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## HIV 음성 환자에서 형질모세포종의 세침흡인 세포소견 - 1예 보고 -

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= Abstract =

### Fine Needle Aspiration Cytology of the Plasmablastic Lymphoma in Human Immunodeficiency Virus (HIV) Negative Patient - A Case Report -

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Plasmablastic lymphoma (PBL) is a recently described aggressive B-cell neoplasm, which usually manifests as a localized disease of the oral mucosa in individuals infected with human immunodeficiency virus (HIV). Recently, we encountered a case of plasmablastic lymphoma manifesting in the left maxillary sinus and cervical lymph node of a previously healthy HIV-negative man, 48 years of age. We conducted a fine-needle aspiration smear of the cervical lymph node, and this was found to be highly cellular with numerous large cells exhibiting eccentrically positioned nuclei, prominent nucleoli, and moderate quantities of basophilic cytoplasm. A biopsy of the mass in the maxillary sinus evidenced diffuse growth of similar plasmablastic cells. These tumor cells were negative for the leukocyte common antigens, CD20, CD3, CD30, and EMA. However, the cells tested positive for CD79a and CD138/syndecan-1. The tumor cells also exhibited L-light-chain restriction. The Ki-67 proliferation index was measured at almost 100%. The patient was diagnosed with plasmablastic lymphoma. After three cycles of combination chemotherapy and radiotherapy, the patient went into complete remission, and currently remains in this state.

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**Key words:** Plasmablastic lymphoma, HIV, Fine needle aspiration cytology

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## INTRODUCTION

Plasmablastic lymphoma (PBL) is a recently described variant of diffuse large B-cell lymphoma (DLBCL), which occurs preferentially in the oral cavities of patients infected with the human immunodeficiency virus (HIV).<sup>1</sup> PBL accounts for 2.6 to 3% of all AIDS-related non-Hodgkin's lymphomas.<sup>2</sup>

Plasmablastic lymphoma was initially described in 1997, by Delecluse et al.<sup>1</sup> The condition is characterized by the presence of large cells which exhibit plasmacytoid differentiation, with one or two prominent central nucleoli. The tumor cells are also characterized by the marked expression of the plasma cell-associated antigens, VS38c or CD138/syndecan-1 and CD79a, as well as the presence of immunoglobulin heavy-chain gene rearrangement and light chain restriction. In plasmablastic lymphoma, a high Ki-67 labelling index is also normally detected. PBL does not typically involve the expression of leukocyte common antigen (LCA), CD19, or CD20. This condition is also frequently associated with a positive result for Epstein-Barr virus (EBV)-encoded RNA (EBER).<sup>1</sup>

Since the initial description of PBL, this entity has been occasionally reported to occur in extra-oral locations, including the stomach and the lung,<sup>3-5</sup> and has also been reported to occur sporadically in HIV-negative individuals.<sup>6,7</sup> The cytological features of this tumor in the lymph node, though, have been described only rarely. In this report, we describe the findings of a fine-needle aspiration (FNA) of a plasmablastic lymphoma occurring in the cervical lymph node of a HIV-negative patient.

## CASE

A 48-year-old man visited our institution with a one-year history of nasal stuffiness and rhinorrhea, and also complained of recent episodes of epistaxis. The patient's previous medical history was unremarkable, except for some gross hematuria due to a renal stone, which had occurred 6 years ago. The patient worked as a taxi driver, and had no prior history of homosexuality or

drug abuse.

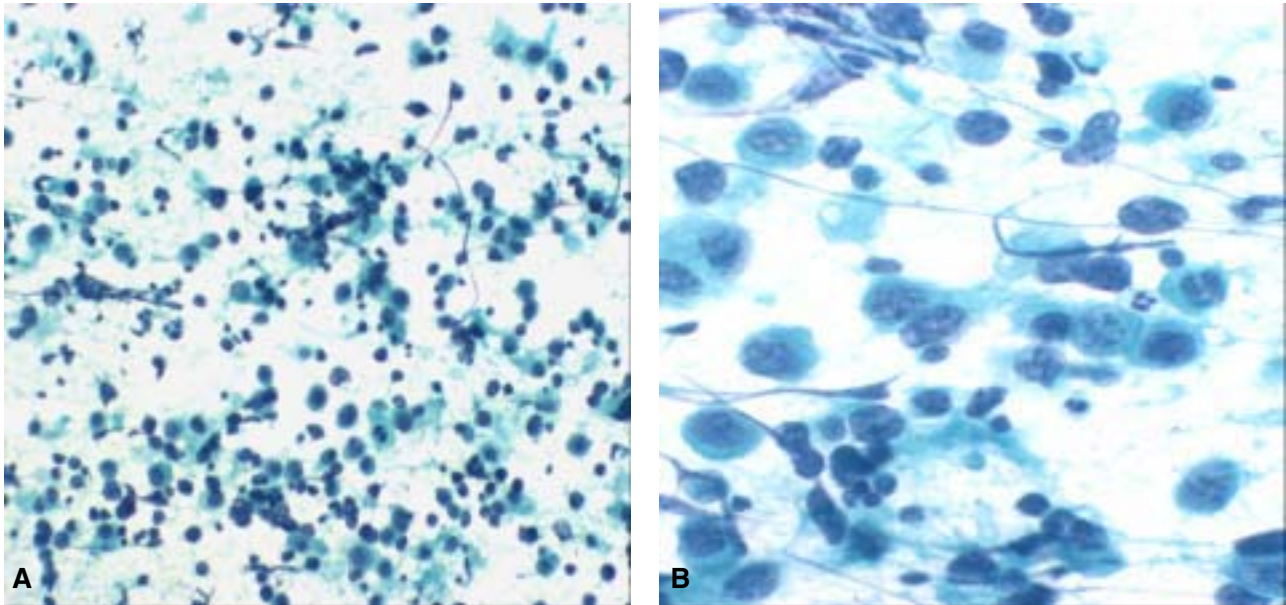
Upon physical examination, the patient was determined to have edematous nasal mucosa, as well as several enlarged cervical lymph nodes. Magnetic resonance imaging (MRI) of the paranasal sinuses revealed an ill-defined, heterogeneous, and enhancing solid mass, which involved the left maxillary sinus, and extended to the anterior and medial walls. On a computed tomography (CT) scan of the neck, we noted multiple enlarged lymph nodes at levels II, III, and IV along the left jugular vein. All laboratory findings were within normal limits. We then conducted a fine needle aspiration biopsy of the cervical node, and a Caldwell-Luc biopsy of the maxillary sinus. On the basis of these results, the patient received a diagnosis of plasmablastic lymphoma. Our extensive stage work-up revealed no evidence of spread. The patient was administered 3 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy, coupled with a radiotherapy regimen. 4 months after the initiation of treatment, the patient exhibited complete remission.

## Cytologic Findings

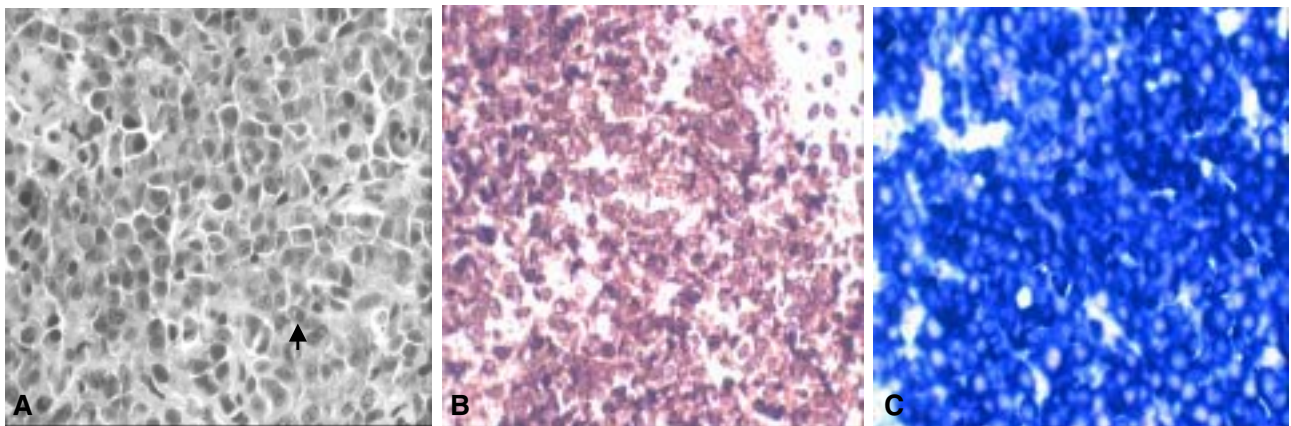
The cervical lymph node smears were very cellular, and featured large atypical cells with plasmacytoid characteristics. The tumor cells themselves were diffusely scattered, and exhibited indistinct cell borders, with variable nuclear to cytoplasmic ratios. The nuclei were oval to round, and were positioned erratically for the most part. They also exhibited a fine chromatin structure, and one or two prominent nucleoli each. The cytoplasm of the tumor cells was found to be dense, basophilic, and of variable amounts (Fig. 1). The cells were sporadically binucleated, and featured paranuclear haloes. Many atypical mitoses were also identified in these cells. In the background, we noted infrequent lymphoglandular and apoptotic bodies, as well as small quantities of mature plasma cells, benign lymphocytes, and neutrophils.

## Histologic Findings

The incisional biopsy specimen of the maxillary sinus



**Fig. 1.** Cytologic findings of plasmablastic lymphoma. (A) There are diffusely scattered large atypical cells with small mature lymphocytes. (Papanicolaou) (B) Tumor cells have eccentric nuclei with one or two prominent nucleoli and fine chromatin, and abundant cytoplasm. Occasionally, binucleated cells are present. (Papanicolaou)



**Fig. 2.** Histologic findings of plasmablastic lymphoma. (A) Tumor shows highly cellular sheet of large atypical cells with prominent nucleoli, admixed with mature plasma cells (arrowhead). (B) Tumor cells are strongly positive in a diffuse fashion for CD138. (C) In situ hybridization for lambda light chain mRNA is strongly positive in tumor cells.

revealed morphologic features comparable to those of the prior FNA of the cervical lymph node, including large plasmablastic cells which contained one or two medium-sized nucleoli and paranuclear hofs, mature plasma cells, and atypical mitoses. We also noted confluent necrotic regions. The tumor cells were wholly negative for LCA, CD20, and CD3, and were strongly positive for CD138/syndecan-1, and weakly positive for CD79a. We determined that the cells were not immunoreactive to

CD43, CD10, CD30, EMA, BCL-6, or IgG heavy chain. The Ki-67 proliferation index was almost 100%. In situ hybridization for lambda and kappa light chain mRNA revealed some lambda light chain restriction (Fig. 2). In situ hybridization for EBV using the EBER-1 probe resulted in the labeling of virtually every nucleus in every tumor cell. We conducted PCR, but did not detect any HHV-8 genome in the tumor tissues. Protein electrophoresis and immunoelectrophoresis, conducted on

both serum and urine, revealed no monoclonal proteins.

## DISCUSSION

In 1997, Delecluse *et al.* reported a highly malignant DLBCL variant, which was characterized by plasmacytoid differentiation and a unique immunological phenotype. This DLBCL variant was first reported to occur in the oral cavities of 15 HIV-positive patients, and also in one elderly (HIV-) patient.<sup>1</sup> At the time of presentation, the lesions tended to be localized within the oral cavity, although extraoral dissemination, once it began to occur, was both rapid and relentless in general. Serum monoclonal immunoglobulin was not detected in any of these patients. Delecluse *et al.* referred to these tumors as plasmablastic lymphomas (PBL), on the basis of their immunoblastic histology and their plasma cell-like immunophenotypes; this appellation was also predicated on the following factors: negative reaction for CD45, CD20, and bcl-6, frequent reaction to CD79a, strong reaction to CD38, and the presence of intracytoplasmic immunoglobulin G or light chains. Since its initial discovery, PBL has been described in a host of reports. In many of these reports, the PBL manifests in extra-oral locations, including the lung, stomach, anorectal regions, skin, soft tissue, bone marrow, nasal cavity, paranasal sinuses, central nervous system, orbits, eyelids, testes, or lymph nodes.<sup>3-5</sup> The occurrence of this condition in HIV-negative individuals has also been reported, particularly in transplant patients receiving immunosuppressive or steroid therapy.<sup>3-7</sup> In some cases, no obvious causes of immunosuppression, other than old age, can be identified.<sup>1,8</sup>

Recently, in a review of a large series of DLBCL exhibiting plasmablastic differentiation, Colomo *et al.*<sup>8</sup> observed large that the B-cell lymphomas evidencing plasmablastic features--the so-called PBLs--constituted a heterogeneous group, and were composed of several distinct subgroups. In that study, the PBL subtypes were designated as the following: PBL of oral mucosa type, PBL with plasmacytic differentiation, and extramedullary plasmablastic tumors associated with plasma cell neo-

plasms, *et cetera*. PBL of the oral mucosa type was characterized by the presence of large lymphoid cells with immunoblastic features. The nuclei in this case were generally ovoid, with open chromatin and prominent central nuclei. The cytoplasm was generally abundant and basophilic, exhibiting occasional paranuclear hofs. This neoplasm also manifested a plasma cell immunophenotypic profile, and was associated with higher rates of immunosuppression (HIV+ in 87%), EBV positivity (74%), and extranodal manifestation (oral in 48%, other extranodal sites in 39%, and nodal in 13%). However, PBL with plasmacytic differentiation contained mature plasma cells, in addition to plasmablasts and immunoblasts. The plasmablasts could be readily differentiated from the immunoblasts by virtue of their more rounded nuclei, coarser chromatin, and smaller nucleoli. Occasional binucleate cells with characteristic cartwheel configurations of chromatin were also identified in this type. This lesion was associated with lower immunosuppression (HIV+ in 38%), EBV positivity (62%), and extranodal presentation (56%) rates than were seen with the oral mucosal PBL subtype. In the current case, we noted some binucleated atypical cells and mature plasma cells, in addition to the presence of immunoblasts and plasmablasts. The third group in the same study was referred to as secondary extramedullary plasmablastic tumors associated with plasma cell neoplasms. However, morphologically, the cells in this group were identical to the cells termed "PBL with plasmacytic differentiation". In the current case, we identified no plasma cell neoplasms, such as multiple myeloma. Therefore, the current case appears to fall into the category of plasmablastic lymphoma with plasmacytic differentiation, on the basis of both morphology and clinical manifestation.

According to the report of Stewart *et al.*,<sup>9</sup> the differential diagnosis of a neoplasm comprised exclusively of large cells exhibiting plasmablastic differentiation can include the following: immunoblastic diffuse large cell lymphoma, anaplastic plasmacytoma/ plasma cell myeloma, and plasmablastoma. The clinical presentation as well as the immunophenotypical features of the constituent tumor cells may prove helpful with regard to the rendering of an accurate diagnosis, as can the labora-

tory findings. Unlike plasmablastic lymphoma, which is normally CD20 negative, diffuse large cell lymphoma of the immunoblastic type is one of the most frequently encountered AIDS-defining high-grade lymphomas, most of which are either systemic in distribution or restricted to the CNS.<sup>10</sup> These tumors invariably exhibit CD45 and CD20 expression, with kappa or lambda light chain restriction, an immunophenotype which is clearly unlike that of the plasmablastic tumor.

The differentiation of plasmablastic lymphoma from anaplastic plasmacytoma on the basis of morphology alone is a difficult proposition. Anaplastic plasmacytoma cells may have more abundant cytoplasm, more eccentrically located nuclei, and more binucleation or multinucleation than PL, and may also occasionally exhibit a higher proportion of mature plasma cells. AP cells also tend to exhibit much lower Ki-67 labelling indices and stronger cytoplasmic kappa or lambda staining than are observed in PL cells. Both plasmablastic lymphoma and plasma-cell malignancies may be associated with signs of EBV infection, although this association appears to be much more pronounced in the former than in the latter.<sup>10</sup> Therefore, evidence of EBV positivity does not constitute a great help in the definitive diagnosis of a plasmablastic neoplasm. In addition, bone marrow involvement and serum monoclonal protein are both common findings in cases of anaplastic plasmacytoma. In the current case, although we detected both mature plasma cells and binucleated cells, the clinical findings, including the absence of serum monoclonal protein and the lack of bone marrow involvement, as well as the pathologic findings, most notably the high Ki-67 labelling index, appear to favor a diagnosis of PBL with plasmacytic differentiation, rather than anaplastic plasmacytoma.

PBLs are also commonly confused with plasmacytomas, with which they share a similar immunoprofile. However, plasmacytoma is composed principally of mature plasma cells with condensed chromatin and inconspicuous nucleoli. In addition, a plasmacytoma would be unlikely to exhibit an extremely high proliferation index, and would also not normally manifest numerous mitotic figures, or an absence of serum monoclonal protein and

bone marrow involvement.

The current case represents a rare manifestation of PBL emerging in the maxillary sinus and cervical lymph node of an HIV-negative patient with no identifiable cause for immunosuppression. In this case, the PBL assumed an immunoblastic appearance, with a typical plasmablastic phenotype, a very high Ki-67 labelling index, and EBV positivity, all of which were determined in virtually all of the tumor cells.

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