CLINICAL VIGNETTE

EBV-Positive Diffuse Large B-Cell Lymphoma Presenting as Knee Pain

Alina Katsman, MD

Case Report

An 82-year-old female presented for an initial PCP visit for worsening knee pain. She reports it hurts to bear weight for ten days and feels like it locks up when she takes a few steps. She denies trauma or any constitutional symptoms but feels it might be a little swollen. She has been using diclofenac gel daily for the pain and is interested in physical therapy. Limited unremarkable physical exam was not performed due to video visit. Knee radiographs were ordered and revealed a large lytic lesion in the proximal right tibia without pathologic fracture. There was also severe bilateral patellofemoral osteoarthritis, and possible CPPD arthropathy. Due to the high risk of impending fracture and likely malignancy, she was directed to the ER for additional evaluation. MRI revealed a "large destructive marrow replacing mass in the proximal tibia, with large surrounding soft tissue component. The marrow infiltration extends throughout the proximal and mid tibial shaft to the level of the distal shaft, with adjacent surrounding soft tissue components. Additional large marrow replacing lesion in the left posterior iliac bone, large partially imaged soft tissue mass anterior to the left hemisacrum adjacent to at least the left S1 and L5 nerve roots, as well as partially evaluated marrow infiltrative lesion in the left proximal femoral shaft without obvious cortical defect. Findings are suspicious for lymphoma although metastatic disease/myeloma not excluded." Past medical history includes paroxysmal atrial fibrillation hypothyroidism, HTN, obstructive sleep apnea, Celiac disease, congestive heart failure, and a history of small bowel obstruction s/p colectomy.

The patient was admitted underwent right tibial ORIF. She was evaluated by hematology/oncology and a CT-guided bone biopsy of the right tibia revealed EBV-positive diffuse large B-cell lymphoma (DLBCL). Immunostaining identified large lymphoma cells positive for CD20, PAX5, BCL2, BCL6, cMYC and MUM-1 with a Ki-67 proliferation index of 70%. FISH study showed IGH-BCL2 fusions [t(14;18)] and gains of 3q, 8q, 14q and 18q. There was no MYC or BCL6 gene rearrangement. The patient initially received daily radiation therapy (400 cGy x 5) to the right lower extremity. She then was started on lenalidomide plus Rituximab for 6 monthly cycles. This was followed by maintenance lenalidomide and Tafasitamab plus lenalidomide x 6 completed over 18 months. Two and a half years after initial presentation at age 85, PET CT scan showed no evidence of recurrent lymphoproliferative disease, consistent with ongoing complete response.

Discussion

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma accounting for approximately 25 percent of non-Hodgkin lymphoma cases. Most patients present with an enlarging mass of lymph nodes in the neck or abdomen. One third of patients have "B" symptoms with fever, weight loss, and sweats. Thirty percent have bone marrow involvement and 40 percent have extranodal disease. Tumor cells generally express B-cell antigens (CD19, CD20, CD22, CD79a) and molecular studies can sometimes reveal t(14;18) or abnormal BCL6 but no single finding is typical or diagnostic. The eight are listed below:

(1) T cell/histiocyte-rich large B cell lymphoma;
(2) Primary mediastinal large B cell lymphoma;
(3) Intravascular large B cell lymphoma;
(4) Lymphomatoid granulomatosis, Epstein-Barr virus (EBV)-positive large B cell lymphoma;
(5) EBV-positive DLBCL, not otherwise specified (NOS);
(6) Primary DLBCL of the central nervous system (CNS);
(7) Primary cutaneous DLBCL, leg type;
(8) DLBCL associated with chronic inflammation.

Our patient has sub-type EBV-positive DLBCL, not otherwise specified (NOS), a variant of DLBCL that replaced EBV-positive DLBCL of the elderly in the 2017 WHO classification, since this subtype can occur in patients of any age.[1,2] This clonal B cell lymphoproliferative disorder develops in patients without known immunodeficiency or prior lymphoma and is most common in Asia.[3] It has a more aggressive clinical course with median survival of 2 years in Asian patients.[4] Most patients present with extranodal disease with or without nodal involvement. Sites of primary extranodal involvement include the skin, soft tissue, bones, nasal cavity, pharynx/hypopharynx, tonsils, tongue, lung, pleura, stomach, liver, spleen, peritoneum, cecum, and bone marrow. EBV-positive tumor cells express the immune checkpoint marker PDL-1 and indoleamine 2,3-dioxygenase (IDO), an enzyme that participates in metabolic pathways implicated in induction of immune tolerance. Both may contribute to "escape" of EBV-positive tumor cells from immune surveillance.[5] It has been postulated that EBV-positive DLBCL of the elderly might be caused by the senescence of the immune system as a part of the normal aging process, based largely on shared features with immunodeficiency-associated lymphoproliferative disorders (LPDs).[4]

Treatment generally involves rituximab-based chemotherapy and is aimed at achieving remission and long-term survival, seen in more than two thirds of patients. For patients 80 and older with adequate heart, kidney and liver function and for patients 60 to 80 with modest impairments, the treatment recommend is R-mini-CHOP to reduce adverse effects associated with more intensive regimens. R-mini-CHOP includes rituximab 375 mg/m2, cyclophosphamide 400 mg/m2, doxorubicin 25 mg/m2, vincristine 1 mg on day 1 of each cycle, with 40 mg/m2 prednisone on days 1 to 5. Newer therapeutics including Lenalidomide (Revlimid) and Tafasitamab, which our patient received, are being used in clinical trials with promising results.[6,7]

In summary, diffuse large B cell lymphoma generally presents as lymph node enlargement; however, extranodal involvement is common and needs to be recognized in the clinical setting. Our patient presented with knee pain and an urgent X-ray revealed an unstable lytic lesion necessitating surgery and bone biopsy to confirm the diagnosis.

REFERENCES

1. **Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES**. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016 May 19;127(20):2375-90. doi: 10.1182/blood-2016-01-643569. Epub 2016 Mar 15. PMID: 26980727; PMCID: PMC4874220.
2. **Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, (Eds)**. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition*. Lyon: International Agency for Research on Cancer (IARC); 2017.
3, **Castillo JJ, Beltran BE, Miranda RN, Paydas S, Winer ES, Butera JN**. Epstein-barr virus-positive diffuse large B-cell lymphoma of the elderly: what we know so far. *Oncologist*. 2011;16(1):87-96. doi: 10.1634/theoncologist.2010-0213. Epub 2011 Jan 6. PMID: 21212426; PMCID: PMC3228047.
4. **Ok CY, Papathomas TG, Medeiros LJ, Young KH**. EBV-positive diffuse large B-cell lymphoma of the elderly. *Blood*. 2013 Jul 18;122(3):328-40. doi: 10.1182/blood-2013-03-489708. Epub 2013 May 6. PMID: 23649469; PMCID: PMC3779382.
5. **Adam P, Bonzheim I, Fend F, Quintanilla-Martínez L**. Epstein-Barr virus-positive diffuse large B-cell lymphomas of the elderly. *Adv Anat Pathol*. 2011 Sep;18(5):349-55. doi: 10.1097/PAP.0b013e318229bf08. PMID: 21841405.
6. **Hu P, Ben Y, Liu J, Zheng W, Yan X, Zhang Y, Shi W**. Promising Response to Lenalidomide-Combination Therapy in a Discordant Lymphoma Consisting of EBV-Positive Diffuse Large B-Cell Lymphoma and Angioimmunoblastic T-Cell Lymphoma: A Case Report. *Onco Targets Ther*. 2021 Apr 12;14:2489-2495. doi: 10.2147/OTT.S297539. PMID: 33883903; PMCID: PMC8053605.
7. **Salles G, Duell J, González Barca E, Tournilhac O, Jurczak W, Liberati AM, Nagy Z, Obr A, Gaidano G, André M, Kalakonda N, Dreyling M, Weirather J, Dirnberger-Hertweck M, Ambarkhane S, Fingerle-Rowson G, Maddocks K**. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol*. 2020 Jul;21(7):978-988. doi: 10.1016/S1470-2045(20)30225-4. Epub 2020 Jun 5. PMID: 32511983.