CASE REPORT: IVIG-INDUCED HEMOLYSIS

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NO DISCLOSURES

CASE INFO

Patient history:

- 53 year-old female patient
- History of MDS (myelodysplastic syndrome)
- Day+ 90 of allogeneic hematopoietic stem cell transplant
- Presented for IVIg (intravenous immunoglobulin) infusion*

*Support immunoglobulin levels, prevent opportunistic infection, prevent CMV reactivation, reduce GVHD

CASE INFO

- Developed slight fever (100.5 F) after infusion
- Rechecked after 30 minutes (decreased to 99.2 F)
- Called blood bank to report transfusion reaction…

  - Not technically a blood product
  - Distributed by pharmacy at our hospital
  - Pharmacy responsible for reporting adverse events to FDA

CASE INFO

Recommendations:

- Monitor patient for signs/symptoms of hemolysis
  - Fever
  - Back/flank pain
  - Red or dark urine
  - Jaundice, scleral icterus
- Monitor hemolytic indices/lab indicators of hemolysis
  - Hemoglobin/hematocrit
  - Haptoglobin
  - LDH
  - Bilirubin
  - Reticulocyte indices
  - Urobilinogen (urine)
  - Microspherocytes or schistocytes on peripheral smear

Patient already left (outpatient) – follow-up in clinic in 7 days

CASE INFO

- Unfortunately, no recent labs for baseline
- Initial lab values (immediately after IVIg):
  - DAT = negative
  - LDH = 545 U/L ↑
  - Reticulocyte count/% = 8% ↑
  - Haptoglobin = 14 mg/dL ↓
  - Total bilirubin = 1.1 mg/dL
  - Hemoglobin = 8.6 g/dL
  - No microspherocytes/schistocytes on smear

CASE INFO

- Initial lab values:
  - DAT = negative
  - LDH = 545 U/L ↑
  - Reticulocyte count/% = 8% ↑
  - Haptoglobin = 17 mg/dL ↓
  - Total bilirubin = 0.4 mg/dL
  - Hemoglobin = 10.3 g/dL ↓
  - No microspherocytes/schistocytes on smear

- One week later:
  - DAT = negative
  - LDH = 588 U/L ↑
  - Reticulocyte count/% = 13% ↑
  - Haptoglobin = 14 mg/dL ↓
  - Total bilirubin = 1.1 mg/dL
  - Hemoglobin = 8.6 g/dL ↓
  - Rare microspherocytes on smear

-No fever or other signs/symptoms

-Subsequent improvement in labs

BACKGROUND: IVIG

BACKGROUND

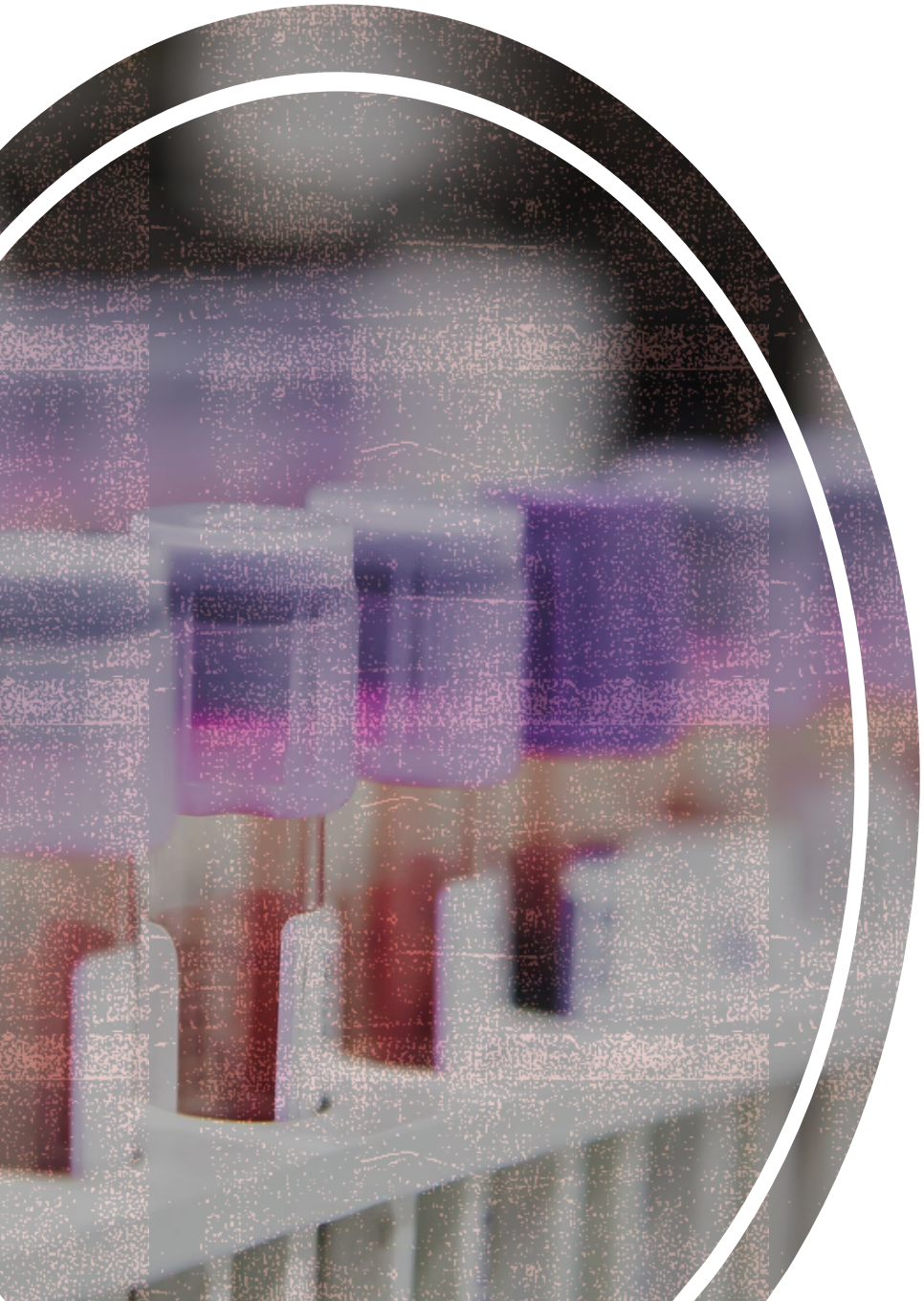
- Around since 1930s
- Steep increase in use the past 2 decades
- Broad clinical utility
  - FDA approved for many diseases
  - Replacement therapy for immune deficiency
  - Hematologic, neurologic, immunologic, rheumatologic diseases
  - Immunomodulatory effects in autoimmune disorders
    - Guillain–Barre syndrome
    - Myasthenia gravis
    - Chronic inflammatory demyelinating polyneuropathy (CIDP)
    - Others
    - Exact mechanism unknown

BACKGROUND

- Prepared from plasma from 10,000-60,000 donors
- Apheresis plasma
- For U.S. use: can only be collected in U.S.
- Predominantly IgG, with small amounts of IgA and IgM
  - Suggested to screen for IgA deficiency prior to treatment (risk of anaphylaxis)
- Viral transmission is rare
  - Rigorous donor screening
  - Stringent manufacturing process

BACKGROUND

- Immunoglobulin can be administered via IV route or SubQ
  - SubQ formulation is typically more concentrated (smaller volume)
  - Less severe side effects with SubQ (injection site reaction,delayed headache)
- IVIg generally well-tolerated
  - <5% of patients with adverse effects (AEs)
  - Can lessen some AEs with slower infusion rate and/or analgesics:
    - Headache, backache, fever, chills/rigors during infusion
  - Certain AEs seen with high doses
    - Thrombosis, aseptic meningitis, hemolysis, renal failure



IVIG-RELATED HEMOLYSIS

MECHANISMS

- Most cases due to donor anti-A and/or anti-B antibodies
  - IgG thought to play the largest role, via extravascular hemolysis
    - IgG attaches to RBC antigens and tagged RBCs are removed/destroyed in spleen
  - IgM/complement only thought to play a minor role
    - May account for early positive DATs and small amount of hemolysis (intravascular)
- Type A, B, or AB patients most affected
  - Especially type AB

INCIDENCE

- Previously:
  - Considered quite rare
  - ~1 per 1000 IVIg administrations treatment (most within 48 hours)
  - ~8% of IVIg administrations
- More recently (prospective studies):
  - Increased incidence documented by FDA since 2011
  - Incidence rate as high as 35-37% for non-type O patients receiving high doses
    - Highest incidence in type AB patients
  - Can be seen up to several days after dose
- Likely underrecognized and underreported

INCIDENCE

- Of those reported, most are:
  - Self-limited with minor decrease in hemoglobin
  - Positive direct antiglobulin test (DAT)
- Occasionally causes severe hemolysis requiring transfusion
- Very rarely fatal

WAYS TO INCREASE DETECTION

- Monitoring (labs and signs/symptoms)
- Consider elution in cases with high suspicion but negative DAT
  - Include A and/or B cells instead of type O reagent cells
- Plasma free hemoglobin

PRIMARY RISK FACTORS

- Administration of high-dose IVIG (especially greater than or equal to 2 g/kg)
- Non-O blood group recipients (esp. type AB)

TREATMENT

- Cessation of IVIG infusion
- Otherwise similar to treatment for hemolytic transfusion reaction (largely supportive)
- Monitor vital signs and urine output
- Proper hydration
- RBC transfusions if necessary, but **only with type O blood**

PREVENTION

- Stop IVIG altogether (if possible)
- Limit dosage amount
- Consider SubQ administration
- Processing – certain methods can greatly reduce isohemagglutinins
- Possibly type-specific IVIg in future?

CASE REPORT

- No further hemolysis beyond one week
- Patient asymptomatic – no need to transfuse
  - Patient was blood type A+ (no antibody history)
  - Recommended type O blood if transfusion needed
  - Monitor for hemolysis with future IVIg doses

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THANK YOU!

QUESTIONS?