



## Case report

# Primary lung intravascular large B-Cell lymphoma clinically mimicking sarcoidosis: A rare case report and review of literature

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## A B S T R A C T

We present a case of a 73-year-old male who initially presented with night sweats, intermittent fever, worsening dry cough and shortness of breath. CT scans revealed atelectasis and calcified mediastinal lymphadenopathy, raising a suspicion for sarcoidosis. Multiple lung biopsies were performed. Microscopically, atypical lymphocytes were identified within capillaries, small arteries and veins. These lymphocytes were large with prominent nucleoli. Immunohistochemical staining demonstrated tumor cells positive for CD20, CD79a, Pax-5, CD10 and Mum-1, while negative for CD3, cytokeratin, S100, and CD34. LDH serum level was increased (480 IU/L). Extra pulmonary lymphoma was not detected elsewhere in the patient. These findings support the diagnosis of primary lung intravascular large B cell lymphoma (IVLBCL). Literature review of 52 cases demonstrated occurrence of primary lung IVBCL in patients between the ages (35–85) with a slight male predominance (1.167:1). The most common clinical presentation was fever associated with dyspnea.

## 1. Introduction

IVLBCL is a rare extra-nodal subtype of non-Hodgkin's diffuse large B-cell lymphoma (DLBCL), characterized by presence of atypical large lymphocytes in the lumina of small vessels [1]. IVLBCL typically occurs in elderly patients with male to female ratio of 1.3 to 1 [21]. It is a rare entity of lymphoma characterized by the predominant, if not exclusive, growth of large lymphocytes within the lumen of different-sized blood vessels [14]. The exact mechanism of selective intravascular location of IVBCL is still unknown. Several studies have shown defective interactions between lymphoma cells and High Endothelin Venues [HEV] in vessels. HEV helps lymphocytes traverse the vessel wall and enter lymphoid organs. It appears that some endothelial cells have surface determinants that causes homing of these lymphocytes into the endothelial cells [22].

## 2. Case report

We present a case of a 73-year-old man presenting with a 2-month history of progressive exertional dyspnea and fever. He had no prior history of lung disease or tobacco use. At presentation, he was febrile and hypoxic with no other abnormal physical findings, including palpable lymph nodes or skin lesions. His white blood cell count was slightly elevated with a normal differential count and a peak serum LDH level of 480 (IU/L). Chest X-Ray appeared normal. CT scans revealed atelectasis and calcified mediastinal lymphadenopathy, raising a

suspicion for sarcoidosis. The patient underwent bronchoscopy with EBUS for biopsy of subcarinal, right hilar lymph nodes and bronchoalveolar lavage of right lung, all of which were non-diagnostic. Subsequently patient underwent mediastinoscopy for mediastinal lymph node biopsies and video-assisted thoracoscopic wedge biopsy of the right lung.

## 3. Histologic findings

Microscopically, atypical lymphocytes were identified within capillaries, small arteries and veins. These lymphocytes were large and pleomorphic, with prominent nucleoli. Immunohistochemical staining demonstrated tumor cells positive for CD20, CD79a, Pax-5, CD10 and Mum-1, while negative for CD3, Cytokeratin, S100, and CD34 (Fig. 1; A-I). Fluorescent in situ hybridization study for high grade B cell lymphoma was normal, indicating the absence of gene rearrangements involving BCL2, BCL6, MYC, and IGH. A bone marrow biopsy and aspiration revealed rare large lymphoid cells which occupied less than 1% of the core biopsy. The atypical lymphoid cells were positive for CD20, PAX5 and MUM-1. The changes were suggestive of minimal involvement by large B-cell lymphoma.

## 4. Radiologic findings

Chest CT scan revealed ground glass opacities and calcified mediastinal lymphadenopathy. PET/CT scan demonstrated increase uptake

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in celiac and peripancreatic lymph nodes with focal uptake at T4, T9, L2, L4, concerning for lymphomatous involvement of the thoracic and lumbar spines (Fig. 2; A-E).

## 5. Treatment

The patient was admitted for respiratory failure which necessitated the urgent initiation of chemotherapy (R-CHOP) on September 2017. Rituximab with Neupogen was administered after the first cycle. Intrathecal methotrexate was administered in cycle 2, 3, 4, 5, and 6. A repeat PET scan showed decreased spinal uptake.

## 6. Outcome and follow up

A follow up PET scan on January 2018 demonstrated regression of the disease. The patient also underwent three weeks of radiation therapy to the lumbar spine from February to March 2018. No recent follow-up bone marrow or PET scan has been performed since then.

## 7. Discussion

In 1958, Pflieger and Tappeiner first described an entity known as malignant angioendotheliomatosis. Following thereafter, Sheibani et al. postulated the term angiotropic (Intravascular) large cell lymphoma to replace the earlier term "malignant angioendotheliomatosis" [13]. In 2008, the WHO classified it as a rare, specific type of non-Hodgkin lymphoma (NHL).

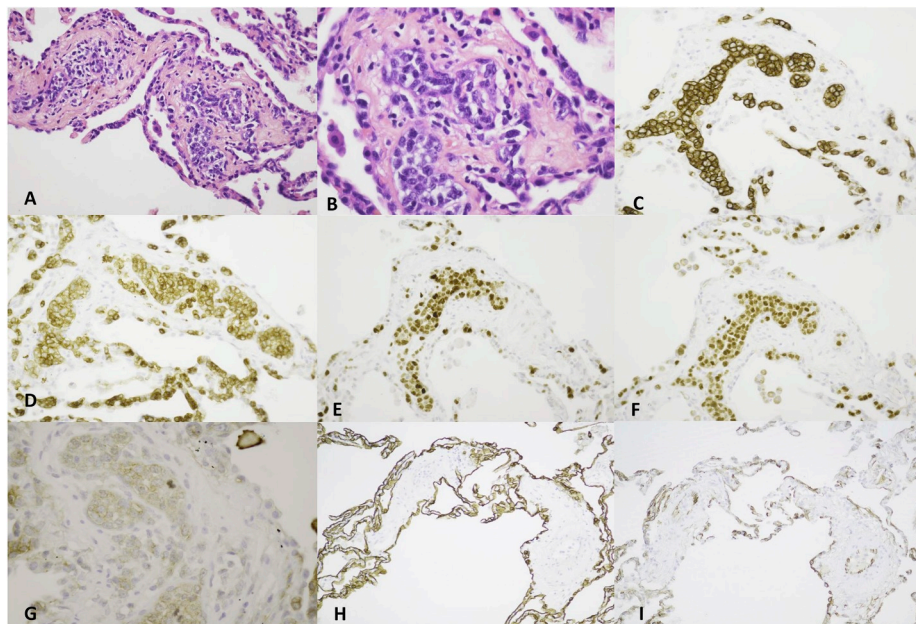
The natural history of IVLBCL has been substantially modified by improvements in early clinical recognition and therapy with recent data reports of an ante-mortem diagnosis in about 80% of patients [5]. The literature review of 52 cases (see attached supplement data; Table 1) demonstrated primary pulmonary presentation of primary lung IVBCL in middle to elderly patients (35–85 years) with a slight male predominance (M: F ratio = 1.167:1). The most common clinical presentation was fever associated with dyspnea. Clinical manifestation and presenting symptoms at initial diagnosis are extremely variable based on geographic origin [2,3]. Western countries exhibit a relatively higher frequency of CNS and skin involvement, while patients from Asian countries preferentially show hematophagocytic syndrome, bone marrow involvement, fever, hepatosplenomegaly, and thrombocytopenia [4–7,15]. However recently updated WHO classification has

suggested that it is more appropriate to consider IVLBCL variants according to their clinical features (i.e., classic, cutaneous and hemophagocytic syndrome-associated) rather than to their geographical distribution [14,17]. Fever of unknown origin is by far the most common systemic symptom, while initial presentation with pulmonary symptom is rare. Definitive diagnosis needs to be established by histopathological examination. Radiological presentation of IVBCL on CT scan of the chest can be nonspecific, ranging from normal, ground glass, to solitary or diffuse multiple small nodules [8–10,16]. Tissue biopsies such as surgical lung biopsy, random transbronchial lung biopsy, CT guided percutaneous lung biopsy, skin biopsy, percutaneous renal biopsy are among the different modalities documented to have been used to obtain a pathological diagnosis of IVBCL with pulmonary presentation [8]. Newer techniques of lymphoma cell detection by pulmonary microvascular cytology and transbronchial cryobiopsy have also been mentioned in the literature [8,11,12].

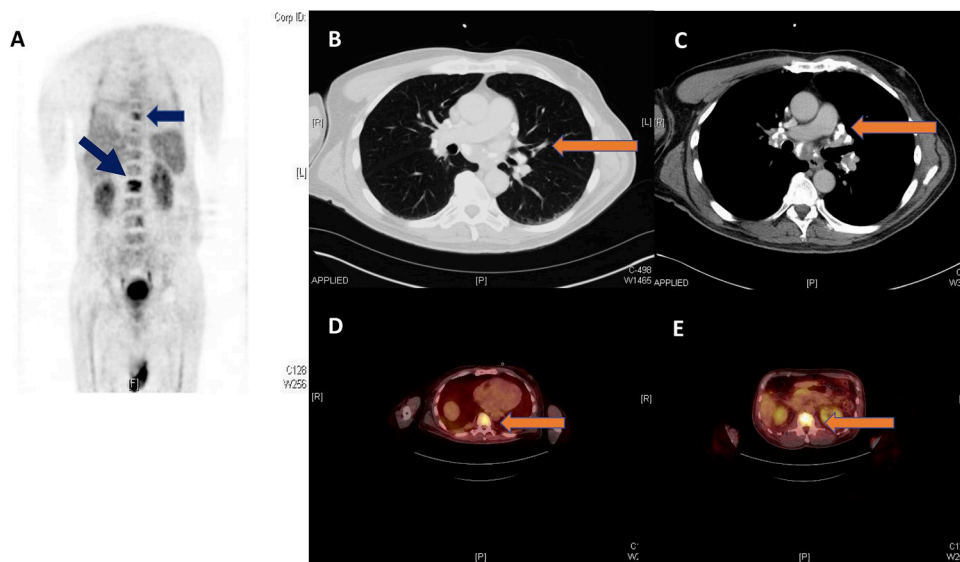
Given that 60% of IVLBCL patients present with stage IV disease and the absence of prospective trials, the most appropriate therapeutic approach for IVLBCL has been difficult to define. The available data often refer to individual case reports. The first choice of treatment for these patients is the use of anthracyclines and the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimen. Patients with IVLBCL treated with CHOP achieved an overall response rate (ORR) of 59% and 33% with a 3-year overall survival (OS) in Western countries [18,19]. The addition of rituximab to CHOP in patients of the Western world, has yielded an 88% complete remission rate, 91% ORR, and an 81% 3-year OS [20,21]. The cutaneous variant of IVLBCL, in spite of being less aggressive, should be treated the same way as the other variants. CNS prophylaxis and treatment is another important therapeutic component in IVLBCL patients [1]. Extravascular CNS dissemination is the main site of relapse among Western patients treated with rituximab-CHOP [21]. Addition of drugs with a better CNS bioavailability, such as high dose methotrexate represents a possible strategy [1]. A recent population-based study reported a 5-year overall survival of 46.4% and 46.5% respectively, with intrathecal methotrexate therapy [2]. Autologous stem cell transplantation (ASCT) still remains a matter of debate.

## 8. Conclusion

IVLBCL is an aggressive disease and a timely diagnosis is pivotal for a



**Fig. 1.** A) 20x magnification, H & E section shows atypical and pleomorphic lymphocytes with prominent nucleoli and vesicular chromatin; (B) 40x magnification demonstrates atypical lymphocytes in the lumina of vessels; (C) CD 20 and (D) CD79a demonstrates strong membranous staining; (E) Mum1 and (F) Pax 5 staining demonstrates strong nuclear positivity; (G) CD 10 demonstrates weak membranous staining in atypical B lymphocytes; (H) Cytokeratin and (I) CD34 demonstrate negative staining in atypical B lymphocytes.



**Fig. 2.** A): Whole body FDG PET scan, coronal non-attenuation corrected image demonstrating hypermetabolic activity in thoracic and lumbar vertebral bodies (arrows); (B): Axial CT lung window with diffuse ground glass opacities; (C): Axial CT soft tissue window showing bilateral hilar calcified lymph nodes; (D): Axial fused PET/CT image through the T9 vertebral level identifies hypermetabolic activity in the vertebral body; (E): Axial fused PET/CT demonstrating hypermetabolic focus in the L2 vertebral body.

successful treatment and overall survival. Due to the nonspecific clinical presentation and radiological findings, there may be a delay in the diagnosis. Keeping this entity in the spectrum of differential diagnosis and with appropriate tissue biopsy, an accurate diagnosis and efficacious treatment can be rendered.

#### Declaration of competing interest

Disclosure: The authors declare no conflict of interest.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2019.100989>.

#### References

- M. Ponzoni, A.J.M. Ferreri, E. Campo, et al., Definition, diagnosis, and management of intravascular large B-cell lymphoma: proposals and perspectives from an international consensus meeting, *J. Clin. Oncol.* 25 (2007) 3168–3173.
- D.J. Rajyaguru, C. Bhaskar, A.J. Borgert, A. Smith, B. Parsons, Intravascular large B-cell lymphoma in the United States (US): a population-based study using surveillance, epidemiology, and end results program and national cancer database, *Leuk. Lymphoma* 58 (9) (2017 Sep) 1–9.
- K. Shimada, T. Kinoshita, T. Naoe, S. Nakamura, Presentation and management of intravascular large B-cell lymphoma, *Lancet Oncol.* 10 (9) (2009), 895e902.
- A.J.M. Ferreri, E. Campo, J.F. Seymour, et al., Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the ‘cutaneous variant’, *Br. J. Haematol.* 127 (2004) 173–183.
- J.E. Chapin, L.E. Davis, M. Kornfeld, et al., Neurologic manifestations of intravascular lymphomatosis, *Acta Neurol. Scand.* 91 (1995) 494–499.
- T. Murase, S. Nakamura, K. Kawauchi, et al., An Asian variant of intravascular large B-cell lymphoma: clinical, pathological and cytogenetic approaches to diffuse large B-cell lymphoma associated with haemophagocytic syndrome, *Br. J. Haematol.* 111 (2000) 826–834.
- T. Murase, M. Yamaguchi, R. Suzuki, et al., Intravascular large B-cell lymphoma (IVLBCL): a clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5, *Blood* 109 (2007) 478–485.
- T. Takeshige, N. Harada, Y. Sekimoto, R. Kanemaru, T. Tsutsumi, K. Matsuno, S. Shiota, A. Masuda, A. Gotoh, M. Asahina, et al., Pulmonary intravascular large B-cell lymphoma (IVLBCL) disguised as an asthma exacerbation in a patient with asthma, *Intern. Med.* 56 (14) (2017) 1885–1891.
- H.J. Bae, G.R. Chon, D.J. Kim, S.H. Lee, J.Y. Ahn, A case of intravascular large B-cell lymphoma of lung presenting with progressive multiple nodules on chest computed tomography, *Respir Med Case Rep* 21 (2017 Apr 12) 108–112.
- Y. Chen, C. Ding, Q. Lin, K. Yang, Y. Li, S. Chen, Primary intravascular large B-cell lymphoma of the lung: a review and case report, *J. Thorac. Dis.* 6 (10) (2014). E242eE245.
- H. Yamakawa, M. Yoshida, M. Yabe, et al., Useful strategy of pulmonary microvascular cytology in the early diagnosis of intravascular large B-cell lymphoma in a patient with hypoxemia: a case report and literature review, *Intern. Med.* 54 (2015) 1403–1406.
- V. Poletti, C. Gurioli, S. Picciocchi, et al., Intravascular large B cell lymphoma presenting in the lung: the diagnostic value of transbronchial cryobiopsy, *Sarcoidosis Vasc. Diffuse Lung Dis.* 31 (2015) 354–358.
- K. Sheibani, H. Battifora, J.S. Burke, J. Ben-Ezra, G.M. Ellinger, N.J. Quigley, et al., Further evidence that ‘malignant angioendotheliomatosis’ is an angiotropic large-cell lymphoma, *N. Engl. J. Med.* 314 (15) (1986) 943–948.
- S. Nakamura, M. Ponzoni, E. Campo, Intravascular large B-cell lymphoma, in: S. H. Swerdlow, E. Campo, N.L. Harris, E.S. Jaffe, S.A. Pileri, H. Stein, J. Thiele (Eds.), *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* (Revised 4th Edition). IARC: Lyon, 2017, pp. 317–318.
- V. Brunet, S. Marouan, J.P. Routy, M.A. Hashem, V. Bernier, R. Simard, et al., Retrospective study of intravascular large B-cell lymphoma cases diagnosed in Quebec: a retrospective study of 29 case reports, *Medicine (Baltim.)* 96 (5) (2017), e5985.
- K. Katayama, K. Tomoda, T. Ohya, H. Asada, C. Ohbayashi, H. Kimura, Ground-glass opacities and a solitary nodule on chest in intravascular large B-cell lymphoma, *Respirol Case Rep* 3 (3) (2015) 108–111.
- A.J. Ferreri, G.P. Dognini, E. Campo, R. Willemze, J.F. Seymour, O. Bairey, et al., International Extranodal Lymphoma Study Group (IELSG), Variations in clinical presentation, frequency of hemophagocytosis and clinical behavior of intravascular lymphoma diagnosed in different geographical regions, *Haematologica* 92 (4) (2007) 486–492.
- A.J. Ferreri, E. Campo, A. Ambrosetti, F. Ilariucci, J.F. Seymour, R. Willemze, et al., Anthracycline-based chemotherapy as primary treatment for intravascular lymphoma, *Ann. Oncol.* 15 (8) (2004) 1215–1221.
- A.J. Ferreri, G.P. Dognini, O. Bairey, A. Szomor, C. Montalbán, B. Horvath, et al., International Extranodal Lymphoma Study Group. The addition of rituximab to anthracycline-based chemotherapy significantly improves outcome in ‘Western’ patients with intravascular large B-cell lymphoma, *Br. J. Haematol.* 143 (2) (2008) 253–257.
- A.J. Ferreri, G.P. Dognini, S. Govi, R. Crocchiolo, M. Bouzani, C.R. Bollinger, et al., Can rituximab change the usually dismal prognosis of patients with intravascular large B-cell lymphoma? *J. Clin. Oncol.* 26 (31) (2008) 5134–5136.
- Yingwei Zhang, Lintao Bi, Yuying Qiu, Tingting Zhao, Mengshu Cao, Jingjing Ding, Fanqing Meng, Hourong Cai, Primary pulmonary intravascular large B-cell lymphoma: a report of three cases and literature review, *Oncol Lett* 15 (3) (2018 Mar) 3610–3613. PMID: PMC5796294.
- E.C. Butcher, R.G. Scollay, I.L. Weissman, Lymphocyte adherence to high endothelial venules: characterization of a modified in vitro assay, and examination of the binding of syngeneic and allogeneic lymphocyte populations, *J. Immunol.* 123 (1979) 1996–2003.