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Intravascular Lymphoma – The Creepy Crawler: A Case Series and Brief Literature Review

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Abstract. *Background: Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of extranodal B-cell lymphoma, which has traditionally been associated with poor outcomes. Despite increasing recognition, IVLBCL requires a high degree of clinical suspicion on the part of the clinician for its diagnosis. Case Series: We present four patient cases: A 69-year-old female with constitutional symptoms and cognitive decline; a 78-year-old female with kidney injury and constitutional symptoms whose disease rapidly progressed to multiorgan failure and death; a 70-year-old asymptomatic female with an incidentally found, enlarged thyroid; and a 63-year-old male with cytopenia and constitutional symptoms. Retrospective chart analysis was performed on these four patients diagnosed with IVLBCL at our Institute to identify the pathognomonic features of the disease and compare these to the published evidence. IVLBCL has a heterogeneous presentation, as seen in our four patients. The disease is characterized by the exclusive presence of malignant cells inside the blood vessels and lack of organ infiltration. Traditional preliminary diagnostic modalities such as imaging are usually inconclusive, given the paucity of lymphomatous aggregates. A bone marrow biopsy, random skin biopsies, or a focal organ biopsy in appropriate cases is required for diagnosis. Immunosuppression might play a role in the pathogenesis. Timely initiation of aggressive cancer-directed therapy was associated with improved outcomes. Monitoring for disease response and relapse continues to be a challenge. Conclusion: Our mini-series highlights the significance of timely diagnosis and intervention in IVLBCL and emphasizes the importance of further research to determine its association with immunosuppression.*

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Intravascular B-cell lymphoma (IVLBCL) is a rare form of extranodal diffuse large B-cell lymphoma, with an incidence rate of approximately one per 10,000,000 (1). Increased recognition of this entity has led to an increase in the number of reported cases over time. Three different subtypes of IVLBCL have been identified: Classical variant (more common in Western countries), hemophagocytic syndrome-associated (more common in Asian countries), and a cutaneous variant (2). Herein, the natural history of IVLBCL is described for four patients, each with a unique presentation of the disease. A brief review of the available literature on this topic is additionally provided.

Case Series

This study was performed in accordance with the Declaration of Helsinki. This human study and its associated processes were approved under study ID: STUDY21010148 by the University of Pittsburgh Institutional Review Board and the University of Pittsburgh Office of Research Informatics,

which are academic affiliates of the University of Pittsburgh Medical Center. Adult participant consent was not required because the study was retrospective and posed minimal risk to the subjects. All identifying information that could be traced back to the subjects was removed from the article. A waiver under the Health Insurance Portability and Accountability Act of 1996 was obtained from the Institutional Review Board.

Case 1. A 69-year-old female was admitted with a 6-month history of episodic fevers, an almost 22 kg weight loss, anemia, and cognitive decline. Prior to admission, she had undergone extensive workup for cognitive decline, including brain magnetic resonance imaging (MRI), electroencephalogram and cerebrospinal fluid (CSF) analysis for viral, bacterial, fungal, and tuberculous infections. No cause of her symptoms could be identified. Her fevers had been evaluated with a comprehensive rheumatological workup, which was inconclusive. Imaging of the chest, abdomen, and pelvis did not show any occult malignancies. Peripheral blood flow cytometry and bone marrow biopsy were unremarkable. Pertinent laboratory analyses on presentation included a white blood cell (WBC) count of 10.3×10^9/l, hemoglobin 9.6 g/dl, platelets 157×10^9/l, total bilirubin 0.6 mg/dl, ferritin 1432 ng/ml, lactate dehydrogenase (LDH) 404 IU/l, erythrocyte sedimentation rate (ESR) 53 mm/h and international normalized ratio (INR) of 1.5. Given her non-focal symptoms and lack of a definitive infectious or malignant etiology, intravascular lymphoma was suspected. Random deep skin biopsies were taken and showed several dilated blood vessels with sparse collections of large atypical lymphoid cells with irregular nuclei, prominent nucleoli, and moderately abundant cytoplasm (Figure 1A). Cells stained positive for CD20 (Figure 1B) and interferon regulatory factor 4 (MUM1), and negative for CD10, B-cell lymphoma 2 (BCL2), and BCL6. The patient urgently received one cycle of dose-reduced (dose level –1) combination regimen: rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) with granulocyte colony-stimulating factor (G-CSF) support, which resulted in significant cognitive improvement over the next few weeks. The treatment course was complicated by neutropenic fever, recurrent hospital admissions, and functional decline. At that point, it was recommended that therapy be switched to rituximab with dose-reduced cyclophosphamide, doxorubicin, vincristine, and prednisone (mini-R-CHOP) but the patient's poor functional status only allowed single-agent rituximab therapy. She had follow-up imaging which showed that she was in remission and at that point, a decision was made to switch to active surveillance as rituximab by itself was considered insufficient for maintaining remission. She was disease-free at the time of the last contact with the system, which was 3.5 years after her initial diagnosis.

Case 2. A 78-year-old female with stage IV chronic kidney disease and active warfarin use for venous thromboembolism was admitted with 6 weeks of progressive generalized weakness, lethargy, and a few months of functional decline. Pertinent laboratory analyses on admission included WBC 3.8×10^9/l, hemoglobin 8.3 g/dl, platelets 55×10^9/l, total bilirubin 0.7 mg/dl, ESR 120 mm/h, INR 3.2, creatinine 5.5 mg/dL, estimated glomerular filtration rate 9 ml/min/1.73m^2. Workup was initiated for kidney injury. Several days into admission, her laboratory analyses indicated worsening of her condition (WBC 1.4×10^9/l, hemoglobin 5.5 g/dl, platelets 31×10^9/l, ferritin 1,316 ng/ml, LDH 2,289 IU/l and INR 3.4). Peripheral blood smear showed normal morphology of all cell lineages. A bone marrow biopsy was planned; however, her overall condition deteriorated rapidly, and she went into shock and respiratory failure. She subsequently had a cardiac arrest requiring brief cardiopulmonary resuscitation. After return of spontaneous circulation, she was found to be in disseminated intravascular coagulation that was refractory to blood products. Supportive measures such as continuous hemodialysis and pressors were initiated but were ultimately unsuccessful and were followed by her death. An autopsy showed extensive vascular involvement in all histological sections (bone marrow, liver, kidney, large bowel, and pancreas) by large, atypical, malignant lymphoid cells (Figure 1C). Cells were positive for CD20 and BCL2, with scattered positivity for CD5 and CD10, and negative for BCL6 and MUM1. The cause of death was multiorgan failure secondary to systemic hemorrhage from coagulopathy due to intravascular lymphoma.

Case 3. A 70-year-old female was found to have incidental enlargement of the thyroid gland on a routine outpatient visit. Thyroid ultrasound showed multiple heterogeneous nodules in the right and left lobes and isthmus. No neck adenopathy was seen. Thyroid function tests were normal (thyroid stimulating hormone 0.73 mIU/l and free T4 1.25 ng/dl), and the patient was asymptomatic. Fine-needle aspiration of the two largest thyroid nodules was performed, and pathology showed scattered highly atypical epithelioid cells suspicious for carcinoma. The patient underwent total elective thyroidectomy for a definitive diagnosis. Pathology showed large pleomorphic B-cells in small vascular channels in both thyroid lobes (Figure 1D and E). Cells were positive for CD10, CD5 and BCL6, and partially positive for MUM1; BCL2 staining was negative. No primary thyroid malignancy was found. Staging positron-emission tomography paired with computerized tomography (PET/CT) and brain MRI were negative for systemic involvement. CSF analysis was deferred given the lack of clinical and radiological evidence of central nervous system involvement. The patient continues to be monitored off chemotherapy with serial imaging and remains disease-free 2 years after her diagnosis.

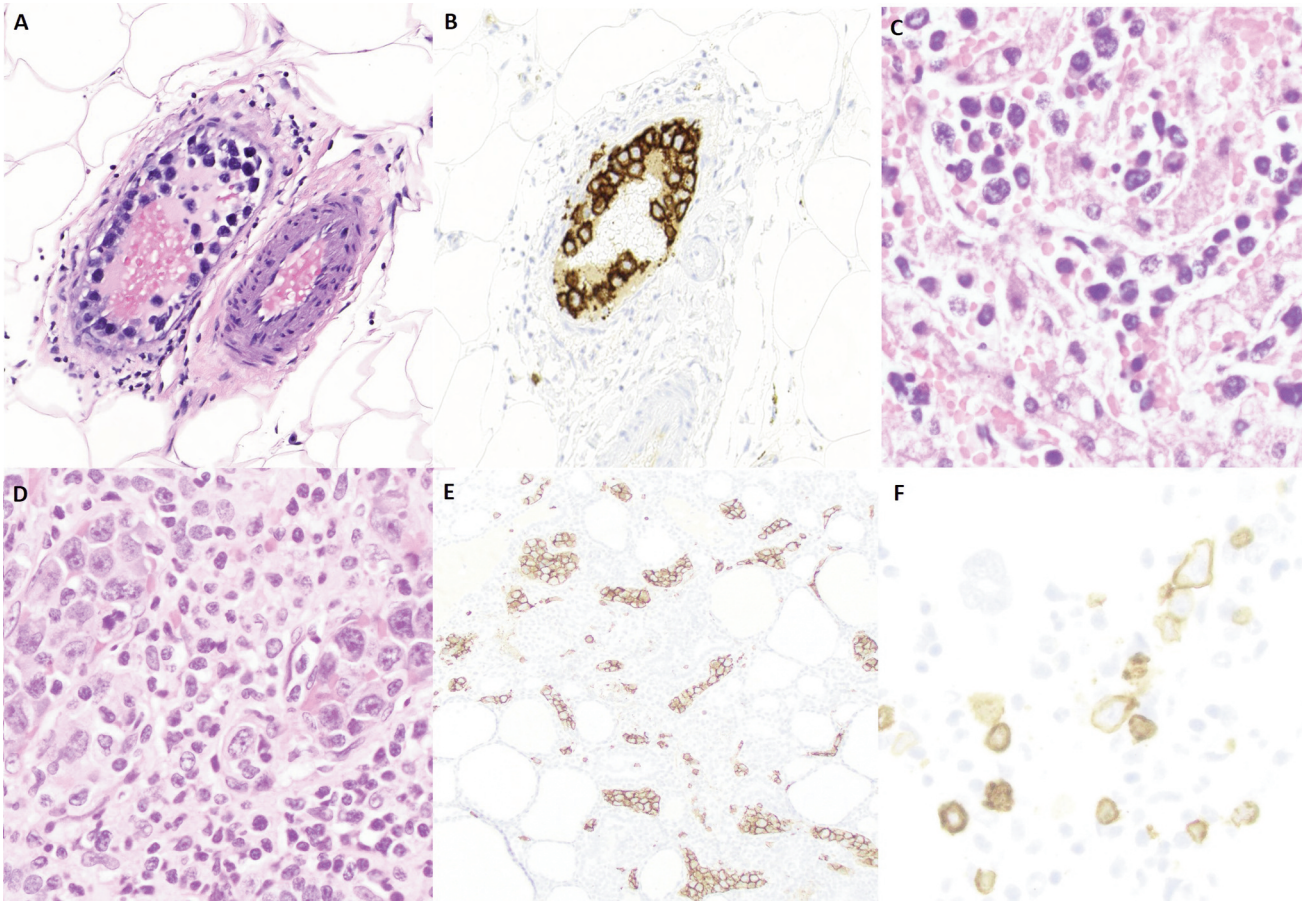

Figure 1. *Biopsy findings of cases 1-4; Case 1: Small vessels in the subcutis of thigh skin featured atypical hyperchromatic lymphoid cells in the lumen as revealed by hematoxylin and eosin (HE) stain (A), and were CD20-positive (B); original magnification ×400. Case 2: Liver sinusoids were filled and expanded by large atypical B-cells (C); HE, original magnification ×400. Case 3: Small vessels in the thyroid were filled with large pleomorphic B-cells (D; HE, original magnification, ×400) and were CD20-positive (E; original magnification, ×200). Case 4: CD20 staining of the bone marrow biopsy, highlighting occasional atypical B-cells in the vessels (F); original magnification ×400.*

Case 4. A 63-year-old male on tacrolimus and mycophenolate mofetil (MMF) for prior renal transplant was admitted for a several-week history of episodic fevers. His prior workup, including cultures and serologies for viral infections, was negative. Pertinent laboratory analyses at admission were: WBC 2.1×10^9/l, hemoglobin 10.2 gm/dl, platelets 60×10^9/l, total bilirubin 0.9 mg/dl, LDH 554 IU/l and ESR 11 mm/h. Peripheral blood smear showed moderate anisocytosis and normal WBC and platelet morphology. Bone marrow biopsy showed trilineage hematopoiesis with occasional large, atypical lymphoid cells in small vessels. Cells were positive for CD20 (Figure 1F), CD79s, and CD5, and mostly negative for BCL2, BCL6, and CD10. Cytogenetic studies showed abnormal clones with structural rearrangements of chromosomes 3, 5, 9, 10, and 14 along with loss of 6q. Follow-up random skin biopsies showed rare, atypical intravascular B cells positive for CD20. Staining for Epstein–Barr virus DNA was negative. Computerized tomography of the neck, chest, abdomen, and pelvis were negative for lymphadenopathy. CSF was negative for malignant cells. He received six cycles of R-CHOP with intrathecal methotrexate, leading to the recovery of blood cell counts. MMF was discontinued at the time of diagnosis. Follow-up PET/CT did not show any evidence of disease. Post-treatment bone marrow biopsy was negative for any morphological or immunophenotypic evidence of lymphoma. The patient continues to be in remission on follow-up 3 years after his initial diagnosis.

Discussion

In the Western world, IVLBCL is a disease of the elderly, with the median age of diagnosis being 70 years (1, 2). This

malignancy is poorly understood and appreciated as an aggressive disease with dismal outcomes. In historical cohorts, most cases were diagnosed postmortem, however, as we continue to learn more about this elusive disease, the rate of diagnosis in living patients is improving. IVLBCL is characterized by the exclusive growth of malignant cells in medium-sized blood vessels. As described in our patients, distinct lymphomatous masses are usually not seen (3), which renders routine imaging modalities such as PET/CT ineffective at identifying this malignancy. IVLBCL symptoms are extremely heterogenous and are caused by the occlusion of blood vessels from tumor cells which has led to this disease being called the 'great mimicker'. The most common symptoms include fever, weight loss, and deterioration of functional status. Timely diagnosis remains a challenge as these non-specific symptoms and a high index of suspicion are usually the only clues for clinicians. Involvement of specific organ vasculature such as the gastrointestinal tract, endocrine organs, or lungs can produce focal symptoms (4, 5) and in cases with heavy infiltration of blood vessels, may be visualized on CT/PET imaging (6). In patients with neurological signs and symptoms, brain MRI can show non-specific changes in white matter (4, 6). As described in our patient cohort, bone marrow biopsy, random skin biopsies, or biopsies of specific organs in cases with focal symptoms remain the mainstay of diagnosis (7).

The genetic profile of IVLBCL is complex and the pathophysiology of this disease including the proclivity of tumor cells for blood vessels is not well understood. On immunohistochemistry, malignant cells are invariably positive for CD20; however, tests for T-cell markers such as CD5 can also be positive. Most cells exhibit a non-germinal center or activated B-cell phenotype, which is seen as BCL2 and MUM1 positivity, and CD10 and BCL6 negativity on immunohistochemistry (2, 8). Cytogenetics of this disease is also complex. Implicit genetic mutations have been identified in the B-cell receptor/nuclear factor-κB signaling pathways which bear similarity to the genetic landscape of activated B-cell-type diffuse large B-cell lymphoma (9). Loss of expression of intercellular adhesion molecule 1, a surface glycoprotein integral to leukocyte transendothelial migration, and integrin β1, a cell surface adhesion molecule involved in cell migration, has been described as a reason for the lack of tumor invasion into surrounding tissues (7). The underlying drivers for these genetic alterations are not well understood and are a focus of ongoing research.

In literature, there are some rare reports of patients developing IVLBCL in the setting of HIV/AIDS (particularly with concomitant Kaposi's Sarcoma), rheumatological disorders on active immunosuppression, or in post-kidney transplant setting (10-21). Interestingly, two of our patients were on active immunosuppression at the time of diagnosis. In case 2, our patient was on adalimumab for inverse psoriasis, while the patient in case 4 was on tacrolimus/MMF for renal transplant. Withdrawal of immunosuppression was used as an adjunct to chemo-immunotherapy in case 4, which resulted in complete remission of the disease, a strategy reported in other cases of IVLBCL arising in the setting of systemic immunosuppression (14, 15, 17-19). These findings point to a possible link between the emergence of IVLBCL, similar to post-transplant lymphoproliferative disorder, and the immunosuppressive state. The role of other comorbidities in the development and prognosis of IVLBCL remains unclear and warrants further research which could help understand the milieu in which IVLBCL is born. The comorbidities of our patients are listed in detail in Table I.

There are no definitive guidelines regarding the treatment of IVLBCL given the rarity of this disorder and resulting lack of prospective studies. Most patients are treated as having disseminated disease along the lines of advanced diffuse large B-cell lymphoma. Systemic therapy with anthracycline-based regimens (CHOP or EPOCH) in combination with the anti-CD20 agent rituximab, along with CNS prophylaxis with intrathecal methotrexate, is the most commonly utilized strategy with a reported 53% complete response rate with CHOP/R-CHOP (5). In one study of patients with IVLBCL treated with R-CHOP, a median overall survival of 135.3 months with a 5-year survival rate of 62·0% [95% confidence interval (CI)=39.4-74.6%] have been reported (6). The survival outcomes in IVLBCL have been found to be similar to those of diffuse large B-cell lymphoma, not otherwise specified (1). Similar to other forms of lymphoma, the addition of rituximab to cytotoxic chemotherapy has been associated with improved rates of complete response (82% *vs*. 51%; p=0.001), progression-free survival [hazard ratio (HR)=0.45, 95% CI=0.25-0.80; p=0.006] and overall survival (HR=0.42, 95% CI=0.21-0.85; p=0.016) (8, 22). This anthracycline-based treatment strategy was also utilized for two of our patients. In case 1, remission was achieved with only one cycle of dose-reduced R-EPOCH despite being diagnosed 6 months from symptom onset. This case suggests a potentially more indolent cohort that may benefit from aggressive chemo-immunotherapy despite a delayed diagnosis. Case 1 contrasts with case 2, where the patient presented with a similar duration of symptoms but rapidly developed malignancy-related complications and died. The time course of this latter case concurs with the historical portrayal of IVLBCL as an aggressive and fatal disease. The disease was thought to have been too far advanced in this case to allow timely receipt of cancer-directed therapy. In comparison to these two cases, case 3 demonstrated focal end-organ involvement with IVLBCL and achieved remission upon resection of the affected organ. This patient continued to be in remission despite not receiving any systemic therapy. Maintenance of remission in this case with simple resection of the involved organ may represent a novel approach to

Table I. *Overview of study patients*.

Case	Age at diagnosis	Sex	ECOG PS at diagnosis	Comorbidities at diagnosis	Time from symptom onset to diagnosis	Biopsy site for diagnosis	Treatment received	Last known status	Time from diagnosis to last known disease status
1	69 Years	F	3	Hypertension Anemia of chronic disease Excision for superficial recurrent melanoma of the nose 14 years before presentation Thyroidectomy due to thyroid cancer 30 years prior to presentation	~ 6 Months	Skin	One cycle R-EPOCH (−1 dose level). Then one cycle single-agent rituximab weekly × 4 doses *q6* months. Then single-agent rituximab, one dose *q2* months for 2 months	NED	3.5 years
2	78 Years	F	3	CKD stage IV secondary to hypertension and MTX use. Inverse psoriasis treated with adalimumab Recurrent VTE Anticoagulation with warfarin Hypothyroidism Definitive resection for pancreatic neuroendocrine neoplasia 10 years earlier	~ 6 Months	Autopsy	None	DOD	(Diagnosed postmortem)
3	70 Years	F	1	Type 2 diabetes AKI requiring transient hemodialysis 2 years before Stage III CKD secondary to diabetic nephropathy CAD status post PCI	Incidental finding	Thyroid	Total thyroidectomy	NED	2 Years
4	63 Years	M	2	ESRD secondary to ADPKD Renal transplant 6 years earlier Immunosuppression with tacrolimus and MMF	1 Month	Bone marrow	Six cycles of R-CHOP with intrathecal MTX Discontinuation of MMF	NED	3 Years

ADPKD: Autosomal dominant polycystic kidney disease; AKI: acute kidney injury; DOD: dead from disease; CAD: coronary artery disease; CKD: chronic kidney disease; ECOG PS: Eastern Cooperative Oncology Group performance status; ESRD: end-stage renal disease; F: female; M: male; MMF: mycophenolate mofetil; MTX: methotrexate; PCI: percutaneous coronary intervention; R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-EPOCH: rituximab plus etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; NED: no evidence of disease; VTE: venous thromboembolism.

managing patients with single-organ involvement. This approach is, however, is not an option for more commonly observed variants involving the bone marrow. Stem cell transplant after initial induction remains a treatment option, although it cannot be offered to many patients due to their advanced age at diagnosis and poor functional status (4).

Disease monitoring is another challenging aspect of the management of IVLBCL. As the cancer has a propensity to remain in blood vessels, it renders the use of PET/CT ineffective except in cases with involvement of vasculature of specific organs, in which case PET/CT may be helpful. Serial bone marrow biopsies in patients with marrow involvement remains an option. A small study (n=21) in Japanese patients with IVLBCL evaluated the use of circulating tumor DNA (ctDNA) in assessing disease response and relapse (23). ctDNA has proven to be useful for

disease monitoring in solid organ tumor such as colorectal cancer. This study in IVLBCL demonstrated a strong correlation between ctDNA concentration and disease activity. However, a significant limitation of this monitoring modality is the need for whole-exome sequencing given the lack of pathognomonic mutations in IVLBCL. As whole-exome sequencing is generally reserved only for experimental procedures, its limited availability and the associated cost would likely hinder widespread adoption of this technique for disease monitoring.

Conclusion

IVLBCL has traditionally been associated with an aggressive course and poor outcomes, mostly due to the vast variations in presentation and natural histology of the disease as noted within our case series. The observed potential for improved outcomes hinges on timely diagnosis and early initiation of systemic therapies when indicated, with consideration for end-organ resection in patients with single organ disease such as thyroid or kidney which can potentially induce remission without the need for systemic therapy. More research is warranted to understand the pathophysiology of this disorder with special focus on the milieu seen in immunosuppressed patients.

Conflicts of Interest

The Authors do not have any interests to declare, financial or otherwise.

Authors' Contributions

Kainat Saleem: Investigation, data curation, writing – original draft and visualization. Azadeh Nasrazadani: Conceptualization, investigation, writing – reviewing and editing. Chaoyuan Kuang: Conceptualization, writing – reviewing and editing. Vanya Jaitly: Investigation and data curation. Jonhan Ho: Investigation and data curation. Anastasios Raptis: Writing – reviewing and editing. Roy Smith: Writing – reviewing and editing. Craig Seaman: Writing – reviewing and editing, and supervision.

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