25 year old female presents with persistent flu-like symptoms

A 25 year old female presents to her primary healthcare clinic complaining of flu-like symptoms which consist of a fever, headache, myalgia, abdominal pain, nausea and fatigue.

Acknowledgement
This case study was kindly provided by Dr Monica Mercer from Immunopaedia

History

Ms L is a 25 year old female who lives in an informal settlement in Johannesburg. She shares a 2 roomed house with two adult cousins and her boyfriend. They have electricity and running water. She is employed part time as a domestic worker and is often the only breadwinner for the household.

8 months ago
She was admitted to hospital for cryptococcal meningitis for which she was successfully treated. At this time she was diagnosed as HIV infected with a CD4 count of 115 and a viral load (VL) of 25000 copies. She was started on an antiretroviral regimen which consists of lamivudine (3TC), stavudine.
(d4T) and efavirenz (EFV).

**2 months ago**
She was responding well to therapy and her CD4 count increased to 450 and her viral load was undetectable at <25 copies.

**1 week ago**
She came to the clinic complaining of weakness, myalgia, headache, nausea and general flu-like symptoms. She also complained of a non-tender lump on her left thigh. She was prescribed acetaminophen and told to return in one week if her symptoms did not improve.

**Differential Diagnosis**
- Influenza
- Cryptococcus meningitis
- IRIS- unlikely because she has been on treatment for 8 months
- Defaulting on treatment
- Drug toxicity

**Examination**

**Vitals:**
BP: 105/55
Temp: 37.5°C
Respiratory rate: 24
Pulse: 100

**Abdominal Examination:**
Right upper abdomen is very tender on palpation.
Hepatomegaly is noted

**Lower Limb Examination:**
Small, soft, mobile, non-tender tumor found on medial aspect of left thigh. This has been identified as a lipoma.

The remainder of the examination is nil of note

**Investigations**
<table>
<thead>
<tr>
<th>Leukocyte Esterase</th>
<th>Trace</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Negative</td>
</tr>
<tr>
<td>Protein</td>
<td>Negative</td>
</tr>
<tr>
<td>Ketones</td>
<td>Trace</td>
</tr>
<tr>
<td>Blood</td>
<td>Negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Na</th>
<th>138</th>
<th>(135-147 mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>4</td>
<td>(3.3-5.0 mmol/l)</td>
</tr>
<tr>
<td>Cl</td>
<td>100</td>
<td>(99-103 umol/l)</td>
</tr>
<tr>
<td>HC03</td>
<td>14</td>
<td>(18-29 mmol/l)</td>
</tr>
<tr>
<td>Urea</td>
<td>7.2</td>
<td>(2.5-6.4 mmol/l)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>170</td>
<td>(62-115 mmol/l)</td>
</tr>
<tr>
<td>Anion Gap</td>
<td>28</td>
<td>(10-18 mmol/l)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Bilirubin</th>
<th>3</th>
<th>(3-18 umol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Bilirubin</td>
<td>1.7</td>
<td>(0-5 umol/l)</td>
</tr>
<tr>
<td>ALP</td>
<td>52</td>
<td>(30-120 U/L)</td>
</tr>
<tr>
<td>GGT</td>
<td>15</td>
<td>(5-35 U/L)</td>
</tr>
<tr>
<td>ALT</td>
<td>90</td>
<td>(5-45 U/L)</td>
</tr>
<tr>
<td>AST</td>
<td>85</td>
<td>(5-45 U/L)</td>
</tr>
<tr>
<td>Lactate</td>
<td>8</td>
<td>(&lt;1.5 mmol/l)</td>
</tr>
</tbody>
</table>

Ultrasound of her abdomen confirmed the hepatomegaly and showed fatty infiltration.
From our results we see this patient has a metabolic acidosis. The diagnosis of metabolic acidosis is based on a calculation which estimates the unmeasured anions and is called the anion gap. The formula used is 

$$\text{(Na} + \text{K}) - (\text{Cl} - \text{HCO}_3)$$

In this case we have a raised anion gap which indicates the patient has a metabolic acidosis.

**Causes of metabolic acidosis**
This occurs due to an increase in production of organic acids, resulting in a fall in HCO₃ or other unmeasured anions and is thus associated with the accumulation of acids.

*Causes include:*
- Lactic acidosis caused by sepsis, shock or hypoxia
- Urate caused by renal failure
- Ketones caused by diabetes mellitus, alcohol or starvation
- Drugs (salicylates, biguanides, ethylene, NRTIs)

**Treatment**
- Patient was admitted to hospital
- All HIV medication was stopped
- L-carnitine 50mg/kg was given per day
- Blood lactate levels measured daily

**Final outcome**
After 20 days her blood results were within normal ranges.

Her CD4 count has however dropped down to 250 and her viral load has increased to 10000 copies. Her declining CD4 count requires that she be carefully monitored and as soon as she reaches 200 she must go back onto ARV therapy. Which will again consist of two NRTIs and an NNRTI, but she will be given two different NRTIs. Fortunately toxicity does not extend to all the drugs in this class.

<table>
<thead>
<tr>
<th>Urea Creatinine and Electrolytes</th>
<th>Values</th>
<th>Normal Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>136</td>
<td>135 – 147 mmol/l</td>
</tr>
<tr>
<td></td>
<td>Values</td>
<td>Normal Limits</td>
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<tr>
<td>----------</td>
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</tr>
<tr>
<td>K:</td>
<td>4</td>
<td>3.3 – 5.0 mmol/l</td>
</tr>
<tr>
<td>Cl:</td>
<td>103</td>
<td>99 – 103 µmol/l</td>
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<tr>
<td>HCO3:</td>
<td>21</td>
<td>19 – 29 mmol/l</td>
</tr>
<tr>
<td>Urea:</td>
<td>6</td>
<td>2.5 – 6.4 mmol/l</td>
</tr>
<tr>
<td>Creatinine:</td>
<td>110</td>
<td>62 – 115 mmol/l</td>
</tr>
<tr>
<td>Anion Gap</td>
<td>16</td>
<td>10 – 18 mmol/l</td>
</tr>
<tr>
<td>Lactate</td>
<td>1</td>
<td>&lt;1.5 mmol/l</td>
</tr>
</tbody>
</table>

**References**


[Link to Article](#)


Additional discussion points have been adapted from a similar case located in [The Body](#).

**Evaluation – Questions & answers**

**What is the diagnosis?**

A drug induced lactic acidosis specifically a NRTI induced lactic acidosis with evidence of hepatic steatosis and lipodystrophy.

**How does lactic acidosis occur?**

Mitochondria are the energy organelles of all cells. Through the process of cellular respiration the mitochondria produce and store adenosine triphosphate (ATP). This is broken down when energy is
needed by cells. The distribution of mitochondria varies depending on the energy requirements of the tissue they reside in. Furthermore mitochondria have their own DNA called mtDNA which is replicated by the enzyme polymerase gamma. Studies have shown that this is a very similar enzyme to reverse transcriptase in HIV. Therefore antiretroviral drugs which inhibit reverse transcriptase may also inhibit polymerase gamma, affecting the replication of mitochondria and the organelles’ repair processes. This results in increasing numbers of non functioning mitochondria with a decreased ability to produce energy aerobically. Anaerobic energy production becomes activated which produces lactate as a by- product. This is released into the blood stream and cleared by the liver. Typically anaerobic respiration is a reserve system and only used when tissue demands are high. However in this case anaerobic respiration becomes excessive, more lactate is produced and accumulates causing lactic acidosis. Thus NRTIs can cause dysfunctions which result in toxicity.

What are the signs and symptoms of mitochondrial toxicity which occur with NRTIs?

Metabolic – lipodystrophy
Hepatic or gastrointestinal- steatosis, lactic acidosis, pancreatitis
Neuromuscular – myopathy or polyneuropathy
Haematologic – pancytopenias
Nephrologic – proximal renal tubular dysfunction

What are the clinical features of NRTI toxicity?

- Nausea and vomiting
- Abdominal pain
- Hepatomegaly
- Tachypnoea
- Asthenia
- Metabolic acidosis
- Lactic acidosis

How does hepatic steatosis occur?

Due to mitochondrial dysfunction hepatic mitochondria cannot adequately oxidize fatty acid, with the result that triglycerides accumulate as lipid vesicles in the hepatocytes. This causes acute microvascular steatosis which can result in liver failure and even death.

What are the risks of prolonged lactic acidosis?

Progression of lactic acidosis can lead to irreversible multi-organ failure and death despite drug withdrawal.

What is the importance of performing blood lactate levels?
Initial lactate levels can predict the course in symptomatic lactic acidosis related to the use of NRTIs. Initial blood lactate levels below 9mmol/L are associated with a less severe disorder and treatment is usually successful. When levels are above 9mmol/L it is often predictive of a fatal outcome.