Intractable hiccups as a rare gastrointestinal manifestation in severe endocrine and metabolic crisis: case report and review of the literature

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Abstract: Diabetic ketoacidosis (DKA) and thyroid storm (TS) are severe metabolic and endocrine disorders. Both usually manifest with multiple systemic clinical signs and symptoms, and digestive symptoms, such as nausea and vomiting, are most common in these patients. Moreover, the presence of a concurrent severe or rare complication may worsen the condition or even cause death due to misdiagnosis, delayed diagnosis, or inappropriate treatment. The identification of these symptoms is usually closely related to the severity and prognosis of the disease. Although clinical prognosis might be improved by prompt diagnosis and aggressive treatment, some rare and insidious metabolic complications are difficult to identify early. Moreover, life-threatening gastrointestinal symptoms are very rare in patients with DKA and TS. Here, we report an inpatient diagnosed with DKA and Graves’ disease who developed life-threatening intractable hiccups resulting in TS and respiratory failure during the treatment of DKA. In addition, we review the literature to discuss the possible underlying mechanism of intractable hiccups in the development of TS.

Keywords: diabetic ketoacidosis, Graves’ disease, intractable hiccups, thyroid storm

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Introduction

Endocrine and metabolic emergencies, such as diabetic ketoacidosis (DKA) and thyroid storm (TS) are life-threatening clinical conditions.1–3 Typical endocrine emergencies may be characterized by sudden onset with severe symptoms. Furthermore, prompt and aggressive treatment may significantly decrease mortality risk.4 DKA, one of the most common metabolic disease crises, occurs when there is insufficient insulin available for cellular uptake of glucose.5 Common clinical manifestations in patients with DKA are severe polyuria, polydipsia, dehydration, shock and even coma.6 In addition, nausea, vomiting, abdominal pain, acute gastrointestinal bleeding, hiccup and diabetic gastroparesis are uncommon digestive manifestations of DKA.7–9

TS is a relatively rare endocrine crisis but is probably misdiagnosed and mismanaged in many cases.10 Despite its rarity, TS has a significantly high mortality rate of over 10%.11 Common causes of TS are infection, surgery, discontinuation of anti-thyroid drugs and worsening mental and disease status in patients with Graves’ disease.12 Particularly when TS is complicated by DKA, the diagnosis of TS is usually delayed because the level of thyroid hormone is suppressed by some factors, such as fever.13 To the best of our knowledge, uncommon digestive complications as a cause of TS have not been reported in the literature. We herein report a rare digestive complication (intractable hiccups) during the treatment of DKA that resulted in TS and acute respiratory failure. Both DKA, TS and respiratory failure are severe clinical emergencies, which can result in high mortality without appropriate management. Although the condition is rare, the mortality rate is quite high. Thus, in severe cases, clinicians should pay close attention to the progress of rare endocrine emergencies with timely diagnosis and prompt treatment. In addition, we
review the literature to explore the possible underlying mechanism of intractable hiccups in the development of TS.

**Case presentation**

A 55-year-old female was transferred to the emergency department with chief complaints of nausea, vomiting and expectoration. In addition, she also presented with cough, palpitation, hyperhidrosis, dizziness, anorexia, poor sleep and weight loss of 5 kg. The patient had no history of diabetes but a recent diagnosis of hyperthyroidism with methimazole treatment (10 mg tid) in another hospital. Before referral from a community hospital, laboratory results revealed the following: pH 7.23; serum blood glucose level 15.4 mmol/L; β-hydroxybutyric acid level 4.0 mmol/L (normal reference range of 0.0–1.0 mmol/L); and severely positive urine ketones. The patient was diagnosed with DKA, type 2 diabetes, hyperthyroidism and upper respiratory tract infection in the community hospital.

The patient was admitted with signs of dehydration; she was awake and alert, ill looking, had an

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**Table 1.** Laboratory examination on admission.

| Laboratory Examination | Blood count | Reference |
|------------------------|-------------|-----------|
| Blood glucose (mmol/L) | 7.82        | 3.9–6.1   |
| Haemoglobin A1c (%)    | 110         | 4.0–6.5   |
| GAD antibody          | (–)         | (–)       |
| IA-2 antibody         | (–)         | (–)       |
| Serum beta-hydroxybutyric acid | 3 | 0.0–1.0 |
| Urinary ketone bodies | (+ +)       | (–)       |
| Plasma osmolarity (mOsm/L) | 292 | 280–320 |
| Arterial blood gas analysis | *PH* | 7.23 | 7.35–7.45 |
| PCO₂ (mmHg) | 26.4 | 35.0–45.0 |
| PO₂ (mmHg) | 105.9 | >75 |
| Bicarbonate (mmol/L) | 16.1 | 21.3–24.8 |
| Base excess (mmol/L)  | –10.5 | –3–+3 |
| Lactic acid (mmol/L)  | 0.52 | 0.60–2.20 |

**Blood chemistry**

| Blood count | Reference |
|-------------|-----------|
| WBC (G/L)   | 14.61     |
| NGP [%]     | 83.6      |
| RBC (T/L)   | 5.02      |
| Haemoglobin [g/L] | 138 | 115–150 |
| Platelet [G/L] | 192 | 125–350 |
| AST (U/L)   | 25        |
| ALT (U/L)   | 22        |
| LDH (U/L)   | 228       |
| GGT (U/L)   | 15        |
| CK (U/L)    | 75        |
| BUN (mmol/L)| 2.65      |
| Creatinine (µmol/L) | 30.1 | 35.0–81.0 |
| Sodium (mmol/L) | 137.3 | 135–145 |
| Lactic acid (mmol/L) | 3.5 | 3.5–5.0 |
| Potassium (mmol/L) | 98.1 | 99.0–110.0 |
| hsCRP (mg/L) | 0.9 | 0.0–3.0 |
| Procalcitonin (ng/mL) | 0.04 | 0.0–0.05 |

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatinine kinase; GGT, γ-glutamyl transferase; hsCRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; NGP, neutrophilic granulocyte percentage; PCO₂, partial pressure of carbon dioxide; PO₂, partial pressure of oxygen; RBC, red blood cell; WBC, white blood cell; G/L, 10⁹/L; T/L, 10¹²/L; PH, Pondus Hydrogenii.
active position, and answered correctly to inquiries; her body mass index was 24.4 kg/m². Regarding vital signs, she had a body temperature of 36.9°C, blood pressure of 146/80 mmHg, heart rate of 105 beats/min and respiration rate of 20 times/min. The thyroid gland showed no enlargement or murmur. Her breast sound was rough. Assessments of muscular strength, visual fields and postural tremor were unremarkable.

Based on whole blood count analysis, the total amount of leucocytes was $14.61 \times 10^9$/L, and the percentage of neutrophil granulocytes was 83.6%. The blood lactic acid level was 1.02 mmol/L (the normal reference range was 0.60–2.20 mmol/L). High-sensitivity C-reactive protein was 0.9 mg/L, and serum procalcitonin was 0.04 ng/mL (Table 1). Urinalysis, electrocardiography, and liver and kidney function analyses were unremarkable. Thyroid ultrasound scanning showed a normal size with a heterogeneous, reduced echo and abundant flow signals, with no nodules. Thyroid function tests revealed very high tri-iodothyronine and thyroxine levels under the normal range of undetectable thyroid-stimulating hormone (Table 2). Immediate treatments included rehydration, anti-infection (levofloxacin, 0.6 g intravenous guttae qd), glycaemic control and anti-thyroid therapy (methimazole and propranolol). Her blood glucose was adjusted to the range of 5.0–14.0 mmol/L; blood plasma $\beta$-hydroxybutyric acid was controlled at approximately 1.1–3.8 mmol/L.

On the second day of hospitalization, the patient exhibited extremely sudden hiccups, profuse sweating and nausea with a high fever (39.8°C). Her heart rate was 170 beats/min (sinus rhythm). The following was sequentially implemented: fever control, metoclopramide (10 mg injection intramuscular bid), omeprazole (40 mg intravenous guttae q12h), hydrotalcite, domperidone, promethazine (25 mg injection intramuscular bid), chlorpromazine (500 mg intravenous guttae q12h), acupuncture, continuous infusion of traditional herbal drugs (Yi Wei Tang, the soup beneficial to stomach), esmolol (intravenous guttae 0.05 mg/kg per min–0.25 mg/kg per min) and rhubarb enema. Intractable hiccups were not controlled but progressively worsened. Brain computed tomography scan and magnetic resonance imaging revealed no acute haemorrhagic or ischaemic lesions. Abdominal computed tomography scan, chest X-ray and cerebrospinal fluid examination also were negative. On the fourth day of hospitalization, the intractable hiccups progressively worsened, accompanied by mental changes. TS was diagnosed based on the Burch–Wartofsky score (total score of 60). The patient was immediately treated with hydrocortisone (100 mg/6h), propylthiouracil (200 mg/6h), propranolol (20 mg/8h), paracetamol and intravenous fluids. On the sixth day of hospitalization, her intractable hiccups were still not controlled and she developed respiratory failure. Transcutaneous oxygen saturation quickly decreased to 47% (under continuous and high flux inhalation of oxygen with a facemask). Tracheal intubation was immediately performed, with artificial ventilation, and the patient became tranquil and calm. Her hiccups gradually slowed. De-ventilator and extubation were conducted after 1 week of treatment. According to the clinical manifestations and experimental examination results, Graves’ disease (Table 2, Figure 1) was definitively diagnosed. The dosages of hydrocortisone, propranolol and propylthiouracil were reduced gradually, and her free T4 and T3 levels were nearly normal after 16 days of therapy (Table 2). She was maintained on a treatment with propylthiouracil (with a discharge dose of 100 mg bid) and propranolol (with 20 mg tid). She had completely recovered from her intractable hiccups 2 weeks later, and her metabolic parameters of diabetes had improved significantly. Her pulse rate was 84 beats/min, blood pressure was 118/70 mmHg, and temperature was 36.5°C when she was discharged. After a 1-year follow-up in the endocrinology department, the patient had no recurrence of hiccups.

| Items                          | The first day | The second week | The third week | Reference range |
|-------------------------------|--------------|-----------------|----------------|----------------|
| TT3 (nmol/L)                  | 1.84         | 0.738           | 0.695          | 1.30–3.1       |
| TT4 (nmol/L)                  | 226.2        | 98.51           | 81.56          | 66.0–181.0     |
| FT3 (pmol/L)                  | 5.78         | 2.67            | 2.91           | 3.1–6.8        |
| FT4 (pmol/L)                  | 73.07        | 17.76           | 13.58          | 12.0–22.0      |
| TSH (mIU/L)                   | <0.005       | <0.005          | 0.098          | 0.27–4.2       |
| TG (ng/mL)                    | 33.84        | 20.27           | 18.2           | 3.50–77.0      |
| TRAb (IU/L)                   | -            | 3.06            | 3.77           | 0.000–1.75     |

**Table 2. Thyroid function tests.**

FT3, free triiodothyronine; FT4, free thyroxine; TRAb, thyrotropin receptor antibody; TT3, triiodothyronine; TT4, thyroxine; TSH, thyroid-stimulating hormone.
Discussion and literature review

The incidence of endocrine emergencies is quite low but not negligible because once it occurs, the mortality is very high. DKA is a severe metabolic crisis induced by absolute or relative insufficiency of insulin activity, which is mainly associated with type 1 diabetes. However, DKA is increasingly recognized in patients with type 2 diabetes in recent years. The incidence of hospital admission for DKA increased from 0.70 to 0.98 per 1000 person-years in adults with T2DM.\(^{15}\) One in five cases of DKA is reported to have a history of type 2 diabetes, which leads to higher mortality, with infection, myocardial infarction and stroke as triggering factors in these patients.\(^{16,17}\) It is noted that some DKA cases caused by type 2 diabetes may not have an obvious precipitating cause.\(^{18–20}\)

Hiccups are usually benign and self-limiting. Intractable hiccups is hiccups lasting more than 48 h.\(^{21}\) Intractable hiccups may produce significant discomfort and may also represent the clinical manifestation of life-threatening clinical conditions such as lateral medullary lesions, myocardial infarction, respiratory failure and pulmonary embolism.\(^{22}\) Hiccups are caused by stimulation of the diaphragm, phrenic nerve, vagus nerve, or central nervous system, causing paroxysmal spasm of one or both the diaphragm and intercostal muscle or anterior scalene muscle.\(^{23}\) Hiccups refers to a short, loud sound accompanied by a sudden closing of the glottis during inhalation.\(^{24}\) Intractable hiccups can cause severe anxiety, depression, reduced physical strength, respiratory failure and even death without timely treatment. Previous studies have
revealed that cerebrovascular disorders, intracranial infectious diseases, severe pneumonia, uremia, gastrointestinal problems, toxic or metabolic disorders and DKA all can cause intractable hiccups.25,26

TS has been reported in 0.20 people per 100,000 in the Japanese population annually and occurs in 0.22% of patients with thyrotoxicosis.27 TS is a life-threatening exacerbation of hyperthyroidism that has a very high mortality rate of 8–25%.12,28 Symptoms and signs of endocrine crisis may overlap with those of other severe disease states. In general, failure to recognize endocrine crises results in delayed diagnosis, and a lack of rapid specific therapy may have fatal consequences.10,29 Therefore, the early identification of TS is very important to reduce the mortality rate. TS is characterized by decompensation of multiple organ functions, leading to severe clinical manifestations such as high fever, disturbed consciousness, marked tachycardia, congestive heart failure, and gastrointestinal and hepatic disturbances.30 TS usually occurs in patients with previously undiagnosed or poorly treated hyperthyroidism, even subclinical hyperthyroidism.13 Graves’ disease is a leading cause of TS and may be the first clinical presentation.14,31 The usual cause of TS is associated with infection, withdrawal of anti-thyroid drugs, radioiodine therapy, surgical procedure and severe emotional stress.32 Common clinical manifestations are central nervous system manifestations and gastrointestinal symptoms, including nausea, vomiting, diarrhoea and abdominal pain. Diarrhoea is the most common gastrointestinal symptom in thyrotoxicosis as well as in TS.11 The literature related to TS was searched from 2016 to 2019, and the clinical characteristics of gastrointestinal symptoms in patients with TS were found to mainly be nausea, and the main cause of TS to be Graves’ disease with unknown or poor compliance with anti-thyroid drugs (Table 3).33-46

Considering that hiccups are not common in either DKA or TS, we speculate that the incidence of intractable hiccups is rare when DKA overlaps with TS. By carefully searching the literature, we found the following related cases. A case of TS associated with Graves’ disease masked by DKA in a 59-year-old woman was reported by Osada et al.47 However, this patient had no history of diabetes, Graves’ disease or respiratory failure compared with the present patient. Management of the functional gastrointestinal tract in patients with severe thyrotoxicosis represents a difficult but significant clinical challenge associated with a high mortality rate.48 Monteiro et al. reported a 70-year-old male who was diagnosed with type 2 diabetes and TS. The patient presented gastrointestinal and neurologic symptoms such as nausea, vomiting, asthenia, psychomotor retardation and generalized decrease in muscle strength but no hiccups.34 Ahmed et al. reported a case of hiccups as an extremely rare presentation of thyrotoxicosis in Graves’ disease.49 To the best of our knowledge, this is the first case of a woman with DKA who developed TS by intractable hiccups that subsequently induced respiratory failure.

In the present case, evaluation results on the usual causes of intractable hiccups were negative. Firstly, we excluded almost all neurologic causes with computed tomography (CT) scan, magnetic resonance (MR) imaging and cerebrospinal fluid examination. Neither acute haemorrhagic nor ischaemic lesions was found in the patient. Secondly, because area postrema syndrome, as one typing of neuromyelitis optica, may be characterized by intractable hiccup, nausea and vomiting that cannot be explained by other causes, MR imaging shows a T2-hyperintense in dorsal medulla/area postrema lesion,50 the cause of hiccup in this patient should be considered. However, AQP4-IgG monitoring was not conducted because MR imaging did not show positive manifestation, and cerebrospinal fluid examination was not found abnormal. Importantly, the hiccup was eventually relieved after aggressive treatment on TS. All these do not support the diagnosis of neuromyelitis optica. Thirdly, negative CT scan of chest excluded pleurisy, pneumonia, enlarged lymph nodes, mediastinitis, mediastinal tumour. Fourthly, some digestive system diseases which may cause hiccup, such as abdominal abscess, pancreatitis, biliary tract diseases, abdominal tumours, intestinal obstruction, have been excluded with clinical manifestation and CT scan of the abdomen. Gastroscopy was not performed because the patient’s severe clinical condition would not have tolerated it. Furthermore, proton pump inhibitor and gastric mucosal protectants cannot take effect to hiccups, which was supported that peptic ulcer, gastritis, duodenitis might not be the reason of hiccups. Finally, acute myocardial infarction was not considered because the patient’s clinical symptoms,
Table 3. The literature review of clinical characteristics in thyroid storm.

| Authors                  | Number of case | Basic information | Inducement                                   | Clinical manifestation                                      | Physical examination                                         | Burch-Wartofsky score | Aetiology                                                                 |
|--------------------------|----------------|-------------------|----------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|------------------------|---------------------------------------------------------------------------|
| Jorge I Conte            | 1              | 32-year-old female| Sexually assaulted and strangled            | Nausea, shortness of breath                                | Proptosis, ocular chemosis, and soft tissue swelling of the neck | 75                     | Unknown Graves’ disease                                                   |
| Ana Margarida Monteiro   | 1              | 70-year-old male  | Not mentioned                               | Nausea and vomiting, asthenia, anorexia, dysphagia        | Postural tremor                                             | 50                     | Unknown Graves’ disease                                                   |
| Toshiyuki Ikeoka         | 1              | 46-year-old female| Influenza A                                  | Nausea                                                     | A diffuse goitre with bilateral exophthalmoses             | 55                     | Graves’ disease, poor compliance with anti-thyroid drugs                  |
| Sabir AA                 | 1              | 30-year-old female| Not mentioned                               | Vomiting                                                   | Lid lag, exophthalmos, and goitre with a bruit             | 50                     | Graves’ disease, non-compliant with medication and follow-up              |
| You-Wen Tan              | 1              | 52-year-old female| Not mentioned                               | Nausea and vomiting accompanied by yellowing of the skin and mucosa | Not mentioned                                              | Not mentioned          | Not mentioned                                                             |
| Ba JH                    | 1              | Female            | Not mentioned                               | Nausea, vomiting, abdominal pain with diarrhoea           | Ocular proptosis, bilateral thyroid gland swelling         | 40                     | Unknown Graves’ disease                                                   |
| Takehara T               | 1              | 50-year-old male  | Not mentioned                               | Chronic diarrhoea                                          | An exophthalmos; the thyroid gland was soft and diffusely enlarged | Not mentioned           | Basedow’s disease, thyroid abscess caused by *Helicobacter cinaedi*       |
| Yonezaki K               | 1              | 85-year-old male  | Combination therapy of ipilimumab and nivolumab | Nausea, vomiting                                          | A diffuse goitre without exophthalmoses                    | 60                     | Hashimoto’s disease                                                       |
| Godo S                   | 1              | 30-year-old female| Diffuse peritonitis secondary to duodenal perforation; underwent an emergency operation | Sudden onset of abdominal pain                           | Diffuse goitre                                             | 95                     | Unknown Graves’ disease                                                   |
| Sophie Degrauwe          | 1              | 70-year-old female| Urgent percutaneous coronary intervention for acute coronary syndrome | Nausea and vomiting                                       | Not mentioned                                              | 55                     | Amiodarone-induced thyrotoxicosis                                         |
| Kiriyama H               | 1              | 54-year-old female| Not mentioned                               | Nausea and vomiting                                        | Not mentioned                                              | Not mentioned          | Unknown Graves’ disease                                                   |
| Salih AM                 | 1              | 29-year-old male  | Cough and generalized body ache             | Vomiting                                                   | Neck was tender in the area of the thyroid gland, mostly at the right side | 75                     | Subacute thyroiditis                                                      |
| Jack M                   | 1              | 32-year-old female| Postpartum                                  | Nausea                                                     | Not mentioned                                              | 60                     | Graves’ disease, poor compliance with anti-thyroid drugs                  |
| Zeng F                   | 1              | 36-year-old male  | Had caught a cold                           | Diarrhoea                                                  | The thyroid gland was diffusely enlarged without pain      | Not mentioned          | Graves’ disease                                                           |
electrocardiogram and myocardial zymogram were not supported.

DKA can cause hiccups, although this is quite rare in clinical practice and the mechanism is also not clear. Therefore, we speculate that the intractable hiccups in the present patient was likely caused by severe endocrine and metabolic diseases. The other possible reason is that intractable hiccups may be an early rare clinical manifestation in patients with TS.

TS manifests as multiple organ dysfunction syndrome often triggered by severe conditions, including accompanying illness, radiation thyroiditis, DKA, toxaemia of pregnancy or perioperative events. The diagnosis of TS is usually based on the Burch–Wartofsky score in patients with severe and life-threatening manifestations of hyperthyroidism. DKA concurrent with TS is relatively uncommon in clinical practice; it commonly occurs in patients with type 1 diabetes but not type 2 diabetes. Based on weight status, glycated haemoglobin of 11% and the oral glucose tolerance test, the present patient was diagnosed with type 2 diabetes. Examination results on admission suggested that her hyperthyroidism and blood glucose were poorly controlled. Acute tracheobronchitis is a common high-risk factor for DKA and TS that is worsened by abnormal glucose metabolism and increased oxygen consumption. DKA can be effectively corrected by fluid infusion and glucose control. Treatment goals for TS are reduction of thyroid hormone synthesis and secretion of thyroid hormones, control of peripheral effects, resolution of systemic manifestations and treatment of the precipitating illness. In our case, hydrocortisone was immediately used to control the peripheral effects of thyroid hormone, and the synthesis and secretion of thyroid hormone was inhibited by propylthiouracil. Nonetheless, a long time, approximately five half-lives of thyroid hormones, may be needed for thyroid function to recover from TS, until thyroid hormone production has been suppressed by anti-thyroid medications. The half-life of thyroid hormones is as long as 6.7 ± 0.7 days in normal subjects but 4.4 ± 1.1 days in patients with hyperthyroidism. Thus, upper respiratory tract infection and continuous gastrointestinal disease worsen the condition and cause the disease state to develop into a vicious circle. In the hyperthyroid state, the insulin level decreases because of the increase in the glomerular filtration rate, and the ratio of C-peptide to proinsulin is very low. These factors aggravate the underlying abnormal glucose metabolism and intensify insulin deficiency, which in this case served as a trigger for the onset of DKA. It has been reported that the identification of TS tends to be delayed in patients with DKA because of suppression by fever and relatively low thyroid hormone levels. Our patient presented a high fever even after DKA was corrected, and this clinical presentation might delay the diagnosis of TS. In addition, thyroid hormones may decrease the possible compensation mechanism, leading to multi-organ dysfunction.

As to the therapeutic measures of intractable hiccups, a wide range of treatment attempts have been conducted, including pharmacological and non-pharmacological, to this date. However, chlorpromazine remains the only Food and Drug Administration-approved drug in this context due to the lack of large-scale studies on efficacy and tolerance of other therapeutic strategies. Gabapentin, baclofen and metoclopramide have been reported to accomplish promising results in reports on the therapy of persistent singultus; they may also be effective when given in combination with other drugs, for example, proton pump inhibitors, prokinetics or as conjoined therapy. As another approach of note, acupuncture treatment was able to abolish hiccups in a number of studies. In therapy-refractory cases, invasive procedures such as the selective phrenic nerve block are available. More studies are needed to help deal with the diagnostic and therapeutic challenges that hiccups presents for clinicians. Finally, we successfully saved the patient’s life with artificial ventilation under general anaesthesia to correct respiratory failure as well as intractable hiccups.

Conclusion
DKA and TS are potentially life-threatening endocrine emergencies, with high morbidity and mortality if not promptly recognized and treated. When DKA is accompanied by TS, it is essential to consider the possibility of coexisting rare complications with uncommon clinical manifestations.

In general, endocrine emergencies have a rapid and aggressive clinical course and pose significant diagnostic challenges. Physicians should be aware of possible presenting features and diagnose and manage promptly to prevent life-threatening severe complications.
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Conflict of interest
The authors declare that there is no conflict of interest.

Ethics statement
This is a case report with a review of the literature for which the patient signed informed consent, providing her approval for publication.

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