Concomitant Revelation of Graves' Disease During Diabetic Ketoacidosis: Report of Two Clinical Cases.

Abstract

Introduction

Type 1 diabetes mellitus (T1DM) and autoimmune thyroid diseases, particularly Graves' disease, are frequently associated within the framework of autoimmune polyglandular syndrome type 3 variant (APS3v). Approximately 15–30% of patients with T1DM develop autoimmune thyroid disease; however, the concomitant occurrence of diabetic ketoacidosis (DKA) and Graves' disease remains exceptional. This complex association may delay the diagnosis of hyperthyroidism, as its clinical manifestations can be masked by the symptoms of diabetic ketoacidosis.

Case Reports

Two female patients aged 26 and 28 years, followed for type 1 diabetes mellitus, were admitted to the intensive care unit for confusion, vomiting, diarrhea, and polyuria. The diagnosis revealed diabetic ketoacidosis associated with Graves' disease, consistent with APS3v.
In both patients, DKA was characterized by the severity of ketosis, difficulty in management, and the absence of an identifiable precipitating factor. Treatment included fluid resuscitation, insulin therapy, and correction of electrolyte disturbances.
A thyroid work-up, prompted by the persistence of atypical clinical signs (tachycardia up to 180 bpm and polyuria of 4 L/day), led to the diagnosis of hyperthyroidism. Both patients were treated with carbimazole and beta-blockers, resulting in clinical improvement.

Discussion

This rare association between diabetic ketoacidosis and Graves' disease highlights the importance of systematic screening for autoimmune disorders in patients with type 1 diabetes presenting with atypical symptoms. Furthermore, genetic studies may play a key role in identifying high-risk HLA profiles, allowing better prediction of APS3v.

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Introduction

Type 1 diabetes mellitus (T1DM) and autoimmune thyroid diseases, particularly Graves' disease and Hashimoto's thyroiditis, are common autoimmune endocrinopathies. When they coexist in the same patient, they fall within the spectrum of autoimmune polyglandular syndrome type 3 variant (APS3v) [1].

Epidemiological data suggest a shared genetic predisposition between T1DM and autoimmune thyroid diseases. Among patients with T1DM, 15–30% develop autoimmune

thyroid involvement, either Graves' disease or Hashimoto's thyroiditis [2]. However, the simultaneous onset of newly diagnosed T1DM and Graves' disease remains rare.

As autoimmunity is more prevalent in women, approximately 80% of hyperthyroidism cases occur in females. Overall, about 1% of adults with T1DM will develop hyperthyroidism, with Graves' disease being the most common etiology. Nevertheless, the concomitant presentation of inaugural T1DM with diabetic ketoacidosis and Graves' disease is exceptional and represents a major diagnostic and therapeutic challenge.

In this context, the diagnosis of Graves' disease may be delayed, as its clinical manifestations can be masked by diabetic symptoms, particularly in cases of severe glycemic imbalance. In diabetic patients presenting with unusual or persistent symptoms despite appropriate management, an associated autoimmune disorder should be considered.

We report two clinical cases of patients with T1DM who presented with severe diabetic ketoacidosis, leading to the concomitant diagnosis of Graves' disease. These observations highlight the importance of rigorous clinical assessment and close endocrine monitoring in diabetic patients with atypical presentations.

Case 1

A 26-year-old woman, followed for type 1 diabetes mellitus for 8 years and treated with a basal-bolus insulin regimen, was admitted to the intensive care unit for diabetic ketoacidosis. Clinical presentation was dominated by vomiting, diarrhea, polyuria-polydipsia syndrome, and confusion.

Physical examination revealed a somnolent patient with a Glasgow Coma Scale score of 13/15, fever of 38°C, sinus tachycardia at 180 bpm, tachypnea at 26 breaths/min, generalized abdominal tenderness, and urine output reaching 15 L/day.

Initial laboratory investigations confirmed diabetic ketoacidosis, with capillary blood glucose of 2.44 g/dL, ketonuria (+++), leukocytosis at 13,300/mm³, C-reactive protein at 43 mg/L, and hyperlipasemia at 666 IU/L.

The patient received fluid resuscitation with replacement of losses, insulin therapy, and correction of electrolyte disturbances. Improvement in consciousness and metabolic acidosis was observed; however, persistent polyuria (4 L/day) and tachycardia (160 bpm) remained.

A thyroid function test revealed suppressed TSH at 0 µIU/mL, elevated free T4 at 2.04 ng/dL, elevated free T3 at 4.42 pg/mL, and positive TSH receptor antibodies at 36 IU/L.

Treatment with carbimazole (60 mg/day) and beta-blockers was initiated. After four weeks, the patient showed good tolerance, normalization of heart rate, and resolution of polyuria.

Case 2

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A 28-year-old woman with type 1 diabetes mellitus for 5 years, who had experienced two episodes of acute diabetic decompensation, was admitted to the intensive care unit. Clinical symptoms included vomiting and diarrhea.

On examination, the patient was somnolent, tachycardic at 111 bpm, and afebrile (temperature 37°C).

Laboratory tests confirmed diabetic ketoacidosis, with capillary blood glucose of 1.93 g/dL, ketonuria (+++), leukocytosis at 20,200/mm³, C-reactive protein at 18 mg/L, negative procalcitonin, and bicarbonate levels below 5 mmol/L.

Thyroid function tests showed suppressed TSH at 0 µIU/mL, elevated free T4 at 1.6 ng/dL (normal range 0.70–1.48), and elevated free T3 at 4.74 pg/mL (normal range 1.71–3.71). The clinical course was marked by normalization of thyroid function following treatment.

Discussion

The association between type 1 diabetes mellitus and Graves' disease within the framework of autoimmune polyglandular syndrome type 3 variant is well documented but remains uncommon, particularly when both diseases occur simultaneously.

The concomitant occurrence of diabetic ketoacidosis and thyrotoxic crisis is rare but potentially fatal, with a reported mortality rate of up to 15% [3]. Their simultaneous presentation appears to be favored by shared predisposing factors, including physiological stress, infections, and especially poor adherence to antidiabetic treatment, which is the main precipitating factor of diabetic ketoacidosis [4].

Horie et al. reported that among 30 Japanese patients with APS3v, 10% developed both diseases simultaneously, 60% developed Graves' disease before T1DM, and 30% developed T1DM first [5]. A study of 60 cases of autoimmune polyglandular syndrome type IIIa over 27 years showed that the time interval between autoimmune diseases depended on the order of their occurrence. The mean interval between diabetes and thyroid disease (10.3 years) was longer than that between thyroid disease and diabetes (4.3 years), with a significant difference ($p = 0.02$) [6].

Osaki et al. reported that among 10 patients with APS3v, 9 developed Graves' disease before T1DM, and only one presented the reverse sequence [7]. In reported cases of acute T1DM associated with Graves' disease, hyperthyroidism generally precedes diabetes [7]. These data confirm that simultaneous onset is rare, making our cases particularly noteworthy.

Hyperthyroidism plays a key role in worsening metabolic imbalance in diabetic patients. It promotes hyperglycemia by increasing intestinal glucose absorption, stimulating hepatic glycogenolysis and gluconeogenesis, and reducing peripheral insulin sensitivity [8]. The use of propranolol may further aggravate glucose intolerance [9]. In addition, increased glomerular filtration rate enhances insulin clearance, contributing to relative insulin deficiency and promoting ketogenesis [10].

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The lipolytic effect of hyperthyroidism also increases ketone body production by enhancing hepatic fatty acid oxidation [11]. These mechanisms explain how hyperthyroidism can precipitate diabetic ketoacidosis by exacerbating underlying insulin deficiency [12]. Our patients illustrate this pathophysiological interaction, presenting with severe initial metabolic decompensation.

APS3v is based on a shared immunogenetic background between T1DM and Graves' disease. HLA susceptibility genes, particularly DR3 and DR4, play a major role in these conditions [13]. Non-HLA genes such as CTLA4, PTPN22, and FOXP3, involved in T-cell regulation, are also associated with an increased risk of developing these diseases [13].

Ethnic variations in genetic predisposition may explain differences in the frequency and chronology of disease onset [14]. For example, the DRB1*04:05–DQA1*03:03–DQB1*04:01 haplotypes found in our patients are not specific to simultaneous disease onset but are commonly implicated in APS3v [7].

Early recognition of the T1DM–Graves' disease association is essential to prevent severe metabolic complications. Diagnosis may be delayed due to the complex interactions between the two conditions, as hyperthyroidism can mask certain diabetic symptoms or worsen pre-existing glycemic instability [12].

Management should be multidisciplinary and include:

- Rapid control of hyperthyroidism (antithyroid drugs, beta-blockers, and radical treatment if necessary);
- Adjustment of insulin therapy according to metabolic fluctuations related to thyrotoxicosis;
- Close monitoring of drug interactions between antithyroid and antidiabetic treatments [12].

Given the rarity of this association, prospective studies are difficult to conduct; however, continued reporting of new cases is essential to improve understanding and optimize management strategies. Enhanced surveillance of patients with diabetes and hyperthyroidism is therefore crucial, along with therapeutic education to improve adherence to treatment.

Conclusion

The association between type 1 diabetes mellitus and Graves' disease within the framework of autoimmune polyglandular syndrome type 3 variant is based on shared immunological and metabolic mechanisms. Although Graves' disease usually precedes T1DM, our cases illustrate a rare situation in which both conditions occur simultaneously, leading to severe metabolic decompensation.

Hyperthyroidism plays a decisive role in worsening glycemic instability and may precipitate diabetic ketoacidosis. Early recognition and appropriate management are therefore essential to limit complications. Systematic screening for thyroid disorders in diabetic patients, particularly in cases of unexplained glycemic imbalance, allows early diagnosis and prevention of severe metabolic complications.

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