Plasmablastic Lymphoma of the Stomach: An Unusual Presentation

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Abstract

Plasmablastic lymphoma (PBL) is listed in the World Health Organization (WHO) classification as a subtype of diffuse large B-cell lymphoma (DLBCL). Some morphologic features of PBL are similar to DLBCL; however, PBL has minimal or no expression of CD20 and leukocyte common antigen. Instead, PBL has been characterized by the plasmablastic morphology of the cancer cells, with high mitotic figures. It is believed to be an aggressive lymphoma. We describe a case of a patient who seemed to pose a diagnostic dilemma, and who was later found to have PBL.

Case Report

A 41-year-old man presented with a 3-week history of left upper quadrant abdominal pain associated with nausea and vomiting. He reported a gradual decrease in his oral intake and a 50-pound weight loss over the past 3 months. There was no history of immunosuppression or steroid use.

Physical examination revealed a firm, palpable mass in the left upper quadrant. It did not move with respiration and it extended towards the umbilicus. His abdomen was otherwise soft, with no guarding or rebound tenderness, and bowel sounds were positive.

Initial laboratory data showed the following: hemoglobin of 12.2 g/dL; hematocrit of 39.2%, with a mean corpuscular volume (MCV) of 86.9 fL; white blood cell (WBC) count of 5,300 cells/mL; and platelet count of 298,000/µL. Liver function tests revealed albumin of 4.2 g/dL; total protein of 7.3 g/dL; total bilirubin of 0.3 mg/dL; alkaline phosphatase of 75 IU/L; alanine transaminase (ALT) of 12 IU/L; aspartate transaminase (AST) of 16 IU/L; and normal serum LDH at 215 IU/L. The hepatitis A, B, and C serology was negative, and Epstein-Barr virus (EBV) testing was not performed. A computed tomography (CT) scan of the abdomen and pelvis showed diffuse marked thickening of the stomach body and fundus with an associated large left adrenal mass (Figure 1).

The patient subsequently underwent an endoscopic biopsy of the stomach, the results of which showed a severe chronic gastritis and nonspecific necrotic debris. However, in view of the history and strong clinical suspicion, a repeat endoscopic ultrasound-guided biopsy, including a fine needle aspiration (FNA) of the adrenal mass via a transgastric approach, was performed. The adrenal biopsy showed necrotic tissue mixed with a group of discohesive cells that were positive for CD45 and CD43, and negative for AE1/3, CD20, CD138, and CD3. The FNA also showed cells staining positive for LCA and CD43, with some cells partially 138-positive. Stains for keratin, MAK-6, CD20, CD3, UCHL-1, CK7, CK20, CD10, cyclin D1, synaptophysin, and chromogranin were negative. The cells stained diffusely for kappa and negative for lambda in situ hybridization. In view of these results, the suspicion for a plasmacytoma was high. However, the stomach biopsy was still inconclusive. During the hospital course, the patient then underwent a bone marrow biopsy and third endoscopic stomach biopsy, all of which did not conclude an appropriate diagnosis.

General surgery was consulted, and a laparoscopic gastric biopsy with wedge excision was performed. Flow cytometric analysis of the gastric wall biopsies revealed aneuploid plasmacytoid cells, which were CD19-positive, CD20-negative, CD138-positive, CD38-positive,
CD56-negative, IgG-positive, and kappa light chain-positive. The Ki67 was not checked. These findings were consistent with plasmablastic lymphoma. Notably, human immunodeficiency virus (HIV) screen was negative. The serum protein electrophoresis (SPEP) revealed a monoclonal spike (0.42 g/dL) in the gamma region, and the serum immunofixation (IFE) showed an IgG kappa monoclonal paraprotein, but the free light chain ratio was a normal 1.05. The patient was started on the following chemotherapy regimen: cyclophosphamide 600 mg/m², doxorubicin 50 mg/m², vincristine 2 mg, with intrathecal methotrexate for central nervous system (CNS) prophylaxis due to the highly aggressive nature of plasmablastic lymphoma, alternating with high-dose methotrexate 1,000 mg/m² and cytarabine 3 g/m² (hyper-CVAD) every 3–4 weeks for a total of 8 cycles. The patient tolerated treatment well and had an excellent response; after 8 cycles of chemotherapy, positron emission tomography (PET)/CT scans, esophagogastroduodenoscopy (EGD), and biopsy of the stomach were negative for any residual disease. Currently, the patient is doing well and has returned to work.

**Discussion**

Initially believed to have a predilection for the jaw or oral mucosa of human immunodeficiency virus (HIV)-infected patients, PBL was later reported in patients with and without HIV. PBL can involve sites other than head and neck, and can have discrete morphologic appearances. The largest case series of about 50 patients was reported by Colomo and associates, who defined PBL as a diffuse large B-cell lymphoma with morphologic and immunophenotypic features indicative of terminal B-cell differentiation and expression of plasma cell-associated markers (CD38 and/or CD138). This series also described a second major category that included cells with more prominent plasmacytoid appearance, which they distinguished as PBL with plasmacytic differentiation. A third variation associated with Castleman’s disease, with nodal and splenic involvement, has also been described. Some morphologic features of PBL are similar to DLBCL; however, PBL has minimal or no expression of CD20 and leukocyte common antigen. Instead, PBL has been characterized by the plasmablastic morphology of
the cancer cells, with high mitotic figures, the expression of plasma cell markers such as Vσ38c and CD138/syndecan-1,\textsuperscript{1,5,12} and EBV-encoded RNA (EBER) positivity.\textsuperscript{13}

Differential diagnoses of these tumors based on a morphologic basis include poorly differentiated carcinoma, anaplastic large cell lymphoma, immunoblastic variant of DLBCL, Burkitt lymphoma, primary effusion lymphomas (PEL), and anaplastic plasmacytoma. Carcinomas can be differentiated from PBLs based on more cluster formation in carcinomas, absent lymphoglandular bodies, increased cell size, and positive immunoreactivity for cytokeratin. It should be noted that CD138 can also be positive in neoplasms of the epithelium.\textsuperscript{14} Anaplastic large cell lymphomas are not immunoreactive for CD38 or CD138;\textsuperscript{46} PBLs are negative for CD20, while immunoblastic variants of DLBCLs are negative for CD138.\textsuperscript{10} In Burkitt lymphoma, CD20 is immunoreactive and CD138 is negative, as opposed to PBLs, which are the opposite.\textsuperscript{10} PEL is a neoplasm that usually presents with serous effusions and without detectable tumor masses.\textsuperscript{15}

It is usually associated with HIV infection and positive for human herpesvirus (HHV)-8.\textsuperscript{15} This peculiar tumor has many immunophenotypic similarities with PBL, such as expression of CD45, CD38, and CD138, while it is negative for CD19, CD20, CD79a, and immunoglobulin expression.\textsuperscript{15} Thus, flow cytometric studies are essential to help confirm the diagnosis.

The most common site of origin of extranodal lymphomas is the stomach.\textsuperscript{16} Most of these are marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT)-type.\textsuperscript{17} They are divided into low-grade and high-grade tumors with a low-grade component. PBL differentiates from high-grade MALT lymphomas in the absence of a low-grade component, as well as any sign of Helicobacter pylori infection diffuse plasmablastic differentiation, and it lacks CD45 and CD20, but has CD38 expression.\textsuperscript{17} De Mascarel and colleagues reported the case of a patient with a gastric large cell lymphoma composed by plasmablasts, which expressed cytokeratin and monotypic IgA but no leukocyte common antigen.\textsuperscript{18} These data suggest that PBL may develop in extranodal locations other than the oral mucosa, and the presence of HIV infection is not necessary.

There is no clear-cut explanation regarding the pathogenesis of PBL. In a study by Delecluse and colleagues, Bcl-2 protein overexpression was found in only a fraction of cases, there was no evidence of Bcl-2 gene rearrangement, and all cases also lacked Bcl-6 expression. They concluded that PBL probably does not arise from the follicular center cells.\textsuperscript{1}

In summary, PBL is a variant of large cell lymphoma with heterogeneous cytologic findings, but distinct immunophenotypic features. PBL is believed to be an aggressive lymphoma. In the original report by Delecluse and coworkers,\textsuperscript{1} 10 of 12 patients with available follow-up died, nearly all within 12 months of diagnosis. Although most of these neoplasms display a fairly good response to initial chemotherapy, this response is transient, and others have also reported such short survival durations.\textsuperscript{10,19,20}

The cytomorphic spectrum of PBL and detection of CD138 expression by flow cytometry can aid in achieving a correct diagnosis.

The rapid rate of proliferation and associated necrosis in this patient’s tumor confounded the initial diagnosis, since it was difficult to obtain viable tissue for analysis and flow cytometry via conventional EGD-guided biopsy. A laparoscopic surgical approach was required, and biopsy of the gastric muscle finally secured tissue for adequate diagnosis. This outcome underscores the necessity of understanding the tumor characteristics and the importance of clinical suspicion in the approach to managing these patients.

References


Review

Plasmablastic Lymphoma of the Stomach

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Discussion

Plasmablastic lymphoma (PBL) is a unique lymphoma, first described by Delecluse and associates as a rare variant of diffuse large B-cell lymphoma (DLBCL) involving the oral cavity. It is associated with human immunodeficiency virus (HIV) and latent Epstein-Barr virus (EBV) infection. PBL is an aggressive form of lymphoma associated with poor survival, usually presenting in the oral cavity with rapid progression to extra oral sites. It has also been known to present in other sites, including the orbits, paranasal sinuses, cervical lymph nodes, lungs, rectum, and extremities. Only a few cases of PBL involving the stomach have been reported. PBL is usually diagnosed in the setting of HIV infection, and is characterized as an AIDS-defining lymphoma. While the most common types of AIDS-associated non-Hodgkin lymphoma (NHL) are Burkitt lymphoma and DLBCL, including immunoblastic lymphoma, other rare types are seen, including human herpesvirus (HHV)-8-positive primary effusion lymphoma (PEL), primary central nervous system lymphoma (PCNSL), and PBL. PBL has also been described in association with other forms of immunosuppression, including autoimmune disorders and advanced age. Recently, cases of PBL have been reported in immunocompetent patients in extraoral locations.

DLBCL with plasmablastic differentiation represents a clinically heterogeneous spectrum with different clinicopathologic characteristics representing distinct entities. Important subtypes include PBL of oral mucosa type, PBL with plasmacytic differentiation, extramedullary plasmablastic plasmacytomas, and plasmablastic myelomas. Differentiation of these discrete disease entities is often very difficult, albeit still important, as it may guide therapeutic recommendations. Morphologically, PBL can vary from a diffuse and cohesive proliferation of cells resembling immunoblasts to cells with plasmacytic differentiation.

Immunophenotypically, the tumor cells characteristically express plasmacytic markers: CD38, CD138, VS38c (p63), MUM-1, and cytoplasmic immunoglobulins. They may have weak to absent expression of mature B-cell markers, such as CD45, CD20, and PAX5. EBV viral association is found in 80% of PBL patients. Remarkably, recent studies have shown a high incidence of MYC deregulation through translocation or amplification of the MYC gene region, suggesting an important role in the pathogenesis of PBL, and possibly accounting for the aggressive nature of this lymphoma. Furthermore, the immunoglobulin (IG) genes were the MYC partners in the majority of examined tumors. A similar genomic rearrangement pattern, involving MYC/IG gene rearrangement, has been implicated in the pathogenesis of multiple myeloma (MM). The cytogenetic features of PBL linking it to aggressive lymphoma and MM may provide insight into the pathophysiology, treatment paradigm, and possible targeted therapies.

Because of the low incidence and prevalence of the disease, no standard recommendations have emerged for the treatment of PBL. Thus, common systemic multidrug chemotherapies used for lymphoma are commonly employed for the treatment of PBL. Examples of reported regimens include: cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexametha-
sone); and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with intrathecal methotrexate.\textsuperscript{20} Rituximab (Rituxan, Genentech/Biogen Idec) is unlikely to play a role in the treatment of PBL because of the lack of CD20 expression on the neoplastic cells. The majority of patients with PBL have a median survival of less than 1 year.\textsuperscript{20} Improvement in outcome has been observed in HIV-infected patients with the combination of highly active antiretroviral therapy (HAART) and lymphoma-specific chemotherapy.\textsuperscript{21} Interestingly, it was reported that immunocompetent patients with PBL actually had a worse prognosis (12 months) compared to HIV-positive patients with PBL (22 months),\textsuperscript{20} supporting aggressive induction chemotherapy and adding to the heterogeneity of the disease. A recently published literature review described 76 cases of HIV-negative PBL based on morphology and minimal immunohistochemical criteria.\textsuperscript{22} The authors reported that this group had a median survival of 9 months and a 2-year survival of 10%, consistent with previous literature reports. Despite a small sample size, achievement of a complete response was significantly correlated with survival. In a single institutional case series, 9 HIV-negative PBL patients were treated with CHOP or hyper-CVAD.\textsuperscript{23} Responses were observed in 8 cases (7 complete, 1 partial). Four patients underwent consolidation with autologous hematopoietic stem cell transplant (HSCT) in first complete remission. At a median follow-up of 23.9 months, 7 patients were alive and 5 patients were disease-free. This study supports aggressive induction chemotherapy and consolidation with autologous HSCT for patients with HIV-negative PBL.

The report by Riaz and colleagues\textsuperscript{24} illustrates an unusual presentation of PBL in a seemingly immunocompetent patient without associated EBV infection. There is a paucity of data to guide the choice of therapy in this case, and the benefit of traditional lymphoma therapies, such as hyper-CVAD, is as reasonable as any other. New advances in the management of both B-cell lymphoma and MM may provide a premise to evolve the treatment paradigm in PBL. Of course, thinking about drugs that may be used to produce guidance for care.

References