

Ketosis-prone diabetes and SLE co-presenting in an African lady with previous gestational diabetes

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Summary

We describe the case of an African woman who was diagnosed with ketosis-prone diabetes with diabetes-associated autoantibodies, after being admitted for diabetic ketoacidosis (DKA) precipitated by her first presentation of systemic lupus erythematosus (SLE). She had a seven-year history of recurrent gestational diabetes (GDM) not requiring insulin therapy, with return to normoglycaemia after each pregnancy. This might have suggested that she had now developed type 2 diabetes (T2D). However, the diagnosis of SLE prompted testing for an autoimmune aetiology for the diabetes, and she was found to have a very high titre of GAD antibodies. Typical type 1 diabetes (T1D) was thought unlikely due to the long preceding history of GDM. Latent autoimmune diabetes of adults (LADA) was considered, but ruled out as she required insulin therapy from diagnosis. The challenge of identifying the type of diabetes when clinical features overlap the various diabetes categories is discussed. This is the first report of autoimmune ketosis-prone diabetes (KPD) presenting with new onset of SLE.

Learning points:

- DKA may be the first presentation of a multi-system condition and a precipitating cause should always be sought, particularly in women with a history of GDM or suspected T2D.
- All women with GDM should undergo repeat glucose tolerance testing postpartum to exclude frank diabetes, even when post-delivery capillary blood glucose (CBG) tests are normal. They should also be advised to continue CBG monitoring during acute illness in case of new onset diabetes.
- KPD comprises a spectrum of diabetes syndromes that present with DKA, but subsequently have a variable course depending on the presence or absence of beta cell failure and/or diabetes autoantibodies.
- KPD should be considered in a patient with presumed T2D presenting with DKA, especially if there is a personal or family history of autoimmune diabetes.
- LADA should be suspected in adults presumed to have T2D, who do not require insulin therapy for at least six months after diagnosis and have anti-GAD antibodies.
- Patients with autoimmune diabetes have an increased risk of other autoimmune diseases and screening for thyroid, parietal cell, coeliac and antinuclear antibodies should be considered.

Background

Diabetes mellitus is a common condition characterised by chronic hyperglycaemia. Traditionally, diabetes was classified according to age at diagnosis and the need for

insulin therapy as type 1 (insulin dependent with onset in childhood, often with diabetes-associated autoantibodies) and type 2 (adult onset, not insulin dependent) forms.



This is now known to be a major oversimplification and many hybrid forms exist (1).

LADA is one such hybrid. LADA is a form of autoimmune diabetes (also known as type 1.5 diabetes or slowly progressive insulin-dependent diabetes mellitus (SPIDDM)) with onset in adulthood, but insulin treatment is not required for a period after diagnosis.

DKA is usually seen as a presenting feature or complication of T1D due to insulin deficiency, but DKA may also occur in T2D during acute infection or other stress, when it should always prompt review of the original diabetes classification, particularly in younger, slim patients (2).

KPD is another hybrid form of diabetes in which patients present with DKA, but most patients do not remain insulin dependent lifelong. Also known as Flatbush diabetes after the USA suburb in which it was first described, KPD is more common in Afro-Caribbean patients.

GDM is a state of insulin resistance causing hyperglycaemia in the second or third trimester of pregnancy, often requiring insulin therapy. GDM tends to recur in future pregnancies and confers a greater risk to the mother of developing T2D in later life.

With an increasing variety of diabetes presentations and pathogenic mechanisms being recognised, identifying the type of diabetes at diagnosis to plan treatment can present a dilemma.

Here, we describe one such case – a patient with a history of recurrent GDM who presented postpartum in DKA with autoimmune diabetes and SLE.

Case presentation

A 26-year-old African woman presented to the emergency department six weeks postpartum with a four-day history of left-sided pleuritic chest pain and progressive breathlessness.

The pregnancy had been complicated by GDM treated with metformin and by pre-eclampsia necessitating induction of labour at 34 weeks. After delivery, she remained euglycaemic on no glucose-lowering therapy. She was discharged home on Labetalol for blood pressure control and advised to return in six weeks for an oral glucose tolerance test.

This had been her fourth pregnancy, GDM having been diagnosed in the final trimester of all except her first pregnancy. Insulin therapy had not been required in any of the GDM pregnancies. She had no history of miscarriage or thromboembolism and no personal or family history of autoimmune disease or diabetes.

On further questioning, she gave a one-month history of drenching night sweats and feeling feverish. There had been no unusual weight loss, cough or haemoptysis. Her last foreign travel had been to the Congo five years earlier, and she had no known contact with tuberculosis.

Bedside observations demonstrated a slim woman (weight 58.9 kg), with a resting tachycardia (118 bpm), low grade pyrexia (37.8°C), reduced oxygen saturation (78% on room air) and normal blood pressure of 114/79 mmHg. Examination revealed an elevated jugular venous pressure (5 cm), left-sided chest wall tenderness, a pansystolic murmur and left basal crepitations. There was no oedema, peripheral stigmata of endocarditis or signs of deep vein thrombosis. Abdominal, thyroid, neurological and musculoskeletal examinations were all unremarkable.

Investigation

Arterial blood gas analysis on 15 L of oxygen administered via a non-rebreathing mask confirmed a relative hypoxaemia, a marked metabolic acidosis with hyperglycaemia and a raised anion gap (pH: 7.16, pCO₂: 3.33 kPa, pO₂: 33.1 kPa, HCO₃: 8.1 mmol/L, base excess: –22.6 mmol/L, lactate: 0.4 mmol/L, glucose: 18 mmol/L). Blood ketones were elevated at 5.3 mmol/L.

Portable chest radiograph demonstrated cardiomegaly and resting ECG showed a sinus tachycardia.

A urinary pregnancy test was negative and a urine dipstick was positive for blood (3+), protein (3+), glucose (4+) and ketones (3+).

Venous blood tests revealed a microcytic anaemia, mild neutrophilia and elevated D-dimers and C-reactive protein (Table 1). Liver and kidney function and TSH were normal. Paracetamol and salicylate levels were undetectable, and she tested negative for HIV.

CTPA excluded pulmonary embolism, but did identify a pericardial effusion, bilateral small pleural effusions with atelectasis and bilateral axillary lymphadenopathy (up to 2.1 cm).

Treatment

The patient was treated for DKA and possible lower respiratory tract infection with oxygen, intravenous fluids, fixed rate intravenous insulin (0.1 units/kg/h (6 units/h)) and antibiotics. She required 8 L of intravenous fluids over 24 h. She was transferred to the intensive care unit for close monitoring, where she responded well to treatment, and 24 h later was stepped down to a medical ward.

Table 1 A table summarising the patient's blood results, at presentation, with normal laboratory reference ranges.

Laboratory tests	Values	Normal range
Haemoglobin	10.4	12–15 g/dL
Mean corpuscular volume	70.1	83–101 fL
White cell count	11.7	4–10 × 10 ⁹ /L
Neutrophils	7.8	2–7 × 10 ⁹ /L
Platelets	198	150–410 × 10 ⁹ /L
Sodium	132	133–146 mmol/L
Potassium	4.1	3.5–5.3 mmol/L
Urea	2.3	2.5–7.8 mmol/L
Creatinine	71	62–106 mmol/L
Bilirubin	5	5–21 µmol/L
Alkaline phosphatase	124	30–130 IU/L
Alanine aminotransferase	7	0–35 IU/L
D-dimers	3.58	0–0.44
C-reactive protein	161.2	0–10 mg/L
Blood ketones	5.3	
Bicarbonate	8.1	22–29 mmol/L
Thyroid-stimulating hormone (TSH)	1.13	0.4–4.5 µL

Figure 1 demonstrates the patient's biochemical response to DKA treatment over 36 h.

Outcome and follow-up

Over the subsequent 48 h, she developed persistent high-grade fevers with no clear focus of infection; blood and urine cultures remained sterile.

Differential diagnoses at this point included infective endocarditis, an autoimmune process, a lymphoproliferative condition and a postpartum cardiomyopathy precipitating DKA.

Transthoracic echocardiography confirmed the presence of a small pericardial effusion, right heart dilatation and pulmonary hypertension, but no evidence

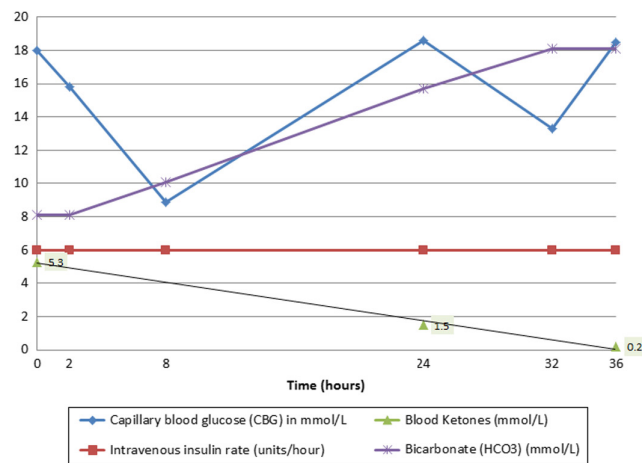


Figure 1 A graph showing the biochemical response to DKA treatment over 36 h.

of endocarditis. Left ventricular function was preserved. Cardiac MRI scan showed no signs of cardiac sarcoidosis or cardiomyopathy.

Serum angiotensin-converting enzyme level was normal and axillary lymph node biopsy showed a reactive node.

Immunological testing revealed strongly positive ANA, dsDNA, anti-Ro and anti-RNP antibodies, consistent with an autoimmune connective tissue disorder.

Urinary protein/creatinine ratio was elevated (62 mg/mmol (normal range <30 mg/mmol)).

A diagnosis of SLE was made on the basis of the immunology, cardiopulmonary involvement and proteinuria. She received three doses of intravenous methylprednisolone (500 mg) before being transferred to a tertiary rheumatology centre where she was treated with a combination of cyclophosphamide, hydroxychloroquine and high-dose prednisolone with good response.

Anti-GAD antibodies were also strongly positive (1357 kunits/L (normal range 0–5 kunits/L)), whilst islet cell antibodies were negative. She was established on subcutaneous insulin therapy (1 unit/kg/day). Eighteen months later, she continues to require insulin therapy and has recently commenced metformin to improve its action.

Discussion

This case illustrates the challenge in determining the type of diabetes when the clinical features overlap the traditional diagnostic classification. This patient had a history of GDM, which is known to confer an increased risk of future T2D, especially in Asian and Afro-Caribbean women (3). Therefore, the finding of hyperglycaemia in this African woman six weeks postpartum following a period of normoglycaemia in the immediate postpartum period, might initially suggest she had developed T2D.

The profound metabolic acidosis (pH <7.3, HCO₃ <15 mmol/L) accompanied by ketonaemia (>3 mmol/L) and hyperglycaemia (glucose >11 mmol/L), fulfilled the diagnostic criteria for DKA (4). Although more commonly seen in T1D, DKA can occur in patients with T2D (2), usually when there is an identifiable trigger such as infection. In this case, we initially considered a diagnosis of DKA precipitated by an acute respiratory infection, with underlying newly presenting T2D, though DKA is not usually an early feature of T2D.

However, this patient was later found to have a strongly positive titre of anti-GAD antibodies, which would rule out T2D (5).



T1D typically presents in children or young adults with severe hyperglycaemia and DKA usually due to autoimmune beta cell destruction (type 1a) by diabetes-associated autoantibodies (GAD, protein tyrosine phosphatase insulinoma-associated protein IA-2, IA-2 beta, insulin or zinc transporter 8) or by non-autoimmune beta cell destruction (type 1b) (6). Yet, T1D may also present in older adults as LADA, where the presenting clinical features can be more suggestive of T2D. LADA patients possess diabetes-associated autoantibodies, especially GAD antibodies, but only slowly progress to insulin dependence over a period ranging from six months to years (6, 7).

This patient possessed GAD autoantibodies and presented with DKA, so a diagnosis of LADA was considered. However, she required insulin therapy from diagnosis, which would exclude LADA, in which insulin therapy is not required for the initial 6–12 months. Although this patient had a history of glucose intolerance during pregnancy, she was demonstrated to have normoglycaemia postpartum and her first presentation of diabetes outside pregnancy was with DKA.

KPD is defined by presentation with DKA and occurs particularly in the Afro-Caribbean population, both features of this case. KPD was initially thought to be a variant of T2D, but is now recognised to be heterogeneous, encompassing varying degrees of beta cell function and diabetes autoimmunity (8). KPD is classified into four subgroups according to the presence or absence of beta cell functional reserve (B+ or B–) and diabetes autoantibodies (A+ or A–) (8). KPD patients who lack beta cell reserve (A+B– or A–B–) remain totally insulin deficient and require insulin therapy lifelong. Those KPD patients who retain beta cell function (A+B+ or A–B+) may not require insulin therapy for life (8).

The patient described presented with DKA, possessed diabetes autoantibodies and has since continued to require insulin therapy. These features suggest she has A+B– ketosis-prone diabetes.

We believe this is the first description of a patient presenting with ketosis-prone autoimmune diabetes simultaneously presenting with SLE.

The underlying pathogenic mechanism linking KPD and SLE is speculative. Both are autoimmune conditions, but although autoimmune diabetes is known to confer an increased risk of positive thyroid and parietal cell antibodies, diabetes and/or DKA are not widely recognised presentations of SLE (9). Furthermore, given the heightened immune tolerance in pregnancy, it is not

uncommon for autoimmune conditions to first present in the postpartum period, as we observed in our patient.

Diabetes and SLE are each strongly associated with specific HLA class II alleles and with polymorphisms in the TNF gene, but it is not known whether these associations are related to the HLA DQ and HLA DR loci. A further mechanism proposed involves co-stimulatory molecules. T lymphocytes are stimulated by CD80 or CD86 molecules expressed on antigen-presenting cells. The CTLA4 molecule (a T cell stimulator) and the CD28 molecule (a T cell inhibitor) act as receptors for CD80 and CD86. The CD80 gene has been associated with SLE and the CTLA4/CD28 locus is associated with T1D (10).

In summary, this case reports co-presentation of ketosis-prone autoimmune diabetes and SLE, adding to the repertoire of diverse diabetes presentations.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Patient consent

Informed consent has been obtained from the patient for publication of this article.

Author contribution statement

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