Hypoalbuminemia as Warning Sign for Paraneoplastic Nephrotic Syndrome In Squamous Lung Cancer

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Learning Objectives:

1. Presentation and physical findings
2. Pathophysiology
3. Diagnosis
4. Medical Management

Clinical Overview:

- **Clinical Presentation:** Patient with squamous lung cancer (SLC) most commonly presents with cough (45-75%), hemoptysis (57%), bronchial obstructions, asymptomatic (10%) & paraneoplastic syndrome (8-12%). This makes very challenging the diagnosis. [2]
- **Pathophysiology:**

  -Paraneoplastic Membranous nephropathy (MN) is caused by the cross-reaction between glomeruli and tumor antigens, providing evidence of immune complex in paraneoplastic glomerulopathy (Figure 1)

  -MN promotes a prothrombotic stage increasing the risk for deep vein thrombosis (DVT), and pulmonary embolism (PE).
- **Diagnosis**: Biopsy is the goal standard test to diagnosis MN as well as SLC. In MN, the electron microscopy (EM) shows presence of subepithelial immune-complex deposit. Immunoflurescence (IF) shows diffuse global granular capillary wall staining for IgG and C3.
- **Management:**

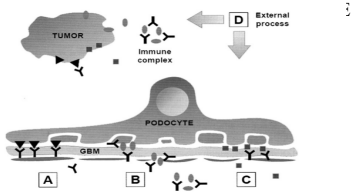


Figure 1. Mechanisms by which solid tumors MN may be generated against an antigen identical to, or bearing an epitope similar to, an endogenous podocyte antigen, thereby leading to in in situ immune complex formation. Shed tumor antigens and any circulate forming immune complexes that can be trapped in the capillary wall. This process initiates inflammation and MN.

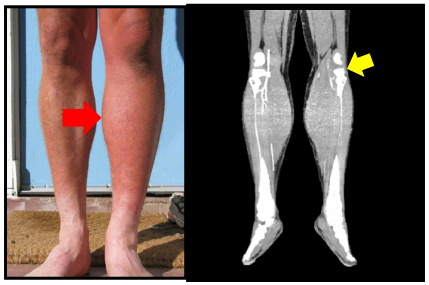


Figure 2. A. Shows swelling of the leg compare with the right (red arrow). **B.** CT angiogram of abdominal aorta runoff showed focal occlusion of the left popliteal artery near its origin (yellow arrow). No flow is seen along the left foot.

Clinical Case:

- A 51-year-old Caucasian male with history of heavy tobacco user (16/PPY) presented to the hospital with left lower leg pain for 3 days with limited range of motion (Figure 2A)

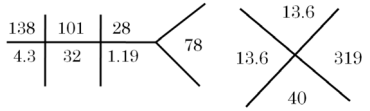
ROS:

Positive: left leg swelling, limited range of motion, tenderness on palpation, cough, SOB
Negative: any acute injury, recent weight loss, hemoptysis, fever

Physical exam

•Respiratory: bilateral wheezing
•Lower extremity: Peripheral vascular examination revealed absent of left dorsalis pedis and posterior tibial artery pulsation confirmed with Doppler ultrasound.

Laboratory:



Laboratory	Value	Normal Range
Albumin	1.6 g/dL	3.4-5g/dL
Urine protein	4+	Negative
Urine blood	Trace-intact	Negative
Urine pH	8	5-7
Urine protein/creatinine	12.72 mg/mmol	0-30 mg/mmol

Table 1

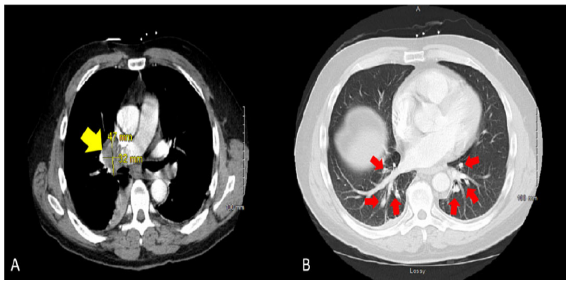


Figure 3. CT angiogram showed: A. Large right hilar mass measuring 47 x 32 mm (yellow arrow) in association with consolidation to the medial right lower lobe having compressive effect upon the second order airway branches to the right lower lobe. B. Presence of bilateral hilar lymphoadenopathies (red arrows).

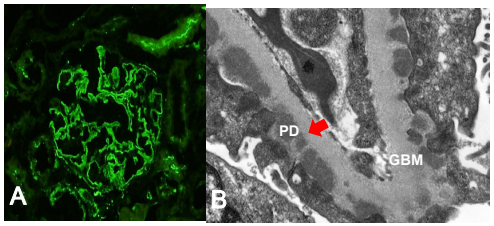


Figure 4. Pathology report of renal biopsy: A. IF study showed glomeurli with granular staining for IgG (3+), C3 (3+), kappa ligh chain (3+), and lambda chain (3+) along the capillary walls, and the anti-PLA2R stain was negative. B. EM showed glomerular basal membrane (GMB), and diffuse effacement of the foot process (red arrow) of the podocyte (PD).

Hospital course:

- **Day #1:** Computerized tomography angiogram (CTA) of the abdominal aorta showed occlusion of the left popliteal artery (Figure 1B) and patient underwent to catheter-directed thrombolysis (CDT) and started on tissue plasminogen activator (TPA) 1mg/hr.
- **Day #2:** Patient had episodes of SpO2 85% and needs 2L of nasal cannula with breathing treatment. On the lab **albumin noticed low** for age and urinalysis was ordered which showed 4+ proteinuria (Table 1). Chest X-ray (CXR) showed mild prominence of the right hilum. Nephrology was consulted for nephrotic range proteinuria.
- **Day#3**: With nephrotic range proteinuria and DVT, following labs were ordered: ANA, C3, C4, hepatitis panel, serum protein electrophoreis (SPEP), urine protein electrophoresis (UPEP), and anti-phospholipase A2 receptor (anti-PLA 2R) to distinguish between possible primary and secondary MN. CTA pulmonary was ordered with history of tobacco use and scheduled for kidney biopsy. Differentials diagnosis was: MN, Focal segmental glomerulosclerosis (FSGS), minimal-change disease, and amyloidosis
- **Day#4:** SPEP suggested acute or subacute inflammation or neoplastic disease (Table 2). Autoimmune test was unremarkable, and anti-PLA 2R was negative. CTA pulmonary showed large right hilar mass (Figure 3). Patient underwent to kidney biopsy which revealed MN (Figure 4).
- **Day#5**: Endobronchial ultrasound bronchoscopy (EBUS) was performed and biopsy was sent to the pathology which reported SLC. Hem/Oncologist was consulted and patient was scheduled on chemo/radiation therapy as outpatient.

Learning Points & Discussion:

Diagnostic:

This case shows the important of being meticulous during diagnosis and finding the etiology. In this case, patient presented with hypoalbuminemia without the whole picture of nephrotic proteinuria which was a key finding to elaborate subsequent workup quickly.

New finding:

Showed the role of the anti-PLA2R discovered in 2009 to help distinguish **primary from secondary** MN[6]. This new biomarker was recently introduced by FDA to use as non-invasive diagnosis test. Anti-PLA2R is recently identified podocyte antigen which a family of M-type transmembrane phospoliase A2 receptor (Figure 5).

The uses of biopsy with the stained PLA2R antigen potentiate the sensitivity to 80% (6). The treatment of secondary forms should be based at the underlying systemic disease. For example, the treatment of a tumor in malignancy-associated MN as this case

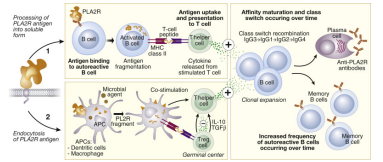


Figure 5. Pathophysiology of primary MN by the exposition of PLA2R from the podocyte and development of antibodies.

Key Points:

- It is essential to do a thorough workup in any patient keeping in mind differential diagnosis and reviewing labs.
- Try to investigate the clinical presentation that may explain the whole situation.
- The role of anti-PLA2R to differentiate between primary and secondary MN
- The importance of an interdisciplinary teamwork

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