Winter Surge

Dr. KM Chow
Prince of Wales Hospital
A Call from Chemical Pathology

- Plasma potassium 7.9 mmol/L
- From a 53-year-old outpatient after blood test at the Blood Taking Centre
Headache for Bed Availability
<table>
<thead>
<tr>
<th>Test</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
<th>Value 4</th>
<th>Value 5</th>
<th>Reference</th>
<th>Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>139</td>
<td>136</td>
<td>143</td>
<td>142</td>
<td>137-144</td>
<td>mmol/l</td>
<td></td>
<td></td>
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<tr>
<td>Potassium</td>
<td>4.3</td>
<td>7.8</td>
<td>*</td>
<td>7.9</td>
<td>3.5-5.0</td>
<td>mmol/l</td>
<td></td>
<td></td>
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<tr>
<td>Urea</td>
<td>5.2</td>
<td>6.8</td>
<td>7.1</td>
<td>5.3</td>
<td>3.1-7.8</td>
<td>mmol/l</td>
<td></td>
<td></td>
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<tr>
<td>Creatinine</td>
<td>103</td>
<td>104</td>
<td>108</td>
<td>111</td>
<td>65-109*</td>
<td>umol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Protein</td>
<td>74</td>
<td>69</td>
<td>68</td>
<td>66-80</td>
<td>g/l</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Albumin</td>
<td>47</td>
<td>45</td>
<td>45</td>
<td>46</td>
<td>35-52</td>
<td>g/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>15</td>
<td>23*</td>
<td>25*</td>
<td>&lt; 19</td>
<td>umol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ALP</td>
<td>71</td>
<td>68</td>
<td>70</td>
<td>76</td>
<td>43-105%</td>
<td>IU/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/GPT</td>
<td>72*</td>
<td>41</td>
<td>50</td>
<td>&lt; 53</td>
<td>IU/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urate</td>
<td>0.30</td>
<td>0.25</td>
<td>0.52</td>
<td>0.30</td>
<td>mmol/l</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Calcium</td>
<td>2.30</td>
<td>2.27</td>
<td>2.20</td>
<td>2.20</td>
<td>2.15-2.55</td>
<td>mmol/l</td>
<td></td>
<td></td>
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<tr>
<td>Adj Calcium</td>
<td>2.22</td>
<td>2.20</td>
<td>2.11</td>
<td>2.11</td>
<td>2.15-2.55</td>
<td>mmol/l</td>
<td></td>
<td></td>
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<tr>
<td>Phosphate</td>
<td>1.17</td>
<td>1.24</td>
<td>1.14</td>
<td>1.14</td>
<td>0.72-1.39</td>
<td>mmol/l</td>
<td></td>
<td></td>
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<tr>
<td>LDH</td>
<td>289</td>
<td>230</td>
<td>332</td>
<td>106</td>
<td>218</td>
<td>IU/l</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment:
Patient History

– 53-year-old smoker
– Family history unremarkable
– Beta thalassaemia trait
– Asymptomatic gallstone
– Haemolytic anaemia under haematologist
Recurrent hyperkalaemia

- Multiple *ad hoc* admission for abnormal potassium level
- K 6.0 – 7.9 mmol/L
- Not on slow K replacement and denied NSAID
- Serum Cr 103-111 µmol/L
Further Medical History

- Found cold agglutinin (titre 1:2048) in Union Hospital on year ago
- No documented Mycoplasma disease; denied Raynaud’s
- Direct Coomb’s test anti-C3d positive
- Bone marrow biopsy and CT scan no definite lymphoma
Further Medical History

– Recurrent haemolytic anaemia, usual Hb 9-10 g/dL
– G6PD activity normal
– Repeated cold agglutinin titre > 1:4096
A form of autoimmune haemolytic anaemia

Exposure to cold precipitates formation of thrombi (classically involving ears and acral sites)

Pathogenic cold agglutinins lead to haemolysis and haemagglutination (IgM mediated and complement cascade)

Two forms: Cold Agglutinin Disease

**Primary**: no underlying systemic cause

**Secondary**: associated with *infection* (infectious mononucleosis, HIV, Mycoplasma, etc) or lymphoproliferative disease
Cold agglutinin disease: diagnosis

- presence of chronic haemolytic anaemia
- positive direct antiglobulin test DAT (anti-C3 positive and negative anti-IgG)
- cold agglutinin titre > 1:64 (>1:512 usually clinically significant)

Back to Our Case of Hyperkalaemia and Management
Salient Features

Severe and recurrent hyperkalaemia in a patient without risk factors
Asymptomatic
Normal electrocardiogram ECG
Factitious hyperkalemia (pseudohyperkalemia) should be excluded
Box 3. Key Teaching Points

- Serum potassium measurement should be repeated to exclude pseudo-hyperkalemia in patients with a normal electrocardiogram and no risk factors for hyperkalemia.
- Hyperkalemia typically observed in patients with diabetic ketoacidosis is caused by insulin deficiency and the hypertonic state and not the result of the underlying organic acidosis.
- Hyperkalemia that is chronic is caused by impaired renal potassium excretion and not cell shift.
- Impaired renal potassium excretion can be the result of conditions that severely limit distal sodium delivery, decreased mineralocorticoid levels or activity, or a distal tubular defect; in many instances, one or more mechanisms are present.
- Withholding drugs that block the renin-angiotensin system only on the basis of impaired kidney function can potentially deprive many patients of the cardiovascular benefit they would otherwise receive because numerous steps can be taken to minimize the risk of hyperkalemia.
Risk Factors: Hyperkalaemia

– Chronic kidney disease: risk inversely related to GFR, increases substantially with eGFR < 30 mL/min/1.73m²
– Diabetes mellitus
– Decompensated congestive heart failure
– Medications

Palmer BF, Clegg DJ. Hyperkalemia. JAMA 2015;314:2405-2406
Drug Factors: Hyperkalaemia

- **Inhibition of renin release from juxtaglomerular cells**: β-blockers; calcineurin inhibitors: cyclosporine, tacrolimus; NSAID
- **Inhibition of aldosterone release from the adrenal gland**: heparin; ketoconazole
- **Mineralocorticoid receptor blockade**: spironolactone; eplerenone
- **Blockade of epithelial sodium channel in renal collecting duct**: amiloride; triamterene; trimethoprim
- **Potassium** supplements, salt substitutes, certain herbs, and potassium-enriched foods in setting of impaired renal excretion
How is Potassium Measured?

- Ion-selective electrode that converts activity of dissolved potassium in solution into an electric potential measured by a voltmeter

- **Serum potassium**: blood samples collected in tubes containing a clot activator

- **Plasma potassium**: blood samples collected in tubes containing heparin
Serum *versus* plasma Potassium

Serum potassium concentration is typically 0.1 to 0.4 mmol/L greater than plasma

- due to release of potassium from platelet granules during the clotting process
Pseudohyperkalaemia

First reported in 1955 as a marked elevation of serum potassium levels (due to leakage from platelets *in vitro*) in the absence of clinical evidence of electrolyte imbalance

Hartmann RC, Mellinkoff SM. Relationship of platelets to serum potassium concentration. *J Clin Invest* 1955;34:938
Pseudohyperkalaemia
(Factitious hyperkalemia)

- Thrombocytosis (> 600 x 10⁹/L)
- White blood cell neoplasia (> 200 x 10⁹/L)
- Potassium moves out of red cells (stomatocytosis), or release from erythrocyte cytosol (in vitro haemolysis)
Pseudohyperkalaemia (Factitious hyperkalemia)

- Mechanical factors (prolonged application of a tourniquet and fist clenching during the phlebotomy procedure; very high white blood cell counts and mechanical disruption of WBC via pneumatic tube systems)
Pseudohyperkalaemia
(Factitious hyperkalemia)

- Prolonged storage of blood / delayed analysis
- Blood collected from vein into which potassium is infused
- Haemolysis via small needle or traumatic venepuncture
How Do We Confirm / Exclude Pseudohypermolekulaemia?
Experiment for Patient and Control

- Blood taking from the same doctor (KM Chow)
- Samples from patient and healthy control (a chemical pathologist)
Experiment for Patient and Control

- Transport and storage of blood sample at three environment: (i) 37°C, (ii) room temperature (hospital setting), (iii) -4°C
- Three different storage time before centrifuge to separate plasma: (i) immediately, (ii) 2 hours, (iii) 4 hours
Hemolytic index

Patient

Healthy control

A-37°C
B-RT
C-4°C

Time 0
Time 2
Time 4
Diagnosis

Pseudohyperkalaemia secondary to temperature and time-dependent haemolysis *in vitro*  
(*cold agglutinin disease with haemolysis*)
Minor Point on Workup for Cold Agglutinin Disease

- Part of the workup for this IgM disease is searching for secondary causes
- Including measurement of serum electrophoresis and immunofixation
- Remember to obtain and keep the blood specimen at 37-38°C (until the serum has been removed from the clot)
Why temperature precaution

– If the blood sample is cooled and not kept warm, the cold agglutinin will attach to the RBCs and be removed from the serum, causing a false-negative result
Second Case

– Another call from Chemical Pathology before Lunar New Year
– K 7.5 mmol/L
Patient History

- 75-year-old male ex-smoker
- Beta thalassaemia trait
- Cold autoimmune haemolytic anaemia (AIHA) under haematologist since 2013
- Haptoglobin < 0.2, DAT Coomb’s positive C3d
- Bone marrow B cell lymphoproliferative disorder
Result on Chinese New Year Eve

<table>
<thead>
<tr>
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<tr>
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</tr>
<tr>
<td>Total Protein</td>
<td>65</td>
<td>65 - 1094 umol/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>38</td>
<td>35 - 52 g/L</td>
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<td>MFRD</td>
<td>41</td>
<td>&gt; 60 unit</td>
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Happy Ending
Final Solution: Educate and Tag

Precaution in renal function or LDH test of Mr. [Name Redacted] (to avoid pseudohyperkalaemia due to cold antibody)

For sending out blood specimen (renal function test or LDH level):

- Arrange warm flask from urgent laboratory (ext 3353)
- Store in warm flask and transport to laboratory within 1–2 hours
- Chem Path urgent laboratory (ext 3353) in PWH will process the specimen as urgent sample

Division of Nephrology & Dept of Chemical Pathology
### Adverse Drug Reaction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Drug Reaction</th>
<th>Additional Information</th>
<th>Level of Severity</th>
<th>Update</th>
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</thead>
<tbody>
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### Alert

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional Information</th>
<th>Validity From</th>
<th>Validity To</th>
<th>Update</th>
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</thead>
<tbody>
<tr>
<td>cold AI-A with pseudohyperkalaemia</td>
<td>ensure transport of renal function blood test to laboratory within 2 hours, and stored in warm flask during transport</td>
<td>25-10-2016</td>
<td>27-10-2025</td>
<td>25-10</td>
</tr>
</tbody>
</table>

**Disclaimer:** Records in **RED** are NOT checked by system against medications prescribed.
Summary

- Two cases of cold agglutinin disease causing laboratory artefacts as a result of *in vitro* temperature dependent haemolysis
- Pseudohyperkalaemia confirmed by repeating blood sample stored in warm flask and sent to laboratory within 2 hours