An Overview of the Thyroid Gland and Thyroid-Related Deaths for the Forensic Pathologist

Marianne E. Beynon, Kathryn Pinneri

ABSTRACT

The thyroid gland is a butterfly-shaped organ situated in the anterior neck whose functions have system-wide effects. Thyroid diseases represent some of the most commonly encountered endocrine disorders and therefore are commonly encountered at the time of autopsy. Knowing how the gland functions and the effects it may have on vital organs is important when determining the cause of death and significant contributory conditions. Endocrine-related deaths may be anatomically subtle, therefore histologic examination, review of medical records, and selected postmortem testing must be performed to correctly identify and document their presence. For this reason, it is recommended that pathologists consider regularly examining the thyroid gland histologically, particularly on decedents where no apparent anatomic cause of death is identified after the autopsy. This article provides an in-depth review of the thyroid gland, thyroid hormones, and thyroid diseases, including potential thyroid-related deaths and incidental autopsy findings. *Acad Forensic Pathol.* 2016 6(2): 217-236

AUTHORS

Marianne E. Beynon MD, Baylor College of Medicine - Department of Pathology & Immunology

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, writing assistance and/or technical editing.

Kathryn Pinneri MD, Harris County Institute of Forensic Sciences

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general supervision, writing assistance and/or technical editing.

CORRESPONDENCE

Kathryn Pinneri MD, 1885 Old Spanish Trail, Houston TX 77054, kpinneri@hotmail.com

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INTRODUCTION

Endocrine disorders can be difficult to detect at the time of autopsy due to their manifestations primarily through hormonal imbalance. Anatomic findings, such as nodules or organomegaly, may suggest an abnormality that should prompt further investigation through microscopic examination or laboratory tests. Thyroid disorders have a wide range of presentations and may affect many different organ systems. This article provides an in-depth review of the thyroid gland, thyroid hormones, and thyroid diseases, including potential thyroid-related deaths and incidental autopsy findings.

DISCUSSION

Anatomy

The thyroid gland is a butterfly-shaped organ composed of bulbous right and left lobes connected in the midline by a thin structure called the isthmus (1, 2). Located in the neck, the thyroid wraps around the anterior trachea directly inferior to the larynx, at the level of the C5 through T1 vertebrae (2). On average, it measures 5 cm in height, 5 cm in width, and weighs 20-30 g in adults, with slightly heavier thyroids seen in women (2). A richly vascular structure, the thyroid receives its blood supply predominantly from two sources. The superior thyroid artery, which is the first branch of the external carotid artery, supplies the upper half of the thyroid in over 95% of people. The lower portion of the thyroid is most commonly supplied by the inferior thyroid artery, branching from the thyrocervical trunk, itself a branch of the subclavian artery; in a subset of the population, the inferior thyroid artery may be absent or duplicated (3). In addition, the thyroid has extensive lymphatic drainage involving multiple levels of lymph nodes, including but not limited to the prelaryngeal (or Delphian), pre- and paratracheal, retropharyngeal, retroesophageal, and internal jugular lymph nodes. This becomes very important in the staging of thyroid carcinoma, during which careful lymph node dissection may be necessary in the search for metastases (4).

Embryology

The thyroid gland is the first endocrine organ to form during fetal development (5). It begins to develop at four weeks gestation as an epithelial diverticulum arising from the foregut endoderm near the base of the primitive tongue, which extends progressively inferiorly starting at week five as the fetus develops (2, 5, 6). It reaches its final shape and relative size by seven weeks gestation (5). The connection between the thyroid and the foregut, called the thyroglossal duct, later regresses in normal development; if this regression does not occur, a thyroglossal duct cyst may form (2). The most common congenital anomaly of the thyroid, thyroglossal duct cysts are seen in 7% of adults, appearing as 2-3 cm fusiform or spherical nodules in the midline neck, which move upon swallowing (1, 6). Histologically, the cyst lining varies based on location; superiorly, the lining is stratified squamous, and inferiorly, it is thyroid epithelium (1). On occasion, thyroglossal duct cysts may become infected, and, rarely, squamous cell and/or thyroid carcinoma may arise from the cyst lining (1). The thyroglossal duct may also leave behind an anatomic remnant known as the pyramidal lobe, which is a third, narrow thyroid lobe extending superiorly from the isthmus in 18-60% of people (4-6). Finally, due to the thyroid's intimate association with branchial structures during development, several clinically insignificant anatomic variations can occur, including intrathyroidal ectopic thymus, parathyroid gland, salivary gland, and cartilage (4).

Normal Histology

The normal thyroid is comprised of numerous follicles surrounded by a fibrous capsule, which forms septae that divide the parenchyma into multiple lobules (2). The septae also contain the nerves and blood vessels supplying each lobule (2). Each lobule contains 20-40 round follicles, 200 μ m in average diameter and lined by simple, flat to low columnar epithelium, depending on the state of functional activity; the more active the follicle, the taller the follicular epithelium (1, 2, 4). Follicular cells have uniform dark, small nuclei that are centrally located, and some have abun-

dant granular cytoplasm, a variant known as Hürthle cells (2, 4). Sanderson polsters, which are small follicles extending into the central spaces of larger follicles, can be seen scattered throughout the thyroid, and should not be mistaken for papillary structures (4). Follicles contain colloid, a viscous material composed predominantly of the thyroid hormone precursor protein thyroglobulin (2). The normal thyroid gland contains up to three months' worth of thyroglobulin stored within colloid (2). The final cell type of the thyroid is the parafollicular, or C cell, a derivative of the neural crest by way of the ultimobranchial body (2, 4). Parafollicular cells form clusters – as the name suggests – within and in between follicles, and are found in highest concentration within the mid- and upper portions of the lobes (2, 4). These cells form and secrete calcitonin, thereby participating in calcium homeostasis, which is a subject not included in this review (2).

Hyper- and Hypothyroidism

Hyper- and hypothyroidism are two of the most common disorders of the endocrine system worldwide (7). Approximately 4-5% of the population of the United States are affected, and the number is even higher in iodine-deficient countries (7). Most importantly, both symptomatic and silent versions of these two conditions are associated with increased mortality – in particular, due to cardiovascular disease (8).

Normal Physiology

In order to discuss hyper- and hypothyroidism and their sequelae, one must first recall the normal physiology of the thyroid gland. The primary function of thyroid follicular cells is the synthesis of thyroid hormones, of which there are predominantly two: tetraiodothyronine (T_4), more commonly known as thyroxine, and triiodothyronine (T_3) (2). These hormones are extremely important for a significant variety of functions throughout the body, including development, growth, and basal metabolic rate (BMR) control, which will be discussed further below (2). Thyroid hormone production and release is stimulated through the hypothalamic-pituitary axis. Thyrotro-

pin-releasing hormone (TRH) from the hypothalamus causes the anterior pituitary to release thyrotropin, also called thyroid-stimulating hormone (TSH) (2, 7). In response to TSH, thyroid follicular cells produce thyroglobulin, an inactive protein, which is then released from the apical surface into the follicle as colloid (2). Sodium-iodide cotransporters on the basal surface of follicular cells take up iodide from the bloodstream, which is then released via transport protein, pendrin, into the follicle and oxidized by thyroid peroxidase into iodine (2). Next, tyrosine residues on thyroglobulin are iodinated and then conjugated via oxidative coupling, forming T_3 and T_4 (2). Iodinated thyroglobulin is taken back into the follicular cell, where lysosomal protease degradation releases the T_3 and T_4 to exit into capillaries. Thyroid hormones travel in the bloodstream bound predominantly to thyroxine-binding protein (7). T_4 is significantly more abundant, making up 90% of the total thyroid hormone; however, T_3 is two to ten times more bioactive (2, 7). To combat this problem, the target tissues contain 5'-iodinase, which can convert T_4 into T_3 (7). The activity of thyroid hormone is very broad, as it can act by essentially three main mechanisms: 1) directly at the cellular level, 2) via the sympathetic nervous system, and 3) through changing metabolism and affecting the circulation (9). Thyroid hormone increases BMR, body temperature, gluconeogenesis, lipolysis, proteolysis, and glucose absorption. It increases stroke volume and heart rate, leading to increased cardiac output. In the young, it promotes growth and leads to bone maturation and fusion of growth plates. It is essential for central nervous system (CNS) maturation during fetal development (7).

This series of biochemical events leading to thyroid hormone formation is controlled by a negative feedback loop whereby increased levels of thyroid hormone, especially T_3 , inhibit release of TSH from the anterior pituitary (7). The opposing forces of TRH and T_3 allow for maintenance of a relatively steady thyroid state in the normal individual (7). However, when derangements occur within this delicate system, serious and potentially fatal conditions may result (10).

Hyperthyroidism

Increased concentration of thyroid hormone has many causes, the most common of which is Graves disease, which will be discussed in detail below (1, 7, 11). Less common causes of hyperthyroidism include hyperfunctional (or toxic) adenoma, toxic multinodular goiter, thyroid malignancy, increased TSH from pituitary adenoma (secondary hyperparathyroidism), increased TRH (tertiary hyperparathyroidism), exogenous thyroid hormone ingestion, or thyroid damage from amiodarone toxicity, radiation, or trauma (1, 7, 11). No matter the inciting factor, for the most part, the signs and symptoms of hyperthyroidism are the same, related to the previously described activity of thyroid hormone. These include weight loss despite adequate or increased caloric intake, heat intolerance, tremor, hyperreflexia, sweating, skin flushing, weakness, irritability, and nervousness (1, 7, 11).

Most important to the discussion of thyroid-related mortality, however, are the substantial cardiac manifestations of hyperthyroidism. Indeed, symptoms related to effects on the heart are a consistent feature, and often the presenting complaint, of a hyperthyroid patient (1). These include tachycardia, palpitations, and arrhythmias, notably atrial fibrillation, which is not only the most common cardiac arrhythmia in this population, but also a substantial contributor to cardiovascular disease-related morbidity and mortality, particularly cerebrovascular events (CVE) or stroke (1, 8, 9, 12, 13). Many other arrhythmias can occur as well, including sinus tachycardia, supraventricular tachycardia (SVT), premature atrial contractions, and complete heart block (8, 14). The atria are more sensitive to the effects of thyroid hormone than the ventricles, and as such, ventricular arrhythmias are very rarely caused by hyperthyroidism (9). Other cardiac manifestations of hyperthyroidism that have been reported include coronary spasm, mild interstitial fibrosis, and mild lymphocytic and eosinophilic myocarditis. In more severe cases, thyrotoxic cardiomyopathy, myocardial infarction (MI), CVE, and congestive heart failure (CHF) can occur (1, 8, 9). Congestive heart failure may be the sole symptom of so-called “apathetic” hyperthyroidism in a subset of elderly patients (9). Almost 6%

of patients with hyperthyroidism present with CHF and atrial fibrillation (13). Thyrotoxic cardiomyopathy often presents as acute heart failure in young patients without cardiovascular risk factors, and may be fatal if not treated properly. Stabilization of thyroid function status may reverse the process; however, chronic dilated cardiomyopathy can also result (13).

Graves Disease

Causing approximately 85% of clinically-apparent hyperthyroidism, Graves disease was first reported by Caleb Hillier Parry in 1786 (1). It presents most commonly in Caucasian and Asian women between the ages of 20-40 years, and affects 1.5-2% of women in the United States (1, 8). The pathophysiology is autoimmune in nature; specifically, autoantibodies to the TSH receptors of the follicular cells lead to stimulation of thyroid hormone production (1, 2). Because of the negative feedback effect of thyroid hormone on the anterior pituitary gland, TSH levels will be low in this disease (7). Along with the signs and symptoms of hyperthyroidism discussed previously, Graves disease has several unique characteristics due to autoimmunity, including thyroid ophthalmopathy (or proptosis), which occurs in 50% of patients, exophthalmos from hypertrophy of the extraocular adipose tissue, generalized lymphadenopathy, and late findings including pretibial myxedema (thickened, indurated, and scaled skin overlying the shins), which occurs in only 1-2% of patients, and acropachy (clubbing of all digits from new bone formation) (1, 2, 4, 8).

However, at the time of autopsy, clinical history may be unavailable, the decedent may not have a diagnosis of Graves disease, and the above findings may not be present; therefore, diagnosing Graves disease in the forensic setting requires examination of the thyroid gland. Grossly, the thyroid gland of Graves disease is symmetrical, with mild-to-moderate, diffuse enlargement (4) (**Image 1**). It is firm on palpation, and the cut surface is uniform, solid, and grey-to-red; to some, it resembles pancreas (4). Histologic examination reveals severely hyperplastic follicles with papillae extending into the follicles (**Image 2**), which contain pale colloid with somewhat characteristic scalloped

edges (4) (**Image 3**). Within the interstitium may be lymphoid aggregates and/or mild fibrosis (4). Graves disease is often treated with radioactive iodine ablation (RIA), which changes the thyroid histology significantly. Soon following RIA, thyroid histology shows nuclear atypia, follicle dropout, and alterations of the vasculature. When these changes subside, the thyroid becomes atrophic and fibrotic (4) (**Image 4**).

Although the association between Graves disease and increased mortality is well-known, deaths associated with Graves disease are not often encountered in the forensic setting (8). In 2013, Wei et al. reported a case of a 30-year-old woman with poorly-controlled

Graves disease, who died as a result of cardiac arrhythmia secondary to physical and mental stress related to an altercation with her husband (8).

Several additional case reports of Graves disease-related deaths can be found in the literature, mostly in the emergency medicine context, which share common elements. The immediate cause of death in nearly all cases was cardiovascular in nature, including arrhythmia (SVT), cardiomyopathy, and congestive heart failure (14–17). The decedent often had a history of poor compliance with anti-thyroid medication (8, 17, 18). In several instances, the decedent was previously healthy, and the diagnosis of Graves disease was

Image 1: Diffusely and symmetrically enlarged thyroid gland weighing 125 g.

made during the postmortem examination through a combination of autopsy findings and postmortem thyroid hormone concentrations, highlighting the importance of careful gross and, if indicated, histologic examination of the thyroid during autopsy (14–16). As the above cases indicate, Graves disease leads to increased morbidity and mortality most often through its effects on the cardiovascular system. Although somewhat controversial, the incidence of thyroid carcinoma in patients with Graves disease is essentially the same as in euthyroid people; however, Graves disease may coexist with its sister autoimmune thyroid disease, Hashimoto (lymphocytic) thyroiditis, in 15–20% of patients, and Hashimoto thyroiditis is associated with increased incidence of papillary thyroid

carcinoma (4, 19). These concepts will be discussed in more detail below.

Thyroid Storm

Thyrotoxic crisis, or thyroid storm, is one of the few true thyroid emergencies (20). First described as “*the crisis of exophthalmic goiter*” by Frank Howard Lahey in 1926, this severe condition most commonly occurs in those with Graves disease (1, 20). Thyroid storm is an acute, often life-threatening exacerbation of the signs and symptoms of hyperthyroidism that have been described previously in this review (1, 11, 15). It is thought to result from a sudden spike in catecholamines due to a variety of inciting factors, in-

Image 2: Colloid-filled follicles with papillae (Sanderson's polsters) (H&E, x100).

cluding infection, trauma, surgery (particularly on the thyroid), pregnancy, childbirth, stress, RIA, sudden cessation of antithyroid medications, and medications such as amiodarone (an iodine-rich antiarrhythmic), steroids, and tricyclic antidepressants (1, 11, 14, 15, 21, 22). Yoon et al. reported a case of thyroid storm resulting from an overdose of exogenous thyroid hormone in an 18-year-old female for the purposes of weight loss (23). Thyroid storm has even rarely been reported in the setting of silent (subacute) thyroiditis (22). Overall, the most common precipitating factor for thyroid storm is infection (22).

Thyroid storm, like Graves disease, is more common in women than men, and occurs most commonly between

the ages of 20-49 years (11). It is rare, occurring in less than 10% of patients hospitalized for hyperthyroidism (11). In addition to worsening of hyperthyroid symptoms, thyroid storm presents with an otherwise non-specific triad of findings: high fever, tachycardia out of proportion to said fever, and altered mental status (24, 25). The patient may also display seizures or coma, and laboratory testing may reveal metabolic derangements including hyperglycemia, ketoacidosis, and/or lactic acidosis (11). The patient may also be hypercoagulable (11). Perhaps counterintuitively, the thyroid hormone levels may not be significantly elevated from the patient's baseline during the crisis (11). As mentioned previously, thyroid storm is a medical emergency, with reported mortality rates varying from 10-75%, even

Image 3: Scalloping in colloid filled follicles (H&E, x400).

with early diagnosis and treatment (15, 22). Causes of death include high-output heart failure, cardiac arrhythmia, multiple organ failure, disseminated intravascular coagulation (DIC), hypoxic brain injury, and sepsis (11, 20). Eighteen percent of deaths from thyroid storm are due to the sequelae of thromboembolism (11). In particular, thyroid storm associated with RIA and amiodarone have been reported to have increased morbidity and mortality as compared to other inciting factors (21, 24). Factors that increase the risk for poor outcome include, perhaps unsurprisingly, elderly age group, severe hyperthyroidism, preexisting diseases, and the need for more aggressive care measures, including intubation, mechanical ventilation, therapeutic plasma exchange, and hemodialysis (21, 26).

Hypothyroidism

Described in 1850, hypothyroidism was the first reported endocrine deficiency disorder (7). This is a very common condition, with approximately 4% of the population having subclinical disease and symptomatic hypothyroidism seen in 0.3% (1). It most commonly presents in women and the incidence increases with age (1, 27). Just like hyperthyroidism, hypothyroidism has many causes, the most common of which is also autoimmune in nature – in this case, Hashimoto thyroiditis (1, 7). In Hashimoto thyroiditis, patients form various autoantibodies that affect different steps in the synthesis of thyroid hormones, leading to hypothyroidism (1, 7). These autoantibod-

Image 4: Thyroid gland, status post ablation treatment (H&E, x100).

ies include antithyroglobulin and antithyroid peroxidase (recall from above that thyroid peroxidase is the enzyme that converts iodide into iodine within the follicle) (1, 7). Hashimoto thyroiditis will be discussed in greater detail in the section on incidental findings of the thyroid below. Other causes of hypothyroidism include iodine-deficient diet, surgical removal or radioablation of the thyroid gland for hyperthyroidism or malignancy, medications such as lithium, and loss of upstream signaling due to pituitary or hypothalamic disease (secondary and tertiary hypothyroidism, respectively) (7, 11). During the autopsy, especially external examination only cases, careful examination of the neck should be performed to look for a thyroidectomy scar (28). Hypothyroidism may also be congenital. The signs and symptoms of hypothyroidism are in many respects the opposite of those seen with hyperthyroidism including bradycardia, weight gain despite decreased intake, cold intolerance, dry skin, constipation, alopecia, hyporeflexia, slowed speech, and lethargy (7, 11, 28). Chronic hypothyroidism also increases total cholesterol and low-density lipoprotein concentrations while decreasing high-density lipoproteins, which increases cardiovascular mortality risk (1). Depression is also a common symptom of hypothyroidism and therefore may be encountered in the medical history of individuals who commit suicide (29).

Myxedema Coma

Although much rarer than thyroid storm, end-stage hypothyroidism, also known as myxedema coma, is also a thyroid-related medical emergency. First described by Sir William Gull in 1873, myxedema coma has an estimated incidence of only 0.22 per million per year (1, 11). It most commonly affects women over the age of 60 years who have a long history of hypothyroidism, and tends to occur during cold weather (11, 30). Of note, 5-15% of patients presenting with myxedema coma have a history of secondary or tertiary hypothyroidism (22). Other inciting factors include infection, CVE, MI, trauma, pregnancy, and medications including lithium and amiodarone (11, 22). One unusual case of myxedema coma resulted from ingestion of large amounts of bok choy, which contains glucosino-

late, a compound that suppresses iodine uptake and hormone production by follicular cells (22).

The condition presents with many of the signs and symptoms of hypothyroidism described above as well as progressive slowing of physical and mental prowess as the disease progresses (1). Initially, symptoms may mimic depression or early dementia, with fatigue, apathy, and forgetfulness as the predominant complaints (1). If not treated, patients may develop severe hypothermia (temperatures down to 74°F have been reported), urinary retention, respiratory depression, bradycardia, hypotension, and arrhythmias including heart block and torsades de pointes (11). Diffuse mucopolysaccharide deposition occurs, leading to airway obstruction through involvement of the tongue and larynx, cardiac tamponade through pericardial effusion, and nonpitting edema through involvement of the skin and subcutaneous tissues (1, 7, 11). Electrolyte abnormalities, especially hyponatremia, and coagulopathy, including acquired von Willebrand disease, also result, and are associated with increased mortality (11). Altered mental status worsens from lethargy to stupor to coma, which increases risk of aspiration pneumonia, urinary tract infection, and sepsis (22, 28).

Mortality in patients with myxedema coma is currently estimated to be 20-25%, representing a significant improvement from past reports of 60-70% due to better recognition and treatment of this disease (11). Survival rates are worse in elderly patients and those with severe and/or persistent hypothermia, bradycardia, and hypotension, lower Glasgow Coma Score at presentation, and multiorgan disease (11, 22). The most common immediate causes of death are sepsis, gastrointestinal bleeding secondary to coagulopathy, and respiratory failure (22).

Congenital Hypothyroidism

Thyroid hormone is exquisitely important for proper central nervous system development in the fetus. In order to ensure adequate thyroid hormone availability, β -human chorionic gonadotropin from the placenta directly affects the maternal thyroid, leading to increased T_3 and T_4 production during the first tri-

mester (27). After the first trimester, the fetal thyroid takes over as the main source of thyroid hormone. The placenta also expresses type 3 deiodinase, an enzyme which degrades T_4 into inactive reverse T_3 , as a protection against overly high thyroid hormone levels; however, despite this safeguard, abundant thyroid hormone crosses into the fetus (27).

It is estimated that 100-200 000 fetuses per year develop in hypothyroid mothers, mostly in iodine-deficient parts of the world (27). Decreased fetal levels of thyroid hormone during the crucial period of early neurodevelopment lead to severe mental retardation, also called cretinism (1, 27). Other clinical features include skeletal anomalies, macroglossia, and coarse facies (1). This condition is irreversible if it is not diagnosed early; therefore, in the United States, the newborn screen in all states includes thyroid function tests to allow for immediate thyroid replacement therapy (7). Although not associated with mortality, congenital hypothyroidism may nevertheless be encountered during the course of fetal and pediatric autopsies for other reasons and should be considered in the differential diagnosis of mental retardation.

Euthyroid Mortality

The association between thyroid hormone levels and mortality in the euthyroid population is a controversial subject, and has been the focus of a number of large prospective clinical cohort studies worldwide with no consensus (10). In a study of 212 456 euthyroid patients in South Korea, Zhang et al. found that low-normal free T_3 and T_4 levels were associated with increased mortality from all causes and that low-normal T_3 level was associated with increased mortality from cancer, especially liver cancer, independent of other risk factors or comorbidities (10). No clear association was found with cardiovascular mortality in their study population (10). On the other hand, two other studies both found that high-normal T_4 was associated with increased mortality; however, they disagreed regarding TSH, with Cappola et al. reporting a negative association with mortality and Van de Ven et al. reporting a positive one (31, 32). Others still have shown TSH levels having an association with cardio-

vascular mortality only in women, or no association at all (10). In general, study results have been variable and inconsistent, likely because of differences in the patient population, including size, age, sex, ethnic distribution, and iodine intake, as well as length of follow-up (10, 12). Overall, it appears that more studies are necessary in order to elucidate the true association between mortality and thyroid hormone levels in euthyroid patients.

Postmortem Thyroid Function Interpretation

Both pre- and postmortem diagnosis of hyper- or hypothyroidism rely on the same set of laboratory values, the thyroid function tests. The most useful initial test for thyroid disease screening in living patients is TSH, which is decreased in hyperthyroidism and increased in hypothyroidism. The TSH interpretation is then confirmed by testing for free T_4 , which will be increased or decreased, respectively. Blood submitted in a red-top tube should be centrifuged and an aliquot of serum can be submitted for this testing. These basic guidelines are only true in primary thyroid disease; in cases of pituitary or hypothalamic primary, TSH levels may be normal or altered in the same direction as free T_4 (1).

Interpretation of postmortem thyroid function testing is further complicated by changes that occur after death that lead to alterations of the levels of TSH, free T_3 , and free T_4 . Since the first publication on this topic by Coe et al. in 1973, several attempts have been made to characterize the nature of these changes, with varying, often contradictory results (33). Coe, in his original work and later update, reported that T_4 decreases in the postmortem period, and that TSH levels are stable (33, 34). Edston et al. found that free T_4 increases after death in 57% of cases, free T_3 may increase or decrease, and that TSH almost always decreases (35). Rachut et al. agreed that postmortem free T_3 levels are unpredictable, but report that T_4 decreases, supporting Coe's conclusion (36). Their study also compared blood from the inferior vena cava (IVC) with femoral blood and found that thyroid hormone levels were higher in the IVC than femoral artery, suggesting that one mechanism behind alteration in postmortem lev-

els may be diffusion of thyroid hormone out of the decomposing thyroid gland (8, 35, 36). Another suggested mechanism, supported by those studies showing decreasing T_4 and increasing T_3 , is that residual 5'-iodinase continues to convert T_4 to T_3 after death; however, studies have not shown any association with T_3 and T_4 levels and time since death (8, 35). Thyroid function tests have also been performed on vitreous humor. Although thyroid hormone was historically described not to enter the vitreous at all, Edston was able to detect free T_3 and T_4 at lower levels than the femoral blood (35). For this reason, Wei et al. report that postmortem vitreous T_3 and T_4 levels are unreliable compared to femoral blood (8).

Postmortem changes notwithstanding, it is most important to ascertain whether thyroid function tests can be used reliably after death to diagnose antemortem hyper- and hypothyroidism. Edston et al. compared postmortem TSH and thyroid hormone levels in decedents with and without Graves disease, and found that free T_3 was significantly increased in decedents with thyroid histology revealing hyperplasia, irrespective of confounding factors including age, sex, thyroid size, and postmortem interval; however, differences in T_4 and TSH levels were not statistically significant (35). Bonnell et al. found that T_4 decreased in the pre-mortem period in patients with prolonged hospitalization and pain, and counseled that low postmortem T_4 levels should not be used to diagnose hypothyroidism in that population (37). Similarly, increased postmortem T_3 and T_4 levels should be used hesitantly to diagnose hyperthyroidism in decedents with a history of hanging or strangulation, as thyroid hormone may be released from the thyroid gland as a result of neck trauma (38).

In summation, postmortem thyroid function tests are a useful tool in the forensic pathologist's arsenal for the diagnosis of hyper- and hypothyroidism; however, they must be used judiciously in the presence of suspicious clinical history or autopsy findings, interpreted in combination with gross and histologic examination, and tempered as necessary by an understanding of test limitations and possible confounding factors.

Carcinoma of the Thyroid

Thyroid cancer is the most common type of endocrine malignancy, representing 1.5% of all cancers in the United States (1, 39). The incidence of thyroid carcinoma is rising by 5% each year, possibly due to increased detection of smaller nodules as imaging techniques improve (39, 40). The major risk factors for the development of thyroid carcinoma are ionizing radiation exposure and dietary iodine deficiency (1). Although thyroid cancer is the ninth most common cancer and the fifth most common cancer of American women, it has the lowest mortality rate of any cancer in the top ten; however, death rates have been increasing by 0.9% per year (40, 41).

There are four main subtypes of thyroid carcinoma in two overarching categories: 1) those arising from follicular epithelium, including papillary thyroid carcinoma (85%), follicular carcinoma (5-15%), and anaplastic carcinoma (<5%), and 2) medullary thyroid carcinoma (5%), which arises from the parafollicular, or C cells (1). Each of these types of thyroid carcinoma will be discussed in detail under its respective subheading. In general, the well-differentiated epithelial thyroid carcinomas (papillary and follicular) have good prognoses, with survival rates surpassing 90%, whereas anaplastic and medullary thyroid carcinoma are aggressive and associated with increased mortality (4, 39).

Papillary Thyroid Carcinoma

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer by a wide margin, making up 85-88% of primary thyroid malignancies (1, 41). It most often presents in 25-50 year old patients with a history of exposure to ionizing radiation, and is associated with Hashimoto thyroiditis (1, 4). On gross examination of the thyroid gland, PTC appears as solid, white, mostly unencapsulated nodules of varying sizes, which may contain papillary structures that are visible to the naked eye (4) (**Image 5**). Histologically, the traditional form of PTC is composed of numerous true papillary structures with an irregular, complex branching pattern (4). The cytologic features are

Image 5: Colloid nodule with small focus of papillary thyroid carcinoma (white nodule in center).

characteristic and essentially required for diagnosis, displaying large, oval nuclei with clear chromatin (so-called Orphan Annie eyes), as well as nuclear grooves and pseudoinclusions (**Image 6**) due to irregular folding of the nuclear membrane (4). Psammoma bodies may also be present (4). Occult PTC's are encountered at autopsy with a prevalence rate ranging from 3-36%, depending on geographic location (42). In the United States, the prevalence rate falls between 6-13% (42). Occult PTC may be small (less than one centimeter), solitary, and can occur in the setting of multinodular goiter. Extracapsular extension and metastatic disease are unlikely in the setting of occult PTC (42).

Despite commonly involving cervical lymph nodes (see Anatomy section for more information), PTC rarely metastasizes and generally has a very good

Image 6: Nuclear features of papillary thyroid carcinoma. Nuclear grooves are represented with the thin arrows and a nuclear pseudo-inclusion is represented by the larger open arrow. Normal thyroid follicular cells are to the left of the image (H&E, x400).

prognosis, with ten-year survival greater than 95% (1, 39, 41). There are many variants of PTC, of which only a handful affect prognosis. The encapsulated variant of PTC, as the name suggests, is entirely surrounded by a capsule, essentially never metastasizes, and is not associated with mortality (4). The follicular variant of PTC is composed entirely of follicles (**Image 7**), which may mimic follicular thyroid carcinoma, which has a worse prognosis than PTC; however, the nuclei display classic PTC features (4) (**Image 8**). Finally, the tall cell variant, in which the PTC cells are three times taller than they are wide, is associated with extra-thyroidal extension and poorer prognosis (4). Overall, factors associated with poorer prognosis include age over 40 years, male sex, large tumor

size, extra-thyroidal extension (seen in 25% of cases), and distant metastasis (seen in 10-15% of cases, most commonly the lung) (1, 4).

Follicular Thyroid Carcinoma

The second most common primary thyroid carcinoma (5-15%), follicular thyroid carcinoma (FTC), most often presents as a slow-growing nodule in women age 40-60 years, and is associated with dietary iodine deficiency (1). It is usually not possible to differentiate FTC from follicular adenoma on gross examination alone, since the diagnosis of FTC requires evidence of capsular, vascular, or extrathyroidal invasion, which may necessitate histologic examination

Image 7: Follicular variant of papillary thyroid carcinoma (left) adjacent to normal thyroid parenchyma (right) (H&E, x100).

of the entire capsule of the lesion (4). FTC is more likely to invade blood vessels than lymphatics, and as such is more likely to present with distant metastases to the bone, lungs, and liver than with cervical lymph node involvement (1, 4). It is important to note that metastatic foci of FTC may be very well-differentiated and resemble normal thyroid tissue (4). Prognosis is generally favorable but worse than PTC, with ten-year survival of 50-90% (1, 39). Adverse risk factors include age over 40 years, absence of capsule, and distant metastasis (4).

Anaplastic Thyroid Carcinoma

Undifferentiated, or anaplastic thyroid carcinoma (ATC), is the third epithelial thyroid carcinoma and least common primary thyroid carcinoma (<5%) (1, 39). There are approximately 500 cases of ATC per year in the United States (39). It is one of the most aggressive malignancies, and usually presents in older females as a rapidly growing neck mass with symptoms secondary to involvement of neck structures by extra-thyroidal disease, including dysphagia, dyspnea, and hoarseness (39, 41, 43). More than half of patients with ATC have a history of or concurrent differentiated thyroid carcinoma, although ATC may arise *de novo* as well (26, 39, 44). Over one third of patients have extra-thyroidal extension and/or lymph node in-

volvement, and more than 50% have distant metastasis at presentation (39, 43). ATC has extremely poor prognosis. The reported mean survival ranges from nine weeks to six months, with ten-year mortality rate of >95% (41, 43-45). Death is most often caused by direct compromise of vital neck structures (1, 46).

Due to its undifferentiated nature, ATC has many different histologic appearances, most commonly squamoid or sarcomatoid, and can be difficult to distinguish from a variety of other high-grade malignancies (4, 26, 44, 47). Squamoid ATC may have areas of keratinization and mimic metastatic poorly-differentiated squamous cell carcinoma of the head and neck or lung (26). Sarcomatoid ATC may be spindled, pleomorphic, or rhabdoid, among other patterns, and may contain heterologous elements such as cartilage or bone (4, 26). As in other types of malignancy, rhabdoid morphology, seen in 10% of ATC, is associated with increased aggressiveness and even poorer prognosis (26, 47). The differential diagnosis of rhabdoid-predominant ATC includes rhabdomyosarcoma, melanoma, and medullary thyroid carcinoma with plasmacytoid morphology (47). Other considerations for ATC include high-grade sarcomas and diffuse large B cell lymphoma (44). In general, with a combination of clinical history, examination for primary site during autopsy, and appropriate utilization of immunohistochemistry, these mimickers can be systematically excluded in all but the most exceptional cases (44).

Image 8: Nuclear features of follicular variant of papillary thyroid carcinoma with nuclear grooves (thin arrow) and pseudoinclusion (open arrow) (H&E, x400).

Medullary Thyroid Carcinoma

The last major type of thyroid carcinoma is the only one not arising from the follicular epithelium; instead, medullary thyroid carcinoma (MTC) is derived from the parafollicular, or C cells, which, as discussed previously, are of neural crest origin and as such express neuroendocrine markers, (1, 39). MTC represents 5% of thyroid carcinomas, and is familial in 25-30% of cases – most commonly associated with multiple endocrine neoplasia type 2 (MEN2a and 2b) due to *RET* proto-oncogene activating mutations (1, 39, 48). Along with MTC, patients with MEN2a or MEN2b may develop other malignancies. The more common subtype, MEN2a, is associated with pheochromocytoma

toma in 50% of cases, and parathyroid adenoma or hyperplasia in 5-10% (1, 49). MEN2b also has an association with pheochromocytoma in approximately half of cases, as well as mucosal neuromas in greater than 95% and marfanoid body habitus (1, 49). Any of these findings noted during autopsy may be a clue to the presence of an underlying MEN syndrome, and as such, it is a critical duty of forensic pathologists to educate the families of these decedents regarding the importance of appropriate genetic counseling.

In general, familial cases tend to occur in younger patients (average 35 years) as multiple, bilateral masses, whereas sporadic cases occur in 40-50 year olds as solitary, unilateral masses (1, 4). Grossly, MTC appears as a solid, well-circumscribed but unencapsulated lesion with grey-to-yellow cut surfaces, and tends to arise in the mid-to-upper portion of the thyroid gland, where C cells are most numerous (4). On histologic examination, the malignant cells show neuroendocrine features, with solid sheets of round, relatively uniform cells with salt-and-pepper chromatin (4). Amyloid is invariably present in the surrounding stroma, and displays apple-green birefringence under polarized light when stained with Congo red (4). In familial cases, the background thyroid gland will often show hyperplastic C cell nodules (4). Immunohistochemistry with neuroendocrine markers, including chromogranin, synaptophysin, and CD56, as well as calcitonin, can be helpful for confirming the diagnosis of MTC.

Overall, MTC is a fairly aggressive tumor with moderate prognosis. Cervical lymph node involvement and distant metastasis are noted at presentation in 70% and 10-15% of patients with MTC, respectively (39). An additional 18-38% of patients will have distant metastasis during their clinical course, most commonly to the liver, lungs, and bone (48). MTC does not respond well to radiation or chemotherapy, and overall five-year survival rate is 70-80% (4). Mortality increases significantly with higher stage tumors; if distant metastases are present, five-year survival rate drops to 26% (48). According to Erovcic et al., angioinvasion was the most reliable predictor of mortality. They found that, of the 43% of MTC cases with an-

gioinvasion, 60% developed distant metastases (50). Additionally, familial cases are more aggressive than sporadic ones, and as such, risk stratification guidelines have been created based on specific RET mutations, with the M918T substitution at codon 918 (exon 16) of MEN2b having the highest risk of all (4). Due to this increased risk, many patients with MEN2b are offered prophylactic thyroidectomy (1). Finally, other poor prognostic factors include older age, small cell morphology, and loss of calcitonin positivity by immunohistochemistry (4).

Occult MTC is rare but does occur, predominantly in individuals over the age of 60 years, with a fairly equal male to female predominance (51). Tumor nodules were found to be less than one centimeter and had not metastasized (51). The prevalence rate of these tumors was found to be 0.14%, much less than that of PTC (51).

Incidental Thyroid Autopsy Findings

Most thyroid pathology identified at the time of autopsy will be incidental to the cause of death. That said, it is still important to document, as some conditions may be familial, as described above. The following entities represent the most commonly encountered incidental autopsy findings.

Solitary Nodules

Thyroid nodules are very common and may be palpable in up to 1.5% of men and 6% of women (51). High resolution ultrasonography imaging studies detect nodules in 19 to 67% of patients randomly selected for examination (52). The autopsy prevalence is estimated to range from 30 to 60%; however, the majority of the studies cited are from the 1950s (52, 53). Most incidental nodules are benign colloid nodules, with the rest made up of benign adenomas, cysts, or localized thyroiditis (52). Nodules larger than 1.5 cm are thought to be more clinically significant and are more likely to undergo ultrasound-guided biopsies and regular surveillance than smaller ones (53) (**Image 9**).

Multinodular Goiter

The presence of multinodular goiter may not be incidental if it occurs in the setting of functioning nodules resulting in toxic multinodular goiter, which would have symptoms of hyperthyroidism as previously discussed. Another rare but important complication is the potential for acute hemorrhage to occur in one of the nodules, resulting in acute pain, tenderness, and sudden increase in size of the gland, which may cause respiratory distress (54). More often than not, it is a nontoxic, sporadically occurring goiter with an incidence of approximately 5% in the United States (54). The incidence increases with age, which may result in an increase in the number encountered at the time of autopsy.

Hashimoto Thyroiditis

Now considered the most common autoimmune disease, Hashimoto thyroiditis (HT, also called lymphocytic thyroiditis) occurs as the result of antithyroglobulin and antithyroid peroxidase antibodies. First described in 1912 by Dr. Hakaru Hashimoto, it typically presents as a painless, slowly enlarging gland which results in hypothyroidism (55). A short period of transient hyperthyroidism may also occur. It typically occurs in middle aged (45-65 years) women and may cluster in families (55). Hashimoto thyroiditis

has an incidence of approximately one case per 1000 persons per year, based on clinical data (56). Increased concentrations of dietary iodine have been associated with an increase in the incidence of HT. Grossly, the thyroid gland will be enlarged, firm and have more of a grey-tan color than the typical dark red color (**Images 10 and 11**). Histologically, the interstitium will be infiltrated by lymphocytes forming reactive follicles, often having germinal centers, and Hürthle cell metaplasia of the follicular epithelium will commonly be present (**Image 12**). Life-long daily thyroid hormone replacement therapy is typically the treatment of choice for the progressive thyroid hormone deficiency (55). Interestingly, although this disorder is associated with hypothyroidism, Cina et al. found no association between Hashimoto thyroiditis and suicide (57).

Black Thyroid

The finding of a thyroid gland that is discolored black is the result of prior minocycline or other tetracycline therapy, typically for the treatment of acne or other dermatologic condition (**Image 13**). Associated pigmentation of the bone, nearby blood vessels, and skin have also been reported (58). Many mechanisms have been proposed for this change, including the combination of the drug with lipofuscin, accelerated accumulation of lipofuscin, oxidative changes from breakdown products of the medication, altered tyro-

Image 9: Solitary thyroid nodule.

Image 10: Firm, atrophic thyroid gland.

sine metabolism due to minocycline-inhibited thyroid peroxidase, and disruption of lysosomal transport resulting in pigment deposition (59). Whatever the underlying mechanism for the color change, it is thought to be a benign process.

Thyroidectomy

Absence of the thyroid gland is indicative of previous underlying thyroid pathology and it may be important to determine when and why it was removed. Individuals who undergo removal of the thyroid gland must initially undergo monitoring of their calcium levels to detect potential iatrogenic hypoparathyroidism and will need to take thyroid hormone replacement medication for the rest of their lives (56). Abuse and misuse of thyroid medications can occur; therefore, attempts at measuring thyroid hormone levels may be helpful in some cases.

CONCLUSION

The thyroid gland is a small but mighty organ whose function has system-wide effects. While not commonly the direct cause of death, thyroid disease may be an underlying condition contributing to the death for the reasons previously discussed. Thyroid pathology is one of the most commonly encountered incidental findings at the time of autopsy. Detection of postmortem TSH levels may be useful in appropriately selected cases for the detection of hyperthyroidism/thyrotoxicosis. Due to the effects it has on so many vital organs, it is recommended that the thyroid gland be examined microscopically in cases where there is no apparent cause of death and subtle or obvious pathology is grossly visible. Histologic sections should also be examined whenever cancer is suspected in order to provide this important information for the surviving blood relatives.

Image 11: Cut sections of firm atrophic thyroid gland.

Image 12: Thyroid parenchyma infiltrated by lymphocytes and reactive follicles (H&E, x40).

Image 13: Black thyroid gland due to minocycline therapy.

EDITORIAL COMMENT

It should be noted that in the April 14, 2016 issue of *JAMA Oncology*, an international panel of pathologists and clinicians reclassified the encapsulated follicular variant of papillary thyroid carcinoma to a nonmalignancy – noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) (60).

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