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CASE REPORT

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Intravascular large B-cell lymphoma in Hispanics: a case series and literature review

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ABSTRACT

Intravascular large B-cell Lymphoma (IVLBCL) is a rare subtype of extra nodal non-Hodgkin's lymphoma, which is challenging to diagnose and has a poor prognosis. Here we describe three non-White Hispanic patients newly diagnosed with IVLBCL within 14-month period. All of them presented with persistent fever of unknown origin and symptomatic severe anemia as the initial manifestations. Two out of three cases were successfully diagnosed in a timely manner by fat pad biopsy and have remained disease free up to 34 months after chemotherapy. The third case was diagnosed by bone marrow biopsy and deceased one week later after choosing home hospice care. To date, this is the largest published case series of IVLBCL in non-White Hispanics.

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1. Introduction

Intravascular large B-cell lymphoma (IVLBCL) is aggressive, characterized by selective growth of lymphoma cells within the lumen of small to intermediate-sized blood vessels [1]. In many instances, the diagnosis has been made postmortem. Delayed diagnosis is mainly due to its highly variable and non-specific clinical presentation. Currently, IVLBCL is classified into two variants: classic form (Western type) and hemophagocytic syndrome-associated form (Eastern/Asian type). In this case series, we present three non-White Hispanic patients in North America with Eastern/Asian variant IVLBCL.

2. Presentation

Case 1) A 78-year-old male presented to Emergency Department (ED) with progressive generalized weakness for a few months and flu-like symptoms with fever for one week. His medical history included diabetes mellitus type 2, benign prostatic hyperplasia, and hypothyroidism. The patient had no prior personal or family history of autoimmune disease, bleeding disorders, or malignancy. Of note, two weeks prior, he was hospitalized for hemoglobin (Hgb) of 6.5 g/L and near syncopal episode. At that time, anemia work-up was negative with unremarkable upper esophagogastroduodenoscopy and colonoscopy. He was discharged after blood transfusion.

Case 2) A 64-year-old female presented to ED with subjective fever, shortness of breath, and progressive fatigue for one month. Her medical history was significant for hypertension, myocardial infarct status post stent placement more than ten years ago, chronic kidney disease stage III, chronic gastritis without hemorrhagic stigmata, and anemia on iron supplement for the past 3 months. Family history was remarkable for two sisters with gastric cancer in their 60s.

Case 3) An 86-year-old female was sent to ED from primary care office due to severe anemia and hyponatremia. In addition, the patient complained of subjective fever, progressive fatigue and diffuse body pain for two months. Her medical history was significant for hypertension and controlled diabetes mellitus. Of note, she was hospitalized 3 weeks prior at a different facility for sepsis secondary to Pseudomonas pneumonia. Her recent colonoscopy was unremarkable. Her father and three siblings had nonspecified lymphoma at unknown ages.

All three cases were non-White Hispanic. They did not endorse nausea/vomiting, chest pain, hematochezia, melena, or hematuria. They also denied recent travel, sick contact, prior history of smoking, heavy drinking, or illicit drugs.

Vital signs of these three patients showed febrile with maximal temperature (T_m) at 101–102°F, hypotensive, sinus tachycardia with heart rate of 100–120

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beats per minute, hyperventilating with respiratory rate of mid-20s per minute otherwise adequate saturation at room air. Physical examination (PE) was insignificant with no lymphadenopathy or rash.

3. Work-up and hospital course

3.1. Lab studies

Pertinent laboratory findings are summarized in Table 1. Infection work-up was negative for influenza A/B, Cytomegalovirus (CMV), human immunodeficiency virus (HIV), hepatitis A/B/C, blood and urine cultures. Tuberculosis (TB) and fungal studies were not done at the time due to low suspicion. Polymerase chain reaction was positive for Epstein Barr virus (EBV) only in Case 3 at 976 copies/mL (<200 copies/mL). Autoimmune work-up was negative for antinuclear antibody with elevated erythrocyte sedimentation rate and C-reactive protein. For anemia work-up, ferritin was elevated in Case 1 and Case 2 and was not ordered in Case 3. Folate and vitamin B12 were unremarkable. LDH was elevated in all three cases but indirect bilirubin was mildly elevated only in Case 2. Peripheral smear showed normocytic normochromic anemia without blast.

In Case 1, immunoglobulin A (IGA) was elevated to 586 mg/dL (81–463 mg/dL). Serum protein electrophoresis (SPEP) showed positive M spike 0.3 g/dL. Urine protein electrophoresis (UPEP) showed elevated 24-hour total protein up to 788 mg. Serum and urine immunofixation confirmed presence of a faint monoclonal free lambda light chain. In Case 2, immunoglobulin M (IGM) was elevated to 331 mg/dL; while IGA and immunoglobulin G (IGG) were within the normal range. Serum immunofixation showed a faint monoclonal free lambda light chain. In Case 3, Immunoglobulins screening was not ordered. SPEP indicated acute phase reaction with decreased total protein to 4.7 g/dL (6.1–-8.1 g/dL). UPEP, serum, and urine immunofixation were not ordered. Fluorescent in situ hybridization (FISH) was negative for BCR-ABL1 fusion.

3.1.1. Imaging

Imaging studies including chest X-ray, abdominal ultrasound and Computed Tomography (CT) scan of head-neck-chest-abdomen-pelvis were negative except splenomegaly in Case 1 and Case 3 without lymphadenopathy. Skeletal survey was done with no focal lytic lesions in Case 1 and Case 2.

Table 1. Clinical and imaging findings of the 3 patients. Lactic Acid Dehydrogenase, LDH. Aspartate Aminotransferase, AST. Alanine aminotransferase, ALT. Erythrocyte sedimentation rate, ESR. C-reactive protein, CRP. Real-time Epstein-Barr virus Polymerase chain reaction, EBV PCR. Partial thromboplastin time, PTT. Prothrombin time, PT. Not Done, ND.

Profile of Patient			
Patient	**#1**	**#2**	**#3**
Years of age	78	64	86
Gender	Male	Female	Female
Ethnicity	Non-White Hispanic	Non-White Hispanic	Non-White Hispanic
Laboratory findings			
White blood cells (x10^9/L)	3.9	5.5	15.8
Hemoglobin (g/L)	7.9	6.1	5.5
Mean corpuscular volume	85.2	82.2	84
Platelet ((x10^9/L)	77	98	64
Corrected retic count (0–1.5%)	2.3	1.8	1.0
LDH (84–246 U/L)	900	1054	1871
Alkaline phosphatase (45–117 units/L)	83	44	87
AST (15–37 units/L)	39	38	51
ALT (12–78 units/L)	23	10	15
Total bilirubin (0.2–1 mg/dL)	0.7	2.6	0.7
Direct bilirubin (0–0.2 mg/dL)	N/A	0.36	N/A
Albumin (3.4–5.0 g/dL)	2	3.3	1.8
Creatinine (mg/dL)	0.98	2.46	0.35
ESR (0–20 mm/hour)	100	52	105
CRP (0–0.3 mg/dL)	N/A	1.82	19.8
Ferritin (26–388 ng/mL)	822	3172	ND
EBV PCR	-	-	+
PTT (23.4–35.7 seconds)	43	29.1	30
PT (12–14.2 seconds)	17	18.2	14.3
Procalcitonin (0–0.5 ng/mL)	0.2	0.65	0.66
Lactate (0.56–1.39 mmol)	1.19	1.4	1.37
Beta-2-microglobulin (<2.51 mg/L)	7.6	9.28	ND
Monoclonal gammopathy serum/urine	+	+	ND
Imaging findings			
Hepatomegaly	-	-	-
Splenomegaly	+	-	+
Lymphadenopathy	-	-	-
Pathology			
Bone marrow biopsy	-	-	+
Fat pad biopsy	+	+	ND

3.2. Pathology

In Case 1, bone marrow biopsy (BMBx) and aspirate morphology evaluated by in-house pathologist showed no evidence of malignancy. Outside flow cytometry and core immunohistochemical (IHC) studies did not find evidence of malignancy (Figure 1(1C)). However, fat pad biopsy of lower abdominal wall (FPB) showed microvasculature distended by highly atypical lymphoid-appearing cells. In Case 2, BMBx evaluated by in-house pathologist was described suboptimal. H&E stains were unremarkable. No aspirate was available for flow cytometry analysis. Meanwhile, random FPB evaluated by in-house pathologist showed dysplastic intravascular cellular proliferation without amyloid. Outside pathologist interpretation of FBP showed adipose tissue with capillaries filled with atypical medium to large lymphoid cells. The IHC staining of FPB in both cases were positive for CD5, CD20, PAX-5, MUM-1, BCL-2, BCL-6 with Ki-67 70–80% and negative for CD10, CD43, BCL-1 (Figure 1(1–2A and 1–2B)), confirming diagnosis of IVLBCL. In Case 3, BMBx morphology was described by in-house pathologist as injury-like pattern and atypical appearing cells of uncertain origin. The bone marrow core and aspirate evaluated by reference laboratory pathologist showed reactive hypercellular bone marrow with large B cell lymphoma cells in the sinusoids (Figure 1(3C)). IHC was positive for CD5, CD20, CD43, PAX5, MUM-1, BLCL-2, BLC-6, Ki-67 80% and negative CD10, BCL-1; confirming IVLBCL.

3.3. Treatment course

Case 1) The patient was treated with R-CHOP (Rituximab, Cytoxan 750 mg/m2, Adriamycin 50 mg/m2, Oncovin 2 mg, and Prednisolone 125 mg) every 3 weeks for total of 6 cycles with cure intent. Three months after completion of chemotherapy, Positron Emission Tomography (PET) scan showed no fluorodeoxyglucose (FDG) avid sites suspicious for lymphoma. He was then given intrathecal methotrexate (IT-MTX) at 10 mg/m^2 weekly × 4 for central nervous system (CNS) prophylaxis. The patient has been in surveillance and doing well 34 months after diagnosis without evidence of relapse.

Case 2) Subsequent Magnetic Resonance (MR) imaging of the brain did not show enhancing lesions concerning for metastatic disease or leptomeningeal involvement. Lumbar puncture was negative for CNS involvement. Therefore, she received R-CHOP (the doses and frequency were similar to former case) and concurrent IT-MTX at 12 mg/m^2 for 6 cycles. Follow-up PET scan two days after completion of chemotherapy was negative. The patient has been doing well without evidence of relapse 28 months after diagnosis.

Case 3) The patient chose palliative care with home hospice. She was deceased 3 days after discharge.

4. Discussion

In 2008, the World Health Organization (WHO) classified IVLBCL as a specific type of non-Hodgkin lymphoma. Recently in 2019, WHO suggested to classify IVLBCL variants according to their clinical

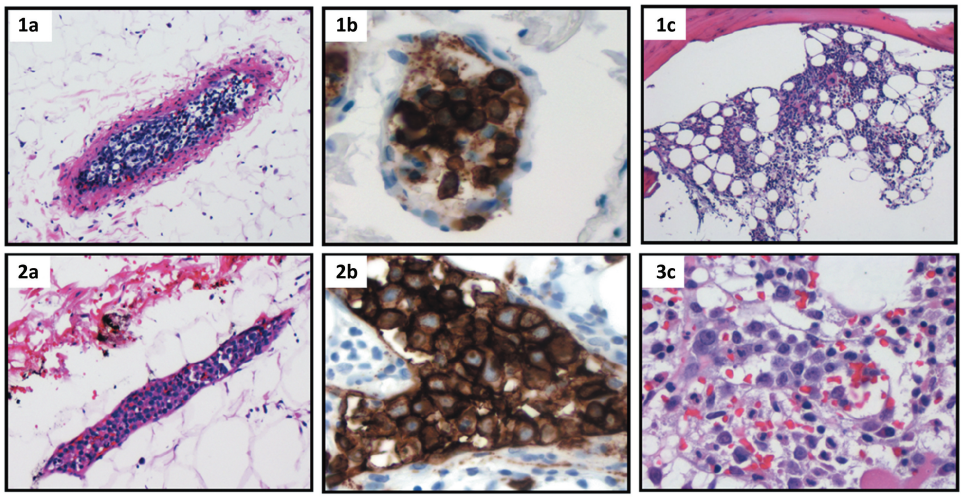

Figure 1. Fat pad and bone marrow infiltration patterns of three patients with IVLBCL. In Case 1, (1A) Histopathology of fat pad biopsy (H&E, x100) showed IVLBCL mainly in lumens of small vessels; (1B) Aggregated abnormal lymphocytes were positively stained by CD20 marker (x400); (1 C) Histopathology of bone marrow biopsy showed trilineage hematopoiesis without lymphoma involvement (H&E, x100). In Case 2, (2A) Histopathology of fat pad biopsy (H&E, x100) showed IVLBCL in lumens of small vessels; (2B) Aggregated abnormal lymphocytes were positively stained by CD20 marker (x400). In Case 3, (3 C) Histopathology of bone marrow biopsy showed the presence of IVLBCL with sinusoidal pattern (x400). Hematoxylin and eosin stain, H&E. Intravascular large B-cell lymphoma, IVLBCL.

features: classic form (Western type) and hemophagocytic syndrome-associated form (Asian/Eastern type) [2].

The clinical presentation of IVLBCL is widely variable, depending on geographical origin. It is recognized that patients in Western countries manifest with neurological symptoms and varied skin involvement from purpura to telangiectasias, plaques, and vasculitis. Meanwhile, in Eastern countries, the patients present more commonly as hemophagocytic syndrome with symptoms of cytokine release syndrome, such as: anemia and circulatory insufficiency leading to fatigue, fever, abdominal fullness, and respiratory disturbance. Moreover, other common findings included splenomegaly and/or hepatomegaly with no associated lymphadenopathy [3,4]. Interestingly, all of our three non-White Hispanic patients in North America had clinical manifestations similar to those in Eastern countries. To our knowledge, these presentations are exceedingly rare and limited in a few case reports [5,6].

The median age at diagnosis for IVLBCL is sixth and seventh decades with no difference between gender [7]. Its incidence is rare, less than 1 in 1 million general population. However, the true incidence is suspected to be higher since the diagnosis was mainly made at autopsy in the past. In the first and largest epidemiologic study of IVLBCL conducted in the USA, the incidence rate of IVLBCL was highest amongst Asian/Pacific Islanders (0.165 per 1,000,000), followed by American Indian/Alaska natives (0.121), White (0.09), and Blacks (0.06) [8]. Meanwhile, the incidence rate of IVBCL in Hispanic population remained infrequent and unknown. This case series contributes to the understanding of this rare type of lymphoma in non-White Hispanics, in which all of our three patients were diagnosed within 14 months.

Often, diagnosis was delayed or missed due to nonspecific symptoms. Fever of unknown origin (FUO) is the most common systemic symptom in IVLBCL [9]. In general, FUO is a common and challenging clinical condition. Over 200 causes of FUO have been described in the literature. The suspicion for IVLBCL was often low due to its nonspecific symptoms. Similarly, our three patients initially presented with persistent fever without lymphadenopathy. Each of them underwent extensive work-up for infection, autoimmune, and malignancy etiologies before leading to the definitive diagnosis. Interestingly, the common laboratory tests altered in our three cases were severe anemia, thrombocytopenia, hypoalbuminemia, elevated ferritin, ESR, CRP, and serum LDH without sign of hemolysis. Moreover, beta-2 microglobulin was also elevated in the setting of slight monoclonal gammopathy (MG), which gave suspicion for possibility of an underlying lymphoma. As such, the association of MG with B-cell non-Hodgkin's lymphomas is well known and is not only a highlight of plasma cell disorders. These findings are also common clinical characteristics of IVLBCL in the large study conducted by Murase et al., 2007 [10]. While the presence of MG in diffuse large B-cell lymphoma (DLBCL) predicted an inferior overall survival and progression-free survival [11], prognostic role of MG in IVLBCL is not yet known. In our series, two patients presented with MG and were treated with good outcome. The third patient was not screened for MG as her initial bone marrow evaluation already established the diagnosis of lymphoma.

Radiological imaging plays a little role in diagnosis of IVLBCL with absence of lymphadenopathy as in our cases [12,13]. Imaging of the abdomen frequently showed splenomegaly, which was also found in two of our three patients. Meanwhile, whole body FDG PET scan may demonstrate hypermetabolic activity in vertebral bodies or diffuse hypermetabolic bilateral pulmonary FDG uptake in cases of lung involvement without corresponding CT abnormality [14,15]. Unfortunately, PET scan prior to treatment was not performed in our patients due to the limited availability at our community institution.

While BMBx is a standard procedure for diagnosis of hematological diseases and work-up for FUO; its role seems to be limited in detecting IVLBCL. In the largest series conducted by Matsue et al. [12], among the forty-two studied patients, twenty-nine (69%) patients were diagnosed via random skin biopsy (RSB) and only eight (19%) patients were diagnosed by BMBx alone. Meanwhile, the use of RSB in healthy-appearing skin still remains controversial [16]. While abdominal FPB has been used to diagnose amyloidosis as a less invasive approach; it was also useful in diagnosis of IVLBCL [17]. In addition, although punch biopsy is easily performed, if not deep enough, it may not contain sufficient amounts of hypodermal adipose tissue for diagnosis [18]. This finding was consistent with our case series. Only one patient was diagnosed by BMBx alone while the other two were diagnosed by FPB. Often, the neoplastic cells expressed B cell markers (such as CD20, CD79a, PAX5); and in some cases, T cell marker CD5 was present. In DLBCL, CD5 positive B-cells only present in up to 5–10% patients and is associated with poorer overall survival when treated with R-CHOP regimens as compared to CD5 negative cases [19]. Interestingly, CD5 was positive in our three patients and two of them who received R-CHOP remain disease free up to the time of this submission.

5. Summary and conclusion

IVLBCL is an aggressive disease with highly variable clinical manifestations. Timely diagnosis is vital for efficacious treatment. Our case series discussed the atypical presentation of IVLBCL in three non-White Hispanic patients. To date, this case series is the largest existing report of IVLBCL in non-White Hispanic patients. In addition, it emphasizes that the absence of lymphadenopathy and a negative BMBx do not rule out lymphoma. As such, IVLBCL should be considered in patients with FUO with negative standard approach, elevated inflammatory markers, elevated LDH in the absence of hemolysis and presence of monoclonal gammopathy. Lastly, it also suggests that FPB could be a useful complimentary tool for diagnosis of IVLBCL. FPB may be considered as a quick and easy additional diagnostic method for oncologists practicing at the community and rural areas, during the long wait for final bone marrow results which may often be nondiagnostic in IVLBCL. Further investigation is needed for better epidemiology, classification, and prognosis of IVLBC lymphoma in non-White Hispanic population.

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Disclosure statement

All authors stated that they had no relevant conflicts of interest.

References

[1] Ponzoni M, Campo E, Nakamura S. Intravascular large B-cell lymphoma: a chameleon with multiple faces and many masks. Blood. 2018;132 (15):1561–1567.
[2] Grimm KE, O'malley DP. Aggressive B cell lymphomas in the 2017 revised WHO classification of tumors of hematopoietic and lymphoid tissues. Ann Diagn Pathol. 2019;38:6–10.
[3] Ferreri AJ, Campo E, Seymour JF, 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. 2004;127:173–183.
[4] Murase T, Nakamura S, Kawauchi K, et al. An Asian variant of intravascular large B-cell lym- phoma: clinical, pathological and cytogenetic ap- proaches to diffuse large B-cell lymphoma asso- ciated with haemophagocytic syndrome. Br J Haematol. 2000;111:826–834.
[5] Duan X, Lapus A, Brown RE, et al. Intravascular large B- cell lymphoma presenting as cholecystitis and pancytopenia: case report with literature review. Ann Clin Lab Sci. 2011;41:262–266.
[6] Hall JM, Meyers N, Andrews J. Hemophagocytosis-related (Asian Variant) Intravascular Large B-Cell Lymphoma in a Hispanic patient: a case report highlighting a micronodular pattern in the spleen. Am J Clin Pathol. 2016;145(5):727–735.
[7] Goyal A, Goyal K, Bohjanen K. Mortality in intravascular large B-cell lymphoma: A SEER analysis. J Am Acad Dermatol. 2018;79(6):1163–1165.
[8] Rajyaguru DJ, Bhaskar C, Borgert AJ, et al. Intravascular large B-cell lymphoma in the USA (US): a population-based study using surveillance, epidemiology, and end results program and national cancer database. Leuk Lymphoma. 2017;58 (9):2080–2088.
[9] Mulders-manders C, Simon A, Bleeker-rovers C. Fever of unknown origin. Clin Med (Lond). 2015;15 (3):280–284.
[10] Economopoulos T, Papageorgiou S, Pappa V, et al. Monoclonal gammopathies in B-cell non-Hodgkin's lymphomas. Leuk Res. 2003;27(6):505–508.
[11] Zhang Y, Wei Z, Li J, et al. Monoclonal gammopathies regardless of subtypes are associated with poor prognosis of diffuse large B-cell lymphoma: A STROBE-compliant article. Medicine (Baltimore). 2018;97(30):e11719.
[12] Matsue K, Abe Y, Narita K, et al. Diagnosis of intravascular large B cell lymphoma: novel insights into clinicopathological features from 42 patients at a single institution over 20 years. Br J Haematol. 2019;187 (3): 328–336.
[13] Bae HJ, Chon GR, Kim DJ, et al. A case of intravascular large B-cell lymphoma of lung presenting with progressive multiple nodules on chest computed tomography. Respir Med Case Rep. 2017;21:108–112.
[14] Yamashita H, Suzuki A, Takahashi Y, et al. Intravascular large B-cell lymphoma with diffuse FDG uptake in the lung by 18FDG-PET/CT without chest CT findings. Ann Nucl Med. 2012;26(6):515–521.
[15] Spencer J, Dusing R, Yap W, et al. Intravascular large B-cell lymphoma presenting with diffusely increased pulmonary fluorodeoxyglucose uptake without corresponding CT abnormality. Radiol Case Rep. 2019;14 (2):260–264.
[16] Cho HG, Sheu SL, Kuo KY, et al. Limited role of random skin biopsy in the diagnosis of intravascular lymphoma in adult patients with hemophagocytic lymphohistiocytosis. Acta Haematol. 2017;138:33–38.
[17] Sinha N, Lantigua L, Niazi M, et al. An elderly lady with Fever of unknown etiology and severe pulmonary hypertension: intravascular lymphoma-an elusive diagnosis. Case Rep Med. 2013;2013:153798.
[18] Enzan N, Kitadate A, Tanaka A, et al. Incisional random skin biopsy, not punch biopsy, is an appropriate method for diagnosis of intravascular large B-cell lymphoma: a clinicopathological study of 25 patients. Br J Dermatol. 2019;181(1):200–201.
[19] Thakral B, Medeiros LJ, Desai P, et al. Prognostic impact of CD5 expression in diffuse large B-cell lymphoma in patients treated with rituximab-EPOCH. Eur J Haematol. 2017;98(4):415–421.