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CASE REPORT

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Three sudden deaths in men associated with undiagnosed chronic thyroiditis

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Abstract Three cases of sudden death associated with undiagnosed chronic thyroiditis are described. All were young or middle-aged men who were found dead, and death appeared to have occurred suddenly. Two of them had not previously experienced any serious medical problems, the third suffered from well-controlled Addison's disease. None had been investigated or treated for thyroid disease previously. Microscopically all showed a severe chronic thyroiditis with parenchymal destruction and reactive hyperplasia of the acinar epithelium. In the first case elevated triiodothyronin (T3), thyroxin (T4) and low thyroid stimulating hormone (TSH) were present, in the second case low T3 and T4 and normal TSH, and in the third an isolated elevation of T3 were found. Anti-thyroid antibodies were found in two cases. The possible causal relationship between silent chronic autoimmune thyroiditis and sudden death is discussed.

Key words Sudden death · Thyroiditis · Hyperthyroidism · Cardiac arrhythmia

Introduction

Thyroiditis is commonly classified into three clinical and histological forms, i.e. acute, subacute/granulomatous and chronic/lymphocytic [1]. In the last decades the so-called „painless" or „silent" thyroiditis has been recognized as clinically similar to subacute thyroiditis, but with a histological picture of chronic lymphocytic thyroiditis [2–7]. The overall incidence and prevalence of painless thyroiditis has not yet been studied. In clinical studies the prevalence has been estimated to be between 5 and 20% of all cases of hyperthyroidism [1]. Compared with Hashimoto's thyroiditis this condition shows a greater degree of parenchymal destruction and less oxyphilic epithelial changes and fibrosis, but follicular lymphoid infiltration and thyroid autoantibodies have often been observed [8]. Whether painless thyroiditis represents a variant of Hashimoto's thyroiditis is not established with certainty. Thyroid function during the course of painless thyroiditis is characterized by an initial phase of thyrotoxicosis, followed by hypothyroidism which usually resolves spontaneously [3].

Thyrotoxicosis, if untreated, might lead to sudden death by several mechanisms including cardiac arrythmia [9], hyperpyrexia, electrolytic disturbances and epileptic seizures [10]. Hypothyroidism may give rise to hyper- or hypokalemia that might induce cardiac arrhythmia [11, 12].

The prevalence of thyroiditis in forensic autopsies is not known with certainty as the thyroid is only studied carefully if conspicuous alterations of the thyroid gland alert the examiner's attention, and histological sections from the thyroid are not studied routinely. When thyroiditis is observed it is most commonly in the form of mild non-specific lymphocytic infiltration. In a clinico-pathological autopsy study the prevalence of chronic thyroiditis was 12% [13].

Sudden death in young individuals without significant coronary artery disease is commonly attributed to infections and cardiovascular accidents, whereas only a few cases have been associated with thyroid dysfunction [14].

Case histories

In this report three cases of sudden death are presented. A complete autopsy and toxicological tests were done. The thyroid glands were not weighed because no enlargement of the glands were observed and the macroscopical changes were discrete. Histological sections from the thyroid and other organs were studied, by staining with hematoxylin-erythrosin-saffron. The pituitary gland was only studied in Case 3. Triiodothyronin (T3), thyroxin (T4), and thyroid stimulating hormone (TSH) were measured in femoral blood. In two cases anti-thyroid antibodies were measured, namely microsomal antibodies (TMAb), anti-thyroglobulin (TgAb) and thyrotropin-receptor antibody (TRab) (Table 1). No special tests for other autoimmune diseases were carried out.The hospital records of the deceased were collected and evaluated.

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Table 1 Laboratory values in three cases of sudden death with thyroiditis. Triiodothyronin (T3) and thyroxin (T4) are expressed in pmol/L; thyrotropin (TSH) in mU/L; thyroid microsomal antibody (TMAb) and anti-thyroglobulin antibody (TgAb) in titres; thyrotropin receptor antibody (TRab) is expressed in U/L

Case	T3	T4	TSH	TMAb	TgAb	TRab
1→	1.2*	2.0*	7.3*	Not done	Not done	Not done
2→	13.6*	9.3	1.0	1/1600*	1/20	15*
3→	12.6*	31*	0.44	1/6400*	1/40	7.4
Normal	3–9	9–24	0.4–4.0	≥ 1/1600	≥ 1/160	< 8

* indicates abnormale value

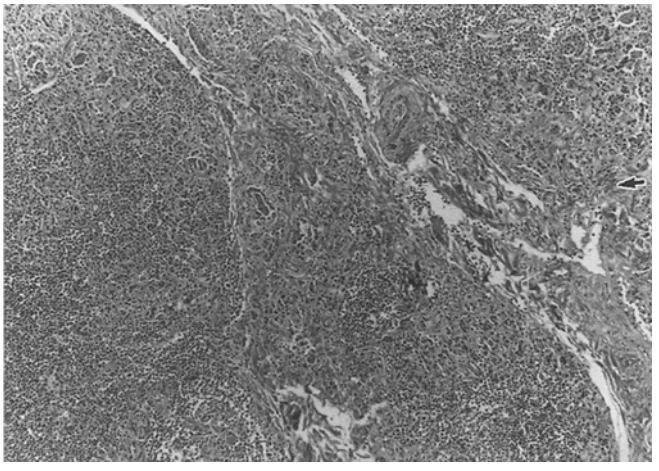

Fig. 1 Thyroid gland in case 1 shows extensive inflammatory lymphocytic infiltration, parenchymal destruction and moderate fibrosis (arrow). Erythrosin-hematoxylin-saffron stain × 100

Case 1

A 31-year-old teacher was found dead lying in bed in his apartment. Two days earlier he had called his school and indicated that he was ill. Shortly before death he appeared to have had severe diarrhoea. He had no previous hospital records, but his father reported that he had said he had felt tired and had a feeling of uneasiness in the bowel during the previous months. He took no medication and did not abuse alcohol or narcotics. His height was 187 cm and weight 72 kg. He was thin and the skin appeared slightly hyperpigmented. At autopsy 5 days postmortem no abnormalities were found except a slightly enlarged thyroid gland with a yellow and granular cut surface. Histologically (Fig. 1) the gland showed diffuse and follicular lymphocytic infiltration, parenchymal destruction and fibrosis. Oxyphil epithelial changes were sparse. No giant cells or granulomas were observed. Histological sections from the lungs, heart, liver, kidneys, pancreas and the intestines were studied, but no pathological changes were seen. Toxicological screening was negative.

Analysis of autopsy serum at the laboratory for Clinical Chemistry, Huddinge Hospital, Stockholm for free T4, free T3 and TSH indicated hypothyroidism with values of 2.0 (normal range: 9–24) pmol/L, 1.2 (3–9) pmol/L, and 7.3 (0.4–4.0) mU/L respectively.

Case 2

A 47-year-old farmer was found dead in a barn. He was last seen alive and well within an hour before death. He had no recent complaints about his health. The medical records showed frequent episodes of sinusitis during the last 20 years. He had symptoms of respiratory insufficiency when exposed to dust; allergy had been suspected but not verified. A few years before his death, when visiting his doctor he had complained of asthenia. Recently he had problems with eczema. At the time of his death he took no medication and he had never abused alcohol or drugs. He was a short and thin man, 168 cm tall, weighing 61 kg. At autopsy 3 days postmortem acute pulmonary edema and congestion were found, but no coronary atherosclerosis or other cardiac abnormalities. The thyroid gland was of normal size, but with a light-brown cut surface. Microscopically (Fig. 2) parenchymal infiltration of lymphocytes was seen, both diffuse and in follicular arrangement.The thyroid parenchyma showed acini lined by hyperplastic and oxyphilic follicular epithelium, but no giant cells or granulomas. In the myocardium, two small foci of subepicardial contraction-band necrosis with a few inflammatory cells were seen. Toxicological screening showed no alcohol or drugs in the blood. To exclude anaphylactic shock, total IgE and mast cell tryptase were analysed in blood but were found not to be elevated. Analysis of thyroid hormones and TSH were performed at the Laboratory of Clinical Chemistry, University Hospital of Linköping. Free T3 was found to be elevated (13.6 pmol/L, normal range 3–9 pmol/L), whereas free T4 was normal (9.3 pmol/L, normal range 9–24 pmol/L) and TSH was within the normal range (1.0 mU/L, normal range 0.4–4.0). The titre of TMAb was increased (1/1600) whereas TgAb (1/20) was low. TRab was elevated to 15 U/L (normal < 8 U/L).

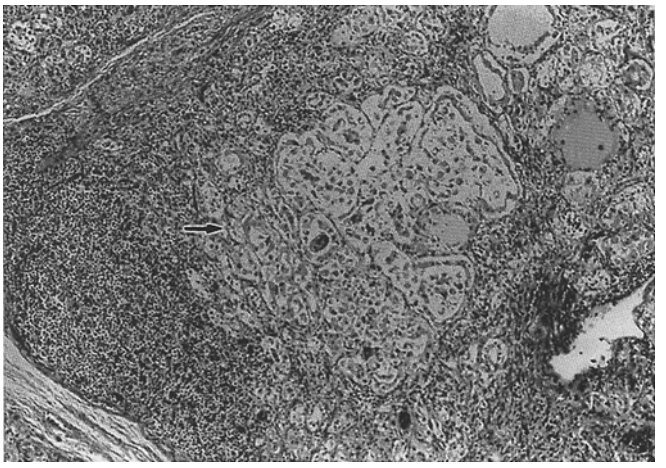

Fig. 2 Thyroid gland in case 2. Moderate to severe lymphocytic infiltration, parenchymal destruction and focal hyperplasia and oxyphilia of the follicular epithelium (arrow), slight to moderate fibrosis. Erythrosin-hematoxylin-saffron stain × 100

Case 3

A 29-year-old man was found dead at home. He was an unemployed, former factory worker. Ten years before death he had suffered from pneumonia, and in the postinfectious period he had pronounced asthenia. Addison's disease had been diagnosed; no hereditary endocrine disease was found in his family. However, no antibodies to adrenal cortical tissue were found, and he had no insufficiency of the pituitary gland. He was given substitution medication with fludrocortison and cortison and appeared to be well at subsequent yearly visits.The last time he was seen by his doctor was 8 months before his death, at which time he had an uncomplicated rhinitis. The autopsy was performed 3 days postmortem. He was a thin man weighing 58 kg and measuring 178 cm. There was no hyperpigmentation of the skin, including the nipples, or the mucous membranes. He had alopecia areata-like changes in the scalp. At autopsy he had cerebral edema, the brain weight was 1800 g. There was no evidence of cardiovascular disease. The adrenal glands were difficult to identify and microscopically they showed a total fibrosis of the cortices without inflammation. The thyroid gland was thin, but consistency was normal to firm and the cut sur-

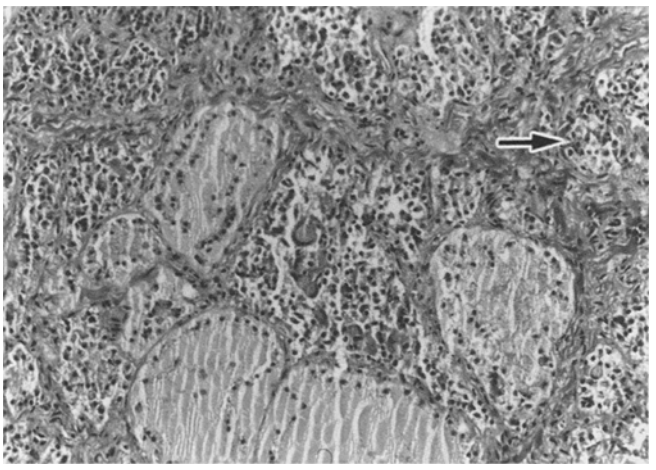

Fig. 3 Thyroid gland in case 3. Moderate lymphocytic infiltration, parenchymal destruction and diffuse epithelial hyperplasia with loss of colloid (arrow); slight fibrosis.Erythrosin-hematoxylin-saffron stain × 200

face was light brown and homogeneous. The pancreas, parathyroid and the pituitary gland appeared normal histologically. No immediate cause of death could be elicited. The toxicological screening for alcohol and drugs was negative. Analyses of glucose and lactic acid in vitreous humour showed no signs of hyperglycaemia. Histologically (Fig. 3) the thyroid was diffusely infiltrated with lymphocytes and in follicles. Parenchymal destruction and hyperplastic reactive and oxyphil epithelial changes were pronounced and there was moderate fibrosis. No granulomas were seen. In the vicinity a hyperplastic parathyroid gland was found. The pituitary gland was histologically normal. Analyses of free T3, free T4 and TSH at the laboratory of Clinical Chemistry at the University Hospital, Linköping, gave the following results: 12.6 pmol/L (elevated), 31 pmol/L (elevated) and 0.44 mU/L (normal in the lower range) respectively. The TMAb titre was 1/6400 (elevated), TgAb 1/40 (low) and TRab was normal (7.4 U/L).

Discussion

Postmortem changes of thyroid and related hormones in blood have been reviewed by Coe [15]. Elevated concentrations of T4 and TSH correlate well with antemortem values, although T4 might decrease somewhat in the postmortem period [16]. T3 is known to be an unreliable marker of hyperthyroidism postmortem [17]. The diagnosis of hypothyroidism postmortem is more difficult to ascertain than that of hyperthyroidism due to a natural decrease in thyroid hormones in blood in the antemortem period [18], making interpretation difficult in the individual case. For postmortem concentrations of thyroid antibodies there are no reference values, but antibodies of IgE and IgG types are known to be stable in blood for several days in refrigerated bodies and samples even at room temperature.

Chronic, autoimmune and "painless" thyroiditis might have more than one etiology [1]. During the course of the disease the patients can be hyper-eu-or hypothyroid [6]. In "painless" thyroiditis restoration of thyroid function is seen within months or years and the disease can remain undetected both by the patient and the doctor. In the three cases presented here the subjects had not complained of neckpain or had no significant enlargement of the thyroid. The histological picture was that of lymphocytic thyroiditis with variable parenchymal destruction and fibrosis, indistinguishable from Hashimoto's thyroiditis. Moreover anti-thyroid antibodies were detected in the two cases in which these were looked for. The general picture is thus consistent with painless thyroiditis. Case 1 was found to be hypothyroid biochemically and had had diffuse symptoms in agreement with disturbance of thyroid function some time before his death. Diarrhoea, which this patient seemed to have had shortly before death, is not a feature of hypothyroidism. Unfortunately, no microbiological or other tests were done to identify the cause of his diarrhoea.

Case 2 had elevated T3 and a low value of T4 and normal TSH. Isolated T3 thyrotoxicosis is uncommon [19]. The subject had elevated titres of TMAb and TRab. The latter might corroborate hyperthyroidism as 80% of cases with elevated TRab are hyperthyroid due to thyrotropism of these antibodies [20]. This patient had discrete myocardial contraction bands in two subepicardial areas in the absence of coronary artery disease. These might have been caused by resuscitation procedures [21], which were undertaken during the ambulance transport. Focal myocardial necrosis can also be seen in cases of thyroid hormone abuse [22].

Case 3 had elevated T3 and T4 and TSH in the lower normal range, all in agreement with thyrotoxicosis due to a fulminant thyroiditis. TMAb titres were elevated and TRab was high in the normal range. Grave's disease cannot be excluded, as Hashimoto's disease is interrelated with primary hyperthyroidism [23].This patient also had Addison's disease, which can be seen concomitantly, then called Schmidt's syndrome [24], and might have the same, possibly autoimmune, etiology [25].

During the last 20 years there have only been a few reports of sudden death associated with functional thyroid disease [12, 19, 26, 27].Two of the cases displayed hyperplastic goiter [12, 26] and one Hashimoto's thyroiditis [19]; the remaining case did not include histological examination. In a clinical study of 33 deaths in thyrotoxicosis some 15% died suddenly and unexpectedly in the absence of demonstrable myocardial infarction [28].

In summary the three deaths described in the present study, were apparently sudden and showed nearly identical thyroid histopathological changes and abnormal thyroid hormone values, which may have been caused by destruction of the thyroid parenchyma. None of the case histories showed a causal relationship between sudden death and thyroiditis. No cause of death was found by careful autopsy, histological study of internal organs and toxicological tests. Thyroid disease, therefore, might have been the cause of death, per exclusion – and this indicates that lymphocytic thyroiditis might be rapidly fatal. In cases of sudden death in young and middle-aged men and women without signs of vascular disease, sampling for histology from the thyroid gland would be highly recommended.

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