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Iodoform induced thyrotoxicosis in the elderly: case report and review of literature

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Background. Drug-induced hyperthyroidism is a rare condition linked to dietary supplements, iodine-containing medications and intentional or unintentional over ingestion of levothyroxine; its detection is important since, if left untreated, thyroid storm can develop, carrying a mortality rate of 20-50%.
Case presentation. Here we describe the case of an oldest old (84 years) woman, with severe cognitive impairment and immobilization syndrome attending our geriatric ward for aspiration pneumonia. During the fifth day of hospitalization, while pneumonia and respiratory symptoms were improving, tachycardia persisted (heart rate 130 bpm), associated with tremors and lack of sleep. The patient was affected by multinodular goiter and, a diagnosis of thyrotoxicosis was documented by elevated serum free thyroxine and free triiodothyronine levels (4.7 ng/dL and 6.6 ng/L, respectively), associated with undetectable thyroid-stimulating hormone (TSH 0.04mIU/L), elevated urinary iodine excretion (849 µg/L) and normal serum thyroglobulin levels (10 ng/mL).131I thyroid scan showed diffuse low uptake, suggesting iatrogenic thyrotoxicosis. The patient suffered from immobilization syndrome with bedsores that had been medicated twice a week with iodoform gauzes for one year. Prior to starting the use of iodoform dressings the patient was documented euthyroid.
Conclusions. Over the past century, few cases have been described regarding possible severe toxicity caused by the use of iodoform gauzes, all of them presenting with neurovegetative symptoms as vomiting, altered sensor, which disappeared after withdrawn of the medication, but iatrogenic thyrotoxicosis was never demonstrated. Thus, to our knowledge, this is the first report documenting the onset of thyrotoxicosis induced by lasting use of iodoform gauzes.

Key words: Thyrotoxicosis, Iodoform gauzes, povidone-iodine, decubitus ulcer, urine iodine

BACKGROUND

Thyrotoxicosis is a common condition characterized by an excess of circulating thyroid hormones. It may result from a variety of conditions the origin of which can be either endogenous or exogenous: Graves' disease (autoimmune hyperthyroidism) is the most frequent cause, other important causes include autonomous thyroid nodules (toxic nodular goiter, thyroid adenoma) and, rarely, excessive iodine intake [1]. Iatrogenic thyrotoxicosis may be caused by *i*) destructive thyroiditis (a result of lymphocytic infiltration, cellular injury, trauma, irradiation) with release of preformed hormones into circulation; *ii*) excessive ingestion of thyroid hormones ("thyrotoxicosis factitia"); *iii*) iodine-induced hyperthyroidism: (radiologic contrast agents, topical antiseptics, amiodarone etc.) [2]. Several drugs can interact with thyroid homeostasis, with different biochemical pathways and clinical presentations. We present a rare form of iodine-induced hyperthyroidism, which is caused by intrathyroidal iodine pool expansion and consequent escape from the acute inhibitory effect (Wolff-Chaikoff

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effect) thus, releasing an excess of thyroid hormones [1]. This latter etiology is probably the most susceptible to both pre-existing gland condition of the patient and environmental iodine. Therefore, iodine-induced thyrotoxicosis is more common in iodine-deficient areas and in patients with thyroid disease, especially multinodular goiter. A characteristic of iodide thyrotoxicosis in patients suffered from multinodular goiter is its usually transient course. In these forms serum Thyroid Stimulating Hormone (TSH) is undetectable, free thyroxine (FT4) is increased and free triiodothyronine (FT3) is usually but not always elevated. Radioactive iodine uptake is generally low, but occasionally is normal or increased [2].

Here we present the first case described in literature of an 84-year-old Caucasian female suffered from transient iodine-induced thyrotoxicosis caused by the prolonged use of iodoform gauzes to treat trochanteric and sacral bedsores.

CASE PRESENTATION

An 84-year-old woman with Alzheimer's dementia was admitted to the Emergency Department because of sudden onset of shortness of breath, dizziness, and vomiting immediately after choking while having lunch. On admission, the patient was drowsy, febrile (38.2°C) with severe shortness of breath and tachycardia (130 bpm). Her skin was warm and sweaty, she showed fine tremors of the hands. Respiratory examination revealed mild tachypnea with dullness to percussion over the lower-right lung. Auscultation revealed decreased breath sounds and crackles in the same area. Blood investigation showed a total leucocyte count of 16,310/mm^3, Hb 8.8 g/dL, C-reactive protein (CPR) 18.53 mg/dL, Procalcitonin (PCT) 2.19 ng/L Fibrinogen 569 mg/dL, Ferritin 475 mcg/L, Creatinine 0.95 mg/dL, liver and pancreatic enzymes (Amylase, Lipase, AST/ALT) were within the normal range. Chest XR revealed a pulmonary consolidation in the right lower lung, consistent with aspiration pneumonia. Once admitted to our Geriatric ward, blood samples for bacterial cultures were collected and, *i.v.* antimicrobial broad-spectrum therapy along with crystalloid solution infusion were started. Five days after, despite a good clinical response in terms of fever resolution and the decrease of inflammation markers (CRP 2.53 mg/dL, PCT 0.05 ng/L), the patient still suffered from tachycardia (around 120 bpm) without relief of the fine tremors. She had increased systolic and decreased diastolic blood pressure (160/60 mmHg). At neurological examination she presented psychomotor agitation only. Cardiac US, EKG and BNP were normal. Given that the patient had a history positive for multinodular goiter, thyroid function was assessed, revealing suppressed thyroid-stimulating hormone (TSH) (0.01 mIU/L, normal range: 0.40-4.00) along with slightly increased FT3 (6.5 ng/dL, normal range: 2.70-5.70) and substantially elevated FT4 (4.7 ng/L, normal range 0.70-1.70) levels; a hormone profile consistent with a condition of thyrotoxicosis (namely T4-toxicosis). Accordingly, circulating anti-thyroglobulin (TgAb), anti-thyroid peroxidase (TPOAb) and anti-thyrotropin receptor antibodies (TRAb) were measured, resulting all undetectable. Moreover, serum thyroglobulin level was low (10 ng/mL, normal value < 35 ng/mL) in the face of elevated urinary iodine excretion (849 µg/L, normal < 300 µg/L), confirming the hypothesis of iodine induced thyrotoxicosis. In this setting, it is noteworthy that the patient six months before hospital admission had measured circulating thyroid hormone levels, showing normal values: TSH 1.2 mIU/L, FT4 1.2 ng/L. She was not given drugs known to interfere with thyroid function as amiodarone, interferon-α, interleukin-2 or lithium nor had received iodinated contrast agents. Conversely, the patient has started using iodoform gauzes (four times a week) to treat her extended femoral and sacral pressure sores for about five months. An ultrasound of the neck was then performed, confirming a small multinodular goiter (diffuse isoechoic parenchyma with several bilateral micronodules with diameters < 1 cm); ^{131}I scintiscan showed a diffuse reduced radioactive iodine uptake (Fig. 1).

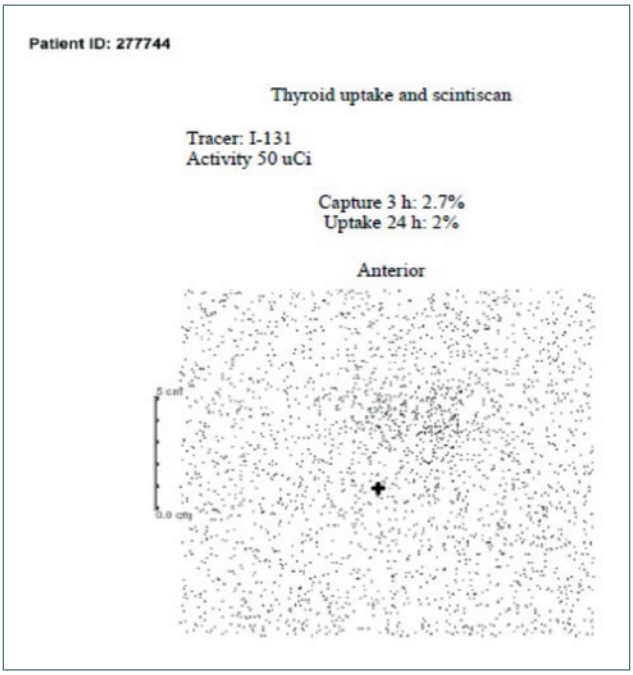

Figure 1. 131I Thyroid scintiscan shows a substantial decrease in uptake in both lobes.

In order to treat thyrotoxicosis, methimazole 5 mg/bid was prescribed along with atenolol 50 mg/day for persistent tachycardia while, iodoform gauze treatment of bedsores was withdrawn. The patient was discharged after seven days of hospitalization and, at six-week follow up thyroid hormone profile was normalized: TSH 0.70 mUI/L, FT3 3.4 pg/mL, FT4 1.8 ng/mL; similarly, the urinary iodine excretion had returned within the normal range (280 µg/L). Accordingly, methimazole therapy was reduced to 5 mg/day and then discontinued. Over the following 6 months the patient remained asymptomatic with normal thyroid hormone profile.

DISCUSSION AND CONCLUSIONS

Drug-induced thyrotoxicosis is more frequent in older than younger patients and shares a similar pathogenic mechanism of destructive thyroiditis. Lithium, interferon-α, intravenous contrast, amiodarone and some topical antiseptics like povidone iodine are commonly involved in drug-induced thyroid dysfunction (Tab. I). Exogenous thyrotoxicosis – factitious or iatrogenic – develops after ingestion of an excessive amount of thyroid hormone, and is associated with low serum TSH and thyroglobulin concentrations [2 3].

In elderly patients, it is extremely important to obtain a detailed clinical history and perform an accurate physical examination, since the signs and symptoms of hyperthyroidism can be uncertain (apathetic thyrotoxicosis). Clinical manifestations of hyperthyroidism often affect the cardiovascular system, presenting with palpitations, especially during stress, associated with tachycardia and, less frequently, with atrial fibrillation. Fine tremors and mild cognitive symptoms (e.g. irritability, depression) can occur as well. In our case, the persistent tachycardia associated with fine tremors in the absence of cardiovascular disease suggested a possible thyrotoxicosis [1].

Iodoform gauze is one the most adopted dressing in clinical practice to treat open wounds and bedsores; it consists of a medical standard gauze impregnated with iodoform, which releases continuous limited iodine doses in the wounds [4]. Although modest, the chronic

Table I. Clinical cases reported in the literature.

Author	Cases	Age	Sex	Symptoms and signs	Urinary/plasma iodine ratio	Thyroid hormone levels
Muir AH [5] (1903)	1	35	M	Delirium, fever, tachycardia and vomiting	N.E.	N.E.
Short L [6] (1910)	1	N.A.	F	Weight loss, tachycardia, distal tremors, nervousness and restlessness	N.E.	N.E.
Buccellato T [7] (1950)	1	N.A.	F	Not specified	N.E.	N.E.
Harry P [8] (1992)	3	N.A.	N.A.	Delirium, fever, tachycardia, vomiting, coma (a patient of the three described) and slight transaminases increase and proteinuria	N.E.	N.E.
Kasahara T [11] (1992)	2	N.A.	N.A.	Delirium	N.E.	N.E.
Martins CA [9] (1994)	1	N.A.	N.A.	Delirium	N.E.	N.E.
Yamasaki K [10] (1997)	1	66	M	Delirium, mild liver dysfunction	Plasma Iodine 471 g/dL	N.E.
Tada M [14] (2002)	1	76	M	Tachycardia, Altered mental status (EE demonstrated slow, widespread and random activities)	Plasma Iodine 151 ug/dL	Normal levels
Numata S [12] (2004)	1	78	M	Stupor, involuntary motion of lower extremities, abnormal muscle tone of the upper extremities	Plasma iodine 715 mg/dL Urinary iodine 3930 µg/L	N.E.
Matsumura Y [15] (2005)	1	64	M	Delirium, altered mental status	Plasma Iodine 125 µg/dL	N.E.
Araki K [13] (2007)	1	71	M	Altered mental status	Plasma iodine 6.280 µg/dL	N.E.

N.E.: not evaluated, N.A.: not available

release of iodine by iodoform gauzes could trigger a state of overt thyrotoxicosis but, it has never been described till now. To our knowledge, this the first case described in literature, in whom the onset of thyrotoxicosis is associated with long-lasting use of iodoform gauzes. Nonetheless, few articles had reported potential toxicity related to the use of iodoform gauzes since the beginning of the 20th century (Tab. I).

Indeed, in 1903 Miur at al. described a 35-year-old male with a non-tubercular abscess in the left leg, treated with surgical intervention and medicated with iodoform gauzes. 24 hours after the medication the patient presented neurovegetative symptoms (nausea, vomiting, tachycardia, altered mental status), that disappeared once the iodoform gauzes were removed [5].

In 1910 Short et al. hypothesized for the first time that an excessive quantity of iodoform could determine thyroid hyperfunction; in particular, he reviewed 100 cases previously reported, supposing that thyrotoxicosis was misdiagnosed but, at that time, it was impossible to confirm the diagnosis [6]. At odds, in 1950 Buccellato et al. described a case of severe poisoning following packing of the uterus with iodoform gauzes, without hypothesizing thyroid dysfunction [7] (Tab. II).

For more than 40 years no further studies were published regarding iodoform toxicity, presumably because of the nuanced symptoms overlapping with those sepsis-related. In 1992, Harry et al. reported three cases of intoxication after starting iodoform dressings on extended wounds. The patients presented with neurovegetative symptoms (nausea, vomiting, tachycardia with ventricular extrasystoles), hallucinations and, one of them subsequently became comatose. Within a few days after discontinuation of iodoform gauze dressing, the symptoms disappeared; however, the Authors did not evaluate thyroid function, but reported a slight increase of transaminase and proteinuria [8]. Two years later, Martins et al. reported a case of poisoning caused by the use of iodoform gauzes after occlusive surgical dressings of a diffuse hemorrhage in the pelvic cavity [9]. Interestingly, in 1997 Yamasaki et al. described a case of prolonged delirium with both hallucinations and psychomotor excitement after the use of iodoform gauzes in an abdominal wound and subclavian abscess; routine laboratory analysis indicated only hypoalbuminemia, anemia, and mild liver dysfunction, nevertheless plasma iodine concentration was found high. With withdrawn of the dressing application and subsequent reduction of plasma iodine levels, the patient's delirium improved [10]. Moreover, other Japanese authors reported delirium and altered consciousness that disappeared a few days after removal of iodoform gauzes, with concomitant decrease in plasma iodine levels [11-13].

Matsumura et al reported the case of a patient with diabetes mellitus and multiple foot ulcers, in whom altered consciousness developed after local use of iodoform gauzes; the Author points out that it would be very difficult to distinguish toxic symptoms resulting from iodoform itself from those resulting from released iodine, as measurement of the blood iodoform is not possible. They underlined the importance of iodine renal excretion, suggesting a careful use of iodoform gauzes in patient with decreased kidney function [14].

Interestingly, Tada et al. in 2002 described a case similar to our report: a 76-year-old man with supranuclear palsy who developed consciousness disturbance following treatment of a decubitus ulcer in the sacral region by iodoform-gauzes. In that report, however, plasma free iodine concentrations were high (151 μg/dL) in the face of normal thyroid function tests. The symptoms and laboratory abnormalities of the patient recovered soon after removal of iodoform-gauzes [15].

Previous reports have also called attention to the use of BIPP (Bismuth Iodoform Paraffin Paste) preparations, where symptoms arising from bismuth should also be considered. Sharma et al. described a rare case of relapsing toxic encephalopathy due to the absorption of bismuth from BIPP [16].

Our report and literature review suggest that sporadic cases of recurrent thyrotoxicosis caused by iodoform impregnated gauze might partially explain the so-called "iodoform poisoning".

In conclusion, the devious signs and symptoms previously reported in the literature caused by iodoform toxicity could be attributable to iodine-induced thyrotoxicosis which, in the elderly, mostly occurs with uncertain presentation (apathetic hyperthyroidism) and might be ascribed to other preexisting patient's comorbidities. Thus, in case of signs and symptoms, although slight, nonmatching with the underlying diseases in patients using iodoform gauzes the possible presence of iodine-induced thyrotoxicosis should be considered.

Table II. Topical antiseptics containing iodine.

Topical antiseptics	Iodine concentration
Diiodohydroxyquin cream	6 mg/g
Iodine tincture	40 mg/mL
Iodochlorhydroxyquin cream	12 mg/g
Iodoform gauze	4.8 mg/100 mg
Povidone iodine	10 mg/mL

Conflict of interest

The Authors declare to have no conflict of interest.

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