Chapter 14
Introduction

Kenneth D. Burman

In this Thyroid Section, we have presented several cases and clinical scenarios that are commonly encountered by clinicians. Drs. Chindris and Bernet describe a patient with a recently discovered thyroid nodule. Thyroid nodules are frequent and by autopsy study occur in about 12–37 % of individuals with 2.1 % having thyroid cancer [1]. The important issue is how to discriminate a thyroid nodule that is likely to be benign that can be monitored from a nodule more likely to harbor malignancy and should be more aggressively treated with thyroid surgery. Clinical history and features play an important role in this discrimination with, for example, a history of neck radiation, a family history of thyroid cancer, and local compression symptoms being worrisome for the presence of thyroid cancer [2]. Thyroid ultrasound characteristics are also important with shape (taller than wide), hazy borders, hypoechogenicity, increased internal vascularity, and microcalcifications suggesting (but not proving) the presence of thyroid cancer [3]. Serum TSH in the upper portion of the normal range is statistically correlated with the presence of thyroid cancer [4]. Of course, the cornerstone of the diagnostic approach is the performance of a thyroid Fine Needle Aspiration (FNA) [2]. Drs. Chindris and Bernet discuss the interpretation of an FNA in detail, but, in general, a thyroid FNA will be interpreted as benign, indeterminate, or consistent with malignancy (usually papillary thyroid cancer). Benign nodules generally can be monitored (with some exceptions) and malignant nodules (e.g., papillary thyroid cancer) require a thyroidectomy. The approach to an indeterminate cytology has improved recently due to the ability to perform molecular diagnostics. The likelihood of an indeterminate nodule harboring cancer is about 5–15 % for Atypia of Undetermined Significance (AUS), 15–30 % for follicular lesion, and 60–75 % for suspicious for papillary thyroid cancer [5]. There are two available molecular diagnostic tests or approaches presently available that can

K.D. Burman, M.D. (✉)
Endocrine Section, Medstar Washington Hospital Center, Washington, DC, USA

Department of Medicine, Georgetown University, Washington, DC, USA
e-mail: kenneth.d.burman@medstar.net

T.F. Davies (ed.), *A Case-Based Guide to Clinical Endocrinology*,
DOI 10.1007/978-1-4939-2059-4_14

assist in helping to determine if an indeterminate nodule contains cancer [5, 6]. Drs. Chindris and Bernet discuss the molecular analysis and its clinical applicability in detail. They also discuss the appropriate management and monitoring for each type of thyroid nodule.

Drs. Goyal and Burman then discuss a patient with about a 3 cm nodule that on thyroid FNA was suspicious for papillary thyroid cancer. Thyroid cancer is increasing at an alarming rate with about 60,220 new cases projected to occur in 2013 [7]. The stages of thyroid cancer are reviewed. The TNM staging system is commonly utilized. Interestingly, patients under age 45 can only have Stage 1 (disease localized to the neck) or Stage 2 disease (disease outside of the neck). However, patients; 45 years and above are classified as having Stage 1 through 4 disease, where Stage 1 is localized to the thyroid and Stage 4 represents metastatic disease outside the neck area [2]. This TNM Staging System has been useful in predicting mortality, but it may not accurately represent recurrence rates. The TNM Staging System (as noted above), however, has been noted to have discrepancies in predicting mortality, especially in some (but not all) patients with metastatic thyroid cancer who are under age 45. In an effort to improve prognostication, it has now become commonplace to reassess patients approximately a year after treatment [8]. This risk adapted strategy seems to aid in the long term assessment of patients. That is, a patient, for example, may have metastatic disease to the lungs and bones at presentation, but then responds to the initial treatment (e.g., surgery and radioactive iodine and perhaps external radiation therapy to selected sites). If re-evaluation at 1 year reveals resolution of the metastatic lesions, these patients are considered to have a good long-term prognosis as compared to their original evaluation. Drs. Goyal and Burman review the common somatic molecular mutations that occur in thyroid cancer, with approximately 40–70 % of patients with papillary thyroid cancer having a BRAF mutation (BRAF V600E) and a lesser percentage having a RAS or Ret/PTC or a PAX8/PPAR gamma translocation (that occurs more frequently in follicular thyroid cancer) [5]. There is active debate whether a somatic BRAF mutation is associated with a worse prognosis as compared to patients who do not possess this mutation. Indications, benefits, and possible side effects of treatment modalities, surgery, and radioactive iodine are discussed [9–11].

Dr. Burch discusses a patient who presents with osseous metastasis from papillary thyroid cancer. This situation is serious and appropriate diagnosis and therapy are discussed. When analyzing tissue from a patient with metastatic disease and when it is relevant to consider thyroid cancer, tissue staining with thyroglobulin may be very useful. Patients who present with a distant metastatic lesion from thyroid cancer, after the diagnosis of thyroid cancer is confirmed, a total thyroidectomy is recommended following by radioactive iodine [2]. Dr. Burch discusses the importance of assessing such a patient for exposure to recent previous radiocontrast dye (e.g., CT with IV contrast). Such a dye load will preclude radioactive iodine scanning and treatment for perhaps 4–8 weeks and such patients should have serial spot urine iodine measurements to help determine when it would be appropriate to proceed with radioiodine scans and treatment. Preparation for radioactive iodine therapy may be either levothyroxine withdrawal or maintenance of levothyroxine

therapy and the use of rhTSH stimulation [12]. Use of rhTSH stimulation for metastatic disease is not presently approved by the FDA but it is increasingly frequently being used clinically in this circumstance. Levothyroxine withdrawal may be associated with symptoms of fatigue, electrolyte abnormalities (e.g., hyponatremia) and decreased ability to perform routine daily activities including work. Two recent articles suggest that the use of rhTSH preparation for radioactive iodine therapy is associated with comparable beneficial effects as levothyroxine withdrawal [12, 13]. Further treatment of patients with distant metastatic lesion depends on the site, location, size, and clinical associations. External radiation may be effective as it is usually performed in patient with large osseous lesions, especially if they are impinging on vital structures (e.g., spinal cord) and/or are painful. Newer treatment techniques include radiofrequency ablation, laser ablation and/or tumor embolization [14]. Patients with osseous thyroid cancer metastases are also treated with bisphosphonates (usually IV) or denosumab (SQ) [14]. The frequency of these treatments is controversial in thyroid cancer.

Dr. Jonklaas reviews a patient with medullary thyroid cancer. Medullary thyroid cancer is distinct from differentiated thyroid cancer (papillary and follicular) in that is may occur sporadically or may be part of a familial genetic syndrome in which a germline RET oncogene mutation is present [15]. The pathologic and clinical manifestations and treatment modalities may be different than differentiated thyroid cancer. For example, medullary thyroid cancer does not respond to and is not treated with radioactive iodine therapy. Further, a normal serum TSH is maintained, rather than TSH suppression which is the goal in many patients with differentiated thyroid cancer. Depending on the series and the referral patterns, perhaps 20–30 % of patients with medullary thyroid cancer will have a germline RET mutation. RET mutations are most commonly part of the Multiple Endocrine Neoplasia (MEN) 2 syndrome, but also may be part of familial medullary thyroid cancer [15]. All patients with medullary thyroid cancer should be screened for a germline RET oncogene mutation. Frequently it is clear a patient has a family history of medullary thyroid cancer or a relevant genetic syndrome, but even some patients with apparently sporadic medullary thyroid cancer may actually have a RET mutation. Patients with a RET mutation must be screened initially and periodically for an associated pheochromocytome and hyperparathyroidism with hypercalcemia. It is recommended that a detected pheochromocytoma be removed prior to a thyroidectomy [15]. Moreover, all first degree relatives of a patient with a RET mutation must similarly be screened. A prophylactic thyroidectomy is considered in a screened RET oncogene positive first degree relative of a patient with known RET positive medullary thyroid cancer. Specific RET mutations are classified as low, medium and high risk disease and the timing of the thyroidectomy in the screened RET oncogene positive relative depends on clinical factors and the genetic site of the mutation [15]. The most important aspect of care of a medullary thyroid cancer patient is an expeditious total thyroidectomy with removal of lateral and central compartment lymph nodes as appropriate [15]. The prognosis of medullary thyroid cancer depends on the initial clinical and pathological findings. Patient with medullary thyroid cancer are monitored closely with serial calcitonin and CEA levels, neck ultrasounds, and neck

examinations. Serum calcitonin is an excellent marker for the presence and extent of persistent or recurrent disease. The doubling time of serum calcitonin helps predict the progression and course of disease [16]. If the serum calcitonin is higher than approximately 250–400 pg/ml CT scans of neck and chest as well as MRI of the spine and liver (or a liver protocol CT) are indicated as medullary thyroid cancer typically metastasizes to these locations [15]. Appropriate therapy may include external radiation, chemo-or bland embolization of hepatic lesions, and/or directed therapy at a specific lesion (e.g., cryotherapy, laser therapy). Recently, two multikinase inhibitors, Vandetanib and Cabozantanib, have been approved by the FDA for systemic therapy for metastatic, progressive medullary thyroid cancer [17, 18]. These agents have multiple potential adverse effects, including fatigue, neutropenia, proteinuria, hypertension, and hand–foot syndrome. Prolongation of the QT interval may occur and there are specific physician requirements to administer Vandetanib and for EKG and cardiac monitoring of both of these agents. Further, they generally cause temporary stabilization of disease and experience with their long term use is limited [19–21].

In summary, these related thyroid nodule and cancer articles bring us up to date on how to diagnose, evaluate, treat, and monitor common presentations of thyroid cancer. This effort to manage aggressive thyroid cancer is optimally integrated into a multidisciplinary team. Entry into an appropriate clinical trial should also be considered when appropriate. Future studies will no doubt focus on improved molecular analysis of thyroid FNAs and histologically obtained thyroid tissue, and on better treatment modalities, for example, the development of better more targeted TKIs and, also, on combination TKI therapy in an attempt to decrease the development of thyroid cancer resistance to single TKI therapy.

References

1. Mortensen JD, Woolner LB, Bennett WA. Gross and microscopic findings in clinically normal thyroid glands. J Clin Endocrinol Metab. 1955;15:1270–80.
2. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19:1167–214.
3. Kim GR, Kim MH, Moon HJ, Chung WY, Kwak JY, Kim EK. Sonographic characteristics suggesting papillary thyroid carcinoma according to nodule size. Ann Surg Oncol. 2013;20:906–13.
4. Jonklaas J, Nsouli-Maktabi H, Soldin SJ. Endogenous thyrotropin and triiodothyronine concentrations in individuals with thyroid cancer. Thyroid. 2008;18:943–52.
5. Nikiforov YE, Steward DL, Robinson-Smith TM, et al. Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules. J Clin Endocrinol Metab. 2009;94:2092–8.
6. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med. 2012;367:705–15.
7. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA. 2006;295:2164–7.

8. Tuttle RM, Tala H, Shah J, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid. 2010;20:1341–9.
9. Xing M, Alzahrani AS, Carson KA, et al. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA. 2013;309:1493–501.
10. Guerra A, Sapio MR, Marotta V, et al. The primary occurrence of BRAF(V600E) is a rare clonal event in papillary thyroid carcinoma. J Clin Endocrinol Metab. 2012;97:517–24.
11. Sarne DH. A piece of the puzzle: what does BRAF status mean in the management of patients with papillary thyroid carcinoma? J Clin Endocrinol Metab. 2012;97:3094–6.
12. Klubo-Gwiezdzinska J, Burman KD, Van Nostrand D, Mete M, Jonklaas J, Wartofsky L. Radioiodine treatment of metastatic thyroid cancer: relative efficacy and side effect profile of preparation by thyroid hormone withdrawal versus recombinant human thyrotropin. Thyroid. 2012;22(3):310–7.
13. Tala H, Robbins R, Fagin JA, Larson SM, Tuttle RM. Five-year survival is similar in thyroid cancer patients with distant metastases prepared for radioactive iodine therapy with either thyroid hormone withdrawal or recombinant human TSH. J Clin Endocrinol Metab. 2011; 96:2105–11.
14. Wexler JA. Approach to the thyroid cancer patient with bone metastases. J Clin Endocrinol Metab. 2011;96:2296–307.
15. Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid. 2009;19:565–612.
16. Gawlik T, d'Amico A, Szpak-Ulczok S, et al. The prognostic value of tumor markers doubling times in medullary thyroid carcinoma – preliminary report. Thyroid Res. 2010;3:10.
17. Durante C, Paciaroni A, Plasmati K, Trulli F, Filetti S. Vandetanib: opening a new treatment practice in advanced medullary thyroid carcinoma. Endocrine. 2013;44(2):334–42.
18. Viola D, Cappagli V, Elisei R. Cabozantinib (XL184) for the treatment of locally advanced or metastatic progressive medullary thyroid cancer. Future Oncol. 2013;9:1083–92.
19. Wells Jr SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30:134–41.
20. Haddad RI. New developments in thyroid cancer. J Natl Compr Canc Netw. 2013;11:705–7.
21. Nixon IJ, Shaha AR, Tuttle MR. Targeted therapy in thyroid cancer. Curr Opin Otolaryngol Head Neck Surg. 2013;21:130–4.