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Primary Extra-Medullary Plasmacytoma with Diffuse Lymph Node Involvement, Lymphoma Diagnostic Mimicry: A Case Report and Review of the Literature

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Abstract

Background: Plasmacytoma is a localized clonal proliferation of plasma cells that occur in the absence of bone marrow and systemic involvement. Extra medullary plasmacytoma most commonly involves the aerodigestive tract in 80% of cases, mainly in the head and neck with lymph nodes involvement. It usually results from the metastasis of the primary extra-medullary plasmacytoma or as part of a systemic MM involvement or plasma cell leukemia. Moreover, primary lymph node extra-medullary plasmacytoma is exceedingly rare, and it constitutes around 2% of EMP. Most cases are of solitary lymph node involvement. Nevertheless, PLNEMP with widespread lymph nodes involvement is rarer, with less than 10 reported cases worldwide. The localized nature of plasmacytoma is generally treated with localized measure *i.e.*: Radiotherapy and less commonly surgical excision, however, in cases of diffuse involvement such as our case -when the radiotherapy is not feasible- there is no consensus treatment guideline. Here, we present a case of wide spread PLNEMP that is treated with myeloma specific regimen followed by autologous stem cell.

Case Report: A case of a 51-year-old man presented with progressive shortness of breath in the setting of a thick-walled cystic subcutaneous lesion, noted in the suprasternal area and several mildly enlarged left lower cervical, mediastinal and right hilar lymph nodes. Diagnosis of lymphoma was initially suspected; however, a lymph node biopsy was consistent with plasmacytoma. Also, a bone marrow biopsy was unremarkable, and a monoclonal band was present in the Gamma area, measuring approximately 0.4 gm/dL. It is found to be IgG Lambda by Immunofixation. Moreover, there was no evidence of end organ damage; thus establishing a diagnosis of primary extra-medullary plasmacytoma of the lymph nodes. The patient was treated with a myeloma-adapted regimen consisting of 3 cycles of VTD that result in VGPR ,however due to thalidomide related SNHL the cyclophosphamide substitutes thalidomide and 3 more cycles of VCD regimen given and was referred to autologous stem cell transplant as consolidation.

Conclusion: The importance of this extra-medullary plasmacytoma case came from its rare presentation, location and type of treatment received. There was only one previous case with this presentation treated with novel myeloma therapy and it is the only case that received ASCT as consolidation treatment according to literature review included in this case report.

Keywords: Primary plasmacytoma; Plasmacyte dyscrasia; Myeloma; Lymph nodes; Bortezomib; thalidomide

Introduction

Plasmacytoma may involve any organ and can be solitary or multiple. However, it can be categorized into two distinct groups namely: Osseous plasmacytoma and extra-medullary plasmacytoma [1]. Even though both are treated similarly, they differ in prevalence, clinical behavior and prognosis [2]. Osseous plasmacytoma is more common but with worse prognosis in terms of PFS and OS as it is more likely to progress in multiple myeloma [3]. Primary plasmacytomas are an uncommon form of plasma cell dyscrasias and constitute around 1.6-4% of all plasma cell disorder. They are characterized by localized clonal proliferation of plasma cells that can involve the bone or soft tissue, but without the bone marrow and systemic involvement [4,5].

Diagnosis of solitary extra-medullary plasmacytoma requires a tissue confirmation of clonal plasma cell involvement, and absence of or less than 10% of all nucleated cells in the bone marrow aspirate and biopsy. In addition to this, no osteolytic bone lesions and no evidence of CRAB is present. The updated diagnostic criteria for multiple myeloma based on IMWG also refined the diagnosis of plasmacytoma with abnormal free light

chain, that should be less than 100, and no focal bone lesion is visible based on MRI and PET scan [6].

The incidence of osseous plasmacytoma is 40% higher than EMP [2], and it most commonly involves the axial skeleton as vertebrae, while the extra-medullary plasmacytoma in 80% of cases involves the aerodigestive tract [7-9]. Also, only 2% of EMP is presented with primary lymph node involvement, of this single lymph involvement constitutes the majority [10]. On the other hand, diffuse lymph node plasmacytoma is reported only in 8 previous cases worldwide.

In general, the EMP have better prognosis with lower rate to progression to MM, and longer PFS and OS when compared to osseous plasmacytoma. Among extra-medullary plasmacytoma, the survival is the same regardless of the site, however, PLNEMP rarely progress to MM in comparision to other sites of extra-medullary plasmacytomas, and tend to recur occasionally [10,11].

Due to the localized nature of solitary plasmacytoma either osseous or extra-medullary, the treatment also in the local form namely radiotherapy [12] and less commonly surgical excision [13], and this can be applied for limited distribution plasmacytomas when radiotherapy to multiple lesion is anatomically feasible. Nonetheless, as in our case with widespread dissemination of plasmacytoma , there is no consensus agreement on the treatment of such cases, and of the 8 reviewed cases in the literature, only one case received novel myeloma therapy in the form of VD/VTD, however, none of these cases received ASCT as a consolidation.

Methods

A 51-year-old man with unremarkable past medical history, was presented for the first time with shortness of breath, he was complaining for six months before. Physical examination was unremarkable; without palpable lymphadenopathy or hepatosplenomegaly CT scan done as presented in Figure 1 (A-E). The CT images have shown multiple pathologically enlarged right hilar and right paratracheal lymph nodes, as well as, a thick-walled cystic subcutaneous lesion in the suprasternal region measuring 2 x 3.3 x 1.9 cm. In addition to this, PET scan have revealed a hyper-metabolic malignant suprasternal subcutaneous lesion, multiple hyper-metabolic mediastinal and hilar lymph nodes, suspicious for disease infiltration, and no hyper-metabolic concerning skeletal lesions as shown in Figure 2 (A and B). Moreover, a biopsy was taken from subcutaneous lesion in the suprasternal area and reported as fibrous tissue with few, multinucleated giant cells and polarized material. Right paratracheal lymph node biopsy was done and it reported that the lymph node is infiltrated by a monomorphic population of plasma cells focally effacing its architecture (Figures 3A and 3B). The neoplastic plasma cells were found to have positive staining for CD138 and CD56, while are negative for CD20 and PAX5 immunostains. There is light chain restriction in these cells as lambda immunostain is positive while kappa immunostain is negative as shown in Figure 3 (C-G). The immunoprofile and histopathology are those of plasma cell tumor in the lymph node correlating with the serum immunofixation result of IgG lambda.

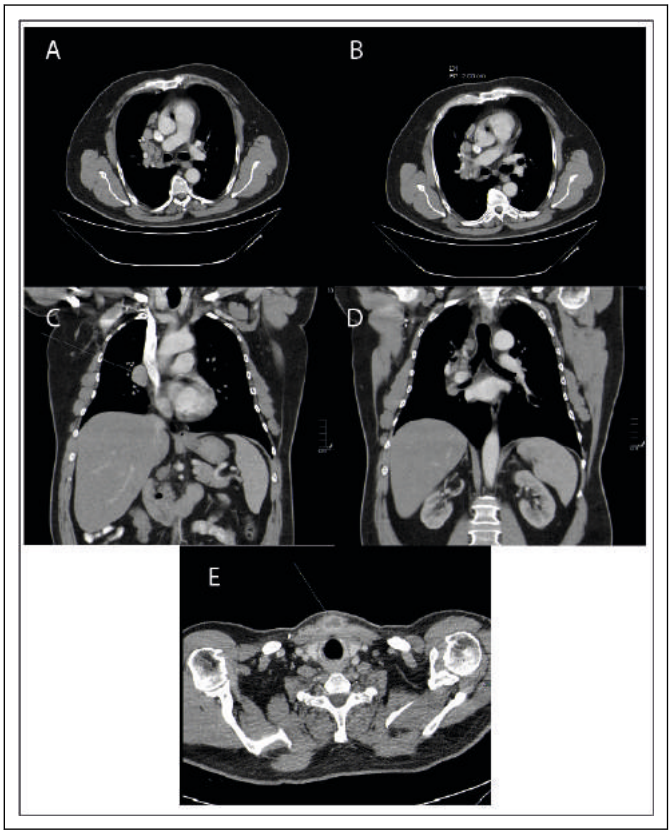

Figure 1: A. Axial CT image at presentation showing multiple pathologically enlarged right hilar and right paratracheal lymph nodes. B. Axial CT scan image at presentation showing multiple pathologically right hilar and right paratracheal lymph nodes, measuring up to 2 cm in short axis. C. Coronal CT scan image showing the largest hilar lymph node. D. Coronal CT scan at presentation showing few of the multiple enlarged paratracheal and hilar lymph nodes. E. Axial CT showing a thick-walled cystic subcutaneous lesion noted in the suprasternal region measuring 2 x 3.3 x 1.9 cm.

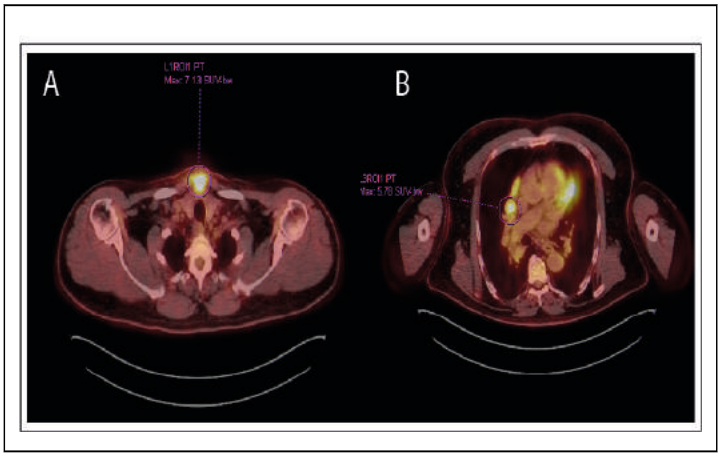

Figure 2: A. PET CT scan showing hyper-metabolic malignant suprasternal subcutaneous lesion with SUV max=7. B. PET scan showing hyper-metabolic malignant mediastinal and right hilar lymph nodes with SUV max=5.7.

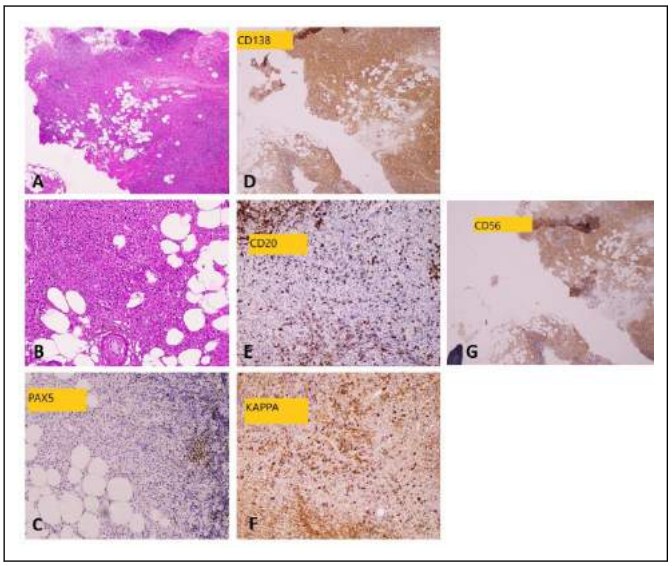

Figure 3: A. Right Paratracheal lymph node is in iltrated by a monomorphic population of plasma cells focally effacing its architecture. B. Lymph node is infiltrated by a monomorphic population of plasma cells focally effacing its architecture presented as fibrous tissue with few, multinucleated giant cells and polarized material. C. The neoplastic plasma cells were found to have negative staining PA X 5 immunostains. D. The neoplastic plasma cells were found to have positive staining for CD138. E. The neoplastic plasma cells were found to have negative staining CD20 immunostains. F. There is light chain restriction in these cells as lambda immunostain is positive while kappa immunostain is negative. G. The neoplastic plasma cells were found to have positive staining for CD56.

Initial laboratory values showed normal hemoglobin, leukocyte, and platelet counts. Blood Urea Nitrogen (BUN), creatinine, calcium, inorganic phosphate, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and serum electrolyte levels were also found to be normal. Tests for HIV (Human Immunodeficiency Virus) and HCV (Hepatitis C Virus) antibodies and HBV (Hepatitis B Virus) antigens were negative (FLC Kappa : 22.9, Lambda : 675 and ratio : 0.034 , IgG : 1207.IgA : 129 IgM : 48.6). Serum Protein Electrophoresis (PEP) and Immunofixation (IF) were also conducted.

Serum PEP revealed a monoclonal band present in the Gamma area, measuring approximately 0.4 gm/dL, and is found to be IgG Lambda by Immunofixation. However, no monoclonal bands were seen in the urine PEP and immunofixation. The β2-microglobulin level was found to be (2.54 mg/L), Serum albumin was 4.4 g/dL, and total protein was 7.4 g/dL. Also, bone marrow aspiration and biopsy from the iliac crest revealed Normocellular bone marrow with trilineage hematopoiesis and no morphologic evidence of infiltrative marrow disease with quantitatively normal plasma cells.

Results

Patient was treated with VTD regimen (bortezomib 1.3 mg/m2 sc weekly, thalidomide 100 mg po daily, and dexamethasone: 40 mg PO once on day 1,8,15 and 22) after 2 cycles. Moreover, patient achieved VGPR after 2 cycles and after cycle 3 of VTD he started complaining of impaired hearing audiometry done and showed bilateral SNHL at high frequency and attributed to thalidomide and accordingly switched to VCD and received 3 cycles. The axial and sagittal CT in Figure 4 scans have shown resolution of the suprasternal subcutaneous thick walled cystic lesion, as well as regression of the enlarged hilar and mediastinal lymph nodes (≤ 1 cm in short axis). The latest PET scan showed complete resolution of the previously mentioned hyper-metabolic malignant suprasternal subcutaneous lesion, almost complete metabolic resolution of the previously mentioned multiple hyper-metabolic mediastinal and hilar lymph nodes, and no interval development of any hyper-metabolic concerning skeletal or extra-skeletal lesions as shown in Figure 5. It was seen from the serum protein electrophoresis, a decreased gamma globulin, and no monoclonal bands (Serum free light chain: Kappa 14 lambda 27 ratio 0.5). Later on, the patient underwent ASCT in 14/Oct/2021 as consolidation therapy.

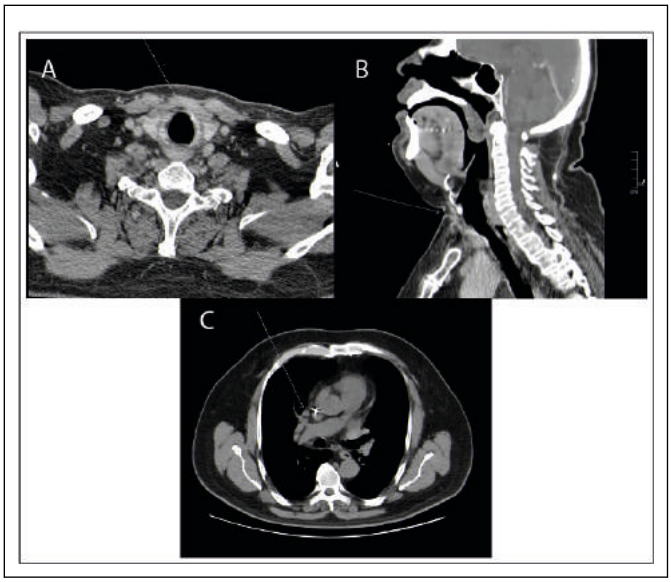

Figure 4: A. Axial CT image a ter treatment showing resolution of the suprasternal subcutaneous thick walled cystic lesion. B. Sagittal CT scan showing the resolution of the thick walled cystic lesion. C. Axial CT scan showing regression of the enlarged hilar and mediastinal lymph nodes, none of which exceeds 1 cm in short axis.

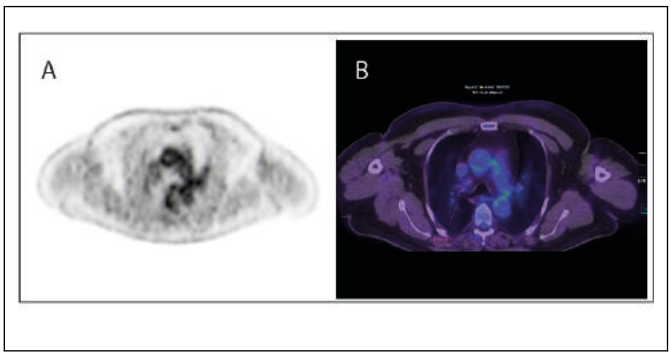

Figure 5: A.PET scan showed complete resolution of the previously mentioned hyper-metabolic malignant suprasternal subcutaneous lesion, almost complete metabolic resolution of

the previously mentioned multiple hyper-metabolic mediastinal. B. Hilar lymph nodes, and no interval development of any hyper-metabolic concerning skeletal or extra-skeletal lesions.

Literature Review

After reviewing the literature about primary extramedullary plasmacytoma with diffuse lymph node involvement as presented in Table-1, we found only eight reported cases worldwide with only five that diffused enough to be treated with systemic treatment. However, only 1 case received the currently approved line of MM treatment. Therefore, our case is unique, as it had received autologous stem cell transplant as consolidation treatment.

Author	Age and Sex	Pattern of lymph nodes involvement	Ig isotype	Serum monoclonal protein	Initial therapy	Outcome
Salem et al. [14]	48 M	Paratracheal, precarinal, subcarinal, aortopulmonary	IgG λ	M-Spike 2.1 g/dL, λ FLC 1613 mg/L	Involved field radiation (50 Gy in 25 fractions)	Persistant disease ,received VTD-PACE, then auto SCT, then lenalidomide maintenance achieved CR
Matsushima et al. [15]	56 F	Mandibular, cervical, axillary, para-aortic	IgA K	Present, though not quantified	Cyclophosphamide and prednisolone 10 Cs	CR after intial treatment,relapse after 6 years ,treated with Melphalan and prednisolone (10C)
Gorodetskiy et al. [16]	48 F	Diffuse LAD, most prominent at supraclavicular, femoral nodes	IgA K	M-Spike 7.2 g/dL	CHOP for 9 Cs	CR after intial therapy relapse after 3 months,treated with 1C CEVD,relapse again after 19 months and received 1C CHOEP
Menke et al. [10]	N/A	Disseminated involvement, not specific	Not specified	Not specified	Chlorambucil for 8 Ws	Achieved CR on follow up
Menke et al. [10]	N/A	Disseminated involvement, not specific	Not specified	Not specified	Chlorambucil and prednisone for 8 Ws	Persistent disease afetr intial therapy and died after diagnosis by 2 months
Lim et al. [17]	56 M	Right submental and submandibular	IgG λ	M-Spike 1.6 g/dL	Involved field radiation (50 Gy in 25 fractions)	Residual mass(1*2cm),previously (6.7×4.7 cm) plan to be monitored by PETscan and ct scan to assess viability of the remaining mass

Lin et al. [18]	58 F	Bilateral cervical	K light chain	Present, though not quantified	Excision	Achieved CR on follow up
Naymagon L et al. [19]	71M	Diffuse LAD,nech,chest, abdomen and pelvis	---	absent	four cycles of bortezomib/ dexamethasone followed by two continuous 28-day cycles of thalidomide 100 mg orally administered with prednisone	near CR ,remain in remission after 18 months of follow up

Table1: Primary extramedullary plasmacytoma with diffuse lymph node involvement as presented.

Discussion

Solitary plasmacytoma is a rare entity of plasma cell disorder in which the monoclonal plasma cell proliferates in localized manner either in the bone osseous plasmacytoma or in the so t tissue EMP. Bony plasmacytoma are more common than EMP with poorer prognosis and higher risk of progression to multiple myeloma [19,20]. In most cases (80%) EMP involves the aerodigestive tract and all other sites are as equally rare [21]. Lymph nodes EMP is exceedingly rare, accounting for 0.08 of plasma cell disorder and in most cases presented as a metastasis from primary EMP of head and neck origin or as a part of systemic involvement of MM or plasma cell leukemia [22].

Diagnosis of diffuse lymph node plasmacytoma without underlying MM as in our case. Bone marrow aspirate and biopsy, serum free light chain, PET scan, and lab work up including CBC, KFT, LFT, urine analysis with serum/urine protein electrophoresis and immuno ixation were done and no evidence of MM was evident. PLNEMP differentiated from other disorders as Mucosa-Associated Lymphoid Tissue (MALT lymphoma), follicular lymphoma, monocytoid B-cell lymphoma, which may also show plasmacytic differentiation which are usually accompanied with many small neoplastic lymphocytes. Immunohistochemistry with Immunoglobulin light and heavy chain expression can also support the diagnosis of primary plasmacytoma [23]. Radiotherapy and to a lesser extent surgical excision are the two major treatment modalities for plasmacytoma. Solitary extra medullary plasmacytomas are highly radiosensitive tumors, and with even moderate doses of radiotherapy, local control rates have been reported to be as high as 80%-100% [24,25]. Most of the reported cases of PLNEMP are solitary lesion, while only 8 reported cases in literature of diffuse lymph node involvement. Most of these cases are treated with local treatment (resection, radiotherapy for multiple sites) or using chemotherapy plus prednisolone with only one previous case treated as our with novel myeloma treatment.

In our case, hilar and mediastinal lymph nodes were involved which are diffused enough to make radiotherapy not feasible. Therefore, systemic therapy was deployed and the patient was treated with myeloma speci ic regimen VTD/VCD. This makes our case the ninth case reported and the second that received such treatment. None of the previous cases received consolidation or maintenance therapy after first line, making our case the first case that underwent ASCT as consolidation in PLNEMP.

Conclusion

In our case, hilar and mediastinal lymph nodes were involved which are diffused enough to make radiotherapy not feasible. Therefore, systemic therapy was deployed and the patient was treated with myeloma specific regimen VTD/VCD. This makes our case the ninth case reported and the second that received such treatment. None of the previous cases received consolidation or maintenance therapy after first line, making our case the first case that underwent ASCT as consolidation in PLNEMP.

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