Immunohematology Case Study 2017 - #7

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Clinical History

Medical History:

A 30 years old Caucasian female hospitalized for dorsal meningioma

Transfusion history: no history of recent transfusion. Patient received 2 units of red blood cells approximately five years ago during a gynecologic surgery

Pregnancy history: no history of pregnancy

Serologic History

- Routine serological workup was performed

- The referring hospital transfusion service observed that antibody screen and identification were positive with all cells, DAT negative

- Due to limited resources, a sample was submitted to Immunohematology Reference Laboratory at Policlinico Hospital of Milan (Italy) for further testing

Current Sample Presentation Data

ABO/Rh/K: A Rh positive, ccee, kk

DAT: negative

Antibody Screen Method: Indirect Antiglobulin Test (IAT) using Column Agglutination Technology (CAT) polyspecific (Biovue, Ortho Clinical Diagnostics)

Antibody Screen Results: 2+ with all tested cells

Antibody Identification Method: IAT using CAT-Polyspecific, polyethylene glycol (PeG), LISS and ficin-treated cells

Antibody Identification Preliminary Results: all cells positive in IAT with untreated and ficin-treated red cells

Antibody Identification
Preliminary Results

	D	C	c	E	e	Cw	K	k	Fya	Fyb	Jka	Jkb	Lea	Leb	P1	M	N	S	s	CAT	PEG
1	+	+	0	+	+	0	0	+	0	+	0	+	0	+	+	+	+	0	+	2+	2+
2	+	+	0	0	+	+	0	+	+	0	+	0	0	+	0	+	+	0	+	2+	2+
3	+	0	+	+	0	0	0	+	0	+	0	+	0	+	+	+	+	0	+	2+	2+
4	+	0	+	0	+	0	0	+	0	0	+	0	+	0	+	+	+	0	0	2+	2+
5	0	+	+	0	+	0	0	+	+	0	+	0	0	+	+	+	+	0	+	2+	2+
6	0	0	+	+	+	0	0	+	+	+	0	+	0	+	+	+	+	+	+	2+	2+
7	0	0	+	0	+	0	+	+	+	0	0	+	0	+	0	+	0	+	0	2+	2+
8	0	0	+	0	+	0	0	+	+	0	+	0	0	+	+	0	+	0	+	2+	2+
9	0	0	+	0	+	0	0	+	0	+	+	+	+	0	0	+	+	0	+	2+	2+
10	+	+	0	0	+	0	+	+	+	+	0	+	+	0	+	0	+	0	+	2+	2+
11	0	0	+	0	+	0	0	+	0	+	+	+	0	0	+	+	+	0	+	2+	2+
AC	+	0	+	+	+	0	0	+	0	+	+	+	0	+	+	+	0	+	+	0	0

AC: autocontrol

Antibody Identification
Preliminary Results

	D	C	c	E	e	Cw	K	k	Fya	Fyb	Jka	Jkb	Lea	Leb	P1	M	N	S	s	LISS	FICIN
1	+	+	0	+	+	0	0	+	0	+	0	+	0	+	+	+	+	0	+	2+	2+
2	+	+	0	0	+	+	0	+	+	0	+	0	0	+	0	+	+	0	+	2+	2+
3	+	0	+	+	0	0	0	+	0	+	0	+	0	+	+	+	+	0	+	2+	2+
4	+	0	+	0	+	0	0	+	0	0	+	0	+	0	+	+	+	0	0	2+	2+
5	0	+	+	0	+	0	0	+	+	0	+	0	0	+	+	+	+	0	+	2+	2+
6	0	0	+	+	+	0	0	+	+	+	0	+	0	+	+	+	+	+	+	2+	2+
7	0	0	+	0	+	0	+	+	+	0	0	+	0	+	0	+	0	+	0	2+	2+
8	0	0	+	0	+	0	0	+	+	0	+	0	0	+	+	0	+	0	+	2+	2+
9	0	0	+	0	+	0	0	+	0	+	+	+	+	0	0	+	+	0	+	2+	2+
10	+	+	0	0	+	0	+	+	+	+	0	+	+	0	+	0	+	0	+	2+	2+
11	0	0	+	0	+	0	0	+	0	+	+	+	0	0	+	+	+	0	+	2+	2+
AC	+	0	+	+	+	0	0	+	0	+	+	+	0	+	+	+	0	+	+	0	0

AC: autocontrol

Challenge with the Current Presentation

- All cells are positive independently of the antigen patterns
- The autocontrols (AC) are negative
- The most frequent causes for the “all cells positive/autocontrols negative” pattern are:
  - Multiple antibodies to common antigens
  - An antibody to an antigen of high prevalence
  - An antibody to reagent components
- The laboratory suspected an alloantibody to a high-prevalence antigen due to the similar strength and phases for all the red cells, DAT and AC negative

Challenge with the Current Presentation

- Antibodies to a high-prevalence antigens can be identified by:

• typing the patient's red cells with antisera to high-prevalence antigens

• testing selected red cells of rare phenotypes

• testing reagent red cells sample that match the patient's phenotype in order to rule out the presence of a complex mixture of antibodies of common specificities

- The laboratory performed further tests

Further Serologic Work

The extended phenotype for common red blood cell antigens and other rare high frequency antigens was investigated, with the following results:

Antigens	Serology	Antigens	Serology	Antigens	Serology
C^w	0	**s**	+	**Lu^b**	+
K	0	**Le^a**	0	**PP_1P^k**	+
k	+	**Le^b**	0	**U**	+
Jk^a	+	**P1**	+	**Vel**	**0**
Jk^b	+	**Kp^b**	+	**Yt^a**	+
Fy^a	0	**Gy^a**	+	**Co^a**	+
Fy^b	+	**Lan**	+		
S	+	**Ge2**	+		

Further Serologic Work

Testing Vel negative red cells:

	D	C	c	E	e	C^w	K	k	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	P_1	M	N	S	s	Vel	CAT-AS
ID 411623	+	+	0	0	+	0	0	+	0	+	+	+	/	/	/	/	/	0	+	0	0
Cell 12 Panel RC0016S DRKBSD	+	0	+	0	+	0	0	+	0	+	+	+	0	+	+	+	0	0	+	0	0

- Antibodies to high-prevalence antigens may mask the concomitant presence of additional antibodies to common antigens
- Exclusion of additional antibodies is an important step in the interpretation process and must be performed to ensure proper identification of all of the antibodies present
- Patient's serum must be tested against a sufficient number of reagent red cell samples that express the antigens that are negative on patient's red cell (ideally 2 for antigens with dosage effect)

Further Testing Results and Interpretations

- To exclude the presence of additional alloantibodies, allogenic adsorption was performed with a cell carrying a patient's complementary phenotype for the most common red cell antigens: rr, K-,Fy(a+b-), Vel+

- Adsorptions (x2) were made at 37° C without additive

	D	C	c	E	e	Cw	K	k	Fya	Fyb	Jka	Jkb	Lea	Leb	P1	M	N	S	s	CAT
1	+	0	+	+	0	0	0	+	+	0	0	+	0	+	w	+	+	0	+	0
2	+	0	+	+	0	0	0	+	+	0	+	+	+	0	+	0	+	+	+	0
3	0	0	+	0	+	0	0	+	0	+	+	0	0	+	+	0	+	0	+	0
4	0	0	+	0	+	0	0	+	0	+	0	+	0	+	0	0	+	+	0	0
5	+	+	0	0	+	+	0	+	+	+	+	+	0	+	0	+	0	0	+	0
6	+	0	+	+	0	0	0	+	0	0	+	0	+	0	+	+	0	0	+	0
7	+	0	+	+	0	0	0	+	+	0	+	0	+	0	+	+	0	+	+	0
8	+	+	+	0	+	0	0	+	+	+	+	+	0	+	0	+	+	+	+	0
9	+	+	+	+	+	0	0	+	0	0	0	+	0	+	+	+	+	+	+	0
10	+	+	0	0	+	+	0	+	0	+	+	+	+	0	+	+	0	0	+	0
11	+	+	0	0	+	+	+	+	+	+	+	+	+	0	+	+	0	0	+	0
12	+	0	+	+	0	0	0	+	0	+	0	+	0	+	+	+	0	+	0	0
13	0	0	+	0	+	0	+	+	+	0	+	0	0	+	+	+	+	+	+	0

NO ADDITIONAL ALLOANTIBODIES

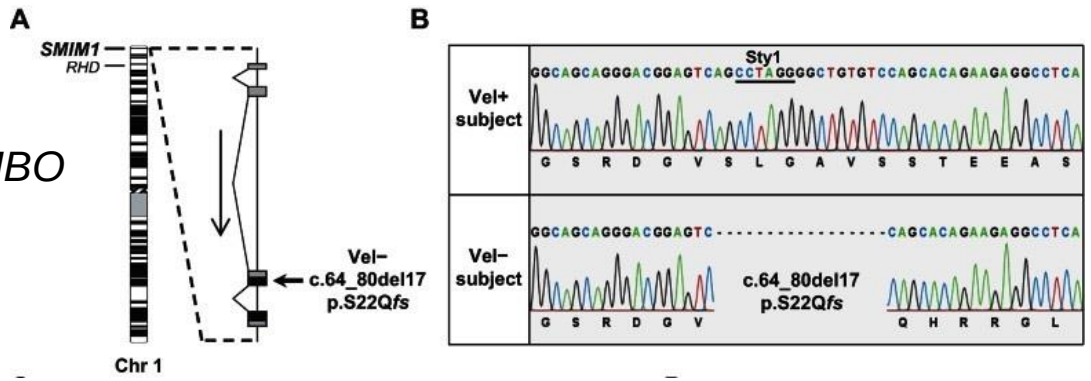
The Vel system (ISBT number 34)

- Vel antigen was recognized in 1952 by Sussman and Miller
- Anti-Vel antibodies are usually responsible for severe and acute hemolytic transfusion reactions but rarely cause significant hemolytic disease of the fetus and newborn
- The prevalence of Vel- individuals is estimated at 1 in 4,000 in Europe, but the prevalence is somewhat higher (1 in 1,700) in northern Scandinavia
- Serologic screening for the Vel- phenotype is complicated. Some individuals appear to express very low levels of the Vel antigen that can be challenging to detect, especially since anti-Vel does not work well in adsorption-elution studies

The Vel system (ISBT number 34)

- The transmembrane protein SMIM1 was identified as carrying the Vel antigen
- The *SMIM1* gene is located on the chromosome 1 and is composed of four exons
- Vel negative phenotype is caused by the homozygous presence of a 17-bp deletion in exon 3 of *SMIM1* gene (*SMIM1*64_80-del* allele) that completely abolishes the expression of the SMIM1 protein
- The allele frequency of the *SMIM1*64_80-del* allele is 1,46% in the Caucasian population, 0,56% in the African black population

Ballif B, Helias V, Peyrard T & al. *EMBO Mol Med* 2013



The Vel system (ISBT number 34)

- Weak expression of the Vel antigen is most often caused by the heterozygous presence of *SMIM1*64_80-del* allele in combination with a wild type allele

- Variation in Vel expression levels is also related to two single heterozygous missense mutations, at the same nucleotide position of *SMIM1* resulting in a different aminoacid substitutions (c.152T>A encoding p.Met51Lys and c.152T>C encoding p.Met51Arg)

Haer-Wigman L, Stegmann T,Solati S & al.Transfusion 2015;55;1457–1466

Further Work

Searching for compatible blood:

- At that time, no Vel negative blood was available and autologous donation was not possible
- Family study can be useful:
  - The absence of high-prevalence antigens is usually associated with the inheritance of the same rare recessive blood group gene from each heterozygous parent
  - Siblings are much more likely to have the rare blood type (25%) than the general population

Parents and brother were phenotyped and genotyped for Vel antigen:

	Serology	Molecular Biology
Mother	Vel positive	heterozygous *SMIM1*64_80-del* allele
Father	Vel positive	heterozygous *SMIM1*64_80-del* allele
Brother	Vel negative	homozygous *SMIM1*64_80-del* allele

Updated Clinical Information

- No autologous units were available
- No units were available in our inventory but possible matches were detected when consulting the International Rare Donor Panel
- No transfusion support was required

Conclusions

- Emergency blood transfusion in alloimmunized patients with a rare blood type is a challenge

- The role of IRL in identifying rare antibodies and in finding compatible blood for a rare phenotype is very relevant

- If the clinical situation allows, autologous RBC transfusion should be considered for patients with rare phenotypes

Lessons Learned by the Case

- The reaction pattern of the antibody identification gives important information

- The ability to identify an antibody to a high-prevalence antigen depends on the “rare“ cells and antisera available in a laboratory

- Family members are a potential source of rare blood when rare blood is needed

References

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- *SMIM1* underlies the Vel blood group and influences red blood cell traits. Cvejic A and al. Nat Genet. 2013 May; **45**(5):542-5