CASE REPORT

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

P.P. Landburg1, J.J.J. de Sonnaville2, J.A. Romijn3, N.P. Juffermans4
1Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; 2Department of Internal Medicine, Tergooi Hospital, Hilversum, the Netherlands; 3Department of Internal Medicine and 4Intensive 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. Well-known risk factors for the development of ARDS include sepsis, trauma, aspiration, massive transfusions, drug overdose, pancreatitis, and inhalation injury. 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 ºC 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. 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein</td>
<td>250mg/l</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>25.2x10 ^9/l</td>
</tr>
<tr>
<td>Absolute neutrophil granulocyte count</td>
<td>18x10 ^9/l</td>
</tr>
<tr>
<td>Rods</td>
<td>2x10 ^9/l</td>
</tr>
<tr>
<td>Myelocytes</td>
<td>0.25x10 ^9/l</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>0.25x10 ^9/l</td>
</tr>
<tr>
<td>Monocytes</td>
<td>2.0x10 ^9/l</td>
</tr>
<tr>
<td>Lymphocytic count*</td>
<td>2.3x10 ^9/l</td>
</tr>
</tbody>
</table>

* with toxic granulation
New-onset type 1 diabetic ketoacidosis complicated by acute respiratory distress syndrome

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 ºC, 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. 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein</td>
<td>166 mg/l</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>11.3 x 10^9/l</td>
</tr>
<tr>
<td>Absolute neutrophilic</td>
<td>13 x 10^9/l</td>
</tr>
<tr>
<td>granulocyte count</td>
<td>1.5 x 10^9/l</td>
</tr>
<tr>
<td>Lymphocytic count</td>
<td>0.8 - 3.2 x 10^9/l</td>
</tr>
</tbody>
</table>

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 flucoxacin 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.

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.
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. 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. 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. 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. Results on whether DM is protective or deleterious in ARDS are conflicting. We previously showed that not DM but the financial support was received.

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

References