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Hematolymphoid neoplasms with a plasma cell phenotype

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Introduction

This article reviews the histopathologic and clinical features of pulmonary hematolymphoid neoplasms with a plasma cell phenotype. This topic includes entities under the umbrella of plasma cell neoplasms, namely, extraosseous plasmacytoma and light chain amyloidosis, as well as a few subtypes of large B-cell lymphomas. Small B-cell lymphomas with plasmacytic differentiation, such as marginal zone lymphoma, will be discussed separately.

The plasma cell neoplasms reviewed in this article encompass plasma cell myeloma, characterized by the identification of mature clonal plasma cells, and light chain amyloidosis, characterized by the deposition of clonal immunoglobulin as amyloid protein.

The types of large B-cell lymphoma discussed in this article are those derived from a B-cell that has turned on the expression of plasma cell proteins, namely, plasmablastic lymphoma and primary effusion lymphoma (including the "extracavitary" variant). These are rare and aggressive types of large B-cell lymphomas that occur in the setting of immunosuppression. The entities in this category are characterized by the proliferation of plasmablasts (large immunoblastic cells with plasma cell phenotype), frequently in association with demonstrable Epstein Barr virus (EBV) and/or Human Herpes virus 8 (HHV-8) infections.

Extraosseous plasmacytoma

Extraosseous (or extramedullary) plasmacytomas are a subtype of plasma cell neoplasm defined by the identification of clonal plasma cells identified in sites other than bone marrow or bone. The lungs, specifically, the upper respiratory airways are commonly involved, followed by head and neck, the gastrointestinal tract, lymph nodes and other solid organs. [1,2]

Pulmonary involvement by extraosseous plasmacytoma (PEP) can occur as a secondary spread in a patient with known marrow-based plasma cell myeloma. [3] PEP may also arise primarily in the lungs, in patients who do not meet the criteria for plasma cell myeloma. Cases confined to the lungs may later spread secondarily to involve regional lymph nodes.

The majority of reported patients with PEP presented with a solitary mass. [1] However, patients with bilateral masses or multiple infiltrative lesions or consolidations, either parenchymal or peribronchial, have also been reported. [1] The patients tend to present with symptoms related to the mass, especially when there is associated compression of the airways. The demographic distribution of PEP differs from that of plasma cell myeloma in that the patients tend to be younger (median 52 years for PEP, versus 70 years for plasma cell myeloma). There is also equal gender distribution in PEP, whereas there is a trend towards a male predominance in plasma cell myeloma. [4] When a small paraprotein is identified (approximately 20% of cases), it is more likely to be of IgA type than osseous plasmacytomas. [4]

Aside from the distinct clinical presentation, PEP is otherwise similar to their bone marrow counterparts in terms of their histopathologic and immunophenotypic features. A targeted biopsy will typically show sheets of mature-appearing plasma cells (Fig. 1) that are light chain restricted by immunophenotyping or in situ hybridization and display the plasma cell phenotype (CD138+, CD38 bright +, vs38+, PAX5 -, MUM1 +). Phenotypic aberrancies, when identified, are similar to those seen in plasma cell myeloma (CD19-, CD56+). However, some phenotypic, morphologic and genetic differences from plasma cell myeloma have been reported.[4] Specifically, PEP is less likely to display a plasmablastic morphology and MYC rearrangements, and is less likely to be positive for cyclin D1 or CD20. [5] The expression of CD56 in PEP is typically weak by immunohistochemistry. [5]

The morphologic differential diagnosis includes reactive and neoplastic processes with a predominance of mature plasma cells. Among the reactive or inflammatory disorders, pulmonary nodular lymphoid hyperplasia and IgG4-related disease are considerations.[6] Utilization of multiparameter flow cytometry, immunohistochemistry or in situ hybridization studies to evaluate kappa and lambda immunoglobulin light chains can easily determine the clonal neoplastic nature of PEP.

It may be more challenging to distinguish PEP from MALT lymphoma with extensive plasmacytic differentiation.[7] The presence of plasmacytoid cells expressing CD20, and the presence of an associated lymphocytic infiltrate would favor the diagnosis of lymphoma. Flow cytometry is helpful in establishing the clonal relationship between plasma cells and B-lymphocytes in lymphoma, in which case both populations share the same light chain restriction. In lymphomas with plasmacytic differentiation, the clonal plasma cells are also more likely

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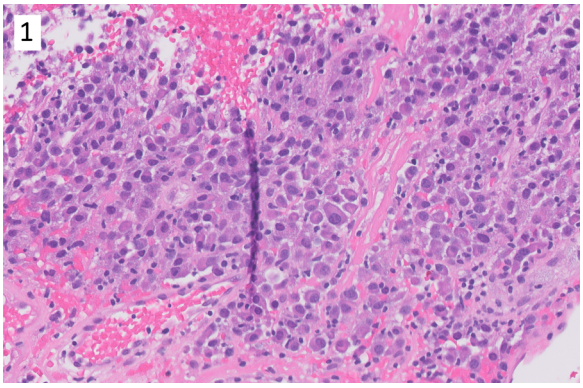


Fig. 1. Plasmacytoma: Cluster of mature-appearing plasma cells with slight cytologic atypia (H&E, 40x).

to express CD19, while in the plasmacytoma counterpart the plasma cells are almost always CD19-negative. [8] The expression of CD45 is also reported to be more frequent in lymphoma than in myeloma. [7]

The prognosis of PEP is generally better than that of plasma cell myeloma. Excision may be curative, although recurrences may occur. [7] The majority of patients remain disease free at 10 years, [7] while a minor subset of patients may progress to meet the criteria for plasma cell myeloma. [7] The risk of progression increases upon identification of minimal bone marrow involvement by a plasma cell neoplasm. [9]

Amyloidosis

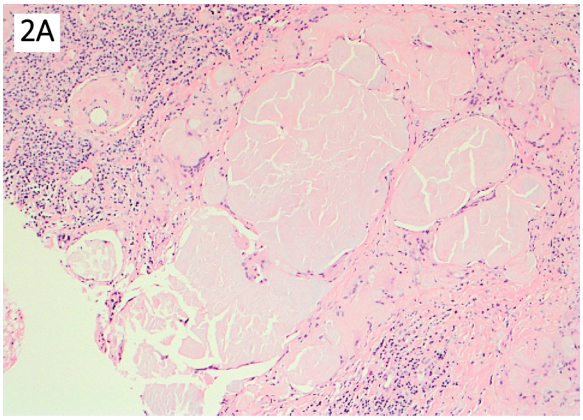
Amyloidosis is defined by the deposition of protein with the beta-pleated sheet structure configuration characteristic of amyloid. In primary amyloidosis, the amyloid protein is an abnormal immunoglobulin produced by neoplastic plasma cells or lymphoplasmacytic cells. Amyloid formation is more likely to occur with lambda light chain than with kappa light chain or heavy chain paraprotein. [7]

The symptoms of the disease occur due to tissue deposition of the amyloid protein and may be serious and debilitating, in spite of a small, sometimes undetectable level of clonal plasma cells. The most frequent sites of amyloid deposition include subcutaneous fat, kidneys, heart, liver, GI tract, peripheral nerves and bone marrow. Lung involvement has been reported infrequently. [10]

In the lungs, amyloid deposition is thought to be relatively common, albeit rarely symptomatic, thus most likely to be identified incidentally or in autopsies. [10] The diagnosis is made with the identification of Congo red positive deposits that show the characteristic apple-green birefringence under polarized light.[10] In small deposits, a high index of suspicion is needed for the diagnosis, and interpretation of Congo red stain may be difficult. Amyloid subtyping with mass spectrometry is recommended to confirm the subtype of amyloid (light chain versus others), which is crucial to determine the appropriate therapy. [10,11]

Although immunohistochemistry is an alternative for determining the amyloid subtype, mass spectrometry is overall superior. Pulmonary amyloidosis can be subdivided into three different categories according to its histologic pattern (1) diffuse alveolar septal amyloidosis, (2) nodular parenchymal amyloidosis, and (3) tracheobronchial amyloidosis.[10]

In the diffuse alveolar-septal amyloidosis, also known as diffuse parenchymal amyloidosis, amyloid deposits are identified within the alveolar septa and vessel walls. This pattern occurs more often as a manifestation of systemic AL amyloidosis, although other types of amyloidosis may rarely present with this pattern. [12-14] Sections of the lung show a diffuse thickening of the alveolar septa and vessels with amorphous eosinophilic amyloid deposits without architectural distortion of the lungs. Given that amyloid resembles collagen, these cases may be mistaken for a fibrosing type of interstitial pneumonia.



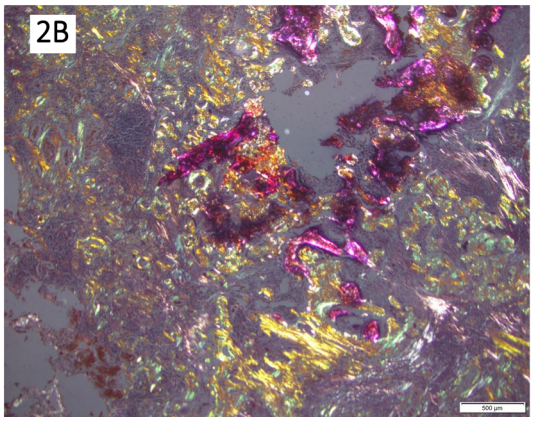


Fig. 2. Nodular amyloidoma: amyloid deposition appears as eosinophilic amorphous material (2a, H&E stain, 10x) and displays the characteristic apple green birefringence using polarized light on a Congo red-stained section (2B, Cong red stain, 10x).

Identification of vascular deposits help to raise suspicion for amyloidosis.[10]

Nodular pulmonary amyloidosis (or nodular amyloidoma) is defined by the presence of at least one mass-forming amyloid deposit in the lung parenchyma (Fig. 2). The deposits are grossly visible well-circumscribed nodules measuring usually 0.4 to 5 cm in greatest dimension. [15] This pattern is usually seen in localized types of amyloidosis, although sometimes seen in the setting of systemic AL amyloidosis. [10] It can be also seen in the setting of an underlying lymphoproliferative disorder with plasmacytic differentiation such as extranodal marginal zone lymphoma of mucosa-associated. Histologically, the nodules are composed of Congo red positive amorphous eosinophilic material. At the periphery of the nodules usually scant infiltrate of lymphocytes or plasma cells may be seen. In cases associated with a B-cell lymphoproliferative disorder, the B-cell component may be only identified using sensitive clonality studies. [16-18] The differential diagnosis includes pulmonary hyalinizing granuloma and light chain deposition disease, which may show amyloid-like deposition. [19] However, the nodules in pulmonary hyalinizing granuloma are composed of thick distinct collagen bundles, and not of the amorphous eosinophilic material seen in amyloidosis. In light chain deposition disease, a Congo red stain will be negative allowing for the distinction from light chain amyloidosis.

Tracheobronchial amyloidosis is the least common type of pulmonary amyloidosis. It shows deposition of amyloid within the trachea and proximal mid and distal bronchial airways. The majority of cases are systemic AL amyloidosis. The biopsy demonstrates thickening of the tracheobronchial walls with submucosal deposits surrounding glands and cartilage, often with associated narrowing of the lumen.[10]

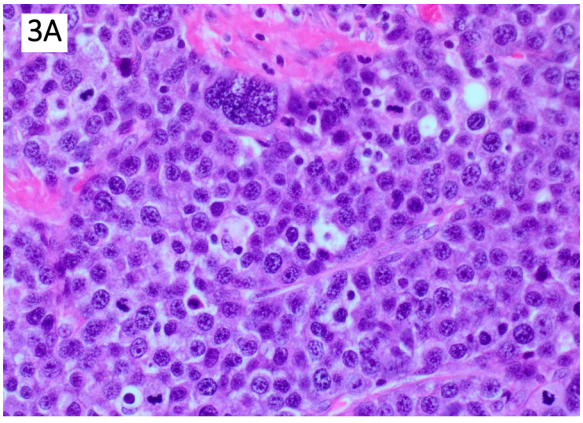
Plasmablastic lymphoma (PBL)

Plasmablastic lymphoma (PBL) is a type of large B-cell lymphoma in which the neoplastic cells display a plasma cell phenotype. This type of lymphoma arises typically in association with Epstein Barr virus (EBV) infection in immunosuppressed individuals, particularly those with advanced Acquired Immunodeficiency Syndrome (AIDS).[20] Cases occurring in HIV-negative patients appear to show different clinical and prognostic features.[21] PBL is an aggressive disease, with poor response to therapy and short overall survival (<1 year).[22]

The lymphoma presents more frequently as an extranodal mass, preferably at mucosal sites. Isolated nodal involvement is unusual. [23] The head and neck region, specifically the oral cavity, followed by the gastrointestinal tract are the most frequently involved sites. However, PBL can arise in any extranodal location. [23] Lung involvement appears to occur more often in association with involvement of other sites.[23] Isolated lung involvement appears to be rare. [24] In the rare cases reported primarily in the lungs, the patients presented with 1–2 enlarging parenchymal nodules. [24,25]

A microscopic evaluation of PBL shows a diffuse infiltrate of large cells with plasmablastic features, defined as central to slightly off-center large nuclei, vesicular chromatin, prominent nucleoli, and moderate amount of slightly basophilic cytoplasm (Fig. 3). In some cases, the large cells are seen admixed with smaller plasmacytoid cells [23, 25]

PBL shows a plasma cell phenotype characterized by the positive expression of CD138, CD38, IRF4/MUM1, Blimp1, VS38c, and cytoplasmic immunoglobulins, without CD19, CD20, PAX5 and surface immunoglobulins. The expression CD43, CD79a, and CD117 is variable, and CD45, CD27, or CD81 are either negative or diminished. [23, 26-29] The markers CD30 and EMA are positive in most cases, CD10 and CD56 in a minority of cases, and bcl2, bcl6 and cyclin D1 are consistently absent.[23] Ki-67 proliferation rate is typically high, at greater than 90%.[23] Aberrant expression of T-cell markers and keratin has been reported in multiple studies and may represent a diagnostic pitfall. [20, 22, 23, 29-33]



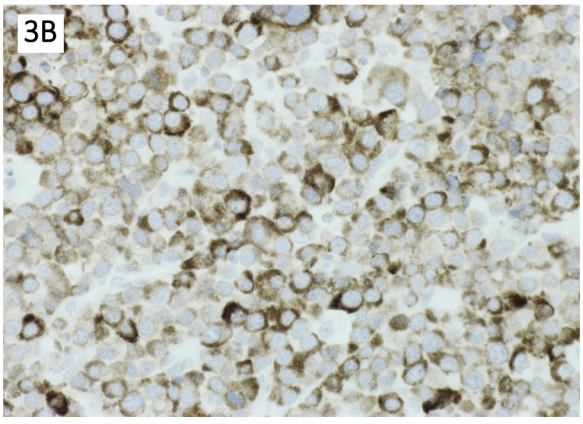
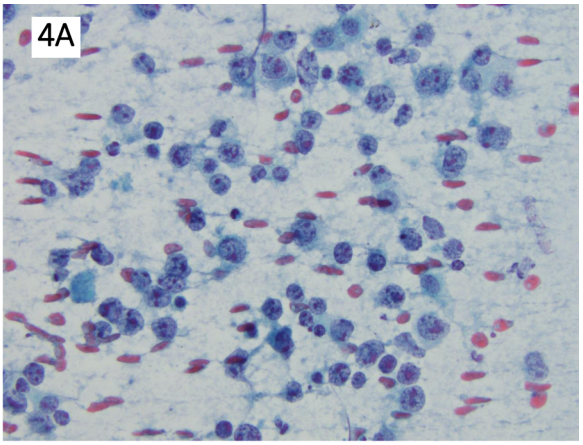


Fig. 3. Plasmablastic lymphoma: sheets of large plasmacytoid cells with immunoblastic cytology (large nuclei and prominent nucleoli) (3A, H&E, 40x). The cells are positive for one or more plasma cells markers (3B, VS38 immunostain, 40x) and are negative for B-cell markers such as PAX-5 and CD20.



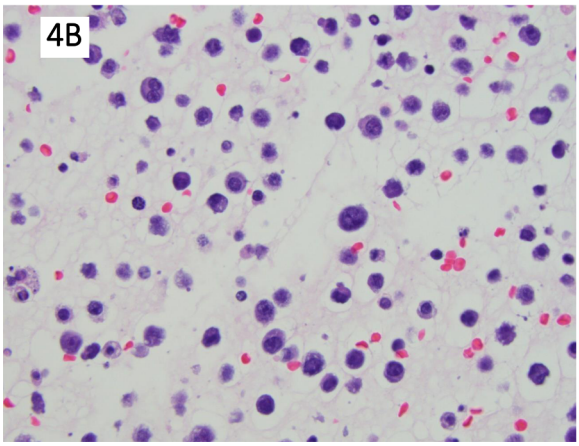


Fig. 4. Primary effusion lymphoma in pleural fluid: The variably-sized tumor cells in the cytospin (4A, pap stain, 100x oil) and cell block (4B, HE, 100x oil) are atypical, showing large nuclei and prominent nucleoli. Few cells display plasmacytoid cytology, with slightly off center nuclei and more abundant cytoplasm.

The frequent EBV association can be identified with EBV-encoded RNA in situ hybridization (EBER); however, PBL is usually negative for EBV-LMP.[23] Cases without association with EBV account for 14–28% of cases and tends to occur more frequently in HIV-negative patients. [22,23,34-36]

At least 50% of plasmablastic lymphomas harbor *MYC* gene rearrangements by FISH, with the partner being in most cases the IgH gene.[20,23,37] Rearrangements of MYC with BCL2 and BCL6 are not seen.[20, 38]

The differential diagnosis includes other EBV-associated diffuse large B cell lymphomas, other large B-cell lymphomas with plasma cell phenotype (e.g., primary effusion lymphoma), and plasmablastic myeloma. PBL is by definition negative for HHV8 distinguishing it from primary effusion lymphoma and negative for ALK distinguishing it from ALK positive diffuse large B-cell lymphoma. [23] Strong expression of CD20 and PAX5 warrants the classification of diffuse large B-cell lymphoma, rather than PBL. [23] The distinction from plasmablastic types of myeloma or EBV-positive plasmacytoma may be problematic when no clinical history is available. [23, 26] A positive EBV study in the

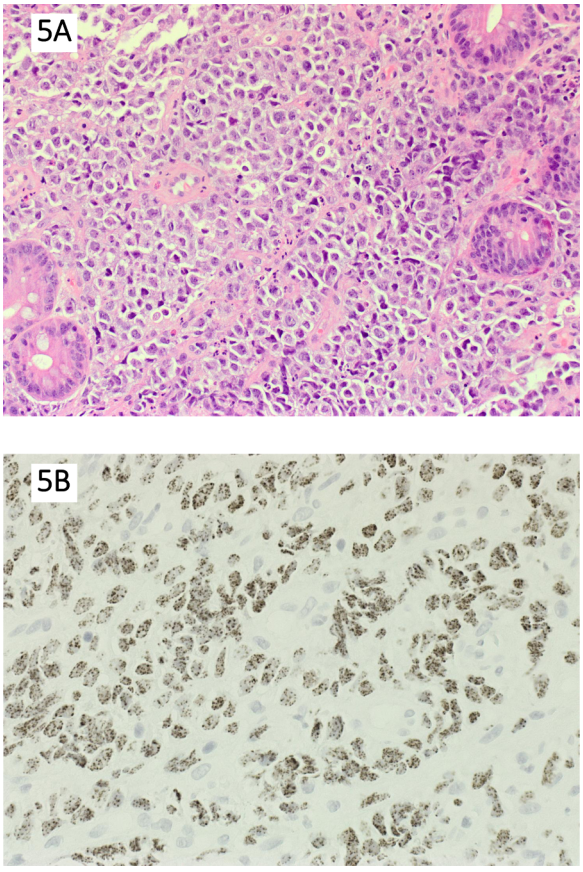


Fig. 5. Extracavitary variant of primary effusion lymphoma: Sheets of large cells infiltrate the colonic mucosa (5A, HE, 20x). The tumor cells are positive for HHV8 (5B, HHV8 immunostain, 40x) and Epstein Barr virus by in situ hybridization.

appropriate clinical setting of immunosuppression helps to distinguish PBL and plasmablastic myeloma; however, cases of EBV-positive plasmacytoma/myeloma have been recently described in immunocompetent, further complicating the distinction of between lymphoma and myeloma when history is unknown. [39] The differential diagnosis in cases that are negative for CD45 also includes non-hematopoietic malignancies such as mesothelioma, melanoma or carcinoma.

Primary effusion lymphoma (PEL)

Primary effusion lymphoma (PEL) is a rare, aggressive type of large B-cell lymphoma with plasma cell phenotype defined by its association with Human Herpesvirus-8(HHV8) and EBV co-infection. It is most frequently seen in patients with advanced Acquired Immunodeficiency Syndrome (AIDS) or in otherwise immunosuppressed patients in HHV8-endemic areas. [40-43]

PEL presents as recurrent malignant effusions in the pleural, pericardial, or abdominal cavities. The symptoms vary according to the site of involvement and size of the effusion. In cases involving the pleural cavity, the most common presentation is shortness of breath leading to the radiologic identification of unilateral pleural effusion.[40]

Although typical cases are confined to the pleural cavity, cases with an associated extracavitary masses have been reported. [43-45] Rarely, the lymphoma presents with extranodal or nodal disease without pleural involvement and are termed “extracavitary primary effusion lymphoma”. [39, 46]

The morphologic features of PEL are also similar to PBL, with sheets of large cells with immunoblastic cytology and plasma cell phenotype (Fig. 4). Some cases may show prominent pleomorphism with RS-like cells.[46, 47] The co-identification of HHV8 (LANA1) using immunohistochemistry and EBV with in situ hybridization allow for the appropriate classification of most cases. As such, obtaining an adequate cell block for HHV8 and EBV testing is needed. Similar to PBL, the neoplastic cells of PEL are usually positive for plasma cell markers CD138, CD38, vs38, MUM-1, without expression of surface immunoglobulin and B-cell markers CD19, CD20, CD22, CD79a and PAX-5.[46] There is often expression of activation markers such as CD30 and HLA-DR.. [46] The extracavitary variant of PEL is more likely to express B-cell markers. [46] Similarly to PBL, there have been reports of PEL cases expressing T-cell markers, particularly, CD2, CD3, CD4, and/or CD5. [47–49] Unlike PBL, PEL is not associated with structural abnormalities of the *c-MYC* gene. [50] The extracavitary variants of PEL are morphologically and phenotypically similar to the cavitary counterpart (Fig. 5). However, Extracavitary PEL is more likely to show partial expression of B-cell markers CD20, PAX-5 or surface immunoglobulins.[43,51,52]

The differential diagnosis includes other EBV-positive or HHV8 positive B-cell lymphomas, and in cases with more anaplastic morphology, classic Hodgkin lymphoma and anaplastic large cell lymphoma. However, unlike classical Hodgkin lymphoma, anaplastic forms of PEL are usually positive for CD45 and negative for CD15.[43] In the difficult cases such as PEL cases expressing multiple T-cell markers including CD3, CD4 and/or CD5, in situ hybridization for kappa and lambda light chains and the molecular studies for IgH and TCR rearrangements are helpful in determining the B- cell lineage of the neoplastic cells.

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