Nodular Diseases in the Thyroid

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Introduction

A thyroid nodule is a discrete lesion within the thyroid gland that is palpably or radiologically distinct from the surrounding thyroid parenchyma. Nodular diseases of the thyroid are very common, seen in about 8.5% of the population. They are commoner amongst women. Thyroid cancer is relatively rarer - the incidence is 8.7 per 100000 people per year, though this seems to have been increasing over the years. Hence, whenever a patient presents with a thyroid swelling, the task of the clinician is to distinguish the benign nodule from the malignant one. This is a difficult task, and no test is perfect in this regard. However, a reasonable amount of success can be achieved by good clinical evaluation and appropriate investigations.

Etiology

The etiology of thyroid nodules is diverse. Benign causes include the colloid nodule and the classical multinodular goiter. Occasionally, Hashimoto’s thyroiditis and Graves Disease may present with nodularity. Malignant causes include thyroid cancer, lymphoma as well as metastasis to the thyroid gland. The important causes are listed in table 1. This article will not discuss nodules in association with hypothyroidism or hyperthyroidism in detail, and will focus only on the commonly encountered problem of euthyroid thyroid nodules.

Clinical Evaluation

The focus of clinical evaluation is to differentiate thyroid cancers from benign swellings. The following features are suspicious and should suggest a malignant thyroid swelling: family history of thyroid cancer, rapid nodule growth, a very firm/hard nodule, clinical signs of fixity to surrounding structures, vocal cord paralysis/hoarseness of voice, regional lymph node enlargement or the presence of another lesion (for e.g. a lung nodule on chest x-ray) that suggests a distant metastases. While the above mentioned features are classical features, it must be remembered that many patients do not come with these typical features, and the presence of the following factors in addition to the thyroid nodule should evoke further investigations: male gender, extremes of age (<20 or >70 years), history of neck irradiation, nodule >4cm in size or the presence of any pressure symptoms.

Investigations

Blood tests: A TSH value that is < 0.2 mU/L indicates hyperthyroidism and a TSH that is >4 mU/L indicates hypothyroidism, and both are situations where medical therapy may be considered.

Ultrasonography (USG): The USG is a very cost-effective imaging procedure, and is highly sensitive in assessing nodule size and number. By itself; USG is not very useful in determining whether a nodule is benign or malignant. However, combining the USG with a Doppler can result in a better estimation of malignant potential: risk of malignancy is lower when a nodule has an exclusively perinodular vascular pattern than when there is a purely central vascular pattern. In addition, the following patterns suggest malignancy: irregular shape, ill-defined borders, hypoechogeneity, solidity, heterogeneous internal echoes, microcalcifications, absence of a halo, an anteroposterior to transverse diameter ratio (A/T) greater than one, infiltration into regional structures and suspicious regional lymph nodes. Of note, while multinodularity does not exclude malignancy, the absence of a truly dominant nodule in this setting may make cancer an unlikely possibility.

Fine needle aspiration biopsy (FNAB): This is unarguably the best single test, and uses a 23-27 gauge needle to aspirate samples for cytological assessment. With experience, adequate samples can be obtained in >95% cases. USG-guided FNAB can lower the occurrence of non-diagnostic smears. Degenerating and cystic nodules are problematic to aspirate. In this setting, the accuracy is improved by using ultrasound-guided aspirations from the appropriate solid zones. Overall all, a USG-guided FNAB with an onsite confirmation of adequate cellularity of the smear by a trained cytopathologist is the investigation with the highest sensitivity and specificity. In suspicious nodules, taking multiple aspirates will help to improve the sensitivity.

Radionuclide scanning: Nuclear scans use either one of the isotopes of iodine or technetium. These are handled differently by the follicular cells. Normal follicular cells take up both, but only radiiodine is organified and stored. Most benign and malignant neoplasms concentrate isotopes less avidly leading to a “cold” area on scanning. The rate of malignancy is about 10-15% in cold nodules, whereas malignancy is very unlikely in hot nodules. A hot nodule suggests hyperthyroidism- such nodules are usually not malignant.

Investigations to detect airway obstruction: Upper airways obstruction is rare in patients with goiter and is indicated by symptoms such as breathlessness and choking. There is a lack of correlation between the clinically assessed size of the goiter and the likelihood of upper airways obstruction. Plain radiography of the thoracic inlet and respiratory flow volume loops are specific means of identifying patients with functional tracheal compression who may need surgery.

Other tests: Antibody peroxidase antibodies are useful if Hashimoto’s thyroiditis is suspected. However, thyroiditis can coexist with thyroid cancer and therefore a euthyroid patient with a nodule will still need evaluation despite antibodies being positive. The routine use of serum calcitonin measurements to detect medullary thyroid cancer in the evaluation of thyroid nodules is controversial.

Combining investigations into a practical approach: It is often important to use a logical and step-wise approach in the management of thyroid nodules, and figure 1 lists such a strategy.

Management

General considerations

Despite the many investigative options available to the clinician, the management of the nodule essentially depends on the FNAB result. The possible reports from the cytopathologist
The disadvantages of suppressive levothyroxine therapy are modest efficacy, need for long-term suppression, post-therapy regrowth, risk of atrial fibrillation/cardiac arrhythmias and reduction in bone mineral density. therapy is an option in slightly enlarged, benign goiters, but benefits are limited by the very slow onset of action and need for contraception in female subjects. Ethanol injection into nodules (especially the symptomatic cystic nodules) may be useful. This can reduce the goiter size by 45% at the end of 6 months, but has severe adverse effects: seepage of ethanol, hemorrhage into nodule, pain and even vocal cord paralysis. Laser therapy is still experimental, but it offers similar benefits as ethanol injection with lesser side effects. This is probably because of the higher degree of control and consequently lower risk of extra-nodular damage that laser therapy entails. Laser therapy is useful in the mini-debulking of benign thyroid nodules with local pressure symptoms in cases of high surgical risk. The beneficial effect of laser therapy on the long term control of nodule size is uncertain.

**Thyroid incidentalomas**

An impalpable thyroid nodule in a euthyroid patient detected incidentally by ultrasonography is termed a “thyroid incidentaloma”. The prevalence of non-palpable thyroid nodules discovered on sonography in Asian adults is about 13%.

The same study, the malignancy rate among these incidentalomas was 28.8%. These nodules are detected when sonography is performed for nonthyroid related neck problems. It is important to perform a TSH estimation to detect a toxic nodule. A general management approach is to observe those nodules that are less than or equal to 1.4 cm in size and perform an FNAB under ultrasound guidance for nodules greater than 1.4 cm. Routine FNAB for all nodules < 1.4cm is less desirable. However, it is important to remember that the prevalence of malignancy in subjects with a non-palpable nodule is the same as that in a palpable nodule: hence, close follow up is quintessential. If 6-monthly ultrasounds document an increase in size, an attempt at US-guided FNAB may be appropriate. If other additional risk factors for malignancy exist (like family history or past radiation or typical USG features), then further evaluation of even nodules <1.4 cm is justified. With the increasing use of PET scanning, many incidentalomas are being detected. Further evaluation of these lesions must be based on clinical and USG-based assessment of malignant potential.

**Cystic thyroid lesions**

Most cystic lesions are degenerating benign adenomas, which may be seen on USG within the cyst wall or adjacent to the nodule. A cyst that is encountered in the course of performing FNAB should be drained completely since many such lesions are adequately treated by aspiration alone. The cyst fluid may be sent for cytological evaluation. However, this is unlikely to provide much diagnostic information as the fluid usually contains only degenerative debris. The color of the cyst fluid can offer a clue: an amber colored fluid is indicative of a benign lesion and a crystal clear fluid may be seen in a parathyroid cyst. It is important to note that both benign and malignant cysts may yield a bloody fluid. Cysts that recur after aspiration are best operated upon. Solid-cystic thyroid nodules have a higher incidence of malignancy than the purely cystic lesions. USG can differentiate between a solid and cystic lesion, but 80% of thyroid nodules are solid/cystic. Hence if the ultrasound report is the sole criteria to decide about surgery then 80% of patients will proceed to surgery. A better option is to perform an FNAB from the solid portion of the solid-cystic lesion using USG guidance, and then decide on therapy of these cystic thyroid lesions.
New Advances in Diagnosis and Therapy

A major problem in the evaluation of thyroid nodules is the high prevalence of indeterminate cytology cases (as high as 10-15%) on FNAB. Nuclear scintigraphy has not been able to completely overcome this problem. In this regard, two important modifications to the FNAB have been attempted: immunocytochemical studies (particularly with galectin-3 immunostaining) and molecular cytogenetic studies. Galectin-3 is not expressed in normal thyroid cells. It has been suggested that cells which have a tendency to malignancy express galectin-3. Galectin-3 has been found to be useful in differentiating benign from malignant thyroid lesions.16 It has been shown that over 90% of thyroid cancer express galectin-3, while only about 2% of benign nodules express galectin-3. Galectin-3 has been shown to be useful in diagnosing small (minimally invasive) follicular cancers.17 This is important, because an FNAB cannot differentiate follicular adenoma from a follicular cancer. A combination of molecular and cytogenetic studies after FNAB offers an exciting pre-surgical insight into whether a lesion is benign or malignant. The important mutations studied in relation to thyroid cancer are: BRAF, RAS, RET/PTC and PAX8/PPAR\gamma mutations. In cases with indeterminate cytology, a recent study showed that 97% of subjects who were mutation-positive harbored a malignancy.18 If these results are corroborated, then the clinician will have a new tool for deciding which nodules should undergo thyroidectomy.

Finally, a recent advancement in the management of thyroid nodules has been the use of recombinant TSH for amplifying the effect of I\textsubscript{131} in shrinking benign goiters. Recombinant TSH can increase the uptake of iodine by thyroid cells, and can thus augment the effect of I\textsubscript{131} on nodule size. A recent study showed that recombinant TSH (rTSH) injections prior to I\textsubscript{131} therapy facilitated goiter shrinkage by an additional 50% as compared to I\textsubscript{131} alone.19 However, in that study, pain and compressive symptoms were more frequent with rTSH therapy. In another study on very large multinodular goiters, rTSH-based I\textsubscript{131} therapy was shown to improve tracheal compression and improve inspiratory capacity.20 Though rTSH is now available in India; this therapy is both controversial and experimental.

Conclusions

- A thyroid nodule is a discrete lesion within the thyroid gland that is palpably or radiologically distinct from the surrounding thyroid parenchyma
- Whenever a patient presents with a thyroid swelling, the task of the clinician is to distinguish the benign nodule from the malignant
- Features suggestive of a malignant thyroid swelling are family history of thyroid cancer, rapid nodule growth, a very firm/hard nodule, clinical signs of fixity to surrounding structures, vocal cord paralysis/hoarseness of voice, regional lymph node enlargement or the presence of another lesion (for e.g., a lung nodule on chest x-ray) that suggests a distant metastases
- In addition to thyroid nodule, male gender, extremes of age (<20 or >70 years), history of neck irradiation, nodule >4cm in size or the presence of any pressure symptoms should evoke further investigations
- Investigations include TSH, TS, T4, ultrasonography, Radionuclide Scanning and FNAB
- Surgery is required if malignant or suspicious cytology is reported. Rapid growth and increasing pressure effects (breathing difficulty, dysphagia), and cosmetic reasons due to the size of the goiter are indications for surgery
- Patients with a suspicious FNAB report are subjected to radio nuclide scanning and surgery is performed on those nodules that are cold or warm, and simply following up those with hot nodules without surgery as the risk of malignancy in these nodules is very low
- In malignant/ suspicious cases, total thyroidectomy is the treatment of choice
- In patients with a benign cytology total or hemi- or subtotal thyroidectomy is done
- Total thyroidectomy is advocated for bilateral benign multinodular goiters

References

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