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Review article

Mimickers of pulmonary lymphoma

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ABSTRACT

There are multiple entities that involve the lung that have radiographic, clinical, and morphologic overlaps with pulmonary lymphoma. In this review, we will discuss these entities in detail and provide relevant updates.

Lymphomatoid granulomatosis

Lymphomatoid granulomatosis (LYG) is a rare angiocentric and angiodestructive EBV-associated B-cell lymphoproliferative disease. It was first described in 1972 by Liebow et al. based on 40 cases of patients who had nodular lesions primarily in the lungs. Although it is specified as a lymphoproliferative disorder in place of a lymphoma, the disease is driven by EBV and express monoclonality, similar to post-transplant lymphoproliferative disorder.[1,2] It has been reported that 12% of LYG cases transform to lymphoma.[3] LYG must be distinguished from the aggressive nasal type extranodal NK/T cells lymphoma which is related to EBV infection and shares the same angiodestructive features.[4]

Etiology

EBV is essential in the pathobiology of LYG. Patients with underlying acquired or inherited immunodeficiency diseases (eg, Wiskott-Aldrich syndrome, X-linked severe combined immunodeficiency (SCID), Dedicator of cytokinesis 8 (DOCK8) deficiency, post-solid organ transplantation, and HIV/AIDS) generally have a higher risk of developing LYG. It has been also linked to autoimmune diseases such as Sjogren syndrome, rheumatoid arthritis, ulcerative colitis and sarcoidosis.[3–10]

Patients who are immunosuppressed due to medications (such as azathioprine, methotrexate or imatinib) might develop LYG, although rare. Few studies have shown LYG resolution upon medication discontinuation further supporting this is a lymphoproliferative disease.[11–15]

Epidemiology

LYG is a rare disorder which affects mainly adults between the ages of 30 and 50 although it can be seen at any age. Men are affected almost twice as often as women.[16,3,5,17,18,1,19,20] It is observed at a higher prevalence in Western countries compared to Asia.[4]

Clinical presentation

Although the infected cells are B cells in origin, the disease presents as an extranodal disease with involvement in the lungs being the most commonly affected (>90%), then kidneys (45%), skin (25–50%), and central nervous system (25–50%). Other reported involved organs include liver, spleen, lymph nodes, bone marrow, adrenal glands, heart, eyes, hard palate, gastrointestinal tract, genitourinary tract.[21,4,3,22–24] Central nervous system involvement may be an adverse prognostic sign.[3,21] If there is a lack of lung involvement, a diagnosis of LYG is very unlikely since the lung is almost always involved.

The most common presenting symptoms include fever, persistent productive cough, dyspnea, chest tightness together with skin rash, malaise, weight loss, arthralgias, myalgias, gastrointestinal symptoms and neurologic abnormalities (altered mental status, ataxia, cranial nerve palsies, hemiparesis, seizures and peripheral paresthesia).[3,4,21]

Imaging

Radiologically, pulmonary lesions are characterized by multiple bilateral nodules with variable size involving mid and lower lobes with central necrosis/cavitation without hilar lymphadenopathy.

Extrapulmonary organs (e.g. liver, kidneys) commonly show focal

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nodular lesions on imaging. Central nervous system involvement demonstrated by magnetic resonance imaging may show multiple focal lesions with punctate linear enhancement consistent with their perivascular nature. These lesions can be seen in the white matter, deep gray matter or brainstem. Enhancement of the leptomeninges may be radiologically visualized.[21,25]

Pathology features

Macroscopy

LYG characteristically presents as bilateral pulmonary nodules, typically in the mid and lower lobes. The nodules vary in size and the large ones are commonly centrally necrotic or cavitated.[4]

Extrapulmonary macroscopic manifestation also include nodular lesions with central necrosis (seen in kidneys and brain). Skin presentation is relatively heterogeneous with scattered subcutaneous or dermal nodules in varying size primarily on the extremities.[4,21]

Microscopy

LYG is distinctively recognized by its angiocentric and angiodestructive pattern with remarkable transmural lymphocytic infiltration as well as varying degrees of necrosis particularly dependent on the grade of the lesion.[21] The infiltrate is polymorphous and admixed with small lymphocytes, histiocytes and occasional plasma cells. The majority of small lymphocytes are T cells, which are typically CD4 positive.[7,4,20] Within this polymorphous background are variable number of atypical medium-to-large lymphoid cells, related to grade (Table 1). These cells are typically irregular and have vesicular chromatin and occasional prominent nucleoli. They can have a pleomorphic appearance resembling Hodgkin cells but Reed-Sternberg variants are not usually seen.[7,4] These cells are positive for CD20, CD79a and EBER by in situ hybridization (ISH), proving they are indeed EBV infected B cells. Other EBV markers including LMP1 and EBNA2 are positive consistent with latency type III.[7,4] The atypical cells commonly express CD30 but are negative for CD15.[4] Neutrophils, eosinophils and well-formed granulomas are not typically seen. The infiltrate is often well-demarcated, separated from unremarkable surrounding pulmonary parenchyma.[7] Vascular infiltration may lead to infarct-like tissue necrosis or fibrinoid necrosis, which is mediated by chemokines induced by EBV.[26]

Variable degree of coagulative necrosis in absence of neutrophils and apoptotic bodies are seen in relation to grade. CD20 stain can be expressed by the “ghost cells” in the necrotic areas, which is usually associated with high grade[7] but since the tumor cells in these areas are non-viable, they will be negative by EBER-ISH.

Peripheral fibroblastic foci, intra-alveolar macrophages, and edema could be present but a frank organizing pneumonia is not characteristic.[7]

Grading

LYG can be divided into 3 grades based on the proportion of large atypical EBV-positive B cells and necrosis relative to the reactive lymphocyte background[21,7,4] (Table 1).[4] It is essential to differentiate high grade (grade 3) from low grade (grade 1 and 2) (Fig. 1) due to different therapeutic regime, where grade 3 (Fig. 2) are treated like diffuse large B-cell lymphoma (DLBCL). In addition, LYG diagnosis should be avoided in cases of uniform large atypical EBV-positive B cells without a polymorphous background. These cases should be considered as an EBV-positive, DLBCL. When present, necrosis in DLBCL is frequently focal or patchy and does not show angiocentric pattern.[7]

Diagnosis

While the clinical presentation of LYG can be non-specific, the histopathology finding is quite distinctive. Biopsy of the lesion is essential. If multiple lesions are present, it is important to obtain multiple biopsies including ones from the larger nodules for better grading as each nodule can exhibit different grade in some cases (see Table 2 for the diagnostic criteria).[7]

It is worth noting that although EBV serology test is commonly positive, the EBV viral load is minimally increased despite finding EBV infected tumor cells.[7]

LYG should be differentiated from certain lymphomas that share similar features including extranodal NK/T cell lymphoma, nasal type when present in lungs, due to EBV association and angiodestructive growth pattern.[4] However, LYG does not typically involve the nasal cavity or GI tract. The characteristic of necrosis in LYG is quite different with absence of apoptotic debris, unlike extranodal NK/T cell lymphoma.[4,7] Additionally, LYG is seen more in Western countries than Asia where the NK/T cell lymphoma is predominant. Lastly, while the lymphocyte in the background is predominantly T cells, the large atypical cells in LYG is B cell in origin.[4,7,21]

Another lymphoma that occasionally poses a challenge in the diagnosis of LYG is classic Hodgkin lymphoma (CHL) as the large atypical cells in LYG may have a pleomorphic appearance reminiscent of Reed-Sternberg cells. These cells are positive for CD30 and EBER and the Hodgkin cells in CHL might have variable expression of CD20 making it difficult to exclude Hodgkin lymphoma. It should be emphasized that in LYG, the EBER positive cells show a range of cell size, from small to medium to large. In CHL, only the large HRS cells are highlighted by EBER.[2,4,7,21]

LYG almost never involves the lymph node, which is helpful in distinguish it from other lymphomas. If lymph node involvement is present without lung involvement, this is unlikely to be LYG.

Treatment and prognosis

The treatment should be approached in reference to the underlying immunosuppression, the symptom severity, extrapulmonary extent and histological grade of the lesion.[4,7,20,21,27]

In iatrogenic immune dysfunction (e.g. medication), the suspected agents should be ceased and patients with low grade lesions should be carefully observed as studies have shown spontaneous remission can be achieved in a subset of cases.[3,21] However, observation is not an appropriate option for high grade disease, which requires more aggressive treatment like that for diffuse large B cell lymphoma.

In HIV-associated LYG, case report on using antiretroviral showed complete remission of the disease.[28]

Corticosteroids are the most common medication used in LYG.[21] Although it shows initial symptomatic improvement, the disease consistently recurs. Steroid usage with dose adjustment is recommended in conjunction with other therapies to avoid worsening the immune

Table 1
Summary of Lymphomatoid Granulomatosis grading.

Grade	Background	Large atypical EBV(+) B cells	Necrosis
1	Polymorphous lymphoid infiltrate (prominent T cells). No cytological atypia	Rare (<5/HPF)	Focal
2	Polymorphous background	Occasional, ± small clusters (5–20/HPF, <50/HPF)	Commonly seen
3	Less inflammatory background	Readily identified, ± large aggregates (>50/HPF), ± pleomorphic and Hodgkin-like cells	Extensive

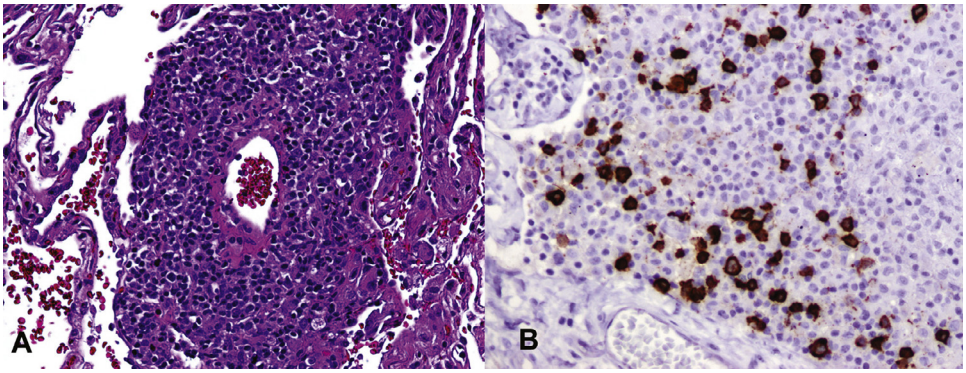

Fig. 1. Lymphomatoid granulomatosis, grade 1. A. The lesion is angiocentric with numerous small lymphoid cells and scattered large atypical cells that are B. highlighted by CD20 immunostaining. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dysfunction.

Based on a National Cancer Institute (NCI) study, the use of interferon (INF) in low-grade disease resulted in an increased progression-free survival and greater complete remission (CR) rate of 60%. In addition, most of patients who had CNS involvement achieved CR that prevented them from intrathecal chemotherapy or whole brain radiation.[29] High-grade LYG was treated with EPOCH-R (rituximab, prednisone, etoposide, vincristine, cyclophosphamide, and Adriamycin) regimen and showed improved overall survival of 68% with a median of 4 years.[21,4,29]

Table 2
Diagnosis of LYG (reprinted from Lymphomatoid granulomatosis, a single institute experience: pathologic findings and clinical correlations, Song et al.).

Clinical	High clinical suspicion
	Multiple lung lesions (predilection for the lower lobes)
	Extrapulmonary sites common (CNS, kidney, liver, skin)
	Absence of lymph node, spleen, or bone marrow involvement
	Normal or minimally-elevated EBV viral load
Morphologic	Angiocentric/angioinvasive
	Polymorphous infiltrate (histiocytes, small T-cells, plasma cells)
	Small T-cells are prominent with CD4 > CD8
	Large atypical B-cells present (density dependent on grade)
	Presence of EBV (by EBER or EBNA PCR), number of EBER positive dependent on grade
	Necrosis seen in all grades but more prominent in LYG grade 2 and 3
	Patchy infiltrate with largely normal surrounding lung parenchyma

IgG4-related lung disease

IgG4-related disease (RD) is characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and often elevated serum IgG4 concentrations.[30] The involvement of the lung, was first reported in 2004[31] and is a rare disease which is difficult to diagnose and can mimic primary lung malignancy on imaging.[32]

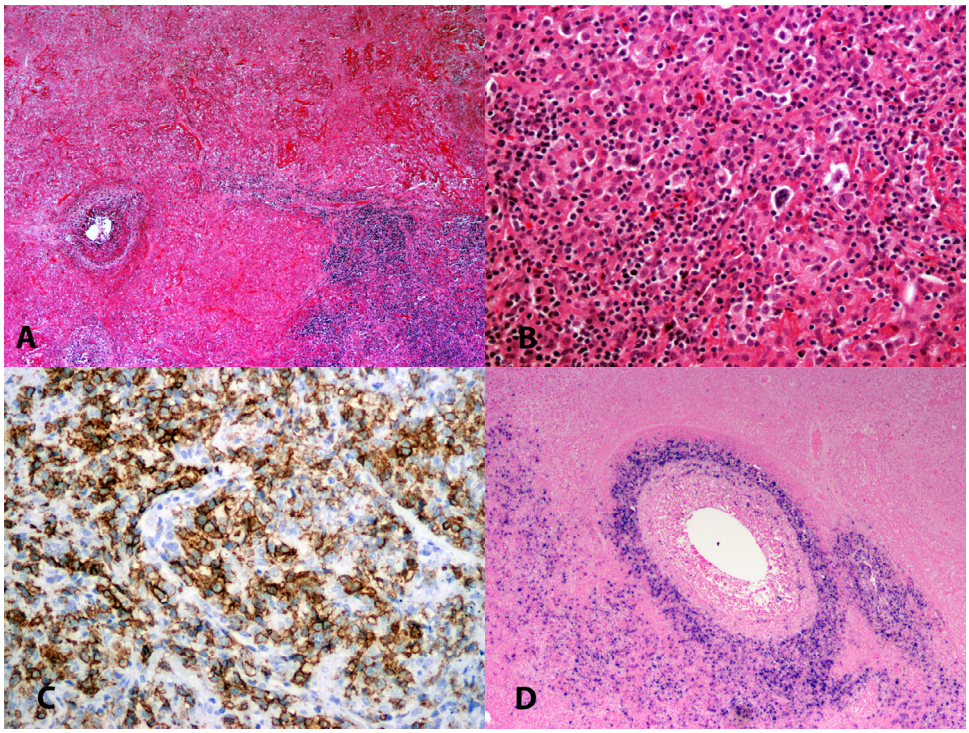

Fig. 2. Lymphomatoid granulomatosis, grade 3. A. In high grade lesions there is geographic necrosis with B. increased large atypical cells, some with Hodgkin-like morphology. C. CD20 immunostain shows increased large B-cells that are D. positive for EBER-ISH.

Etiology and pathogenesis

The mechanism of IgG related disease remains largely unknown with many proposed theories.

IgG4 is a T helper (Th) cell type 2-dependent isotype. The Th2-type cells accumulate in one third of the cases, suggesting a possible relation with allergic responses since IL-4, IL-5, and IL-13 are induced by Th2 cells. Also, Th2 cytokine expression and regulatory cytokines are noticeably up-regulated in the affected tissues of patients with IgG4- related cholangitis and sclerosing pancreatitis. IL-5, IL-13 produced by Th cells and TGF-β from T-reg cells induce recruitment of eosinophils and activate fibroblasts.[33] The increased Th2 cytokines activate macrophages which produce fibrogenic factors. These elements recruit macrophages, neutrophils, dendritic cells, among others, that contribute to the fibrotic lymphoplasmacytic infiltrate, which is characteristic of the disease.[34,35]

Another theory involves B cells, which enter the affected tissue, differentiate and proliferate into IgG4 B cells, due to the tolerogenic environment of the inflammation.[36]

IgG4 antibodies are considered to have anti-inflammatory activity given the fact that they can undergo Fragment antigen-binding (Fab)-arm exchange and limit immune complex formation. These elements make IgG4 less likely to be active element in the pathogenesis of the disease. IgG1 could be associated with IgG4 and be responsible for the inflammatory changes in IgG4-RD.[37]

It has been reported that patients with IgG4-RD likely have a higher incidence of pulmonary malignancies including lymphoma, which might be related to unidentified antigen.[38,39] It is unclear whether the IgG4-related immune response is activated by tumor cells or malignancies arising in chronically inflamed tissue. In addition, some patients with lung cancer have increased IgG4 cell infiltration which has correlated with an improved survival.[40]

Some cases of histoplasmosis or granulomatous disease-associated fibrosing mediastinitis involving the lung may demonstrate histopathologic overlap with IgG4-RD. It is uncertain whether these changes occur as the host immune response against Histoplasma or represent a manifestation of IgG4-RD.[41]

Epidemiology

In general, IgG4-RD is predominantly seen in adults, mostly in older males (70–80%).[41] In autoimmune pancreatitis, lung specific involvement rate varies from 9.5% to 51.2% of patients. IgG4-related lung disease without involvement of other organs is 8% according a Japanese study.[42]

Clinical feature

Clinical symptoms of IgG4-related lung disease have nonspecific symptoms such as cough, fever, dyspnea, and chest pain.[34,41,35]

Patterns of intrathoracic involvement

Parenchymal/interstitium. Radiological patterns include patchy ground-glass opacity or consolidation, reticular opacities, honeycombing, thickening of the bronchovascular bundles and interlobular septa. Pulmonary function is reduced with restrictive pattern. These findings resemble those found in idiopathic interstitial[43] pneumonia,idiopathic nonspecific interstitial pneumonia, cryptogenic organizing pneumonia and sarcoidosis. Also, the round opacities might frequently raise suspicion of malignancy and lead to wedge resection or lobectomy in some patients.

Airways. Case reports in the literature on airway manifestation of IgG4-RD are rare. A possible relation between IgG4-RD and asthma[44] has been noted, in which autoimmune pancreatitis was preceded by clinical features of asthma. Another case was noted to have tracheobronchial stenosis with edematous and hypervascular bronchial mucosa, intrathoracic lymphadenopathy, and thickening of bronchovascular bundles, resembling sarcoidosis. Fibrosing mediastinitis and bronchiectasis causing extrinsic compression of the central airway was also described.[45,46]

Pleural. Pleural disease in IgG4-RLD can present, rarely, as a sole pleural effusion but more commonly with additional pulmonary manifestations of disease. Zen et al[45] studied 21 patients with IgG4-RD, 5 of them had pleural disease with nodular lesions involving the visceral pleura, parietal pleura and chest wall. Another case report described thrombophlebitis and a massive pleural effusion found in a patient with lung-related disease.[47]

Mediastinal. Most common intrathoracic manifestation in IgG4-RD may be mediastinal with or without hilar lymphadenopathy, which have been documented in 40% to 90% of cases.[41] In 2007, Inoue et al. reported the first case of sclerosing mediastinitis with elevated IgG4 plasma cell infiltration and serum levels. The patient was noted to have a remission after steroid therapy suggesting that the serum IgG4 level is a good indicator for steroid therapy in sclerosing mediastinitis.[48]

Histology findings

The histology of IgG4 related lung disease is relatively similar to the findings in other extrapulmonary IgG4-RD. It is characterized by a diffuse interstitial thickening with extensive plasma cell infiltration. The lesions have a mixed inflammatory infiltrate and fibrosis, with irregular storiform pattern of fibrosis. IgG4+ plasma cells were observed to be diffusely distribute in inflamed areas, including the alveolar interstitium, interlobular septa, and peribronchial or peribronchiolar interstitium. IgG4 positive plasma cells are more than 10 per high power field and the ratio of IgG4 positive cells/IgG positive cells is more than 40% (Fig. 3).

Eosinophils are easily identified and no atypical cells suggestive of a neoplastic process are seen. The number of alveolar epithelial cells is

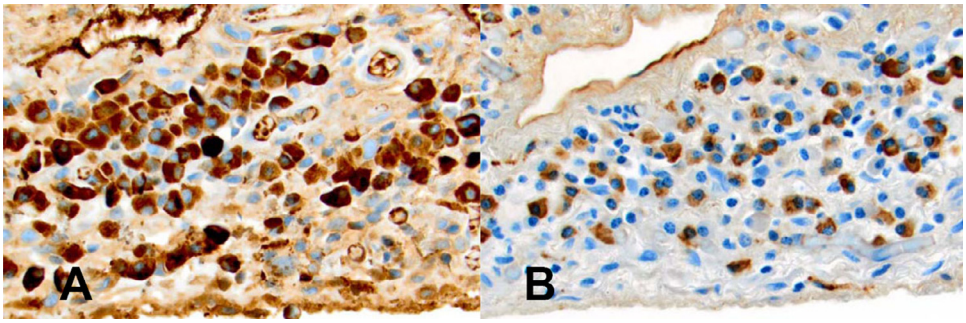

Fig. 3. IgG4-related lung disease. A. Within the interstitial air spaces there are areas of fibrosis with increased plasma cells that are positive for IgG with B. increased IgG4-positive plasma cells.

markedly reduced. Obliterative phlebitis or obliterative arteritis is observed in most patients.[49,35]

Laboratory

IgG4 serum level greater than 135 mg/dl was reported to have a high sensitivity of 97% and specificity of 79.6% in making a diagnosis of IgG4-RD, and serum IgG4/IgG ratios >8% had a sensitivity and specificity of 95.5% and 87.5%, respectively.[50] However, IgG4 serum level elevation can be seen in conjunction with a wide array of disorders including bronchiectasis, asthma, idiopathic pulmonary fibrosis, emphysema, hypersensitivity pneumonitis, but only a small minority of them has IgG4-RD.

Krebs von den Lungen (KL)−6 is a high molecular weight glycoprotein expressed on type 2 alveolar pneumocytes and has been found to be elevated in serum and bronchoalveolar lavage fluid in patients with interstitial pneumonia,[51,52] and decreased with steroid therapy,[53] suggesting the marker of disease activity.

Diagnosis

While IgG4-positive lymphoplasmacytic infiltrates are a characteristic feature in IgG4-RD, it is not entirely specific for a diagnosis.[41] In addition, the clinical presentation can be seen in any benign or malignant pulmonary disease. Making a diagnosis of IgG4-related lung disease can be challenging and requires a series of clinical, radiological, laboratory, and histopathological findings. Histopathological examination of tissue biopsy from the intrathoracic lesion is also useful in distinguishing manifestations related to IgG4-related lung disease from a separate process, such as lung cancer, lymphoma or sarcoidosis.

The Japanese (Table 3)[35] and Boston criteria are two major systems for diagnosis. The 2012 International consensus (Table 4)[35] is the third system. In 2017, Umehara et al. published a diagnostic criteria for IgG4-RLD focusing on chest imaging, serology, histology and other organ involvements.[54]

Morales et al.[35] brought up an IgG4 diagnostic algorithm including specific criteria (Fig. 4)

Treatment

The mainstay treatment for IgG4-RD is corticosteroids. Lung involvement tends to respond favorably to prednisone treatment (20-50 mg daily) and improvement is noticed in both symptoms as well as imaging. An International consensus guidance affirmed that not only symptomatic patients require treatment, but some asymptomatic patients may also benefit with treatment.[55] In recurrent disease, Bortezomib (protease inhibitor) and cyclosporine has shown a good response when use in conjunction with steroids. Patients who do not improve with corticosteroids can be treated with cyclophosphamide, azathioprine, and mycophenolate mofetil with favorable responses.[35,56,57] Rituximab has been used as an alternative to steroids and leads to rapid decline of serum IgG4 levels with prompt clinical improvement of the disease.[58]

Table 3
The Japanese comprehensive clinical diagnostic (CCD) criteria for IgG4-RD.

1.	Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs
2.	Hematological examination shows elevated serum IgG4 concentrations (> 135 mg/dl)
3.	Histopathological examination shows: 1. Marked lymphocyte and plasmacytic infiltration and fibrosis 2. Infiltration of IgG4 + plasma cells ratio of IgG4 + /IgG + cells >40% and > 10 IgG4 + plasma cells/HPF

Definite: 1 + 2 + 3
Probable: 1 + 3
Possible: 1 + 2
• Consider always in the differential of IgG4-RD any malignant tumors (solid organ and blood malignancies).
• Consider similar diseases as Castleman's disease, granulomatous diseases or autoimmune diseases like Sjogren's syndrome.
• When CCD criteria are not met, patients may be diagnosed using organ-specific diagnostic criteria for IgG4-RD.

Prognosis

The long-term prognosis of patients with IgG4-related lung disease is generally favorable with response to steroid. Some patient might develop extrapulmonary IgG4-RD at later time or may not been able to achieve complete resolution of their disease. Malignancies following an IgG-RD have been described.[45,41]

Castleman disease

Castleman disease (CD) is a complex lymphoproliferative disease, which was first described in 1954 by Benjamin Castleman.[59] CD can typically manifest as unicentric (UCD) or multicentric (MCD), clinically. Histologically, hyaline vascular (HV) CD is separated from plasma cell variant (PCV) CD. CD can occur at any site and approximately 70% of CD was found in the thorax.[60,61] However, lung is a rare location[62] and should be considered in the differential diagnosis of primary pulmonary malignancies, including pulmonary lymphoma.

Pathogenesis

Although the pathogenesis of CD has remained to be understood, few scientific ascertainments have been proven. Human herpes virus 8 (HHV8), which has been linked to MCD is now known to encode for interleukin 6 (IL-6), which regulates B-lymphocytes' differentiation to plasma cells, hence contributes significantly to the pathogenesis of PCV CD and MCD. IL-6 levels have also been known to be elevated in MCD. Antibodies to IL-6 have been found to have efficacy in plasma cell disorders and MCD.[63–66]

In addition, MCD has intimately associated with human immunodeficiency virus (HIV), and synergistic interactions between HHV8 and HIV have been described.[67] Some studies have shown HIV-positive MCD patients are all virtually co-infected with HHV-8.[68,69] Retroviral therapy and use of rituximab in HHV8-MCD have effectively changed outcomes in HHV8-MCD.

Vascular endothelial growth factor (VEGF) is observed to be increased in patients with CD,[70,71] that might suggest a potential contribution of VEGF in CD pathogenesis.

In contrast, unicentric Castleman disease (UCD) pathogenesis is considered a clonal neoplastic process and stromal cells, particularly follicular dendritic cells are most likely the cell of origin.[72,68] Li et al. published a study in 2019 showing recurrent *PDGFRB* mutations detected in stromal cells in UCD patients might play a critical role in the pathogenesis of UCD.[73]

Clinical presentation and laboratory tests

One retrospective study of 48 intrathoracic CD cases show no gender predilection between UCD and MCD but patients with MCD tend to be older (41 years) than those of UCD (30 years).[74]

UCD patients do not usually present with obvious symptoms but incidental solitary mass on a routine chest x-ray. Symptomatic manifestation is commonly related to direct compression of adjacent structures, leading to cough, dyspnea, hemoptysis, chest pain or dysphagia.[74–76] Complete blood cell analysis and serum biochemical studies show no significant changes although mild anemia, hypoalbuminemia and elevated lactate dehydrogenase (LDH) can be found in few cases.[74]

MCD patients, conversely, have systemic symptoms in most of the

Table 4
Diagnostic criteria of the 2012 international consensus.

Clinical suspicion that correlates Histopathologic findings: A. Lymphoplasmacytic infiltrate in biopsy and/ or storiform fibrosis and/or coronary/obliterative phlebitis B. IgG4 plasma cells (10–200 cells by HPF) infiltrates in biopsy. Cell count IgG4 + /IgG > 0.4	Highly suggestive: two or more items of *A* + *B* Probable: At least 1 item of *A* + plasma cells that do not meet B criteria. Insufficient: not included in highly suggestive or probable categories.	Confirmation of Probable requires a IgG4 > 135 mg/dl levels and/or involvement of another typical organ(s) of IgG4 -RD demonstrated by images or histopathologic analysis.

cases including fever, cough, dyspnea, fatigue, hepatomegaly, splenomegaly were reported in half of multicentric intrathoracic CD cases.[74,76] Anemia is present in half of the cases. Thrombocytosis, hypoalbuminemia, hyperglobulinemia, elevated erythrocyte sedimentation rate (ESR), elevated serum C-reactive protein (CRP), and positive antinuclear antibody (ANA) are among the reported laboratory abnormalities.[74,76]

Associated disorders such as POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), other autoimmune diseases (Wiskott-Aldrich syndrome, scleroderma, systemic lupus erythematosus, Sjörgren syndrome, polymyositis, paraneoplastic pemphigus, mixed connective tissue disease, and undifferentiated connective tissue disease),[77,78] renal diseases and neoplasm (Kaposi sarcoma, plasmablastic lymphoma, primary effusion lymphoma, other non-Hodgkin lymphoma, angiomatoid and dendritic neoplasm)[79–81,75] can be found in MCD patients.

Pathologic features

The histopathology features are not specific but commonly divided into three categories[82,75]:

Hyaline vascular variant

Most commonly seen in UCD, hyaline vascular variant is characterized by regressed or involuted germinal centers in large follicles. Two or more germinal centers per follicles ("twinning") is not always present but highly suggestive of CD. Vascular proliferation is increased in the interfollicular zones with hyalinized vessel wall. These vessels often contain pink hyaline material ("hyaline vascular") and frequently penetrate the germinal centers ("lollipop"). Mantle zone is expanded and characterized by concentric rings of lymphocytes ("onion skin").

Plasma cell variant

The most common variant of MCD is the plasma cell variant, which can be subdivided into HHV8(-) and HHV8(+).

The HHV8(-) PC—CD is unicentric has preserved lymph node architecture with hyperplastic germinal centers. Atrophic germinal centers can be seen in a small subset. Marked plasmacytosis is characteristically present in the interfollicular areas with no cytologic atypia noted.

The HHV8(+) MCD is strongly associated with HIV infection. The follicles are frequently hyperplastic and not usually atrophic as seen in the HV-CD. Lymphocyte depletion can be present, especially in cases with HIV co-infection. The interfollicular regions are expanded by sheets of plasma cells with immature and atypical forms present. The HHV8 infected cells (with features of immunoblasts or plasmablasts) which are usually located in the mantle zone can form small nodules ("microlymphomas") or confluent sheets (Fig. 5). Vascular proliferation is also increased.

Mixed

Lymph nodes demonstrate extensive regressed germinal centers and sheet-like plasmacytosis, which are features of both HV and PC are considered to have mixed histopathology.

Imaging features

Unicentric CD

Incidental solitary mass on a routine chest x-ray seen in mediastinum, lung hilum, intrapulmonary fissure and pulmonary parenchyma. Punctate calcification in the mass and minimal pleural effusion can be seen in a subset of cases.[74]

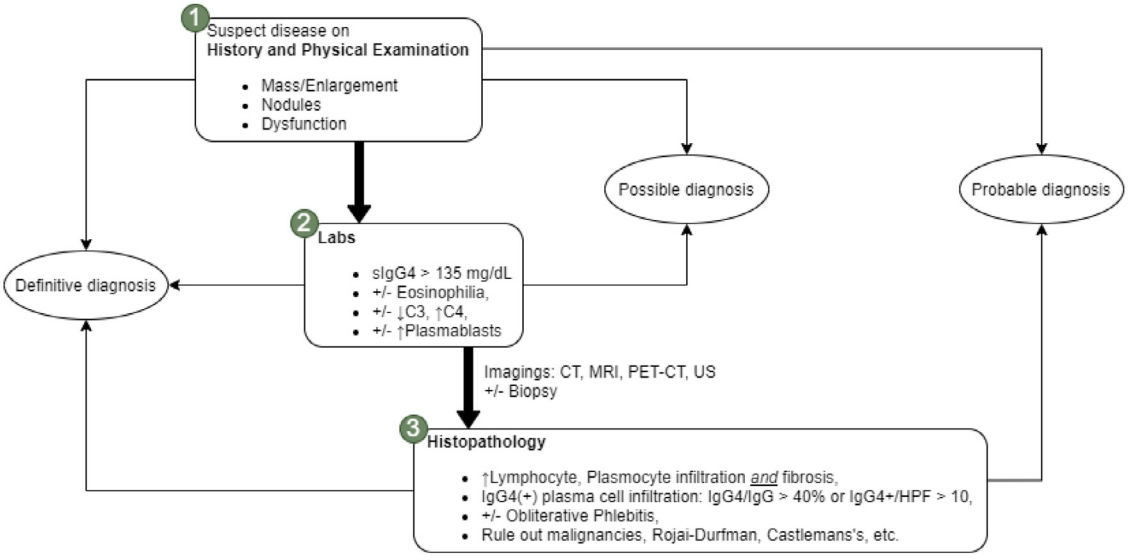

Fig. 4. IgG4 related lung disease specific criteria.

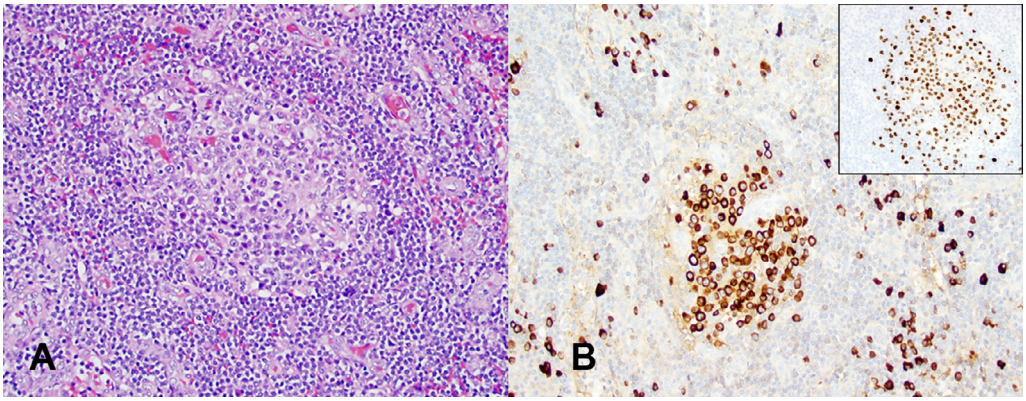

Fig. 5. Multicentric Castleman disease. A. Atrophic germinal centers are seen with increased large transformed cells B. that are lambda restricted and (inset) positive for HHV8.

Multicentric CD

The radiological abnormalities include significant lymphadenopathy with different size in the hilum and/or mediastinum. Cysts of different sizes and shapes, ground glass opacification, air trapping, interlobular septal thickening, thickening of bronchovascular bundles, localized consolidation, pleural effusion, bronchiolitis obliterans, and rarely intrapulmonary masses are among findings that are observed in MCD.[76,74,75,83,84,62]

Diagnosis

Diagnosis of CD should be made after carefully investigating the patient's clinical history and presentation including infectious status of HIV and HHV-8, laboratory testing, radiology, biopsy of the involved tissue with flow cytometry, immunohistochemistry and molecular testing for clonality. HV-CD typically shows polyclonal lymphocyte population and the plasma cells in PC—CD are polytypic as well.[75,85] Monoclonality is rarely seen CD and might herald the development of a lymphoma. Fine needle aspiration is not considered a method for diagnosis of CD.[86]

Treatment and prognosis

The treatment of choice for unicentric CD is a complete surgical resection due to excellent prognosis and rare recurrence.[87,88] When the mass is inoperable due to its involvement of adjacent vital structures, neoadjuvant therapy or embolization can be attempted. Localized radiation is also an alternative choice for unresectable unicentric CD (Fig. 6).[85] However, toxicities after radiotherapy has been documented.[89,90]

Multiple different treatment modalities are available for MCD depending on the viral infection status and institutional practice.[75,85] Monoclonal antibody to CD20 has been shown to improve survival on MCD patients who are HIV and HHV8 co-infected and reduces lymphoma development[91–93] (Fig. 7).[85]

The FDA has approved the use of IL-6 monoclonal antibody, siltuximab, formerly known as CNTO328, which binds and neutralizes human IL-6 (major role in CD pathogenesis) with high affinity and specificity, to treat HHV8-negative idiopathic multicentric Castleman disease (iMCD) who do not have HIV or HHV-8.

Corticosteroids are often given for acute exacerbations of multicentric CD and mostly in conjunction with rituximab or alkylating agents. Studies have reported an increased risk of infection and death due to sepsis associated with steroid therapy.[94,28]

Multiagent chemotherapy (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [CVAD]) has shown complete responses in approximately 50% of patients. However, these cases often recurred with the median survival of 19 months.[95,96] Newer therapies such as VEGF and IL-6 inhibitor, bortezomib, thalidomide and lenalidomide have been introduced[85,97] (Table 5).[85]

Graft-versus-host disease (GVHD)

Pulmonary complication after allogeneic hematopoietic stem cell transplant (allo-HSCT) is approximately 30–60%,[98,99] and is a common cause of morbidity and mortality post transplantation.[100–103] Multiple factors can contribute to pulmonary injury including graft versus host disease (GVHD).

Since primary pulmonary lymphoma can occur in patients who have immunosuppression including the post-transplant population, differentiating between pulmonary complications of graft versus host disease and primary pulmonary lymphoma is necessary.

Clinical presentation

Acute and chronic GVHD is classified by the occurrence of symptoms before or after 100 days, respectively. In acute GVHD, pulmonary complication is rare.[104,105]

In chronic GVHD, a wide spectrum of symptom can be seen depending on the stage of disease. Patients can completely be asymptomatic or experience from mild dyspnea, non-productive cough to shortness of breath, dyspnea from exertion that affect their daily function.[106–110] Many patients also have symptoms from other organ injuries (e.g. skin, GI tract, liver) such as rash, diarrhea, and jaundice.

Clinical tests

Pulmonary function tests (PFTs)

The pulmonary function can be assessed by measuring the total lung capacity (TLC), Forced expiratory vital capacity (FVC), Diffusion capacity for carbon monoxide, Forced Expiratory Volume at 1 s (FEV1), FEV1/FVC ratio, and Lung Function Score (LFS). The usage of these parameters are helpful not only to set up the baseline, evaluate the severity of obstructive as well as restrictive changes, but also to differentiate pulmonary GVHD with other conditions such as scleroderma like-chronic GVHD, steroid related myopathy or conditioning toxicity.[111,112]

PFTs is recommended for screening in population at risk of pulmonary GVHD due to its capacity to detect early sign of restriction despite no apparent respiratory symptoms.[113]

Bronchoalveolar lavage (BAL)

The important differential diagnosis in pulmonary GVHD is infection. A BAL is a good test to help exclude the infectious causes. In addition, it is suggested that BAL cytomorphological analysis should be

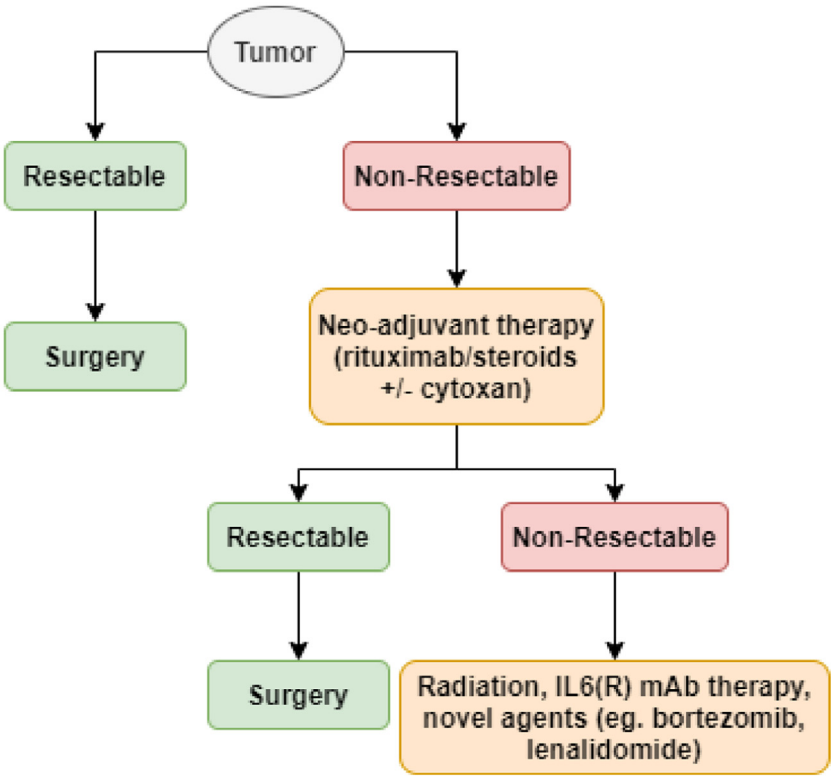

Fig. 6. Treatment algorithm for UCD.

performed on the obtained cells including leukocytes, CD4:CD8 ratio evaluation and atypical epithelial cells detection.[114]

Imaging

In acute GVHD, the CT scan finding is nonspecific, which might demonstrate diffuse interstitial and alveolar opacities.[104] Pulmonary cytologic thrombi is a rare complication and can be present in both acute and chronic GVHD.[104]

Chronic GVHD pulmonary complications may exhibit characteristic findings on imaging. Organizing pneumonia is reversible, with patchy peribronchial and peripheral consolidation, which is often well circumscribed. Elongated consolidation in a perilobular distribution ("reversed-halo" sign) is indicative of organizing pneumonia. Centrilobular nodules and ground glass opacities are frequently observed.[115,116] Bronchiolitis Obliterans is the irreversible stage, which is characterized by mosaic perfusion pattern including areas of low attenuation with reflex hypoxic vasoconstriction due to impaired ventilation and areas of normal perfused lung.[104]

Histopathology

The histopathological spectrum of pulmonary GVHD in a study of 17 cases included 4 major patterns: diffuse alveolar damage (DAD), lymphocytic bronchitis/bronchiolitis with cellular interstitial pneumonitis (BIP), bronchiolitis obliterans organizing pneumonia (BOOP) and cicatricial bronchiolitis obliterans (BO).[117] Xu et al. showed the histological manifestation of GVHD features in lungs as acute lung injury, organizing pneumonia (OP) with or without fibrin, and chronic interstitial pneumonia (CIP). The descriptions are essentially similar since the histopathological features are variable and only BO or obliterative bronchiolitis which is the late stage of disease is considered diagnostic feature of chronic GVHD.[107,118]

Acute lung injury typically exhibits diffuse alveolar damage, which show diffuse interstitial and alveolar infiltrate. Intra-alveolar fibrin with reactive pneumocytes and denudation of alveolar septa is seen. The damaged septa can be lined by a thick eosinophilic hyaline membrane. OP features should not be seen but foci of early organization and alveolar eosinophils are noted in some cases.[107,117–119]

Organizing pneumonia is characterized by nodules of fibroblasts and myofibroblasts arranged in whorls with pale gray matrix within the distal airspace and alveoli. Epithelial apoptosis and chronic interstitial infiltrates are almost present in all cases.[107] Other common findings are epithelial regeneration with moderate to severe epithelial atypia, alveolar eosinophils and relatively prominent lymphocytic perivasculitis.[107,117]

Chronic interstitial pneumonia[107] shows widen alveolar septa infiltrated by mixed chronic inflammation and mild fibrosis. The inflammation includes lymphocytes (mostly T cells), plasma cells and apoptotic bodies. Reactive pneumocyte hyperplasia is diffusely present without residual fibrin or OP pattern.

Bronchiolitis obliterans is characterized by constrictive bronchiolitis with obliterated lumens by submucosal bronchiolar fibrosis, displaying transversed lumens by the cicatrix in some airways. The peribronchial infiltrate percolates into the overlying flattened epithelium where readily found apoptosis. Alveolar pneumocyte atypia is prominent.[104,107,117]

Xu et al[107] noted that increased intraepithelial bronchiolar T cells and apoptosis of bronchiolar epithelium and interstitium are seen in 90% of the cases of all stages. While perivascular infiltrates and apoptosis are not specific, these findings are more consistent with inflammatory changes in GVHD.

Diagnosis

Bronchitis/bronchiolitis with interstitial pneumonitis (BIP) was the most common finding and included a lymphocytic infiltration around bronchial structures along with a mononuclear inflammation in the perivascular zones and alveolar septa. Pulmonary chronic GVHD can present with obstructive and/or restrictive changes, therefore the diagnostic work-up includes high-resolution computed tomography,

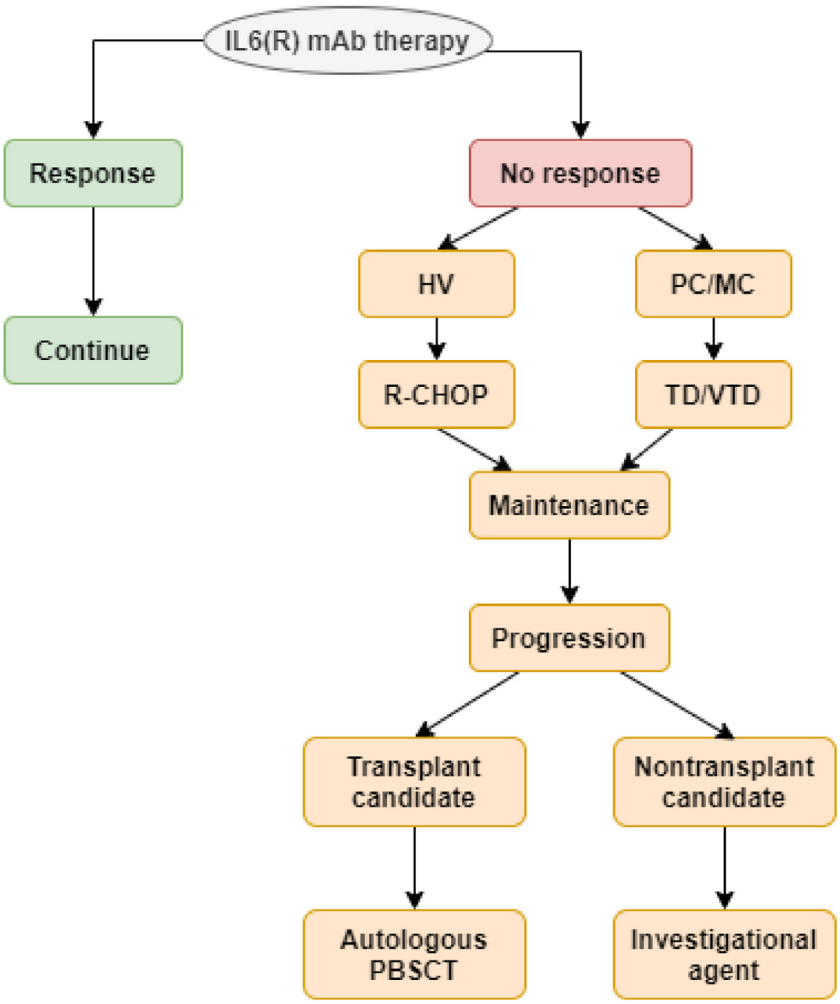

Fig. 7. Treatment algorithm for MCD.

Table 5
Treatment Modalities for Castleman Disease.

Treatment Modality	Agents
Local	Surgery, irradiation
Corticosteroids	Prednisone, Dexamethasone
Chemotherapy	Cyclophosphamide, Etoposide, Vinblastine, Chlorambucil, Liposomal Doxorubicin, Combination chemotherapy (CHOP, CVAD), 2-chloro-deoxyadenosine
Anti-CD20 mAb	Rituximab
Anti-IL6-based	Tocilizumab, Siltuximab, Anakinra, Suramin
Immunomodulatory	Interferon-α, Thalidomide, Lenalidomide, All-transretinoic acid
Antiviral	Valganciclovir, Foscarnet, Cidofovir
Miscellaneous	Bortezomib, Cimetidine
Autologous PBSCT	Melphalan, BEAM

bronchoalveolar lavage and histopathologic analysis. A consensus statement has been established by the German Working Group on bone marrow and blood stem cell transplantation.[118,107] The open lung biopsy, although considered the gold standard for the diagnosis of BO or BOOP/OP,[106] combines with a high morbidity rate and possibly causes severe consequence.[120,121] It is advised that a lung biopsy may not be required if clinical history, pulmonary function tests, chest CT features and characteristic involvement by the other organs are suggestive of GVHD.[122,118]

Treatment and prognosis

Patient who have acute lung injury are at high risk.[107]

Due to the reversible nature, most patients with OP respond favorably to steroid and the condition resolves in majority of cases. However, comparing to those with cryptogenic OP or other secondary forms of OP, patients who have GVHD related OP heralds an inferior prognosis, with respiratory failure and death reported in 20% of cases.[108,123]

40% patients who have CIP develop BO at 30 months of follow-up according to study of Xu et al.[107] The outcome of BO is poor with eventually no adequate response to steroid or immunosuppressant therapies. The overall mortality rate is 12–27% at 5 years. Superimposed infection is the most common cause of death in the late stage.[108,123]

Post-transplant lymphoproliferative disorder (PTLD)

Post-transplant lymphoproliferative disorders (PTLD) develops in approximately 2% of all transplant recipients depending on what type of organ that is transplanted (highest with visceral, 5–20%). The incidence of PTLD in the setting of allogeneic stem cell transplantation is 0.5–1%. It is categorized into non-destructive and destructive. The non-destructive includes plasmacytic hyperplasia, infectious mononucleosis, and florid follicular hyperplasia (new entity in the 2017 WHO classification).[4] These entities do not cause destruction to the underlying architecture which is contrary to the destructive types such as polymorphic, monomorphic, and classical Hodgkin-type (CHL) of PTLD.

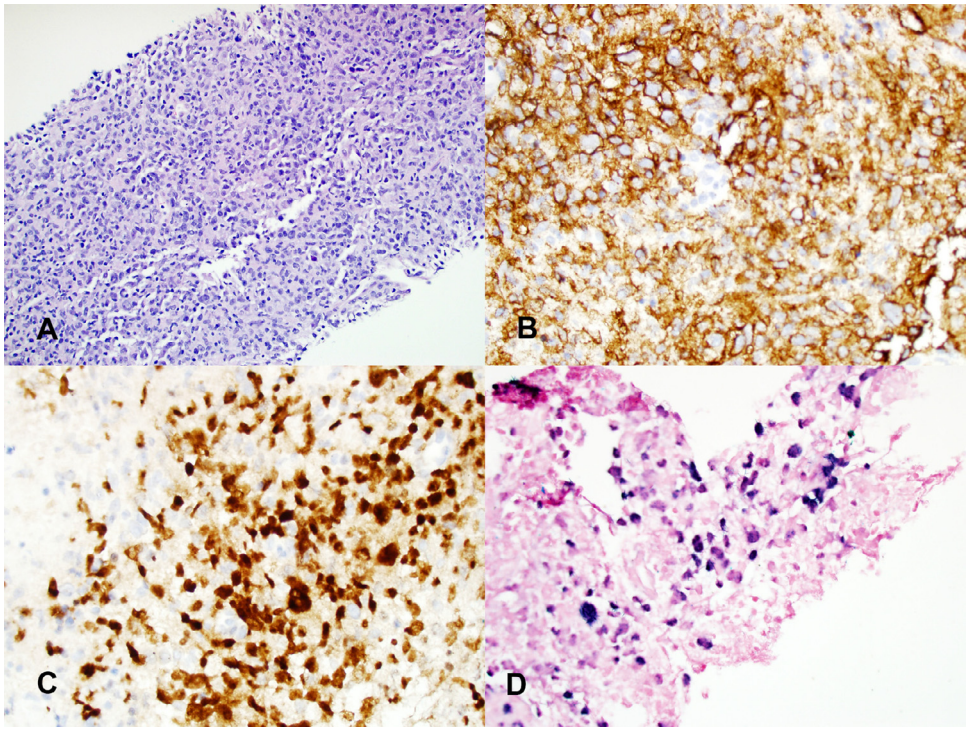

Fig. 8. PTLD, monomorphic, diffuse large B-cell lymphoma. A. The neoplastic cells are large in size with pleomorphism B. that are positive for CD20 C. and show a non-GCB phenotype expressing MUM1 and D. positive for EBER-ISH.

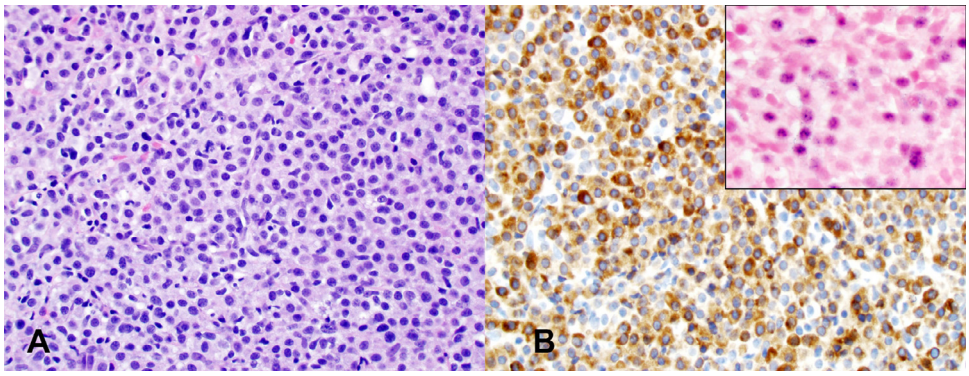

Fig. 9. PTLD, monomorphic, plasmacytoma. A. Sheets of mature appearing plasma cells B. that are positive for CD79a and (inset) positive for EBER-ISH.

Etiology

The vast majority of PTLDs arise after solid organ transplantation derived from the recipient's lymphoid cells. PTLDs are caused by EBV-infected lymphoid or plasma cells that are not controlled by the host's immune system due to immunosuppression. EBV-associated PTLDs can show different states of latency but many of the cases have a type III latency pattern with the next largest being type II.[124] The decrease in EBV-specific CD8+ T-cells and CD4+ T-cells leads to an ineffective immune response to EBV. It is thought to begin with a polyclonal proliferation related to EBV and over time the development of an oligoclonal and eventually monoclonal B-cell population and in rare cases, a T-cell proliferation. There are cases of PTLD that do not show EBV and are seen in higher incidence as “late” PTLDs occurring years after the transplantation. These may be either a “hit and run” where EBV initiated the proliferation but is lost later or chronic antigenic stimulation.

Epidemiology

The majority of PTLDs (80%) develop within the first year of transplantation with the remaining occurring more than 10 years later. Generally, early-onset PTLD are associated with younger patients and present with EBV-positive, non-destructive type lesions. These are seen after bone marrow, lung, and heart-lung transplantations. Extranodal sites can be seen in patients with longer intervals from transplantation and worse prognosis and monomorphic histology. Pulmonary lesions are commonly seen in cases with extranodal involvement (16%) and are usually EBV-positive (75%). The monomorphic type with diffuse large B-cell lymphoma morphology is the most common histologic type but pulmonary lesions can vary with histologic subtype.[125]

Pathology

The histologic findings in PTLD is a spectrum with non-destructive lesions to more destructive lesions seen in polymorphic or monomorphic proliferations.

Non-destructive PTLD

Plasmacytic hyperplasia is usually diagnosed in the lymph nodes and shows intact architecture with increased plasma cells. *Infectious mononucleosis-like PTLD* also shows intact architecture with some distortion and. There is increased plasma cells, and prominent transformed cells present. *Florid follicular hyperplasia* (new entity in 2017 WHO classification) PTLD can also be seen showing expanded germinal centers.[4] All of these lesions can show clonal karyotypic abnormalities. These lesions should show increased number of EBV positive B-cells or plasma cells. Typically, the lesions are polytypic by kappa and lambda IHC or in situ hybridization as well as by *IGH* gene rearrangements. Of note, many of these patterns can be seen in a single case as these are seen as a spectrum of the disease. These lesions are typically considered early lesion.

Polymorphic, monomorphic PTLD and CHL PTLD

These are the destructive lesions and show obliteration or destruction of the underlying architecture. The polymorphic PTLDs show a spectrum of B-cell differentiation from small lymphocytes, transformed cells, sometimes Hodgkin-like, and plasma cells. The monomorphic PTLDs can resemble any of the entities in the WHO classification with the most common being DLBCL for B cell (Fig. 8) and peripheral T-cell lymphoma, NOS for the T-cell type. Classical Hodgkin lymphoma PTLDs can also be seen and have the exact morphologic features as typical CHL, usually mixed-cellularity. CHL PTLDs usually have higher expression of B-cell associated markers such as CD79a, OCT2, or BOB1. The DLBCL monomorphic type is usually of non-GCB phenotype and many of the cases have increased number of CD30-positive tumor cells. Another type of B-cell PTLD that is common are the plasma cell myeloma or plasmacytoma-like lesions. They can be seen in the GI tract, skin, and extranodal sites and contain sheets of plasma cells (Fig. 9).

Detection of EBV is best done by EBER-ISH since there can be varying latency stages within the lesion. Early or non-destructive PTLDs are usually positive for EBV, while cases of monomorphic PTLD have a higher proportion that are negative.

Of note, there may be some cases of PTLD that fulfill the diagnostic criteria of *EBV-positive mucocutaneous ulcer (MCU)* (new entity in the 2017 WHO classification) but these are typically seen in the GI tract or mucosal sites and has not been reported as pulmonary manifestations.[126]

Diagnosis

Biopsy of the lesion for pathologic review is necessary to determine the histologic subtype. Radiographic evaluation is also needed with CT or PET-CT. In one study by Hou et al., they identified 8 patients with pulmonary involvement by PTLD after allogeneic stem cell transplantation. Nearly all cases were positive for EBER-ISH (92%) and had other extranodal involvement at other sites. These pulmonary PTLDs showed an aggressive clinical course and poor response to therapy such as Rituximab likely due to the extent of involvement.[127] In a study by Yoon et al. of 12 patients with thoracic involvement by PTLD, they found that actual pulmonary involvement was rare and that the majority showed lymph node involvement of the mediastinum, hilum, and cervical regions.[128] In addition, many of the lesions had other sites of involvement such as lymph nodes of in the abdomen. EBV serology is also recommended since many patients with show elevated EBV titers.

Treatment/Prognosis

PTLD is usually associated with significant morbidity and mortality. However, with appropriate therapy, patients with monomorphic PTLDs have a similar survival as those with the same lymphoma type in the non-transplantation setting. Typically, the initial step, particularly in non-destructive lesions, is to decrease immunosuppressive therapies and the use of Rituximab has been sufficient after surgical resection. For monomorphic PTLD and CHL PTLD, these usually require a chemotherapy regimen which should be tailored to the histologic subtype of the lesion. There are varying results in the literature in regard to prognosis but in general, non-destructive lesions have shown good prognosis especially with conservative management (e.g. excision with decrease immunosuppression), while cases that are EBV-negative or monomorphic PTLD have a poorer survival and will require chemotherapy or more aggressive management. As mentioned above, pulmonary involvement has shown an aggressive clinical course.

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