Investigation of thyroid nodules

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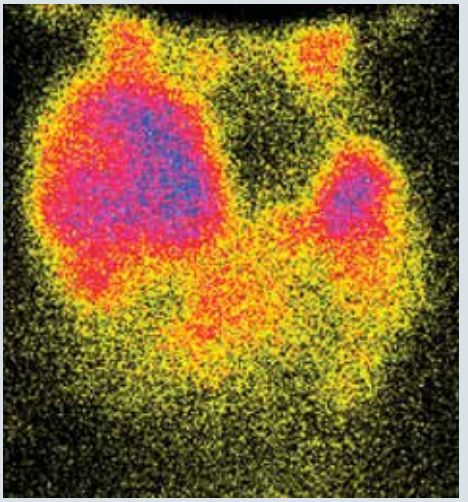
Case scenarios are used in this section to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.



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Thyroid nodules are a very common clinical problem in adults. Detection rates of nodularity are now much higher because of improved availability of neck ultrasonography and other imaging modalities. A prevalence of thyroid nodules of 19 to 67% has been reported using high-resolution ultrasound on randomly selected individuals,[1,2] with higher rates reported in women and with increasing age in both sexes. The risk of malignancy is about 7 to 15%,[3] of which many are probably insignificant microcarcinomas. The remaining vast majority of thyroid nodules are benign. The Bethesda system for reporting thyroid cytopathology has been universally adopted and each diagnostic category portends a risk of malignancy. Indications for fine-needle aspiration (FNA) biopsy based on ultrasound features are summarised in Box 1. Risk factors implicated in thyroid nodular disease include increased age, female sex, low dietary iodine intake, neck irradiation and family history of thyroid cancer.

It is important for GPs to have a clear understanding and a precise approach to the management of thyroid nodules (see Flowchart).[4,5] Selection of appropriate investigations, interpretation of the results, as well as short- and long-term management plans are demonstrated by the following clinical scenarios.

Case 1. A 70-year-old woman presents with atrial fibrillation (AF) and a neck swelling. There is no history of recent iodine load or family history of autoimmune thyroid disease.

How do you investigate this patient?

People with toxic thyroid nodules present with symptoms that are caused by complications arising in other organ systems (e.g. AF, osteoporosis) rather than with local symptoms such as swelling, airway obstruction, hoarseness of voice or difficulty in swallowing. Cardiac symptoms are the most common mode of presentation.

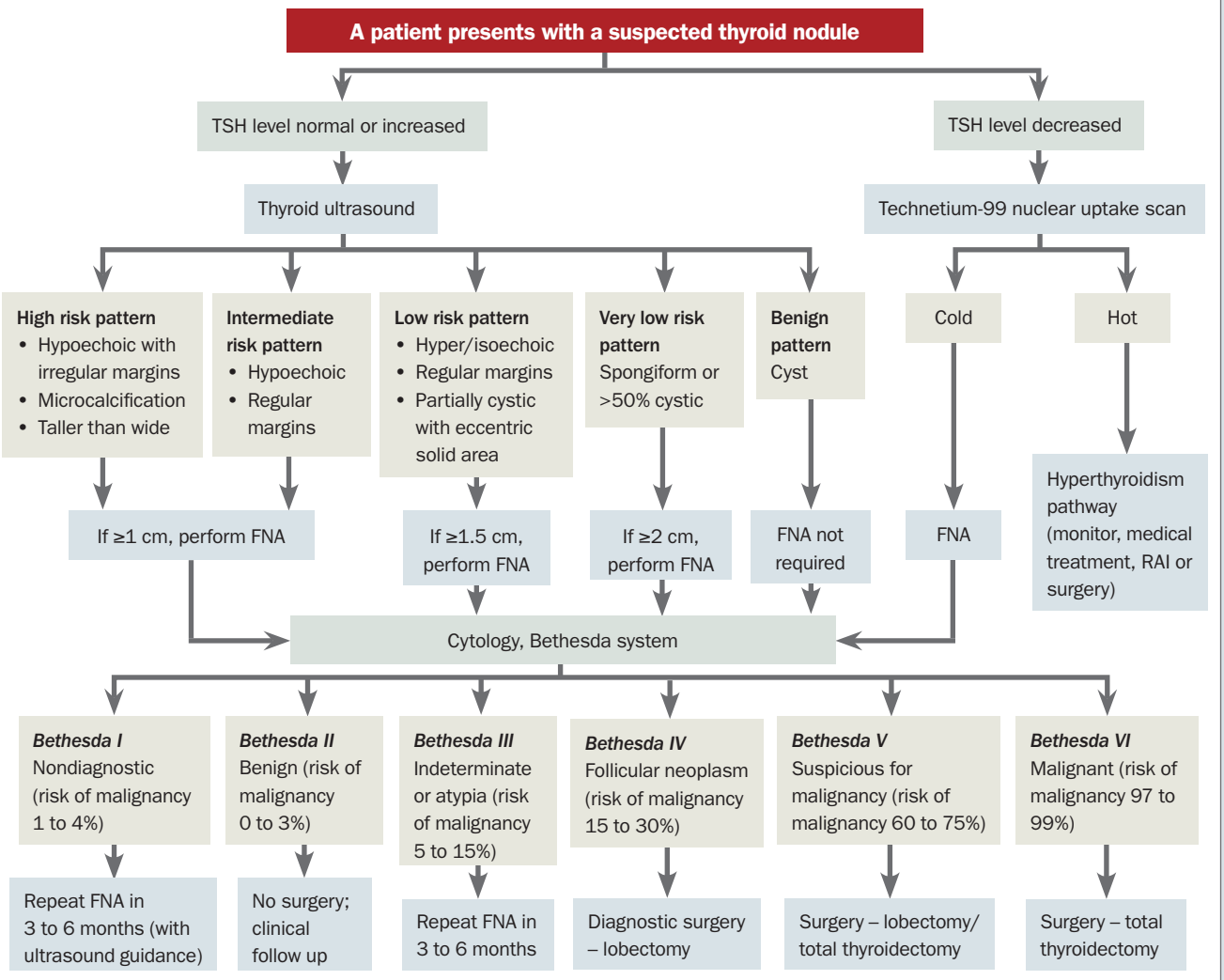
The patient underwent routine investigations for AF, as well as thyroid function tests (using the Roche immunoassay platform), which showed a suppressed thyroid-stimulating hormone (TSH) level of less than 0.01 mIU/L (reference range [RR], 0.27–4.2mIU/L), free T4 level of 33 pmol/L (RR, 12–25 pmol/L) and free T3 level of 7 pmol/L (RR, 2.5–6.0 pmol/L). Thyroid peroxidase, thyroglobulin and TSH receptor antibodies were negative. On a technetium-99 nuclear uptake scan, the right inferior pole nodule appeared 'hot' with suppression of tracer uptake elsewhere in the thyroid gland. A thyroid ultrasound showed increased thyroid volumes with multiple subcentimetre nodules in both lobes and a dominant 1.8 x 1.4 x 1.2 cm right inferior pole nodule. None of the nodules displayed suspicious sonographic features. These results are consistent with a solitary toxic thyroid nodule in a multinodular goitre (MNG).

The risk of malignancy in 'hot' nodules is extremely low (<1%) and FNA is generally not indicated. Nonfunctioning nodules on the technetium-99 nuclear uptake scan with suspicious sonographic features should be thoroughly investigated (Box 1).

What is the recommended management plan?

This patient was treated with 15 millicuries (555 MBq) of radioactive iodine (RAI) as definitive management. She was given a low dose beta blocker to rate-control her AF. Antithyroid drugs (ATDs) such as carbimazole could be considered for immediate short-term management to restore euthyroidism. Discontinuation of ATDs in the absence of definitive therapy will result in relapse of hyperthyroidism.[6] ATDs should therefore only be considered in individuals who refuse definitive therapy, have a contraindication to RAI treatment or who are unfit for surgery. If ATDs are used to restore euthyroidism before RAI therapy, they should be stopped at least one week before RAI treatment. The two definitive treatment options in

A systematic approach for evaluation of thyroid nodules[4,5]



Abbreviations: FNA = fine-needle aspiration; RAI = radioactive iodine.
Adapted from the 2015 American Thyroid Association Guidelines on the management of thyroid nodules and differentiated thyroid cancer.[4]

a toxic MNG or toxic adenoma include RAI or surgery.[6] If surgery is planned, a lobectomy is preferred for a solitary toxic adenoma. In the presence of multiple large nodules or a suspicious nodule/s in the contralateral lobe, with or without symptoms of local neck compression, a total thyroidectomy may be preferred.

How would you monitor this patient?

This patient did not require ATD treatment post RAI. Thyroid function tests were repeated at six weeks, three months and six months post RAI and she remained biochemically euthyroid. In toxic MNG, resolution of hyperthyroidism after RAI treatment occurs in about 55% of patients at three months and 80% of patients at six months.[7,8] The failure rate of RAI is about 15% (in which case a second dose of RAI is required) and is less than 1% with near-total or total thyroidectomy.[7,9] These patients should be monitored until they are rendered euthyroid or hypothyroid (and stabilised on thyroxine treatment). The other subcentimetre nodules remained stable during a two-year follow-up period. These stable subcentimetre nodules do not require long-term monitoring unless the patient develops clinical evidence of nodule enlargement. This patient should be followed up with annual thyroid function tests after RAI treatment as she may become hypothyroid in the long run (risk of hypothyroidism up to 60% at 20 years post RAI).[10]

Case 2. **A 66-year-old woman presents with an incidental 1 cm thyroid nodule detected on a staging CT as part of her investigations for breast cancer. Her TSH level is 0.56 mIU/L (RR, 0.27–4.2 mIU/L), free T4 is 14.4 pmol/L (RR, 12–25 pmol/L) and free T3 is 3 pmol/L (RR, 2.5–6.0 pmol/L) with a low positive thyroid peroxidase antibody titre of 60 IU/mL (RR, <35). The lesion is 18-fluorodeoxyglucose (FDG) avid on positron emission tomography (PET) scan, which was organised as part of her breast cancer investigations.**

How do you investigate this patient?

A thyroid ultrasound should be organised for this woman. This showed a solitary hypoechoic

1. Indications for fine-needle aspiration biopsy based on ultrasound features

- Thyroid nodule 1 cm or more plus one or more of the following high-risk ultrasound features:
  - hypoechoic and solid
  - microcalcification
  - taller than wide (AP diameter to transverse diameter ratio >1)
  - ill-defined/irregular margins
  - disrupted rim calcification
- Hyperechoic or isoechoic solid thyroid nodule ≥1.5 cm with regular margin or partially cystic nodule with eccentric solid area
- Spongiform or partially cystic thyroid nodule ≥2.0 cm with no suspicious features

solid nodule in the left superior pole measuring 1.0 x 0.8 x 0.6 cm with increased internal vascularity. There were no abnormal cervical lymph nodes. FNA of the nodule revealed a Bethesda category III (atypia of unknown significance).

Focal FDG avidity on PET scan in an ultrasound-confirmed nodule of more than 1 cm implies increased risk of malignancy and FNA is indicated in such cases.[4] The risk of malignancy in a FDG-PET positive thyroid nodule may be as high as 35%.[11] FDG-PET is not routinely indicated in further risk stratification of suspicious nodules on ultrasound or indeterminate FNA results.

Further investigation was undertaken due to the nodule's FDG avidity on PET scan. Surgical management should be considered in a hypoechoic PET positive nodule that is Bethesda III on FNA.

What is the recommended management plan?

Surgical management was offered to this patient given the high risk of malignancy. She underwent a lobectomy as the contralateral side did not harbour any nodules. On histopathology, the lesion was confirmed to be a unifocal papillary thyroid microcarcinoma of 0.8 cm with no extrathyroidal extension or lymph node involvement.

Lobectomy alone is sufficient in a small (<1 cm) unifocal intrathyroid carcinoma without lymph node involvement in the absence of other risk factors of thyroid cancer such as familial thyroid cancer and prior neck irradiation.

How should the patient be monitored?

Usual surveillance would include a neck ultrasound and measurement of an unstimulated serum thyroglobulin level at 12 months' post-surgery. If negative, careful annual neck examination thereafter may be sufficient. This patient only had a hemithyroidectomy and hence the benefit of monitoring serum thyroglobulin level is limited. As this is a very low risk intrathyroidal unifocal papillary thyroid carcinoma, there is no indication for remnant ablation with RAI or completion thyroidectomy. Thyroxine replacement was not required as this patient only underwent a hemithyroidectomy. Annual assessment of TSH levels is be warranted due to her positive thyroid peroxidase antibodies, which may increase her long-term risk of autoimmune hypothyroidism.

Case 3. **A 35-year-old woman presents with a neck swelling. Neck ultrasound confirms a multinodular goitre with multiple subcentimetre nodules. Her TSH level is 1.5 mIU/L (RR, 0.27–4.2 mIU/L) and free T4 level is 16 pmol/L (RR, 12–25 pmol/L) with negative thyroid autoimmunity. She has a strong family history of thyroid nodular disease.**

How do you investigate and manage this patient?

There is no indication for FNA of subcentimetre nodules in the absence of suspicious sonographic features (Box 1) because the risk of malignancy is very low. As the biochemistry is normal, there is no indication for a technetium-99 nuclear uptake scan.

Criteria for sonographic evidence of significant nodule growth are either a 20% increase in at least two dimensions with a minimal increase of 2 mm, or more than a 50% change in nodule volume. Significant growth or the presence of new suspicious sonographic features warrants a repeat FNA or continued close monitoring with ultrasound and consideration of FNA if there is continued growth.[4] For nodules that do not require FNA on initial imaging, the frequency of monitoring would be based on the sonographic pattern (Box 2). Nodules of more than 1 cm in size with a low suspicious sonographic pattern or pure cysts do not need routine ultrasound follow up. The ultrasound may be repeated at 24 months in nodules of more than 1 cm and a very low suspicious sonographic pattern, at 12 to 24 months for nodules with a low to intermediate suspicious sonographic pattern and at 6 to 12 months for nodules with a high suspicion sonographic pattern.

2. Red flags requiring immediate specialist referral

- Stridor associated with a thyroid lump
- Rapidly enlarging painless thyroid mass over a period of weeks
- Unexplained new hoarseness associated with goitre
- Cervical lymphadenopathy associated with a thyroid lump

Case 4. **A 48-year-old woman presents with a diffuse nontender goitre with no local neck compression symptoms. She is worried about the mass cosmetically. Her TSH level is 11 mIU/L (RR, 0.27–4.2 mIU/L), free T4 is 7 pmol/L (RR, 12–25 pmol/L), and thyroid peroxidase antibody titre is 868 IU/mL (RR, <35 IU/mL). She has a family history of hypothyroidism.**

How do you investigate this patient?

This patient is clearly hypothyroid and further elicitation of the symptoms on history is warranted. Her thyroid peroxidase antibodies are strongly positive and consistent with Hashimoto's thyroiditis, the most common cause of a diffuse goitre and hypothyroidism.

Hashimoto's thyroiditis is an autoimmune thyroiditis characterised by the presence of antithyroid antibodies and is often asymptomatic. Clinical indications for considering treatment with thyroxine include: symptomatic subclinical and overt hypothyroidism; a TSH level of 10 mIU/L or more regardless of free T4 levels and symptoms; if *in vitro* fertilisation treatment and/or pregnancy is desired; and if concurrent goitre or thyroid nodular disease is present. In contrast, patients with subacute thyroiditis secondary to a viral aetiology present with a painful diffuse goitre with or without transient

3. Differential diagnoses for solitary and diffuse thyroid swellings

Solitary swelling

- Solid or cystic thyroid nodule
- Thyroid adenoma
- Thyroid cancer
- Thyroglossal cyst
- Rare: metastasis from nonthyroid malignancy

Diffuse swelling

- Multinodular goitre (toxic or non-toxic)
- Hashimoto's/chronic lymphocytic thyroiditis
- Lymphoma*
- Acute suppurative thyroiditis†
- Graves' disease
- Subacute thyroiditis

*Presents as a rapidly enlarging thyroid mass with cervical lymphadenopathy.
† More severe pain, swelling, fever and compressive symptoms than subacute thyroiditis, more common in immunocompromised patients.

Key points

- Thyroid nodules are common, particularly with increasing age. The risk of malignancy is approximately 7 to 15%.
- Indications for ultrasound-guided fine-needle aspiration (FNA) biopsy of thyroid nodules are based on ultrasound features and consideration of risk factors (e.g. history of neck irradiation and family history of thyroid cancer).
- If TSH level is suppressed, a technetium-99 nuclear uptake scan is indicated to identify functioning nodules.
- Risk of malignancy in a functioning 'hot' nodule is very low (<1%) and FNA is generally not indicated if there are no suspicious ultrasound features or history.
- Nonfunctioning nodules on technetium-99 nuclear uptake scan with suspicious sonographic features should be thoroughly investigated.
- The Bethesda system for reporting thyroid cytopathology has led to standardisation of FNA reports based on diagnostic categories.
- Clear expert consensus and evidence-based guidelines on investigation and management of thyroid nodules are available via the American Thyroid Association guidelines on thyroid nodules and differentiated thyroid cancer.[4]

thyrotoxicosis from destructive thyroiditis. These patients may have fever and an associated rise in inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate and white cell count. A technetium-99 nuclear uptake scan may be helpful as thyroid uptake will be reduced in the presence of subacute thyroiditis. Differential diagnoses for solitary and diffuse thyroid swellings are listed in Box 3.

How do you manage this patient?

This patient was treated with levothyroxine. Thyroid function tests should be checked six to eight weeks after commencing therapy.[12] The initial starting dose may be at the full estimated dose in younger, healthy patients of 1.6 µg/kg/day and older patients may be started at a lower dose. To ensure that there is no effect on levothyroxine intestinal absorption it should be taken about 60 minutes before breakfast or before bed (with the last meal at least two hours beforehand). It should not be taken with medications that can potentially impair absorption, such as proton pump inhibitors or calcium or iron supplements.[12]

The goitre may reduce in size once the TSH level is normalised with levothyroxine replacement. Most patients with Hashimoto's thyroiditis have a small atrophic thyroid gland eventually and surgery is not indicated unless there are suspicious nodules. This patient is worried about the appearance of her neck and she needs careful discussion of the benefits and risks of surgery such as laryngeal nerve injury and hypoparathyroidism. Surgical management is recommended in patients with goitre associated with compressive symptoms such as dysphagia, dysphonia and dyspnoea.[13]

Case 5. A 40-year-old man presents with an incidentally discovered thyroid nodule on CT scan. Thyroid ultrasound reveals a right lower pole 2 cm cystic nodule with an eccentrically placed solid component with vascularity.

How do you investigate this patient?

This patient is biochemically euthyroid with negative thyroid autoimmunity. Cystic thyroid nodules are usually asymptomatic and occasionally present with pain from rapid expansion due to cystic degeneration, haemorrhage or haemorrhagic infarction.

Simple thyroid cysts are lined by epithelial cells and are less common than complex solid-cystic nodules. The eccentrically placed solid component in complex nodules may require FNA if there is vascularity; the absence of vascularity indicates that the tissue probably represents debris.

FNA revealed a colloidal cyst lined by benign epithelial cells. Purely cystic nodules with no solid components are rare to harbour malignancy (<1%) and FNA is not indicated.[4] Spongiform or partially cystic nodules of more than 2 cm without suspicious sonographic features could be clinically monitored or considered for FNA. The estimated risk of malignancy in complex (cystic and solid) nodules approaches that of solid nodules and FNA is indicated in such nodules if more than 1.5 cm. In any nodule more than 1 cm with intermediate- to high-risk sonographic pattern, FNA should be considered (Box 1).[4] Papillary thyroid cancer is the most common malignancy in complex solid-cystic nodules.[14]

How do you manage this patient?

Cyst aspiration is not routinely recommended as cysts tend to reaccumulate but could be considered if the patient is symptomatic or for cosmetic purposes. Asymptomatic nodules should be managed conservatively. Recurrent cystic nodules with benign cytology may be considered for surgical excision (hemithyroidectomy).

This patient was monitored with careful clinical assessment and annual ultrasound for the next two years. The nodule remained stable on ultrasound and hence FNA was not repeated. He remained asymptomatic. The patient was discharged for follow up with his local GP. **ET**

References

A list of references is included in the website version of this article (www.endocrinologytoday.com.au).

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