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RESEARCH ARTICLE

A CASE OF AGGRESSIVE PLASMABLASTIC LYMPHOMA IN AN HIV-NEGATIVE FEMALE

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Abstract

Plasmablastic lymphoma (PBL) is a rare lymphoma first described around twenty years back as a unique entity typically associated with Human Immunodeficiency Viruses (HIV) and affecting the oral cavity. The authors present a case of a 62 years old female who was diagnosed with Plasmablastic Lymphoma (PBL). She had a long standing history of persistent anemia and presented acutely with gastrointestinal symptoms. She was found to have a picture of Tumor Lysis Syndrome and her investigations were initially going with a diagnosis of Plasma Cell Dyscrasia but further investigations determined a diagnosis of PBL. PBL continues to be an uncommon entity and is thus usually missed as part of an initial differential diagnosis. Ongoing studies are limited because of the aggressive nature of the disease making long-term follow-up a challenge.

Introduction:-

Plasmablastic lymphoma (PBL) is a rare lymphoma first described around twenty years back as a unique entity typically associated with Human Immunodeficiency Viruses (HIV) and affecting the oral cavity.[2] It is now considered a distinct subtype of diffuse large B-cell lymphoma (DLBCL) and is indeed more common in patients with HIV and those with age-associated immunosuppression as well as patients receiving immunosuppressive therapy. However, PBL has also been diagnosed in immunocompetent patients. PBL shares some features with a group of large B-cell lymphomas that exhibit plasmablastic differentiation with an aggressive behavior, refractoriness to chemotherapy, and poor prognosis in most cases. They are characterized by a gradual expression of transcription factors associated with the plasmacytic differentiation, CD38, CD138, MUM1, Blimp1, and XBP1, with decreased expression of CD20 and PAX5.[2]

The most commonly affected sites are the oral cavity, GI tract, lymph nodes, and skin.[2] PBL generally has a poor prognosis with most patients dying within 2 years from initial presentation. [2] Cases of HIV negative PBL may arise from previously existing lymphoproliferative or autoimmune disorders but some cases have been described in otherwise immunocompetent patients. The actual incidence of both HIV-positive and HIV-negative PBL is unknown. PBL is more common in males (3:1 male to female ratio) with a median age of 50 years.[2]

We present here a case of Plasmablastic lymphoma behaving aggressively in an HIV-negative female presenting with non-specific symptoms.

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Our case

Mrs. N, is a 62 years old female, a known case of type 2 Diabetes Mellitus, Hypertension, Dyslipidemia and Chronic kidney disease. She is an ex-smoker with a 10 pack-year history. She was diagnosed a few years back with persistent anemia, for which multiple bone marrow examinations (biopsy and aspirate) were performed abroad, all of which came back inconclusive (no supporting documentation). She presented with a 10-day history of vague gastrointestinal symptoms consisting of abdominal pain, anorexia and repeated vomiting. No other symptoms were reported; no fever, weight loss, bleeding per any orifice or night sweats. However; she gave a history of herpetic eruption one month back for which she was started on Acyclovir.

On examination, she was hemodynamically stable, conscious and oriented but physically dehydrated. She had splenomegaly on abdominal examination, yet no lymph nodes palpable.

Investigations and labs:

12-lead ECG showed no dynamic changes CBC

White blood cells (WBC)	21 x 10^9/L	3.7-10^/L
Hemoglobin	75 g/L	120-150 g/L
Hematocrit	0.206	0.36-0.46
Mean corpuscular volume (MCV)	95 fL	83-101 fL
Platelet count	119 / L	130-430 /L
Neutrophils #	5.8 /L	1.7-7.5 /L
Lymphocyte #	10.3 /L	1-3 /L
Monocytes #	5.5 / L	0.2-1 /L
Eosinophils #	0.1 /L	0.02-0.1 /L
ESR	11	0-20

Table 1:- Serum Urea and Electrolytes.

Troponin 0.02 ng/mL	Glucose 4.8 mmol/L	Urea 23.6 mmol/L	Creatinine501 mmol/L	Sodium 134 mmol/L
Potassium 6.58 mmol/L	Cloride 100 mmol/L	CO2 16 mmol/L	Phos 2.86 mmol/L	Total protein 81 g/L
Albumin 30 g/L	Adjusted calcium 2.45 mmol/L	Total bilirubin 7.9 umol/L	Alkaline Phosphatase 211 IU/L	Gamma GT 62 IU/L
ALT 15 IU/L	AST 55 IU/L	Lactate Dehydrogenase 15024	Uric acid 1588	

Table 2:-Arterial blood gas.

PH	7.07	7.35-7.45
PCO2	2.7 kPA	4.6-6 kPA
PO2	8.6 kPA	11-14.4 kPA
HCO3	7.1 mmol/L	

Table 3

Virology screen:

HIV, Hepatitis B, Hepatitis C, CMV, EBV, Parvovirus all negative.

Peripheral blood smear:

White Blood Cells: moderate absolute lymphocytosis with many activated and lymphoplasmacytoids, rare plasma cells, 0.5% suspicious cells, left shift of neutrophils to myelocyte stage. Red Blood Cells: moderate normocytic normochromic anemia with anisocytosis and normoblastemia (6% normoblasts). Platelets: mild true thrombocytopenia with few large forms.

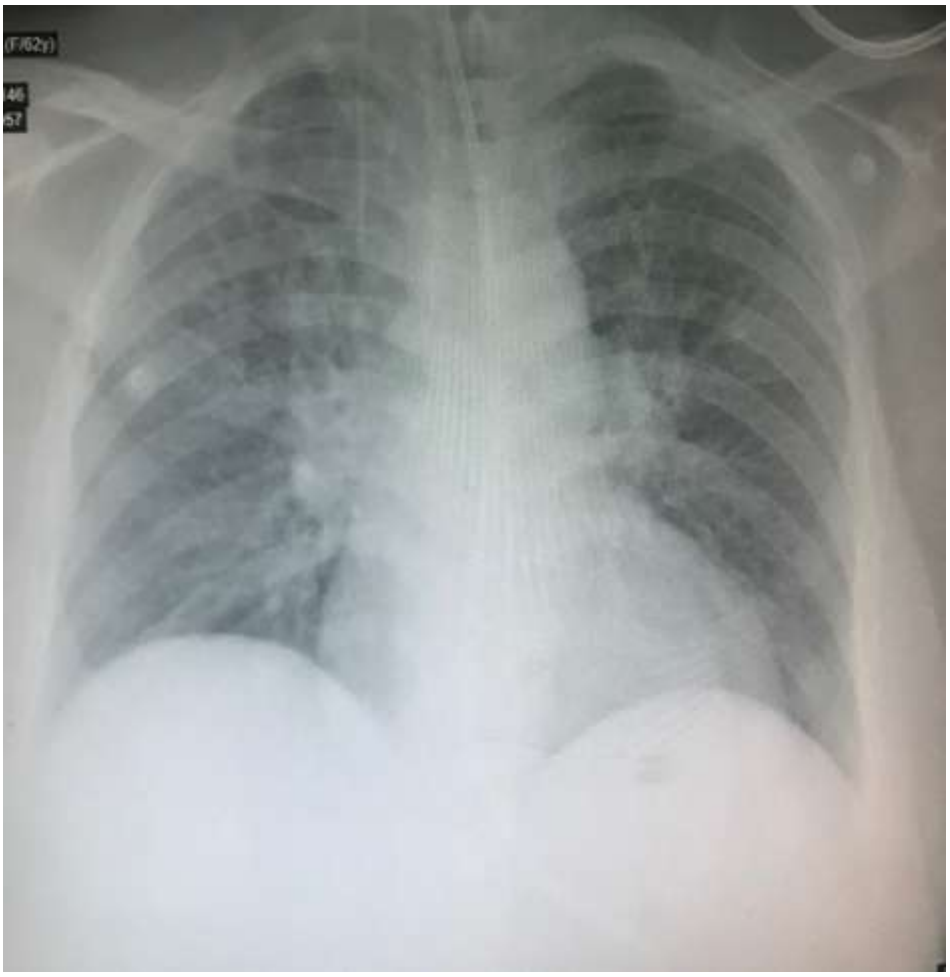

Figure 1:- Chest X-ray: bilateral lymphadenopathy.

Ultrasound abdomen:
Calcular gallstones without cholecystitis. Hepatosplenomegaly; liver measuring 20 centimeters and spleen measuring 20 centimeters. both kidneys are normal in size.

Tumor markers:
CA125: 275 U/mL
CA15.3: 48.5 U/mL

The patient presented with acidosis, hyperuricemia and refractory hyperkalemia; a picture suggestive of tumor lysis syndrome (TLS). A CT chest/ abdomen/ pelvis was obtained and showed: Thoracic and abdominal lymphadenopathy. Prominent breast glandular tissue bilaterally. Thyroid lesions. Pulmonary nodules. Bilateral collapse consolidations more pronounced on the left. Also, a mild pleural effusion. The distal part of the anorectal region showed apparent thickening.

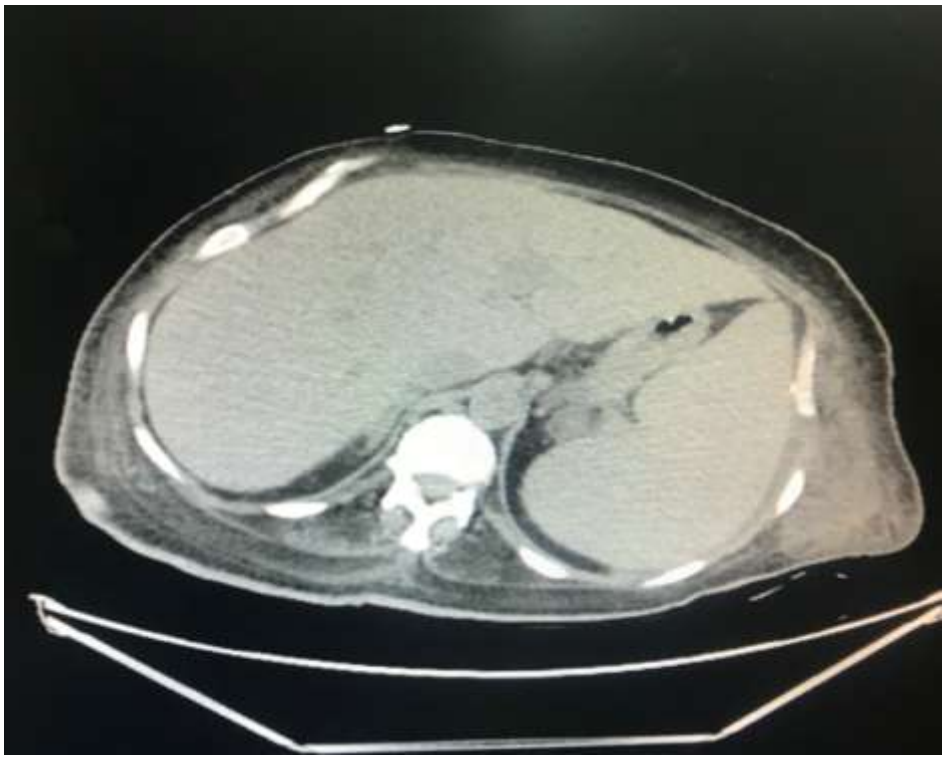

Figure 2:-

Serum protein electrophoresis and immunofixation were sent and showed a monoclonal band; kappa restricted. A lymph node (LN) biopsy was advised but there was no accessible LN.

Table 4:-

IgA	0.46 g/L	0.7-3.8 g/L
IgG	4.53 g/L	6.9-16.1 g/L
IgM	31.7 g/L	0.6-2.6 g/L
Total protein	73 g/L	63-80 g/L
Albumin	25 g/L	32-50 g/L
Alpha 1	3 g/L	0.8-2.2 g/L
Alpha 2	6.7 g/L	6-10 g/L
Beta	5.8 g/L	6-13 g/L
Gamma globin	8.3 g/L	7-15 g/L

Bone marrow aspiration and biopsy:

Hypercellular bone marrow. Infiltration by variable number of moderate to large cells with 1-4 nucleoli and moderate amount of cytoplasm with mitotic figures. Many plasma cells, plasmacytoid lymphocytes and mature lymphocytes. Depressed granulopoeises and erythropoeises. Normal megakaryopoeises. Some dysplastic features in all lineages. Provided down are pictures of bone marrow aspirate.

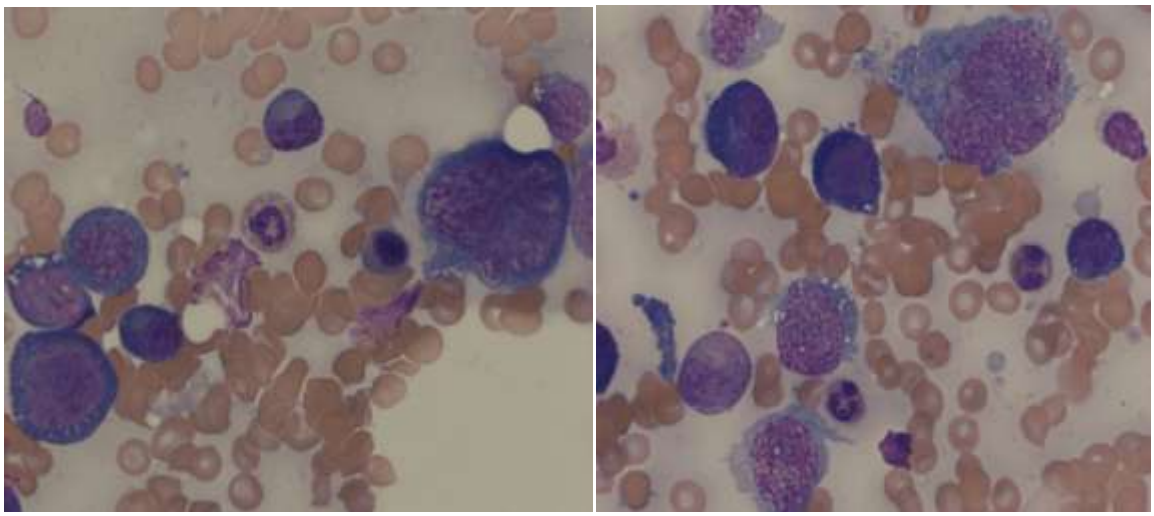

Figure 1:-

Immunohistochemistry was positive for CD 38, CD138, kappa restricted. It was negative for CD 19, CD 20, ALK, and cytokeratin.

Peripheral blood (PB) immunophenotyping showed positive CD 38, CD 138, Kappa light chain. Thirty percent of Bone marrow cells came back positive for the same CD markers present in the PB flow cytometry.

Cytogenetic studies came as complex karyotyping (46 XX, -X, t(8;?), +(13?), -14, -18, +mar). FISH came back negative for IGH/ CCND/ t (11;14)/ (q13; q32)/ TP53 (17p13)/ CCP17.

Based on the clinical picture, lab tests, bone marrow results, she was diagnosed with Plasmablastic Lymphoma. Unfortunately, the patient passed away before obtaining the aforementioned bone marrow examination, flow cytometry and cytogenetic results.

Discussion:-

Plasmablastic lymphoma (PBL) is a rare entity of aggressive diffuse large B-cell lymphoma generally presenting in immunocompromised patients; especially those with HIV.[1] It is associated with a very poor prognosis and patients affected usually present at later stages of the disease.[3]

PBL mainly affects adults. Age range is variable but most commonly within the 50-60 age group. This may be earlier in HIV-positive patients.[3]

Clinical presentation in patients with PBL is variable but mostly extranodal. It mainly presents in the oral cavity followed by the GI tract as was found in our patient. Nodal presentation is not uncommon comprising less than 10% of cases.[3]

Our patient gave a history of persistent anemia along with hepatosplenomegaly for which several bone marrow examinations were done. It is unresolved whether her diagnosis of PBL was a separate unassociated disease or simply a continuum of the same disease process. She presented with advanced stage disease which is the commonly reported scenario in comparable case reports.

Regarding the disease morphology, PBL shows a spectrum varying from a diffuse and cohesive proliferation of cells resembling immunoblasts to cells with more obvious plasmacytic differentiation which may resemble cases of plasmablastic plasma cell myeloma. Mitotic figures are commonly seen.

Typical flow cytometry yields positive CD38, CD138, CD79a (positive in 40% of cases), IRF-4MUM1, BLIMP-1, XBP1. Usually negative for CD20, CD45 and PAX5. Cytoplasmic Ig is commonly expressed as IgG; either kappa or lambda restricted. Ki67 is typically highly expressed in PBL; usually more than 90%.

Cytogenetic findings typical to PBL are a complex karyotype, MYC positive (is seen in almost half of diagnosed cases usually linked to EBV positivity) and a negative BCL-2 and BCL-6. TP53 is positive in around 50% of cases. [9]

The average overall survival usually does not exceed 2 years as patients generally present later in the course of the disease. [3]

Since most patients with PBL commonly present late this renders it harder to establish an optimal treatment regimen. As such, treatment options have been variable and mostly based on trials of different regimen options. Given the resemblance in disease biology between PBL and both multiple myeloma (MM) and lymphoma, treatment plans are usually a combination of both diseases' treatment algorithms.

As aforementioned, there is no well-established treatment for the management of PBL and more than 50% of cases have received Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (CHOP).[3] The NCCN, however, recommends a more intensive approach such as Etoposide, Vincristine, Doxorubicin, Cyclophosphamide, Prednisone (EPOCH), Hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone (Hyper-CVAD) and Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate alternating with Ifosfamide, Etoposide, Cytarabine (CODOX-M/IVAC).[3] Seeing that PBL shares characteristic pathophysiological features with MM, the use of anti-myeloma agents can be a rational option. These agents include the proteasome inhibitor, Bortezomib as well as Linalidomide or Thalidomide, although the evidence on their use in PBL is scarce.[10]

A study currently in progress studies the potential benefit of Daratumumab and dose-adjusted EPOCH in PBL (NCT04139304).

Regrettably, our patient's final diagnosis of PBL was reached after her demise and so we were unable to start any treatment except for best supportive care. It is not straightforward to determine whether our patient was a case of primary PBL or plasmablastic transformation of myeloma given the non-conclusive lab results and overlapping features of both.

Conclusion:-

Plasmablastic lymphoma continues to be an uncommon entity and is thus usually missed as part of an initial differential diagnosis. Ongoing studies are limited because of the aggressive nature of the disease making long-term follow-up a challenge.

From our perspective, collaborated efforts from different medical institutions is paramount. Reporting identified cases of PBL would immensely aid colleagues in diagnosing and planning the best treatment strategy for their patients.

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