

# Possible RBC T Activation in a Pediatric Patient: Suggestion for Transfusion Management

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# CASE REPORT

- A critically ill 2-year-old boy was transferred from a community hospital where he was diagnosed with atypical hemolytic uremic syndrome (HUS) associated with *Streptococcus pneumoniae*.
- The patient had been transfused with two SDP and 1 red blood cell (PRBC) unit without incident

# Hemolytic Uremic Syndrome

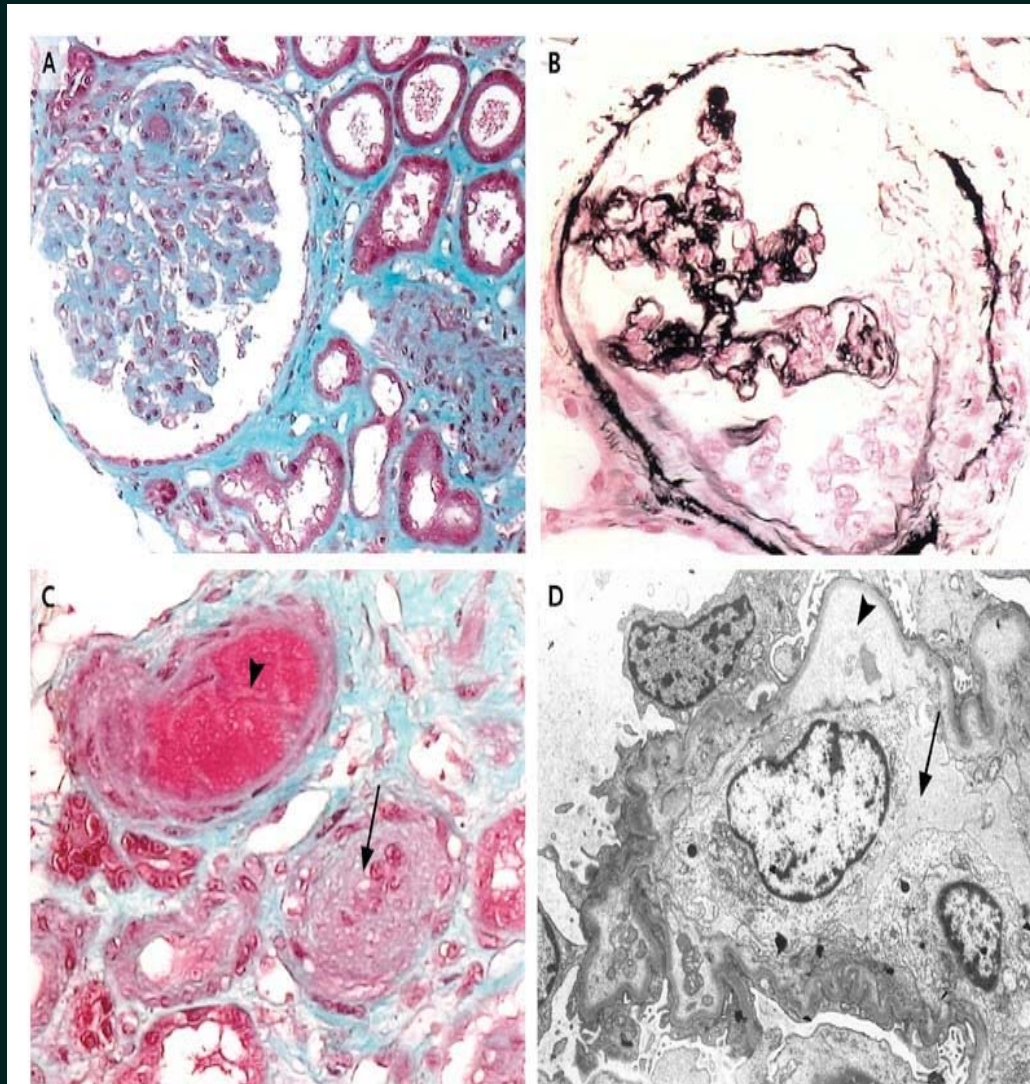
- Hemolytic uremic syndrome is a disease characterized by
  - Microangiopathic hemolytic anemia
  - Thrombocytopenia
  - Renal insufficiency
- This disorder occurs frequently in children under 5 years of age.
- HUS is classified into two different subgroups
  - Typical HUS and Atypical HUS

# Typical and Atypical HUS

- **Typical HUS**
  - 90 % of pediatric cases
  - Associated with shiga-like toxin produced by E. coli 0157:H7
  - Survival > 95% and long term morbidity is <30%
- **Atypical HUS**
  - 10% of pediatric cases
  - ↑ mortality and renal morbidity (death rate of as ↑ as 25%)
  - 50% associated with disorder of complement
- Pneumococcus associated HUS

# HISTOLOGICAL LESIONS OF PATIENTS WITH HUS

- Histological lesions for atypical HUS –same as Typical.
- Characterized by:
- Thickening of the arterioles and capillaries.
- Endothelia swelling and detachment
- Platelet thrombi obstruct vessel lumina
- Sub-endothelial space is widened, and sub-endothelial accumulation of protein and cell debris



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# LABORATORY RESULTS

- **Pre-transfusion sample**
  - A Positive
  - Antibody screen = Negative

WBC (K/ $\mu$ L)	RBC (M/ $\mu$ L)	Hgb (g/dL)	Hct (%)	Plt (K/ $\mu$ L)
8.8	2.40	6.9	19.5	25
6.0-14.5	3.7-5.3	10.5-13.5	33.0-39.0	150-400

–Schistocytes were absent on the peripheral smear

# Timeline of Clinical course

**03:52** 1 unit of RBC was ordered and transfused without incident

	Temperature	Pulse	Respiration	BP
Pre-transfusion VS	38.8	167	46	114/66
Post-transfusion VS	38.9	146	70	134/89

**14:41** 1 unit of SDP was issued ( platelet count was 25 K/ $\mu$ L)

**15:20** Platelet transfusion began in the PICU

**16:12** The patient became apneic.  
Patient was intubated and CPR was initiated.  
60 mL of SDP was transfused  
An emergency bedside thoracentesis was performed and 180 mL of pleural fluid was removed.

**16:40** 1 RBC was issued and 60 mL of was transfused during CPR

**17:15** CPR was unsuccessful. No specimens were drawn from the time of apnea until death.

# TRANSFUSION REACTION INVESTIGATION

	Laboratory Transfusion Reaction Investigation Form			TYPE OF REACTION: CARDIAC ARREST				
	Cell reaction with:		Serum reaction with:	Cell reaction with:	ABO interp.	Cell reaction with:	Anti-D AHG	Rh interp
Tested samples:	Anti-A	Anti-B	A cells	B cells		Anti-D		
Pretransfusion Donor unit (RBC)	<b>4</b>	<b>0</b>	<b>0</b>	<b>4</b>	<b>A</b>	<b>4</b>		<b>POS</b>
	<b>4</b>	<b>0</b>	<b>NT</b>	<b>NT</b>	<b>A</b>	<b>4</b>		<b>POS</b>

Antibody Screen:			
Pre-transfusion		AHG	INT
	I	0	NEG
	II	0	NEG
		DIRECT COOMBS	POS/ C3d ONLY

CROSS MATCH	IMM	AHG
MINOR (SDP)	0	0
MAJOR (RBC)	0	0

**A post transfusion specimen could not be obtained.**

# Transfusion Reaction Investigation

- The initial Blood Bank investigation revealed no clerical check errors.
- Both SDP and PRBC retyped as A+
- No evidence of ABO cell or plasma incompatibility.
- Repeat cross-match with pre-transfusion sample was compatible.
  - A minor cross-match with the SDP bag showed
  - no evidence of incompatibility between patient's RBCs and plasma from the SDP bag.
  - Visual inspection for agglutination or hemolysis was negative at IS and AHG.

# Transfusion Reaction Investigation

- **Microbiology Report:**
  - Gram stain : No organisms seen
  - Culture: Negative
- **CONCLUSION**
  - No serological evidence of hemolysis or red cell antigen incompatibility.

# Polyagglutination Work-Up

- Due the patient's diagnosis RBC T activation investigation was carried out.
  - Literature reports of hemolysis due to polyagglutination of RBCs in infants diagnosed with necrotizing enterocolitis (NEC)
  - Children with invasive pneumococcal infection after transfusion with blood components.

# Pneumococcal-Associated HUS

- Pathogenesis
  - T antigen is found on the surface of RBCs, platelet and glomeruli
- Microbial neuraminidase produced by a wide range of
  - *S. pneumoniae*
  - *Clostridium sp*
  - Influenza viruses

cleaves sialic acid exposing the T antigen.

- This phenomenon called “T activation” was first described in the early 20th century by Thomsen and Friedenreich.

# Polyagglutination

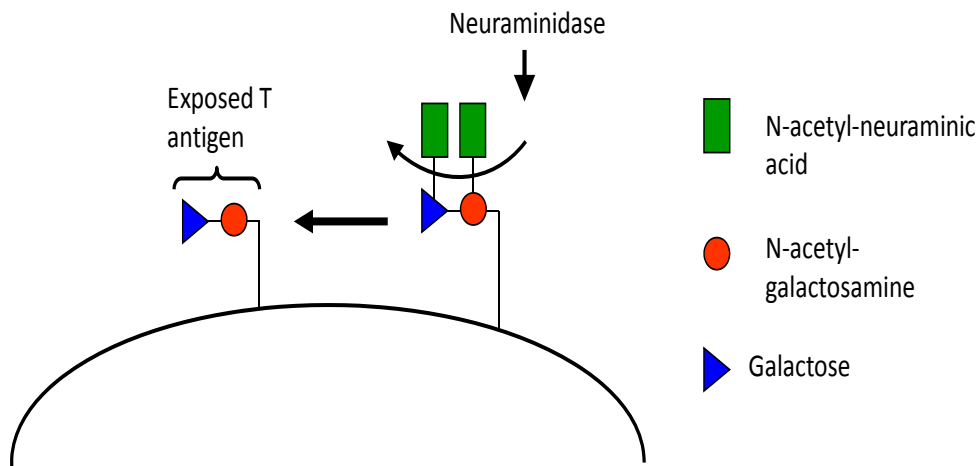
- Polyagglutination is the agglutination of RBCs by normal adult sera.
  - It occurs due to the enzymatic exposure of the T antigen.
  - T antigen can react with naturally occurring IgM anti-T antibody normally present in adult plasma.
- Several forms of polyagglutination have been described:
  - T, Th, Tk, Tx, and Tn.
- T activation is the most common and earliest form of polyagglutination.

# Figure. Schematic Presentation of Microbially-Induced T Activation.

FIGURE 1

## Microbially-induced T-activation

- Sialic acid residues are removed from glycoproteins at the cell surface by neuraminidase, exposing the T antigen



- T activation occurs due to:
  - alteration of the RBC membrane glycoprotein structure.
  - Neuraminidase cleaves sialic acid residue exposing the T antigen.
  - Naturally occurring Anti-T IgM antibodies binds to the exposed T antigen.
  - Resulting in RBC polyagglutination.

Courtesy Melissa Cushing, MD.

- **The Anti-T antibody**

- develops in the plasma of most infants at about 3 months of age and reaches adult levels by the age of 2.
- is present in adult sera as a result of
  - antigenic stimulation by intestinal flora
  - other environmental stimuli.
- has been identified as a potential cause of intravascular hemolysis
- in T activated pediatric patients that lack anti-T antibodies
- Transfused with components from adult donors who possess anti-T antibodies.

# Transfusion Management For Patients At Risk of T Activation

- Transfusion-associated hemolysis is the main concern when transfusing patients with T activation.
  - Some reports have shown minimal risk of transfusion-associated hemolysis.
  - Severe hemolysis and death have been reported in others.
  - Hemolysis has been reported in some patients regardless of transfusion.
- Based on these findings the question has be posed whether to routinely screen infants' erythrocytes for T activation?

# Existing Practice In Transfusion Medicine

- No particular preventative
- Specific measures to identify patients with T activation
  - low-titer anti-T: washed RBCs and platelets, and low titer anti-T plasma.
- Avoidance of plasma-containing products in patients with T activation (not recommended).
- Although several studies suggest an association between hemolysis and passively acquired anti-T
  - the significance of anti-T is still questioned based on several serological grounds.
  - Some authors have demonstrated minimal to zero risk of transfusion associated hemolysis in patients with T-activation.

# Transfusion Management: Washed RBC, Washed Platelet And Other Plasma Products

- Washing has little or no effect on function of RBCs
  - Shelf life shortened from 35-42 days to 24 hours
- The plasma present in platelet concentrates can also be removed by saline washing.
  - ↑ volume loss
  - Benefit of providing lower titer anti-T vs. risk of bleeding due to thrombocytopenia
- Other plasma-derived products
  - coagulation factor concentrates
  - purified albumin

Contain no IgM (not a source of anti-T antibodies).

# Laboratory Evaluation

- The various types of polyagglutination can be distinguished serologically by testing with
  - cord sera (contain no anti-T) → no agglutination
  - normal group AB adult sera → T-activated cells will agglutinate most of adult sera.
- T-activated cells do not agglutinate in their own sera; presumably because the anti-T has been adsorbed onto the exposed cryptantigen.

# Results: Polyagglutination Work-Up (NYBC)

Lectin Extract	Normal Cells	Patient's Cell
<i>Arachis hypogaea</i>	0	+ mf
<i>Salvia sclarea</i>	0	0
<i>Salvia horminum</i>	0	0
<i>Glycine soja</i>	0	+ mf

The pattern reaction revealed that patient's RBCs were T activated

- + = positive (agglutination)
- 0 = negative (no agglutination)
- + mf = positive; mixed field

# Results: Polyagglutination Work-Up

- Anti-T in the SDP unit was tittered using the positive control (neuraminidase-induced T activated cells ).
  - Plasma from SDP had ↓ titer anti-T ( vs. level in a pool of AB inert plasma.)
  - The titer = 2
- Additionally, patient's cell + AB inert plasma = no agglutination or hemolysis

## Case Conclusion

- The T-activation probably had little significance with patient's overall clinical course.
- Reported signs and symptoms are likely due to patient underlying conditions.

# Moving Forward

- T activation remains a topic of concern in neonatal populations. (HUS and NEC)
- Most case reports conflict with each other, and well-executed controlled clinical trials are lacking.
- While many still question the relevance of T activation in transfusion management, most agree that rapid identification is important after evidence of transfusion-associated hemolysis is observed.

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