



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

冬季服務高峰期
WINTER SURGE



Laboratory Result X

Lab: Chem Request No.: 16C8480020 Profile: Bone Profile,LDH,LFT,RFT,UA Request Date : 25-Oct-2016

Collect Date :	13/08/16	09/09/16	09/09/16	20/09/16	25/10/16		
Collect Time :	11:04	14:26	19:25	11:48	14:40		
Arrive Date :	13/08/16	09/09/16	09/09/16	20/09/16	25/10/16		
Arrive Time :	11:08	15:39	19:38	12:25	15:31		
Request No. :	C6373959	C7178289	C7183724	C7463406	C8480020	Reference	
Urgency :	--	--	URGENT	--	--	Range	Units

C

PLASMA

Sodium	139	138	143		142	137 - 144	mmol/l
Potassium	4.3	7.8 *	4.1		7.9 *	3.5 - 5.0	mmol/l
Urea	5.2	6.8	7.1		5.3	3.1 - 7.8	mmol/l
Creatinine	103	104	108		111 *	65 - 109‡	umol/l
Total Protein		74		69	68	66 - 80	g/l
Albumin		47	45	45	46	35 - 52	g/l
Total Bilirubin		18		23 *	25 *	< 19	umol/l
Total ALP		71	68	70	76	43 - 105‡	IU/l
ALT/GPT		72 *		41	50	< 53	IU/l
Urate					0.30	0.25 - 0.52‡	mmol/l
Calcium		2.33	2.27		2.20	2.15 - 2.55	mmol/l
Adj.Calcium		2.22	2.20		2.11 *	2.15 - 2.55	mmol/l
Phosphate		1.17	1.24		1.14	0.72 - 1.39	mmol/l
LDH		289 *		230 *	332 *	106 - 218	U/l

Comment:

CHEMICAL PATHOLOGY 1



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 $\mu\text{mol/L}$



Further Medical History

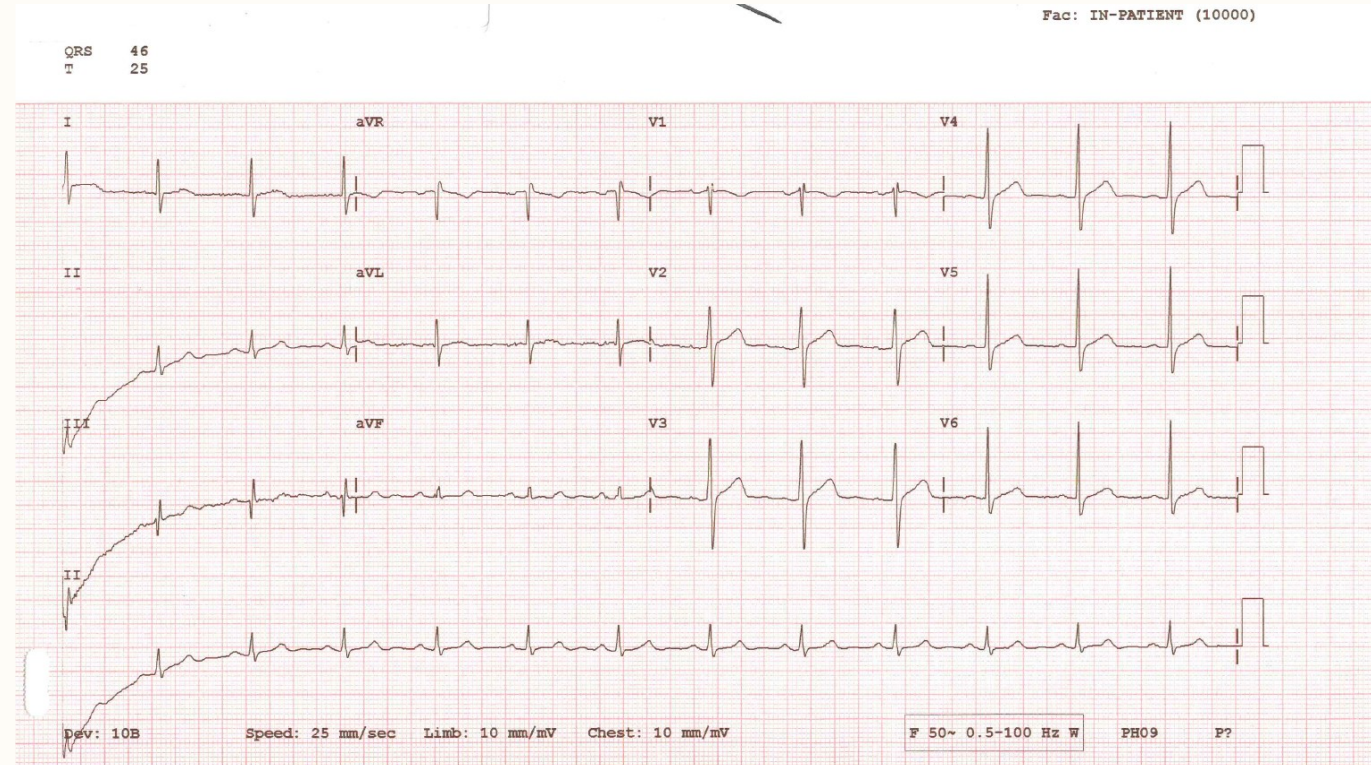
- Found cold agglutinin (titre 1:2048) in Union Hospital on year ago
- No documented Mycoplasma disease; denied Raynaud's
- Direct Coomb's test anti-C3d positive
- Bone marrow biopsy and CT scan no definite lymphoma



Further Medical History

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

ECG





Few Words About Cold Agglutinin Disease

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)

Berentsen S. How I manage cold agglutinin disease. Br J Haematol 2011;153:309-17

Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. Blood 2013 122:1114-1121



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 pseudohyperkalemia in patients with a normal electrocardiogram and no risk factors for hyperkalemia. ~~The 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



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 ($> 600 \times 10^9/L$)
- White blood cell neoplasia ($> 200 \times 10^9/L$)
- 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 Pseudohyperkalaemia?

Experiment for Patient and Control

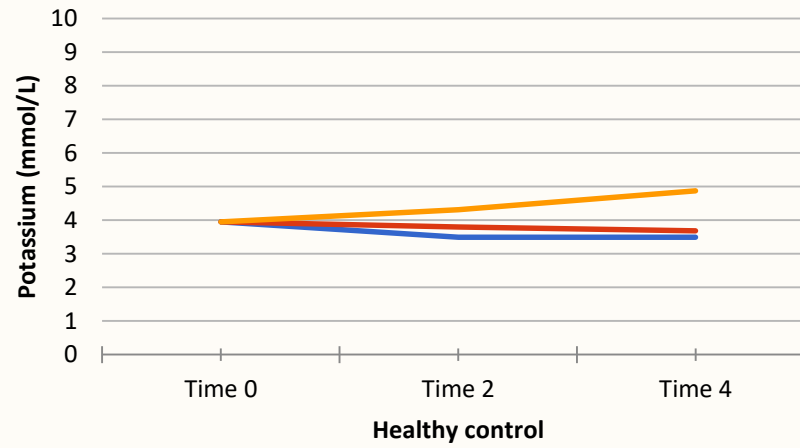
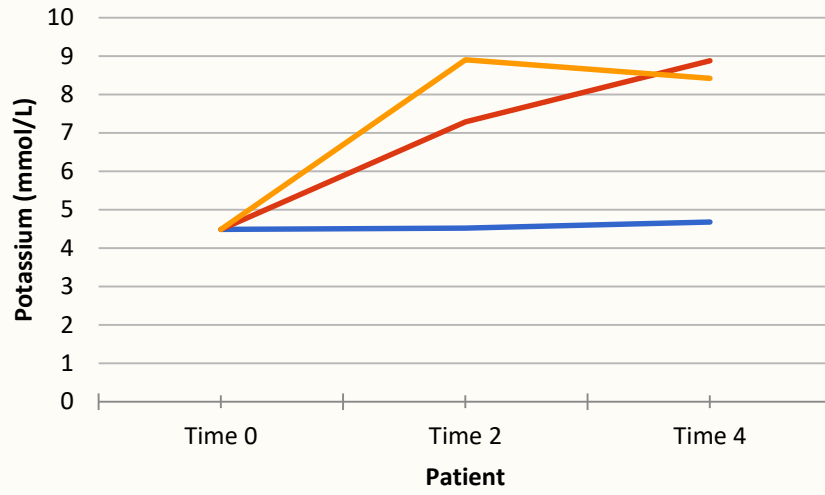
- Blood taking from the same doctor (KM Chow)
- Samples from patient and healthy control (a chemical pathologist)

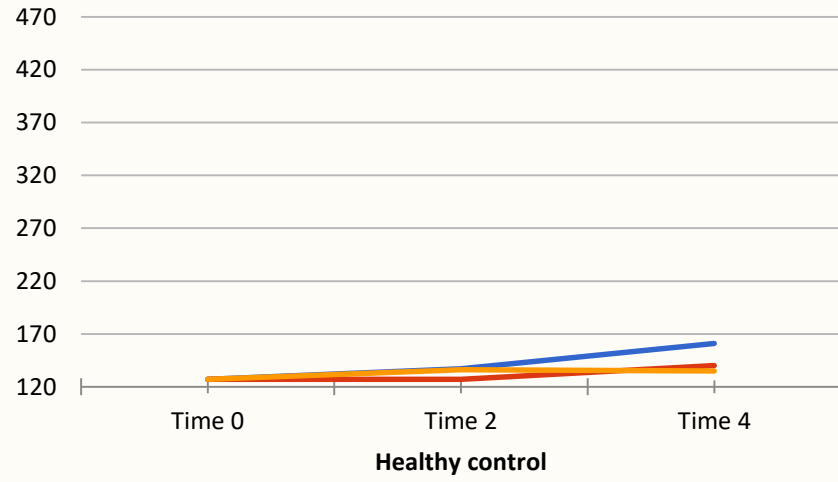
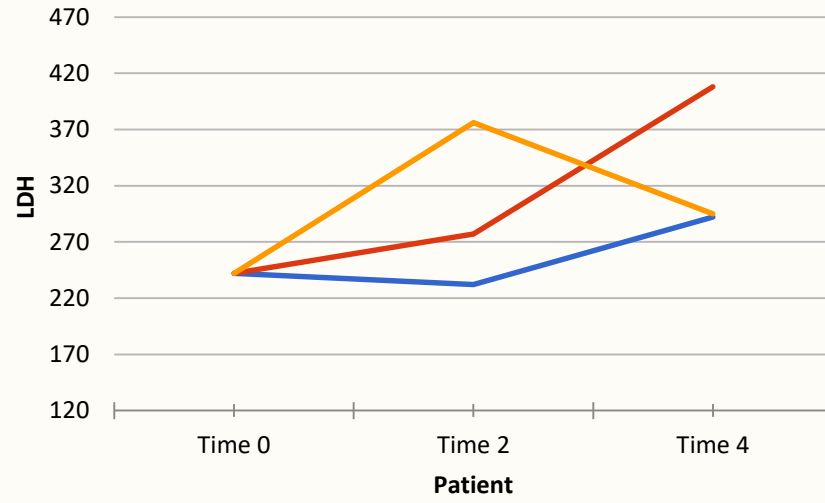


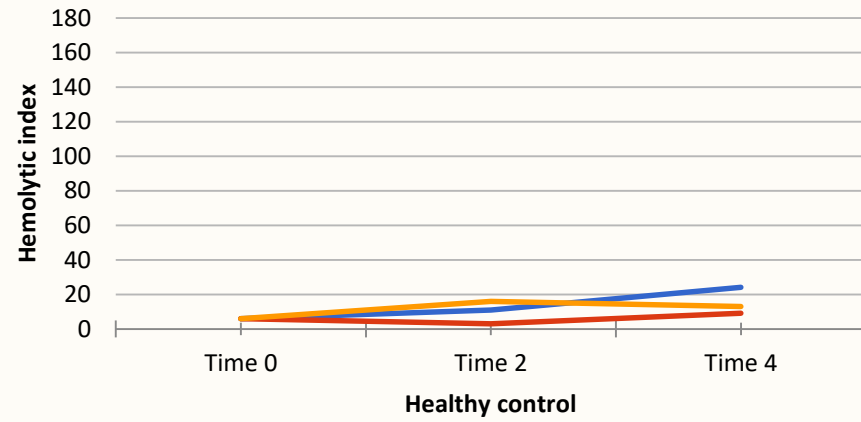
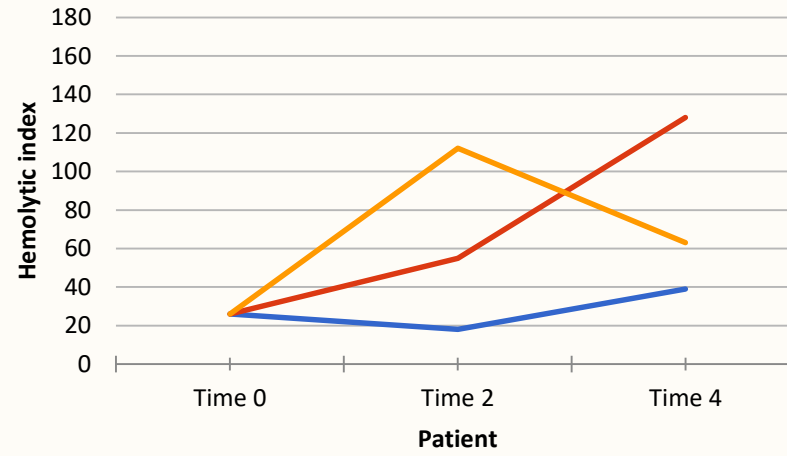


Experiment for Patient and Control

- 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







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

Laboratory Result X							
Lab: Chem	Request No. : 17C0838223	Profile: Bone Profile,CR,LDH,LFT,MDRD,RFT	Request Date : 27-Jan-2017				
Collect Date :	06/09/16	27/09/16	28/09/16	28/09/16	27/01/17		C
Collect Time :	09:28	13:13	09:19	14:16	13:02		
Arrive Date :	06/09/16	27/09/16	28/09/16	28/09/16	27/01/17		
Arrive Time :	11:04	14:42	10:14	14:26	14:24		
Request No. :	C7066029	C7684201	C7704387	C7718120	C0838223	Reference	
Urgency :	--	--	URGENT	URGENT	--	Range	Units
PLASMA							
Sodium	138	145 *	145 *	146 *	137	137 - 144	mmol/l
Potassium	CANCEL	CANCEL	7.2 *	3.8	7.5 *	3.5 - 5.0	mmol/l
Urea	9.9 *	7.4	9.4 *	8.9 *	13.5 *	3.1 - 7.8	mmol/l
Creatinine	132 *	109	116 *	114 *	146 *	65 - 109†	umol/l
Total Protein		65 *			71	66 - 80	g/l
Albumin		38			37	35 - 52	g/l
Total Bilirubin		11			16	< 19	umol/l
Total ALP		70			67	43 - 105†	IU/l
ALT/GPT		24			24	< 53	IU/l
Calcium		2.19			2.28	2.15 - 2.55	mmol/l
Adj.Calcium		2.22			2.33	2.15 - 2.55	mmol/l
Phosphate		0.83			1.04	0.72 - 1.39	mmol/l
LDH		345 *			387 *	106 - 218	U/l
MDRD					41 *	>60	unit

CHEMICAL PATHOLOGY I

Happy Ending

Laboratory Result X

ab : Chem Request No. : 17C0849939 Profile : RFT Request Date : 28-Jan-2017

	27/09/16	28/09/16	28/09/16	27/01/17	28/01/17	Reference	Units
Collect Date :	27/09/16	28/09/16	28/09/16	27/01/17	28/01/17		
Collect Time :	13:13	09:19	14:16	13:02	10:27		
Arrive Date :	27/09/16	28/09/16	28/09/16	27/01/17	28/01/17		
Arrive Time :	14:42	10:14	14:26	14:24	10:47		
Request No. :	C7684201	C7704387	C7718120	C0838223	C0849939		
Urgency :	--	URGENT	URGENT	--	URGENT	Range	Units
PLASMA							
Sodium	145 *	145 *	146 *	137	142	137 - 144	mmo1/l
Potassium	CANCEL	7.2 *	3.8	7.5 *	4.2	3.5 - 5.0	mmo1/l
Urea	7.4	9.4 *	8.9 *	13.5 *	14.1 *	3.1 - 7.8	mmo1/l
Creatinine	109	116 *	114 *	146 *	134 *	65 - 109\$	umo1/l
Total Protein	65 *			71		66 - 80	g/l
Albumin	38			37		35 - 52	g/l
Total Bilirubin	11			16		< 19	umo1/l
Total ALP	70			67		43 - 105\$	IU/l
ALT/GPT	24			24		< 53	IU/l
Calcium	2.19			2.28		2.15 - 2.55	mmo1/l
Adj.Calcium	2.22			2.33		2.15 - 2.55	mmo1/l
Phosphate	0.83			1.04		0.72 - 1.39	mmo1/l
LDH	345 *			387 *		106 - 218	U/l
MDRD				41 *		>60	unit

Comment :

Previous Next Request list Print Close

CHEMICAL PATHOLOGY R

Final Solution: Educate and Tag

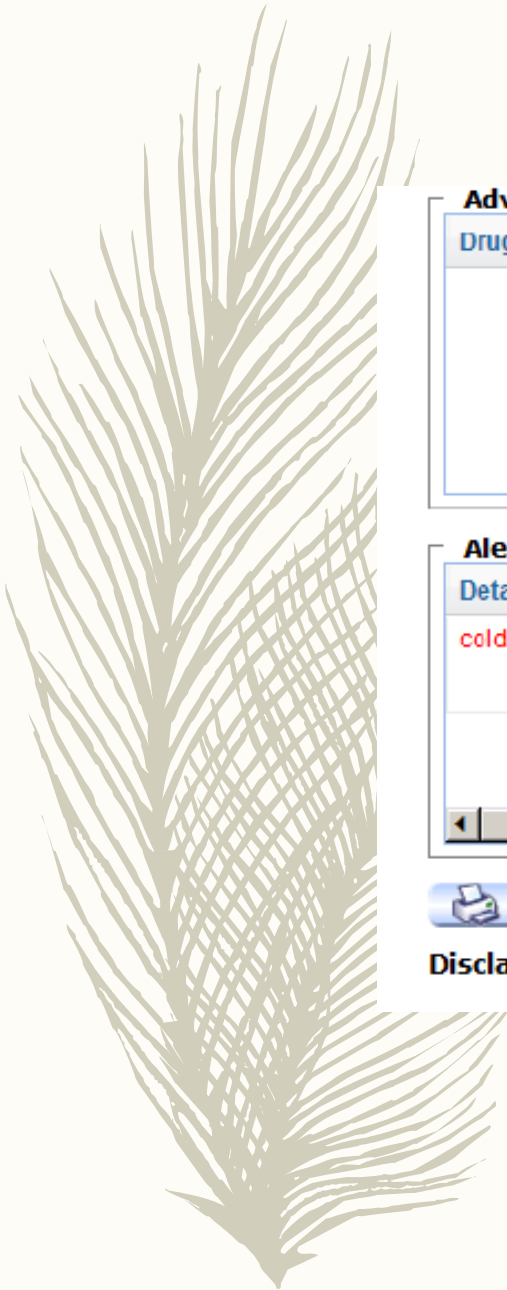
Precaution in renal function or LDH test of Mr. [REDACTED] (to avoid pseudohyperkalaemia due to cold antibody)

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

Drug	Adverse Drug Reaction	Additional Information	Level of Severity	Update

+ Add

Edit

Delete

Alert

Details	Additional Information	Validity From	Validity To	Update
cold AIHA with pseudohyperkalaemia	ensure transport of renal function blood test to laboratory within 2 hours, and stored in warm flask during transport	26-10-2016	27-10-2025	26-10

+ Add

Edit

Delete

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Preview

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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

