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Sudden thyroid death. A systematic review

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Abstract: Sudden death due to thyroid disorders is a rare occurrence in forensic practice. Marked changes of thyroid plasma hormones in short periods of time are known to be life threatening, but they are usually identifiable in patients with known thyroid disorders, and therefore do not comply with the definition of sudden death. In order to properly identify published sudden thyroid death cases we performed an extensive search on Web of Science. We found 31 articles containing case presentations of possible sudden thyroid deaths, from which were identified a total number of 42 cases. There are three main thyroid pathologies associated with sudden unexpected death: hyperthyroidism (usually in the context of a Graves' disease or toxic multinodular goiter), hypothyroidism (usually associated with Hashimoto's thyroiditis), and lymphocytic thyroiditis (most likely associated with lymphocytic hypophysitis). We also present a diagnosis algorithm for detecting thyroid and related pathologies in sudden unexpected deaths.

Key Words: sudden thyroid death, lymphocytic thyroiditis, Graves' disease.

Sudden death due to thyroid disorders is a rare occurrence in forensic practice. Marked changes of thyroid plasma hormones in short periods of time are known to be life threatening, but they are usually identifiable in patients with known thyroid disorders, and therefore do not comply with the definition of sudden death. The main causes of thyroid-related death are thyrotoxicosis and myxedematous coma [1, 2]. For the forensic medicine practitioner the main problems raised by previously unknown thyroid pathology are to suspect a potential sudden thyroid death, and to properly demonstrate it. The purpose of this article is to determine the most common causes of sudden thyroid death as presented in the scientific literature, and to give a diagnosis algorithm for cases in which a suspected thyroid pathology may be considered as a cause of death.

MATERIALS AND METHODS

In order to properly identify published sudden thyroid death cases we performed a Web of Science search using the following words: sudden + thyroid +

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death. A total number of 354 articles were identified, of which 26 contained case presentations of possible sudden thyroid deaths. By analyzing the articles containing case presentations and other relevant articles (reviews, original studies detailing life threatening conditions associated with thyroid pathologies) followed by relevant references search, we found another five articles containing sudden thyroid death cases. A total number of 42 cases were identified in these articles (Table 1). In order to draft a diagnostic algorithm we performed an un-systematized review of forensic endocrinology articles, focused on biochemical and histological criteria for postmortem identification of thyroid pathology.

Table 1. Potential sudden thyroid deaths identified in the scientific literature

Reference	Thyroid pathology	Age	Gender
[3]	Hypothyroidism, pulmonary thromboembolism	42	F
[3]	Hypothyroidism, pulmonary thromboembolism	15	M
[4]	Hyperthyroidism, Graves	43	F
[5]	Hyperthyroidism	30	F
[6]	Black thyroid	20	F
[7]	Hyperthyroidism	20	F
[8]	Gossypiboma	35	M
[9]	Apituitarism, 13q- syndrome	17	M
[10]	Lymphocytic hypophysitis	23	F
[11]	Hyperthyroidism +Type 1 DM	22	F
[11]	Hyperthyroidism +Type 1 DM	18	F
[12]	Lymphocytic thyroiditis	39	M
[12]	Lymphocytic thyroiditis	34	F
[12]	Lymphocytic thyroiditis	34	F
[12]	Lymphocytic thyroiditis	53	F
[13]	Hyperthyroidism	28	F
[14]	Lymphocytic thyroiditis, hypothyroidism	40	M
[15]	Hashimoto	62	F
[15]	Hyperthyroidism	22	M
[2]	Myxedema	48	M
[16]	Hyperthyroidism	34	F
[17]	Hyperthyroidism	16	F
[18]	Subclinical thyroid pathology	22	F
[19]	Hashimoto	Young	F
[20]	Hypothyroidism	31	M
[20]	Hyperthyroidism	47	M
[20]	Hyperthyroidism, fulminant thyroiditis	29	M
[21]	After subtotal thyroidectomy for Hyperthyroidism, laryngospasm	15	F
[22]	Lymphoid thyroiditis	29	F
[23]	Hyperthyroidism	19	F
[23]	Partial thyroidectomy after Hyperthyroidism	39	F
[24]	Hyperthyroidism +hypokalemic periodic paralysis	34	M
[25]	Hyperthyroidism	22	F
[26]	Hyperthyroidism	45	F
[27]	Hyperthyroidism	34	F
[28]	Hypothyroidism	15	F
[29]	Hyperthyroidism	34	F
[30]	Atrophic thyroiditis, hypothyroidism, myxedema related cardiac tamponade	54	F
[31]	Thyroid hormone abuse	50	F
[31]	Thyroid hormone abuse	39	M
[31]	Thyroid hormone abuse	72	F
[32]	Hashimoto associated with anterior hypophysitis	22	F

Major thyroid related pathologies associated with sudden unexpected death

Hyperthyroidism

Hyperthyroidism is associated with a 20% increase in mortality [33] compared to euthyroid patients, mainly caused by complications such as thyroid storm [34] thromboembolic episodes, cardiac arrhythmias or structural cardiac abnormalities [33]. Most of the cases we identified as sudden thyroid deaths in the scientific literature were related to increased thyroid hormone levels (22 cases); however, three of them were related to thyroid hormone abuse[31] and did not comply with the currently accepted definition of sudden death, as the matter of death was violent. It was interesting to note that the average age of the group of sudden deaths associated with hyperthyroidism was very low (32.3 years), and most were women (77%). Hyperthyroidism was usually caused by Graves' disease or toxic multinodular goiter, but other causes were identified as well, including thyroiditis or autonomously functioning thyroid adenoma [35]. Direct cause of death was usually considered thyrotoxic crisis [4, 5, 25, 27]. Three articles presented more particular cases of thyroid involvement in sudden death, and will be summarized below.

Wei *et al.* described a case in which thanatogenesis was initiated by a violent act – a women with untreated Graves' disease was slapped by her husband; immediately after, she collapsed unconsciously and died despite immediate resuscitation. Death was considered to be caused by a cardiac arrhythmia due to Graves' disease complicated with cardiomegaly and left ventricular hypertrophy, and the physical altercation was considered a contributing factor to death by causing emotional distress that favored the development of the arrhythmia. The court decided that the husband was guilty of involuntary manslaughter and was initially sentenced to three years in prison [5]. Yeo presented two cases of hyperthyroidism in thyrotoxic crisis associated with type I diabetes mellitus

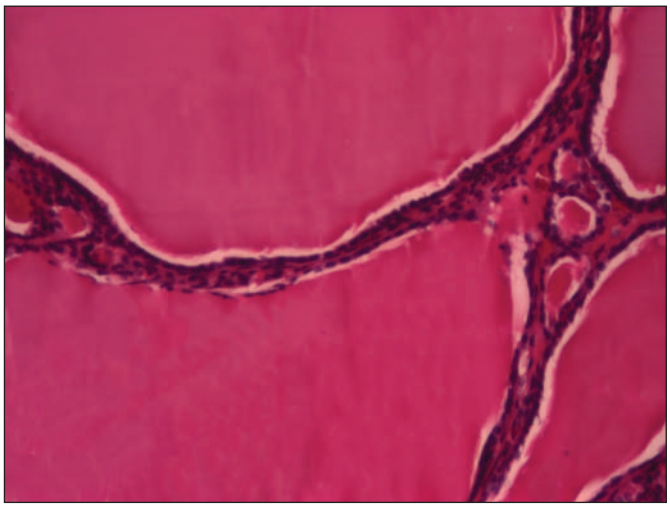

Figure 1. Simple goiter with large follicles, increased colloid, flat lining epithelium. HE, 10x.

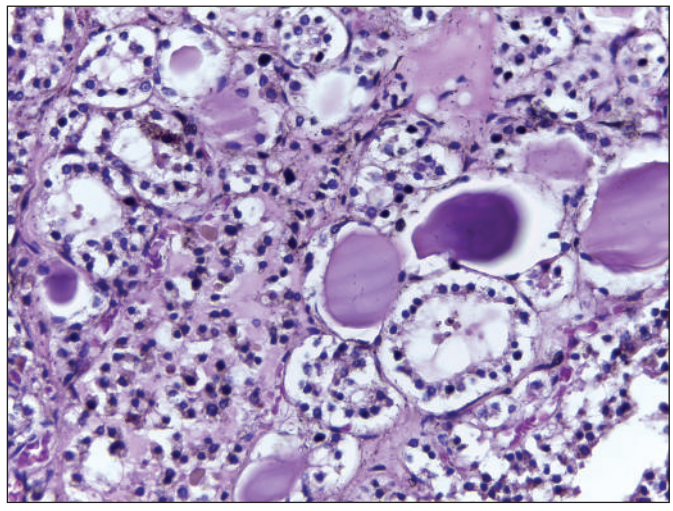

Figure 2. Graves' disease, with columnar epithelial cells, and decreased quantity of colloid. HE, 40X.

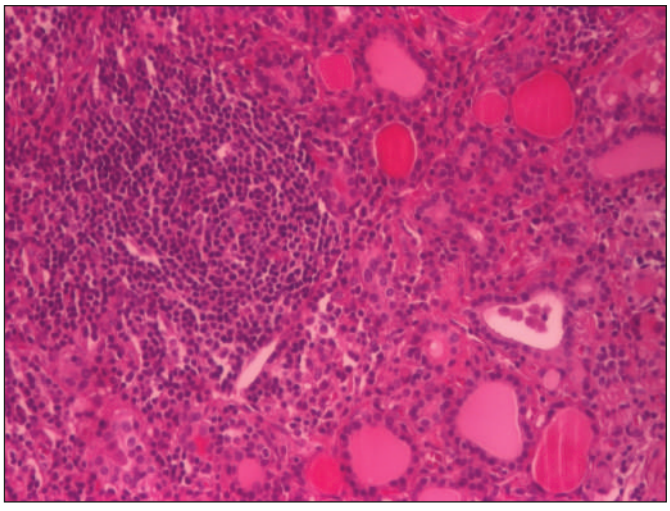

Figure 3. Hashimoto thyroiditis with lymphoid follicles, HE, 10x.

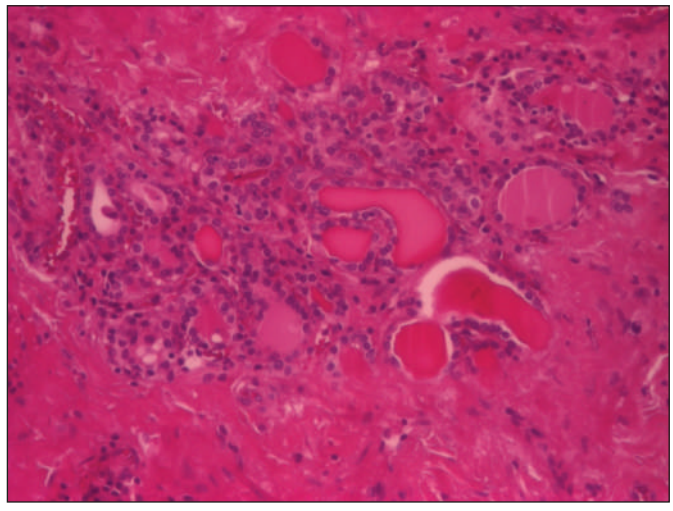

Figure 4. Riedel's thyroiditis, with flat epithelium, atrophy, fibrosis and inflammatory reaction HE, 10X.

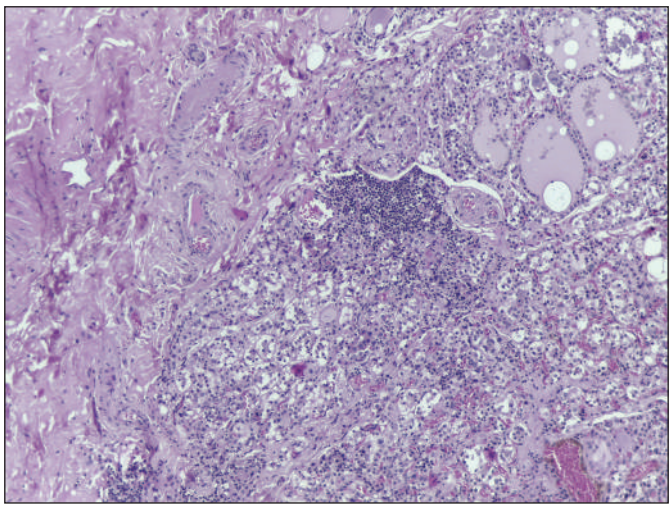

Figure 5. Lymphocitic thyroiditis. HE, 10x.

leading to sudden cardiac arrest that were successfully resuscitated [11, 36, 37]. Even if they were not sudden deaths per se they were included in our analysis because these two pathologies are known to negatively affect each other and subsequently increase their severity [11]; this association could lead in theory, if not treated, to sudden death. Moreover, both pathologies are relatively frequent in the younger population, the association being a potential cause of sudden death in this age group. Randall presented a case of sudden death due to hypokalemic periodic paralysis associated with thyrotoxicosis (TPP). TPP may appear irrespective of the cause of thyrotoxicosis, being associated with Graves' disease, toxic nodular goiter, iodine induced thyrotoxicosis, lymphocytic thyroiditis, solidary toxic thyroid adenoma, etc. [38]. The postmortem diagnosis of this pathology is difficult because potassium levels are very hard to interpret after death [39]. A positive diagnosis can be suspected based on the ethnic grounds (it usually affects Asian people), a familial history suggesting an autosomal dominant inheritance, a history of episodes of flaccid paralysis with rapid installation and recovery, low potassium level during but not between the attacks, and mutations in the CACNA1S gene (60% of cases), SCN4A gene (20% of cases), and KCNJ18 gene (3.5% of cases)[40].

Hypothyroidism

Overt hypothyroidism is rarely a cause of death. A study performed between 1953 and 1996 identified a total number of 200 cases of myxedematous coma, the number of deaths in this subgroup being around 20% [41]. As a cause of sudden death, hypothyroidism has only been cited a few times. De la Grandmaison *et al* presented a case of a 40 years-old man whose cause of death was lymphocytic myocarditis associated with chronic lymphocytic thyroiditis. Postmortem biochemistry was consistent with Hashimoto thyroiditis with hypothyroidism (increased anti-peroxidase antibody, increased TSH) [14]; however, the authors failed to prove that Hashimoto thyroiditis, or the presence of hypothyroidism, was actually involved in thanatogenesis. De Letter presented a 62 years old woman who died suddenly, being diagnosed with pernicious anemia, right ventricular dysplasia, and Hashimoto thyroiditis. Toxicological examination revealed a mixture of analgesics, hypnotics and amphetamines (appetite suppressants), that barely reached a toxic blood level [10]. Thyroid pathology in this case was not enough to explain the death of the patients, which was more likely caused by the effects of the drugs on a pathological heart. Pompeo and Salutari presented the case of a 48 years-old man with sleep apnea and goiter having a significantly enlarged, multinodular thyroid causing tracheal dislocation, and macroglosia. The patient suffered severe O_2 desaturation, secondary to periods of prolonged apnea, that finally caused his death [2]. In this case we think that hypothyroidism could be considered as the underlying cause of death, if proven to antecede the sleep apnea syndrome, as it could lead to a series of morphological and physiological changes that able to cause or increase the severity of the syndrome [42-45]. Edston presented a case of a 31 years-old man who was found dead in his bed; two days earlier he announced he couldn't go to school to teach, because he was feeling ill (a severe diarrhea). Autopsy found nothing out of the ordinary except for a small goiter with follicular lymphocytic infiltration and an increased TSH [20]. Our opinion is that in this case the most likely cause of death is represented by an electrolyte disturbance, as both hypothyroidism and diarrhea are known to negatively affect Sodium, Potassium or pH levels, which in turn may cause electric cardiac disturbances [46, 47]. Guthrie presented the case of a 15 years-old woman with Hashimoto Thyroiditis whose direct cause of death was considered spontaneous arrhythmia due to hypothyroidism [28]. However, no structural changes were highly suggestive for the arrhythmic hypothesis. Kelly and Butt presented the case of a 54 years-old woman with atrophic thyroiditis and severe myxedema, who developed a severe cardiac tamponade (2270 ml)[30]. Fruhwald *et al.* in a study that included 61 patients with subclinical thyroid disorders, found one sudden death; however, they didn't present the case [18]. If, from what is seen above, overt hypothyroidism is only exceptionally proven to be a cause of sudden death, recently there have been some debates regarding the possibility of subclinical hypothyroidism to cause it through the appearance of various coagulation disorders [3, 48-51]. Two cases were recently published in which this subclinical hypothyroidism was associated with pulmonary thromboembolism in sudden deaths [3]; if one patient also had significant risk factors for venous thrombosis (orthopedic surgery), in the second case there were no other significant risk factors that could explain the appearance of the pulmonary thromboembolism.

Table 2. Major morphological criteria in various thyroid disorders

Disease	Gross Pathology	Details
Simple goiter	Diffuse or nodular enlargement (larger in the endemic compared to the sporadic form), amber color. The nodular form presents nodules of varying sizes, sometimes calcification, ossification, hemorrhage or necrosis	Hyperplastic stage (initially): small follicles, little colloid, tall columnar cells. More advanced stages: involution of the follicles, associated with large follicles, increased colloid, flat or cuboidal lining epithelium, sometimes associated with intrafollicular pseudopapillary projections [57] (Figure 1). Secondary changes, associated with the nodular form include: hemorrhage, necrosis, fibrosis, foci of calcification and ossification [56].
Graves' Disease	Diffuse, symmetrical enlargement, smooth surface, decreased consistency, fleshy red-brown on the cut surface	Follicles of various sizes having columnar cells, sometimes forming pseudopapillary structures with a decreased quantity of colloid, scalloping of the colloid in periphery, variable degree of lymphocytic infiltrate, mostly containing CD4+ T cells[58]. See Figure 2.
Hashimoto Thyroiditis	Symmetrical enlargement of the lobules, pale-pink to yellow color, with lobules on the cut surface[56]	Atrophy of the thyroid follicles associated with (1) oncocytic metaplasia of the follicular epithelium (Hurthle cells), sometimes aggregated forming hyperplastic nodules, and sometimes with nuclear enlargements or atypical shapes (not to be confounded with thyroid cancers, and (2) frequent lymphoid folicles, sometimes forming germinal centers. The lymph nodes around the thyroid are often enlarged, showing signs of reactive follicular hyperplasia. Immunohistochemically, this associates positivity for antimicrosomal antibody, antithyreoglobulin antibody, TSH receptor and iodine transporter. The lymphocytic infiltrate contains a mixture of T helper (both CD4 and CD8+) and B cells[59, 60]. See Figure 3.
De Quervain thyroiditis (subacute thyroiditis)	Asymetrical enlargement, increased consistency, nodular on cut sections [61].	Hyperthyroid phase – follicular disruption associated with depletion of colloid, giant multinucleated cells, and signs of acute inflammation [62]. Hypothyroid phase – disappearance of the follicular epithelium, mixed inflammatory infiltrate, granulomas around ruptured follicles. Regenerative period – regeneration of the follicles associated with fibrosis [63, 64].
Riedel's Thyroiditis	Enlarged, hardened (woody), often asymmetrical, caused extensive fibrosis extending in the extrathyroid tissues of the neck[65]. The surface is smooth of finely nodular [66].	Dense, acellular, fibrotic tissue, associated with a mixed inflammatory infiltrate. See Figure 4.
Amiodarone induced thyroiditis	Diffusely enlarged thyroid	Large, involution follicles, with areas of degeneration, filled with swollen and foamy cells, surrounded by areas of fibrosis and chronic inflammation [67].
Black thyroid	Black, associated with Mynocicline use	Black pigment in the apical portion of the thyroid follicular cells [68].
Lymphocytic Thyroiditis	Normal lobar architecture	Foci of lymphocytic infiltrate possibly associated with germinal center formation in the interfollicular regions [56].

Lymphocitic thyroiditis

Vestergaard *et al.* performed, in 2007, a histopathology study of the thyroid on five groups of cases (each comprising 25 patients): opiate overdose, alcoholics dead due to alcohol abuse, other types of fatal poisonings, cases with unknown cause of death, and controls. In five cases they identified an extensive lymphocytic thyroiditis, four of which being in the unknown cause of death group. One patient had arrhythmogenic right ventricular dysplasia, one was known with myxedema that was properly controlled using Eltroxin therapy. In the other two cases there was no discernible cause of death, and the authors concluded that lymphocytic thyroiditis could be, after excluding all other potential causes, a reasonable explanation for the sudden unexpected death [12]. In the scientific literature there are a few case reports in which lymphocytic thyroiditis was associated with lymphocytic hypophysitis [10, 14, 22, 32], the latter being considered as a cause of death. Most cases involved young women in postpartum period (up to a few years),

Table 3. Biological samples to be taken in sudden unexpected death without an apparent cause, needed for the identification of thyroid and related pathologies

Analysis	Biological product	Reason	Details
Histopathology	Thyroid	Identification of thyroid disorders	Initially a Haematoxylin Eosin stain should be performed. If a thyroid pathology is suspected one should additionally performed various immunohistochemical analyses (see above or Hayan and Fan[69] for a more comprehensive set of useful markers).
	Major organs (heart, brain, liver, etc)	Identification of associated pathologies or other causes of death	Initially a Haematoxylin Eosin stain should be performed. Cardiac samples should be screened for early ischemic/necrotic changes (Lee stain, fibronectin, etc).
	Endocrine organs	Identification of associated pathologies or other causes of death	Initially a Haematoxylin Eosin stain should be performed. If an endocrine pathology is suspected one should perform additional histochemical and immunohistochemical analyses, depending on the pathology/organ.
Biochemistry	Blood	Identification of hypo/hyperthyroidism	T4 for the diagnosis of hyperthyroidism. TSH for both hypo and hyperthyroidism. Anti-peroxidase antibody can be useful for identification of an autoimmune thyroiditis.
		HbA1	Test for diabetes, that can be associated in hypopituitarism with a thyroid pathology; differential diagnosis with a sudden death caused by diabetes.
		Hormone profile	As detailed as possible, depending on local availability. Can aid in the diagnosis of associated endocrine pathologies.
	Vitreous humor	Glucose, lactate, ketone bodies	Test for diabetes, that can be associated in hypopituitarism with a thyroid pathology; differential diagnosis with a sudden death caused by diabetes.
	Pericardial fluid	Cardiac enzymes	Aid in excluding a cardiac cause of death. To be used with care if resuscitation measures were performed.
Toxicology	Blood, urine, gastric contents, other	Differential diagnosis	A violent death due to acute intoxication should always be excluded in sudden unexpected deaths.
Genetic	Blood, skeletal muscle	Differential diagnosis	Other causes of sudden unexpected death may be impervious to histology or biochemistry means of detection (e.g. ion channel diseases).

with symptoms suggesting various pituitary hormonal insufficiencies including fatigue, depression (associated with thyroid dysfunction), amenorrhea (gonadotropin deficiency), inability to lactate postpartum (prolactin deficiency), hypoglycemia, dehydration, disorientation, weakness (adrenal insufficiency), diabetes insipidus, etc. [52]. Sudden death in acute hypophysitis is usually caused by adrenal insufficiency or pan-hypopituitarism [53-55], lymphocytic thyroiditis being most likely only an associated condition, not directly involved in thanatogenesis. All four of these cases with sudden, unexplained death from the Vestergaard study were women, three of which were in their reproductive age. However, hypophysis dysfunction or pathology was not presented, and a personal history was not available (including if they were in their early postpartum period).

Diagnosis protocol for the identification of a potential sudden thyroid death

Raising the suspicion for a sudden unexpected death with a potential thyroid pathology involvement

A personal history should be obtained from the relatives, including data about non-specific changes like mood disorders, sleep disturbances, pregnancies, and so on. External examination can be suggestive for thyroid diseases (especially severe myxedema). Obese patients should be routinely checked for macroglosia, and signs of sleep apnea.

The involvement of a potential thyroid disorder in thanatogenesis is difficult to be assessed during the autopsy. Even if most thyroid disorders are associated with various morphological changes (see Table 2), there are instances in which they are not apparent, as is the case of lymphocytic thyroiditis [12, 56]. Therefore, if the causes of death are not clear from the autopsy room, biological samples to assess thyroid (and more generally endocrine function), should be taken (Table 3). Besides the usual organs (brain, heart, lungs, kidney, spleen, liver), during an autopsy of sudden unexpected death one should also take samples from all major endocrine organs, including hypophysis, adrenal gland and ovaries. Moreover the presence of the thymus should be assessed and samples should be taken for pathology examination.

Postmortem diagnosis of thyroid pathology

Thyroid hormones can be used with caution for the diagnosis of either hypo or hyperthyroidism after death. T4 levels tend to decrease starting with 2.75 hours after death [70, 71] except for cases with prolonged agony (when thyroxin levels may start decreasing before death) [72]. Therefore high postmortem T4 levels can be used to diagnose hyperthyroidism. T3 levels tend to have a variable course after death [71] (values either higher than before death, mainly caused by T4->T3 conversion or lower, mainly due to bacterial degradation) and therefore they cannot be used in postmortem diagnosis of thyroid dysfunction. TSH levels however, are known to be stable in serum for at least 24 hours after death and are positively correlated with the values before death [70], being useful for the diagnose of either hypothyroidism or hyperthyroidism. Pathology examination can then pinpoint the underlying cause of the thyroid hormone changes that were identified biochemically.

Postmortem diagnosis of associated disorders

Pulmonary edema [4, 7, 20], interstitial fibrosis [5, 13, 61], cardiomegaly [5], lymphocytic infiltration affecting other organs [13, 25] are often described in literature in association with sudden thyroid death. Another frequent occurrence is thymus lymphocytic hyperplasia, an autoimmune pathology that is known to be associated with Graves' disease [73] especially in younger patients. This pathology was identified by some authors in sudden death cases with hyperthyroidism[13, 25, 26, 29], and its identification is very informative for a possible autoimmune disease. Hypophysis should always be assessed in the sudden death of young women, especially if they are in their early postpartum period. Other endocrine organs can also be affected in sudden unexpected deaths with thyroid pathology, either in the context of hypopituitarism or other general autoimmune endocrine disorders (see Table 3 for details). Coagulation disorders are frequent in patients with thyroid pathologies (for a detailed overview see [48]). During the autopsy their identification is however difficult.

CONCLUSIONS

Thyroid pathology is rarely identified as a cause of sudden, unexpected death. However, thyroid (and more generally endocrine) function should be assessed in each sudden unexpected death case in which a clear cause of death was not identified at the autopsy.

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