A Young Woman with a Thyroid Nodule

Case Study and Commentary, Colleen Veloski, MD, and Elias S. Siraj, MD

Abstract

- **Objective:** To review the diagnosis and treatment of patients with thyroid nodules.
- **Methods:** Review of the literature.
- **Results:** Thyroid nodules are common, with up to 7% of the adult population having palpable nodules. The primary aim in investigating a thyroid nodule is to exclude the possibility of malignancy, which occurs in about 5% of nodules. Evaluation of nodules includes a thorough history and physical examination, serum thyroid-stimulating hormone measurement, ultrasound, and, in some cases, fine-needle aspiration biopsy. Surgical intervention is indicated in cytologically malignant nodules or in cases suspicious for malignancy. In addition to surgical treatment, radioactive iodine ablation and suppressive treatment with levothyroxine are used to optimally manage thyroid cancer.
- **Conclusion:** Clinical decision-making depends on proper evaluation of the thyroid nodule. Only a small percentage require surgical management.

**CASE STUDY**

**Initial Presentation**

A 27-year-old woman with no significant past medical history presents for evaluation after her gynecologist discovered a palpable mass in the right anterior neck. The patient was previously unaware of the mass and has not experienced neck pain, dysphagia, hoarseness, or compressive symptoms. She has no symptoms of thyroid dysfunction and takes no medications. Physical examination reveals an enlarged thyroid with a 2.0-cm thyroid nodule that moves with swallowing. There is no palpable cervical lymphadenopathy. Family history is negative for thyroid carcinoma but several family members have goiters. The patient has no history of irradiation to the head or neck.

- What is the significance of a thyroid nodule?
- What is an appropriate evaluation for a thyroid nodule?

**Thyroid Nodules**

Thyroid nodules are common, with the prevalence of palpable nodules estimated to be 4% to 7% in the U.S. adult population [1]. The prevalence of thyroid nodules detected by ultrasound or at autopsy is much higher, likely 50% or greater [2,3]. Older age, iodine deficiency, female gender, and exposure to ionizing radiation are associated with increased prevalence of thyroid nodules. The various causes of thyroid nodules are listed in Table 1 [4]. Colloid nodules, cysts, and thyroiditis account for 80% of thyroid nodules, whereas benign follicular neoplasms are the cause in 10% to 15%, and thyroid carcinoma account for about 5% [5]. Since only 5% of thyroid nodules are malignant, a systematic approach to the diagnosis and treatment is essential to optimize outcomes and minimize costs. An algorithm for the evaluation and treatment of thyroid nodules has been developed by the American Thyroid Association Guidelines Taskforce (Figure) using an evidence- and consensus-based approach [6]. The primary goal of the evaluation is to exclude the presence of a malignant thyroid lesion.

**Evaluation of Thyroid Nodules**

Generally, nodules larger than 1 cm in diameter should be evaluated. In situations where the risk of malignancy is high (eg, family history, suspicious ultrasound features, a history of head or neck irradiation), smaller nodules may also need evaluation [4,6].

A careful history and the physical examination provide the framework for assessing the risk of malignancy. Rapid or gradual progressive enlargement, compressive symptoms, a family history of medullary or papillary thyroid cancer, multiple endocrine neoplasia type 2 (MEN2), or familial tumor syndromes should raise the level of suspicion for malignancy. Similarly, a firm or hard nodule fixed to adjacent structures or regional lymphadenopathy is suggestive of malignancy (Table 2) [5]. A history of exposure to ionizing radiation such as radiation to the head and neck or exposure to radioactive fallout from Chernobyl before age 14 years has also been associated with increased risk of thyroid malignancy [7].

- Which laboratory and imaging studies should be performed?
Thyroid Nodules

Table 1. Causes of Thyroid Nodules

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
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<tbody>
<tr>
<td>Benign</td>
<td>Multinodular goiter, Hashimoto's thyroiditis, Simple or hemorrhagic cysts, Follicular adenomas, Subacute thyroiditis</td>
</tr>
<tr>
<td>Malignant</td>
<td>Papillary carcinoma, Follicular carcinoma, Hürthle cell carcinoma, Medullary carcinoma, Anaplastic carcinoma, Primary thyroid lymphoma, Metastatic malignant lesion</td>
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Thyroid Function Tests

The initial step in evaluating a patient with 1 or more thyroid nodules is to assess thyroid function by measuring a serum thyroid-stimulating hormone (TSH) level. If the TSH level is suppressed below the lower limit of normal, measurement of free thyroid hormone levels will distinguish between overt and subclinical hyperthyroidism. Additionally, if the TSH level is suppressed, radionuclide thyroid testing should be performed to determine whether the nodule is hyperfunctioning or “hot.” The role of the radionuclide testing in the evaluation of thyroid nodules should be limited to patients found to have a low TSH or an indeterminate fine-needle aspiration (FNA) biopsy as discussed later in this section.

Radionuclide Thyroid Testing

Radionuclide thyroid testing is typically performed using radioisotopes such as iodine 123 (\(^{123}\)I) or technetium 99m (\(^{99m}\)Tc) that are trapped by the thyroid. After oral ingestion of the radiiodine isotope or intravenous injection of technetium, a gamma camera is used to capture images of the thyroid gland. A hyperfunctioning nodule has radioactive tracer uptake greater than the surrounding thyroid tissue. Such hot nodules are rarely malignant and do not require FNA biopsy but may require treatment for the hyperthyroidism, usually by radioiodine ablation. Only about 10% of thyroid nodules are hyperfunctioning. Treatment with iodine-containing medications or exposure to iodinated contrast interferes with radionuclide thyroid testing. The recommended minimum interval between exposure to iodinated contrast and radionuclide scanning is 4 to 6 weeks. An iodine-containing drug with a long half-life such as amiodarone can preclude radionuclide testing for 6 to 12 months.

When the TSH is normal or high, radionuclide scanning is not routinely indicated. Demonstration of a cold nodule on a radionuclide scan is not specific for thyroid cancer since only 5% to 8% of cold nodules are malignant.

Ultrasound

If the TSH is normal or elevated, the evaluation should proceed with ultrasound examination of the thyroid. High-resolution ultrasonography is the most sensitive test to detect thyroid lesions and provides information about the size of the gland and the number, size, and characteristics of specific nodules.

Because of the high prevalence of subcentimeter nodules and the indolent nature of most thyroid cancers, thyroid ultrasound should not be used as a screening test in asymptomatic individuals unless there is a family history of thyroid cancer or MEN2, significant exposure to ionizing radiation, or unexplained cervical adenopathy [8]. Generally, thyroid ultrasound is indicated in patients with a palpable nodule, enlarged thyroid gland, or multinodular goiter [4].

Other Tests

If a patient has a family history of medullary thyroid carcinoma or MEN2, serum calcitonin should be measured [5]. A basal serum calcitonin level greater than 100 pg/mL is suggestive of medullary thyroid cancer [9]. In patients with a negative family history, serum calcitonin is not routinely measured since medullary thyroid carcinoma is relatively rare.

Case Continued

A TSH level and a thyroid ultrasound are performed. The TSH level is normal at 1.5 mIU/L (reference range, 0.29–5.1 mIU/L). Thyroid ultrasound shows a mildly enlarged multinodular goiter with a complex nodule in the right midpole with solid and cystic components measuring 1.9 cm in its largest dimension, and several subcentimeter nodules throughout both thyroid lobes. None of the nodules have suspicious ultrasonographic characteristics.

- What is the next step in the evaluation?

Fine-Needle Aspiration

Patients with multinodular goiters have the same risk of malignancy as those with solitary nodules [10,11], and nodule size has not been shown to be predictive of malignancy [12]. The presence of certain characteristics on ultrasound is superior to nodule size for predicting malignancy in thyroid nodules. Specifically, microcalcifications, irregular margins, hypervascular chaotic arrangement of blood vessels within the nodule by color Doppler ultrasound, or hypoecho-
Figure. Algorithm for the evaluation of patients with 1 or more thyroid nodules. FNA = fine-needle aspiration; I = iodine; Tc = technetium; TSH = thyroid-stimulating hormone. *If the scan does not show uniform distribution of tracer activity, ultrasound may be considered to assess for the presence of a cystic component. (Adapted with permission from Cooper DS, Doherty GM, Haugen BR, et al; The American Thyroid Association Guidelines Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:114.)
Thyroid Nodules

genicity in a solid nodule are ultrasound characteristics that are superior to nodule size for identifying nodules more likely to be malignant [11,13,14]. Consequently, guidelines from American Association of Clinical Endocrinologists, American Thyroid Association, and Society of Radiologists in Ultrasound recommend selecting nodules for FNA on the basis of ultrasound characteristics rather than size [8].

It is important to note that while the previously mentioned suspicious ultrasound features have good specificity, the predictive value is limited by low sensitivity. Therefore, in the absence of suspicious ultrasound characteristics, the largest nodules are preferably aspirated [6].

In this case, the 1.9-cm right lobe nodule requires FNA biopsy because of its size and the lack of suspicious ultrasound characteristics in the other nodules. Since the nodule is palpable, FNA could be performed without image guidance. However, since it has cystic components, ultrasound guidance is preferable to increase the likelihood of sampling from the solid component of the nodule. In general, ultrasound-guided FNA reduces the rate of inadequate sampling and is required for biopsy of nonpalpable nodules [15,16].

Case Continued
FNA biopsy of the right thyroid nodule is performed. The sample is satisfactory and cytologic interpretation is “nodular goiter.”

- What is the significance of the cytologic diagnosis?

FNA Categories
FNA is a highly reliable diagnostic test with both false-negative and false-positive results in less than 5% of cases. FNA results fall into 4 general categories [4,16,17]:

• Inadequate or nondiagnostic (10%–15%)
• Benign (70%)
• Malignant (5%)
• Indeterminate (10%–15%)

Nondiagnostic samples contain inadequate numbers of cells for cytologic analysis and should be repeated. The majority of aspirates yield benign cytology (e.g., colloid nodule or nodular goiter, macrofollicular adenoma, benign cyst, or lymphocytic thyroiditis).

Among malignant cytologic results, papillary thyroid cancer is the most common (70%) followed by follicular (10%–15%), medullary (10%–15%), and anaplastic (5%–15%).

Indeterminate specimens are those for which a clear cytologic diagnosis is not possible and may be reported as follicular neoplasm, suspicious for follicular neoplasm, Hurthle cell neoplasm, or suspicious for papillary carcinoma. The risk of malignancy in indeterminate specimens varies from 15% for “follicular neoplasm” to 60% for “atypical papillary carcinoma [17,18].” When FNA biopsy yields an indeterminate result, surgical excision with review of the pathology is the only way to definitively establish the diagnosis.

The patient in the case has a FNA biopsy result in the benign category and no compressive symptoms from the goiter or the nodule. There is no indication for surgical intervention. Given that the false-negative rate for FNA biopsy is not zero, the size of the nodule should be re-evaluated either clinically or sonographically at 6- to 18-month intervals [6].

Treatment with levothyroxine to suppress the TSH below 0.3 mIU/L was used in the past to prevent enlargement of benign thyroid nodules, but the efficacy of this option has not been convincingly demonstrated [19]. In addition, in view of the increased risk of atrial fibrillation [20,21] and low bone density [22] associated with suppression of TSH, routine suppression therapy of benign nodules is not recommended [6].

Case Continued
The patient is instructed to follow-up in 1 year but was lost to follow-up for 7 years. In the meantime, she has given birth to 3 children. Recently she has noticed an overall increase in the size of her anterior neck. She has no dysphagia but occasionally experiences a choking sensation when lying supine.

Physical examination reveals a moderately enlarged thyroid with a 2.0-cm nodule in the right lobe and an indistinct prominence of at least 1.5 cm in the left lobe near the
Thyroid Neoplasms and Cancer

The cytology is indeterminate and only surgical resection with review of the pathology for extracapsular invasion, vascular invasion, etc. will yield a definitive diagnosis. The risk of malignancy in indeterminate specimens overall is approximately 20%, but varies from 15% for follicular neoplasm to 60% for atypical papillary carcinoma [17–19]. In this case, the risk of malignancy based on the cytology is 15% to 20%. However, the ultrasound features and the presence of an enlarged cervical node ipsilateral to the nodule impart a higher risk of malignancy.

Given the cytologic interpretation, presence of an enlarged cervical lymph node, and suspicious ultrasound characteristics, the patient should be counseled to proceed with total thyroidectomy and appropriate lymph node dissection. A radionuclide uptake and scan could be ordered before proceeding to surgery to further ensure that the nodule is not “hot” but is not necessary given her normal TSH [6]. Preoperative neck ultrasound to evaluate the cervical lymph nodes was already performed and revealed an enlarged left lateral cervical node. Generally, preoperative neck ultrasound to evaluate the thyroid and cervical nodes is recommended for all patients undergoing thyroidectomy for malignant cytology on FNA biopsy [6].

Case Continued

The patient undergoes total thyroidectomy. Left lateral neck dissection is also performed given the presence of an enlarged left cervical lymph node on examination and by ultrasound. Pathology shows follicular variant of papillary thyroid carcinoma in the 1.3-cm nodule in the left superior pole with lymphatic invasion. The 1.7-cm nodule left of the isthmus and the 2.0-cm nodule in the right midpole are follicular adenomas. One lymph node is positive for follicular variant of papillary thyroid cancer.

What additional therapy is indicated in thyroid cancer?

Management of Thyroid Cancer

In addition to surgical treatment, there are 2 therapeutic approaches used to optimally manage thyroid cancer: radioactive iodine treatment (ablation) with 131I and suppressive treatment with levothyroxine.

Radioactive Iodine Treatment

Postoperative radioactive remnant ablation is recommended for most patients with tumors greater than 1.5 cm; stages II, III, and IV disease; evidence of multifocal disease, nodal metastases, extrathyroidal or vascular invasion; or aggressive histology [6]. The goal of radioiodine ablation is to destroy residual thyroid tissue to decrease the risk of local recurrence. Also, the absence of thyroid tissue following ablation allows long-term surveillance for recurrence using TSH-stimulated thyroglobulin and whole body radioiodine scans.

Following successful treatment of thyroid cancer with surgery and 131I ablation, the thyroglobulin level should be undetectable and the radioiodine scans should be negative. A detectable level of thyroglobulin or areas of activity on a
radioiodine scan following surgical resection and radioiodine ablation usually indicates a recurrence or metastasis of a thyroid cancer.

Typically, patients receive 30 to 100 mCi of $^{131}$I for ablation. This treatment is usually administered after artificially raising the TSH level to above 30 mIU/L in order to enhance uptake by residual thyroid tissue or metastases. Most commonly, the elevated TSH is achieved by discontinuing levothyroxine therapy for a few weeks. More recently, though very expensive, recombinant human thyrotropin administration has been used to raise the TSH level without subjecting the patient to symptoms of hypothyroidism associated with levothyroxine withdrawal. Approximately 1 week after radioiodine therapy, whole body iodine scanning is usually performed to visualize any metastases.

**Suppressive Therapy with Supraphysiologic Doses of Levothyroxine**

Supraphysiologic doses of levothyroxine are given to suppress TSH below the lower limit of normal and has been shown to improve outcomes in high-risk thyroid cancer patients [23,24]. For most patients, TSH should be maintained at or slightly below the lower limit of normal (0.1–0.5 mIU/L); however, high-risk patients should be suppressed to below 0.1 mIU/L. TSH levels in the low-normal range (0.3–2.0 mIU/L) may be appropriate in patients free of disease after 5 to 10 years of suppressive therapy [6].

**Case Continued**

Six weeks following surgery, levothyroxine therapy is withdrawn for 3 weeks. When the TSH is greater than 30 mIU/L, the patient is treated with 100 mCi of radioiodine and whole body radionuclide scanning performed 1 week later is negative for metastatic disease. Levothyroxine therapy is restarted and titrated to achieve a TSH level of 0.3 mIU/L.

- What follow-up is necessary after surgery and remnant ablation?

**Surveillance of Thyroid Cancer**

The thyroglobulin assay and neck ultrasonography are the mainstays of surveillance following total thyroidectomy and radioiodine ablation for differentiated thyroid cancer.

**Serum Thyroglobulin**

Serum thyroglobulin is a sensitive indicator of recurrent thyroid cancer provided that it is not falsely lowered by the presence of antithyroglobulin antibodies. Laboratory testing evaluating levels of antithyroglobulin antibodies should be ordered along with thyroglobulin to ensure the validity of the thyroglobulin level. The serum thyroglobulin level should be undetectable in patients following complete thyroidectomy and radioiodine remnant ablation. The sensitivity of serum thyroglobulin testing is increased when stimulated by TSH either by levothyroxine withdrawal or administration of recombinant human thyrotropin.

**Neck Ultrasound**

Since most thyroid cancer recurrences or metastasis occur in the neck, ultrasound of the neck to evaluate the thyroid bed and cervical lymph nodes is highly sensitive in the detection of recurrent disease even when TSH-stimulated thyroglobulin is undetectable [25].

**Diagnostic Whole Body Radioiodine Scans**

Whole body radioiodine scans are less sensitive than TSH-stimulated thyroglobulin levels in detecting metastases [26]. Following the first whole body radioiodine scan performed after remnant ablation, additional whole body scans are not required for follow-up of low-risk patients with negative cervical ultrasound and negative TSH-stimulated thyroglobulin [6].

The American Thyroid Association Guidelines Taskforce recommends measurement of serum thyroglobulin and antithyroglobulin antibodies every 6 to 12 months. If antithyroglobulin antibodies are not present, an undetectable thyroglobulin level is considered negative for the recurrence of disease. In addition, a TSH-stimulated serum thyroglobulin level and antithyroglobulin antibodies should be performed 12 months after ablation to verify the absence of disease. Neck ultrasound to evaluate the thyroid bed and cervical lymph nodes is recommended at 6 and 12 months following remnant ablation and then annually thereafter for at least 3 to 5 years [6].

- What is the prognosis of well-differentiated thyroid cancer following treatment?

Given that our patient is younger than age 45 years with no distant metastases and 1 positive node, she has stage I papillary thyroid cancer. The 5-year survival rate for stage I disease is 100% [27]. Overall, well-differentiated thyroid cancer has a good prognosis with a 30-year cancer-related death rate of approximately 6% for papillary cancer and 15% for follicular cancer.

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References

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