

Cold Agglutinin Disease with Cryoglobulinemia

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Case Study

- 80year old man with severe aortic stenosis presented for evaluation for percutaneous aortic valve replacement with possible conversion to open heart surgery
- Patient had 20year history of cold agglutinin disease with cryoglobulinemia. Cold agglutinin titer in 2010 was 2480. Patient has been asymptomatic throughout the past 20 years.
- Hematology service was consulted to determine how best to manage this patient's procedure given the history of cold agglutinin disease and the possible need to lower his body temperature if cardio pulmonary bypass was needed.

Cold agglutinin disease

- Rare disease accounting for 16%-32% of all autoimmune hemolytic anemias.
- Characterized by IgM antibodies that react strongly at 4°. These antibodies may also react at RT which can lead to difficulties in determining the ABO type.
- Storing collected samples at 37° can eliminate this problem or alternatively the sample can be warmed to 37° for 10-15 minutes and then separated.

CAD

- Most antibodies of these type in adults are anti-I.
- Can cause moderate chronic hemolytic anemia in middle-aged or elderly patients which is often exacerbated by cold temperatures.
- Rarely significant except in situations where titer is high and there is possibility of lowering the patient's body temperature.

Cryoglobulins

- IgM immunoglobulins that precipitate from solution in the cold.
- This patient's serum cryoglobulin level was **36%**
- By electrophoresis this patient was determined to have Type I cryoglobulinemia

(monoclonal IgM kappa)

Type I cryoglobulins are associated with multiple myeloma or Waldenstrom macroglobulinemia.

Livedo reticularis in response to cold

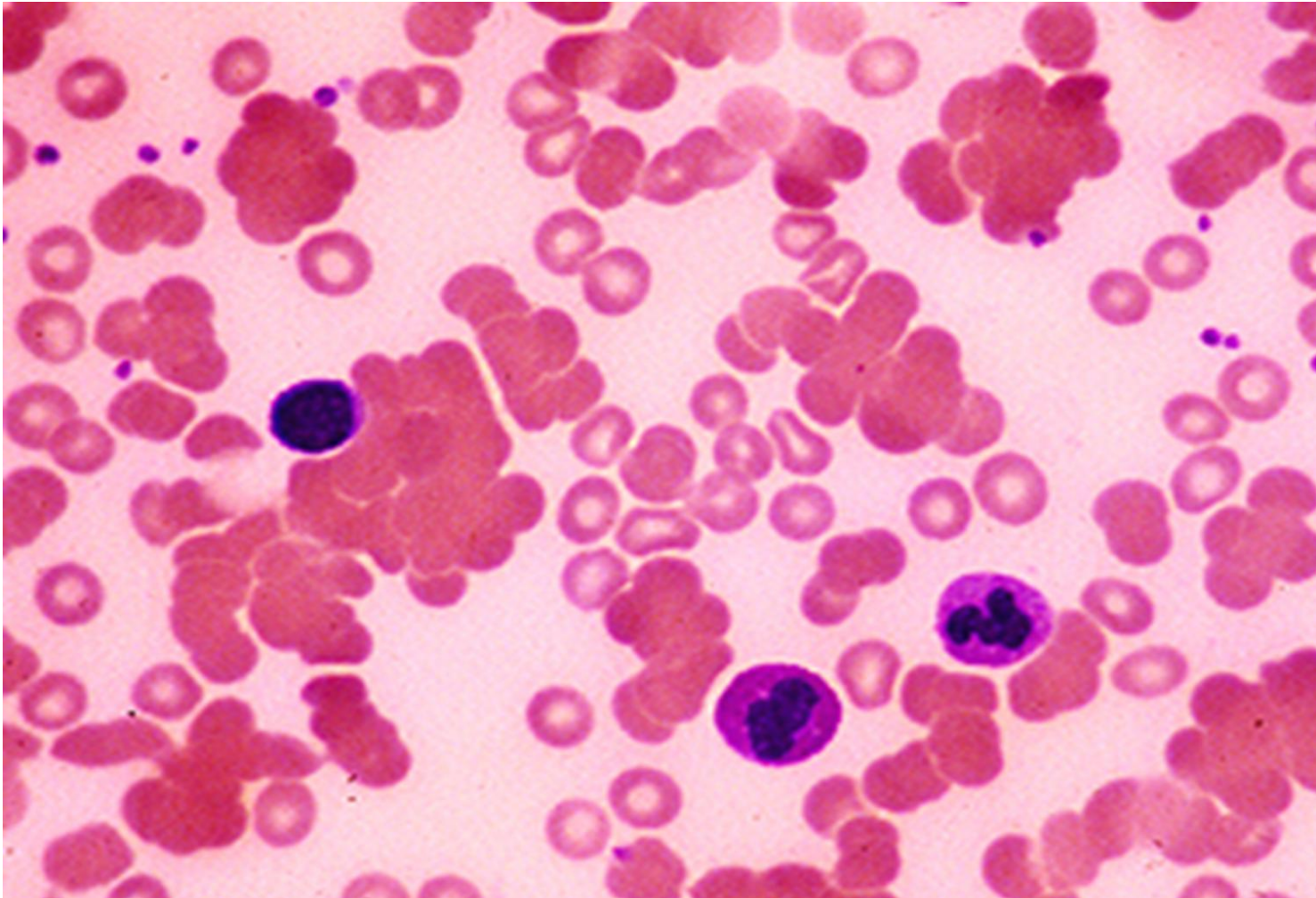
- Severe livedo (blush) reticularis (net-like appearance) following cold exposure
- Skin changes disappear completely without residua within several minutes following warming



Initial laboratory findings

- CBC
 - WBC: 6.9
 - Hgb: **8.8** (stable from 2 years ago)
 - Hct: **24.0**
 - Platelets: 153
- Reticulocyte count: **3.9** (0.5-1.5)
- LDH: **381** (100-250)
- Haptoglobin: **<10.0** (27.0-220.0)

Peripheral smear
Red cell agglutination due to cold antibody



Initial Blood Bank findings

	Anti-A	Anti-B	Anti-D	Rhct	A1cell	Bcell
	2+	2+	2+	2+	4+	4+
DTT tx	0	0	2+	0		
ABO type:	Opos					

Antibody screen (gel)

<u>I</u>	<u>II</u>
2+	1+

Direct antiglobulin test

	POLY	IgG	C3	6% alb
IS	3+	m+	3+	m+
DTT tx	2+	0	2+	0

Antibody Panel

LOT NO: 49076
EXPIRES: 2013/02/08

VIAL	Special Type	Donor	Rh - Hr							Kell					Duffy		Kidd		Lewis		P					MN					Luth-eran		Xg	PATIENT'S SERUM TEST RESULTS TEST METHODS				
			D	C	c	E	e	V	Cw	K	k	Kp ^a	Kp ^b	Js ^{a*}	Js ^b	Fy ^a	Fy ^b	Jk ^a	Jk ^b	Le ^a	Le ^b	P ₁	M	N	S	s	Lu ^a	Lu ^b	Xg ^{a*}	IS	REG ST	WASHED	WASHED	WASHED	WASHED			
1		R1R1 B7516	+	+	0	0	+	0	0	0	+	0	+	0	+	0	+	+	+	0	+	0	+	0	+	0	+	+	+	1	4+	1+						
2		R1wR1 B7306	+	+	0	0	+	0	+	0	+	0	+	0	+	0	+	+	+	0	+	0	+	0	+	0	0	+	+	2	4+	1+						
3		R2R2 C4651	+	0	+	+	0	0	0	0	+	0	+	0	+	+	+	0	+	0	+	+	+	+	0	+	0	+	0	3	4+	0						
4	Go(a+), DiVa-2-ce/DAU0-ce	Ror D699	+	0	+	0	+	0	0	0	+	0	+	0	+	0	0	0	0	0	0	+	0	+	0	+	0	+	+	4	4+	mt						
5		r'r E858	0	+	+	0	+	0	0	0	+	0	+	0	+	+	0	+	0	+	0	+	+	+	0	+	0	+	+	5	4+	1+						
6		r'r F760	0	0	+	+	+	0	0	+	+	0	+	0	+	+	0	+	0	+	+	+	0	+	0	+	0	+	+	6	4+	mt						
7		rr G1350	0	0	+	0	+	0	0	+	+	0	+	0	+	+	0	+	0	+	+	+	0	+	0	+	0	+	+	7	4+	2+						
8	Co(b+)	rr H1368	0	0	+	0	+	0	0	0	+	0	+	0	+	+	0	+	0	+	+	+	0	+	0	+	0	+	+	8	4+	2+						
9		rr N2994	0	0	+	0	+	0	0	0	+	0	+	0	+	+	+	+	0	0	0	+	0	+	0	+	0	+	+	9	4+	1+						
10		R1R1 B6917	+	+	0	0	+	0	0	+	0	0	+	0	+	+	+	0	0	+	+	+	0	+	0	+	0	+	+	10	4+	2+						
TC	I-,Co(b+),Bg(a+),Sc:2	r'r F26	0	0	+	+	+	0	0	0	+	0	+	0	+	+	+	0	+	+	0	W	0	+	0	+	0	+	0	TC	0	0						
		Patient's Cells																												PC	4+	0						

Direct Antiglobulin Test			Equate Result		
	Poly	IgG	C3		
LOT					
RESULT					

NOTES:
An antigen designated with a 'w' represent a weakened expression of the antigen that may or may not react with all examples of the corresponding antibody.

TC: In most individuals, the amount of i antigen present on red blood cells gradually decreases during the first 18 months of age, while the amount of I antigen increases. In rare individuals, this transition does not occur and the i phenotype persists on the adult red blood cells. Trace amounts of I antigen may be detected on cord blood cells and i adult cells with potent examples of anti- I . The frequency of i adult cells is approximately 1 in 4400 samples tested. The ii antigens are closely associated with ABH, Lewis, and P, often forming compound antigens, e.g. IA, IH, iH, etc. Additional information may be found in Blood Groups: P, I, Sd^a and Pr, published in 1991 by the American Association of Blood Banks.

PATIENT'S SERUM:	PANOSCREEN LOT	I				
		II				
		III				
	REVERSE GROUPING CELLS	A1				
A2						
B						

* Indicates those antigens whose presence or absence may have been determined using only one example of a specific antibody.

Thermal amplitude studies

I+ cells

Temperature	Titer
37° C	32
30° C	64
25° C (RT)	512
4° C	>32,000

I - cells

Temperature	Titer
37° C	<1
30° C	<1
25° C (RT)	<1
4° C	2048

Cryoglobulin fraction

I + cells

Temperature	Titer
37° C	0
30° C	0
RT	8
4° C	128

I - cells

Temperature	Titer
RT	0
4° C	<1

Plasma supernatant

I + cells

Temperature	Titer
37° C	64
30° C	64
RT	1024
4° C	32,768

I - cells

Temperature	Titer
37° C	1
30° C	1
RT	<1
4° C	64

Treatment

- Avoidance of cold
- Cytosan - cyclophosphamide. Nitrogen alkylating agent that interferes with DNA replication.
- Rituximab – Anti-CD20. Attaches to B cells and leads to their destruction.
- Plasmapheresis – can provide temporary relief that is transient. Category II recommendation (2nd line therapy).

Hypothermic cardiac surgery in patients with cold agglutinins

- Risks:

- Hemolysis
- Massive hemagglutination
- Microvascular thrombosis
- Myocardial infarction
- Renal and hepatic insufficiency
- Cerebral damage

- Our patient: predicted to have a 50% risk of serious morbidity and mortality from CPB

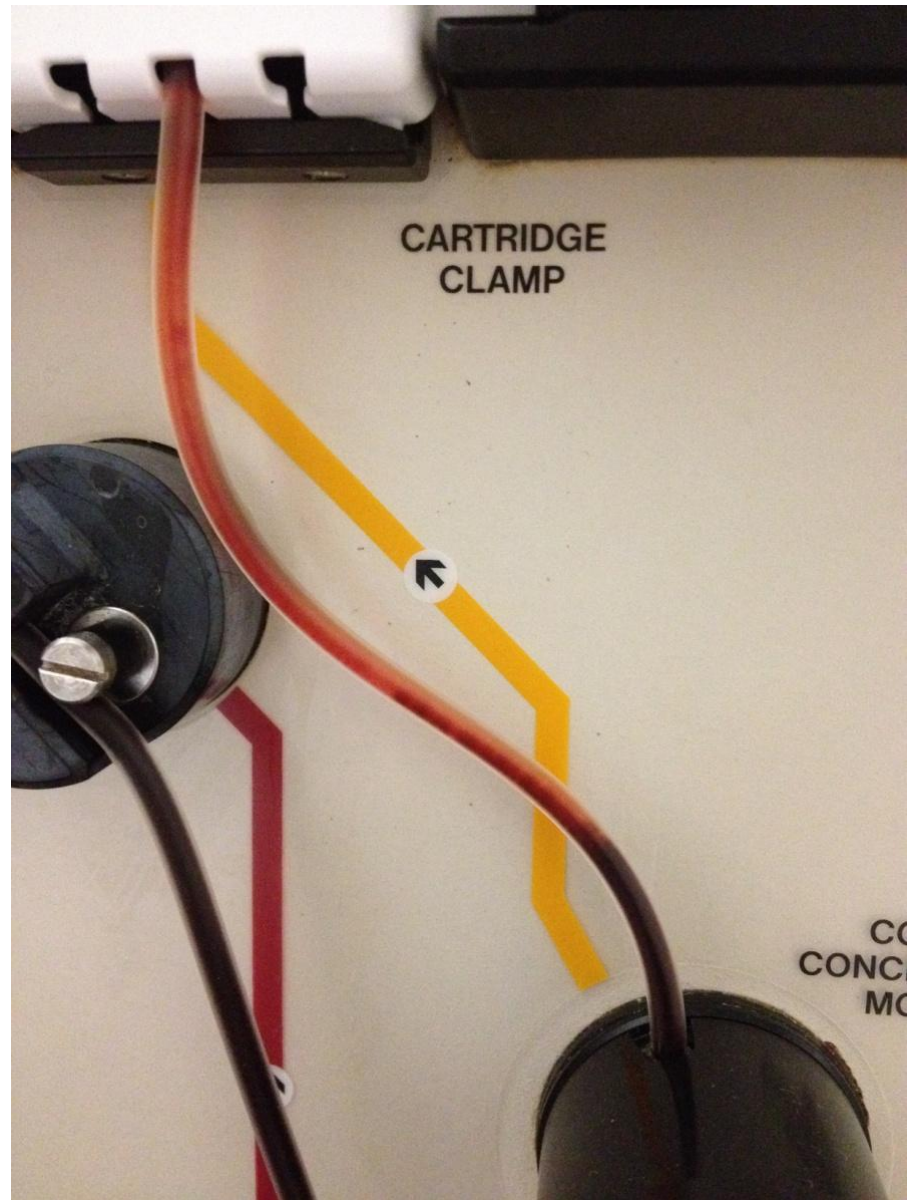
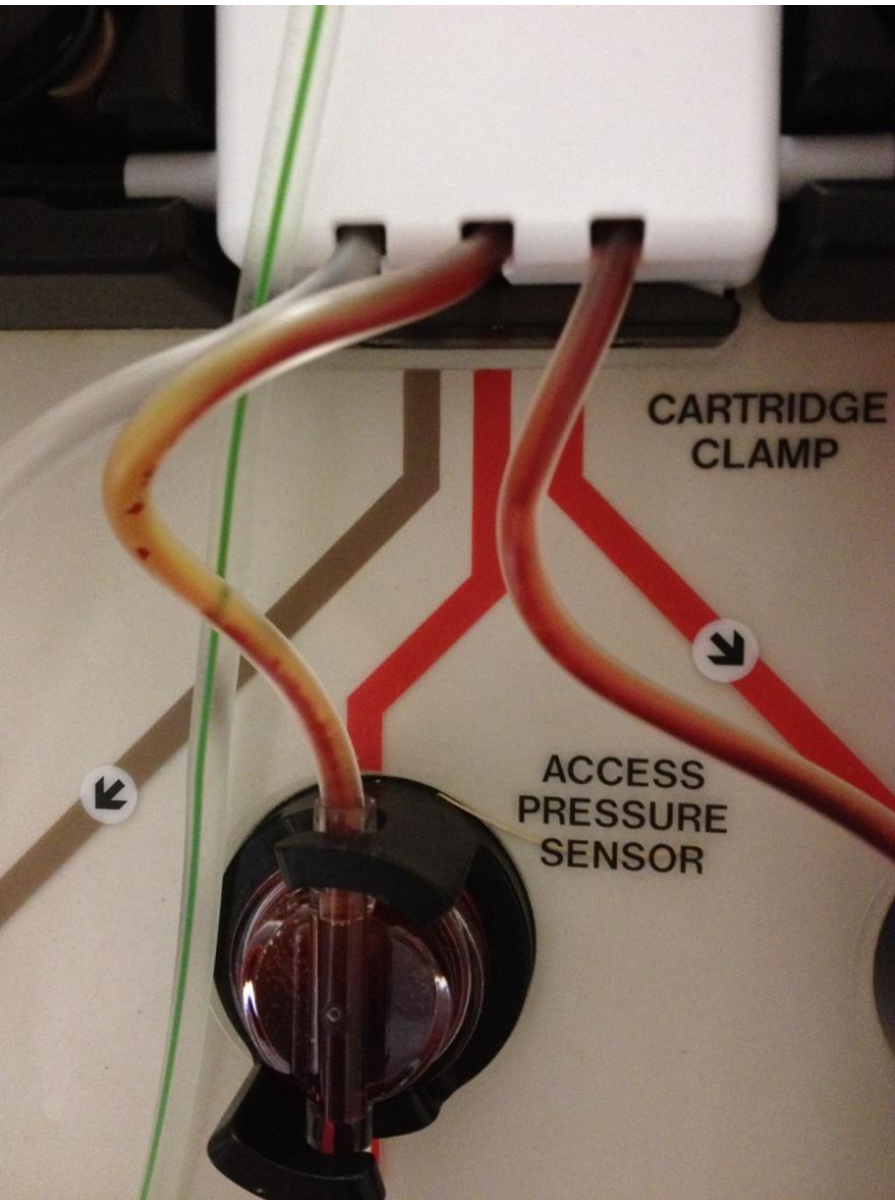
Apheresis plan

- Admit patient to get catheter placed
- 1st procedure 3 days prior to surgery
- 2nd procedure 2 days prior to surgery
- 1 day to recover

Apheresis procedure #1

- Warmed room to 85° (attempted)
- Warm blanket
- Heating pads, 2nd blood warmer and heating packs applied to all exposed tubing.







Procedure 1 events and outcome

- 13 minutes into procedure unable to clear centrifuge alarms, clotting in tubing.
- Several attempts to restart and clear alarms – unsuccessful
- Procedure aborted at 1479ml volume processed.
- Titer reduced from 32,000 to 16,384 (at 4°).

Apheresis procedure #2

- Warmed room to 85°
- Warm blanket
- Heating pads, 2nd blood warmer, and heating packs applied to exposed tubing
- **Placed machine next to heater**
- **Used Bair Hugger (Arizant Healthcare Inc., St. Paul, MN) to blow hot air on machine**





Pheresis #2 outcome

1/15/13 11:20 (before procedure 2)

Temp	Titer
37°C	64
4° C	16,384

1/16/13 9:15 (after procedure 2)

Temp	Titer
37°C	32
4° C	65,000

Apheresis Procedure #3 (1 day before operation)

Warmed room to 85°

Warm blanket

Heating pads, 2nd blood warmer, and heating packs applied to exposed tubing

Placed machine next to heater

Used Bair Hugger to blow hot air on machine

Procedure 3 outcome

1/16/13 9:15 (before 3rd procedure)

Temp	Titer
37°C	32
4° C	65,000

1/16/13 19:01 (after 3rd procedure)

Temp	Titer
37°C	32
4° C	4,096

1/17/13: Operation

- Successful transapical aortic valve replacement
 - Case was technically unremarkable
- Patient under warm blanket
- Fluids warmed

- Patient recovered and was discharged on 1/23/13

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