

A 3-year-old male with severe anemia and dark urine

1-25-2023
Gabor Oroszi MD PhD

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- 11/3/22 at 15:00 - CMH admission
- PMH - previously healthy
- HPI
 - Fever 5 days prior
 - Vomiting 4 days prior (6+ episodes daily)
 - Hematuria and jaundice 1 day prior
 - Cough&congestion (several other family members with URI symptoms)
- Mercy Hospital Joplin ED

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Mercy Hospital Joplin ED
11/2-11/3

- VS
 - T: 98.9, HR: 162, RR: 28, SaO₂: 96% on RA
- PE: scleral icterus and jaundice
- Labs
 - RBC: 1.22
 - Hb: 3.6
 - LDH: 1577
 - AST: 95
 - TBili: 5.7 (Direct Bili: 0.4)
 - 20 mL/kg NS bolus
 - 5 mL/kg RBC

Lab Results
Elin from Mercy Joplin 11/2/22: 11/2/22:
CBC 1.0
Hgb 3.5 (report after pH&G 2.8)
Hct 10 (report after pH&G 3.6)
MCV 107
MCH 32
MCHC 29.9
RDW 15.4
plate 172
wbc 12.2
HbA1c 5.8
LDH 1577
bilirubin 5.4%
RBC: 1.22
Hb: 3.6
LDH: 1577
AST: 95
TBili: 5.7
Direct Bili: 0.4

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Children's Mercy Hospital (CMH)

Lab View	1/16/2022 11:09:27	1/16/2022 11:09:27	Lab View	1/16/2022 11:15	1/16/2022 11:09:27
Chemistry			Urinary/Protein		Hgb/Hct
Bilirubin Total	0.0		Cr/Creat	0.9	18.0
Bilirubin Direct	0.0		Cr/Creat	0.9	18.0
Bilirubin Indirect	0.0		Cr/Creat	0.9	18.0
ALT	18.0		Cr/Creat	0.9	18.0
AST	20		Cr/Creat	0.9	18.0
LDH	70.4		Cr/Creat	0.9	18.0
Renew Transglut			Cr/Creat	0.9	18.0

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Workup

Lab View	1/16/2022 11:15
Blood Bank	1/16/2022 11:15
ABO/Rh	1/16/2022 11:15
Direct Antiglobulin Test	1/16/2022 11:15
Antibody Panel	1/16/2022 11:15

Test Requested		Investigate Positive DAT		Date Tested
				1/16/2022
Immunohematology Testing				
Red Blood Cell		Direct Antiglobulin Test		
ABO Group	Rh Type	Polyspecific Positive	Specific Positive	Completion Positive
Antibody Identification				
Previous Serologic Findings		Current Serologic Findings		
Source	Reactivity	Direct Antiglobulin Test	Source	Reactivity
No Previous History		Plasma	Plasma	Warm Autoantibody Cold Autoantibody No alloantibodies detected
				Clinical Significance See Below See Below

Additional Comments	
Transfusion of patients with autoantibodies carries a greater than normal risk.	
Cold autoantibodies are not usually clinically significant.	
The patient's sample has been submitted to the National Center for Blood Group Genetics, 2002 W 39th Ave., Kansas City, KS 66203 - 913-574-6100 - for Reflex HEA testing (Red Hub order 12628622) to obtain the patient's predicted phenotype.	

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Workup

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Lab View	1/16/2022 11:15	Lab View	1/16/2022 11:15
ABO/Rh		ABO/Rh	
ABO/Rh	1/16/2022 11:15	ABO/Rh	1/16/2022 11:15
Direct Antiglobulin Test	1/16/2022 11:15	Direct Antiglobulin Test	1/16/2022 11:15
Antibody Panel	1/16/2022 11:15	Antibody Panel	1/16/2022 11:15

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- 11/4 "In discussion with blood bank this morning, additional testing showed both warm and cold agglutinins and that cold agglutinins were clinically insignificant. Decision was made to treat for **warm autoimmune hemolytic anemia** by initiating steroids and famotidine"
- "In discussion with blood bank, given hemoglobin relatively stable in the setting of very **low levels of both cold and warm agglutinins**, this may represent that her **hemolytic process is transient and already resolving**, especially in the setting of 3 known infection causes- **RSV, R/E+**, and mycoplasma IgM positive. With this we will choose to support her with transfusions and then monitor her to see if hemolysis is improved or continues. Will have a low threshold to reinstitute steroid treatment."

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- 11/6 "She continues to hemolyze with Hgb 5.9 this morning, so will proceed with another transfusion and will **resume steroid** course."

Hematology	L	WBC	Lab View	1/16/2022 08:30 CST	1/16/2022 16:15 CST
1/16/2022 08:30 CST	2.14		Blood Bank		
1/16/2022 14:55 CST	4.51	45.1	ABO/Rh	LA POS	
1/16/2022 15:30 CST	2.48	4.8	Comments	Complete, Complete, Complete	
1/16/2022 15:30 CST	4.14	4.14	Antibody Screen	Unreactive	
1/16/2022 14:44 CST	8.83	8.83	Direct Antiglobulin Test	Wf Neg/Complement Pos	
1/16/2022 16:15 CST	4.24	4.24	Antibody Result	Warm Autoantibody 1+, 3+ CM	

Dispensed and Presumed Transfused				
Product	Unit Number	Transfused Date and Time	Dispensed Volume	
RBC AS1 LR RRR Pmt	W045022191213	11/09/2022 12:05	100	
RBC ASP A33 LR RRR Pmt	W045022915623	11/05/2022 19:21	110	
RBC ASP A33 LR RRR Pmt	W045022915623	11/04/2022 22:20	100	
RBC ASP A33 LR RRR Pmt	W045022915623	11/04/2022 16:31	100	
RBC AS1 LR RRR Pmt	W045022193516	11/04/2022 19:51	88	
RBC AS1 LR RRR Pmt	W045022193516	11/04/2022 03:54	95	
RBC AS1 LR RRR Pmt	W045022193516	11/03/2022 20:59	105	

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- 11/7 "Her hemoglobin continues to gradually decrease despite blood transfusions and high dose IV steroids yesterday. Discussed at length with hematology and will plan to treat as a **cold autoimmune hemolytic anemia** and **discontinue steroids** as she has not responded."

Test Requested:		Cold Antibody Titration			Date Tested:	1/17/2022
Immunohematology Testing						
Red Blood Cell						
ABO Group (In Type)	Other Antigen Types	Polyspecific	Direct Antiglobulin Test	Indirect	Complement	
A	Pos	Positive	Positive	Positive	Positive	
Antibody Identification						
Previous Serologic Findings			Current Serologic Findings			
Source	Antibody	Clinical Significance	Source	Antibody	Clinical Significance	
Eluate	Warm autoantibody	See below	Plasma	Cold autoantibody	See below	
Plasma	Cold autoantibody	See below				
Additional Comments						
The DAT results are consistent with the previously reported warm autoantibody. An eluate was not prepared from this sample. Transfusion of patients with autoantibodies carries a greater than normal risk.						
Titration studies indicated the cold autoantibody had a titer of 4 against 1 positive cells and a titer of <2 with 1 negative cells at 4°C. Thermal amplitude studies demonstrated no reactivity at 37°C, indicating the cold autoantibody is not clinically significant.						

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- 11/8 "Patient has remained stable on room air for >24 hours. She experienced a drop in hemoglobin from 6.8 to 5.9 over the previous day. She remained asymptomatic so no transfusions were given."

Hematology	U	mg	Lab View	11/08/2022 16:58	11/08/2022 15:02 CPT
11/08/2022 04:21 CPT	S.H.		Source		A TCS
11/08/2022 04:15 CPT	S.H.		Abnorm		
11/08/2022 04:15 CPT	S.H.		Iron studies		
11/08/2022 04:15 CPT	S.H.		Antibody Screen		Negative
11/08/2022 04:15 CPT	S.H.		Direct Antiglobulin Test		
11/08/2022 04:15 CPT	S.H.		Phenology Comment		
11/08/2022 04:15 CPT	S.H.		ABO/Rh Confirm		
11/08/2022 04:15 CPT	S.H.		Reference Lab (See Blood Bank)		(Reference Lab Only)
11/08/2022 04:15 CPT	S.H.				

Product	Unit Number	Transfused Date and Time	Dispensed Volume
RBC ASP A51 LR C1 RRR Plat	W045022102592	11/08/2022 22:37	180
RBC A51 LR RRR Plat	W045022102513	11/08/2022 12:55	100
RBC ASP A53 LR RRR Plat	W04502215823	11/05/2022 18:21	110
RBC ASP A53 LR RRR Plat	W04502215823	11/04/2022 22:26	100
RBC ASP A53 LR RRR Plat	W04502215823	11/04/2022 16:31	100
RBC A51 LR RRR Plat	W045022103516	11/04/2022 09:51	88
RBC A51 LR RRR Plat	W045022103516	11/04/2022 03:54	95
RBC A51 LR RRR Plat	W045022103516	11/03/2022 20:59	105

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- 11/9 "Patient received 10cc/kg PRBC transfusion last night for Hgb 5.9. She remains asymptomatic from anemia. Mom reports improved energy and jaundice today."

Immunohematology Testing					Date Tested	
ABO Group	Rh Type	Test Result	Other Antigen Types	Antigen Specific	W6 Specific	Comments
A	Pos					

Previous Serologic Findings			Current Serologic Findings		
Specie	Antibody	Clinical Significance	Test	Result	See Below
Elute	Warm autoantibody	See Below	Donath-Landsteiner Test	Positive	See Below
Plasma	Cold autoantibody	See Below			

Additional Comments

The DAT results are consistent with the previously reported warm autoantibody. An eluate was not prepared from this sample per the hospital's request. Transfusion of patients with autoantibodies carries a greater than normal risk.

Titrations studies performed on a previous sample indicated the cold autoantibody had a titer of 4 against 1 positive cells and a titer of <3 with 1 negative cells at 4°C. Thermal amplitude studies performed on a previous sample demonstrated no reactivity at 37°C, indicating the cold autoantibody is not clinically significant. Repeat antibody identification was not performed on the current sample per the hospital's request.

The Donath-Landsteiner test performed on the patient's warm separated serum was positive for IgG anti-RhD. Keeping the patient and her environment warm may be helpful in preventing hemolysis. If transfusion is required, we would recommend the use of a blood warmer.

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- 11/10 "Additional testing was obtained, and Donath-Landsteiner test was positive 11/9 which indicates paroxysmal cold hemoglobinuria (PCH). PCH is a rare autoimmune hemolytic anemia most commonly affecting children recovering from a viral infection. Treatment is supportive with avoidance of cold exposure and transfusions as needed. By day of discharge, her hemoglobin was >7, total and indirect bilirubin was downtrending."

Hematology	U	mg	Quantity	U	mg	U	mg	U	mg	U	mg	U	mg
11/08/2022 08:15 CPT	N.L.		11/08/2022 08:15 CPT	11.9		12.9		12.9		12.9		12.9	
11/08/2022 08:15 CPT	N.L.		11/08/2022 14:28 CPT	14.9		14.9		14.9		14.9		14.9	
11/08/2022 08:15 CPT	N.L.		11/08/2022 20:09 CPT	14.9		14.9		14.9		14.9		14.9	
11/08/2022 08:15 CPT	N.L.		11/08/2022 04:05 CPT	14.9		14.9		14.9		14.9		14.9	
11/08/2022 08:15 CPT	N.L.		11/08/2022 21:48 CPT	17.9		17.9		17.9		17.9		17.9	
11/08/2022 08:15 CPT	N.L.		11/08/2022 09:19 CPT	14.9		14.9		14.9		14.9		14.9	
11/08/2022 08:15 CPT	N.L.		11/08/2022 14:58 CPT	17.9		17.9		17.9		17.9		17.9	
11/08/2022 08:15 CPT	N.L.		11/08/2022 03:19 CPT	18.9		18.9		18.9		18.9		18.9	
11/08/2022 08:15 CPT	N.L.		11/08/2022 14:28 CPT	18.9		18.9		18.9		18.9		18.9	
11/08/2022 08:15 CPT	N.L.		11/08/2022 09:08 CPT	18.9		18.9		18.9		18.9		18.9	
11/08/2022 08:15 CPT	N.L.		11/08/2022 01:28 CPT	12.9		12.9		12.9		12.9		12.9	

Product	Unit Number	Transfused Date and Time	Dispensed Volume
RBC ASP A51 LR C1 RRR Plat	W045022102592	11/08/2022 22:37	180
RBC A51 LR RRR Plat	W045022102513	11/08/2022 12:55	100
RBC ASP A53 LR RRR Plat	W04502215823	11/05/2022 18:21	110
RBC ASP A53 LR RRR Plat	W04502215823	11/04/2022 22:26	100
RBC ASP A53 LR RRR Plat	W04502215823	11/04/2022 16:31	100
RBC A51 LR RRR Plat	W045022103516	11/04/2022 09:51	88
RBC A51 LR RRR Plat	W045022103516	11/04/2022 03:54	95
RBC A51 LR RRR Plat	W045022103516	11/03/2022 20:59	105

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CMH

Lab Name	ABO/Rh	Crossmatch	Antibody Screen	Direct Antiglobulin Test
11/05/2022 16:28 CST				
11/05/2022 16:28 CST	A POS	Compatible	Negative	IgG Neg/Complement Pos
11/05/2022 16:28 CST				
11/05/2022 16:28 CST	A POS	Compatible, Compatible, Compatible	Negative	IgG Neg/Complement Pos

CBC

Investigate Positive DAT

Date Tested: 11/3/2022

Direct Antiglobulin Test

Polyspecific	IgG Specific	Complement
Positive	Positive	Positive

Current Serologic Findings

Specie	Antibody	Clinical Significance
Etiology	Warm autoantibody	See Below
Plasma	Cold autoantibody	See Below
Plasma	No alloantibodies detected	

Date Tested: 11/2/2022

Direct Antiglobulin Test

Polyspecific	IgG Specific	Complement
Positive	Positive	Positive

Date Tested: 11/3/2022

Direct Antiglobulin Test

Polyspecific	IgG Specific	Complement
Positive	Positive	Positive

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Paroxysmal cold hemoglobinuria (PCH)
(Donath-Landsteiner hemolytic anemia or Donath-Landsteiner syndrome)

- AIHA - IgG (polyclonal)
 - Molecular mimicry
 - P antigen
 - No RBC agglutination
 - Biphasic antibody (binds to RBCs in the cold and dissociates upon warming)
 - Complement fixation (in the cold)
- Intravascular hemolysis
 - Complement cascade completed at 37°C
- Associated conditions
 - Children - viral infection
 - Adults - (tertiary) syphilis
- Indications for testing
 - Intravascular hemolysis with a positive Coombs test for complement (negative for IgG) and no RBC agglutination on the peripheral blood smear

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Paroxysmal cold hemoglobinuria (PCH)
(Donath-Landsteiner hemolytic anemia or Donath-Landsteiner syndrome)

- Testing for the Donath-Landsteiner antibody (biphasic hemolysin)
 - 3 sets of tubes (pt serum + group O RBCs)
 - 4°C → 37°C
 - 4°C
 - 37°C
 - Fresh blood sample
 - Stored at 37°C
 - NO EDTA tube
 - Complement supplementation (normal serum)

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Laboratory characteristics, pathophysiology, and therapy for primary autoimmune hemolytic anemia observed in children

Characteristic	Warm-reactive AIHA	Paroxysmal cold hemoglobinuria	Cold agglutinin disease
Autoantibody isotype	IgG	IgG	IgM
Thermal reactivity	Warm	Cold	Cold
Ability to fix complement	Variable	Yes	Yes
DAT (Coombs test) result	4°C: Not typically performed 37°C: Positive for IgG, ± C3	4°C: Positive for IgG and C3 37°C: Negative for IgG, positive for C3	4°C: Negative for IgG, positive for C3 37°C: Negative for IgG, positive for C3
Antigenic reactivity	Ih, others	I _H	I ₁ or I ₂
Site of hemolysis	Spleen	Intravascular	Liver, intravascular
First-line therapy	Glucocorticoids	Avoidance of cold	Avoidance of cold
Secondary therapy	Splenicectomy, Rituximab ^a	Glucocorticoids	Rituximab ^a

AHA, autoimmune hemolytic anemia; IgG, immunoglobulin G; IgM, immunoglobulin M; DAT, direct antiglobulin test (Coombs test); C, C3; C3, complement component 3; Ih, Rhesus.
^a This is an off-label use of rituximab.

Adapted from: Chou JT, Schneider AB. Autoimmune hemolytic anemia. In: Hatcher and (2015) Hematology and Oncology of Infancy and Childhood (7th ed). DeSa D, Fisher DC, Look L, et al. (Eds). WB Saunders, Philadelphia 2015, p. 471.

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CMH

Lab Value	ABO/Rh	Crossmatch	Antibody Screen	Direct Antiglobulin Test
11/06/2022 18:28 CPT				
11/06/2022 18:28 CPT	A POS	Compatible	Negative	IgG Neg/Complement Pos
11/06/2022 18:28 CPT				
11/06/2022 18:28 CPT	A POS	Compatible, Compatible, Compatible	Negative	IgG Neg/Complement Pos

DAT at RT
 Poly - in tube
 IgG - in gel
 C3 - in tube

ABS at 37°C in gel
 CM at 37°C in gel

CBC

Investigate Positive DAT		
	Date Tested	11/3/2022
Direct Antiglobulin Test		
Polyspecific	IgG Specific	Complement
Positive	Positive	Positive
Current Serologic Findings		
Specie	Antibody	Clinical Significance
Eluate	Warm autoantibody	See Below
Plasma	Cold autoantibody	See Below
Plasma	No alloantibodies detected	
Date Tested: 11/7/2022		
Direct Antiglobulin Test		
Polyspecific	IgG Specific	Complement
Positive	Positive	Positive
Date Tested: 11/9/2022		
Direct Antiglobulin Test		
Polyspecific	IgG Specific	Complement
Positive	Positive	Positive

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References

- Henry's Clinical Diagnosis and Management by Laboratory Methods, 24th Ed, 2022, Chapters 33, 36
- UpToDate, January 2023
- Transfusion Medicine and Hemostasis, Clinical and Laboratory Aspects, 3rd Ed, 2019, Chapter 51

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