Chapter

Multinodular Goiter

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Abstract

Multinodular goiter (MNG) is the most common disorder of the thyroid gland. It is highly endemic in iodine-deficient areas; MNG can be seen in almost all individuals with severe iodine-deficient areas. It starts as a diffuse enlargement of the thyroid gland and ends in a nodular enlarged thyroid. Though MNG can be sporadic, there is a strong correlation between occurrence of MNG and iodine deficiency. The characteristic feature of MNG is its functional and structural heterogeneity. The MNG usually presents as neck swelling; rarely it may produce pressure symptoms, i.e., dyspnea, hoarseness of voice, and dysphagia. It can also present with symptoms of hyperthyroidism particularly in long-standing goiter. Imaging particularly ultrasound is very useful to define characteristic of MNG and surrounding structure. The incidence of malignancy in MNG is 4–14%, and risk factors are family history of thyroid carcinoma, history of neck radiation, prior surgery, and presence of cervical lymphadenopathies. Management of MNG can be done by drugs, surgery, and radioiodine (I-131) depending on results of diagnostic evaluation and associated complications.

Keywords: hyperthyroidism, iodine, goiter, MNG, multinodular goiter, thyrotoxicosis

1. Introduction

Goiter is the enlargement of the thyroid gland which can be due to a variety of conditions. Nodular goiter is one of the most common endocrine disorders affecting the thyroid gland. It is endemic to certain populations and regions especially those with iodine deficiency. It also tends to occur with a higher frequency in women and in the fourth to fifth decades of life [1]. The prevalence of goiter is variable worldwide and is correlated with iodine intake of regional populations. In approximately 3600 B.C., Chinese medical writings were the first to show a decrease in size of goiter after ingestion of seaweed and burnt sea sponge, and they continued to remain as effective remedies for goiter worldwide as was documented in the writings of Hippocrates, Galen, Roger, and Arnold [2].

After initiation of iodine prophylaxis programs in over 2100 school girls in the United States in 1917 by David Marine and colleagues, iodized salt was introduced in the United States in 1922 for prevention of endemic goiter. Later in 1930 iodized salt became widely available in the United States [3]. The salt iodization is a good approach for decreasing iodine deficiency in population, as it is a universal foodstuff, inexpensive, and easily available and intake is relatively consistent [4]. Approximately 120 countries, including the UK, Canada, Brazil, China, India, Thailand, and Singapore, have adopted mandatory iodization of all food-grade salt [5]. Currently the WHO recommends daily intake of 150 mcg iodine for adults,

250 mcg for pregnant and lactating women, and 90 mcg for children <2 years of age that can be easily obtained by iodized salt, processed food, and milk products [6]. Prevalence of goiter still remains 4–7% in the United States even after iodine supplementation [7].

Goiter can be classified as solitary or multiple, diffuse or nodular, and toxic or nontoxic on an anatomical and functional basis. The nontoxic goiter is due to abnormalities of iodine supplies or metabolism without any abnormal thyroid function. In children goiter tends to be smaller and diffuse, whereas in older people they are usually large and nodular.

2. Etiology and pathophysiology

Thyroid hormones affect the function of virtually all organ systems of the body; these are critical determinants of brain and somatic development in infants and of metabolic activity in adults. The thyroid gland is regulated to a large extent by the delicate balance between the hypothalamus, pituitary, and thyroid. Thyrotropin-releasing hormones (TRH) are secreted by the hypothalamus which stimulates the secretion of the thyroid-stimulating hormone (TSH), by the pituitary gland. TSH is a major regulator of the thyroid gland which after binding to its receptor on plasma membrane stimulates each and all steps of thyroid hormone synthesis and secretion.

Goiter is an etiologically and pathogenetically complex disease. The specific role of TSH in its pathogenesis has not been unraveled. It has been variously defined and characterized by the increased volume of the thyroid gland with the formation of multiple nodules. Although a number of definitions exist, the most accepted is the thyroid gland weighing over 20–25 g or a volume of over 19 ml in females and 25 ml in males [8].

Grossly, MNG reveals a heterogeneous array of solid/cystic and mixed nodules. Cystic nodules are typically defined as a cystic component >50%. Typically, pathogenesis of MNG thyroid can be attributed to three main processes: diffuse follicular hyperplasia, focal nodular proliferation, and eventual acquisition of functional autonomy. Development of goiter especially in conditions of iodine deficiency or Hashimoto's disease seems to be TSH driven. However, in addition to TSH, several other growth factors, both TSH dependent and independent, have been known to play a role in the pathogenesis of MNG by influencing thyroid follicular cell growth. Chronic stimulation of follicular cells primarily due to TSH leads to follicular hyperplasia, which usually then enters a resting phase leading to the formation of colloid goiter [9]. This long-standing diffuse goiter may develop into MNG with the potential of autonomy in certain nodules. The role of genetic factors especially in nontoxic MNG is not clear, but some role has been suggested by twin studies, family history, female preponderance, etc. [10]. Certain mutations like those affecting the activation of camp cascade (e.g., TSH-r mutations) which stimulates growth and function mutation in genes encoding thyroglobulin (Tg), thyroid peroxidase (TPO), dual oxidase 2 (THOX2), the sodium-iodide symporter gene (SLC5A5), Pendred syndrome gene (SLC26A4), the TSH receptor gene (TSHR gene), the iodotyrosine deiodinase (DEHAL 1), and the thyroid oxidase 2 gene (THOX2) have been found to be responsible in certain cases for the formation of nodules in a patient with MNG [10]. Familial MNGs have been found to be strongly associated with mutations in the miRNA processing gene DICER1 [11]. Environmental factors have also been incriminated in causation of MNG possibly by aggravating the expression of heterogeneity causing the thyroid to grow and perhaps leading to its autonomy. Naturally occurring goitrogens are thought to work by different

Goitrogens	Agent	Action
Millet, soy	Flavonoids	Impairs thyroperoxidase activity
Cassava, sweet potato, sorghum	Cyanogenic glucosides metabolized to thiocyanates	Inhibits iodine thyroidal uptake
Babassu coconut, mandioca	Flavonoids	Inhibits thyroperoxidase
Cruciferous vegetables: cabbage, cauliflower, broccoli, turnips	Glucosinolates	Impairs iodine thyroidal uptake
Seaweed (kelp)	Iodine excess	Inhibits release of thyroidal hormones
Malnutrition	Vitamin A deficiency Iron deficiency	Increases TSH stimulation, Reduces heme-dependent thyroperoxidase thyroidal activity
Selenium	Selenium deficiency	Accumulates peroxides and causes deiodinase deficiency; impairs thyroid hormone synthesis

Adapted and modified from Medeiros-Neto and Knobel [48].

Table 1.
Natural goitrogens associated with goiter prevalence.

mechanisms, leading to impaired thyroid hormone synthesis or thyroid growth (**Table 1**). For example, iodine-rich substances like seaweed and cruciferous and cassava may impair iodine uptake [12]. In addition to this protein energy malnutrition and deficiency of other nutrients like iron and selenium, vitamin a may also be associated with thyroid enlargement if present with iodine-deficient state. The non-functioning nodules in nontoxic MNG may over time evolve into larger autonomous nodules, leading first to a smoldering subclinical hyperthyroid state which may then progress to overt hyperthyroidism [13]. The Marine Lenhart disease is functioning thyroid nodules associated with Graves' disease.

3. Types of goiter

3.1 Toxic MNG

Toxic MNG is a result of activating somatic mutation of the TSH receptor gene that leads to diffuse hyperplasia of thyroid follicular cells independent of TSH regulation [14–16]. MNG with thyrotoxicosis is also known as Plummer's disease. Toxic MNG presented with clinical features similar to other causes of thyrotoxicosis except ophthalmopathy. Incidence of thyrotoxicosis in MNG is related to the duration of the presence of MNG. So it's more common in elderly people who are harboring MNG for a long time. Hormone profile in toxic MNG is seen with suppressed TSH along with normal or elevated thyroid hormones.

3.2 Graves' disease

Graves' disease is an autoimmune disorder caused by anti-TSH receptor antibody. These antibodies interact with TSH receptor and cause increased thyroid hormone synthesis and secretion [17]. Many risk factors have been found in causation of Graves' disease including high iodine intake and stress [18, 19]. Several drugs have also been implicated in etiology of Graves' disease including lithium,

interferon α, and alemtuzumab [20–22]. Other autoimmune manifestations associated with Graves' disease are pretibial myxedema and ophthalmopathy. Graves' disease is the most common cause of thyrotoxicosis [23]. It is more common in females and usually presents before 30 years of age. Graves' disease presents with classical symptoms of thyrotoxicosis, i.e., irritability, sleeplessness, palpitations, excessive sweating, heat intolerance, and weight loss.

3.3 Hashitoxicosis

Hashitoxicosis, a term coined from Hashimoto's disease and thyrotoxicosis, is a rare condition seen in patients with autoimmune thyroid disease. Hashitoxicosis presents initially with clinical features of thyrotoxicosis and is associated with high radioiodine uptake similar to Graves' disease [24]. Later on it leads to development of hypothyroidism which is caused by lymphocytic infiltration and autoimmune destruction of thyroid gland similar to Hashimoto's thyroiditis. Anti-TSH receptor antibodies are found in nearly 23% of patients with hashitoxicosis [25].

3.4 Subacute (DeQuervain's) thyroiditis

It is a nonsuppurative thyroiditis caused by viral infection or as a result of post-viral illness. In twin study, some link of genetic association was also found [26]. Subacute thyroiditis is characterized by neck pain and tenderness. Initially disease presents with fever, fatigue, and myalgia along with hyperthyroidism that is followed by euthyroidism and then hypothyroidism, and lastly euthyroidism is achieved. A less or absent uptake is seen by radionuclide uptake study. Color Doppler study reveals low blood flow in the hyperthyroid phase which normalizes once euthyroidism is achieved. On laboratory study TSH remains suppressed, and free T4 and free T3 are raised during the hyperthyroid phase.

3.5 Riedel's thyroiditis

Riedel's thyroiditis is a rare condition of unknown etiology occurring in middle-aged women. In this chronic thyroiditis, thyroid follicles are replaced by fibrous tissue. Association with other autoimmune fibrosclerotic disease, i.e., retroperitoneal fibrosis and sclerosing cholangitis, is also found. Initially patients present with goiter with normal thyroid function but later on become hypothyroid. The diagnosis can be made with FNAC, but sometimes biopsy may be required for confirmation.

4. Clinical evaluation of MNG

MNG is usually detected incidentally during routine examination for evaluation of some other disease. Sometimes the patient seeks help for obvious neck swelling and cosmetic disfigurement of the neck. As MNG becomes palpable once the size is more than 1 centimeter, so large MNG mainly presents with neck swelling. Once MNG is detected, a complete history and physical examination focusing on the thyroid gland and adjacent cervical lymph nodes should be performed. Through history including history of childhood head and neck radiation therapy, total body radiation for bone marrow transplantation, exposure to ionizing radiation from fallout in childhood or adolescence, familial thyroid carcinoma, or thyroid cancer syndrome should be sought [27, 28]. Patients with long-standing MNG are more

likely to have clinical features of thyrotoxicosis, and they usually present with subclinical or clinical hyperthyroidism during evaluation. The MNG may present with compressive features, i.e., dyspnea and dysphagia. Respiratory symptoms develop due to tracheal compression. Hoarseness of voice may result from compression of recurrent laryngeal nerve. Very rarely MNG may present with vocal cord palsy, but it is usually seen in malignancy. Retrosternal MNG with thoracic inlet compression can be diagnosed with Pemberton's maneuver, in which raising arm overhead causes flushing and shortness of breath due to compression of neck veins. Information regarding family members, any significant drug use, and radiation exposure should also be enquired. Thyroid examination should be done in sitting position, and during palpation information regarding thyroid shape, nodularity, tenderness, and fixity to the surrounding should be sought. Fixation to trachea, esophagus, and surrounding structure raises the possibility of malignancy. Enlarged painful and tender thyroid can be due to subacute thyroiditis or thyroid abscess. Neck mass with enlarged cervical lymph node again raises suspicion of carcinoma and warrants further evaluation.

5. Laboratory investigation

American Thyroid Association (ATA) recommends serum TSH as the initial laboratory test in evaluation of MNG. If serum TSH is abnormal, then serum FT4 and serum FT3 are recommended to know the thyroid's functioning status. Antithyroid peroxidase (anti TPO) antibody and thyroglobulin (Tg) are other laboratory tests to know about thyroid autoimmunity and Tg gene mutation in patients with MNG. If TSH is high, the risk of malignancy is increased, so it warrants further evaluation with imaging and FNAC [29–30].

6. Imaging study

6.1 Thyroid ultrasonography

Thyroid ultrasound is the most widely accepted imaging modality to know the characteristic of MNG. Ultrasound can give information regarding the number of nodules and the size and location of nodules within the thyroid. It also provides information regarding the presence or absence of any suspicious cervical lymph nodes in the neck. Thyroid sonography can also describe features including composition (solid, cystic proportion, or spongiform), echogenicity, margins, presence and type of calcifications, shape if taller than wide, and vascularity which helps in making decision of FNAC (**Figure 1**). Thyroid ultrasound is commonly used in ultrasound guided FNAC for greater yield in diagnosis.

6.2 Radionuclide scan

Although radionuclide imaging of thyroid gland has been done for a long time, resolution of this modality for thyroid nodule is far behind the ultrasonography [31]. So radionuclide imaging is not having much role in anatomic description of MNG. However radionuclide imaging is very useful in describing physiology of thyroid nodules. If TSH is subnormal, then ATA recommends a radionuclide thyroid scan to know whether nodules are hyperfunctioning ("hot," i.e., tracer uptake is greater than the surrounding normal thyroid), isofunctioning ("warm,"

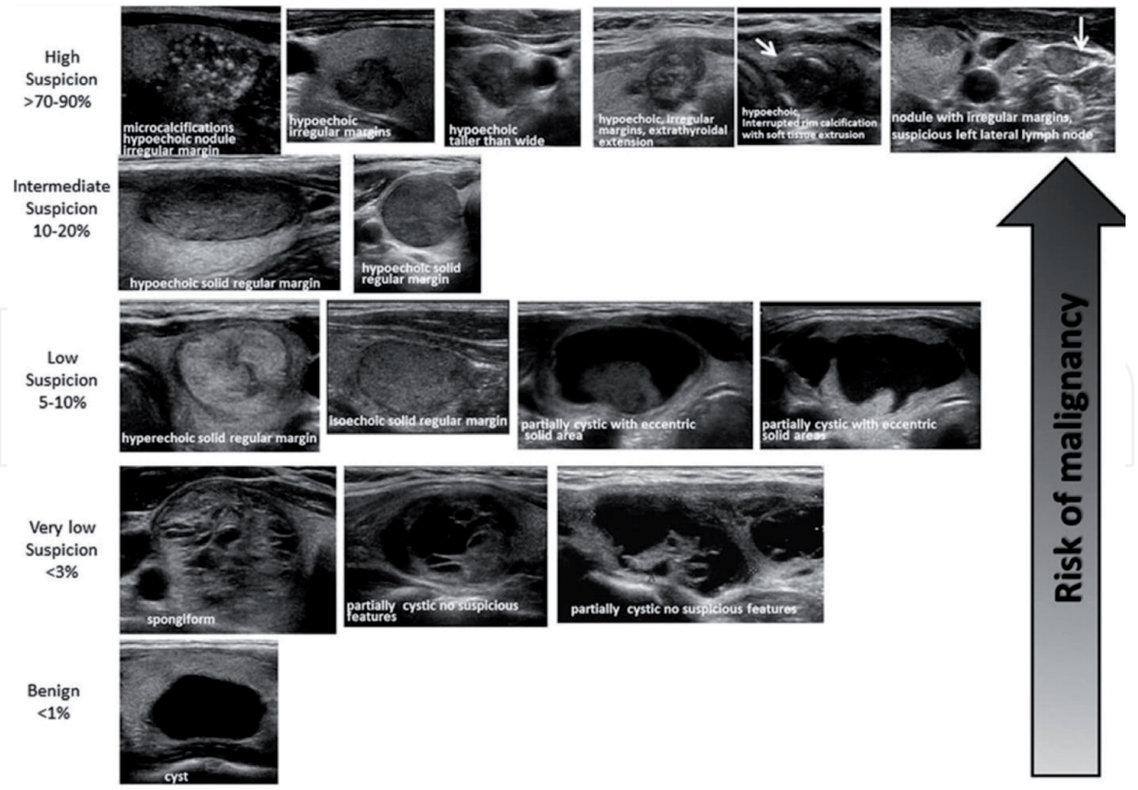

Figure 1.
Nodule sonographic patterns and risk of malignancy.

i.e., tracer uptake is equal to the surrounding thyroid), or nonfunctioning ("cold," i.e., has uptake less than the surrounding thyroid tissue) [32]. Since hyperfunctioning nodules rarely harbor malignancy, so cytologic evaluation is not required in hyperfunctioning nodules. Scan is also useful in distinguishing Graves' disease from (toxic MNG) Plummer's disease.

6.3 CT/MRI

CT/MRI is generally not recommended in evaluation of MNG. These modalities of imaging do not have any advantage over ultrasonography in description of intrathyroidal structure. These imaging modalities are useful only when malignancy is suspected or goiter is retrosternal in which MRI is more precise than CT. CT/MRI provides more information about the surrounding tissue in relation to the thyroid, i.e., trachea, esophagus, and neck vessels. So these imaging modalities are used when features of tracheal compression/deviation, dysphagia, vocal cord paralysis, and weight loss are present. CT/MRI provides additional anatomical information to be helpful preoperatively for planning of surgical excision.

6.4 FNAC

ATA recommends FNAC as the procedure of choice in evaluation of MNG, as it is the cost-effective and most accurate method for thyroid nodule evaluation. FNAC is very reliable and has a low false-negative (7%) and very low false-positive rate near to zero [33]. In one study negative predictive value of case classified as benign was 95% [34]. FNAC provides an algorithm for evaluation and management of patients with thyroid nodules based on sonographic pattern and FNA cytology. ATA recommends FNAC in nodule >1 cm with high or intermediate suspicion of malignancy, nodule >1.5 cm with low suspicion of malignancy, and nodule >2 cm

Diagnostic category	Estimated/predicted risk of malignancy by the Bethesda system, %a	Actual risk of malignancy in nodules surgically excised, % median (range)b
Nondiagnostic or unsatisfactory	1–4	20 (9–32)
Benign	0–3	2.5 (1–10)
Atypia of undetermined significance or follicular lesion of undetermined significance	5–15	14 (6–48)
Follicular neoplasm or suspicious for a follicular neoplasm	15–30	25 (14–34)
Suspicious for malignancy	60–75	70 (53–97)
Malignant	97–99	99 (94–100)

As reported in the Bethesda system by Cibas and Ali.

Table 2.
The Bethesda system for reporting thyroid cytopathology: Diagnostic categories and risk of malignancy.

with very low suspicion of malignancy. FNAC is not recommended for purely cystic nodule. To make a satisfactory FNAC, at least six to eight cell clusters are required in two slides. ATA recommends FNAC to be reported using diagnostic groups outlined in the Bethesda system for reporting thyroid cytopathology (**Table 2**). Based on literature review and expert opinion, the Bethesda system has six diagnostic categories and also provides an estimation of cancer risk within each category. These categories are (i) nondiagnostic/unsatisfactory; (ii) benign; (iii) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); (iv) follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), a category that also encompasses the diagnosis of Hu¨rthle cell neoplasm/suspicious for Hürthle cell neoplasm; (v) suspicious for malignancy (susp); and (vi) malignant.

7. Treatment

Treatment of MNG is directed towards existing thyroid disease associated with MNG and etiology of the disease [35]. Management of toxic and nontoxic MNG is done separately and should be based on the type of MNG. Treatment selection is also based on overall health and comorbidities of the patient. Success of treatment depends on the patient selection and type of treatment. Treatment is broadly divided in surgical and nonsurgical modalities. Surgery is indicated in large MNG, retrosternal extension of MNG, compression of trachea or esophagus, rapid growth, suspicion of malignancy, and MNG associated with vocal cord palsy.

7.1 Surgical treatment

Definitive treatment of toxic MNG is done by surgery when goiter size is large. Two types of surgical procedures are performed: total thyroidectomy and subtotal thyroidectomy. In total thyroidectomy all thyroid tissue is surgically excised, whereas in subtotal thyroidectomy small amount of thyroid tissue 1 gm on each lobe of thyroid is left. Before doing surgical procedure, patient should be rendered euthyroid by antithyroid drugs, beta blockers, and potassium iodide or a combination of one or more of these. Preoperatively cardiac evaluation is mandatory, and patient should be stabilized with appropriate treatment. Surgical procedures are the

same for toxic and nontoxic MNG. In nontoxic MNG preoperative treatment with antithyroid drugs, beta blockers, or potassium iodide is not required.

Although most surgeons prefer to do total thyroidectomy, still controversy exists regarding the removal of thyroid tissue in between total and subtotal thyroidectomy for surgical treatment of MNG. In study temporary or permanent recurrent laryngeal nerve palsy, temporary or permanent hypoparathyroidism, hemorrhage, and wound complications were not significantly different in total thyroidectomy versus subtotal thyroidectomy [36]. In an analysis, goiter recurrence was significantly more in subtotal thyroidectomy than total thyroidectomy, but reintervention due to goiter was not significantly higher. Incidence of permanent recurrent laryngeal nerve palsy and permanent hypoparathyroidism was more in the total thyroidectomy group, but it was statistically nonsignificant [37]. Postoperatively serum TSH level should be monitored, many physicians prefer to start thyroid hormone as theoretically this may prevent recurrence of goiter, but studies have not shown this kind of benefit from thyroid hormone suppressive therapy [38–39].

7.2 Medical treatment

Levothyroxine (LT4) is used as TSH suppression therapy with variable success for nontoxic goiter. But suppressive therapy with LT4 is associated with thyrotoxicosis particularly in elderly patients. In this subset of patients, it is associated with osteopenia and cardiac arrhythmia and is inversely related to TSH concentration. Very rarely thyroid nodules can become functionally autonomous [40–41]. The goal is to keep TSH in between 0.1 mIU/L and 0.4 mIU/L. However the suppressive therapy is still a matter of debate. A meta-analysis of 11 studies has shown a twofold increase of chance in reduction in nodule size with LT4 suppressive therapy with proper selection of patient [42]. In another study with 54 patients 12 months after starting suppressive therapy, 37.1% of patients with single, solid nodules are found to regress more than 50% in nodule volume, and 20.3% of patients had reduction in nodule volume more than 20% but less than 49.9%. One-third of subjects with MNG had 50% or more regression of the glandular volume, whereas 46.8% were considered as nonresponsive. During suppressive therapy with LT4, the mean serum Tg level was also decreased significantly in these patients [43]. Because of lifelong therapy is required for prevention of goiter recurrence and is associated with risk of autonomous functioning of nodules, so in many patients, TSH suppression with LT4 is not feasible.

Antithyroid drugs propylthiouracil and thionamides (carbimazole and methimazole) are used to restore euthyroidism in toxic MNG. They can be used for a long time in patients whom surgery and radioiodine (I-131) treatment are contraindicated. But risk of agranulocytosis remains a major concern. In a recent study, methimazole was used for 8 years in 53 patients for treatment of toxic MNG without any serious adverse effect [44].

7.3 Radioiodine (I-131)

Radioiodine (I-131) is in use for management of thyroid disorder for more than 50 years. Radioiodine (I-131) is used particularly for thyrotoxic disorder mainly in Graves' disease. Radioiodine (I-131) also causes a significant reduction of thyroid gland volume. Due to its effect on reduction of thyroid gland volume, it has been used in management of nontoxic nodular thyroid disease also. In one study, 35 patients with nontoxic large MNG were treated with mean 1806 mbq (range 800–4000) of I-131. The mean reduction in thyroid volume was 43.18% (range −17.23–89.66%) seen after 3 months of treatment with I-131 [45]. In another

study 63.4 ± 3.6% reduction in volume was seen with I-131 in rhTSH-treated nontoxic MNG patients [46]. Treatment with radioiodine (I-131) also relieves symptoms of tracheal and esophagus compression in large MNG. In toxic MNG radioiodine (I-131), euthyroid state is restored in addition to decrease of nodule size in MNG. Pretreatment with rhTSH increases the uptake of radioiodine (I-131) by thyroid tissue in a homogenous manner so that cold areas also take up radioiodine (I-131). In a small study, pretreatment with rhTSH is associated with greater reduction of thyroid volume in radioiodine (I-131)-treated patient [47]. Treatment with radioiodine (I-131) is also associated with adverse effects in a few cases, i.e., hypothyroidism, radiation thyroiditis, and autoimmune hyperthyroidism. Although long-term studies have not demonstrated carcinogenic effect of radioiodine (I-131), still concern regarding thyroid cancer, leukemia, and congenital abnormalities in offspring remains in mind.

8. Conclusion

MNG is the most common thyroid disorder, but usually it is asymptomatic. When large enough it can cause compression to the trachea, esophagus, and neck veins. Other complications of MNG are autonomous functioning nodules, and very rarely it may progress to malignancy. Diagnostic evaluation includes clinical evaluation, thyroid function, and imaging study. Additional testing with FNAC may be required. Treatment modalities include drugs, surgery, and radioiodine (I-131), depending on results of diagnostic evaluation and associated complications.

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