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MOTTLING AS AN EARLY SIGN OF EUGLYCEMIC KETOACIDOSIS INDUCED BY SGLT-2 INHIBITORS

Besard Memeti[1], Felix Brombacher[1], Ludwig Perger[1], Stefan Russmann[1,2,3]

[1] Department of Internal Medicine, Klinic Hirslanden, Zurich, Switzerland
[2] Drugsafety.ch, Kuesnacht, Switzerland
[3] University of Nicosia Medical School, Engomi, Cyprus

Corresponding author's e-mail: besart-memeti@hotmail.com

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ABSTRACT

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have shown benefits in managing heart failure, renal insufficiency and type 2 diabetes, but euglycemic ketoacidosis, while rare, has been reported in several patients on those medications. Therefore, their potential for inducing ketoacidosis, even in the presence of normal glucose levels, requires careful monitoring. We describe the case of a 78-year-old woman with type 2 diabetes treated with the SGLT-2 inhibitor dapagliflozin and the biguanide metformin, who presented after several days of reduced food and fluid intake due to nausea and diarrhoea to the emergency department. A few hours after admission to the medical ward with a working diagnosis of infectious gastroenteritis her condition deteriorated, and mottling served as an early sign of life-threatening euglycemic ketoacidosis. The mottling score increased in parallel with the National Early Warning Score (NEWS). She was treated with intravenous fluids, continuous insulin therapy and supportive measures, resulting in rapid clinical improvement. This report highlights the importance of early recognition to prevent serious complications and underscores that mottling might be a valuable early sign in addition to classical tools such as the NEWS. Although rare, euglycemic ketoacidosis can be precipitated by factors such as starvation, dehydration or infections in patients taking SGLT-2 inhibitors. The risk might be higher in individuals on SGLT-2 inhibitors and metformin. Timely intervention and metabolic correction are essential for improving outcomes in these patients, particularly when they present with atypical symptoms.

KEYWORDS

Euglycemic ketoacidosis, SGLT-2 inhibitors, mottling, dapagliflozin, diabetes management

LEARNING POINTS

- Mottling can serve as an early clinical indicator of euglycemic ketoacidosis (EKA) in patients treated with sodium-glucose co-transporter-2 (SGLT-2) inhibitors, even in the absence of circulatory shock, highlighting the importance of timely detection and intervention.
- Factors such as starvation, dehydration or infections can precipitate EKA in patients using SGLT-2 inhibitors, emphasising the need for careful monitoring in at-risk populations.
- Discontinuation of SGLT-2 inhibitors, rapid metabolic correction using fluids and insulin and avoidance of unnecessary antibiotics are essential for effective management and recovery from EKA.

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INTRODUCTION

Mottling is a clinical sign characterised by patchy skin discoloration due to compromised microvascular circulation. It is frequently observed in critically ill or dying patients and can be an important indicator of reduced oxygenation and perfusion. This report discusses the case of a patient whose mottling was associated with severe euglycemic ketoacidosis induced by starvation while taking the SGLT-2 inhibitor dapagliflozin and the biguanide metformin.

CASE DESCRIPTION

A 78-year-old woman with a history of type 2 diabetes presented to the emergency department because of reduced food and fluid intake due to nausea and recurrent vomiting over the preceding two days. On presentation, the National Early Warning Score (NEWS) was 0[1]. With an initial working diagnosis of infectious gastroenteritis, she was admitted to the medical ward for supportive treatment, including intravenous fluid supplementation. Approximately six hours after admission, her condition suddenly deteriorated.

Aside from type 2 diabetes and hyperlipidaemia, there were no pre-existing medical conditions. The patient's regular medication consisted of dapagliflozin 5 mg/day, insulin degludec subcutaneously, acetylsalicylic acid 100 mg/day for primary prophylaxis of cardiovascular disease, metformin 1,000 mg/day and simvastatin 40 mg/day.

The patient presented tachypnoeic (30 breaths per minute), tachycardic (110 beats per minute) and normotensive (120/44 mmHg). She was responsive to voice, with a normal capillary refill time of 2.5 seconds. On clinical examination, there was advanced mottling (grade 4 out of 5, *Fig. 1*, *Table 1*). Peripheral temperature was mildly cool, with mild bilateral lower extremity oedema. Peripheral pulses were palpable. The NEWS was now 7 (3 points for respiratory rate, 1 point for heart rate, 3 points for vigilance). Neurological, pulmonary and abdominal examination were otherwise normal.

Arterial blood gas analysis revealed severe metabolic acidosis (pH 7.07, HCO_3^- 6.5 mmol/l) without lactic acidosis (lactate 1.1 mmol/l). Blood glucose was normal at 6.2 mmol/l. Renal function was within the normal range (creatinine 48 µmol/l, estimated glomerular filtration rate 83 ml/min/1.73 m^2). C-reactive protein was within normal limits, while leukocyte count, and erythrocyte sedimentation rate were slightly elevated. There was marked ketonuria (> 5.1 mmol/l). Contrast-enhanced CT scan of the thorax and abdomen revealed no signs of infection. Antibody testing results for latent autoimmune diabetes in adults were negative.

The patient was transferred to the intensive care unit. Laboratory findings confirmed severe ketoacidosis without lactic acidosis. This clinical picture, combined with normal blood glucose levels and the patient's history of SGLT-2 inhibitor use under starvation conditions, strongly suggested euglycemic ketoacidosis triggered by dapagliflozin and possibly exacerbated by metformin. Consequently, oral antidiabetic drugs were discontinued, and the metabolic

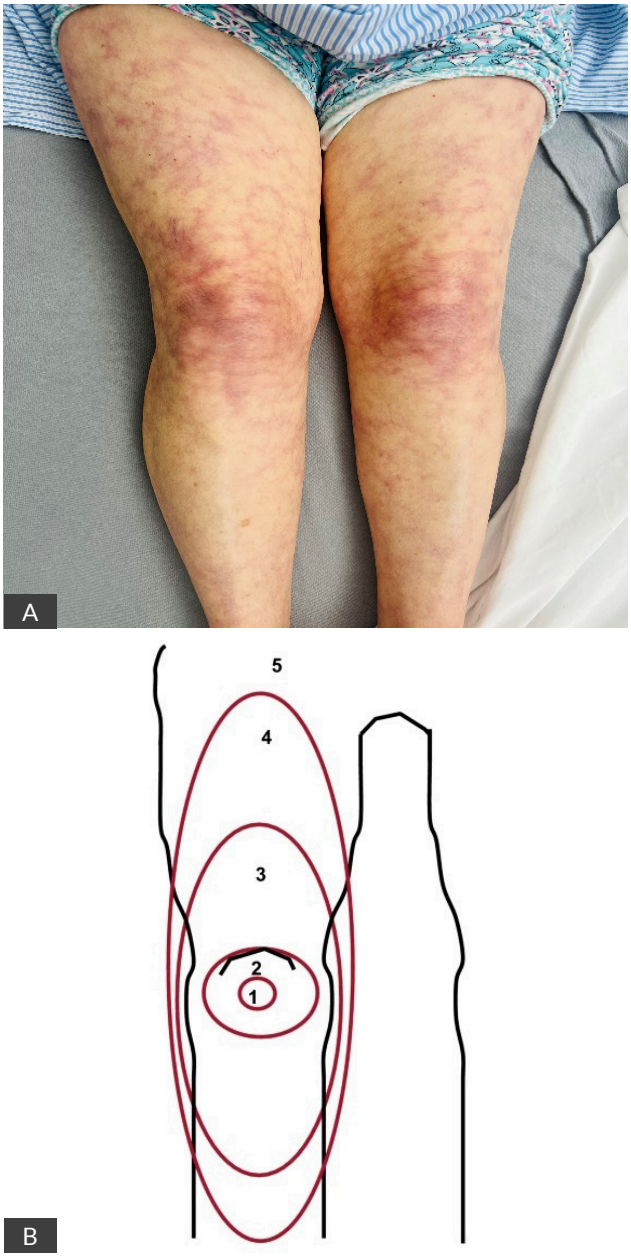

Figure 1. A) Clinical presentation with grade 4 peripheral mottling of the lower extremities and B) the mottling score, based on the extent of the skin mottling area on the legs. Adapted from Hariri et al. (2019), licensed under CC BY 4.0[8].

Score	Clinical presentation
0	No mottling
1	Coin-sized mottling over the knee
2	Mild mottling that does not extend beyond the mid-thigh
3	Moderate mottling that does not exceed the patella
4	Severe mottling that does not exceed the groin region
5	Severe mottling that exceeds the groin region

Table 1. Clinical classification of mottling indicating severity based on localisation.

acidosis was corrected with crystalloid infusions, continuous insulin therapy and moderate glucose supplementation. Due to suspicion of coexisting sepsis, empirical antibiotic therapy with piperacillin/tazobactam (4.5 g three times per day) was initiated. The patient remained haemodynamically stable without the need for vasopressors, and her oxygenation on room air was satisfactory. Potassium and phosphate were supplemented as necessary. Microbiological investigations including multiplex polymerase chain reaction of a stool sample showed no infectious pathogens, and antibiotic therapy was subsequently discontinued. Vomiting and diarrhoea subsided, and a basal bolus insulin regimen was introduced. Dapagliflozin was permanently discontinued, and the patient was gradually reintroduced to a normal diet, with rapid improvement.

DISCUSSION

This report presents the case of a 78-year-old woman with severe euglycemic ketoacidosis (EKA) induced by the SGLT-2 inhibitor dapagliflozin with the notable clinical feature of severe mottling as an early sign of clinical and metabolic deterioration. The SGLT-2 inhibitor was discontinued, and metabolic acidosis was treated with insulin and fluids. The absence of lactic acidosis and detectable pathogens, along with ketonuria, helped to rule out septic shock and facilitated the prompt discontinuation of antibiotics to focus on metabolic correction. The absence of lactataemia argues against metformin as the primary cause of the metabolic disturbance.

SGLT-2 inhibitors have shown benefits in managing heart failure, chronic kidney disease and type 2 diabetes. Euglycemic ketoacidosis is a rare adverse effect that has been reported in several patients on those medications[2]. This highlights the importance of careful monitoring under therapy and early recognition of complications to prevent serious outcomes[2,3].

SGLT-2 inhibitors promote glucosuria and can accelerate ketogenesis and acidosis under conditions of dehydration or fasting, even with normal glucose levels. Such euglycemia might delay timely diagnosis[2]. EKA has also been recognised as a diagnostic dilemma due to its atypical presentation, reinforcing the importance of recognising key clinical signs[4]. In this case, mottling was a sign of early perfusion deficits, linked to ketoacidosis and dehydration, even without circulatory shock. FAERS data has highlighted similar cases where SGLT-2 inhibitors led to EKA, emphasising that patients often remain haemodynamically stable despite significant metabolic disturbances[3].

The risk of euglycemic ketoacidosis may increase in patients who are treated with a combination of SGLT-2 inhibitors and metformin. While one study found this co-medication safe and effective in individuals fasting during Ramadan[5], several case reports describe EKA in patients during prolonged fasting[6]. Additionally, a case series described instances of EKA associated with SGLT-2 inhibitors and metformin even in patients who underwent minor and complication-free surgery[7]. Metformin reduces hepatic glucose production and is associated with a low risk of hypoglycaemia, but it can also limit the capacity for gluconeogenesis during metabolic stress. When combined with SGLT-2 inhibitor-induced renal glucose excretion, this may promote excessive ketone body production.

Mottling is a clinical finding associated with impaired microcirculation, has been well studied especially for septic shock[8], and is also frequently observed in end-of-life care. It can also appear in other states of low or maldistributed perfusion, as in our case due to metabolic stress. Mottling appears as irregular and patchy discolouration of the skin, often presenting as a reddish-purple or bluish marbled pattern. It typically starts around the knees. The mottling score (*Fig. 1B*, *Table 1*) systematically assesses its severity based on spread of the skin manifestations from the knees towards the periphery[8]. Literature has demonstrated that a higher mottling score is associated with worse outcomes and increased mortality in critically ill patients[9]. As a sign of microcirculatory failure, mottling may precede overt haemodynamic instability linked to microcirculatory failure. The mottling score correlates with the NEWS in our case and in the literature[10], suggesting that it might serve as an additional diagnostic and prognostic tool in critically ill patients.

CONCLUSION

This case emphasises the importance of recognising EKA as a potential adverse effect of SGLT-2 inhibitor therapy. Mottling correlated with the well-established NEWS and served as a crucial early indicator of clinical deterioration. Timely identification of EKA and prompt, targeted treatment resulted in a rapid clinical recovery. Given the expanding use of SGLT-2 inhibitors, awareness of this entity and its possible atypical presentation is essential for preventing delayed diagnosis and improving patient outcomes.

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