CLINICAL VIGNETTE

Hyperinflammation Malnutrition Syndrome in a Patient with DLBCL

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A 76-year-old female was brought to the Emergency Department with severe generalized weakness and weight loss. She was cachectic, weighing 65 lbs. Four months earlier, her clinic weight was 98 lbs. She had chronic back pain which was worsened in upper back, but no fever, sweats, cough, or abdominal or chest pain. She was anorexic but without nausea, vomiting or diarrhea. No history of bleeding or other focal symptoms. She was afebrile and highest temperature recorded in hospital was 99.5-degree Fahrenheit. Respiratory rate 12-24/ minute. BP 90-112/ 47-66. Pulse 94-113 beats/ minute.

She lived with her husband in a retirement community. She was lethargic, and extremely weak with difficulty sitting up. Vital signs included normal temperature. Respiratory rate 12-24/min. BP 90-112-47-66. Pulse 94-113 beats/min. Exam was remarkable for scleral icterus.

Admission labs included WBC 20.5 (10 3/uL) Hemoglobin 6.7g/dL, Hematocrit 24%, Platelets 995 (10 3/ uL), 91.2% Neutrophil, 1.8 %Lymphocyte, 6.8% Monocyte, MCV 74, MCH23.3, RDW 16.1. BUN 22, Cr 0.60 TB 3.6, DB 2.6, AST and ALT normal to borderline increased. Alkaline phosphatase elevated at 445 (N 45-117) Total Protein 5.9 g/ dL. Albumin 1.0 g/dL. Calcium adjusted 11.4.

Ammonia, Troponin and BNP normal.

PT INR 1.4, PTT 35, Fibrinogen >1000 mg/dL. D Dimer 885 (Normal <500) ng/mL.

She had old Lumbar and T9 compression fractures and new T6 compression fracture on X ray.

SPEP showed no monoclonal protein, Serum Kappa: Lambda light chain ratio was normal, IgG 701, IgA 313, IgM 25.

PTH was low, Vitamin D 27.5 (decreased), PTH related protein negative. Calcium improved with hydration.

TSH and Free T3 in normal range.

UA 1+ blood, 1+Bili, No RBC and no increased WBC.

Stool guaiac was negative.

LDH was in normal range on repeat testing also, Haptoglobin slightly increased401 (Normal 42-346), Urine hemosiderin Positive.

Uric acid was normal.

Reticulocytes 2.4%. Microcytosis and hypochromic. Smear also showed no increased schistocytes, Target cells were 1+, Rouleau +. Thrombocytosis, leukocytosis, 1+metamyelocytes, and 1+ myelocytes.

Vitamin B12, Hemoglobin electrophoresis normal.

Iron 18, saturation 9%, TIBC 240 all low, Ferritin 1419 v high.

Erythrocyte sedimentation rate was high at > 130 (Normal <30) Beta 2 microglobulin was elevated at > 8 (Normal <2).

ANA and anti-ds DNA, p ANCA and c ANCA negative RF borderline elevated at 24.

COVID-19, Influenza A, B, Cryptococcus Ag negative, Cocci serology negative, Quinteron Gold test negative.

EBV testing no evidence of recent infection or activation but evidence of past infection, CMV negative. Hepatitis A, B and C serologies negative. HIV negative.

Flow Cytometry on blood showed no monoclonal population, normal CD4 and 8 ratios.

FISH and Hem malignancy profile for JAK, CALR and MPN and otherwise negative.

CT Chest: Calcified fibrotic breast implants. Single 2 cm deep left axillary lymph node and another 2 cm LN in anterior prevascular space anterior to Left Pulmonary artery. There was a slightly prominent lymph node in pre-carinal space. Trace BL pleural effusions, left sided small pleural based thickening/ nodule 2 cm near sternum anteriorly, nodule LLL 6 mm in size.

CT abdomen pelvis were normal except bone changes previously described. No hepatosplenomegaly or adenopathy. No suspicious masses. Gallbladder and biliary system was normal without biliary dilatation.

This patient had presented with severe malnutrition and inflammation, with high ESR, fibrinogen and ferritin and significant anemia. Elevated neutrophils and thrombocytosis and elevated bilirubin were also present but no clear evidence of hemolysis or biliary obstruction. Imaging noted only mild, limited adenopathy and no infection or autoimmune disorders.

Bone marrow biopsy showed mildly hypercellular marrow at 50% with tri lineage hyperplasia but no dysplasia or immature cells. Benign reactive lymphoid aggregate was identified. No other pathology was seen and all studies came normal. No morphologic, immunohistochemically or immune phenotypic evidence of any hematological disorder or malignancy. All molecular, FISH and karyotype studies were negative.

Patient was bed bound with extremely poor performance status. She had difficulty even raising her head and was sleeping most of time. She initially refused lymph node biopsy.

She was started on dexamethasone and improved quickly both clinically as well as her lab data. She was stronger and more alert, and agreed to lymph node biopsy. Left axillary Lymph node CT guided core biopsy showed Diffuse Large B cell lymphoma non-germinal center subtype. CD20, bcl2 and bcl6+. C Myc at 40%, Ki 67 at 85%, and mum1+. There were no features of EBV related lymphoma and all staining for EBV including EBER were negative.

This was consistent with malnutrition hyperinflammation syndrome[1,2] with intermediate IPI score (Age and performance status), early stage and very low bulk Diffuse large B cell NHL and no other etiology was identified. The inflammation produced significant anemia, hyperbilirubinemia and transient hypercalcemia, without fever or sweats. These protein energy wasting syndromes with hypoalbuminemia and cachexia have been described in multiple hematological disorders and malignancies but usually in more advanced cancers. Hyper-inflammation and malnutrition are also seen in non-malignant conditions like kidney failure chronic dialysis patients and cardiac diseases as well as infections and some autoimmune and other disorders.[3,4]

Our patient's performance status was extremely poor and had rapidly declined while her inflammation markers were very high. With other testing negative, treating with steroids allowed rapid clinical improvement as well as lab parameters, which allowed biopsy for diagnosis and treatment of DLBCL. Non-GCB lymphomas treatment outcomes have significantly improved with addition of Rituximab to conventional drugs. Some of inflammation associated lymphomas have been associated with activation of EBV or other infections but we found no evidence in this patient. There was no cutaneous or visceral lymphoma involvement seen other than a possible pleural based lung nodule.[5,6]

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