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Unusual Presentation of Non-Hodgkin's Lymphoma Presenting as Anasarca and Protein-Losing Enteropathy: A Case Report

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Abstract Non-Hodgkin's lymphomas (NHL) manifest in a multitude of presentations dependent on the subtype, aggressiveness, and primary location of the lymphoma. Because of varied clinical presentations, NHL can oftentimes be difficult to diagnose. However, a high index of suspicion and timely diagnosis is critical, especially in the case of aggressive NHL, in order to initiate prompt treatment for the most optimal outcomes. Here we describe the case of a 62 year-old Caucasian male who presented to a new primary care provider for further evaluation of edema, at which time he was found to have evidence of progression to anasarca along with evidence of protein-losing enteropathy. This occurred after initial workup for symptoms had been terminated prematurely by the previous provider with a move toward symptomatic management without establishing a diagnosis due diagnostic challenges of his nonspecific symptoms. The disease course had an insidious onset. By the time adenopathy became apparent and was biopsied, a diagnosis of aggressive and advanced angioimmunoblastic T-cell lymphoma and secondary Epstein-Barr virus (+) B-cell lymphoma was eventually made. This case highlights an uncommon form of aggressive NHL (angioimmunoblastic T-cell lymphoma) presenting insidiously as edema most likely secondary to protein-losing enteropathy. Lymphatic invasion can obstruct drainage leading to intestinal lymphangiectasia, ulceration, and inflammatory exudation of protein causing anasarca. Additional mechanisms postulated in the presentation of edema in NHL include an increase in Tumor Necrosis Factor Alpha and vascular endothelial growth factor. Therefore, it is important to consider the diagnosis of NHL in patients with similar manifestations when workup is otherwise inconclusive. Additionally, this case brings to light the critical role that primary care providers can play in maintaining a high index of suspicion for cancer, continuing to work up patients not responsive to initial therapy in a prompt manner to mitigate any delays in diagnosis.

Keywords: *NHL, anasarca, lymphoma, protein losing enteropathy, edema, primary care*

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1. Background

Non-Hodgkin Lymphomas (NHL) are a heterogeneous group of lymphoproliferative B- and T-cell malignancies. They can manifest in a myriad of presentations dependent on the subtype, aggressiveness, and primary location of the lymphoma. The typical presentation for an aggressive NHL consists of a rapidly growing mass (painless lymphadenopathy) accompanied by "B" symptoms of fever, night sweats, and weight loss, and occasionally tumor lysis syndrome. Other general symptoms may include fatigue, pallor, generalized urticaria, or infection. Less common primary presentations include extranodal NHL (gastrointestinal (GI), soft tissue, nasopharynx, bone, etc.), or lymphoma restricted to the nervous system as seen in primary central nervous system lymphoma [1]. Because of this variation, NHL can oftentimes be difficult to diagnose. However, a high index of suspicion and timely diagnosis is critical, especially in the case of aggressive NHL, in order to initiate prompt treatment for the most optimal outcomes.

2. Case Presentation

The patient in this case was a 62-year-old man who presented to establish care with a large outpatient academic internal medicine practice with a 5-month complaint of edema progressing to anasarca, fatigue, and subjective weakness. He had no prior medical history apart from a benign bladder tumor removed around 25 years ago. He otherwise had been previously regularly physically active

with his busy local business and had not sought routine preventive care/cancer screenings due to being generally healthy. He consumed around 1-2 beers per day, but recently quit in the last few months. Otherwise, he denied use of tobacco products or recreational drug use and did not have any specific occupational exposures. His mother was diagnosed with lung cancer in her late 60s, and he denied any family history of colon, breast, or prostate cancer.

Four months prior to presenting to our clinic, he was initially seen by outside primary care and emergency department for evaluation of mild lower extremity edema. At that time, labs including complete blood count, thyroid-stimulating hormone (TSH), free thyroxine, comprehensive metabolic panel, urinalysis, erythrocyte sedimentation rate, C-reactive protein, brain natriuretic peptide, creatine kinase, and troponins were unremarkable apart from eosinophilia of 2.31×10^9/L (25.4%), thrombocytosis of 495×10^9/L, and mildly decreased total protein of 5.9 g/dL. Due to hematologic abnormalities, he was referred to a hematologist who attributed these abnormal values to a reactive/inflammatory process and ordered additional stool ova and parasite testing as well as rheumatologic labs and myeloproliferative diseases panel, which were not completed. His outside primary care provider (PCP) additionally ordered labs including c1 esterase, complement, human immunodeficiency virus (HIV) antibody, cryoglobulins, and antinuclear antibodies (ANA), which were normal. The patient was then started on Lasix daily for treatment of edema. Due to worsening edema extending to his proximal lower extremities, abdomen, and face, which had not improved with an increased dose of Lasix, he decided to get further evaluation with an internal medicine provider.

At that point, in addition to anasarca, the patient also noted dyspnea on exertion. He reported about a 20-pound weight gain early in the course of his illness, but was at present down to his baseline weight, despite worsening edema. On exam, the patient was noted to have tense swelling of his upper and lower extremities, abdomen, and face with no airway compromise. He had clear lung fields with no evidence of jugular venous distension, and his dyspnea seemed likely secondary to inadequate inspiration related to abdominal swelling. No lymphadenopathy was present.

A transthoracic echocardiogram was completed which ruled out cardiac pathology. Further workup of anasarca at that time included 24-hour urine protein which was marginally elevated with notable deficiencies in vitamin A and D with decreasing protein and albumin levels of 5.2 g/dL and 3.2 g/dL respectively. There was also a notable decrease in serum IgG and low-normal IgA/IgM. An abdominal ultrasound ordered to evaluate for liver pathology leading to hypoalbuminemia showed mild splenomegaly and diffuse hepatic steatosis. Alpha-1-Antitrypsin, Fibrinogen, and Ceruloplasmin were ordered to further evaluate liver pathology, all returning normal. In order to evaluate for autoimmune causes of the patient's anasarca (with the presence of new skin ulceration) Celiac antibodies (anti-endomysial IgA), rheumatoid factor, anti-double stranded DNA, and ANA were ordered, all of which were negative. TSH was repeated to evaluate for any contributory hypothyroidism, and it returned normal.

Given the evidence of possible malabsorption and protein loss, Esophagogastroduodenoscopy (EGD)/colonoscopy was ordered to evaluate for the potential cause of protein-losing enteropathy (PLE). However, prior to completion, the patient returned with new complaints of skin lesions on his arms and legs, swelling and "fullness" in bilateral groins and axilla, and weight loss. Physical exam showed bilateral enlarged axillary lymph nodes and inguinal lymph nodes, as well as multiple indurated pink plaques on his arms and legs (Figure 1). Subsequently, an ultrasound of bilateral axilla was ordered showing benign-appearing lymph nodes. Lymph node biopsy was recommended, which the patient opted to defer until after his upcoming colonoscopy. The patient was also referred to rheumatology for further evaluation of his skin ulcerations. rheumatology's workup for syphilis, plasma cell disorders, mastocytosis, Epstein-Barr virus (EBV), HIV, and sarcoidosis was negative. At this point, there was a growing concern for underlying lymphoma with GI involvement, with plans to move forward with endoscopic biopsies to evaluate further and confirm this suspicion.

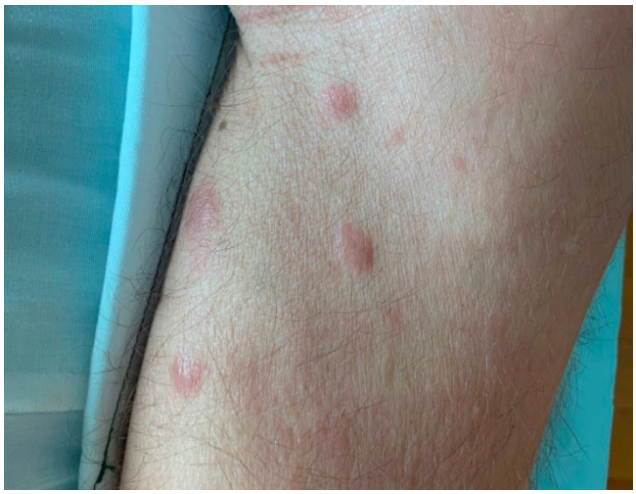

Figure 1. Indurated pink plaques on patient's left leg

Due to anesthesia's concern about the safety of outpatient endoscopy given the patient's anasarca and further deterioration in functional status and nutrition, his PCP directly admitted him for expedited workup. At this point, the patient was having continued weight loss, lymphadenopathy of bilateral axilla and inguinal regions, and a new enlarged left supraclavicular node. He continued to have significant tense edema in bilateral extremities and face, worsening dyspnea, low energy, poor appetite, and discomfort with swallowing. Once admitted, computed tomography (CT) neck, chest, abdomen, and pelvis showed diffuse adenopathy, left-sided pleural effusion as well as a glottic/supraglottic mass (Figure 2). Otolaryngology and GI deferred further evaluation in favor of percutaneous biopsy of superficial axillary lymph nodes by interventional radiology, which showed clonal EBV(+) B cells in a background of immunophenotypically aberrant T cells. Due to concern for angioimmunoblastic T-cell lymphoma (AITL), the case was sent out for expert consultation. Molecular T-cell receptor analysis at this time was oligoclonal, and expert consultation returned as EBV(+) B-cell lymphoma with insufficient material to further classify the aberrant T cells (Figure 3, Figure 4, Figure 5). Punch biopsy of the indurated pink skin plaques revealed diffuse granulomatous dermatitis, favored to represent a reactive process.

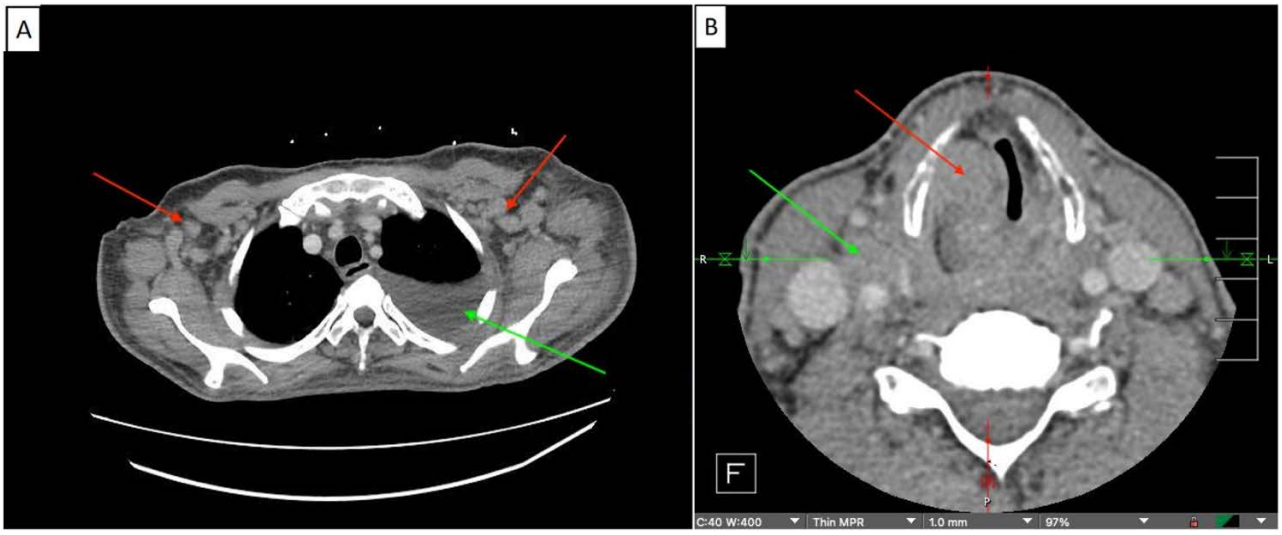

Figure 2. CT chest and abdomen/pelvis with intravenous contrast (A) shows adenopathy, most pronounced in the bilateral axillary regions (red arrows), left side greater than right side, and a moderate left-sided pleural effusion (green arrow). CT larynx/trachea with intravenous contrast (B) shows a 3.6 cm right glottic and supraglottic mass (red arrow) with associated cervical lymphadenopathy (green arrow) bilaterally and mass effect on the airway

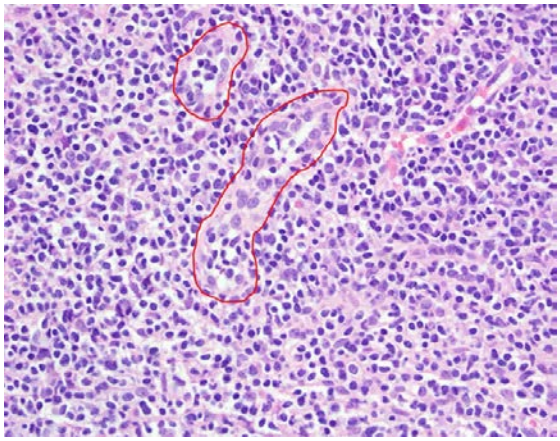

Figure 3. Hematoxylin and Eosin, 400x magnification. The biopsy demonstrates effacement of the nodal architecture, with many small lymphocytes containing abundant, clear cytoplasm, seen here clustering around high endothelial venules (outlined)

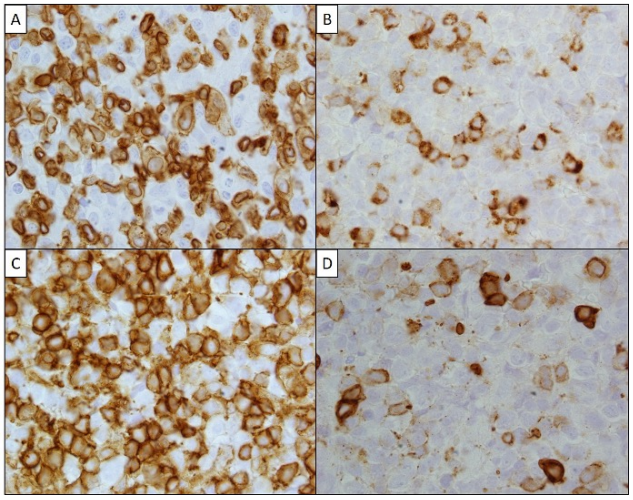

Figure 4. Immunohistochemical stains, 1000x magnification. CD3 immunohistochemical stain (A) demonstrates two populations of T lymphocytes, including small, brightly staining lymphocytes, and large, dimly staining lymphocytes. CD10 immunohistochemical (B) highlights a subset of lymphocytes, consistent with a follicular phenotype. CD4 and CD8 immunohistochemical stains (C and D, respectively) demonstrate a CD4/CD8 ratio of approximately 5:1

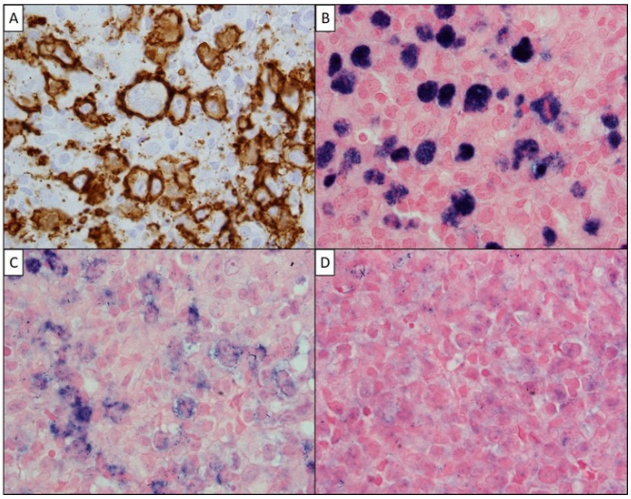

Figure 5. Various stains, 1000x magnification. CD20 immunohistochemical stain (A) highlights many large, atypical B lymphocytes. EBER in situ hybridization (B) demonstrates the presence of many EBV(+) cells, with a similar distribution to CD20. Kappa and lambda in situ hybridization (C and D, respectively) show kappa-restriction within B lymphocytes

One month later, the patient underwent one cycle of rituximab, etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, and doxorubicin hydrochloride (R-EPOCH) and intrathecal methotrexate, which showed radiographic response. However, the patient did not tolerate chemotherapy well and showed continued functional decline, with eventual lymphangitic spread to the lungs. Flow cytometry of the pleural effusion was positive for T-cell lymphoproliferative disorder, with a similar phenotype to those noted in the initial biopsy. Molecular T-cell receptor analysis at this time was monoclonal. Therefore, the overall pathologic and clinical findings were most consistent with advanced AITL with secondary EBV(+) B-cell lymphoma. After subsequent hospitalizations in the coming weeks for failure to thrive, cytomegalovirus viremia and respiratory failure due to recurrent bilateral pleural effusions, the patient ultimately declined further treatment and he passed away in the hospital days later.

3. Discussion/Conclusion

This case highlights an unusual presentation of aggressive NHL (specifically AITL) presenting insidiously as edema secondary to PLE. While it has been described in the literature, anasarca is a relatively uncommon presenting complaint of NHL, and PLE remains a poorly recognized disease process leaving a diagnostic challenge. Our patient's workup showed signs of PLE supported by hypoalbuminemia along with decreased immunoglobulins, low fibrinogen, and deficiency of fat-soluble vitamins A and D. While we were unable to obtain endoscopic biopsy due to concerns of our patient's stability for the procedure, he had CT imaging which demonstrated bulking retroperitoneal lymphadenopathy as well as signs of lymphangitic spread to lungs, similar to what we anticipate would have been found in the gastrointestinal tract.

3.1. Pathophysiology

It is postulated that PLE and anasarca are mediated by several mechanisms including inflammatory exudation, increased mucosal permeability, and intestinal loss of lymphatic fluid. In the case of lymphomas, lymphatic invasion can obstruct drainage leading to intestinal lymphangiectasia, ulceration, and inflammatory exudation of protein, resulting in PLE. In our patient, there was clear significant retroperitoneal lymphadenopathy on imaging with worsening burden of lymphadenopathy correlating with his worsening clinical course and edema. It is also possible for PLE to not only be a manifestation of lymphoma, but the cause itself. Patients with long-standing PLE can lose a significant amount of T cells and immunoglobulins into the gut. This can lead to a prolonged period of immunodeficiency and eventual development of lymphoma [2].

Literature also suggests alternative causes for edema secondary to NHL. One theory suggests that as an increase in Tumor Necrosis Factor Alpha (TNF-α) can be seen in some patients with NHL, this may lead to increased vascular permeability and subsequent anasarca [3]. Other literature points to serum vascular endothelial growth factor (VEGF) secretion from EBV-infected cells as the culprit [4]. Generalized edema is not uncommon in patients with AITL. Because of the immune dysregulation caused by AITL, EBV infection often goes unchecked leading to the potential of a concurrent B-cell neoplasm on top of the T-cell lymphoma. This was the case in our patient given the additional findings on lymph node biopsy of nodal architecture effacement by EBV (+) B-cells in the background of immunophenotypically aberrant T cells. Therefore, it is possible that a combination of the factors above, in addition to a PLE, contributed to his initial presentation.

3.2. Diagnostic Challenges

The diagnosis of AITL was difficult to arrive at in this case. Although generalized edema is not uncommon in AITL, patients usually demonstrate hypergammaglobulinemia, rather than hypogammaglobulinemia as in our patient. Additionally, insufficient tissue was present in the original needle biopsy for definitive classification of the aberrant T cells. While there is clear evidence that large B-cell lymphoma may develop in AITL, its presence in a limited biopsy may represent a diagnostic pitfall. A high index of suspicion is required on both the part of clinicians and pathologists to arrive at the correct diagnosis [5,6].

3.3. Primary Care Perspective

Apart from being an unusual presentation of aggressive NHL, this case also brings to light the critical role that primary care providers can play in the prompt recognition of high-risk and aggressive illnesses such as this one. PCP's are usually the first point of contact for patients who are developing signs and symptoms that may be a result of cancer. They often play the role of "gatekeeper," determining whether referral to specialty providers is warranted, creating the possibility for potential delays in diagnosis. In one clinical audit of cancer diagnosis in general practices in the UK, diagnostic delays occurred in 22% of cases. Patient, clinician, and system factors were deemed responsible for these delays 26%, 28%, and 34% of instances, respectively [7]. In terms of clinician delays, a separate quantitative survey conducted identified time constraints, ease of accessibility to making referrals, and concerns about over-utilizing resources as reasons that factored into diagnostic delays from the clinician's standpoint [8].

Although some of these factors are innate to our healthcare system, maintaining a high index of suspicion for cancer and continuing to work up patients not responsive to initial therapy in a prompt manner can help to mitigate the aforementioned reasons for delays in diagnosis. Unfortunately for the patient in this case, prior to his presentation at our healthcare system, his anasarca was initially treated with a diuretic and no further workup took place until months later. This serves as an important reminder that every patient is owed a thorough workup.

Acknowledgements

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Abbreviations

NHL: Non-Hodgkin's lymphoma
GI: Gastrointestinal
TSH: Thyroid-stimulating hormone
PCP: Primary care provider
HIV: human immunodeficiency virus
ANA: Antinuclear antibodies
EGD: Esophagogastroduodenoscopy
PLE: Protein-losing enteropathy
EBV: Epstein-Barr virus
CT: Computed tomography
AITL: Angioimmunoblastic T-cell lymphoma

R-EPOCH: Rituximab, etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, and doxorubicin hydrochloride

TNF-α: Tumor Necrosis Factor Alpha

VEGF: Vascular endothelial growth factor

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