroid microcarcinoma patients with limited nodal involvement, no evidence of other adverse disease features, and no distant metastatic disease at the time of presentation, the risk of dying of thyroid cancer is likely about 0–2 % and the risk of developing distant metastatic recurrence is likely about 0–4 %.

In patients with papillary thyroid microcarcinoma and lymph node metastases (T1aN1), the risk of local-regional recurrence of disease in the neck or lymph nodes is another relevant consideration. The risk of local-regional recurrence in T1aN1 micro-PTC has been reported to range from 3 to 16 % [15, 17, 21]. Furthermore, the incidence rate of local-regional recurrence has been subdivided according to the level of nodal involvement at the time of initial diagnosis as follows, in two of the more recent studies: N1a (central neck)—0 to 3 % and N1b (lateral neck or mediastinum)—2 to 11 % (excluding individuals with extrathyroidal extension of the primary tumor at initial diagnosis) [15, 19]. Based on these limited data, it appears that nodal recurrence of disease is relatively uncommon in patients with micro-PTC whose initial nodal disease is confined to the central neck, in the absence of other adverse disease characteristics.

Does RAI Adjuvant Treatment Reduce the Risk of Disease Recurrence in T1aN1 Disease?

There are limited data from observational studies examining whether radioactive adjuvant treatment reduces the risk of recurrence after total thyroidectomy in patients with node-positive micro-PTC. Hay et al. reported that of 253 node-positive patients with micro-PTC, RAI adjuvant treatment did not significantly reduce local recurrence in the neck ($p=0.81$) nor distant metastatic recurrence ($p=0.68$) [17]. Ross et al. of the National Thyroid Cancer Treatment Cooperative Study Group also reported that in a subgroup analysis of 135 node-positive patients with micro-PTC who were followed prospectively, RAI treatment did not significantly improve

recurrence-free survival in node-positive patients (17 % without RAI, 11 % with RAI, $p > 0.05$) [16]. Kim et al. reported that in a subgroup of 168 micro-PTC patients who either had nodal disease, microscopic extrathyroidal extension of the primary tumor, or multifocality, RAI treatment did not significantly improve recurrence-free survival ($p = 0.52$) [15]. Chow et al. reported that in 50 micro-PTC patients with N1 disease, the administration of RAI did not significantly impact the risk of lymph node recurrence (nodal relapse rate 12.2 % (5/41) in the RAI-treated patients and 22.2 % (2/9) in those who did not receive RAI, $p = 0.6$) [22]. Creach et al. published a retrospective study of micro-PTC patients, which included a subgroup analysis of 153 individuals with N1 disease [26]. In this study, the 5-year recurrence-free survival rate was significantly higher in node-positive micro-PTC patients treated with RAI (93.2 %) compared to those not treated with RAI (42.9 %) ($p < 0.0001$) [26]. An important limitation of the latter study is that not all of the patients had total thyroidectomy, so it is not clear if the surgical extent was the same in both groups [26]. Thus, there is conflicting evidence on whether RAI adjuvant treatment reduces the risk of disease recurrence in node-positive patients with micro-PTC. The relatively small population size, limited follow-up, retrospective nature, and potential bias in selection of patients for RAI, in many of the aforementioned studies, are limitations that need to be considered in interpreting the results, which appear to be conflicting. Furthermore, none of these studies risk-stratified node-positive patients according to the number, size, or levels of involved nodes or the presence of extranodal extension. Given the low event rates, none of these studies would have been likely to be sufficiently statistically powered to detect differences in incidence rates of distant metastatic recurrence nor thyroid cancer-related mortality between RAI treatment and control groups. These studies also did not examine the potential benefit of RAI adjuvant treatment in disease staging (e.g., pre- or posttherapy RAI scans) or facilitating disease follow-up. So et al. recently reported that in patients with micro-PTC who had positive central neck nodal disease in the absence of preoperative evidence on the examination or ultrasound of abnormal nodes, the intensity of sodium iodine symporter (NIS) expression in affected nodes was highly variable [31] and may potentially lead to variability of RAI treatment efficacy among different individuals and populations. However, there are currently no data examining long-term RAI treatment outcomes according to NIS expression in metastatic nodes of patients with micro-PTC. Randomized controlled trials are clearly needed to better define the role of RAI adjuvant treatment in node-positive micro-PTC patients. Ideally, treatment effect according to potential molecular or other biomarkers should be explored in such trials.

Management Considerations and Outcome

Our patient presented with micro-PTC, with no preoperative evidence of nodal metastases, but with intraoperative palpation of a suspicious paratracheal lymph node prompting ipsilateral para- and pretracheal lymph node dissection, yielding

two small metastatic lymph nodes (maximal diameter 8 mm) out of eight nodes that were removed. The finding of the largest node being palpable intraoperatively in this case would technically upstage the disease to the "higher-risk" nodal disease category as defined by Randolph et al. [6], but the relatively small size and number of involved nodes and negative pre- and postoperative imaging would be more suggestive of a lower-risk nodal disease. The inherent limitations of accuracy of intraoperative detection of nodal disease in the central neck [7, 8] and the lack of data on independent prognostic significance of this finding are important considerations. The risk stratification of this case was largely based on the number, size, and levels of involved lymph nodes, in the context of the patient's young age, the absence of an adverse histologic subtype, the lack of extrathyroidal extension or vascular invasion of the primary tumor, and negative postoperative ultrasound imaging of the neck. Diagnostic I-123 scanning was not available at the treating institution, and I-131 pretherapy scans were generally not employed in the treating institution. However, there are some data, in centers experienced in the use of pretherapy I-123 or I-131 diagnostic scans, that such imaging may be helpful in evaluating disease status and other relevant variables, in patients being considered for RAI remnant ablation or treatment [32, 33]. The addition of single photon emission computed tomography–computed tomography (SPECT-CT) to iodine radioisotope planar imaging may provide additional information, clarifying the structural correlates of areas of increased uptake [34]. If an interfering thyroglobulin antibody were not present, measurement of a stimulated thyroglobulin could have also been helpful in postoperative risk stratification and related deliberation on RAI treatment, as previously respectively reported by Walfish et al. [35] and Rosario et al. [36]. The potential strengths and limitations of various postsurgical diagnostic test options for patients being considered for RAI remnant ablation or therapy are weighed in the new ATA guidelines on the management of thyroid nodules and differentiated thyroid cancer in adults [37].

The patient was counseled on disease prognosis, risks, benefits, and evidence uncertainties relating to RAI treatment in the context of her disease stage. Follow-up implications, including the limitation of biochemical follow-up in the presence of thyroglobulin antibodies, were also explained. The patient ultimately declined RAI treatment, reiterating her general opposition to "radiation" and indicating that the available evidence was not sufficiently convincing, in terms of reducing the risk of dying of thyroid cancer or developing distant metastatic disease, in her situation. She was less concerned about the potential for local-regional recurrence and understood the possibility of needing additional surgery, in the event of a recurrence. The patient agreed to close surveillance by ultrasound imaging of the neck and measurement of thyroglobulin and thyroglobulin antibody levels, with the intention of accepting additional treatment in the event of disease recurrence. She also accepted thyroid hormone suppressive treatment, with the intention of suppressing TSH to levels <0.1 mIU/L.

The thyroglobulin antibody positivity at the time of diagnosis was consistent with the pathologic evidence of Hashimoto's thyroiditis. The baseline thyroglobulin antibody titer (97 IU/L) decreased by 67 % within 10 months following surgery and

continued to slowly decrease to undetectable levels over the next 4 years, with continued concurrent undetectable serum thyroglobulin measurements. The patient was maintained on thyroid hormone suppressive therapy, keeping the TSH <0.1 mIU/L with normal free thyroxine levels. The continuing presence of thyroglobulin antibody has been reported to be associated with the presence of residual disease [38, 39]. However, a decrease in thyroglobulin antibody titers of ≥50 % in the first postoperative year after total thyroidectomy is associated with a risk of disease recurrence or persistence of 0–2 % [38, 39]. Furthermore, Tsushima et al. reported that in a multivariable model adjusted for other relevant prognostic factors, a thyroglobulin antibody reduction of <50 % from baseline or rise in this measurement over 1–2 years following thyroidectomy was independently associated with significantly increased risk of recurrence in lymph nodes [40]. Spencer and Fatemi have proposed a classification system for thyroglobulin antibody trends during long-term follow-up of papillary thyroid cancer, including the following categories: (a) falling thyroglobulin antibody trend (>50 % reduction from initial value, associated with <3 % risk of recurrence), (b) stable but significantly elevated thyroglobulin antibody (<50 % change from initial value, approximately 20 % risk of disease recurrence), and (c) rising thyroglobulin antibody trend (progressive, sustained rise in thyroglobulin antibody of >50 % from initial value, approximately 40 % risk of disease recurrence) [41]. Our patient continues to be followed, but as of 5 years after her surgery, she has had no evidence of structural disease on ultrasound imaging, and her thyroglobulin antibodies are continuing to slowly drop, currently bordering the detection limit of the assay; there has been no change in her undetectable thyroglobulin levels. In follow-up visits, she asserts that she is satisfied and she made the right choice for her, relating to not taking RAI, and she is highly compliant with close surveillance and TSH suppressive therapy.

Clinical Pearls/Pitfalls

- The risk of recurrence of patients with papillary thyroid carcinoma who have nodal metastases is dependent on factors such as the size, number, and presence or absence of extranodal extension of involved nodes and patient age, in addition to consideration of other disease features.
- Lymph node metastases are not uncommon in patients with micro-PTC.
- The risk of disease recurrence or persistence in node-positive patients with papillary thyroid microcarcinoma is variable; however, some of the lowest recurrence rates in this group appear to be in patients with relatively low-volume nodal disease confined to the central neck, in the absence of other adverse prognostic features or clinically detectable disease preoperatively.
- There is conflicting evidence as to whether adjuvant RAI treatment significantly impacts the risk of disease recurrence in node-positive micro-PTC patients, particularly for lower-risk nodal disease; however, RAI use may facilitate follow-up.

- Thyroglobulin antibodies interfere with thyroglobulin interpretation, but monitoring changes in antithyroglobulin antibody titers, in conjunction with structural imaging, may be helpful in disease surveillance.
- Patient preferences are important to consider in RAI decision-making, especially when there is conflicting or unclear evidence of long-term outcome benefit.

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