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Case Report

A case of intravascular large B-cell lymphoma – Our clinical experience

Karthik Kumar[1], Subhajit Hajra[2], Gaurav Dhingra[1], Uttam Kumar Nath[1]

Departments of [1]Clinical Hematology and [2]Pathology and Laboratory Medicine, AIIMS, Rishikesh, Uttarakhand, India.

***Corresponding author:**
Subhajit Hajra,
Department of Pathology and Laboratory Medicine, AIIMS, Rishikesh, Uttarakhand, India.

subhajithajra@gmail.com

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ABSTRACT

Fever of unknown origin is always a diagnostic challenge in establishing etiology. A gentleman in his 70s presented with complaints of fever and dry cough for 2 months duration. We proceeded with contrast imaging of the thorax and abdomen which revealed mild hepatomegaly. Bone marrow examination with bone marrow culture and 18-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG PET/CT). Bone marrow aspirate smears were hypercellular with around 50% atypical lymphoid cells with plasmacytoid and bizarre morphology with few multilobed nuclei. Bone marrow biopsy revealed predominantly sinusoidal involvement by neoplastic cells. On immunohistochemistry, tumor cells were positive for CD45, CD79a, CD20, and MUM1 and were negative for CD5, CD10, and BCL6. Ki-67 was around 60% in tumor cells. FDG PET/CT revealed diffusely increased uptake in the both axial and appendicular skeleton with (SUVmax 5.06) and diffusely increased FDG uptake (SUVmax 3.67) noted in the spleen. As intravascular large B-cell lymphoma is a highly aggressive non-Hodgkin lymphoma with a high risk of central nervous system involvement, we treated it with chemoimmunotherapy (R-CHOP) with intrathecal methotrexate. After a clinical follow of 3 months, the patient developed relapsed with a soft-tissue swelling over the right leg. The patient was treated with two cycles of R-DHAP and had progressive disease and started on Ibrutinib, Lenalidomide, and Rituximab (2 cycles). Post two cycles, the patient had progressive disease and switched to acalabrutinib based therapy. After 1 month of acalabrutinib-lenalidomide-rituximab therapy, the patient had disease progression and succumbed to the disease.

Keywords: Intravascular large B-cell lymphoma, R-CHOP, Central nervous system prophylaxis, Fever of unknown origin, PUO, FUO, PET-CT, Bone marrow, Lymphoma

INTRODUCTION

Fever of unknown origin (FUO) is always a diagnostic challenge in establishing etiology. Although infections and multisystem inflammatory diseases are the most common causes of FUO, a small proportion of the patients remain non-diagnostic despite detailed evaluation.

CASE REPORT

A gentleman in his 70s presented with complaints of fever and dry cough for a 2-month duration. There were no symptoms of breathlessness, chest pain, syncope, or palpitation. No chronic drug intake, no recent travel, no pet animal exposure, and no contact with the open case of tuberculosis could be elicited. On examination, the patient had pallor and bilateral pitting pedal edema. No significant lymphadenopathy was present. Systemic examinations were normal.

Investigations

A complete hemogram showed hemoglobin of 9.6 g/dL, a total leucocyte count of 11,000/mm^3 (neutrophils 70%, lymphocytes 18%, and monocytes 12%), and platelets of 99,000/mm^3. Peripheral smear had normochromic normocytic red blood cells with neutrophilic leukocytosis and monocytosis. The patient had elevated erythrocyte sedimentation rate and high sensitivity C-reactive protein (58 mm/h and 87.9 mg/dL respective) and liver parameters showed hypoalbuminemia with mild transaminitis and raised alkaline phosphatase. The renal function test was normal and viral serology was negative. Serum lactate dehydrogenase (LDH) was 5,990 U/L (0-248 U/L). Chest X-ray was normal and ultrasound sonography abdomen revealed mild hepatomegaly with normal echogenicity.

Differential diagnosis

As an FUO, our first differential diagnosis was infectious etiology. Second, we thought of occult malignancy as the patient was in the elderly age group. Connective tissue disorders were less likely as no other systemic symptoms were present. Pyrexia workup turned out to be negative. Contrast imaging of the thorax and abdomen revealed mild hepatomegaly measuring 16.7 cm without any focal abnormality with intrahepatic biliary radical dilatation. Due to an unidentifiable cause, a bone marrow examination with bone marrow culture and 18-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG PET/CT) was done. Bone marrow aspirate smears were hypercellular with around 50% atypical lymphoid cells with plasmacytoid and bizarre morphology with few multilobed nuclei. Bone marrow biopsy revealed predominantly sinusoidal involvement by neoplastic cells [Figure 1a and b]. Morphological differentials were metastasis, plasma cell neoplasm, and aggressive lymphoma. On immunohistochemistry, tumor cells were positive for CD45, CD79a, CD 20, and MUM1 (>30%) and were negative for CD5, CD10, and BCL6. Ki-67 is around 60% in tumor cells.[1] With this clinical picture, the diagnosis of intravascular large B cell lymphoma (IVLBL) was made. FDG PET/CT revealed diffusely increased uptake in the both axial and appendicular skeleton with (SUVmax 5.06) and diffusely increased FDG uptake (SUVmax 3.67) noted in the spleen. A hypodense lesion with increased FDG uptake was noted in the spleen measuring 1.3 × 1.2 cm, (SUVmax 5.37). No focal uptake or lytic lesions were noted.

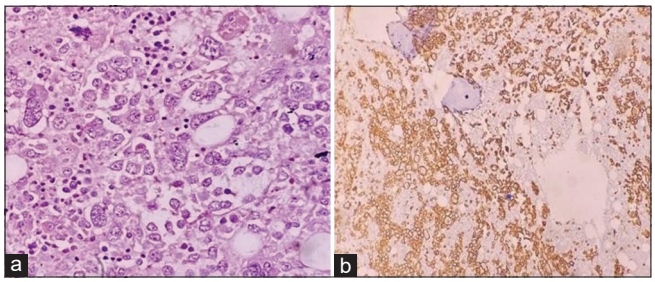

Figure 1: High power (×400) image shows large cells infiltrating bone marrow sinusoids (a). CD20 immunostaining shows the intra-sinusoidal nature of the lymphoma cells (b).

Treatment

As IVLBL is a highly aggressive non-Hodgkin lymphoma with a high risk of central nervous system (CNS) involvement, the patient was treated with standard chemoimmunotherapy R-CHOP with intrathecal methotrexate. No significant toxicity occurred. End of treatment PET/CT revealed no metabolic uptake in the previously described site suggesting a complete metabolic response. The patient was started on lenalidomide maintenance of 10 mg every 21-day cycle.

Outcome and follow-up

After a clinical follow of 3 months, the patient developed soft-tissue swelling over the right leg with an LDH of 2000 U/L. Fine-needle aspiration cytology was consistent with early relapse of IVLBL. The patient was given two cycles of R-DHAP and had progressive disease despite the treatment and started on ibrutinib, lenalidomide, and rituximab (two cycles). Post two cycles, patients still had progressive disease and switched to acalabrutinib-based therapy. After 1 month of acalabrutinib-lenalidomide-rituximab therapy, the patient did not respond and succumbed to the disease.

DISCUSSION

FUO is a diagnostic challenge in clinical practice. Bone marrow examination in the case of FUO can provide a diagnostic yield of around 15–25%.[2,3] The yield of FDG PET in FUO is 16–70%.[4] The focal lesion in the bone marrow is highly suggestive of malignancy. In the case of normal PET/CT, further workup may not be required and the patient can be observed serially for resolution of FUO. IVLBL is a rare hematolymphoid neoplasm with an annual incidence of 0.5 cases/1 million population.[5] The median age of diagnosis is 70 years. Our patient presented with FUO and pure bone marrow involvement without lymphadenopathy and organomegaly. This neoplasm has a high prediction for brain parenchymal involvement, and hence, treatment regimen for this lymphoma should include both systemic and CNS-directed therapy. As per the literature, R CHOP has a complete response rate of 88% and overall survival at 1 year is 42%, at 3 years survival is 11.5%.[6] Regarding CNS, since tumor cells in the vascular compartment lies outside the blood–brain barrier, IT loco-regional therapy may not be beneficial. Hence, for CNS-directed therapy ideally,

cerebrospinal fluid flow cytometry must be performed to delineate the treatment. For CNS prophylaxis, high-dose Methotrexate combined with chemoimmunotherapy should be used. For occult CNS or symptomatic CNS patients, high-dose Methotrexate with high-dose Cytarabine is preferred compared to only high-dose Methotrexate.[7-9] Given the aggressiveness of the disease, a significant number of patients do relapse. Fit patients with IVLBL need to be consolidated with high-dose therapy followed by autologous stem cell rescue to improve survival[10] As Gene Expression Profiling in IVLBL comprise MYD 88 and CD 79b (non-GCB subtype), ibrutinib, lenalidomide, and rituximab can be tried in relapsed/refractory disease as these drugs have a good CNS penetration. Further, treatment options are needed for IVLBL to improve the cure rate and overall survival and the use of novel agents in IVLBL needs to be explored with a good outcome with minimal toxicity.

CONCLUSION

In conclusion, Intravascular Large B cell lymphoma (IVLBL) is a rare hematolymphoid neoplasm that can present as Fever of Unknown Origin (FUO). In this case, the patient presented with fever and dry cough, and on further investigation, was diagnosed with IVLBL with pure bone marrow involvement. Despite treatment with R-CHOP and other chemotherapy regimens, the patient had a relapse and did not respond to subsequent therapies. IVLBL is highly aggressive with a high risk of CNS involvement, and early diagnosis and treatment are crucial. Bone marrow examination and FDG PET can provide valuable diagnostic information in cases of FUO.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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