Acquired von Willebrand Syndrome *secondary to* Immunoglobulin Light Chain Amyloidosis *presenting as an* Intramuscular and Intraabdominal Bleed

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Introduction

Immunoglobulin light chain (AL) amyloidosis

- A plasma cell dyscrasia: overproduction of monoclonal Ig light chain fragments by bone marrow plasma cells → improper folding → deposition into tissues[1]
- Prevalence varies geographically: 1,275 to 3,200 new cases annually in the U.S.[2]
- Complications: Affects heart, kidneys, and nerves → cardiomyopathy, nephrotic syndrome, and neuropathy[1]
- Less common: abnormal bleeding

Acquired von Willebrand Syndrome (AVWS)

- A rare bleeding disorder caused by loss of von Willebrand factor (vWF), a plasma protein that mediates platelet adhesion and aggregation
- vWF can be destroyed or absorbed by amyloid fibrils[3]

Case Presentation

Patient: Middle-aged man with a benign medical history until COVID-19 diagnosis.

Post-COVID-19 recovery: Spontaneous bilateral lower extremity pain, swelling, and bruising.

- Multiple visits with primary care, vascular surgery, and orthopedics.
- Venous doppler ultrasound: Chronic venous insufficiency and small hematoma in the left proximal thigh.
- Worsening leg pain despite conservative measures (naproxen, prednisone, compression socks).

Consultation with Hematology/Oncology due to abnormal CBC findings:

- Chronic leukocytosis with mild neutrophilia and monocytosis.
- Progressive thrombocytosis.
- New onset normocytic anemia.
- Repeat ultrasound: Left thigh hematoma tripled in length and quadrupled in width.

ED visit for abdominal pain, ultrasound revealing cholecystitis.

- Laparoscopic cholecystectomy with post-op hemorrhagic shock and 2.5cm x 2.5cm right abdominal wall hematoma.
- Returned to operating room for diagnostic laparoscopy, abdominal washout, and repair of bleeding trocar sites with multiple blood clots in the omentum.
- Stabilization following platelets and pRBCs administration, discharge on post-operative day three.

Two weeks later, emergency department visit due to progressive left lower extremity swelling.

- CT contrast: Left thigh hematoma expanded throughout vastus intermedius, lateral side of the rectus femoris, and distal vastus medialis.

Diagnostic Assessment

Differential Diagnoses

- Platelet dysfunction
- Coagulation factor disorder
- Myeloproliferative neoplasm (MPN)

Workup for platelet dysfunction and coagulation factor disorders

vWPanel, Factor X assay, CBC:

- Acquired von Willebrand disease (vWD): low ristocetin, absent high molecular weight multimers
  - Echocardiogram negative for aortic stenosis
- Factor X deficiency
- Thrombocytosis (1 million/mm3)

Evaluation for MPN

- Negative JAK2 V617F, JAK2 exon 12-13, CALR, and MPL genes → no polycythemia vera, essential thrombocythemia, JAK2 exon 12-13-positive MPN, CALR-positive MPN, or primary myelofibrosis
- Serum Protein Electrophoresis (SPEP) and multiple myeloma labs:
  - Bence Jones proteinuria
  - Multiple myeloma FISH panel normal
  - Low kappa:lambda light chain ratio
- Bone marrow biopsy:
  - Positive Congo red stain: diagnostic of AL amyloidosis.

Treatment

- Initially treated with hydroxyurea to lower platelets, while receiving recombinant von Willebrand factor and replacement Factor X
  - No resolution of symptoms and values
- Subsequently treated following standard systemic light chain amyloidosis guidelines after diagnosis
  - Daratumumab-CyBorD (cyclophosphamide, bortezomib, and dexamethasone)

Outcome

- Positive response to CyBorD treatment
- Normalization of vWF levels
- Repeat bone marrow biopsies showed plasma cells less than five percent
- Complete resolution of symptoms
- No intention to proceed with hematopoietic stem cell transplantation (HCT) at this time though he did have a stem cell collection

Discussion

- Treatment response suggests bleeding was not solely from thrombocytosis, von Willebrand Disease, or Factor X deficiency, but also related to AL amyloidosis.
- In previous studies, identification of AVWS led to appropriate management of initial bleeding, including transfusions and medication adjustments.[4]
- Clues of AL amyloidosis throughout the patient's presentation, including atraumatic leg hematoma and elevated alkaline phosphatase (ALP) levels.
  - Not high on differential as classic presentation is end-organ damage
  - ALP can be a marker for biliary obstruction but also MPNs
  - COVID-19 related to increased serum amyloid A but less studied on primary amyloid concentrations
- Importance of thorough workup of underlying plasma cell disorders in patients with unexplained bleeding and abnormal coagulopathies.
- A limitation is the lack of information on the patient's long-term outcomes.
- Future studies can explore optimal management approaches for AL amyloidosis in the context of AVWS and thrombocytosis.
- Recognize and manage AL amyloidosis early to prevent complications and improve outcomes in patients with refractory bleeding complications.

Sources

1. Cashen and van Tine. The Washington Manual Hematology and Oncology Subspecialty Consult. Wolters Kluwer; 2016.
2. Falk et al. The systemic amyloidoses. N Engl J Med; 1997.
3. Van Genderen et al. The reduction of large von Willebrand factor multimers in plasma in essential thrombocythaemia is related to the platelet count. Br J Haematol; 1996.
4. Kos et al. Association of acquired von Willebrand syndrome with AL amyloidosis. Am J Hematol; 2007.