

CASE REPORT

A case report of leukemoid reaction in a child with severe diabetic ketoacidosis (DKA) and cerebral edema: When rarity and complexity meet

Abdulla Alfraj¹  | Naser Al-Enazi²

¹Pediatric Intensive Care Unit, Department of Pediatrics, General Ahmadi Hospital (KOC), Ahmadi, Kuwait

²Pediatric Endocrinologist and Diabetologist, Department of Pediatrics, General Ahmadi Hospital (KOC), Ahmadi, Kuwait

Correspondence

Abdulla Alfraj, Department of Pediatrics, General Ahmadi Hospital (KOC), PO Box 9758, Ahmadi 61008, Kuwait.
Email: alfraj.abdulla@gmail.com

Key Clinical Message

In pediatrics, a leukemoid reaction in severe DKA cases with cerebral edema has never been reported. The fluid management was challenging as it required balancing rates to ensure improvement of the condition while preventing neurological sequelae.

Abstract

The combination of diabetic ketoacidosis (DKA), cerebral edema, and leukemoid reaction in pediatrics has never been reported before in the literature. It may lead to significant morbidity and high mortality. Here, we report a case of DKA-induced cerebral edema associated with severe leukocytosis (WBC $98 \times 10^9/L$), which had many challenges in fluid therapy.

KEYWORDS

cerebral edema, diabetic ketoacidosis, leukemoid reaction, pediatric

1 | INTRODUCTION

Leukemoid reaction is one of the relatively benign conditions in children compared to the adult population, where it is associated with high morbidity and mortality.¹ It was initially described by Krumbhaar in 1926 when several patients were reported with non-leukemic conditions having leukemia-like blood film, which was named a “leukemoid reaction.”² It has recently been defined as a leukocyte count of more than $50 \times 10^9/L$, with a significant increase in mature neutrophil counts, left shift of neutrophil activation, absent basophilia, and no dysplastic cells.^{3,4} This reaction is considered benign as the dramatic changes in white blood cell (WBC) count disappear once the underlying etiology improves. Infections are one of the main etiologies of the leukemoid reaction, with pneumonia being

the most associated condition.¹ This hyperleukocytosis increases blood viscosity due to a high WBC count and leukocyte aggregation, which may lead to small blood vessel occlusion predisposing to neurological, pulmonary, or gastrointestinal complications.⁵ Leukapheresis, exchange transfusion, and hyperhydration are the cornerstones of management for symptomatic hyperleukocytosis.⁵

In diabetic ketoacidosis (DKA), patients might present with some degree of leukocytosis with an average leukocyte of $15 \times 10^9/L$; slightly increasing if infection is on board.^{6,7} The causes of leukocytosis in DKA are usually multifactorial, especially in view of infection, stress, blood acidosis, and severe dehydration. On the contrary, one of the serious complications of DKA is cerebral edema, where its exact pathophysiology is not well understood.⁸ It may occur before starting the DKA

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treatment, possibly due to poor blood flow to the brain, leading to cytotoxic injury.^{9,10} Also, it might be worsened during fluid therapy because of the reperfusion injury phenomena.⁸ Clinically significant cerebral injury may occur in three to nine cases in every 100 children with DKA, with a mortality rate between 20% and 25%.^{9,10} Therefore, prevention of DKA is the best way to avoid cerebral injury; of course, this is not possible in newly diagnosed diabetics. However, once it occurs, lowering the intravenous (IV) fluid rate and using hyperosmolar therapy are the two main pillars of management.⁸ Here, we present a rare combination of leukemoid reaction in a child with DKA-induced cerebral edema, where we faced an extreme challenge in fluid therapy.

2 | CASE HISTORY/ EXAMINATION

A 9-year-old girl was diagnosed with type 1 diabetes mellitus (DM) on her fifth birthday based on typical DM symptoms, and the high level of anti-GAD antibodies (1140 IU/mL) with low serum insulin (1.06 μ IU/mL) and C-peptide levels (0.343 ng/mL). Since then, she had been managed with insulin degludec (Tresiba[®]) and insulin aspart (NovoRapid[®]) regimen with regular follow-up. However, due to her poor compliance with the injections over the past year, the insulin regimen was changed to the two-injection insulin regimen of Lispro Mix 50/50 (Humalog[®] Mix 50/50) with degludec. Her home random blood glucose level ranges between 10 and 21 mmol/L, with hemoglobin A1c of 10.4% at the time of presentation, confirming the poorly controlled DM status. She presented to the General Ahmadi Hospital in January 2024 with a one-day history of abdominal pain, nausea, and recurrent vomiting. There was no history of fever, cough, or rash. The condition became very worrisome to the parents when she started to be tachypneic and drowsy. In the emergency room (ER), the diagnosis of severe DKA was confirmed as her random blood glucose was 44 mmol/L (793 mg/dL), associated with a high level of 3-hydroxybutyric acid in the blood (4.6 mmol/L) and a capillary blood gas analysis result of pH of 6.90, a partial pressure of carbon dioxide (pCO₂) 12.7 mmHg, and a bicarbonate level of 3.6 mmol/L. The calculated serum osmolality was 333 mOsm/kg. Her ER vital signs were a heart rate of 160 b/m, respiratory rate of 44 breath/m, oxygen saturation (SpO₂) of 99% on room air, temperature of 37°C, and blood pressure of 115/83 mmHg. Clinically, the patient was lethargic, severely dehydrated, and having Kussmaul breathing. Complete neurological examination revealed a Glasgow Coma Score (GCS) of 12 out of 15, losing two points in the verbal component and one point in eye response. She was noticed to have an

acute onset of slurred speech pattern. The remaining neurological examinations, including the pupils, were unremarkable. There was no hepatomegaly nor splenomegaly by abdominal examination.

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS AND TREATMENT

The patient received 500 mL (10 mL/kg) of 0.9% sodium chloride (NaCl) from the ER over 1 h and was transferred to the pediatric intensive care unit (PICU) to complete her severe DKA management. Insulin infusion started at a rate of 0.05 U/kg/h, and a total fluid rate (including the insulin rate) of 4 mL/kg/h, which is almost double the maintenance fluid rate in pediatrics. Using the two-bag system, 0.9% NaCl was used initially, followed by 5% dextrose with 0.9% NaCl based on the drop rate in blood glucose. Initial laboratory results are shown in Table 1.

Clinically, cerebral edema was suspected, given her decreased GCS and slurred speech in view of severe DKA status. Hyperosmolar hyperglycemic state (HHS) was excluded as the child was a known case of type 1 DM and presented with severe metabolic acidosis and high blood ketone level, which is not the case in HHS. Another differential diagnosis was cerebral central venous thrombosis, which warrants brain imaging. However, given her neuro-instability with the severe degree of dehydration

TABLE 1 Admission blood workup for the patient.

Test [unit]	Result	Normal range
pH	6.90	7.35–7.45
pCO ₂ [mmHg]	12.7	35–45
HCO ₃ [mmol/L]	3.6	22–26
White blood count (WBC) [$\times 10^9$/L]	86.6	4.5–13.5
Hemoglobin [g/dL]	14.0	11.9–15.0
Platelet count [$\times 10^9$ /L]	625	150–450
Neutrophils [%]	81.0	
Lymphocytes [%]	14.4	
C-reactive protein [mg/L]	36	<10
Sodium [mmol/L]	140	135–145
Serum potassium [mmol/L]	5.7	3.5–5.0
Chloride [mmol/L]	100	96–106
Blood urea nitrogen [mmol/L]	9	2.5–6.0
Creatinine [μ mol/L]	114	29–56
Glucose [mmol/L]	44	5.0–10.0

Note: The bold value is to show the very high result compare to normal range.

and the severe DKA status, the CT scan was deferred. Initial blood work results showed a very high WBC count ($86.6 \times 10^9/L$), increasing the risk of blood hyperviscosity in the patient. Therefore, a modified cerebral edema protocol was started to balance the fluid management between the need for fluid restriction for cerebral edema and hyperhydration for hyperleukocytosis to avoid thrombosis. Fluids were kept at the same rate to maintain hyperhydration, with the bed's head elevated by 30 degrees and the patient's head in the midline position. The maximum WBC count level reached $98 \times 10^9/L$, as shown in Table 2. An empiric antibiotic (ceftriaxone) was started at a dose of 75 mg/kg/day once daily, and serial complete blood counts (CBC) were obtained to monitor the WBC trends (Table 2). A blood film test revealed leukocytosis, mainly neutrophilia with left shift, no immature or dysplastic cells, with the presence of rouleaux formation and thrombocytosis—consistent with the leukemoid reaction diagnosis. A respiratory virology panel detected SARS-CoV-2 virus. A BioFire® test for *Bordetella Pertussis* was negative. The chest x-ray and cultures (blood and urine) were negative. Considering the risk of stroke due to the hyperviscosity state, hyperhydration using double the child's maintenance fluids rate was applied with close monitoring of neuro-vitals and fluid chart using a Foley catheter.

4 | OUTCOME AND FOLLOW-UP

The patient's pH improved gradually with a steady reduction in blood glucose levels as aimed by our PICU DKA protocol. More importantly, the child's neurological status improved as the DKA condition resolved (Table 3). She returns to her baseline of 15/15 GCS by 20h from

the admission. The brain CT scan was held due to the marked improvement within a short period, lowering the likelihood of cerebral central venous thrombosis or an ischemic insult. On the third day of hospital admission, the WBC count showed a decline in its level, reaching a normal range. The patient was discharged home without any neurological sequelae. A follow-up in the pediatric diabetologist outpatient clinic confirmed her good general and neurological status.

5 | DISCUSSION

DKA is one of the well-known presentations of type I DM in children. Its severity can be determined by the degree of acidosis, which in our case was considered "severe" as the pH was less than 7.1 and serum bicarbonate was less than 5.¹¹ The goal of DKA management consists of correcting acidosis and dehydration, restoring ketosis and blood glucose, and monitoring for possible complications.¹¹ Cerebral edema is one of the serious complications of DKA, which was clinically suspected in our patient due to altered mentation, confusion, fluctuating level of consciousness, abnormal verbal responses, and slurred speech patterns besides the lethargy and not being easily rousable. These signs and symptoms matched the clinical criteria for diagnosing cerebral edema based on the International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus.¹¹ The literature shows that about 4%–15% of DKA patients will have a mild form of cerebral edema confirmed in neuroimaging, especially when GCS is less than 14.¹¹ Many risk factors for this complication were present in our case, including a low pCO₂ level (12.7 mmHg), high blood urea nitrogen level (9 mmol/L), and severe acidosis at presentation

TABLE 2 Complete blood count (CBC) trends.

Test	Admission (Day 0)	6 h later	Day 2	Day 3	Day 4
WBC ($\times 10^9/L$)	86.6	98	19.9	8.1	5.9
Hemoglobin (g/dL)	14.0	14.2	11.8	12.1	12.6
Platelet count ($\times 10^9/L$)	625	600	238	318	259

Abbreviation: WBC, White blood count.

TABLE 3 Blood gas analysis (BGA) with blood glucose trends.

Test	Admission (Time 0)	6h	12h	18h	30h
Glucose (mmol/L)	44	22.1	15.6	14.2	6
pH	6.90	7.01	7.11	7.24	7.41
PCO ₂ (mmHg)	12.7	16.5	28.2	37.9	38.7
HCO ₃ (mmol/L)	3.6	7.5	11.5	16.2	24.6
Base excess (BE)	−30	−26	−19	−11	0.3

(pH6.90).¹⁰ Neuroimaging is usually required to rule out other differential diagnoses for brain insults rather than diagnosing cerebral edema.¹¹ Osmolar therapies, like mannitol and hypertonic saline, are well-known treatments for cerebral edema in DKA.¹² Although the mechanism of action for these therapies is still not fully understood, it is probably related to the osmotic properties of these therapies.¹³ One of the major drawbacks of mannitol is that it induces osmotic diuresis, which, in our case, may worsen the hyperviscosity state given the leukemoid reaction.¹² On the other hand, hypertonic saline was another option, given its osmotic effect in treating cerebral edema without causing diuresis.¹² However, hypertonic saline is known to cause volume overload, increasing the hyperhydration burden on other organs.¹² Therefore, close monitoring of our fluid management strategy was preferred with a low threshold to start a hypertonic solution when necessary. This is how the leukemoid reaction increased the complexity of our scenario. So, if the usual cerebral edema protocol had been started, the patient would have been at risk for vessels occlusion and stroke—though it is theoretically hypothesized due to the rarity of this combination.

In our case, the etiology of the leukemoid reaction was multifactorial as the patient presented late to the ER, which increased the stress on the body, on top of the severe dehydration and acidosis status. Also, she has an infection with the SARS-CoV-2 virus (COVID-19), which is a well-known factor that induces a leukemoid reaction.¹⁴ The pathophysiology of developing hyperleukocytosis in DKA is not fully understood; However, some theories linked it to blood acidity, insulin deficiency, increased inflammatory processes, adrenaline surge, and cortisol secretion.^{4,15} Management of hyperleukocytosis by cytoreduction can be achieved by either leukapheresis or exchange transfusion.¹⁶ But, these were risky maneuvers for our patient due to the high possibility of central venous catheter or line thrombosis in the presence of high blood viscosity. The main challenge in our case is balancing the need for a high fluid rate to manage the leukemoid reaction versus a low fluid rate (slow correction) for DKA-induced cerebral edema, with the possibility of serious sequelae from both fluid strategies.

6 | CONCLUSION

Having DKA-induced cerebral edema and leukemoid reaction in a child is a rare combination, rendering a critical and delicate approach. We report a child with severe DKA and cerebral edema associated with severe leukocytosis, which improved with hyperhydration therapy. Careful fluid therapy is essential in those cases to prevent morbidity and mortality.

AUTHOR CONTRIBUTIONS

Abdulla Alfraj: Conceptualization; data curation; methodology; writing – original draft; writing – review and editing. **Naser Al-Enazi:** Conceptualization; methodology; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no financial or other conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Abdulla Alfraj  <https://orcid.org/0000-0003-0179-1716>

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