Med & Health Dec 2022; 17(2): 298-304 https://doi.org/10.17576/MH.2022.1702.23

CASE REPORT

Primary Bone Marrow Lymphoma with Secondary Central Nervous System Involvement: A Case Report

HARI PRIYA R[1], ALIA SUZANA A[1] , HAFIZA A[1], REENA RAHAYU MZ[1], NOR RAFEAH T[2], SIVAKUMAR P[2], RAJA ZAHRATUL AZMA RS[1]

[1]Department of Pathology, [2]Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak 56000 Cheras, Kuala Lumpur, Malaysia

ABSTRAK

Limfoma sumsum tulang primer (PBML) ialah keadaan yang jarang berlaku. Kebanyakan PBML ialah limfoma jenis 'non-Hodgkin lymphoma' (NHL), di mana 'diffuse large B-cell lymphoma' (DLBCL) kerap dijumpai. Non-Hodgkin lymphoma dijumpai di luar nodal dalam satu pertiga kes. Limfoma sistem saraf pusat sekunder (SCNSL) ialah keadaan yang jarang berlaku dan ditakrifkan sebagai penglibatan sistem saraf pusat sekunder (CNS) dalam kalangan pesakit yang mempunyai limfoma sistemik. Dalam laporan ini, kami menerangkan kes limfoma sumsum tulang primer dengan penglibatan sekunder CNS. Pesakit menunjukkan defisit neurologi. Filem darah peranti persisian menunjukkan kehadiran sel mononuklear yang tidak normal. Pemeriksaan histopatologi tisu otak menunjukkan ciri-ciri DLBCL dan positif untuk CD10. Pemeriksaan sumsum tulang menunjukkan kehadiran sel limfoma. Pesakit diberikan rawatan dengan Rituximab, methotrexate, vincristine dan procarbazine (R-MPV). Walau bagaimanapun, dia meninggal dunia selepas dua kitaran rawatan kemoterapi.

Kata kunci: limfoma sistem saraf pusat sekunder, limfoma sumsum tulang primer, non-hodgkin lymphoma

ABSTRACT

Primary bone marrow lymphoma (PBML) is a rare condition. Most PBMLs are B-cell non-Hodgkin lymphomas (NHLs), where predominated by the diffuse large B-cell lymphomas (DLBCLs). Non-Hodgkin lymphomas affects extranodal sites in

Address for correspondence and reprint requests: Professor Dr Raja ZahratulAzma bt Raja Sabudin. Department of Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +603-91456640 Email: zahratul@ppukm.ukm.edu.my

one-third of cases. Secondary central nervous system lymphoma (SCNSL) is a rare state which is defined as secondary central nervous system (CNS) involvement in patients with systemic lymphoma. In this report, we described a case of primary bone marrow lymphoma with secondary involvement of the CNS. Patient presented with neurological deficit. Peripheral blood film showed presence of abnormal mononuclear cells. Histopathological examination of the brain tissue showed features of DLBCL with CD10 positivity. Bone marrow examination showed presence of lymphoma cells. He was commenced with Rituximab, methotrexate, vincristine and procarbazine (R-MPV). However, he succumbed after two cycles of chemotherapy.

Keywords: non-Hodgkin lymphoma, primary bone marrow lymphoma, secondary central nervous system lymphoma

INTRODUCTION

Bone marrow involvement by lymphomas is generally considered as a systemic dissemination of the disease that is arising at other location (Martinez et al. 2012). Primary bone marrow lymphoma (PBML) is a rare disorder in which the lymphomatous cells originate in the bone marrow and no other primary locations are found (Martinez et al. 2012). In the 2016 World Health Organisation (WHO) guidelines, no specific entity was mentioned for this. They are primarily B-cell non-Hodgkin lymphoma (NHL) patients (Bhagat et al. 2016). Primary bone marrow lymphoma is said to be more aggressive and has a worse prognosis, despite the fact that its natural history is unknown (Wang et al. 2017). The cells are morphologically large, as found in diffuse large B-cell lymphomas (DLBCL). However, cases of follicular lymphoma type had been documented (Kim et al. 2017).

Secondary central nervous system (CNS) lymphoma can develop during or after the initial presentation of CNS lymphoma (Ferreri 2017). In the absence of other major sites, a serious investigation is required to diagnose these instances. The present study highlighted a case of a 46-year-old man with PBML and subsequent CNS involvement.

CASE REPORT

A 46-year-old man presented with right-sided upper and lower limb weakness for one-week duration associated with headache and dizziness. The initial computerised tomography (CT) scan of brain evaluation revealed a lesion occupying the left temporal parietal region. Magnetic resonance imaging (MRI) of brain revealed a mass measuring 4.5 x 7.3 x 5.7 cm at the left posterior parietal area.

The patient was hemodynamically stable and afebrile with a Glasgow Coma Scale (GCS) of 13 (E4V4M5). There were no palpable lymph nodes.

An examination of the abdomen revealed no organomegaly. His condition suddenly deteriorated and was immediately intubated due to a drop in GCS level from 14 to 3. Patient was proceeded for left decompressive craniectomy and tumor debulking. Intraoperative findings revealed the presence of a massive tumour emerging from the pericranium with extracranial, intracranial, and subdural components. The tumour had spread throughout the parietal cortex.

Patient was diagnosed with DLBCL-germinal centre B-cell subtype after histopathological examination (HPE) of brain tissue. Based on immunohistochemistry, the malignant cells were positive for CD20 and CD10, but negative for GFAP, CD3, BCL6, and MUM-1. Ki67 proliferation index was 80%. A CT scan of thorax, abdomen, and pelvis were performed and revealed no mediastinal, abdominal masses or any enlarged lymph nodes.

During admission, full blood counts revealed a mildly reduced haemoglobin level of 12.8 g/dL, increased white blood cell count ($23.3x10^9$/L) with neutrophilia ($14.2x10^9$/L) and monocytosis ($6.6x10^9$/L). The rest of the differential counts were within the normal range. The platelet count was normal ($233x10^9$/L). The viral screenings were negative. The level of serum lactate dehydrogenase (LDH) was significantly elevated (2122 U/L).

Peripheral blood film showed presence of 5% abnormal lymphoid cells. Bone marrow aspiration smear was hypercellular with presence of numerous abnormal lymphoid cells attributing 81% of cellularity. Their sizes ranged from medium to large, with a moderate to abundant basophilic cytoplasm, homogenous chromatin and prominent nucleoli. Granulopoiesis was diminished to a lesser extent however, megakaryopoiesis appeared to be normal (Figure 1).

A trephine biopsy revealed hypercellular marrow with lymphomatous cell infiltration. The cells were large, with prominent nucleoli and pleomorphic vesicular nuclei. The CD20 stain was positive, however, CD3, CD10, BCL 6, and MUM-1 were all negative. Ki-67 was approximately 80%. There was no evidence of bony trabeculae destruction. These findings

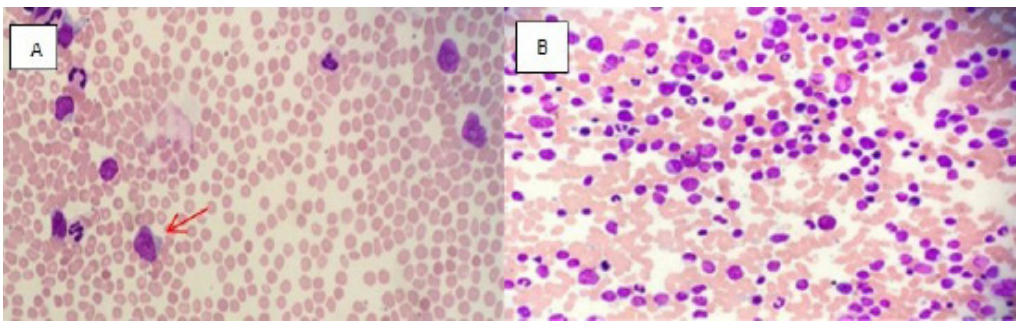

Figure 1: A) Peripheral blood film at diagnosis, showed presence of 5% abnormal lymphoid cells (Wright stain, 400x). B) Bone marrow aspiration smear at diagnosis showed hypercellular marrow with numerous abnormal lymphoid cells (MGG stain, 400x).

were consistent with DLBCL (Figure 2 & 3).

Immunophenotyping of bone marrow sample revealed the presence of 50% mature B-lymphoid cells (Figure 4). Cytogenetic analysis of the G-banded chromosome from cultured bone marrow revealed a male chromosome complement with no evidence of any clonal abnormality in the total cells examined. Karyotype was 46,XY.

Given the lack of lymphadenopathy or any bulk of tumours on CT scan of thorax, abdomen and pelvis; and immunohistochemistry of brain tissue showed presence of CD10 positivity, a diagnosis of primary bone marrow lymphoma with subsequent central nervous system involvement is most plausible according to WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (2016). Patient was categorised as stage IV and he was risk stratified with an International Prognostic Index (IPI) score of four (high risk). He was on intravenous dexamethasone for two cycles before being switched to Rituximab, methotrexate, vincristine, and procarbazine (R-MPV).

After two cycles of R-MPV, patient was admitted again for brain abscess where HPE showed residual disease. While in the hospital, his condition deteriorated and incidentally found he was Covid-19 positive. Patient succumbed on the same day and cause of death was Covid-19 related pneumonia with underlying extensive DLBCL.

DISCUSSION

Primary bone marrow lymphomas are uncommon (Martinez et al. 2012), although secondary bone marrow involvement in a systemic lymphoma is frequently encountered. They are responsible for 1.16% of lymphoma cases and 2.65% of DLBCLs cases. B-cell NHLs account for the majority of primary bone marrow lymphomas, and DLBCLs predominate within those

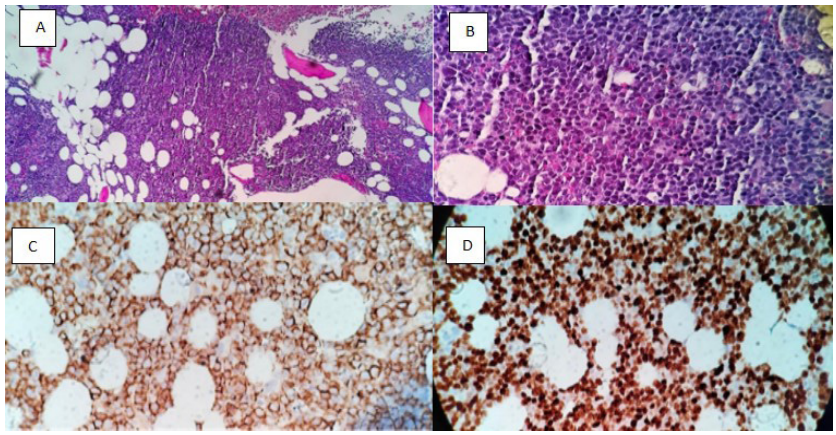

Figure 2: A) Trephine biopsy showed hypercellular marrow (H&E, 200x) with (B) diffuse infiltration by neoplastic lymphoid cells which were large in size, pleomorphic vesicular nuclei with prominent nucleoli (H&E, 400x). These cells showed positivity with C) CD20 (400x) and D) Ki-67: 80% (400x).

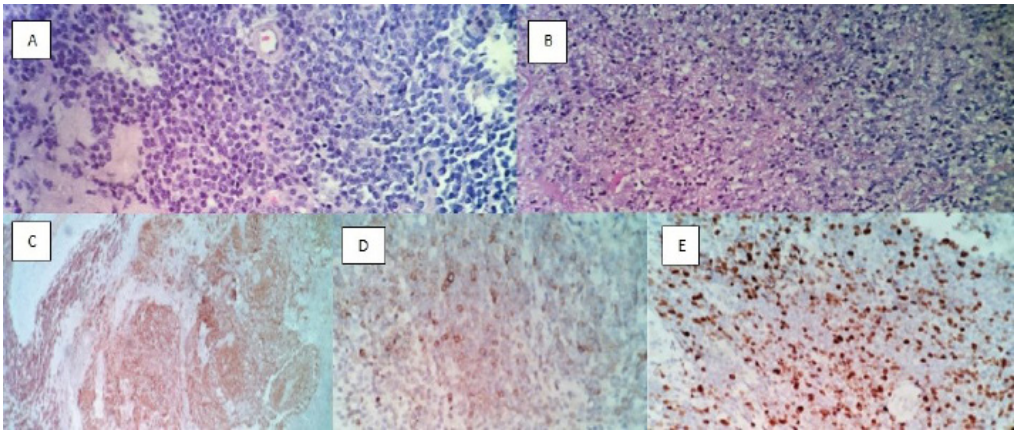

Figure 3: A and B) The brain tissue and meninges were infiltrated by malignant lymphoid cells (H&E, 200x). The cells were positive for C) CD20 (400x) and D) CD10 (400x) and E) Ki-67 : 80-90% (400x)

subtypes (Bhaghat et al. 2016). The majority of PBMLs are discovered late, due to clinical symptoms which are non-specific. They were reported to have the worst prognosis, with a median survival approximately 14.9 months in which 70% of the patients die by two years despite the initiation of chemotherapy (Bhaghat et al. 2016).

Recent diagnostic criteria of PBML were recommended as follows; (i) isolated bone marrow infiltration of lymphoma cells irrespective of peripheral blood involvement; (ii) no evidence of lymph node, spleen, liver, or other additional bone marrow involvement on physical examination or imaging findings; (iii) absence of localised bone tumours; (iv) no evidence of bony trabeculae destruction in the bone marrow biopsy, and (v) exclusion of leukemia/ lymphoma cases (Wang et al. 2017).

Most patients presented with

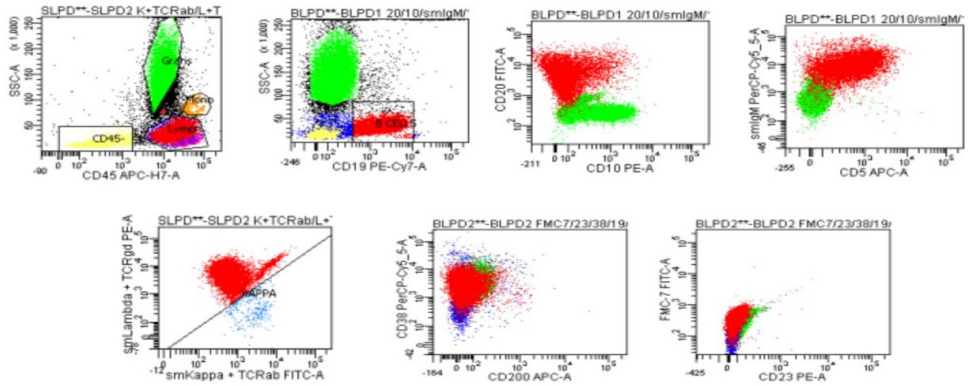

Figure 4: Immunophenotyping analysis showed an abnormal lymphoid population (red), gated at CD45 positive and low to moderate side scatter, which expressed positivity for CD19, CD20, surface IgM, and CD5 (heterogenous). They exhibit lambda light chain restriction. They were negative for CD10, FMC7, CD23, and CD200.

B-symptoms and no signs of lymphadenopathy. Hepatomegaly has been recorded on occasion. In addition, patients with cytopenias frequently have a high serum LDH level. The majority of the patients have bicytopenia or pancytopenia, according to some reports (Bhaghat et al. 2016). However, no cytopenias were found in our case.

Many cases have also revealed a diffuse infiltrate of neoplastic lymphoid cells in the trephine biopsy. Immunohistochemical markers are based on the type of lymphoma that is present (Wang et al. 2017). Although DLBCL is the most prevalent, PBML has also been identified in cases such as follicular lymphoma. The presence of B-cell markers in the tumour, most commonly CD19 or CD20, is required for the diagnosis of primary bone marrow DLBCL. CD5 expression has also been suggested to be clinically and pathologically significant in DLBCL cases, however, the role of CD5 expression in primary bone marrow DLBCL has yet to be determined. In some investigations, haemophagocytosis was observed in the aspirate (Kim et al. 2017), but this was not the case in our patient.

There was also CNS metastasis in our case. Systemic lymphoproliferative disorders with CNS involvement at presentation, relapse, or both stages of the disease are considered as secondary CNS lymphoma (SCNSL) (Ferreri 2017). Secondary CNS lymphoma can manifest as leptomeningeal, parenchymal, cranial nerve or ocular dissemination. Several CNS compartments are frequently involved at the same time. In the general population, the prevalence of SCNSL ranges from 4-23% (DeRosa et al. 2014). They typically have limited long term survivors and the prognosis is inferior to primary central nervous system lymphoma (PCNSL). Studies have reported that age beyond 60 years, high LDH profile, Eastern Cooperative Oncology Group (ECOG) performance status score value of >2, IPI >2, involvement of multiple extranodal site and bone marrow and Ann Arbor stage III-IV are the main identified risk factors for CNS involvement (Ma et al. 2019).

In the present case, the patient had presented with signs and symptoms of CNS involvement. His brain tissue HPE revealed DLBCL with CD10 positivity. Because CD10 expression is more regular in systemic DLBCL, positive CD10 in a CNS DLBCL should prompt a search for systemic DLBCL which has disseminated up to CNS (Swerdlow et al. 2017). Theory could be made inciting that this could be a case of primary CNS lymphoma that has involved the bone marrow. However, according to WHO Classification 2016, primary CNS lymphoma dissemination to extraneural sites are very rare due to the blood brain barrier and preferential spread to testis has been noted. No such findings were seen in our case. From the imaging investigations that had been done, no other primary lesion was seen other than the bone marrow. From here, we concluded that the primary lesion was most likely from the bone marrow with CNS dissemination.

Patients with bone marrow DLBCL

typically have a poor prognosis (Hong et al. 2017). In the early 1990s, the prognosis for large B cell lymphoma was unsatisfactory with a median survival of only 3.5 months, with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or other CHOP-like regimens as the cornerstone of treatment. On top of that, factors like age and comorbidities are taken into account. The elderly fare worse than the others.

Despite the existing dismal setting, emerging treatment and management modalities such as targeted therapies and stem cell transplantation are promising. Rituximab-based therapy found to be more effective than typical CHOP-like regimens in the treatment of primary bone marrow DLBCL. Patients are best treated with rituximab in addition to chemotherapy unless it is contraindicated (Wang et al. 2017). However, as our patient was experiencing CNS symptoms at the same time, the treatment should be able to cross the blood-brain barrier. He was given a high dose of methotrexate (an alkylating drug) in combination with rituximab for this reason.

CONCLUSION

A rare example of PBML with secondary CNS involvement was presented in this case. In comparison to other lymphomas, the presence of extranodal locations with an IPI score of four indicated an aggressive illness with a dismal prognosis. To control the condition, prompt diagnosis and therapy were critical and autologous haematopoietic stem cell transplant (HSCT) will be advantageous in maintaining complete remission status.

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Received: 08 Jun 2022
Accepted: 01 Sept 2022