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CASE REPORT

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Intravascular large B-cell lymphoma (IVLBCL): subtle presentation and challenging diagnosis; a case report

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Abstract

Intravascular large B-cell lymphoma (IVLBCL) is a rare, clinically aggressive lymphoma defined by the proliferation of atypical lymphoma cells in the lumen of all sized blood vessels, particularly capillaries. The reasons for this unusual neoplastic cell proliferation are still only partially understood. IVLBCL is considered stage IV lymphoma and manifests with a variety of nonspecific signs and symptoms. Patients with IVLBCL usually do not present with lymphadenopathy. The tumor cells invade the blood vessels of multiple organs such as the central nervous system, skin, lungs, kidneys, and bone marrow. Common presenting symptoms are based on the organ affected and include mental status changes and fever of unknown origin. Although immunochemotherapy has significantly improved the often-poor prognosis of this kind of lymphoma, a large percentage of patients' relapse. We present a 63-year-old man who had been diagnosed with large B cell lymphoma in the bone marrow in March 2021 and was in remission state after completing six cycles of chemotherapy. There was no abnormal FDG uptake on a post-chemotherapy PET/CT scan. Patient presented to the emergency room (ER) two months later with fever and dyspnea. The entire workup was completed and showed pancytopenia and elevated ESR. While chest CT scan did not show lymphadenopathy or lesions, PET/CT scans revealed a widespread increase in FDG uptake in both the lungs and spleen. Lung biopsy revealed large, atypical cells within alveolar septae and vessels. Immunohistochemical stains demonstrated that these cells were positive for CD20 and PAX-5 and had high proliferation rate based on Ki67. IVLBCL has a low incidence rate with nonspecific clinical presentation. The diagnosis can be easily missed in both clinical, radiological and the corresponding histopathological findings. Radiological finding and CT scan are not sensitive enough and may miss the lesion. Even though the PET/CT scan is more sensitive, the definitive diagnosis of IVLBCL relies mainly on histopathology and immunohistochemistry, at which point awareness of this entity by the pathologist is most necessary.

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare and distinct subtype of extranodal diffuse large B-cell lymphoma (Alaggio et al. 2022). IVLBCL was previously called as intravascular lymphomatosis or angiotropic lymphoma or angioendotheliomatosis proliferans syndrome, but those terms are obsolete. IVLBCL is a highly malignant and disseminated disease with uncommon clinical presentation and poor prognosis. It is characterized by the accumulation of tumor cells in the lumens of blood vessels especially capillaries, with little to no circulating neoplastic cells in the peripheral circulation (Swerdlow, et al. 2016). However, there are rare cases when proliferation in major blood vessels occurs (Ferreri et al. 2004). The underlying mechanism for this angiotropism is not clearly understood. The absence of adhesion molecules on tumor cells, such as b1 integrin,

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(ICAM-1) and metalloproteinases, is thought to alter the transvascular penetration of extracellular matrix for the tumor mass formation (Kinoshita et al. 2008). IVLBCL can present with a wide range of clinical symptoms, such as unexplained fever, night sweats, anemia, weight loss, decreased cognition, and skin lesions. The diagnostic challenge of IVLBCL is mainly due to the fact that subtle histological changes could be easily overlooked, in addition to its rarity, non-specific and diverse clinical presentations, and lack of large mass lesions (Han et al. 2022). The defining feature of IVLBCL diagnosis is the remarkable degree of sparing of the surrounding tissue along with the absence of tumor cells in the lymph nodes and reticuloendothelial system (Kinoshita et al. 2008). R-CHOP chemotherapy (rituximab plus cyclo-phosphamide, hydroxydaunorubicin, vincristine, and prednisone) has significantly improved the previously dismal prognosis of IVLBCL. However, a substantial proportion of patients eventually experience relapse, particularly in the brain, and R-CHOP has minimal efficacy in these patients (Shen et al. 2011).

In this case report, we described the clinicopathological findings of a patient with IVLBCL.

Case presentation

We present a 63-year-old man, a heavy smoker, with a past medical history of hypertension and diabetes. He presented to our institution in March of 2021 with a two-month history of constitutional symptoms (fever, chills, night sweats and weight loss). Extensive workup revealed pancytopenia (hemoglobin 7.2 gm/dL, WBCs <0.1 K/uL, and platelet count 17 K/uL), high BUN (60 mg/dL) and high LDH (520 U/L). A bone marrow biopsy showed atypical large cells involving approximately 10% of the bone marrow. Immunohistochemical analysis showed that the large, atypical cells were positive for CD20, CD79a, and MUM1, and negative for CD3, CD5, CD7, CD10, and CD30. FISH was done and was negative for MYC, BCL2, or BCL6 rearrangements. The patient was diagnosed with large B-cell lymphoma involving the bone marrow. He received six cycles of CHOP chemotherapy and reached remission including no abnormal FDG uptake on post-chemotherapy PET/CT scans.

In March 2022, the patient presented to our institution by flu-like symptoms and tested positive for COVID-19. However, his symptoms completely improved after one week. One month later, the patient presented to the ER with a high fever and dyspnea. The entire workup was completed, showing pancytopenia and elevated ESR. A chest CT scan did not show lymphadenopathy, lesions, or masses within the lung. However, the PET scan showed a mild increase in FGD activity with an SUV peak of 2.2, considered abnormal but not diagnostic of malignancy. Due to the worsening of the patient's dyspnea and fatigue, the decision was made to perform a lung biopsy.

The lung biopsy showed alveolated lung parenchyma with slightly thickened alveolar septa and scant large, atypical cells within alveolar septae and vessels. Immunohistochemistry was performed and highlighted that the atypical cells were strongly positive for CD20 and PAX-5 and had a high Ki-67 proliferation index, leading to the diagnosis of intravascular large B-cell lymphoma (Fig. 1).

Further extensive metabolic workup revealed pancytopenia (hemoglobin 7.8 gm/dL, White blood cells (WBCs) 3.47 K/uL, and platelet count 23 K/uL) along with a mild increase in Blood Urea Nitrogen (BUN) (38 mg/dL) and an elevated Erythrocyte sedimentation rate (ESR) of 70 mm/h. The rest of the laboratory results were within normal values.

An MRI of the brain showed punctate solid enhancement within the anterior left insula and right paramedian parietal subcortical white matter, which was very concerning for central nervous system (CNS) involvement. Although the patient did not show any neurological manifestations, had a negative lumbar puncture, and did not show FDG uptake in the new lesions, the oncology team made a decision to initiate MATRIX chemotherapy.

The patient received two cycles of MATRIX chemotherapy with a complete response. His follow up laboratory workup showed mild thrombocytopenia (platelet count 135 K/ul), with hemoglobin of 13.6 gm/dL, WBCs 5.08 K/uL,a slight elevation of ESR (16 mm/h) and normalization of BUN (18 mg/dL) and LDH (190 U/). The patient was followed up every three months with PET/CT scans, and at the time of writing this paper, the patient is in complete remission (Fig. 2).

Discussion

Here we report a patient who was initially diagnosed with large B-cell lymphoma in the bone marrow and achieved remission after completing six cycles of chemotherapy. The patient presented 1 year later with non-specific and insidious symptoms in the form of fever and dyspnea. The routine imaging did not demonstrate any abnormal findings, however, PET/CT scan revealed suspicious mild FDG uptake in both lungs and spleen. The biopsy of the lung confirmed involvement by intravascular large B-cell lymphoma. Furthermore, the brain MRI was suspicious for CNS involvement and patient was started on MATRIX chemotherapy. After two cycles of chemotherapy the patient had a complete remission. This case demonstrates the challenges and difficulties for radiologists and pathologists in making this diagnosis and highlights complicated management decisions by the oncologist.

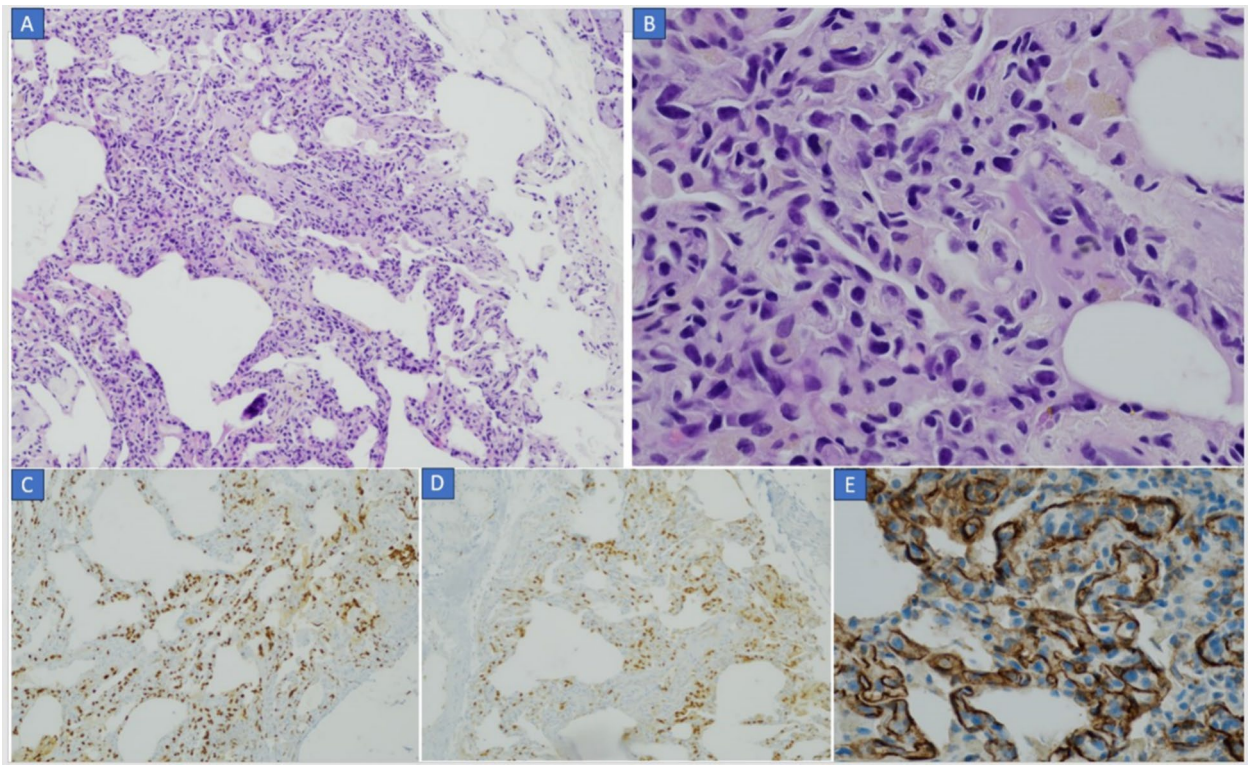

Fig. 1 **A**-10X & **B**-40X: large, atypical cells within alveolar septae and vessels, (**C**-10X): high proliferation rate based on ki67, (**D**-10): atypical cells positive for PAX-5, (**E**-40X) CD34 highlights the endothelial cells of the blood vessels where most of atypical cells are detected. Some atypical cells are detected extravascular

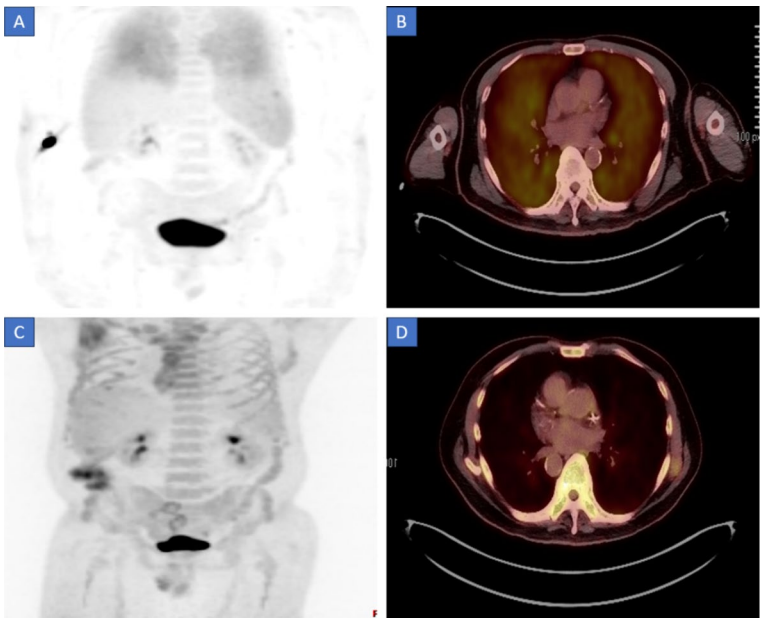

Fig. 2 **A**&**B**: PET/CT scan shows mild FDG activity in both lungs (SUV=2.2), **C**&**D**: PER/CT scan shows no FDG activity after competing 2 cycles of MATRIX chemotherapy

The IVLBCL disease's pathological characteristic is the luminal proliferation of tumor cells in small and medium-sized arteries without lymph nodes or peripheral blood involvement (Ameli et al. 2020). The exclusive intravascular localization of malignant cells is supposed to result from the function loss of adhesion molecules required for tissue homing. Vascular occlusion can cause ischemic, hemorrhagic, or necrotic lesions in any organ, including the lungs, CNS, skin, kidney, or liver. The cause of the affected vessels' obstruction is still unknown. Endothelial surface damage may result in thrombotic microangiopathy, which causes platelet activation, thrombocytopenia, and red blood cell fragmentation, followed by the formation of microthrombi (Fischer et al. 2017).

The clinical presentations of IVLBCL are various and non-specific. The symptoms are often related to organ dysfunction due to blood vessel occlusion, including fever, cutaneous lesions, neurological signs, hepatosplenomegaly, and pancytopenia. The neurological manifestations are often significant and are due to the presence of multiple infarct sites resulting from vascular occlusion. Although the cutaneous manifestations are vague, the most frequent symptoms are nodular, subcutaneous, firm masses or plaques with or without hemorrhage. Patients usually undergo multistep clinical investigations before the final diagnosis due to unpredictable and various clinical presentations. Unfortunately, some cases can be easily overlooked in routine histopathologic evaluation and are not diagnosed correctly due to the insidious intravascular growth pattern of IVLBCL cells (Ameli et al. 2020).

Previously, there were two geographically distinct patterns of IVLBCL presentations (western and Asian forms). However, because of differences in the clinical features and outcome, three distinct types of variants (classical, cutaneous, and hemophagocytic syndrome-associated) have been described recently. The "cutaneous variant" is associated with a better prognosis as it is limited to skin lesions without other systemic involvement, and those patients have a 56% three-year survival rate; if it goes beyond the skin, that rate drops to 22%. On the other side, the worst prognosis form is the hemophagocytic syndrome-associated form, as it is associated with hemophagocytosis and multiorgan failure. According to the recently updated 2022 WHO classification, IVLBCL patients are classified into these three types based on their clinical features rather than their geographic distribution. In addition to these recognized variants of IVLBCL, other case reports highlighted atypical clinical features with challenges in diagnosis (Suehara et al. 2018).

The heterogeneous clinical features of IVLBCL among patients make early diagnosis a challenge. Early diagnosis and early treatment might improve the outcome of IVLBCL. Many studies investigated the strategies for early diagnosis of IVLBCL, such as random skin biopsy, bone marrow biopsy, or FDG PET/CT. However, there has not yet been agreement on methods for early diagnosis of IVLBCL (Matsukura et al. 2018). Complete remission and long-term survival can result from aggressive combined chemotherapy (Ameli et al. 2020). CT or MR imaging usually cannot establish the diagnosis of IVLBCL because there are few or no concomitant solid lesions (Takeoka et al. 2011).

The IVLBCL cell's origin has not yet been confirmed. There is a theory that IVLBCL originated from post-germinal center cells based on the presence of somatic mutations in immunoglobulin heavy chain variable region (VH) gene analyses (Swerdlow et al. 2016). Considering immunohistochemistry subgroups, studies mentioned both germinal center (20%) and non-germinal center (80%) B-cell immunophenotypes. In our patient a germinal center immunophenotype was observed as there was an immunoreactivity for CD10. Murase T et al. reported no significant difference between non-GCB and germinal center B cells (GCB) in clinical features or parameters of 96 IVLBCL cases (Murase et al. 2007).

Liquid biopsy is a promising method for diagnosing IVLBCL, but this method is restricted to institutions that have the facilities to analyze it (Suehara et al. 2018). Suehara et al. reported that liquid biopsies targeting *MYD88*^{L265P} or *CD79B*^{Y196} in cell-free DNA (cfDNA) from plasma were very useful for detection of IVLBCL (Suehara et al. 2018). Anthracycline-based chemotherapy can improve the outcome of IVLBCL patients compared to those without any treatment based on many studies. The addition of rituximab to chemotherapy further improves the outcome of IVLBCL patients, but long-term survival remains dismal. Hence, there are trials to use more intense therapies, such as autologous hematopoietic stem cell transplantation (auto-HSCT). Some reports show longer survival times of treated IVLBCL patients with auto-HSCT, with three-year OS rates between 91% and 100%. Identifying the risk factors for IVLBCL patients with high relapse rates has not been determined. According to the findings of previous studies, auto-HSCT might be an option for a selected number of feasible IVLBCL patients (Suehara et al. 2018). Untreated IVLBCL can be rapidly fatal (Ameli et al. 2020). Lymphoma involving the brain, eye, spinal cord or leptomeninges, has a different treatment approach. Combination of chemotherapy and a targeted therapy drug, known as MATRIX regimen has shown that at a median follow-up of 30 months, patients treated with the MATRIX regimen had significantly higher complete remission rate (49%) as compared to a CR of 23% and 30% in those treated with methotrexate-cytarabine alone

and methotrexate-cytarabine plus rituximab, respectively. This new combination has also shown significant improvement in overall survival of these patients (Ferreri et al. 2016; Cai et al. 2019).

Pulmonary IVLBCL commonly shows on CT scan as a ground glass or nodular opacity (Liu et al. 2014; Iwami, et al. 2020; Xiao et al. 2014; Chen et al. 2014; Zhang et al. 2018; Satoh et al. 2019; Hsieh 2010), pleural effusion (Hsieh , 2010) or mediastinal lymphadenopathy (Masood et al. 2019). This is often accompanied by high LDH (Liu et al. 2014; Iwami, et al. 2020; Xiao et al. 2014; Chen et al. 2014; Zhang et al. 2018; Satoh et al. 2019; Hsieh 2010; Masood et al. 2019) and in some instances hypoxemia (Liu et al. 2014; Iwami, et al. 2020; Zhang et al. 2018). However, in our case these radiologic and laboratory findings were not present, which made the diagnosis very challenging. From our search of the literature, it seems that FDG lung uptake with negative CT scans can be seen in the setting of infection, acute respiratory distress syndrome or IVLBCL (Bikkina et al. 2017). In the right clinical setting, patients with FDG uptake in the lung and negative chest imaging, may benefit from lung biopsies which would lead to prompt diagnosis and quick management of IVLBCL. Despite the absence of these findings, the patient ultimately had a confirmed diagnosis of IVLBCL, highlighting the importance of considering other diagnostic modalities and not solely relying on traditional imaging (CT scan) and laboratory tests for a conclusive diagnosis of this rare and aggressive disease. Prompt diagnosis and management are crucial for improving patient outcomes and survival rates.

Conclusion

Intravascular large B-cell lymphoma (IVLBCL) is a rare and clinically aggressive form of lymphoma with a low incidence rate and non-specific clinical presentation. The diagnosis of IVLBCL can be easily missed due to the non-specific symptoms and the limitations of radiological and histopathological findings. Therefore, it is crucial for healthcare professionals to have a high level of awareness and suspicion for IVLBCL when evaluating these patients and rely not only on histopathology but also immunohistochemistry for an accurate diagnosis.

Abbreviations

IVLBCL	Intravascular large B-cell lymphoma
FDG/PET	F*luorodeoxyglucose* Positron emission tomography
CT	Computed tomography
MR	Magnetic resonance
GCB	Germinal center B cells
MATRIX	Methotrexate, cytarabine, thiotepa and rituximab
SUV	Standardized uptake value
auto-HSCT	Autologous hematopoietic stem cell transplantation
CHOP	cyclophosphamide, hydroxydaunorubicin, Oncovin and prednisone
LDH	Lactate dehydrogenase
ESR	Erythrocyte sedimentation rate
ICAM-1	Intracellular Adhesion Molecule 1
BUN	Blood urea nitrogen
WBCs	White blood cells

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Not applicable.

Authors' contributions

Ahmed Bendari; study design/planning and literature analysis/search, data interpretation, and preparation of manuscript, Aisha Abdelhafez; preparation of manuscript and literature analysis/search, Sunder Sham; preparation of manuscript, and study design/planning, Reham Al-Refai; study design/planning and literature analysis/search, and Alyssa Yurovitsky; literature analysis/search, and preparation of manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

A written informed consent was obtained from the patient for her data to be used anonymously for teaching and publication purposes.

Consent for publication

Written informed consent was obtained from the patient for her data to be used anonymously for teaching and publication purposes.

Competing interest

The authors declare no conflicts of interest.

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