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Delayed CNS Relapse in Diffuse Large B-Cell Lymphoma: Insights into Diagnosis, Management, and Therapeutic Challenges in an Elderly Patient

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ABSTRACT

Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of neoplasms and B-cell-derived (B-NHL) comprises approximately 80% of all NHL in adults. There are differences in B-NHL's appearance, clinical features, prognosis, and response to treatment. This case report involved a 72-year-old male with Non-Germinal Centre B-cell-like (Non-GCB) diffuse large B-cell lymphoma (DLBCL) who had a good response to six cycles of Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) chemotherapy and consolidative radiotherapy. Six years later he developed a delayed Central Nervous System (CNS) relapse with neurological symptoms and a hypermetabolic lesion in the right frontoparietal area. Immunohistochemistry (IHC) revealed aggressive profile: CD20, PAX-5, Bcl-6, MUM-1 and elevated Ki-67 proliferation rate. CNS-directed therapy, including rituximab, corticosteroids, radiotherapy, and supportive measures, stabilized the disease but highlighted treatment challenges in elderly patients, such as toxicity and organ function decline. This case underscores the need for long-term monitoring, individualized therapeutic approaches, and advancements in CNS-targeted therapies for high-risk DLBCL patients.

Keywords

Diffuse large B-cell lymphoma, Immunohistochemistry, Non-germinal center B-cell-like, Radiotherapy.

Abbreviations

DLBCL: Diffuse Large B-cell lymphoma, NHL: Non-Hodgkin Lymphoma, CNS: Central Nervous System, B-NH: B-cell-derived, PET-CT: Positron emission tomography/computed tomography, non-GCB: Non-Germinal Center B-cell-like, R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone, IHC: Immunohistochemistry.

Introduction

Non-Hodgkin lymphomas (NHL) are an extensive category of malignancies, with B-cell-derived (B-NHL) accounting for around 80% of cases. There are differences in B-NHL's appearance, clinical features, prognosis, and response to treatment. Follicle lymphoma makes up around a quarter of occurrences in the United States, whereas diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype, accounting for approximately 30% of cases [1]. Although DLBCL, an aggressive form of lymphoma, responds well to R-CHOP treatments (rituximab, cyclophosphamide, Adriamycin, vincristine, and prednisone), the probability of relapse is a major concern, especially when it comes to brain metastases, which can happen in 5–10% of patients [2]. This case report details the clinical record of a 72-year-old man with DLBCL who developed brain metastases six years after completing treatment. The condition is similar to delayed brain metastases of DLBCL. This case study highlights the importance of serious long-term monitoring for DLBCL patients, even following an apparent remission.

Case Presentation

A 72-year-old male patient was admitted to the hospital with complaints of right lower back pain following a right radical nephrectomy. Clinical examination revealed no significant

cardiovascular and respiratory abnormalities. A positron emission tomography/computed tomography (PET-CT) scan revealed sub-centimeter retroperitoneal lymph node and FDG-Avid soft tissue densities of the peritoneum, omental, and mesenteric fat stranding in the pelvic region. Bilateral subcentimeter lung nodules and minimal ascites were also noted in the imaging; these findings prompt additional examination for confirmation of metastatic disease Figure 1. Biopsy results and gross examination showed a large gray-white tumor involving the kidney in the lower and middle pole pelivical system that is cystically dilated and filled with blood clots. The tumor size is approximately 10x9x7 cm, and the tumor extends into the perirenal fat, reaching up to the rota fascia. On microscopic examination, the tumor is found to infiltrate the perinephric tissue and extend beyond the Gerota fascia, with all margins involved. IHC confirmed DLBCL of Non-Germinal Center B-cell-like (non-GCB subtype), showing that the tumor is immunoreactive to various markers CD20, PAX-5, Bcl-6, MUM-1, and Ki-67. This immune profile indicates aggressive B-cell lymphomas, with Ki-67 expression suggesting a high proliferative index.

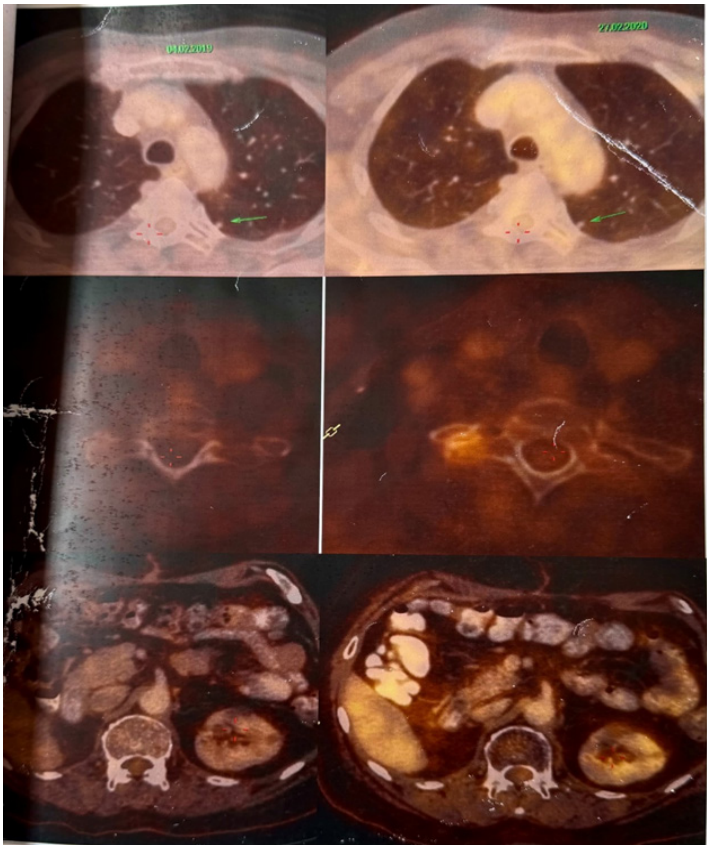

Figure 1: This scan shows sub-centimeter retroperitoneal lymph node and FDG-Avid soft tissue densities of the peritoneum, omental, and mesenteric fat stranding in the pelvic region with bilateral subcentimeter lung nodules and minimal ascites.

The patient was initiated on an R-CHOP regimen of chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) with six cycles followed by radiation therapy to consolidate the response. The patient received a total dose of 36 Gy in 20 fractions and a boost of 9 Gy in five fractions. Regular PET scans as follow-up for three consecutive years revealed no evidence of local or distant recurrence or metastatic disease will be identified, indicating or confirming long-term remission Figure 2. Two years later, the patient developed additional neurological signs and symptoms such as confusion and disorientation. A PET-CT scan of the patient revealed a small, hypermetabolic lesion in the right frontoparietal area, suggesting CNS involvement with persistent mild cerebral edema Figure 3.

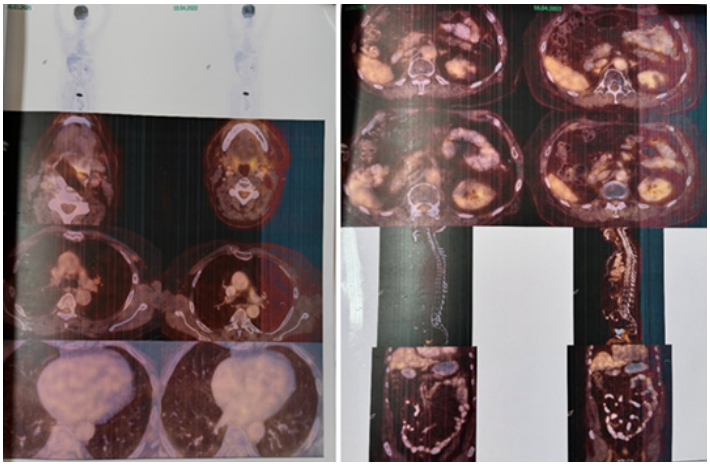

Figure 2: Regular PET scans as follow-up for three consecutive years revealed no evidence of local or distant recurrence or metastatic disease after completing initial chemotherapy.

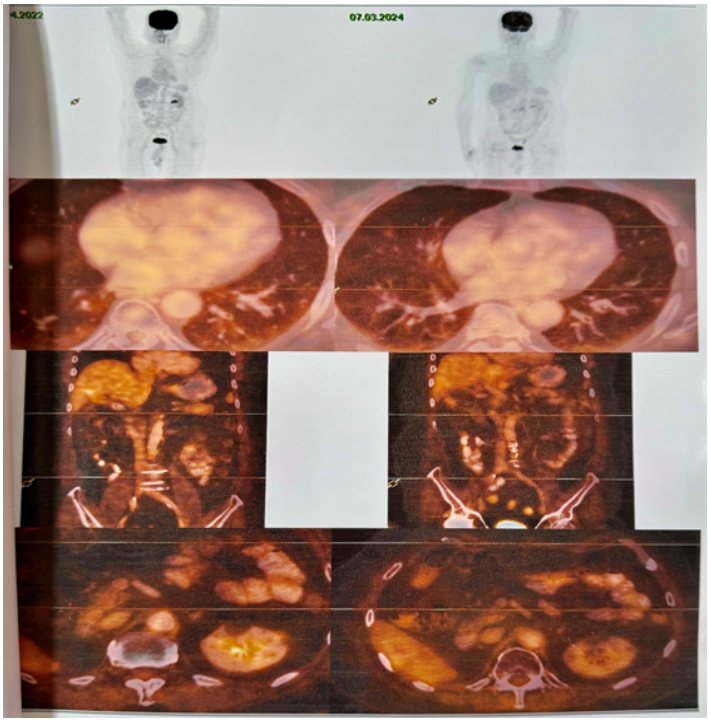

Figure 3: PET-CT scan highlighting increased FDG uptake in the right frontoparietal region consistent with CNS relapse.

After this, the patient started on CNS-directed therapy with rituximab and prednisolone followed by fractionated brain-targeted radiotherapy with a dose of 30 Gy delivered for ten days, alongside supportive treatment for cerebral edema and seizure management the patient received anticonvulsant levetiracetam 750 mg IV, twice a day, mannitol (20%, 100 mL every 6 h); dexamethasone (40 mg IV); and antibiotic treatment, ceftriaxone 1 gram IV, twice a day to prevent the risk of infection, and 2 mL of ranitidine was given three times a day.

After complete remission of treatment, the scans revealed, that the brain lesion size was reduced, and the symptoms of the patient remained stable. However, we also observed a decline in renal function with higher serum creatinine and a decrease in the patient's hemoglobin level due to chemotherapy, but there was no evidence of DLBCL reappearance in the renal area or to other connected lymph nodes.

Despite the initial DLBCL being successfully managed, CNS metastasis reflected on its aggressive course, particularly in non-germinal center subtypes. The complete response to therapy was maintained until CNS involvement, which emphasized the need for observance in routine care in long-term follow-up.

Discussion

DLBCL accounts for the largest proportion of NHL and is classified as an aggressive subtype; however, its clinical characteristics are diverse and therefore affect its prognosis and therapeutic management. IHC and gene expression profiling for DLBCL have been made based on the GCB and non-GCB subtypes alleged to be clinically significant [3]. This non-GCB BCL2 subtype is considerable in this case, associated with poorer prognosis, higher proliferative rates, and a predisposition to CNS involvement. Here, we discuss the complications involved in the management of DLBCL by focusing on immunohistochemical profile, CNS prophylaxis, challenges of chemotherapy in older patients, and emerging future treatment options.

The patient IHC reports showed positive for CD20, PAX-5, Bcl-6, MUM-, and Ki-67, confirming the non-GCB DLBCL diagnosis. This subtype is particularly more aggressive than the GCB subtype with a poor prognosis and higher chances of CNS relapse. CD20 and PAX-5 confirm the B-cell lineage, while Bcl-2 and MUM-1 indicate activated B-cell differentiation and poor prognosis. The Ki-67 index indicates a high proliferation rate and aggressiveness of the tumor [4]. This important molecular profiling in DLBCL helps in diagnosis, treatment decisions, and risk stratification, which assists the clinician in identifying patients who require close monitoring and novel therapies.

Central nervous system involvement in DLBCL is rare and occurs in 5-10% of patients and is associated with significant worsening of progression and represents a challenging part of management [5]. In this case, the patient developed CNS metastasis six years after the initial remission, underlining the unpredictable nature of relapse in high-risk DLBCL cases. This delay highlights the need for long-term monitoring even in patients who respond well to the initial chemotherapy treatment.

Chemotherapy brings numerous problems in elderly patients mainly because it is toxic and older patients have less reserve capacity. The standard R-CHOP regimen has shown good efficacy in DLBCL but implies some risks of hematologic, renal, and cardiotoxic effects which are especially seen in the elderly population [6]. In this case report, CNS relapse treatment and cumulative toxicity led to decreased renal function and low hemoglobin level. This case also illustrates the importance of balancing the treatment intensity with toxicity in elderly DLBCL patients. Although CNS preventive treatment is anticipated for high-risk DLBCL patients, its application in older individuals is still controversial because of the dangers associated with rigorous prophylactic chemotherapy regimens [7]. This patient is a clear example of the fact that existing therapeutic approaches are insufficient to avoid CNS relapse, although the patient achieved a complete response to R-CHOP. While some preventive measures, such as intrathecal chemotherapy or high-dose methotrexate, can be used, they are often difficult for elderly patients and may cause neurological side effects [8]. However, in the given patient's age and functional status, CNS prophylaxis was not given initially, which signifies the need for tailored approaches in older patients. Thus, this case highlights the ongoing challenge of determining when CNS prophylaxis is suitable, particularly in patients with a high risk of relapse.

Emerging therapies in DLBCL include CAR-T cell therapy, antibody-drug conjugation, and targeted molecule inhibitors will help in improving outcomes, especially in high-risk and elderly patients. These therapies offer CNS penetration with fewer toxicities as compared to traditional chemotherapy, presenting a potential option for elder patients who are unable to tolerate aggressive chemotherapy [9]. Advancement of molecular profiling and biomarkers-based strategies provide the development of various personalized treatment approaches and allow for better targeting of high-risk sub-types of DLBCL like non-GCB DLBCL [10]. Future studies are required to focus on optimizing CNS prophylaxis and developing less toxic CNS-targeted chemotherapy which is crucial for improving survival and quality of life in patients with CNS-involved DLBCL.

Conclusion

This case report highlights the importance of utilizing immunohistochemistry in the diagnostic approach of aggressive B-cell lymphomas and the clinical management of patients with atypical presentation post-surgically. The expression of CD20, PAX-5, Bcl-6, MUM-1, and a high Ki-67 index confirms the non-germinal center subtype of DLBCL, bringing into line important markers of high proliferation and poor progression. These findings highlight the aggressive nature of lymphomas and underline the importance of a rapid and targeted therapeutic regimen.

The clinical course of this case underscores the need for developing treatment targeting specific IHC profiles, especially where ploidy

is high and the proliferation index is high. The risk of relapse, especially in the CNS, implies long-term close monitoring after treatment. This case report emphasizes the need for further research in targeted therapies and CNS prophylaxis in high-risk patients of DLBCL to improve patient outcomes. The clinicians can better address the challenge associated with aggressive lymphoma subtypes through comprehensive IHC profiling and targeted therapies.

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