Myxedema Coma Following the Administration of Gonadotropin-releasing Hormone Agonist Complicated by Acute Pancreatitis

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Abstract:
Gonadotropin-releasing hormone (GnRH) agonists have been used for the treatment of various diseases. Although autoimmune thyroid disease has been reported as a rare complication of these agents, the symptoms are almost always transient and non-life-threatening. We herein report a rare case of an 83-year-old man receiving GnRH agonist treatment for prostate cancer who developed myxedema coma complicated by acute pancreatitis. This is the first report of myxedema coma potentially associated with a GnRH agonist. The follow-up of the thyroid function is necessary for patients undergoing treatment with GnRH agonists, especially those known to have or to be susceptible to autoimmune thyroid disease.

Key words: Myxedema coma, gonadotropin-releasing hormone agonist, autoimmune thyroiditis, acute pancreatitis

Introduction
Gonadotropin-releasing hormone (GnRH) agonists have come into widespread clinical use for the treatment of a variety of sex hormone-related diseases, including endometriosis, uterine leiomyoma, and breast or prostate cancer. These agents decrease the amounts of serum estradiol and testosterone to castration or postmenopausal levels (the so-called flare effect) via the desensitization of pituitary gonadotrophs and the down-regulation of pituitary receptors but with possible adverse effects that include decreased libido, erectile dysfunction, gynecomastia, osteoporosis, hot flashes, muscle weakness, anemia, and fatigue (1). A small number of case reports mention thyroid dysfunction in possible association with GnRH agonist treatment, although the association and mechanism remain unclear.

We herein report a case of myxedema coma following the administration of GnRH agonist for prostate cancer that was subsequently complicated by acute pancreatitis and massive retroperitoneal abscesses, which are speculated to be rare complications of myxedema coma. This very rare case highlights the necessity of monitoring the thyroid function in patients undergoing prolonged treatment with GnRH agonists, especially those known to have or to be susceptible to autoimmune thyroid disease.

Case Report
An 83-year-old man presenting with disorientation and weakness since awakening in the morning was transferred to our hospital. The previous evening, he had gone out into the cold for a long time and developed a terrible cough after returning home. He had been treated with a GnRH agonist (sustained-release leuprolide acetate) for prostate cancer for the past eight months. He had been living independently and working as a stonemason but began to notice fatigue, itching, cold intolerance, and whole-body edema three months prior to admission. His medications included bicalutamide, silodosin, and antihistamine, which had been prescribed for pruritus one week earlier. His medical history included tuberculosis treated by transection of the left upper lobe. His thyroid function had not been assessed previously, but the laboratory data had not included abnormal findings indica-
37 beats/min (regular); axillary body temperature, 34.2°C; consciousness (Glasgow Coma Scale of 9; E2V3M4). His vital signs upon arrival were as follows: blood pressure: 100/60 mmHg; pulse: 76 beats/min; respiratory rate: 20 breaths per minute; and oxygen saturation during breathing oxygen at a flow rate of 2 liters per minute through a nasal cannula, 98%. The heart sounds were normal, and the S1 and S2 were clear. The chest X-ray revealed no evidence of pericardial effusion. The echocardiogram revealed a normal cardiac structure and function without pericardial effusion. He was transferred to the intensive care unit under a diagnosis of sick sinus syndrome complicated by profound pitting edema in the lower extremities that resembled elephantiasis.

On arrival, he looked pale with a depressed level of consciousness (Glasgow Coma Scale of 9; E2V3M4). His vital signs were as follows: blood pressure: 77/44 mmHg; pulse: 37 beats/min (regular); axillary body temperature, 34.2°C; respiratory rate: 20 breaths per minute; and oxygen saturation during breathing oxygen at a flow rate of 2 liters per minute through a nasal cannula, 98%. The heart sounds were distant with a regular rhythm, and the breath sounds were decreased. His thyroid was not palpable. His other extremities that resembled elephantiasis.

The results of laboratory examinations are shown in Table 1. A peripheral blood test showed slightly increased levels of aspartate transaminase, creatine kinase, and brain natriuretic peptide without elevations in cardiac enzymes (creatinine kinase MB and troponin I). An electrocardiogram revealed sinus bradycardia and low voltage in the limb and chest leads. Chest X-ray showed cardiomegaly, while an echocardiogram revealed a normal cardiac structure and function without pericardial effusion. He was transferred to the intensive care unit under a diagnosis of sick sinus syndrome complicated by profound pitting edema in the lower extremities that resembled elephantiasis.

The diagnosis of myxedema coma was made based on severe hypothyroidism and the above-mentioned clinical manifestations, and the oral administration of levothyroxine (LT4) and levotirodthronin (LT3) at initial doses of 200 μg and 30 μg daily was begun. The clinical course after admission is shown in Fig. 1. Although the hemodynamics improved, resulting in the withdrawal of catecholamine infusion on the third morning, his consciousness suddenly deteriorated to coma that evening requiring urgent endotracheal intubation, and he entered a shock state (pulse rate: 30 beats/min and blood pressure: 50/30 mmHg). The diagnosis of myxedema coma was made based on severe hypothyroidism and the above-mentioned clinical manifestations, and the oral administration of levothyroxine (LT4) and levotirodthronin (LT3) at initial doses of 200 μg and 30 μg daily was begun. The clinical course after admission is shown in Fig. 1. Although the hemodynamics improved, resulting in the withdrawal of catecholamine infusion on the third morning, his consciousness suddenly deteriorated to coma that evening requiring urgent endotracheal intubation, and he entered a shock state (pulse rate: 30 beats/min and blood pressure: 50/30 mmHg). Thyroid hormone replacement was continued via a nasogastric tube (LT4 100 μg and LT3 30 μg daily), with additional LT4 via subcutaneous injection (400 μg daily) because of the possibility of impaired gastrointestinal absorption.

Along with an elevation in his serum free T4 and T3 levels and low TSH and free T3, he was started on suppository (400 μg daily) because of the possibility of impaired gastrointestinal absorption.
els, his general condition gradually improved accompanied by withdrawal hypothermia (defined as a core body temperature below 35.0°C) on day 5; catecholamine infusion was discontinued on day 6. A sedative agent for vigorous body motion was given beginning on day 7, and recombinant human thrombomodulin was administered for complicated disseminated intravascular coagulation. He regained full consciousness and was discharged from the intensive-care unit on day 11. Extubation was performed on day 15 after remission of the disseminated intravascular coagulation. However, he was placed on noninvasive positive pressure ventilation (NIPPV) on the same day for relapse of hypercapnia, which was speculated to have been induced by macroglossia, hypothyroid myopathy, disuse syndrome, or other entities. Whole-body computed tomography was performed with the suspicion of strangulation or impeded breathing owing to pleural effusion and ascites, which incidentally disclosed overall swelling of the pancreas with surrounding mesenteric edema, effusion, and fat stranding, indicating acute pancreatitis (Fig. 2). There were discrepancies in the levels of pancreatic enzymes, with the amylase and lipase levels remaining within normal limits (57 IU/L and 53 IU/L) while the elastase 1 level was extremely high (1,183 ng/dL). This profile was considered to reflect the differences in the half-time periods of the enzymes, as elastase 1 is suggestive of secondary peripancreatic infection. Percutaneous drainage was thought to be inappropriate for the massive effusion, and surgical debridement was considered. However, his family did not want further invasive treatments and issued do-not-resuscitate orders. Although his respiratory state improved gradually, leading to the cessation of NIPPV, he suddenly complained of massive abdominal pain on day 33. Emergent computed tomography revealed an increase in peripancreatic effusion, expanding to occupy the peritoneal cavity with partial formation of fibrous capsules. A blood examination showed a marked elevation of white blood cells (27,200/μL) and C-reactive protein (14.38 mg/dL) without elevation of pancreatic enzymes, suggesting the possibility of secondary peripancreatic infection. The autopsy showed remarkable necrotic changes in the pancreatic parenchyma in association with extensive necrotic and purulent lesions from the peripancreatic to retroperitoneal cavity (Fig. 3). Disseminated abscesses with yellowish pus were present in every organ in the retroperitoneal cavity, including the stomach, kidney, liver, intestine, and mesentery.

A microscopic examination of the pancreas revealed diffuse inflammatory changes leading to parenchymal necrosis and bleeding, partially complicated by the formation of vacuoles (Fig. 4a). The thyroid was grossly atrophic with

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Clinical course after admission. LT4: levothyroxine, LT3: levo triiodothyronine, CTRX: cef triaxone TAZ/PIPC, tazobactam/piperacillin, VCM: vancomycin, MEPM: meropenem, NIPPV: noninvasive positive-pressure ventilation, CT: computed tomography, DIC: disseminated intravascular coagulation, DOC: disturbance of consciousness, WBC: white blood cell, CRP: C-reactive protein, AMY: amylase
profound involution of the thyroid follicles with lymphocytic infiltration and fibrous lesions observed microscopically, compatible with Hashimoto’s thyroiditis (Fig. 4b). There was an outstanding reduction in his prostate cancer with no remote organ or lymph node metastasis.

Discussion

We herein report an extremely rare case of myxedema coma fulfilling the diagnostic criteria (3rd draft) announced by the Japan Thyroid Association (2) in an elderly man with prostate cancer, potentially associated with the administration of GnRH agonist. This case is also characteristic with respect to the clinical course, in which acute pancreatitis progressing to retroperitoneal abscess was considered an unusual complication of myxedema coma.

Several case reports refer to thyroid dysfunction following the administration of GnRH agonists (3-7). In those cases, however, all of the patients were women, ranging from juvenile to middle-aged, and treated with GnRH agonists as a pseudomenopause therapy for estrogen-related diseases, including precocious puberty (3), leiomyoma (4, 6, 7), and endometriosis (5). The thyroid dysfunction in these was almost always autoimmune thyroiditis with spontaneous resolution or requiring temporary LT4 replacement and rarely Graves’ disease (5, 7) or persistent hypothyroidism (6). The exact pathogenesis by which GnRH agonists provoke autoimmune thyroid dysfunction is unclear, although the abrupt fluctuation of sex hormones has been assumed to activate thyroid autoimmunity, such as in postpartum thyroid dysfunction (4). Indeed, thyroid dysfunction associated with GnRH agonists is generally detected one to six months after the initiation of treatment when the serum sex hormone levels have decreased to castration or postmenopausal levels due to the agent. Even in our case, the patient noticed symptoms of hypothyroidism beginning about five months after the initia-

Figure 2. Abdominal computed tomography imaging findings on days 16 (a) and 33 (b), with axial (1) and coronal (2) views. (a) The findings of overall swelling of the pancreas with surrounding mesenteric edema, effusion, and fat stranding are compatible with acute pancreatitis. (b) The swelling of the pancreas was improved; however, peripancreatic effusion expanded to occupy the peritoneal cavity with the partial formation of fibrous capsules.

Figure 3. A gross photograph of the pancreas shows diffuse infectious necrosis of the pancreatic parenchyma manifested as yellowish green.
tion of GnRH agonist treatment. The reason our patient developed myxedema coma, quite different from the mild thyroid dysfunction in previous case reports, may be due to the difference in age, as our patient was much older than the patients in other cases, and myxedema coma occurs almost exclusively in patients ≥60 years of age with longstanding hypothyroidism (8). It seems strange that our patient developed a myxedema coma shortly after initiating GnRH agonist treatment, since this condition usually occurs in patients with long-standing hypothyroidism over several years to decades. We therefore assumed that drug-induced hypothyroidism may induce a rapidly progressive disturbance in thyroid hormone production in comparison to patients with primary idiopathic hypothyroidism, thus leading to the development of decompensated hypothyroidism within a short period of time. In fact, the occurrence of a myxedema coma, which developed after only five months of amiodarone therapy, similar to our case, has been previously reported (9).

A few small-scale clinical studies have investigated the effect of GnRH agonists on the thyroid function in elderly men and describe a slight decline in the free T4 serum level accompanied (10) or not accompanied (11) by an elevation in the serum TSH during the first twelve months after treatment initiation. However, the observed thyroid dysfunctions in these studies seemed to be mild and without clinical significance, in marked contrast to our patient. This discrepancy suggested that a GnRH agonist is likely to have little influence on normal subjects, while it may induce adverse thyroid dysfunction in patients with preexisting or susceptibility to autoimmune thyroid diseases. This hypothesis may explain the previously reported female predominance of thyroid dysfunction associated with GnRH agonists, although our patient was male but with a strong genetic predisposition to autoimmune thyroid disease, as indicated by his family history of Hashimoto’s thyroiditis. Indeed, the autopsy findings revealed chronic lymphocytic thyroiditis that appeared to precede the GnRH agonist treatment.

Myxedema coma is an extreme expression of decompensated hypothyroidism with an underlying factor. The leading precipitating factors are infection, cardiovascular events, low body temperature, trauma, metabolic disturbances, and the use of certain drugs, such as anesthetics, sedatives, tranquilizers, and narcotics (8). In our case, the antihistamines prescribed for pruritus might have contributed to the myxedema coma because of their sedative effect. In addition, longtime exposure to cold and an upper respiratory infection might be precipitating factors. Myxedema coma remains a severe and life-threatening emergency with a mortality rate of 25% to 60% and complicated by multiorgan involvement, such as shock, cardiac tamponade, fatal arrhythmia, respiratory failure, renal failure, ileus, gastrointestinal bleeding, and disseminated intravascular coagulation (12). However, acute pancreatitis with myxedema coma has seldom been reported as a consequence of hypothermia. In a previous study that investigated the serum amylase levels in the hypothermic state among 15 patients with myxedema coma, 6 patients had elevated serum amylase levels, and 2 had high levels compatible with acute pancreatitis (13). Our patient may also have been affected by acute pancreatitis resulting from hypothermia, since the maximum serum amylase level was found on day 3 during hypothermia; the autopsy did not reveal other pathologies consistent with pancreatitis. In addition, the previously reported patients with acute pancreatitis complicated by hypothermia had no abdominal symptoms (13), similar to our patient in the early phase.

Although whether or not hypothermia is a clinically relevant risk factor for acute pancreatitis is controversial (14), elevations in the serum amylase levels are found in about half of patients with hypothermia (15), and autopsy reports describe various morphological alterations in pancreatic tissues in cases of death due to hypothermia. The reported pancreatic changes are diverse and include vacuoles, bleeding, and inflammation, as seen in our case. These alterations are not all specific to “hypothermic death”, although vacu-
oles in pancreatic adenoid cells appear to be a frequent and characteristic feature of the hypothermic state (16). The pathologies of these microscopic changes remain uncertain, although a hypothermic state has been speculated to induce dysfunction in the metabolism of pancreatic cells, leading to fragility and a loss of protection against auto digestion in the pancreas. In our case, hypoxia and ischemic injury (17) caused by refractory circulatory failure might have contributed to the development of acute pancreatitis. The microcirculatory failure in pancreas tissue, induced by disseminated intravascular coagulopathy associated with myxedema coma and hypothermia, might play an additional role in the development of pancreatic ischemia leading to acute pancreatitis (18).

In conclusion, the present report describes a patient with myxedema coma following the administration of a GnRH agonist for prostate cancer that was subsequently complicated by acute pancreatitis and massive retroperitoneal abscesses, which are speculated to be rare complications of myxedema coma. Although the outcomes in previous clinical studies do not support the routine screening of the thyroid function during GnRH agonist treatment, this case highlights the need to monitor the thyroid function in patients with pre-existing or a strong genetic predisposition to autoimmune thyroid disease, especially during the first six months after the initiation of GnRH agonist administration. Such monitoring is more important in elderly patients, due to the possibility of developing myxedema coma, especially since the number of older prostate cancer patients treated with GnRH agonist has been increasing as the population as a whole ages. Clinicians should also be alert for the onset of acute pancreatitis when managing myxedema coma in patients in a hypothermic state, since it represents a rare but potentially fatal complication and is often difficult to diagnose due to its lack of specific abdominal symptoms, as in the present case.

The authors state that they have no Conflict of Interest (COI).

References

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