CLINICAL VIGNETTE

Paranasal Sinus Diffuse Large B-Cell Lymphoma with Orbital Involvement

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Introduction

Globally, non-Hodgkin lymphomas (NHL) are the most prevalent form of lymphoid malignancy. Within the oral and maxillofacial regions, NHL ranks as the third most frequent category of malignant tumors. Among these, diffuse large B-cell lymphoma (DLBCL) is the predominant histologic subtype.[1,2] There are two molecularly distinct subtypes of DLBCL—germinal center B-cell (GCB) type and activated B-cell (ABC) type, each with a distinct oncogenic mechanism and differing response to treatment.[2-4] DLBCL can grow aggressively, and within the confined maxillofacial regions, it can quickly lead to compressive symptoms. We describe the diagnosis and initial management of paranasal sinus DLBCL with orbital involvement.

Case Presentation

A 44-year-old male presented with right cheek swelling and decreased right eye movement. He had chronic rhinosinusitis with nasal polyposis, recurrent otitis media, and asthma. He noticed painless swelling and indurated right cheek five months prior which did not respond to antibiotics. Two months later, biopsies raised concern for high grade B cell lymphoma. The biopsies were not definitive given insufficient sampling. Two months later, positron emission tomography-computed tomography (PET/CT) imaging revealed a 4-cm FDG avid mass arising from the right maxillary alveolus extending to the right maxillary sinus, right nasal fossa, and right intraconal intraorbital space with 1-2 bilateral FDG avid indeterminate cervical lymph nodes.

Three days prior to presenting to the ED, he noticed that his right eye was not aligning well with his left, with blurry vision. He denied eye pain and issues with his left eye and denied fever, night sweats, chills, weight loss. He also denied ocular pain, erythema, or discharge, as well as weakness, coordination difficulties, or ataxia. He was concerned about enlargement of the mass, prompting the emergency department visit. Complete ophthalmologic exam was notable for afferent pupillary defect, visual acuity and color deficit, optic nerve edema, and ophthalmoplegia of the right eye. Vital signs and remaining physical exam were unremarkable. Labs included complete blood count (CBC) and comprehensive metabolic panel (CMP) and were within normal limits. CT brain without contrast showed a large, homogeneous infiltrative mass within the right orbit, ethmoid air cells, maxillary sinus and hard palate, with resulting proptosis and destructive changes of multiple bones within the right face. MRI of the orbit with and without contrast confirmed CT findings and noted mass effect displacing the right optic nerve and inferior rectus muscle.

He was urgently evaluated by otolaryngology who performed bedside nasal floor biopsy. Biopsy was consistent with DLBCL, non-germinal center subtype, with gain of MYC/8q. He underwent infection screening, lumbar puncture, transthoracic echocardiography (TTE), and scrotal ultrasound prior to starting rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) treatment. He tolerated cycle 1 of R-CHOP and was given the first dose of filgrastim 24 hours after treatment in the hospital. Patient also started daily allopurinol. On discharge, his visual symptoms had begun to improve.

Discussion

DLBCL of otolaryngologic origin may be difficult to diagnose due to the anatomic complexity of the region. Ideally, DLBCL is best diagnosed with excisional biopsy which allows for detailed morphologic examination by a histopathologist, supported by specialized tests including immunohistochemistry, flow cytometry, fluorescence in situ hybridization (FISH), and molecular testing.[2,5] Core biopsy is the next best option, followed by fine-needle aspiration, both of which often yield insufficient sampling, delaying time to diagnosis, as in the case with this patient.[5] Imaging aids in pinpointing the method and location of biopsy. PET/CT is the favored imaging because it can locate areas of disease with the greatest standardized uptake value (SUV), potentially revealing the most aggressive disease.[5] CBC with differential, CMP, LDH, and uric acid are also included in the evaluation of DLBCL.[6]

Soon after diagnosis, this patient received a series of additional tests and imaging prior to the start of treatment, initiated urgently, as the tumor mass caused optic neuropathy and restrictive strabismus. Other essential testing includes hepatitis B and a TTE. Hepatitis B testing is indicated due to the potential for reactivation when undergoing chemoimmunotherapy (CI).[6] For patients without any identified risk factors, the required tests include HBsAg and core antibody. In patients with risk factors or a prior hepatitis B history, e-antigen test should be added.[6] TTE is indicated prior to the administration of anthracycline-based regimen such as R-CHOP to obtain base-

line left ventricular ejection fraction (LVEF).[3] Troponins and TTE can monitor for early signs of cardiotoxicity prior to heart failure symptoms and asymptomatic drop in LVEF.[7]

Case-specific evaluation for DLBCL includes lumbar puncture and bone marrow biopsy.[6] Relatively few patients (7%) with primary paranasal sinus lymphoma, which is most commonly DLBCL, have central nervous system (CNS) involvement at diagnosis.[8] However, due to the proximity of this patient's tumor to the CNS and the invasive nature of primary paranasal sinus lymphoma, a lumbar puncture was performed to assess for leptomeningeal involvement.[8] Due to the possibility of CNS involvement, a scrotal ultrasound was also obtained to assess for primary testicular lymphoma. This has high propensity for CNS dissemination, likely due to their shared origin from an immune privileged site.[9] The majority of patients with primary paranasal sinus lymphoma have evidence of bone invasion at diagnosis (75%).[8] However, because the patient's CBC parameters were normal, lymphomatous bone marrow involvement was unlikely. PET/CT also has variable sensitivity in detecting bone marrow involvement (60%-94%), providing additional reassurance.[3] Because bone marrow infiltration would not affect the initial management, bone marrow biopsy was not pursued during the admission.

The patient received CI with R-CHOP, the prevailing initial treatment approach with reported curative outcome in 50% to 60% of patients.[5] However, ABC subtype has an inferior outcome to GCB subtype (3-year progression-free survival, approximately 40 to 50%, vs. 75%).[10,11] Once treatment is initiated, prophylactic administration of filgrastim or pegfilgrastim is recommended if risk of febrile neutropenia (FN) from the regimen is ≥20%, or if the risk is 10-20% and the patient has additional FN risk factors.[12] Filgrastim and pegfilgrastim are two forms of granulocyte colony-stimulating factor (G-CSF). Pegfilgrastim is longer-acting and administered only once per chemotherapy cycle. Both have been shown to prevent febrile neutropenia, which is often a dose-limiting toxicity of R-CHOP that prevents maintenance of an effective relative dose intensity (RDI).[12,13] G-CSF should be initiated at least 24 hours after chemotherapy completion, as concurrent administration leads to higher incidence of FN.[14] This is thought to be because initial activation of myeloid progenitor cells enhances their susceptibility to the cytotoxicity of chemotherapy.[14] Otherwise, there is no consensus regarding the optimal timing of prophylactic G-CSF initiation.[12] In addition, tumor lysis syndrome is an oncologic emergency that is more commonly seen in hematologic malignancies including DLBCL, especially upon administration of CI.[15] This patient was at lower risk given nonbulky (<7.5 cm) disease and normal LDH. Therefore, the patient received IV fluid with allopurinol with close monitoring whereas high-risk patients are treated with rasburicase and increased hydration.[15]

Conclusion

Prompt diagnosis of DLBCL is crucial, particularly in cases involving the maxillofacial region, as it can quickly result in compressive symptoms and pose challenges for optimal biopsy due to the complex anatomy. In addition to biopsy and PET/CT imaging for diagnosis, comprehensive evaluation for DLBCL should include laboratory tests: CBC, CMP, LDH, uric acid, and hepatitis B testing, and a TTE. Paranasal sinus DLBCL requires specific consideration for bone marrow and evaluation for CNS infiltration, which may prompt additional testing with lumbar puncture, scrotal ultrasound, and bone marrow biopsy. R-CHOP is the typical first-line treatment for both GCB and ABC subtypes, often accompanied by G-CSF to prevent febrile neutropenia and allopurinol with IV hydration to prevent tumor lysis syndrome.

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