CASE OF THE MONTH: MARCH, 2019 (Case study by Jim Perkins)

History: This patient was a 59 year old man who came to the ED with a relatively minor cut on his abdomen that would not stop bleeding and was admitted to the hospital. He admitted to heavy alcohol consumption ("one fifth per day") and had noted intermittent hematochezia (bright red blood per rectum, BRBPR) over the past 2 to 3 weeks as well as increasing abdominal girth. His past history was notable for seizures unrelated to alcohol, and obesity with adult onset diabetes and sleep apnea. He denied any significant surgical procedures and denied transfusion, including on careful questioning by the author after discharge. His admitting hgb level was 9.5g/dL, his platelet count was 174,000/µL, and his PT/INR was 13.3s/1.3. Over the first day in the hospital the patient became increasingly agitated and went into alcohol withdrawal syndrome. A type-and-screen on the first hospital day yielded the following results:

	Anti-A	Anti-B	A1 cells	B cells	6% alb	Anti-D	<D/AHG	Interp
IS	4+	0	0	4+		4+		?

Antibody Screen	
	Gel
SCI	0
SCII	0

Direct Antiglobulin Test (gel)			
	Polyspec.	Anti-IgG	Anti-C3
AHG			
5' incub.			

Over the first night in the hospital the hgb fell to 8.7g/dL, and because of concern that his hgb might underestimate the degree of bleeding one unit of electronically crossmatched RBCs was transfused.

By the 8th hospital day the patient's hgb had fallen to 7.3g/dL. A type-and-screen yielded the same results, and 2 units of transfused RBCs brought the hgb to 9.3g/dL. The patient was discharged on the 11th hospital day with a hgb of 9.1g/dL.

The patient was readmitted 14 days later after of 2 episodes of hematochezia in the past 2 days. The hgb was 9.9g/dL on admission but fell to 9.2 within 11 hours, and a 3rd type-and-screen, 17 days after the previous with the following results:

	Anti-A	Anti-B	A1 cells	B cells	6% alb	Anti-D	<D/AHG	Interp
IS	4+	0	0	3+		3+		?

Antibody Screen	
	Gel, 30'
SCI	0
SCII	1+

Direct Antiglobulin Test, tube			
	Polyspec.	Anti-IgG	Anti-C3
AHG	0	0	
5' incub.	$0^{\surd}$	$0^{\surd}$	

Antibody Screen Cell phenotype

		Rh system					Kell						Duffy		Kidd		Xg	Lewis		MNSs				P	Lutheran					
	Rh	D	C	E	c	e	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a	Le^a	Le^b	S	s	M	N	P1	Lu^a	Lu^b		Cell	Gel	
SC I	R1R1	+	+	0	0	+	0	+	0	+	0	+	0	+	+	0	+	+	0	0	+	0	+	+s	0	+		SC I	0	
SC II	R2R2	+	0	+	+	0	+	+	0	+	0	+	+	0	0	+	+	0	+	+	+	+	0	+s	0	+		SC II	1+	

Plasma Panel

VRA140		Rh system						Kell						Duffy		Kidd		Xg	Lewis		MNSs				P	Lutheran		Other Typings			
Cell	Rh	D	C	E	c	e	V	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a	Le^a	Le^b	S	s	M	N	P1	Lu^a	Lu^b		Cell	Gel	
1	R1wR1	+	+	0	0	+	0	0	+	0	+	0	+	+	+	0	+	+	+	0	+	+	+	+	+	0	+		1	0	
2	R1R1	+	+	0	0	+	0	+	+	0	+	0	+	+	0	+	+	+	0	+	+	0	+	0	0	0	+	HLA+	2	w+	
3	R2R2	+	0	+	+	0	0	0	+	0	+	0	+	0	+	+	0	+	0	+	+	+	+	0	0	0	+		3	0	
4	Ror	+	0	0	+	+	0	0	+	0	+	0	+	+	+	+	0	+	0	+	0	+	0	+	+	0	+		4	0	
5	r'r	0	+	0	+	+	0	0	+	0	+	0	+	+	0	+	+	0	0	+	0	+	0	+	+	0	+		5	0	
6	r"r	0	0	+	+	+	0	0	+	0	+	0	+	+	0	0	+	+	0	+	+	+	+	+	+	0	+		6	0	
7	rr	0	0	0	+	+	0	+	+	0	+	0	+	0	+	+	0	+	0	+	0	+	0	+	+	0	+	HLA+	7	0	
8	rr	0	0	0	+	+	0	0	+	0	+	0	+	+	0	+	0	+	+	0	+	0	0	+	+	0	+		8	0	
9	rr	0	0	0	+	+	0	0	+	0	+	0	+	+	+	+	0	0	0	0	0	+	+	0	+s	0	+		9	0	
10	rr	0	0	0	+	+	0	0	+	0	+	0	+	0	+	0	+	+	0	+	+	+	+	+	0	+	0	+		10	0	
11	R1R1	+	+	0	0	+	0	0	+	0	+	0	+	0	+	+	0	0	0	0	+	0	+	+	+	0	+	HLA+	11	0	
Patient																													AC	0	

Se;ected Cell Panel

VRA140		Rh system						Kell						Duffy		Kidd		Xg	Lewis		MNSs				P	Lutheran		Other Typings		
Cell	Rh	D	C	E	c	e	V	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a	Le^a	Le^b	S	s	M	N	P1	Lu^a	Lu^b		Cell	Gel, 30'
1	rr	0	0	0	+	+	0	+	+	0	+	0	+	+	+	0	0	0	0	+	+	0	+	0	+	0	+		1	0
2	rr	0	0	0	+	+	0	0	+	0	+	0	+	+	0	+	+	+	+	0	+	+	+	+	0	0	+		2	0
3	R2R2	+	0	+	+	0	0	0	+	0	+	0	+	+	0	+	0	+	0	+	+	+	+	+	0	0	+	HLA+	3	0
4	R1R2	+	+	+	+	+	0	+	0	0	+	0	+	0	+	+	0	0	0	+	0	+	+	+	+	0	+		4	2+
5	rr	0	0	0	+	+	0	+	0	0	+	0	+	0	+	+	0	+	0	+	+	+	+	+	+	0	+		5	3+
6	R1R1	+	+	0	0	+	0	+	0	0	+	0	+	+	+	0	+	+	0	+	+	+	+	+	+	0	0	+		6	2+

Extended Phenotype

	Rh system				Kell				Kidd		Duffy		Lewis		MNSs															
	C	E	c	e	K	k	Kp^a	Js^a	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	S	s	M	N	P1	I	H	A_1								
Patient	+	0	+		0																									

*Tested using current specimen

Questions/discussion:

What is the specificity of the patient's antibody? Is it proven? Is there anything notable about this patient's antibody compared to other antibodies of this specificity? What do you think might be going on here? Is there any testing you'd like to do to investigate that possibility?

This patient has an alloanti-K that meets all the criteria for proof (3 K-pos cells reactive, 3 K-neg cells nonreactive, "everything else" ruled out, patient is K neg). This example of anti-K is a little interesting in that it appears to "show dosage" in that it reacts more strongly with double-dose than single-dose K positive RBCs. Given the presence of a new antibody 17 days after transfusion (day 25 overall), the question arises whether the patient may have had a delayed hemolytic transfusion reaction (DHTR). In the evaluation of this possibility one would like to know whether any of the previously transfused units were K positive and whether there was any evidence of hemolysis of the transfused units.

Segments of the 3 units transfused during the previous hospitalization were retrieved and phenotyped for K. The unit transfused on the day of admission was K negative, but both units transfused on day 8 were K positive.

Questions/discussion:

Do you think that we can say there has been a DHTR?

To call this a DHTR we need to show not only that there is a potential causative antibody, as we have already, but also that there has been hemolysis of the donor RBCs. Given the patient's bleeding, the course of his hemoglobin levels is an unreliable guide to whether he had hemolysis. However, note that on the day his antibody was discovered (D25) his K phenotype was negative, so RBCs from the 2 K-positive units were not detected by this method. Moreover, his DAT was negative, again suggesting that K positive RBCs were not circulating 17 days after transfusion.

Calculating his total blood volume from his height and weight (6.4L), his total RBC volume by multiplying this by his hematocrit (1.745L), and assuming 180mL of RBCs per units, on day 9 immediately after transfusion K positive donor RBCs should have represented 20% of his total. One would not expect these RBCs to have become undetectable just on the basis of normal senescence.

Questions/discussion:

So what is special about this case?

Typically we think of DHTRs as being caused by an anamnestic or secondary antibody response in a person who was previously immunized against a blood group antigen, but whose antibody has fallen below a detectable level due to the passage of time. On exposure to the same blood group again a later date antibody appears over just a few days, so that it encounters RBCs bearing the offending antigen and destroys them. However, we typically expect appearance of an antibody to take up to 3 months in a primary immune response, by which time few antigen positive donor RBCs are still circulating and at risk of hemolysis.

In this case the patient denied previous transfusion on careful questioning, and he had never had a surgical procedure that might have caused him to be transfused without his knowledge. He was very cooperative with this questioning and was not cognitively impaired at the time.

There are very few reports of DHTRs due to a primary antibody response, but this case appears to represent one.

The patient still had detectable anti-K a month after it was first detected, but about 7 weeks after that and on subsequent testing it was not detected by the same methods. The patient was not transfused again until his short, terminal hospitalization, 6 months after he first presented.

Take home points

Delayed hemolytic transfusion reactions are generally thought of as due to a secondary immune response but can occasionally be caused by a primary immune response.

The following figure shows the time course of the patient's hemolytic reaction.