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Pemphigus Vulgaris Complicated by SGLT-2 Inhibitor Associated Euglycemic Diabetic Ketoacidosis

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Background	Euglycemic diabetic ketoacidosis (EDKA) is a severe acute metabolic complication observed in patients with both type 1 and type 2 diabetes mellitus. It is characterized by the triad of high anion gap metabolic acidosis, significant ketonemia or ketonuria, and paradoxically normal or near-normal blood glucose levels (typically <250 mg/dL or <13.9 mmol/L). Common precipitating factors include acute physiological stressors such as recent surgery or trauma, infection and sepsis, dehydration, or periods of starvation or significantly reduced carbohydrate intake. The use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors is a well-established risk factor, as these agents promote glycosuria, thereby lowering plasma glucose, and can exacerbate ketogenesis. While EDKA is relatively less common than classic diabetic ketoacidosis (DKA), its incidence is rising, paralleling the increased prescription of SGLT-2 inhibitors. This poses a unique diagnostic challenge in surgical critical care settings, as the absence of marked hyperglycemia can delay recognition and appropriate treatment.
Summary	We present a case of euglycemic diabetic ketoacidosis encountered at our burn center in a male patient with biopsy-confirmed pemphigus vulgaris and poorly controlled type 2 diabetes mellitus, who was receiving an SGLT-2 inhibitor. His extensive desquamating rash was being managed with local wound care and systemic oral corticosteroids. During his admission, he developed acute mental status changes and worsening metabolic acidosis. Laboratory investigations revealed a high anion gap metabolic acidosis and significant ketonuria, in conjunction with normal blood glucose levels, leading to the diagnosis of EDKA. Management involved aggressive intravenous fluid resuscitation, optimization of insulin therapy with an increased insulin infusion rate, and endotracheal intubation for airway protection and respiratory support. His acidosis and electrolyte derangements gradually resolved with this treatment. He was successfully extubated several days later and was ultimately discharged on a comprehensive insulin regimen and a tapering course of oral corticosteroids, as per endocrinology recommendations.
Conclusion	Early recognition of the pathognomonic laboratory findings of EDKA—namely, metabolic acidosis with an elevated anion gap, ketonemia/ketonuria, and euglycemia—coupled with prompt initiation of aggressive fluid resuscitation and insulin therapy, is crucial for successful treatment and improved patient outcomes. Clinicians, particularly those in surgical critical care environments, must maintain a high index of suspicion for EDKA, as its triggers frequently include stressors commonly encountered in this setting. This vigilance is especially warranted in diabetic patients receiving SGLT-2 inhibitors, given their predisposition to this atypical and potentially life-threatening presentation of ketoacidosis.

Key Words	euglycemic diabetic ketoacidosis; pemphigus vulgaris

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Case Description

A 68-year-old African American male with a known history of type 2 diabetes mellitus (T2DM), hypertension, and hyperlipidemia presented with an evolving blistering rash over a six-week period. Initially, partial-thickness lesions appeared on his left upper extremity and subsequently spread despite two outpatient courses of doxycycline. His T2DM was poorly controlled, with suboptimal compliance to insulin and metformin therapy, and he had recently been initiated on empagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor. He continued this medication up to the day of admission; it was not resumed during his hospital course. Physical examination revealed scattered bullous and erosive lesions in various stages of healing across his torso, head, perineum, genitals, and oral mucosa, with a positive Nikolsky sign (Figure 1-4). Due to the extent of skin involvement and systemic illness, he was transferred to our American Burn Association-verified burn center for specialized management.

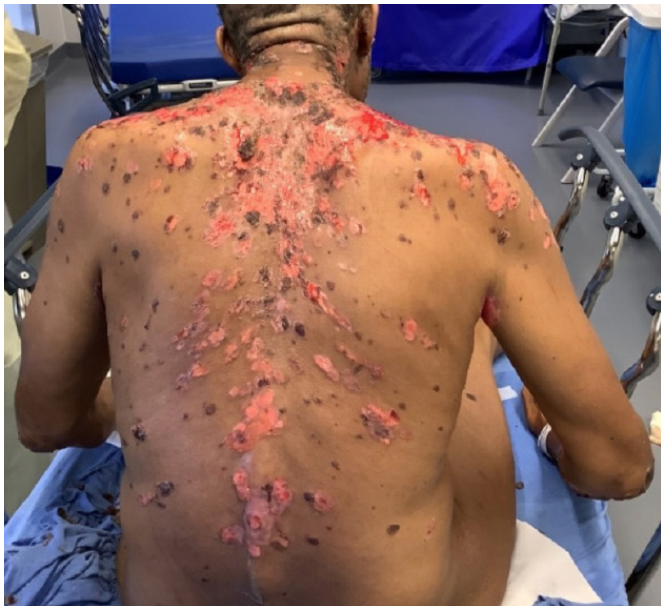
Figure 1. Anterior View of Cutaneous Pemphigus Vulgaris Lesions. Published with Permission

Clinical photograph (anterior view) demonstrating diffuse cutaneous lesions characteristic of pemphigus vulgaris. Note the involvement of the head, neck, and thorax, with lesions in mixed stages of wound healing, including bullae, erosions, and crusted areas. Ocular mucosal involvement is partially visible at the eyelids.

Figure 2. Right Lateral View of Scalp Lesions in Pemphigus Vulgaris. Published with Permission

Clinical photograph (right lateral view) highlighting severe pemphigus vulgaris lesions across the scalp. Areas of active blistering, erosions, and re-epithelialization with associated scarring are evident.

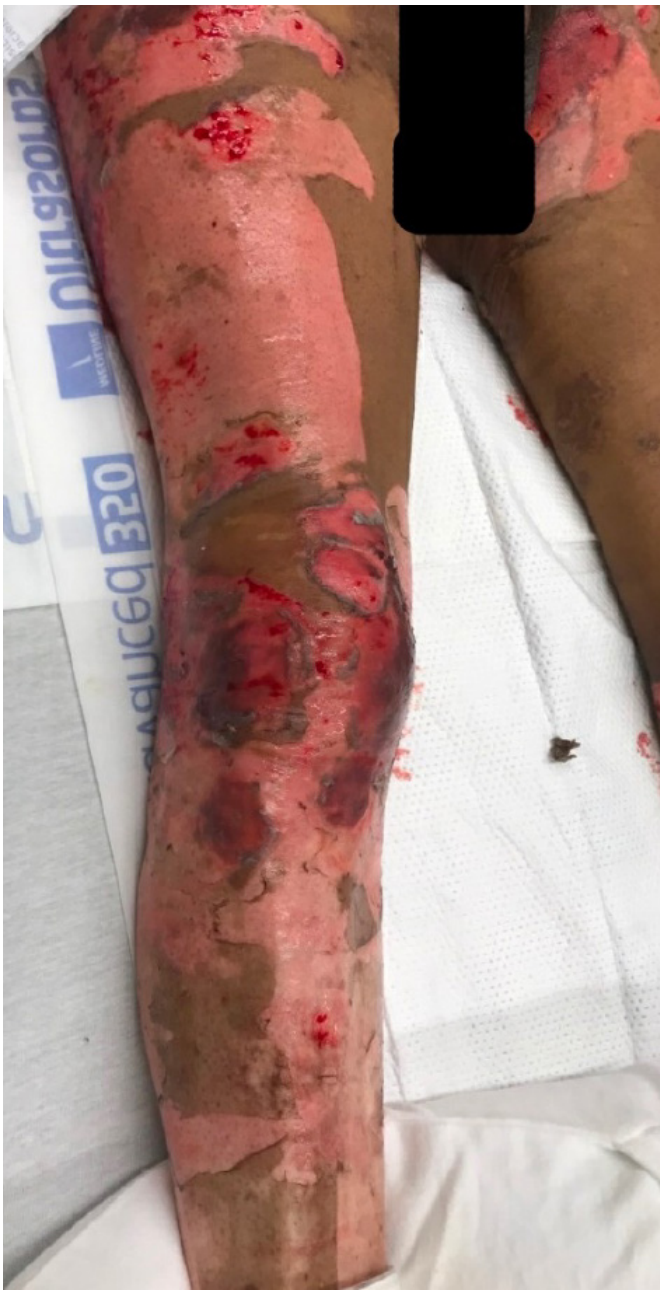
Figure 3. Posterior View of Extensive Pemphigus Vulgaris Lesions. Published with Permission



Clinical photograph (posterior view) showing extensive partial-thickness erosions and bullous lesions across the back and shoulders, with diffuse scabbing and areas of desquamation, characteristic of severe pemphigus vulgaris.

Upon admission to the burn center, the patient was afebrile and hemodynamically stable. Initial laboratory investigations showed euglycemia (blood glucose 85 mg/dL), an elevated hemoglobin A1c (8.9%) indicative of chronic hyperglycemia, and an acute kidney injury (serum creatinine elevated to 1.4 mg/dL from a baseline of 0.9 mg/dL). Nursing staff initiated hydrotherapy for debridement of bullae, followed by daily application of Xeroform petrolatum gauze, triple antibiotic or bacitracin ointment, and dry gauze dressings for local wound care. Urological consultation managed the penoscrotal wounds similarly. Ophthalmologic examination revealed proliferative diabetic retinopathy and blepharitis, without evidence of corneal ulceration. Shave biopsies of skin lesions confirmed the diagnosis of pemphigus vulgaris (PV), with histopathology demonstrating suprabasilar acantholysis. Initial treatment included aggressive intravenous fluid resuscitation, oral prednisone (40 mg daily) for PV, and a sliding-scale rapid-acting insulin regimen (0-10 units subcutaneously every 6 hours) due to his history of poorly controlled diabetes.

Figure 4. Pemphigus Vulgaris Lesions on Lower Extremities. Published with Permission



Clinical photograph displaying an open partial-thickness wound on the right lower extremity and erosions on the left inner thigh following debridement of flaccid bullae, typical of pemphigus vulgaris. (Penoscrotal lesions also present but not depicted).

On the fourth day of admission, the patient developed acute mental status changes characterized by disorientation and agitation. He reported worsening odynophagia despite treatment with topical lidocaine spray. Concurrently, he exhibited worsening tachycardia (heart rate 110-120 beats per minute), hypotension (systolic blood pressure ranging from 70-110 mmHg), and dyspnea. An arterial blood gas analysis revealed a severe metabolic acidosis with a pH of 7.15, pCO2 of 30.3 mmHg, pO2 of 415.2 mmHg (on supplemental oxygen), and bicarbonate (HCO3) of 10.2 mEq/L. Due to the profound acidosis with inadequate respiratory compensation, the patient was endotracheally intubated and mechanically ventilated.

Following intubation, the patient was transferred to the surgical intensive care unit (SICU). His anion gap progressively increased from 27 to 38 mEq/L. While his blood glucose rose modestly to 210 mg/dL, urinalysis indicated 2+ ketones, and serum beta-hydroxybutyrate levels were markedly elevated at 109.6 mg/dL. Based on this constellation of euglycemia (or mild hyperglycemia), high anion gap metabolic acidosis, and significant ketonemia/ketonuria, a diagnosis of euglycemic diabetic ketoacidosis (EDKA) was established. Rather than initiating a continuous titratable insulin infusion, his rapid-acting insulin dosage was increased to 2-15 units subcutaneously every 6 hours, with a target blood glucose of <150 mg/dL, per our institutional pharmacy protocol for this scenario. Chest X-rays were clear of pulmonary edema, and a non-contrast head CT showed no acute intracranial pathology. Serum potassium levels transiently increased from 5.2 to 5.5 mEq/L and were managed with sodium zirconium cyclosilicate (10g). Serum creatinine rose from 1.4 to 1.8 mg/dL, prompting an increase in crystalloid fluid administration rate as per nephrology recommendations. Blood cultures remained negative for bacterial or fungal growth; however, empiric broad-spectrum antibiotic therapy with cefepime and linezolid was initiated for presumed sepsis, as per infectious disease consultation.

Subsequently, the patient's clinical condition steadily improved. By admission day five, his serum beta-hydroxybutyrate level decreased to 59.3 mg/dL, and his serum pH normalized to 7.41. The anion gap closed to 14 mEq/L by the sixth day, and urinalysis was negative for ketones by the seventh day. A basal insulin regimen of 20 units of insulin glargine daily was initiated. After a week of mechanical ventilation, with gradual weaning based on arterial blood gas monitoring and pulse oximetry, the patient was successfully extubated.

By admission day ten, the patient was stable for transfer out of the SICU. His hospital course, extending to 25 days, was complicated by a *Pseudomonas aeruginosa* bacteremia, which was successfully treated with a targeted course of cefepime. His pemphigus vulgaris lesions began to re-epithelialize with continued local wound care and systemic corticosteroids. The endocrinology team closely managed his glycemic control and, upon discharge, prescribed an outpatient regimen consisting of oral prednisone 40 mg daily, insulin detemir 10 units daily, insulin lispro 7 units three times daily with meals, and sitagliptin 25 mg daily.

Discussion

Euglycemic diabetic ketoacidosis represents a significant and potentially life-threatening acute complication of both type 1 and type 2 diabetes mellitus. It is classically defined by the triad of euglycemia or only mild hyperglycemia (blood glucose typically <250 mg/dL), significant ketonemia or ketonuria, and a high anion gap metabolic acidosis (or reduced serum bicarbonate levels).[1] This clinical picture contrasts sharply with classical diabetic ketoacidosis (DKA), where marked hyperglycemia (blood glucose ≥250 mg/dL) is a cardinal feature. Despite this difference in glycemic presentation, both EDKA and DKA can be precipitated by similar physiological stressors commonly encountered in surgical critical care, including infection, sepsis, malnutrition, substance abuse (such as cocaine, as in this case), and major trauma or surgery.[2,3]

In our institution, the burn unit and surgical services collaboratively manage severe dermatological conditions like pemphigus vulgaris (PV) due to the similarities in wound care principles with partial-thickness burns. PV is an autoimmune blistering disease where autoantibodies target desmoglein, a keratinocyte cadherin transmembrane protein, leading to intraepidermal acantholysis and subsequent blistering desquamation.[4] The disruption of cell adhesion affects both cutaneous and mucosal surfaces. Mucosal involvement, particularly of the oral and ocular tissues, along with the presence of easily sloughing, flaccid bullae (Nikolsky sign positive), helps distinguish PV from related autoimmune bullous diseases such as bullous pemphigoid.[5]

While no prior case reports have specifically linked PV as a direct cause of ketoacidosis, the profound physiological and metabolic stressors associated with severe PV exacerbations share commonalities with well-described triggers for DKA and EDKA. Extensive PV wounds lead to significant insensible fluid and proteinaceous losses, predispos-

ing to dehydration and electrolyte derangements.[6] These open ulcerations also create a substantial risk for secondary infection and progression to sepsis. Furthermore, odynophagia from sloughing oral and pharyngeal mucosa often results in decreased dietary intake and malnutrition.[7] Systemic inflammation, a hallmark of active PV, and recent research highlighting unique metabolomic and lipidomic profiles in PV patients, may represent additional, albeit poorly understood, factors contributing to a pro-ketogenic state.[8] The cumulative stress response from these factors leads to increased counter-regulatory hormone production (e.g., cortisol, glucagon), which exacerbates insulin resistance and shifts metabolism towards lipolysis and ketogenesis.[9]

The use of systemic corticosteroids for the treatment of PV, as in our patient, potentially introduces an additional variable that could increase the risk of EDKA. Corticosteroids are a cornerstone of PV management due to their immunosuppressive effects, which diminish autoantibody production and reduce the rate of new lesion formation.[10] However, exogenous corticosteroids are known to induce insulin resistance, partly through inhibition of GLUT-4 transporters, and can stimulate hepatic lipogenesis and adipocyte lipolysis.[11] Despite these metabolic effects, corticosteroid-induced DKA or EDKA remains relatively rare and has been more frequently associated with high-dose intravenous corticosteroid administration rather than oral regimens typically used for PV.[12] Alternative or adjuvant therapies for PV, such as intravenous immunoglobulins (IVIG) or nonsteroidal immunomodulators like rituximab, offer viable treatment options without the significant metabolic complications associated with prolonged or high-dose corticosteroid use.[13]

The patient's use of empagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, represents a well-established and significant risk factor for the development of EDKA, even if the presentation is delayed relative to the last dose. SGLT-2 inhibitors act on the proximal convoluted tubules of the kidneys to inhibit glucose reabsorption, leading to therapeutic glycosuria and osmotic diuresis.[14] The resultant decrease in available carbohydrates for cellular metabolism, coupled with a relative decrease in insulin secretion and an increase in glucagon levels, promotes lipolysis and subsequent ketogenesis via beta-oxidation of free fatty acids.[15] The SGLT-2 inhibitor-mediated renal glucose wasting is thought to be a primary reason for the atypical euglycemia observed in EDKA, as opposed to the marked hyperglycemia seen in classic DKA.[15] Furthermore, because these drugs undergo renal clearance, their clinical effects can be prolonged in patients with acute or chronic renal impairment or significant volume depletion, conditions often present in critically ill patients.[16,17] Although empagliflozin has a reported half-life of approximately 12-13 hours, case reports investigating other SGLT-2 inhibitors have documented persistent glucosuria and ketonemia for several days after the last dose.[17,18] Current guidelines generally recommend discontinuing SGLT-2 inhibitors 24 hours before elective surgery or immediately before emergent surgery; however, a definitive consensus regarding the optimal timing for discontinuation, particularly in patients with acute illness, is still evolving.[19]

The management of EDKA largely mirrors the principles of classic DKA treatment. Both conditions respond to the initiation of continuous insulin infusion, which stimulates cellular glucose uptake and glycolysis while simultaneously inhibiting ketogenesis. Insulin therapy is critical for resolving the ketoacidosis and should be continued until there is closure of the anion gap metabolic acidosis and resolution of ketonuria.[20] A key distinction in EDKA management, however, is the often necessary concomitant administration of intravenous dextrose to prevent hypoglycemia, particularly while the patient remains in a glucose-wasting state due to the effects of SGLT-2 inhibitors or other factors.[21] Early and aggressive intravenous fluid resuscitation is essential in both EDKA and DKA to correct electrolyte derangements and dehydration secondary to osmotic diuresis and other losses.[21] In this case, a crystalloid-based fluid resuscitation strategy, combined with a sliding-scale regimen of subcutaneous rapid-acting insulin administered every 6 hours (with a pharmacy-guided blood glucose target of <150 mg/dL), successfully resolved the EDKA. This approach presents a viable alternative to a continuous insulin infusion, which typically requires more intensive monitoring and frequent nursing titration, particularly in settings where such resources may be constrained.

Conclusion

This case highlights an episode of euglycemic diabetic ketoacidosis precipitated by an acute exacerbation of pemphigus vulgaris in a patient with poorly controlled type 2 diabetes mellitus who was concurrently taking a SGLT-2 inhibitor. Pemphigus vulgaris presents a unique constellation of physiological stressors—including extensive skin barrier disruption, fluid and protein losses, risk of infection, and pain leading to poor oral intake—which, when compounded by the metabolic derangements induced by

SGLT-2 inhibitor therapy (e.g., glucose wasting, enhanced ketogenesis), can synergistically precipitate the development of EDKA.

Lessons Learned

Clinicians managing patients in surgical and burn critical care settings should maintain a high index of suspicion for EDKA when confronted with the pathognomonic laboratory findings of a high anion gap metabolic acidosis, ketonemia or ketonuria, and paradoxically normal or near-normal blood glucose levels. Prompt recognition and initiation of appropriate treatment, primarily involving aggressive fluid resuscitation and optimized insulin therapy (with consideration for concurrent dextrose administration to prevent hypoglycemia), are crucial for successful outcomes. This vigilance is particularly warranted in diabetic patients with significant physiological stressors, such as severe dermatological conditions like pemphigus vulgaris, and especially in those receiving SGLT-2 inhibitor therapy.

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