Submitted December 2014, accepted May 2015

CASE REPORT

New-onset type 1 diabetic ketoacidosis complicated by acute respiratory distress syndrome

P.P. Landburg[1], J.J.J. de Sonnaville[2], J.A. Romijn[3], N.P. Juffermans[4]

[1]Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands,[2]Department of Internal Medicine, Tergooi Hospital, Hilversum, the Netherlands, Department of [3]Internal Medicine and [4]Intensive Care Medicine, Academic Medical Center, Amsterdam, the Netherlands

Correspondence

P.P. Landburg – p.p.landburg@umcg.nl

Keywords - acute respiratory distress syndrome, diabetes mellitus, ketoacidosis, extracorporeal membrane ventilation

Abstract

A young female patient was admitted to the intensive care unit with severe acute respiratory distress syndrome following diabetic ketoacidosis. Intubation and mechanical ventilation were necessary to ensure adequate gas exchange. However, severe hypercapnia with respiratory acidosis persisted despite high ventilatory pressures potentially aggravating ventilator-associated lung injury. A veno-venous extracorporeal membrane ventilator was used to effectively eliminate carbon dioxide. Within a week, the patient could be weaned from the extracorporeal membrane circuit and mechanical ventilator. This case report highlights the importance of considering ARDS as a consequence of diabetic ketoacidosis.

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterised by an acute pulmonary inflammatory response resulting in bilateral opacities on chest imaging and hypoxaemia, often requiring mechanical ventilation. ARDS is able to develop within one week of a clinical insult.[1]

Well-known risk factors for the development of ARDS include sepsis, trauma, aspiration, massive transfusions, drug overdose, pancreatitis, and inhalation injury.[2-4] This report draws attention to the rare development of ARDS due to ketoacidosis as part of the differential diagnosis in a young female presenting with new-onset type 1 diabetes mellitus (DM).

Case report

A 19-year-old Caucasian female with no significant medical history was admitted to the intensive care unit with severe ketoacidosis triggered by new-onset type 1 DM. Five days prior to admission she suffered from a sore throat for which amoxicillin-clavulanic acid was started two days before admission. On the day of admission she was conscious, had polydipsia, polyuria, dysphagia, difficulty in breathing and a non-productive cough. Upon presentation in the emergency room, her blood pressure was 160/105 mmHg with a sinus tachycardia of 126 beats/minute, her temperature was 38.3 °C and her saturation was 98% on room air. Oral inspection revealed an inflamed oropharynx, a red swollen tongue and palpable cervical lymphadenopathy. Initial physical examination of heart and lungs revealed no abnormalities. C-reactive protein and leukocytes were elevated *(table 1)*. Severe metabolic acidosis with an arterial pH of 6.8 was present, as well as hyperglycaemia of 30.9 mmol/l and 3+ ketonuria. The anti-streptolysine test was negative. Chest X-ray on admission was normal. The patient was diagnosed with new-onset type 1 DM with ketoacidosis presumably triggered by a respiratory viral infection, possibly with oral candidiasis. Standard treatment for diabetic ketoacidosis was started with saline infusion and intravenous insulin.[5] Although the diabetic ketoacidosis was thought to be triggered by a viral respiratory infection, amoxicillin- clavulanic acid was continued and nystatin was administered. The sputum culture turned positive for *Candida albicans*. The viral swab for respiratory viruses,

Table 1. Infection parameters on day of admission

		Reference range
C-reactive protein	250mg/l	<10mg/l
Leukocytes	25.2x10 ^{9}/l	4.0 - 10x10 ^{9}/l
Absolute neutrophilic granulocyte count	18x10 ^{9}/l	2.0 - 7.5x10 ^{9}/l
Rods	2x10 ^{9}/l	
Myelocytes	0.25x10 ^{9}/l	
Metamyelocytes	0.25x10 ^{9}/l	
Monocytes	2.0x10 ^{9}/l	
Lymfocytic count*	2.3x10 ^{9}/l	0.8 - 3.2x10 ^{9}/l

* with toxic granulation

which included influenza viruses, turned positive for rhinovirus and enterovirus, while the urinary pneumococcal rapid test, legionella PCR on respiratory material and Ziehl-Neelsen on sputum remained negative. With the antibiotic treatment the patient improved, her body temperature normalised, the inflammatory parameters decreased (C-reactive protein of 143 x 10^9/l and leukocytes of 15.1 x 10^9/l) and her blood cultures remained negative. On recovery, amoxicillin-clavulanic acid was switched to azithromycin in order to reduce the burden of taking pills.

After switching from continuous intravenous insulin to subcutaneous insulin injections on the third day of admission, she became ketoacidotic again with a pH of 7.17 and development of ketonuria. On the fifth day of admission she became dyspnoeic, had a spiking fever of up to 40.2 °C, with an increase of C-reactive protein *(table 2)*. Chest X-ray was repeated and showed bilateral infiltrates. A thoracic CT scan revealed intra-thoracic lymphadenopathy and pulmonary peribronchial cuffing with ground-glass and nodular lesions. There were no pulmonary embolisms. Azithromycin was stopped, amoxicillin-clavulanic acid was administered again and ciprofloxacin was added according to the Dutch Working Party on Antibiotic Policy (SWAB) guideline on pneumonia, and an oral viral swab was repeated.[6] At this point the patient was transferred to the intensive care unit of our hospital.

Table 2. Infection parameters on the fifth day of admission

		Reference range
C-reactive protein	166mg/l	<10mg/l
Leukocytes	11.3x10 ^{9}/l	4.0 - 10x10 ^{9}/l
Absolute neutrophilic granulocyte count	13x10 ^{9}/l	2.0 - 7.5x10 ^{9}/l
Lymfocytic count	1.5x10 ^{9}/l	0.8 - 3.2x10 ^{9}/l

Progressive respiratory failure necessitated intubation and mechanical ventilation. A bronchoscopy with lavage was performed and cultures from blood, urine and saliva were repeated. Sputum yielded a few isolated *Staphylococcus aureus* colonies and the viral swab was positive for rhinovirus and enterovirus. Broncho-alveolar lavage fluid was, however, negative for bacteria and viruses. After the results of the bronchoscopy with lavage were known to be negative, corticosteroids were started in the treatment of ARDS and a thoracic CT scan was repeated *(figure 1)*, which showed increased infiltrates in accordance with the clinical diagnosis of ARDS. Our patient rapidly progressed to severe ARDS necessitating high ventilatory pressures in prone positioning. Although *Staphylococcus aureus* pneumonia was considered unlikely, amoxicillin-clavulanic acid and ciprofloxacin were stopped and flucloxacillin was started, because of her worsening condition. The clinical course also did not seem to fit a viral pneumonia and fungi were not cultured either. Alternatively, the differential diagnosis included ARDS precipitated by the initial diabetic ketoacidosis. On the second day of ICU admission, the hypercapnia became worse, with progressive haemodynamic instability due to high ventilator pressures. There was no other organ failure. In order to decrease the risk of ventilator-associated lung injury, the patient was put on a veno-venous extracorporeal membrane device to facilitate carbon dioxide removal and enable lung protective ventilation, with a blood flow of 1.5 l/min. Other rescue strategies were not given, such as nitric oxide or paralysing agents. Within hours, the ventilatory pressures and vasopressor therapy could be considerably reduced. The pulmonary lesions subsided and after one week the veno-venous extracorporeal membrane device could be removed followed by extubation. The following week she was discharged to the internal medicine ward for further recovery and treatment of her type 1 DM. She is currently well with no impairment of pulmonary performance.

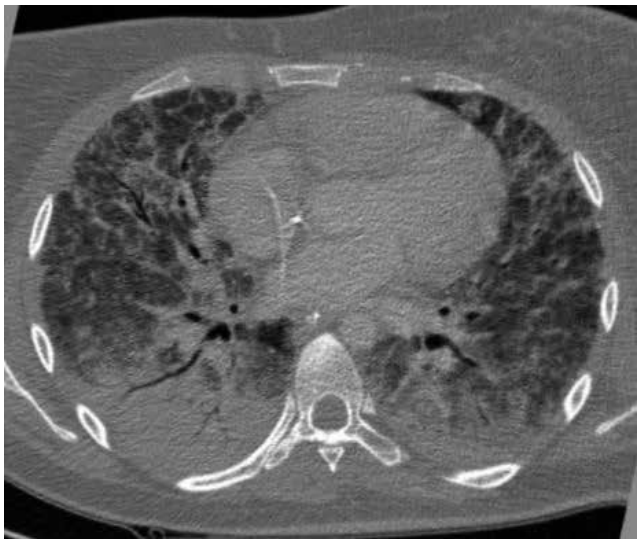

Figure 1. High-resolution CT scan on the eighth day of admission (compared with the same level on earlier CT scan): showing lower lung fields with increasing and confluent consolidations with air bronchograms and diffuse ground-glass in the dependent zones, matching with the clinical diagnosis of ARDS.

Discussion

We present the case of a young female patient with new-onset diabetic ketoacidosis that was complicated by severe ARDS and ultimately a veno-venous extracorporeal membrane device was used. Considering the clinical course related to severe ketoacidosis and the negative cultures it seemed less likely that ARDS developed due to an infectious pathogen, hence the differential diagnosis included ARDS precipitated by severe ketoacidosis.

The incidence of ARDS due to diabetic ketoacidosis is not known. It seems to be less than the incidence of cerebral oedema triggered by diabetic ketoacidosis that is seen in 1-3% of episodes of diabetic ketoacidosis in the paediatric population.[7]

The exact clinical sequence is not well defined, neither is the time frame, yet ARDS usually develops 12-48 hours after treatment for diabetic ketoacidosis. The exact mechanism of ARDS in diabetic ketoacidosis is not clearly understood either. Possibly, high plasma glucose concentrations, low pH and electrolyte disturbances can induce pulmonary oedema, thereby resembling the pathophysiology of cerebral oedema developing as a complication of ketoacidosis.[8,9] Of note, the arterial pH in our patient was very low. In accordance, severe ketoacidosis was also noted in previous case reports that described uncontrolled DM complicated by ARDS.[10-15] Alterations of the alveolar surfactant lining due to acidosis may be a possible mechanism for increased pulmonary capillary permeability, in particular in young patients, which is in line with this case.[9,11,13,16,17] On the other hand, many patients with diabetic ketoacidosis present with a low arterial pH and high glucose levels, but do not develop ARDS. In our patient, the second ketoacidotic episode is probably responsible for further enzymatic impairment or demise on a not fully recovered pulmonary lining, shortly after the first insult, leading to impaired surfactant lining resulting in ARDS.

There is debate about the role of DM in ARDS and the mechanisms underlying the association between DM and ARDS are not clear. Diabetic medications, hyperglycaemia, and the impact of the metabolic syndrome on inflammation may intersect to alter the development of ARDS.[18] Results on whether DM is protective or deleterious in ARDS are conflicting.[19-23] We previously showed that not DM but the use of statins, which are frequently prescribed to patients with DM, protects against the development of ARDS.[24] Of note, DM is associated with cardiac overload. If cardiac overload, as an alternative explanation for bilateral oedema, is not ruled out this may account for a false association between DM and ARDS. However, our patient had normal cardiac function as assessed by repeated echocardiography. In addition, fluid overload following resuscitative treatment of the ketoacidosis as a cause of the pulmonary oedema in our patient is unlikely given that deterioration followed days after resuscitation.

In conclusion, we report a case of severe ARDS presumably precipitated by diabetic ketoacidosis in a young female, who made a full recovery. Ketoacidosis as a cause of ARDS is rare.

Disclosure

All authors declare no conflict of interest. No funding or financial support was received.

References

1. Ranieri VM, Rubenfeld GD, Thompson BT, et al. ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526-33.
2. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000;342:1334-49.
3. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353:1685-93.
4. Wheeler AP, Bernard GR. Acute lung injury and the acute respiratory distress syndrome: a clinical review. Lancet. 2007;369:1553-64.
5. Lutterman JA, Elving LD, van Haeften TW, Verschoor L, Jorna ATM. Richtlijn voor de behandeling van acute ontregeling van diabetes mellitus, diabetische ketoacidose en hyperosmolaire hyperglycemische non-ketotisch syndroom. 2005.
6. Wiersinga WJ, Bonten MJ, Boersma WG, et al. Nederlandse richtlijn voor de behandeling van community acquired pneumonie in volwassenen. 2011
7. Koves IH, Leu MG, Spencer S, et al. Improving care for pediatric diabetic ketoacidosis. Diabetic Ketoacidosis Guideline Development Workgroup. Pediatrics. 2014;134:848-56.
8. Durr JA, Hoffman WH, Sklar AH, El Gammal T, Steinhart CM. Correlates of brain edema in uncontrolled IDDM. Diabetes. 1992;41:627-32.
9. Harris GD, Fiordalisi I. Physiologic management of diabetic ketoacidemia. A 5-year prospective pediatric experience in 231 episodes. Arch Pediatr Adolesc Med. 1994;148:1046-52.
10. Mitsuishi S, Matoba K, Yamazaki H. Acute respiratory distress syndrome in diabetic ketoacidosis. Intern Med. 2014;53:1961-4
11. Kumar B, Ruff ST. Adult respiratory distress syndrome in diabetic ketoacidosis. Intensive Care Med. 1984;10:269.
12. Breidbart S, Singer L, St Louis Y, Saenger PJ. Adult respiratory distress syndrome in an adolescent with diabetic ketoacidosis. J Pediatr. 1987;111:736-8.
13. Carroll P, Matz R. Adult respiratory distress syndrome complicating severely uncontrolled diabetes mellitus: report of nine cases and a review of the literature. Diabetes Care. 1982;5:574-80.
14. Leonard RCF, Asplin C, McCormick CV, Hockaday TDR. Acute respiratory distress in diabetic ketoacidosis: possible contribution of low colloid osmotic pressure. Br Med J (Clin Res Ed). 1983;286:760-2.
15. Young MC. Simultaneous acute cerebral and pulmonary edema complicating diabetic ketoacidosis. Diabetes Care. 1995;18:1288-90.
16. Brun-Buisson CJL, Bonnet F, Bergeret S, Lemaire F, Rapin M. Recurrent high-permeability pulmonary edema associated with diabetic ketoacidosis. Crit Care Med. 1985;13:55-6.
17. Sprung CL, Rackow EC, Fein IA. Pulmonary edema: a complication of diabetic ketoacidosis. Chest. 1980;77:687-8.
18. Honiden S, Gong MN. Diabetes, insulin, and development of acute lung injury. Crit Care Med. 2009;37:2455-64.
19. Kor DJ, Warner DO, Alsara A, et al. Derivation and diagnostic accuracy of the surgical lung injury prediction model. Anesthesiology. 2011;115:117-28.
20. Gu WJ, Wan YD, Tie HT, Kan QC, Sun TW. Risk of acute lung injury/acute respiratory distress syndrome in critically ill adult patients with pre-existing diabetes: a meta-analysis. PLoS One. 2014;27;9:90426.
21. Moss M, Guidot DM, Steinberg KP, et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Crit Care Med. 2000;28:2187-92.
22. Gong MN, Thompson BT, Williams P, Pothier L, Boyce PD, Christiani DC. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. Crit Care Med. 2005;33:1191-8.
23. Iscimen R, Cartin-Ceba R, Yilmaz M, et al. Risk factors for the development of acute lung injury in patients with septic shock: an observational cohort study. Crit Care Med. 2008;36:1518-22.
24. Koh GC, Vlaar AP, Hofstra JJ, et al. In the critically ill patient, diabetes predicts mortality independent of statin therapy but is not associated with acute lung injury: a cohort study. Crit Care Med. 2012;40:1835-43.