May-Hegglin and other Platelet Dysfunctions as Complications to Compartment Syndrome:
A case report

by Jason R. Miller, FACFAS, FAPWCA [1]✉ , Peter Moyer, DPM [2]

Compartment syndrome is a well known surgical emergency encountered by physicians on trauma call. When compounded by platelet dysfunction, the management of a compartment syndrome becomes exponentially more difficult for the surgeon. The following case describes a twenty-four year old male who sustained multiple comminuted tarsal and metatarsal fractures after a crush injury that was further complicated by an existing platelet dysfunction known as May-Hegglin anomaly (MHA). This article reviews May-Hegglin and other rare hematological conditions that often obscure otherwise straightforward surgical cases.

May-Hegglin anomaly (MHA) is a familial disorder that is a rare type of autosomal dominant platelet disorder. From 2000-2005, only 85 families with MHA were reported.[6] It is associated with thrombocytopenia with varying degrees of purpura, bleeding, giant platelets, and cytoplasmic inclusion bodies that resemble Döhle bodies in the granulocytes (neutrophils, eosinophils, monocytes).[4,6] In these patients, neutrophil and platelet function is considered to be normal. Thrombocytopenia occurs in almost all patients and severe bleeding is rare but has been reported.

These patients may have a range of symptoms from asymptomatic to recurrent epistaxis, gingival bleeding, easily bruising to menorrhagia. MHA has not been associated with higher rates of infection.[4]

In 1909, German physician May described a young female patient who had leukocytic inclusions, who was asymptomatic.[6] In 1945, Swiss doctor Hegglin described a father and his two sons who had a triad of thrombocytopenia, giant platelets, and leukocytic inclusions.[6]

These patients have a mutation of the MYH9 gene, encoding non-muscle myosin heavy chain IIA, present in chromosomal region 22q12-13.[4,6] This mutation results in disordered production of non-muscle myosin heavy-chain type IIA.

Address correspondence to: Jason R. Miller, FACFAS, FAPWCA
Chief, Foot and Ankle Surgery, Pennsylvania Orthopaedic Center
Adjunct Associate Professor, Dept. of Surgery, TUSPM
Office: 215-644-6900 , FAX: 215-644-7160
Email: jrmiller71@pol.net
[1] Chief, Foot and Ankle Surgery, PA Orthopaedic Center. Adjunct Associate Professor, Dept. of Surgery, TUSPM, Philadelphia, Pa. 19107.
[2] PGY-4, Foot and Ankle Surgery, Temple University Hospital, Philadelphia, PA, 19140.

Figure 1 Initial presentation after crush injury of the left foot.

Figure 2 Radiograph reveals first and second metatarsal crush fracture.

The result is macrothrombocytopenia, secondary to defective megakaryocyte maturation and fragmentation. Other associated syndromes are Sebastian, Fechtner, or Epstein syndromes. Differential diagnosis associated with thrombocytopenia and large platelets include Alport syndrome, Bernard-Soulier syndrome, Montreal platelet syndrome, immune thrombocytopenia, and gray-platelet syndrome.[6] The differential diagnosis for leukocytic inclusions includes septicemia, myeloproliferative disorders, and pregnancy.

A case report describes a twenty-four year old male who sustained multiple comminuted tarsal and metatarsal fractures after a crush injury that was further complicated by an existing platelet dysfunction known as May-Hegglin anomaly (MHA).

Case Report

A twenty- four year old deaf man was transported from a local hospital to our Level 1 trauma center for evaluation. He was at work when a steel industrial loading dock door came crashing down and landed across his left foot. (Fig. 1) Initial evaluation in the trauma bay was significant for left foot swelling, pain, and mottled skin. His sensory function was compromised while gross motor function remained intact. He presented with stable vital signs.

His past medical history was positive for the May-Hegglin anomaly. He reported living with his parents, denied allergies, and had an otherwise unremarkable review of systems. A full physical exam was normal with the exception of his left lower extremity.

Figure 3 Sagittal CT view of crush injury. Displaced metatarsal, calcaneal, and cuneiform fractures are evident.

Figure 4 Surgical exploration shows dark, non-coagulated blood and hematoma associated with the compartment syndrome.

The lower extremity exam was positive for: diminished pulses, exquisite pain on palpation of the mid-foot area, pain with range of motion of digits 1,2,3 and 4, decreased temperature, color changes, and swelling. Arterial line pressure monitoring revealed compartment pressures between 75 mmHg and 100 mmHg in the foot, therefore the operating room was called and prepared for emergent surgery.

Plain film and CT scan revealed the following fractures: comminuted intra-articular fracture of the calcaneus, comminuted fractures of the navicular, cuboid, proximal portions of the cuneiforms and fractures at the base of the second and third metatarsals. (Figs. 2,3) Stat labs revealed the following abnormalities: WBC 4.9, HgB 8.6, HCT 25.9 and platelets were 39,000mm^3. He was then typed and crossed for surgery.

Surgical Procedure

In the operating room, general anesthesia was administered and an emergent fasciotomy was preformed following typical sterile preparation. His left foot was noted to be severely cyanotic, mottled, and cool to touch. An 8-10 cm medial incision was made to the level of the deep fascia.

After the deep fascia was penetrated via blunt dissection, copious amounts of dark, non-coagulated blood flowed from the incision site. (Fig. 4) Both the medial and plantar compartments were explored through this incision. Approximately one to two minutes after initial incision was made, the hallux changed from a mottled, blanched, cyanotic color to a healthy pink hue with appropriate capillary refill time. A second incision was then made between the shafts of the second and third metatarsals. Blunt dissections in to the deep fascia revealed additional copious amounts of dark blood that was evacuated from the compartment. A third incision was placed between the fourth and fifth metatarsals, and again this compartment was relieved of congestion. Within five minutes after initial incision, the entire foot was pink and warm with a dramatic decrease in the swelling. Further evaluation noted that the rear-foot remained mottled and cyanotic. At that point a fourth incision was made anterior to the Achilles tendon into the deep fascia, and approximately 5 cc of dark blood was evacuated from the calcaneal compartment. The incisions were flushed and packed with saline soaked nu-gauze packing. Attention was then paid to the medial aspect of the calcaneus where a closed reduction of the sustentacular fragment was performed under fluoroscopy.

Figure 5 Patient post reduction with functional left foot and no residual pain or deformity.

An external fixator device was placed in triangular fashion under fluoroscopy to maintain proper alignment of the destabilized midfoot and forefoot fractures.

Post-operatively, a posterior splint with a mild compressive dressing was applied and CBC was collected. Medical and hematology consults were activated, neurovascular evaluations were ordered every two hours, cefazolin 1g every 8 hours was started, and repeat radiographs and CT scans were performed.

On post-operative day number one (POD #1), hematology recommended transfusions of both platelets and packed red blood cells prior to the surgical procedure scheduled for POD #5. While they recommend the use of SCD's, compression stockings, and out of bed to chair three times per day, they discouraged the use of heparin or enoxaparin for DVT prophylaxis. Hematology also recommended that in monitoring the patient for active bleeding, the hemoglobin, hematocrit and platelet count should be drawn every 12 hours and to consider desmopression (DDAVP) if the labs worsened.

On POD #4, he was transfused with four units of platelets, two units of packed red blood cells, and was given prophylactic diphenhydramine.

The patient tolerated the transfusion well with no evidence of reaction. On POD # 5, he was taken back to the operating room for a successful wash out, minor debridement and primary delayed closure. The patient was discharged on POD #6 after two normal CBC evaluations.

His uneventful postoperative course was interrupted on his second office visit when it was noticed that there was some displacement at the comminuted first metatarsal-cuneiform joint. He was taken back to the operating room for a possible fusion or re-manipulation/stabilization procedure. Intra-operatively, the joint was easily manipulated back into place, and small Steinman pins were introduced for stability. Additionally, the sustentacular fragment of the calcaneal fracture was definitively fixated with 4.0mm cannulated screw fixation under fluoroscopy by percutaneous technique. The fixation pins and external fixator were removed six weeks later and he has since returned to regular employment approximately 8 months following this injury. He reports no residual deformity or pain and is able to ambulate freely in regular shoegear. (Fig. 5)

Discussion

It is important to note that platelets play a central role in normal hemostasis and thrombosis. Platelets originate from pluripotent stem cells that undergo differentiation to the megakaryoblast and then to platelets. Normal platelet counts are between 150,000 to 300,000mm^3, with thrombocytopenia being defined as a platelet count less than 100,000mm^3. Spontaneous bleeding typically becomes evident after counts drop below 20,000mm^3 (spontaneous head bleeds < 5,000mm^3).[6]

In the circulating form, platelets appear as a smooth discs enclosed within a plasma membrane. This membrane contains a number of receptor glycoproteins that are responsible for platelet function. Within the platelet are two specific types of granules.
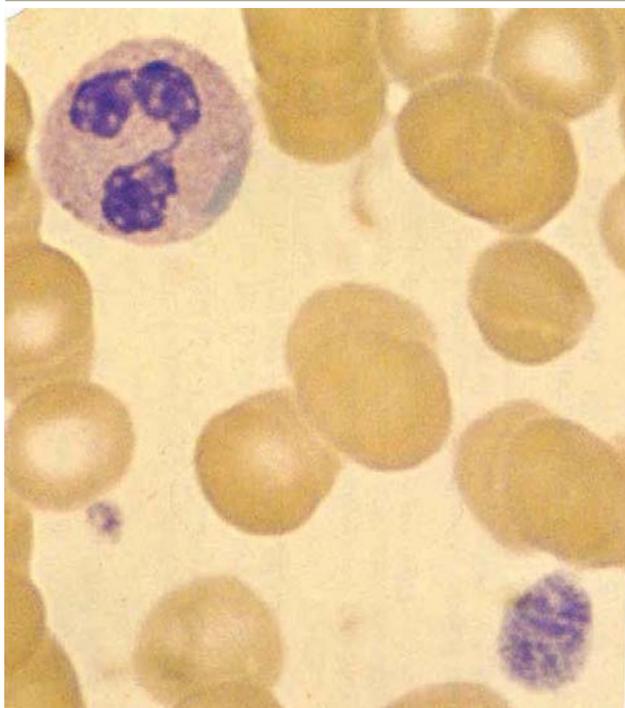
From May-Hegglin Anomaly, eMedicine, 2008.

Figure 6 2000x blood smear of a MHA patient demonstrating a typical giant platelet with ill defined granulation. A normal sized platelet is also seen here. The cytoplasmic inclusion body represents a Dohle body.

The first, alpha granules contain fibrinogen, fibronectin, factors V and VIII, platelet factor 4 and platelet-derived growth factor and transforming growth factor beta. The second type of granule is for non-metabolic pool adenine nucleotides (ADP & ATP), ionized calcium, histamine, serotonin, and epinephrine.[6] When a vessel wall is damaged, platelets undergo three reactions: (1) adhesion and shape change, (2) secretion, and (3) aggregation collectively referred to as platelet activation.[4] (Fig. 6)

A cell blood count is essential in starting a workup in these patients. The platelet count is decreased, usually between 40,000-80,000mm^3. The platelets are enlarged up to 15mm^3 in diameter, with normal morphology.[4] Evaluation at the electron microscopy level reveals normal cell organelles with an increased amount of disorganized microtubuli.

The Wright-stained peripheral blood smear shows cytoplasmic inclusion bodies, most dominant in the neutrophils, but some are present in the eosinphils, monocytes, and basophils.

The inclusions are up to 5μm in size, they are spindle shaped, pale, blue-staining bodies that consist of ribosomes, endoplasmic reticulum, and microfilaments.[4] The inclusions are similar to Döhle bodies and are found in the periphery of the cytoplasm.[4] Bleeding time is typically prolonged in concordance with the degree of thrombocytopenia.

Since patients with MHA do not have significant bleeding problems, treatment should be based on clinical evaluation, laboratory evaluation and following recommendations from a hematologist pre- and post operatively. Though it is rare for a MHA patient to develop severe bleeding intra- and post operatively, the skilled foot and ankle surgeon should be aware of the risk of bleeding requiring transfusions.[5]

Desmopressin acetate (DDAVP), is a synthetic vasopressin analogue that has been used peri-operatively in patients with MHA. It is an altered form of vasopressin in which deamination of hemicysteine at position 1 and substitution of D-arginine for L-arginine at position 8 has occurred.[2] Desmopressin binds to the V2 receptor in renal collecting ducts, increasing water resorption. It also stimulates release of factor VIII from endothelial cells due to stimulation of the V1a receptor.[2] This change in stereochemistry eliminates vasopressor (V1) receptor agonist activity and enhances the antidiuretic (V2) receptor agonist action and prolongs duration of action from 2-6 hours to 6-24 hours.[2]

Desmopressin stimulates the endothelial release of factor VIII and von Willebrand factor into the plasma (V2 receptor effect).

After a slow infusion of 0.3mcg/kg, plasma concentrations of factor VIII and von Willebrand factor is 2-4x greater.[2] Although it can be unpredictable, desmopressin has been shown to shorten bleeding time in a variety of platelet dysfunctional diseases.

DDAVP has become the drug of choice for prevention and treatment of bleeding in patients with mild hemophilia A and von Willebrand's disease because of the increase in factor VIII and von Willebrand factor, but its mechanism in platelet disorders is still one of debate.[5]

Sehbai, et al., reported a case where 34-year old woman with known MHA underwent a craniotomy secondary to an intractable seizure disorder since childhood.[5] After an extensive family history, past medical history of the patient, and extensive workup which included; magnetic resonance imaging (MRI) of the brain, positron emission tomography (PET) scan, and 24 hour video EEG, the woman underwent craniotomy and resection of the temporal lobe foci of seizure activity. She was admitted one day prior to surgery and transfused with 6 units of platelets, and one hour before surgery was given DDAVP. Platelets were on standby if needed intra or post operatively. Her postoperative course was uneventful except for mild hyponatremia secondary to the DDAVP.[5]

Chabane, et al., reported a 24 year old female that was diagnosed with severe thrombocytopenia after giving birth. She was later diagnosed with MHA. She later went on to have a second and third child via cesarean section, and she did not receive platelets for either. The third child was affected by the MHA with a platelet count of 49,000mm^3 as well as inclusion bodies on blood smear.[1]

Matzdorff, et al., reported on a patient with Fechtner syndrome that underwent a tonsillectomy and was given DDAVP pre-operatively.[3]

The patient was a 24 year old woman with a past medical history of thrombocytopenia and bruised easily in childhood. She had been diagnosed with Sebastian platelet syndrome, had also noted a impairment with her hearing as well as mild hematuria. After a detailed family history it was noted that some relatives had thrombocytopenia and hearing impairment. At the time, a blood smear was obtained and evaluated with electron-microscope, which confirmed that the inclusions were consistent with Fechtner syndrome. The woman underwent extensive laboratory evaluation: modified Ivy bleeding test, platelet aggregation studies with ADP, collagen, and ristocentin, and standard coagulation test. The patient also had a bone marrow biopsy. The pertinent test in this case was the bleeding test which was greater than thirty minutes, normal being 5-8 minutes.[3] The test was repeated after DDAVP was given, and her bleeding time normalized to 7 minutes 30 seconds, and her von Willebrand factor (her base line was above average) antigen had increased from 150% to 282%. On the day of surgery the women received DDAVP 0.4 μg/kg over 30 minutes 1 hour before the start time, and the surgery went uneventful.[3]

Conclusion

May-Hegglin is a rare platelet disorder associated with macrothrombocytopenia, leukocyte inclusions, deafness and nephritis. Patients may experience easy bruising, recurrent epistaxis, gingival bleeding, menorrhagia, and excessive bleeding associated with surgical procedures. A patient that presents with MHA and an un-witnessed fall should get a CT scan to rule out intracranial hemorrhage and internal bleeding. Patients that present with MHA should be evaluated by a hematologist to recommend DDAVP and platelet transfusions when necessary. In this case, MHA likely played a compounding role in the rapid development of the foot compartment syndrome encountered and could have certainly compounded the post-operative course.

This case demonstrates the need for a multi-disciplinary approach to patients exhibiting May Hegglin anomaly and expeditious surgical intervention when this rare patient population experiences a traumatic event. Additionally, it demonstrates the need to take a thorough history to reveal rare disorders, like this one, in an elective surgery population. A lack of proper treatment in patients with rare platelet disorders can certainly lead to devastating complications. It is our sincere hope that this article will serve to guide the foot and ankle surgeon to appropriately recognize and treat complicating disease processes when they present.

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