An Atypical Association of Hepatitis C Infection With Extramedullary Marginal Zone Lymphoma

Manisha Jakkidi, Satyajeet Roy

Abstract
Marginal zone lymphomas (MZLs) are an uncommon form of B-cell non-Hodgkin lymphomas (NHLs). They can be further classified into three specific groups depending on the tissue involved: extranodal MZL or mucosa-associated lymphoid tissue (MALT) lymphoma, splenic MZL and nodal MZL. MALT lymphoma is among the most common malignant lymphomas of the ocular adnexa as seen with this case. Infectious agents play a decisive role in the development of these ocular adnexal lymphomas. *Chlamydia psittaci*, HSV1, HSV2, ADV8 and ADV19 are usually linked with these lymphomas. We present a rare case of extranodal MZL of the ocular adnexa with nodal and bone marrow involvement likely due to hepatitis C infection. Hepatitis C infection has been associated with diffuse large cell lymphoma, small lymphocytic lymphoma, splenic and nodal MZL, but to the best of our knowledge, there are very few documented cases of extranodal MZL of the ocular adnexa with hepatitis C infection. The paucity of evidence of this association makes our case rare and also offers a different therapeutic outcome with treatment of hepatitis C infection in conjunction with the traditional chemotherapy.

Keywords: Hepatitis C infection; Ocular adnexal lymphoma

Introduction
Marginal zone lymphomas (MZLs), an uncommon form of B-cell lymphomas, account for a small percentage of non-Hodgkin lymphomas (NHLs). Extramedullary MZLs originate in tissues or organs outside of the lymph nodes and mucosal-associated lymphoid tissue (MALT) lymphoma develops in MALT such as the gastrointestinal tract, lungs and eyes including the orbit. MZL of the MALT type is the most common subtype of the ocular adnexa lymphomas [1, 2]. Infectious agents play a decisive role in the development of ocular adnexal MALT lymphoma. *Chlamydia psittaci*, HSV1, HSV2, ADV8 and ADV19 are usually linked with these lymphomas, an association that varies in different geographical areas [3].

Ocular adnexal lymphomas, composing approximately 1-2% of NHLs and 8% of all extranodal lymphomas are a rare heterogeneous group of malignancies. The most common subtype is the MZL of MALT type. The MALT lymphomas of the ocular adnexa have been associated with certain infections, which can influence the therapeutic outcome. Among these infectious etiologies, *C. psittaci* infection has been extensively studied. Although the association of hepatitis C virus infection is documented with splenic MZL (SMZL) and nodal MZL (NMZL) subtypes of MZLs, nevertheless there is a paucity of evidence of this association with MZL of MALT type in the ocular adnexa. We present a case of ocular adnexal MALT lymphoma presenting with painless progressive proptosis. Hepatitis C infection can have rare associations which are yet to be studied and hepatitis C infection was the potential cause of this B-cell lymphoma. It is important to remember that infectious agents play a critical role in the development of ocular adnexal MALT lymphoma and identification of the infection is critical for the management of these lymphomas.

Case Report
A 68-year-old African American male with history of hypertension and transient ischemic attack in 2011 presented with a 3-week history of right eye swelling and pain associated with eye movement. Patient’s friends and family noticed gradually increasing swelling in his eyelids. He also had blurry vision and diplopia. He had no associated vision loss, redness, floaters or eye trauma. He denied headache, confusion, weakness, fevers or night sweats. He had a 54 pack year smoking history and an unintentional weight loss of 20 pounds in 2 months. He was an active cocaine user. He had no blood transfusions prior to 1980 and no tattoos. He denied alcohol use. He had no personal or family history of malignancy, vasculitis, autoim-
mune or thyroid disease. On exam, his vital signs were within the normal range. Abnormal physical exam findings included marked proptosis of the right eye, painful right eye movements and bilateral eye lid swelling with no congestion or visible discharge (Fig. 1). He also had bilateral non-tender axillary and inguinal lymphadenopathy. A complete blood count with differential revealed a white count of 9.86 (granulocytes 68.2%, lymphocytes 17.8%, monocytes 11.6%, eosinophils 0.6% and basophils 0.9%), hemoglobin of 12 g/dL (reference range 14 - 18 g/dL) and a platelet count of 350,000/mL (reference range 150,000 - 400,000/mL). He tested positive for hepatitis C infection with an elevated viral load, PCR with active virus, 1a genotype, F1-2 fibrosis, and UDS was positive for cocaine. His hepatitis B core IgG antibody testing was positive with a negative surface antigen/antibody and HBV DNA testing. He acquired hepatitis C infection likely from intranasal use of cocaine. CT scan of the head and orbits showed a mass like enlargement of the right superior rectus muscle and mild enlargement of the left superior rectus muscle with resultant proptosis of the right globe (Fig. 2). Additionally, there was abnormal enhancement of the right temporalis muscle which was asymmetrically enlarged and subcutaneous nodules overlying the left temporalis muscle. CT scan of the chest/abdomen and pelvis revealed mediastinal and axillary lymphadenopathy, along with scattered mild lymphadenopathy in the abdomen and pelvis. Subsequent excision biopsy of the right axillary lymph node established the diagnosis of MZL (Fig. 3). Bone marrow biopsy revealed hypercellularity with morphological evidence of involvement with malignant lymphoma (Fig. 4). A tandem flow cytometry study demonstrated a small lambda light chain restricted B-cell population with immunophenotypes: CD5+, CD10-, CD19+, CD20+, and CD22+. His proptosis and blurred vision improved with a 5-day course of prednisone 80 mg daily. He was discharged home with a plan to follow-up with oncology and gastroenterology for initiation of chemotherapy and treatment of hepatitis C infection.
Discussion

Extranodal MZL or the MALT lymphoma is the most common subtype of the MZLs [1]. MALT lymphoma develops in MALT such as the gastrointestinal tract, lungs, salivary glands and eyes including the orbit. The presence of lymphoid infiltrates in sites that are normally without any lymphoid tissue can be explained by long standing antigen stimulation either in the form of an autoimmune disease or a chronic infectious process. Examples include lymphoma of the salivary glands seen in Sjogren’s syndrome, MALT lymphoma of the stomach and its association with Helicobacter pylori. Other infectious agents implicated in the pathogenesis of the extranodal MZL include Helicobacter heilmannii (gastric MALT lymphoma), Campylobacter jejuni (immunoproliferative small intestinal disease), Chlamydia psittaci (orbital MALT lymphoma), and Borrelia burgdorferi (cutaneous MALT lymphoma) [3-6].

There is growing evidence that supports the association of hepatitis C virus with B-cell NHLs. Although various subtypes can be associated with hepatitis C infection, diffuse large B-cell lymphoma, small lymphocytic lymphoma, splenic and nodal MZLs have been commonly associated [1-3]. Extranodal MZLs are not associated with hepatitis C infection. Our case of orbital MZL, a form of extranodal MZL, had an atypical association with hepatitis C infection, which makes the case unique. To the best of our knowledge, there have been very few reported cases of such an association. Hepatitis C virus was the potential cause of the patient’s orbital MZL and this needs to be further validated in future research as it has significant therapeutic implications.

References