Platelet Transfusion in Immune Thrombocytopenia: A Patient With a Measureable Response to Platelet Drip

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Patient Presentation

- A 13 year old male without significant past medical history was transferred to the pediatric intensive care unit at our institution from an outside hospital for further management of new onset intraparenchymal brain hemorrhage.
History of Present Illness

- He had been in his usual state of health until five weeks prior to admission when he began experiencing intermittent epistaxis and noted an associated petechial rash and several ecchymoses.
- Approximately three weeks after the onset of these symptoms, the patient fell while skateboarding, striking the back of his head against concrete.
  - At the time of the injury he denied loss of consciousness, nausea, vomiting, or significant headache.
  - In the days following the fall, he reported persistent intermittent frontal headaches unresponsive to acetaminophen and non-steroidal anti-inflammatory medications.
Outside Hospital

- He was found to be anemic and thrombocytopenic
  - Hemoglobin: 6.0 g/dL
  - Platelet count: Undetectable

- Imaging
  - CT scan: two intraparenchymal hemorrhages
    - left frontal lobe
    - right temporal lobe
On Admission

- Complete blood count revealed a
  - Hgb: 5.6 g/dL,
  - WBC: 10.3x10³/µL
    - normal differential
  - Plt: 5x10³/µL.
- Peripheral smear revealed
  - Severe normochromic normocytic anemia
  - Mild reticulocytosis without schistocytosis
  - Severe thrombocytopenia
- Bone marrow biopsy
  - Mildly hypercellular, normoblastic bone marrow
  - Increased megakaryocytes
  - No evidence of hematologic malignancy
- Bacterial blood cultures negative
- Serology for ehrlichia negative
Diagnosis

- Immune Thrombocytopenia (ITP)
  - Having excluded hypoplastic, infectious, and neoplastic etiologies for thrombocytopenia

- Initial Treatment
  - IVIg
    - 1 gm/kg
      - Initiated almost immediately
  - Bolus platelet transfusion
    - 2 apheresis units
Clinical Course

- **2nd Hospital Day**
  - Increasing intracranial hemorrhage (ICH)
  - Intravenous corticosteroid was added to his regimen
    - Methylprednisolone
      - 1.8g every 24 hours
  - Slightly abnormal coagulation test results
    - PT 16.3s
    - PTT 31.3s
    - INR 1.2
  - Received a total of 4 doses of intravenous recombinant factor VII
    - rVIIa
      - 4 mg every 3 hours
  - Despite this, his ICH continued to worsen
Clinical Course

- **3rd Hospital Day**
  - IVIG discontinued in favor of corticosteroids
  - Received a third unit of apheresis platelets via bolus infusion.
  - These measures continued to fail to produce significant rise in platelet count
    - Maximum uncorrected increment: 2x10^3/µL
    - Maximum corrected count increment: 1104 m^2/µL
  - **Low-dose continuous platelet infusion (platelet drip) initiated**
    - Transfusion rate: ½ apheresis unit every 3 hrs

- **4th Hospital Day**
  - He began showing some evidence (albeit intermittent) of rising platelet counts
    - Maximum platelet count: 25x10^3/µL
  - Hemorrhage stabilized
  - Infusion of intravenous rVIIa discontinued
  - Methylpredinsolone taper begun

- **5th and 6th Hospital Days**
  - Ongoing platelet drip
  - Platelet count continued to fluctuate
    - Range of 4x10^3/µL to 21x10^3/µL
  - ICH remained stable
Clinical Course

- **7th Hospital Day**
  - Splenic artery embolization
  - Platelet drip continued

- **8th Hospital Day**
  - Platelet count rose as high as \(40 \times 10^3/\mu\text{L}\)
    - Radiologic assessment of embolization showed 70-80% of the spleen to be embolized
  - Methylprednisolone taper was continued.

- **9th Hospital Day**
  - Treatment regimen continued
  - Platelet count continued to rise
    - Reaching \(121 \times 10^3/\mu\text{L}\)

- **10th Hospital Day**
  - Open Splenectomy
  - Platelet drip was discontinued following surgery
Splenic Artery Embolization

Pre-embolization

Post-embolization
Splenectomy

O = megakaryocyte
Splenectomy

Viable

Infarcted
Clinical Course

- **11th Hospital Day**
  - Platelet count dropped to 41x10^3/µL in the morning
  - Continued to decline throughout the day
    - Low of 11x10^3/µL
  - **Platelet drip re-initiated**
    - Platelet count rose to 29x10^3/µL.

- **12th Hospital Day**
  - Platelet count remained stable
    - Mid to high 20x10^3/µL range

- **13th Hospital Day**
  - Platelet counts again fell
    - Possibly in response to continued methylprednisolone taper
  - No increase in ICH and no overt bleeding
  - **Platelet drip was increased**
    - One full unit every four hours
  - Corticosteroid dose was increased

- **14th Hospital Day**
  - Platelet count rose to a high of 141x10^3/µL

- **15th Hospital Day**
  - Platelet count rose to 172x10^3/µL
  - **Platelet drip discontinued**
    - Decline in platelet count to 41x10^3/µL

- **16th Hospital Day**
  - Platelet count gradually decreases
    - Low of 14x10^3/µL

- **17th Hospital Day**
  - **Platelet drip re-initiated**
    - Platelet count gradually increases to 32x10^3/µL
Clinical Course

Days 18-24
- Platelet drip continued
- Platelet count fluctuates
  - Peaks at 104x10^3/µL
  - Danazol (started day 23)
    - 300 mg bid

25th Hospital Day
- Platelet drip discontinued
  - Decline in platelet count to 14x10^3/µL

26th Hospital Day
- Platelet count drops continuously to 3x10^3/µL
  - Epistaxis
  - Bleeding from incisions
- Aminocaproic acid started
  - 3,000 mg q6h
- Platelet drip re-initiated

27th and 28th Hospital Days
- Platelet count rose incrementally
  - 15x10^3/µL to 20 x10^3/µL range

29th Hospital Day
- Platelet drip continued
- Azothioprine added
  - 50 mg daily

30th Hospital Day
- No changes
- Platelet count increased to 104 x10^3/µL

31st Hospital Day
- Platelet drip discontinued
- Platelet count decreased to 13x10^3/µL
Clinical Course

- **32\(^{nd}\) Hospital Day**
  - Platelet drip re-initiated

- **33\(^{rd}\) and 34\(^{th}\) Hospital Days**
  - Platelet count increased to 63x10\(^3\)/µL

- **35\(^{th}\) Hospital Day**
  - Platelet drip discontinued
  - Platelet count decreased to 9x10\(^3\)/µL

- **Days 36-40**
  - Condition remained stable
  - Platelet count remained stable
    - 10x10\(^3\)/µL - 13x10\(^3\)/µL

- **41\(^{st}\) Day**
  - Discharged!!!!
  - Platelet count 13x10\(^3\)/µL
Platelet Count in Relation to Platelet Drip

- ▲ = platelet drip started
- * = platelet drip stopped
Total Platelet Use

- **Apheresis Platelets**
  - 12 units over the course of his hospitalization

- **Platelet Drip**
  - 193 platelet aliquots over the course of his hospitalization
Immune Thrombocytopenia (ITP)

- acquired autoimmune disease characterized by isolated thrombocytopenia (<100x10^3/µL) in the absence of a known underlying etiology
- Previously known as Idiopathic Thrombocytopenic Purpura
  - Nomenclature changed in light of consensus opinion of an International Working Group on ITP
  - Patients rarely show signs of bleeding (purpura)
  - Research points toward an autoimmune pathogenesis
Immune Thrombocytopenia (ITP)

- **Pathogenesis**
  - Conventional theories of pathogenesis have centered on increased autoantibody-mediated destruction of platelets via the mononuclear phagocyte (reticuloendothelial) system
  - Evolving theories of pathogenesis are more complex
    - Inhibition of platelet production \( (2,3) \)
    - T-cell mediated platelet destruction \( (4) \)
  - Additional research into potential genetic mechanisms is underway \( (5) \)
Immune Thrombocytopenia (ITP)

- **Diagnosis**
  - ITP is a diagnosis of exclusion
  - Other etiologies of thrombocytopenia must be ruled out

- **Work-up**
  - History
  - Physical exam
  - Complete blood count
  - Peripheral blood smear
  - Bone marrow biopsy
Immune Thrombocytopenia (ITP)

- Clinical Features
  - Onset
    - Adults
      - Insidious onset
      - Chronic course
    - Children
      - Acute onset
        - Often following a viral illness
      - Generally short-lived
  - Symptoms
    - Variable
      - Absent to minimal bleeding/bruising versus widespread hemorrhage from the GI tract, skin, and/or mucosal surfaces
      - Intracranial hemorrhage (ICH) is a rare, potentially life-threatening, complication\(^7\)
Immune Thrombocytopenia (ITP)

- **Treatment**\(^{(8)}\)
  - **Medical**
    - **First line**
      - Corticosteroids
      - Intravenous immunoglobulin (IVIg)
      - Rh immunoglobulin (Rhogam, Winro)
        - Only effective in Rh+ patients
    - **Second line**
      - Additional immunotherapy
        - azathioprine, cyclosporine A, cyclophosphamide, rituximab, danazol, dapsone, mycophenolate mofetil, thrombopoeitin receptor agonists, or vinca alkaloids
  - **Interventional**
    - Splenic artery embolization
  - **Surgical**
    - Splenectomy
Platelet Transfusion in ITP

- Controversial topic
- No absolute contraindication
- Generally ineffective$^{(9,10)}$
  - Transfused platelets are vulnerable to the same destructive mechanisms as native platelets
  - Rarely results in significant post-transfusion increments
  - Potentially useful in the setting of life-threatening hemorrhage
Platelet Transfusion in ITP

- Conventional wisdom regarding platelet transfusion in ITP has recently been challenged.
  - Some studies have shown significant post-transfusion increments in ITP patients\(^{(11)}\).
  - Platelet transfusion, when given concurrently with immunosuppression, may effectively control bleeding\(^{(12)}\).
Our Patient

- Platelet transfusion was initiated in an attempt to stabilize the ICH, while hopefully increasing platelet count to a level where splenectomy would be a safe option
  - Plt goal = $50 \times 10^3/\mu L$
    - *per surgeon request
  - Initial bolus platelet infusions were ineffective
    - Maximum uncorrected increment $2 \times 10^3/\mu L$
    - Maximum corrected count increment $1104 \text{ m}^2/\mu L$
- Platelet drip started with three initial goals
  1. Provide a steady stream of platelets in the hopes that some would reach the bleeding sites and stabilize the ICH
  2. Minimize donor exposure in a patient requiring serial transfusions
  3. Manage platelet supply in the blood bank of a hospital that is a level 1 trauma center and has an active cardiothoracic/vascular surgery service
Our Patient

- Platelet drip in combination with immunosuppression worked!
  - ICH stabilized
  - Platelet count increased, allowing for a safe surgery
- Platelet count rose in excess of the stated goal (50x10³/µL)
  - Peaks ranged from 73x10³/µL to 172x10³/µL
    - Remained elevated as long as the platelet drip continued
- Platelet count plummeted when the drip was stopped
  - Bottomed out at 3x10³/µL to 9x10³/µL
  - Significant recovery occurred only when the drip was re-initiated
Our Patient: Response to Platelet Drip

^ = platelet drip started
* = platelet drip stopped
Our Patient

- Why did the platelet drip work?
  - Perhaps duration of platelet transfusion is more important than volume of platelets transfused
    - PLADO study\(^{(13)}\)
      - In the setting of prophylactic platelet transfusion for patients with hypo-proliferative thrombocytopenia, there was no significant difference in bleeding risk, regardless of the dose of platelets transfused.
        - Low
        - Intermediate
        - High
    - Platelet drip use has been proposed for prophylactic and therapeutic use in thrombocytopenic patients with non-immunologic platelet refractoriness\(^{(14,15)}\)
      - Efficacy confined to isolated case reports
Conclusions

- In ITP patients with severe persistent thrombocytopenia despite aggressive medical therapy, alternative treatments should be considered.
  - Especially in the presence of clinically significant or potentially life-threatening bleeding.
- Conventional wisdom regarding platelet transfusion in ITP should be reconsidered.
- The use of platelet drip in patients with ITP resistant to conventional therapy needs further investigation.
  - Randomized, controlled, prospective trials are needed to validate platelet drip as a potential treatment modality.
Long Term Follow-Up

- **@ 1 week**
  - Platelet count 15-16x10^3/µL
  - Epistaxis

- **@ 2 months**
  - Platelet count 185x10^3/µL

- **@ 2.5 months**
  - MRSA abscess at site of surgical excision

- **@ 5 months**
  - Platelet count 635x10^3/µL

- **@ 8 months**
  - Platelet count 100x10^3/µL
    - Likely chronic ITP
    - Interval development of psychiatric symptoms
      - Self-mutilation and insomnia

- **@ 11 months**
  - Platelet count 123x10^3/µL

- **@ 13 months**
  - Platelet count 105x10^3/µL
  - Began danazol wean

- **@ 15.5 months**
  - Danazol stopped

- **@ 16 months**
  - Platelet count 67x10^3/µL
  - Continued azothiaprine
References


References


