Lymphoproliferative Disorders of the Lung

Raphaël Borie^a Marie Wislez^{b, d} Martine Antoine^{c, d} Jacques Cadranel^{b, d}

^aService de Pneumologie A, Centre de compétences maladies pulmonaires rares, AP-HP, Hôpital Bichat, ^bService de Pneumologie, Centre constitutif maladies pulmonaires rares, and ^cService d'Anatomie pathologique, AP-HP, Hôpital Tenon, and ^dGRC-THERANOSCAN, Université Pierre-et-Marie-Curie, Université Paris 6, Paris, France

Keywords

Primary pulmonary lymphoma · Mucosa-associated lymphoid tissue · Epstein-Barr virus · *Human herpesvirus 8* · Multicentric Castleman disease

Abstract

This review aims to describe some of the most frequent lymphoproliferative disorders arising from the lung: pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma, lymphomatoid granulomatosis (LG), multicentric Castleman disease (MCD), primary effusion lymphoma (PEL), and nodular lymphoid hyperplasia (NLH). Primary pulmonary lymphoma is defined as a clonal lymphoproliferative disorder affecting one or both lungs, without extrapulmonary involvement 3 months after diagnosis, and includes pulmonary MALT lymphoma and LG. MALT lymphoma is the most common pulmonary lymphoma. The disease is slow growing, most often asymptomatic, and revealed by chronic alveolar opacity on radiography. The diagnosis should involve minimally invasive techniques, and the prognosis is typically excellent. LG is a rare B-cell lymphoma driven by Epstein-Barr virus infection. The disease may mimic pulmonary vasculitis, often revealed by systemic signs. The diagnosis usually requires surgical lung biopsy. Its evolution is unpredictable, but median

survival is poor and chemotherapy is usually proposed. MCD and PEL are both driven by *Human herpesvirus 8* infection. Patients with MCD present with fever and lymphadenopathy associated with interstitial lung disease. PEL provokes a febrile, lymphocytic-exudative pleural effusion, without any pleural mass on CT. Specific chemotherapy is urgent for both MCD and PEL. NLH is a benign lymphoproliferative disorder of the lung that is usually asymptomatic and revealed by a single nodular opacity. The prognosis is good, without recurrence after surgical resection.

© 2017 S. Karger AG, Basel

Introduction

Primary pulmonary lymphoma is defined as a clonal lymphoid proliferation affecting the parenchyma and/or bronchi of one or both lungs, with no detectable extrapulmonary involvement at diagnosis or during the following 3 months [1, 2]. The most common primary pulmonary

Previous articles in this series: 1. Lazor R, Nicod LP: The lung in rare systemic diseases. *Respiration* 2017;94:1. 2. Tran C, Barbey F, Lazor R, Bonafé L: Pulmonary involvement in adult patients with inborn errors of metabolism. *Respiration* 2017;94:2–13.

Table 1. Typical presentation of some lymphoproliferative disorders of the lung

	Pulmonary MALT lymphoma	Nodular lymphoid hyperplasia	Lymphomatoid granulomatosis	Multicentric Castleman disease	Primary effusion lymphoma
Symptoms	>50%, asymptomatic	Usually asymptomatic	Asthenia, fever, or dyspnea	Dyspnea, fever, polyadenopathy, and hepatosplenomegaly	Dyspnea, fever, altered performance status
CT scan and PET scan	Unique or multiple lesions with air bronchograms with mild FDG uptake	2- to 4-cm nodule(s) without FDG uptake	Nodules and mass with poorly defined margins with FDG uptake	Peripheral and mediastinal lymphadenopathies; small pleural effusion, reticular and micronodular opacities; FDG uptake	Pleural effusion with FDG uptake
Diagnostic strategy	Transbronchial biopsy or percutaneous biopsies	Transbronchial biopsy or percutaneous biopsies	Surgery	Lymph node biopsy and PCR HHV8 in blood	Pleural fluid examination
Histology	Infiltration by clonal small B cells with lymphoepithelial lesions	Follicular hyperplasia, interfollicular plasmacytosis	Necrosis and large aberrant B cells infected by EBV	Follicular hyperplasia, involution of germinal centers, and hyperplasia of the mantle zone with “onion-skin” layers; high HHV8 level in blood	Large aberrant lymphoid cells infected by HHV8 and frequently by EBV; high HHV8 level in blood and pleura
Treatment	Localized: Surgery or radiotherapy Disseminated: non-urgent chemotherapy	Surgical excision or watch and wait	Usually aggressive chemotherapy	Urgent chemotherapy; antiviral and antiretroviral therapy	Urgent chemotherapy; antiretroviral therapy

MALT, mucosa-associated lymphoid tissue; PET, positron emission tomography; HHV8, *Human herpesvirus 8*; EBV, Epstein-Barr virus.

lymphoma types in order of decreasing frequency [1, 3] are (1) pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma, (2) diffuse large B-cell lymphoma, and (3) lymphomatoid granulomatosis (LG).

We review the kinds of lymphoproliferative disorder that the pneumologist may encounter and that require specific attention, although they may extend beyond this definition. Indeed, nodular lymphoid hyperplasia (NLH) and multicentric Castleman disease (MCD) are not clonal disorders, and primary effusion lymphoma (PEL) does not affect the lung but will be discussed here – but not diffuse large B-cell lymphoma. Each of these lymphoproliferative disorders clinically presents in different ways and is associated with a distinct histological subtype and a specific therapy (Table 1).

Pulmonary MALT Lymphoma

Mucosa-Associated Lymphoid Tissue

MALT is a lymphoid tissue that functions to defend the mucosa [1]. Functional B lymphocytes of MALT are

memory B cells, involved in immune responses. MALT is physiologically absent from the lung and initially recognized in lungs with infections of an undetermined nature [1]. MALT can also be associated with autoimmune disorders such as Sjögren syndrome.

MALT lymphoma belongs to the group of marginal-zone B-cell lymphomas that also include nodal and splenic marginal-zone lymphomas. However, these three subtypes present distinct clinical, morphological, and molecular features [4–8]. In all, 8% of adults with non-Hodgkin lymphoma have MALT lymphoma [9]. MALT lymphoma usually develops from tissues typically devoid of MALT, such as the stomach, salivary glands, lungs, and thyroid. The stomach is the most commonly affected organ, and several features of stomach MALT lymphoma have been extrapolated to other locations such as the lungs.

Etiology

MALT lymphoma may be considered a model of lymphoma driven by chronic antigen stimulation, whether from autoantigens or a microbial origin [10]. However, an

infectious agent does not infect or directly transform the lymphoid cells, unlike in lymphomas associated with *Human herpesvirus 8* (HHV8) infection (see below) [11]. In MALT lymphoma, the infectious agent increases the risk of lymphoma by chronically stimulating B lymphocytes.

For instance, MALT develops in the stomach with *Helicobacter pylori* infection that can later transform to lymphoma. *H. pylori* was formerly detected in 90% of gastric MALT lymphoma cases, and its eradication was associated with complete remission of the disease in 60–80% of cases of gastric MALT lymphoma [12, 13]. The increased use of antibiotics and proton pump inhibitors may have increased the rate of *H. pylori*-negative gastric MALT lymphoma to 50% [14].

Other infectious agents have been suggested as possible causes of MALT lymphoma at other sites [10, 15, 16]. A causal relationship has been suggested between *Campylobacter jejuni* infection and small-intestine MALT lymphoma and between *Hepatitis C virus* infection and some cases of splenic marginal-zone lymphoma. Several studies have also found associations but no proven causal relationship between *Borrelia burgdorferi* infection and skin MALT lymphoma and between *Chlamydophila psittaci* infection and ocular adnexal MALT lymphoma.

A causative antigen associated with MALT lymphoma in the lungs has yet to be found. Several studies of pulmonary MALT lymphoma used PCR to detect DNA from Chlamydiaceae, *Mycoplasma*, or *Mycobacterium* infection, or a 16S ribosomal RNA-based approach, but the results remained inconclusive [17–19]. In one study, Chlamydiaceae DNA was detected more frequently in MALT than in control tissue, although the difference was not statistically significant. In another study, no mycobacterial DNA was detected. A third study detected DNA from *Achromobacter xylosoxidans* in 57/124 cases of pulmonary MALT lymphoma versus 15/82 controls ($p = 0.004$) but with no proven causal relationship. Powerful tools developed for analyzing all DNA and RNA present in a given sample [20] could provide evidence for the presence of an unsuspected pathogen in pulmonary MALT lymphoma [21].

Chronic antigen stimulation may also have an autoimmune origin, particularly in the salivary and thyroid glands. A meta-analysis of 29,423 patients showed patients with Sjögren syndrome or systemic lupus erythematosus with an increased risk of marginal-zone lymphoma [22]. Indeed, patients with Sjögren syndrome showed a 6.5-fold increased risk of any type of lymphoma and a 1,000-fold increased risk of salivary gland MALT lymphoma.

Environmental risk factors have not been evidenced in pulmonary MALT lymphoma, although bakers and oil workers have shown increased risks of ocular adnexal and cutaneous MALT lymphoma, respectively [23].

Epidemiology, Clinical Tests, and Imaging

Pulmonary MALT lymphoma, although rare, represents almost 80% of primary pulmonary lymphoma cases [24–26]. The disease usually occurs at an age of 50–60 years, very occasionally affecting those under 30 years old [27]. Smoking rates (approx. 35%) are not higher among people with pulmonary MALT lymphoma than in the general population, and women are affected as often as men [26]. Up to 16% of patients present features of autoimmune disease [26].

In nearly half of MALT lymphoma cases, patients are asymptomatic at diagnosis, and investigations are initiated after abnormal findings on chest X-ray or CT. When present, symptoms are nonspecific, including cough, dyspnea, and chest pain. Crepitant rales are detected by pulmonary auscultation in less than 20% of cases. General symptoms such as fever and weight loss are particularly associated with aggressive disease forms [27].

On radiography, MALT lymphoma typically presents as a chronic alveolar localized opacity less than 5 cm in diameter, and is associated with air bronchograms in nearly 50% of cases [28–32]. CT (Fig. 1) most frequently shows bilateral and multiple lesions (in 60–77% of cases) and an intact bronchial lumen in the lesions [33, 34]. Less than 10% of cases show diffuse reticulonodular opacities, atelectasis, pleural effusion, or hilar or mediastinal lymphadenopathy [28–30]. The time between the initial abnormal clinical or radiological findings and diagnosis varies from 15 days to 8 years (mean 9 months) [26, 28–31].

Initial staging includes CT scanning of the chest, abdomen, and pelvis, with contrast injection. Bone marrow biopsy is not mandatory but may show MALT lymphoma dissemination in 13–30% of cases [5, 26, 35–37]. Similarly, concomitant disease in other sites, such as the stomach, is present in 25–35% of cases and justifies gastroscopy [36–38]. Other mucosal sites that must be assessed in symptomatic patients include the eyes, ears, nose, and throat by MRI or ultrasonography, and the small bowel by camera capsule. The sensitivity and specificity of positron emission tomography (PET) varies depending on the organ involved. The sensitivity in the stomach is 50–89%, versus 80–100% in the lung, and is very weak in bone marrow [26, 39–42].

The lactate dehydrogenase (LDH) level is usually normal. The β_2 -microglobulin level may be an independent

Fig. 1. Representative CT scans of pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma with chronic alveolar opacities, all confirmed histologically to be MALT lymphoma. **a** Right upper lobe consolidation with air bronchogram. **b** Left lower lobe consolidation with air bronchogram. **c** Multifocal consolidations from the right lower lobe and the middle lobe with air bronchogram (the bronchi are distended within the lesions); reticulonodular opacities from the left lower lobe and the left upper lobe. **d** Middle lobe ground-glass opacity with a solid component.

prognostic factor [36]. Monoclonal gammopathy is found in 20–60% of cases, more frequently with plasmacytic differentiation and disseminated disease [26, 28, 30–32].

Diagnostic Strategy

Tissue biopsy, the gold standard for diagnosis, may be achieved with bronchoscopy or CT-guided needle biopsy. Macroscopic findings of bronchoscopy are usually normal, although abnormalities such as inflammatory mucosa and bronchial stenosis may be observed [28]. Polypoid endobronchial lesions are rare and usually evoke small-cell non-Hodgkin lymphoma. Bronchial and transbronchial biopsies are more fruitful when performed on endobronchial lesions or guided by CT [28]. The sensitivity of bronchial and transbronchial biopsies in detecting MALT lymphoma was reported to be 31 and 88%, respectively [26].

Bronchoalveolar lavage (BAL) performed during bronchoscopy may also aid in the differential diagnosis of chronic alveolar opacities. This technique can indicate the absence of the tumor epithelial cells found in other malignancies such as lepidic adenocarcinoma or the presence of pathogens pointing to a chronic infection. The presence of lymphocytic alveolitis in BAL fluid can also indicate MALT lymphoma [43]. A B-lymphocyte level >10% and the demonstration of the clonality of lymphocytes or presence of t(11;18)(q21;q21) translocation in BAL fluid could be a powerful diagnostic tool, currently underemployed in clinical practice [28, 43–50]. However, a B-cell clone may be absent in BAL fluid in up to 29% of cases [51].

The sensitivity of CT-guided percutaneous biopsies has been reported to be 80% [26]. MALT lymphoma has anecdotally been diagnosed on endobronchial ultraso-

Fig. 2. Representative histology of pulmonary mucosa-associated lymphoid tissue lymphoma with positive CD20 staining (**a**) and cytokeratin staining in epithelial cells to highlight the lymphoepithelial lesions (**b**). Courtesy of Dr. Claire Danel, Hôpital Bichat, Paris, France.

nography in experienced hands, with flow cytometry performed on samples [52].

Cryobiopsy could be discussed by experienced teams before diagnostic surgery is performed as a last resort [53]. However, with a localized lesion, surgery provides the opportunity for ultimate treatment performed at the same time as the biopsy.

Diagnosis

MALT lymphoma is characterized by a lymphoid infiltrate composed of small cells with variable cytologic appearance, including small round lymphocytes, centrocyte-like cells, or monocytoid cells. The tumor cells infiltrate the bronchiolar or alveolar epithelium, thereby causing lymphoepithelial lesions [25, 29, 54–56]. Cohesive sheets of large B cells must suggest the diagnosis of diffuse large B-cell lymphoma.

Plasma cells may be numerous with or without light-chain restriction (κ or λ). The density of infiltration often produces a widening of the alveolar walls and a collapse of the residual alveolar lumen. The airways are often left

intact, which agrees with air bronchograms seen on CT. Amyloid deposits, granulomatous reactions, vascular invasion, or fibrosis may be evidenced [56–60].

Immunohistochemistry excludes reactive follicular hyperplasia or secondary localization to the lung with other lymphomas. Tumor cells express B-cell antigens (CD20 and CD79a) but not CD5, a marker of mantle cell lymphoma or chronic lymphocytic leukemia (Fig. 2) [25, 29, 31, 32, 54–57, 61]. Residual lymphoid follicles (CD21/CD23-positive) and small reactive T lymphocytes (CD3) may be seen [55, 57]. The proliferative index is usually low (Ki-67 <10%). Analysis of B-cell clonality is helpful but not sufficient to establish the diagnosis.

The main histological differential diagnoses are NLH and lymphocytic interstitial pneumonia, follicular bronchiolitis, chronic aspecific inflammatory reaction, and other low-grade B-cell lymphomas [56, 62]. The presence of an intraepithelial CD20/CD43-positive lymphocytic infiltrate is a strong indicator of MALT lymphoma [56]. Molecular analysis is useful to differentiate reactive conditions from lymphoma.

Fig. 3. Event free survival (a) and overall survival (b) in the IELSG randomized study: chlorambucil versus chlorambucil + rituximab in extranodal marginal-zone lymphoma [76]. The 5-year event-free survival was better with double therapy; however, the 5-year overall survival was not improved.

Lymphoid interstitial pneumonia is a benign lymphoproliferative disorder characterized by diffuse infiltration of the alveolar septa by dense collections of lymphocytes mixed with plasma cells and other cellular elements. The most frequent CT pattern is cysts associated with ground-glass infiltrates. Most cases are associated with connective tissue disorders, especially Sjögren syndrome, AIDS, or primary immunodeficiency.

Cytogenetic Abnormalities

Several cytogenetic abnormalities, although neither related to targeted therapy nor sufficient for diagnosis, have been associated with MALT lymphomas. The frequency and type of cytogenetic abnormalities may vary depending on the lymphoma site.

The most common cytogenetic abnormality is t(11;18)(q21;q21) translocation [63]. This translocation results in the production of a chimeric protein, API2-MALT1; it is

detected in approximately 40% of pulmonary cases, about 20% of gastric cases, and circa 15% of intestinal cases, but is absent in most cases of thyroid, salivary gland, and liver MALT lymphoma [64, 65]. In gastric MALT lymphoma, the presence of t(11;18)(q21;q21) translocation is associated with nodal dissemination and resistance to *H. pylori* antibiotics.

Other, rarer translocations or cytogenetic abnormalities include t(1;14)(p22;q32) (IGH-BCL10), t(14;18)(q32;q21) (IGH-MALT1), t(3;14)(p14.1;q32) (FOXP1-IGH), and trisomy 3 and 18 [63, 64]. Most of these translocations result in the constitutive activation of the NF- κ B signaling pathway, which may be specifically targeted. The translocations can be detected by an interphase fluorescence in situ hybridization assay of formalin-fixed paraffin-embedded tissue or RT-PCR of frozen tumor samples [63].

Finally, MALT lymphoma could develop as a result of both cytogenetic abnormalities and antigenic stimulation. Illustrating this point, a mouse genetically modified to overexpress API2-MALT1 showed lymphoma only after antigenic stimulation [66–68].

Treatment and Prognosis

Recent recommendations for gastric MALT lymphoma have been reported [69, 70]. Because no microorganism is identified in the lung, therapeutic options are surgery, chemotherapy, immunotherapy, radiotherapy, or “watch and wait” [71]. In localized lesions, surgical resection or radiotherapy may be considered; radiotherapy is associated with lower morbidity than is surgery [28, 30, 72–74].

In other cases, chemotherapy is preferred. Treatment with single-agent chemotherapy (chloraminophene or fludarabine) is not less preferred than multiple-agent chemotherapy (cyclophosphamide, adriamycin, vincristine, and prednisone; CHOP) [26, 28]. Rituximab alone is effective, with a 70% response rate, but associated with a 36% disease recurrence [75].

The first double-blind, phase III study of MALT lymphoma included 231 patients and compared chlorambucil to rituximab-chlorambucil [76]. The 5-year event-free survival was better with double therapy than with monotherapy (68 vs. 50%, $p = 0.02$) (Fig. 3). Double therapy increased the complete response rate (78 vs. 65%) [76]. However, the 5-year overall survival (89%) was not improved, and grade 3–4 neutropenia was more common with double therapy than with monotherapy. Rituximab alone was also evaluated and the results are still expected.

In a retrospective cohort of gastric MALT lymphoma cases, rituximab-chloraminophene was more efficient than rituximab alone in t(11;18)-positive patients, and rituximab alone was as efficient as double therapy in t(11;18)-negative patients [77, 78].

Numerous currently available therapies have had antitumoral effects, such as purine analogues (fludarabine and cladribine), pentostatin, NF- κ B inhibitors (bortezomib), or a combination of mitoxantrone and bendamustine [70, 79–85]. However, the respective value of each treatment is difficult to estimate [86]. Moreover, numerous phase II/III studies of marginal-zone lymphoma are evaluating compounds currently developed for other lymphomas (anti-btk, anti-CD20 antibody, etc.) [87].

The prognosis with MALT lymphomas is good, with 5-year overall survival >80% and a median survival of >10 years [25, 26, 28–32, 36–38, 54, 59, 88]. A long period of monitoring is required, even after surgical resection, because almost 50% of patients show recurrence, either at the same location or outside the thoracic region [28, 32, 54, 59, 61].

None of the following factors are associated with prognosis: gender, delay to diagnosis, symptoms, bilateral or unilateral lesions, or extrapulmonary involvement [26]. With a multivariate analysis including all localizations of MALT lymphoma, predictors of prognosis were an elevated β_2 -microglobulin level and stage IV classification according to the Ann Arbor system [36, 89].

Very recently, Thieblemont et al. [90] proposed a simple classification including age >70 years, Ann Arbor stage >2, and elevated LDH level. In a cohort of 393 patients, the addition of these three factors discriminated three risk groups with different 5-year progression-free survival rates (78, 63, and 29%; $p < 0.001$) and 5-year overall survival rates (99, 92, and 74%; $p < 0.001$).

Nodular Lymphoid Hyperplasia

Definition

NLH is a rare disease characterized by a nonclonal lymphoproliferation that usually forms a single nodule or, more rarely, multiple pulmonary nodules.

Clinical Presentation and Complementary Examinations

NLH may occur as a solitary lesion in patients without autoimmune disease or immunodeficiency. It may also be associated with combined variable immunodeficiency or, less frequently, with Sjögren syndrome and form a disease

called granulomatous-lymphocytic interstitial lung disease that is frequently associated with extrapulmonary localizations [91]. For clarity, only idiopathic NLH is discussed here.

There is no gender predominance, and the mean age at diagnosis is 60 years (range 18–80) [62, 92]. Some patients may present with cough or dyspnea, particularly with tracheal involvement, although the most frequent localization is parenchymal. Indeed, most patients are asymptomatic.

CT reveals a unique 2- to 4-cm nodule in 64% of cases (Fig. 4). One-third of the patients present with multiple nodules, and one-third with lymphadenopathy, hilar or mediastinal [62]. NLH usually does not show FDG uptake on PET scans, although a mild increase in uptake may be seen, particularly with cavitory lesions [93]. Blood tests are not helpful.

Diagnosis

The diagnosis of NLH is established by histology and requires exclusion of the differential diagnoses, particularly MALT lymphoma [94]. Although the diagnosis may be attempted with transbronchial or transthoracic biopsy, NLH features may also be involved in lung cancer or lymphoma, which cannot be excluded without surgical excision.

The typical histology is follicular hyperplasia, interfollicular plasmacytosis, and a variable degree of fibrosis. Immunohistochemical analysis (of CD3, CD20, etc.) is consistent with a reactive process, without an aberrant lymphocyte phenotype (Fig. 4) [62].

Unlike MALT lymphoma, none of the following features is present: lymphoepithelial lesions, amyloid deposits, B-cell clonality, light-chain restriction, or presence of t(11;14) translocation. NLH and hyper-IgG4 syndrome may coexist. However, in a recent series of 26 cases of NLH retrospectively assessed, none fulfilled the diagnosis of hyper-IgG4 syndrome. Moreover, none showed positive Epstein-Barr virus (EBV)-encoded RNA (EBER) staining [95].

Prognosis and Treatment

The only treatment reported is surgical excision, with excellent prognosis without recurrence. However, Kajiwara et al. [96] reported a case of natural regression. A watch-and-wait policy may be also discussed with this nonclonal disease. Because the disease is not fully understood from an etiological or evolutionary viewpoint, and with the risk of transformation to lymphoma, long-term follow-up is required.

Fig. 4. **a** CT scan of nodular lymphoid hyperplasia from the left lower lobe in the context of granulomatous-lymphocytic interstitial lung disease associated with combined variable immunodeficiency. **b, c** Lymphoid hyperplasia with lymphoid nodules along bronchioles in common variable immunodeficiency.

Fig. 5. Representative CT scans of lymphomatoid granulomatosis with nodules or a mass. **a** Spiculated 6-cm mass from the right upper lobe. **b** 1.5-cm nodule from the middle lobe associated with interstitial lung disease with diffuse ground-glass opacities. **c** Multiple nodules of different size with lower lobe predominance. All patients required surgical biopsy for the diagnosis.

Lymphomatoid Granulomatosis

Definition

LG is a rare B lymphoma associated with EBV infection [97]. It is frequent with immunodepression: autoimmune disease, AIDS, or solid-organ transplantation [98]. The prevalence is unknown, and about 600 cases have been reported [99–102].

Clinical Presentation and Complementary Examinations

The median age at diagnosis is 30–50 years, with a male/female ratio of 2/1 [100]. About 90% of patients are symptomatic, and the symptoms are frequently present for several months: general signs (50%) or respiratory signs (75%) [99].

The lung is involved in 80% of cases [99]. Nodules and a mass with poorly defined margins are frequent patterns seen on CT. Nodules are more frequent along the bronchovascular structures or interlobular septa and in the base (Fig. 5). The nodules may grow, form cavities, or spontaneously disappear [97]. Skin manifestations occur in 30–50% of cases: erythematous plaques, and nodules with predominance on the trunk and extremities [99].

Neurological manifestations occur in approximately 30% of cases. Symptoms may vary depending on the localization of the disease: the central or peripheral nervous system (confusion, paraplegia, hemiparesis, and ataxia), cranial nerves (hearing loss, diplopia, and dysarthria), or neurovegetative system (atonic bladder) [103]. MRI reveals multiple focal intraparenchymal lesions with increased signals on FLAIR and T2-weighted MRI images. This pattern may also be seen with neurological involvement of sarcoidosis, lymphoma, or vasculitis. Cerebrospinal fluid analysis may show an increased number of lymphocytes or a heightened protein level [103].

Ear, nose, and throat manifestations occur in 10–30% of cases and may mimic granulomatosis with polyangiitis (formerly Wegener granulomatosis) [104]. Renal involvement occurs in 10–40% of cases, mostly presenting as a mass seen on CT without renal insufficiency or proteinuria [105]. Other manifestations such as enlarged lymph nodes are rare.

Clinical staging requires specialized neurological and cutaneous evaluation, and radiological staging requires brain MRI and PET. PET may reveal renal, skin, nodal, and pulmonary involvement and may be used to evaluate response to therapy [106].

The complete blood count is normal in more than 50% of cases, although lymphopenia or hyperleukocytosis

may be seen [97, 100]. Half of the cases present polyclonal hypergammaglobulinemia. EBV serology is positive, and the EBV viral load is increased without specificity, with a mean of 18 copies/10⁶ genome equivalents [97].

Diagnosis

A diagnosis of LG requires histology, most frequently obtained by surgical lung biopsy for lung involvement, because tissues obtained by bronchoscopy rarely allow for a diagnosis. However, a diagnosis may be obtained by skin biopsy or by ear, nose, and throat biopsy [97]. Sampling from all accessible sites is recommended, because tumoral infiltration and EBV staining vary between sites [97].

The distribution of the lesions is patchy and the surrounding lung is almost normal, although fibroblastic foci may be seen at the periphery, as well as organizing pneumonia or edema. The lesions are angiocentric and associated with various degrees of necrosis [97, 107]. Contrary to the name of the disease, there is no granuloma, but a polymorphous infiltrate compound of lymphocytes and histiocytes is seen – and, rarely, plasma cells [100].

Most of the small lymphocytes are T cells (CD3/CD4). Atypical large cells and “ghost cells” are lymphoid (CD45) and are highlighted by CD20 immunostaining within the necrotic area. They may present an aberrant phenotype (CD20/CD43) [108]. They are stained on in situ hybridization for EBER, whereas staining for the latent membrane protein of EBV is positive in only 70% of cases (Fig. 6). The B cells are monoclonal, but clonality analysis is not required for the diagnosis, whereas EBER staining is almost mandatory, even if findings may be negative for up to 50% of cutaneous lesions [97, 99].

Finally, LG is histologically classified from grade 1 to grade 3 depending on the number of tumoral cells: grade 1, no large atypical cells, little necrosis, rare EBV-positive cells; grade 2, occasional large atypical cells, moderate necrosis, 5–20 EBV-positive cells/field; and grade 3, predominant population of large atypical cells that may be confluent and associated with extensive necrosis [109]. Indeed, atypical large lymphoid cells may be difficult to detect in low-grade lesions without specific immunostaining.

An infectious disease must be excluded particularly in localized diseases. Differentiating LG from granulomatosis with polyangiitis and necrotizing sarcoidosis may be difficult. Hodgkin lymphoma and other aggressive lymphomas also must be excluded.

Fig. 6. Representative histology of lymphomatoid granulomatosis with positive CD20 staining (**a**) and positive Epstein-Barr virus-encoded RNA (EBER) staining (**b**). Courtesy of Dr. Claire Danel, Hôpital Bichat, Paris, France.

Treatment and Prognosis

The median survival is 4 years. Causes of death in order of frequency are respiratory insufficiency (38–88%), hemoptysis (44–89%), neurological complications (7–31%), and infection (23–38%) [97, 100, 107].

Factors for good prognosis are older age, no symptoms, and unilateral lung involvement, and those for poor prognosis are age <25 years, neurological involvement, hepatosplenomegaly, leukopenia, persistent fever, and, histologically, the number of tumoral cells and amount of necrosis [97, 100, 107].

No therapeutic recommendations or clinical trials have been reported. Localized LG has been successfully

treated with surgery or radiotherapy [110]. Steroids, rituximab, and polychemotherapy are frequently prescribed, but rituximab is inconsistently effective [111, 112]. A striking response to interferon- α was reported [113]. Autologous or allogeneic stem cell transplantation may be considered [114]. Spontaneous regression may be observed, particularly with grade 1 LG. The prognosis for patients not in remission is poor [100].

Multicentric Castleman Disease

Human Herpesvirus 8

HHV8 was discovered in 1994 in Kaposi sarcoma lesions and was later associated with MCD and PEL [115–118]. Pulmonary manifestations of HHV8 infection occur almost exclusively in immunocompromised patients, mostly during HIV infection, and very rarely in older patients or during immunosuppressive therapy [119, 120].

HHV8 has two modes of viral replication. During the latent phase, HHV8 persists in infected cells without detectable replication in the blood [121]. During the lytic phase, replication may be detected in the blood, and viral genes such as viral interleukin-6, are expressed. Most of the clinical effects of MCD are secondary to the presence of viral cytokines such as viral interleukin-6 [122–124].

The reservoir of HHV8 is strictly human. The prevalence is almost 50% in sub-Saharan Africa, 30% in Sicily, and <1% in Northern Europe and Asia [125]. In low-prevalence countries, HHV8 transmission is mostly sexual, essentially in populations with high-risk sexual behavior, with a high frequency of HIV and HHV8 coinfection [125, 126]. In high-prevalence countries, the prevalence increases during childhood, and transmission occurs probably mostly through saliva [127, 128]. Primary HHV8 infection is asymptomatic or results in nonspecific signs of infection and is rarely diagnosed [129].

Definition

The definition of MCD is histological: angiofollicular lymph node hyperplasia. The most frequent form is localized, occurs in nonimmunocompromised patients, and is not associated with HHV8 infection [130]. Localized MCD may take the form of a single mediastinal node (Fig. 7). As developed below, HHV8-associated MCD is clinically and histologically different from classic hyaline-vascular or plasma-cell-type MCD [116, 131].

MCD is rare. The largest series reported were 173 patients with MCD-associated HIV infection in France,

whereas approximately 150,000 patients are living with HIV infection in France [131–133].

Clinical Presentation and Complementary Examinations

The initial presentation of MCD may suggest lymphoma with fever, polyadenopathy, and hepatosplenomegaly. Questioning may reveal previous flares that spontaneously resolved and remained without diagnosis.

Cutaneous or mucosal localization of Kaposi sarcoma may be present in up to 75% of cases [134]. Cough, dyspnea, and expectoration are present in 33–75% of cases, but hemoptysis is rare. Nasal obstruction is frequent. Pulmonary auscultation may show crackles [132, 134, 135].

When respiratory symptoms are present, chest X-ray shows bilateral interstitial and alveolar opacities. A small pleural effusion may be present. Chest CT reveals reticular and micronodular opacities with lymphatic distribution: subpleural, peribronchovascular, or septal. Nodular or ground-glass opacities may be present. CT reveals 1- to 3-cm mediastinal lymphadenopathies. CT findings return to normal with resolution of the flare (Fig. 7) [136].

Almost always, the C-reactive protein level is >200 mg/L and anemia occurs [137]. Liver enzyme and creatinine levels may be increased. Renal insufficiency may be related to autoimmune thrombotic thrombocytopenic purpura [138, 139]. In about 50% of cases, protein electrophoresis shows polyclonal hypergammaglobulinemia and hypoalbuminemia. Autoantibodies are present in 30% of cases: antiglobulin or anticardiolipin, antiphospholipid, or anti-ADAMTS13 antibodies [139]. CD4 counts are generally <350/mm³.

The viral HHV8 load as assessed by PCR is usually between 2 and 4 log copies/10⁵ peripheral blood mononuclear cells, and thus HHV8 serology is not helpful [140]. HHV8 PCR has a good negative-predictive value [121, 137]. A high HHV8 viral load may predict an MCD flare, whereas PCR results are often negative for patients in remission [121, 141, 142].

Diagnosis

MCD is usually diagnosed by lymph node biopsy [143]. Histology shows follicular hyperplasia, hyalinization, and involution of germinal centers and hyperplasia of the mantle zone with concentric rings of lymphocytes called “onion skin” layers. Vascularity is increased, with capillary proliferation and endothelial hyperplasia. Sheets of plasma cells are present in interfollicular areas. The results of only one surgical lung biopsy have been reported, and they showed lesions similar to those in lymph nodes [136].

Fig. 7. a Chest CT scan of multicentric Castleman disease (MCD) with 3-cm mediastinal (zones 4R and 7) lymphadenopathies. **b** Positron emission tomography CT scan of MCD with multiple peripheral and mediastinal adenopathies with FDG uptake.

HHV8-infected cells, dispersed in the mantle zone, are detected by immunohistochemistry with latent nuclear antigen antibody [144, 145]. HHV8-infected cells are not infected with EBV and are not stained with EBER. Kaposi sarcoma and MCD lesions may coexist in the same lymph node in almost two-thirds of cases [146].

HHV-8 infected cells are polyclonal, although the characterization of surface immunoglobulin shows only IgMλ B cells [147]. B cells may group in a sheet of monoclonal cells called microlymphoma; however, the consequences of this observation remain to be determined [145].

The main differential diagnoses are tuberculosis and lymphomas, which both require a histological diagnosis. With a high HHV8 viral load, HHV8-related disease is likely and non-HHV8-related disease is unlikely. How-

ever, an unusual evolution during therapy should suggest reconsidering the diagnosis in the absence of histological proof. During HIV infection, pulmonary manifestations of MCD should exclude infections that justify bronchoscopy with BAL fluid analysis [135]. Pleural effusion may be secondary to MCD-associated hemophagocytosis but also Kaposi sarcoma or PEL, which must be excluded by pleural fluid analysis.

A syndrome called “thrombocytopenia, anasarca including pleural effusion and ascites, fever, renal insufficiency, and organomegaly” (TAFRO) has recently been defined in Japanese patients [148]. This syndrome resembles MCD without HHV8 infection but responds to corticosteroids and tocilizumab.

Prognosis and Treatment

Median survival was reported to be <1 year and mortality 47% [134, 149]. The main reported causes of death are infections (24%), multiple organ dysfunctions (15%), non-Hodgkin lymphomas (15%), and MCD (9%). More recent series reported >75% 5-year survival partially due to the introduction of combined active antiretroviral therapy [134, 149, 150]. Although not demonstrated, delayed MCD diagnosis is probably associated with poor prognosis [134].

The risk of lymphoma, mostly related to HHV8, was previously found to be 10- to 20-fold increased with MCD [150]. This risk has been greatly reduced with the expanded use of rituximab and antiretroviral therapies [151].

MCD flares may spontaneously resolve, but they are likely to recur and be life-threatening without a specific therapy. Therapeutic recommendations rely on only expert opinions that propose treating (1) the HIV infection, (2) the lymphoid proliferation, and (3) the HHV8 infection [143, 152].

Although active against HHV8 infection in vitro, cidofovir alone has no effect on MCD. A retrospective series showed transient remission with high-dose zidovudine and valganciclovir, but only 23% long-term responders [153, 154].

MCD does not exhibit monoclonal lymphoid proliferation but is aggressive and lethal. The evidence supports the use of chemotherapy. Chemotherapy is urgent and induces rapid remission. Indeed, in a retrospective analysis of patients with hemophagocytosis in an intensive care unit, MCD diagnosis was associated with good prognosis [155]. Remission of MCD symptoms is achieved at about 24–48 h with intravenous etoposide. Etoposide may be given orally and once a week thereafter. Corticosteroids may have a partial effect on MCD flares, but they

are associated with worsening of Kaposi sarcoma lesions and are not recommended [143].

However, long-term therapy with etoposide is associated with an increased risk of myelodysplasia, and alternative long-term treatment should be considered [134, 156, 157]. Although not effective as first-line therapy, rituximab led to prolonged MCD remission in almost 80% of cases [143, 149, 158–161]. With rituximab, 5-year overall survival may be >90% [149]. However, Kaposi sarcoma worsens after rituximab injection in almost half of the cases. Prolonged remission has also been reported after polychemotherapy with CHOP or equivalent regimes [134, 162, 163]. Finally, some MCD experts propose etoposide as first-line therapy to control the disease and a maintenance treatment combining ganciclovir, etoposide, and rituximab, along with optimizing antiretroviral therapy [143, 152].

Primary Effusion Lymphoma

Definition

PEL involves the pleura, pericardium, or peritoneum in immunocompromised patients. PEL is distinguished from solid lymphoma with secondary effusion localization [109, 117]. However, PEL has also been described in a solid form – called extracavitary PEL – that may occur as a relapse of classic PEL or as an initial presentation [164, 165]. PEL is a rare lymphoma corresponding to 0.5% of all lymphoma cases and 1–8% of HIV-associated non-Hodgkin lymphoma cases [165–167].

Clinical Presentation and Complementary Examinations

Patients mostly present with fever, altered performance status, and dyspnea [168]. Pleural effusion is present in 85% of cases and is associated with ascites in 50% of cases [169]. PEL may also provoke a specific pericardial localization with a risk of secondary cardiac tamponade [168]. Hepatomegaly and splenomegaly are present in two-thirds of cases [168]. Cutaneous or mucosal localization of Kaposi sarcoma is present in 25–100% of cases, and 9–50% of patients present with concomitant MCD. However, enlarged peripheral lymph nodes are rare. Neurological deficit or a maxillary lesion should lead to suspicion of the specific localization of extracavitary PEL [169].

Anemia is frequent and is associated in 50% of cases with thrombocytopenia and hypoalbuminemia [169]. LDH levels are frequently elevated [168]. The mean CD4 count is 150–200/mm³ [168].

Fig. 8. Cytology of a primary effusion lymphoma confirmed by latent nuclear antigen staining and human herpesvirus 8 PCR. Courtesy of Dr. Claire Danel, Hôpital Bichat, Paris, France.

Bone marrow biopsy may show hemophagocytosis, but only rarely tumor cells [168, 169]. CT reveals pleural effusion without pulmonary lesions or a detectable mass. A small pleural thickening may be present. Pericardial or peritoneal effusion may occur [170]. Pleural fluid analysis, mandatory for a diagnosis, shows serohematic exudative fluid [168].

Diagnosis

Diagnosis is by cytologic examination of the pleural fluid. Pleural biopsy is generally not required or helpful. Cells are polymorphous and large, sometimes immunoblastic, with some plasma cell differentiation and irregular polylobular nuclei (Fig. 8). Cytoplasm is abundant and hyperbasophilic. Mitoses are numerous. Cells generally do not express B-cell markers (CD19 or CD20) or T-cell markers (CD3) but do express CD45, which confirms the lymphoid origin, and may express aberrant T-cell markers such as intracytoplasmic CD3 or CD4. They may coexpress activation markers (CD30, CD38, CD71, or MUM1) and plasma cell markers (CD138) [171, 172]. The B cells are monoclonal, but clonality analysis is not helpful for the diagnosis [173].

In contrast, HHV8 infection must be confirmed by immunohistochemistry with latent nuclear antigen staining on tumor cells or PCR evaluation of the viral load in pleural fluid. In blood, the HHV8 viral load is generally >4 log copies/ 10^5 peripheral blood mononuclear cells, and there is a 3:4 log ratio between pleura and blood [121, 140].

In 70% of cases, tumor cells are coinfecting with EBV. However, immunostaining with latent membrane pro-

tein is negative, whereas EBER staining or PCR analysis of the pleural fluid is positive [169]. Cytogenetic analysis shows a complex karyotype without common or recurrent chromosomal abnormality [174].

Detection of HHV8 is helpful to differentiate PEL from other lymphomas [175, 176]. Pleural effusion with fever in an immunocompromised patient is more often secondary to Kaposi sarcoma or an infectious disease such as tuberculosis than due to PEL. In these cases, pleural fluid analysis does not reveal tumor cells, and HHV8 PCR findings in pleural fluid are negative or weak.

Prognosis and Treatment

No recommended therapy for PEL exists. Median survival is <1 year, with a 39% 1-year survival [169]. Absence of antiretroviral therapy at diagnosis is associated with poor prognosis, and optimized antiretroviral therapy alone can have antitumoral activity and may lead to remission [169, 177]. The number and type of involved cavities could be associated with median survival [178]. However, a retrospective single-center study did not find any statistical difference between patients with involvement of only one cavity and those with involvement of more than one cavity [165]. LDH level and CD4 positivity may be prognostic factors [179].

Polychemotherapy such as CHOP with or without methotrexate is most often prescribed. Although associated with high morbidity, the treatment may result in complete remission in up to 61% of cases [169, 180]. Rituximab should not be prescribed, because tumor cells do not express CD20 and rituximab increases the immunodeficiency. Bortezomib has been investigated, and rapamycin, anti-vascular endothelial growth factor therapy, or interferon has been found to be effective in anecdotal cases [169, 181, 182]. Pleurodesis with talc or intrapleural cidofovir may be discussed in palliative situations [183, 184].

Conclusions

In lymphoproliferative disorders, lung involvement can be widespread, is varied, and may be of concern to lung specialists. Unfortunately, the rarity of these diseases frequently leads to delays in diagnosis or unnecessary examinations. The first step always is to make an assessment of the background: whether or not immunodeficiency is involved, and whether or not it is an autoimmune disease. The second step is to evaluate the presence of general signs that then require a rapid diagnosis.

However, minimally invasive procedures (such as pleural fluid analysis and transbronchial biopsy) with specialized and oriented analysis (immunohistochemistry and molecular biological techniques) most frequently allow for a diagnosis. Finally, there are neither clinical tri-

als nor recommendations on pulmonary lymphoproliferative disorders, and treatment is based on expert opinion, which justifies seeking advice from a specialized center.

References

- Isaacson PG, Norton AJ: Extranodal Lymphomas. New York, Churchill Livingstone, 1994.
- Freeman C, Berg JW, Cutler SJ: Occurrence and prognosis of extranodal lymphomas. *Cancer* 1972;29:252–260.
- Jaffe E, Travis W: Lymphomatoid Granulomatosis and Lymphoproliferative Disorders of the Lung. Philadelphia, Lippincott, 1991.
- Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, De Wolf-Peters C, Falini B, Gatter KC, et al: A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994;84:1361–1392.
- Nathwani BN, Anderson JR, Armitage JO, Cavalli F, Diebold J, Drachenberg MR, Harris NL, MacLennan KA, Müller-Hermelink HK, Ullrich FA, Weisenburger DD: Marginal zone B-cell lymphoma: a clinical comparison of nodal and mucosa-associated lymphoid tissue types. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol* 1999;17:2486–2492.
- Remstein ED, James CD, Kurtin PJ: Incidence and subtype specificity of API2-MALT1 fusion translocations in extranodal, nodal, and splenic marginal zone lymphomas. *Am J Pathol* 2000;156:1183–1188.
- Campo E, Miquel R, Krenacs L, Sorbara L, Raffeld M, Jaffe ES: Primary nodal marginal zone lymphomas of splenic and MALT type. *Am J Pathol* 1999;23:59–68.
- Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES: The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood* 2011;117:5019–5032.
- A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood* 1997;89:3909–3918.
- Suarez F, Lortholary O, Hermine O, Lécuit M: Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven lymphoproliferation. *Blood* 2006;107:3034–3044.
- Borie R, Cadranel J, Guihot A, Marcelin AG, Galicier L, Couderc LJ: Pulmonary manifestations of human herpesvirus-8 during HIV infection. *Eur Respir J* 2013;42:1105–1118.
- Amedei A, Bergman MP, Appelmeik BJ, Azzurri A, Benaglio M, Tamburini C, van der Zee R, Telford JL, Vandenbroucke-Grauls CM, D'Elia MM, Del Prete G: Molecular mimicry between *Helicobacter pylori* antigens and H⁺,K⁺-adenosine triphosphatase in human gastric autoimmunity. *J Exp Med* 2003;198:1147–1156.
- Parsonnet J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, Orentreich N, Vogelmann JH, Friedman GD: *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med* 1994;330:1267–1271.
- Raderer M, Wöhrer S, Kiesewetter B, Dolak W, Lagler H, Wotherspoon A, Muellauer L, Chott A: Antibiotic treatment as sole management of *Helicobacter pylori*-negative gastric MALT lymphoma: a single center experience with prolonged follow-up. *Ann Hematol* 2015;94:969–973.
- Bertonni F, Zucca E: State-of-the-art therapeutics: marginal-zone lymphoma. *J Clin Oncol* 2005;23:6415–6420.
- Ferry JA: Extranodal lymphoma. *Arch Pathol Lab Med* 2008;132:565–578.
- Chanudet E, Zhou Y, Bacon CM, Wotherspoon AC, Müller-Hermelink HK, Adam P, Dong HY, de Jong D, Li Y, Wei R, Gong X, Wu Q, Ranaldi R, Goteri G, Pileri SA, Ye H, Hamoudi RA, Liu H, Radford J, Du MQ: *Chlamydia psittaci* is variably associated with ocular adnexal MALT lymphoma in different geographical regions. *J Pathol* 2006;209:344–351.
- Catherinot E, Longchamp E, Ferroni A, Rivaud E, Cahen P, Couderc LJ: Pulmonary mucosa-associated lymphoid tissue lymphoma revisited. *Eur Respir J* 2016;48:1250–1251.
- Adam P, Czapiewski P, Colak S, Kosmidis P, Tousseyn T, Sagaert X, Boudova L, Okoń K, Morresi-Hauf A, Agostinelli C, Pileri S, Pruneri G, Martinelli G, Du MQ, Fend F: Prevalence of *Achromobacter xylosoxidans* in pulmonary mucosa-associated lymphoid tissue lymphoma in different regions of Europe. *Br J Haematol* 2014;164:804–810.
- Foulongne V, Sauvage V, Hebert C, Dereure O, Cheval J, Gouilh MA, Pariente K, Segondy M, Burguière A, Manuguerra JC, Caro V, Eloit M: Human skin microbiota: high diversity of DNA viruses identified on the human skin by high throughput sequencing. *PLoS One* 2012;7:e38499.
- Lécuit M, Eloit M: The diagnosis of infectious diseases by whole genome next generation sequencing: a new era is opening. *Front Cell Infect Microbiol* 2014;4:25.
- Ekström Smedby K, Vajdic CM, Falster M, Engels EA, Martínez-Maza O, Turner J, Hjalgrim H, Vineis P, Seniori Costantini A, Bracci PM, Holly EA, Willett E, Spinelli JJ, La Vecchia C, Zheng T, Becker N, de Sanjosé S, Chiu BC, Dal Maso L, Cocco P, Maynadié M, Foretova L, Staines A, Brennan P, Davis S, Severson R, Cerhan JR, Breen EC, Birmann B, Grulich AE, Cozen W: Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood* 2008;111:4029–4038.
- Bracci PM, Benavente Y, Turner JJ, Paltiel O, Slager SL, Vajdic CM, Norman AD, Cerhan JR, Chiu BC, Becker N, Cocco P, Dogan A, Nieters A, Holly EA, Kane EV, Smedby KE, Maynadié M, Spinelli JJ, Roman E, Glimelius B, Wang SS, Sampson JN, Morton LM, de Sanjosé S: Medical history, lifestyle, family history, and occupational risk factors for marginal zone lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr* 2014;2014:52–65.
- Kurtin PJ, Myers JL, Adlakha H, Strickler JG, Lohse C, Pankratz VS, Inwards DJ: Pathologic and clinical features of primary pulmonary extranodal marginal zone B-cell lymphoma of MALT type. *Am J Surg Pathol* 2001;25:997–1008.
- Li G, Hansmann ML, Zwingers T, Lennert K: Primary lymphomas of the lung: morphological, immunohistochemical and clinical features. *Histopathology* 1990;16:519–531.
- Borie R, Wislez M, Thabut G, Antoine M, Rabbat A, Couderc LJ, Monnet I, Nunes H, Blanc FX, Mal H, Bergeron A, Dusser D, Israël-Biet D, Crestani B, Cadranel J: Clinical characteristics and prognostic factors of pulmonary MALT lymphoma. *Eur Respir J* 2009;34:1408–1416.
- Cadranel J, Wislez M, Antoine M: Primary pulmonary lymphoma. *Eur Respir J* 2002;20:750–762.
- Cordier JF, Chailleux E, Lauque D, Reynaud-Gaubert M, Dietemann-Molard A, Dalphin JC, Blanc-Jouvan F, Loire R: Primary pulmonary lymphomas. A clinical study of 70 cases in nonimmunocompromised patients. *Chest* 1993;103:201–208.

- 29 Herbert A, Wright DH, Isaacson PG, Smith JL: Primary malignant lymphoma of the lung: histopathologic and immunologic evaluation of nine cases. *Hum Pathol* 1984;15:415–422.
- 30 Kennedy JL, Nathwani BN, Burke JS, Hill LR, Rappaport H: Pulmonary lymphomas and other pulmonary lymphoid lesions. A clinicopathologic and immunologic study of 64 patients. *Cancer* 1985;56:539–552.
- 31 Le Tourneau A, Audouin J, Garbe L, Capron F, Servais B, Monges G, Payan H, Diebold J: Primary pulmonary malignant lymphoma, clinical and pathological findings, immunocytochemical and ultrastructural studies in 15 cases. *Hematol Oncol* 1983;1:49–60.
- 32 L'Hoste RJ Jr, Filippa DA, Lieberman PH, Bretsky S: Primary pulmonary lymphomas. A clinicopathologic analysis of 36 cases. *Cancer* 1984;54:1397–1406.
- 33 Lee DK, Im JG, Lee KS, Lee JS, Seo JB, Goo JM, Kim TS, Lee JW: B-cell lymphoma of bronchus-associated lymphoid tissue (BALT): CT features in 10 patients. *J Comput Assist Tomogr* 2000;24:30–34.
- 34 Wislez M, Cadranet J, Antoine M, Milleron B, Bazot M, Mayaud C, Carette MF: Lymphoma of pulmonary mucosa-associated lymphoid tissue: CT scan findings and pathological correlations. *Eur Respir J* 1999;14:423–429.
- 35 Thieblemont C, Bastion Y, Berger F, Rieux C, Salles G, Dumontet C, Felman P, Coiffier B: Mucosa-associated lymphoid tissue gastrointestinal and nongastrointestinal lymphoma behavior: analysis of 108 patients. *J Clin Oncol* 1997;15:1624–1630.
- 36 Thieblemont C, Berger F, Dumontet C, Moullet I, Bouafia F, Felman P, Salles G, Coiffier B: Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. *Blood* 2000;95:802–806.
- 37 Zinzani PL, Magagnoli M, Galieni P, Martelli M, Poletti V, Zaja F, Molica S, Zaccaria A, Cantonetti AM, Gentilini P, Guardigni L, Gherlinzoni F, Ribersani M, Bendandi M, Albertini P, Tura S: Nongastrointestinal low-grade mucosa-associated lymphoid tissue lymphoma: analysis of 75 patients. *J Clin Oncol* 1999;17:1254.
- 38 Raderer M, Vorbeck F, Formanek M, Österreicher C, Valencak J, Penz M, Kornek G, Hamilton G, Dragosics B, Chott A: Importance of extensive staging in patients with mucosa-associated lymphoid tissue (MALT)-type lymphoma. *Br J Cancer* 2000;83:454–457.
- 39 Enomoto K, Hamada K, Inohara H, Higuchi I, Tomita Y, Kubo T, Hatazawa J: Mucosa-associated lymphoid tissue lymphoma studied with FDG-PET: a comparison with CT and endoscopic findings. *Ann Nucl Med* 2008;22:261–267.
- 40 Beal KP, Yeung HW, Yahalom J: FDG-PET scanning for detection and staging of extranodal marginal zone lymphomas of the MALT type: a report of 42 cases. *Ann Oncol* 2005;16:473–480.
- 41 Bae YA, Lee KS, Han J, Ko YH, Kim BT, Chung MJ, Kim TS: Marginal zone B-cell lymphoma of bronchus-associated lymphoid tissue: imaging findings in 21 patients. *Chest* 2008;133:433–440.
- 42 Hoffmann M, Wöhrer S, Becherer A, Chott A, Streubel B, Kletter K, Raderer M: ¹⁸F-fluorodeoxy-glucose positron emission tomography in lymphoma of mucosa-associated lymphoid tissue: histology makes the difference. *Ann Oncol* 2006;17:1761–1765.
- 43 Drent M, Wagenaar SS, Mulder PH, van Velzen-Blad H, Diamant M, van den Bosch JM: Bronchoalveolar lavage fluid profiles in sarcoidosis, tuberculosis, and non-Hodgkin's and Hodgkin's disease. An evaluation of differences. *Chest* 1994;105:514–519.
- 44 Costabel U, Bross KJ, Matthys H: Diagnosis by bronchoalveolar lavage of cause of pulmonary infiltrates in hematological malignancies. *Br Med J (Clin Res Ed)* 1985;290:1041.
- 45 Pisani RJ, Witzig TE, Li CY, Morris MA, Thibodeau SN: Confirmation of lymphomatous pulmonary involvement by immunophenotypic and gene rearrangement analysis of bronchoalveolar lavage fluid. *Mayo Clin Proc* 1990;65:651–656.
- 46 Schwaiger A, Prior C, Weyrer K, Umlauf F, Gattringer C, Grünwald K, Tötsch M, Fend F: Non-Hodgkin's lymphoma of the lung diagnosed by gene rearrangement from bronchoalveolar lavage fluid: a fast and noninvasive method. *Blood* 1991;77:2538–2539.
- 47 Shiota T, Chiba W, Ikeda S, Ikei N: Gene analysis of pulmonary pseudolymphoma. *Chest* 1993;103:335–338.
- 48 Subramanian D, Albrecht S, Gonzalez JM, Cagle PT: Primary pulmonary lymphoma. Diagnosis by immunoglobulin gene rearrangement study using a novel polymerase chain reaction technique. *Am Rev Respir Dis* 1993;148:222–226.
- 49 Zompi S, Couderc LJ, Cadranet J, Antoine M, Epardeau B, Fleury-Feith J, Popa N, Santoli F, Farcet JP, Delfau-Larue MH: Clonality analysis of alveolar B lymphocytes contributes to the diagnostic strategy in clinical suspicion of pulmonary lymphoma. *Blood* 2004;103:3208–3215.
- 50 Kido T, Yatera K, Noguchi S, Sakurai Y, Nagata S, Kozaki M, Tokuyama S, Ogoshi T, Kawanami T, Yoshii C, Mukae H: Detection of *MALT1* gene rearrangements in BAL fluid cells for the diagnosis of pulmonary mucosa-associated lymphoid tissue lymphoma. *Chest* 2012;141:176–182.
- 51 Borie R, Wislez M, Antoine M, Fleury-Feith J, Thabut G, Crestani B, Monnet I, Nunes H, Delfau-Larue MH, Cadranet J: Clonality and phenotyping analysis of alveolar lymphocytes is suggestive of pulmonary MALT lymphoma. *Respir Med* 2011;105:1231–1237.
- 52 Nunez AL, Jhala NC, Carroll AJ, Mikhail FM, Reddy VV, Xian RR, Jhala DN: Endoscopic ultrasound and endobronchial ultrasound-guided fine-needle aspiration of deep-seated lymphadenopathy: analysis of 1,338 cases. *Cytojournal* 2012;9:14.
- 53 Poletti V, Gurioli C, Piciocchi S, Rossi A, Ravaglia C, Dubini A, Asiola S, Casoni GL: Intravascular large B cell lymphoma presenting in the lung: the diagnostic value of transbronchial cryobiopsy. *Sarcoidosis Vasc Diffuse Lung Dis* 2015;31:354–358.
- 54 Addis BJ, Hyjek E, Isaacson PG: Primary pulmonary lymphoma: a re-appraisal of its histogenesis and its relationship to pseudolymphoma and lymphoid interstitial pneumonia. *Histopathology* 1988;13:1–17.
- 55 Nicholson AG, Wotherspoon AC, Diss TC, Butcher DN, Sheppard MN, Isaacson PG, Corrin B: Pulmonary B-cell non-Hodgkin's lymphomas. The value of immunohistochemistry and gene analysis in diagnosis. *Histopathology* 1995;26:395–403.
- 56 Bégueret H, Vergier B, Parrens M, Lehours P, Laurent F, Vernejoux JM, Dubus P, Velly JF, Mégraud F, Taytard A, Merlio JP, de Mascarel A: Primary lung small B-cell lymphoma versus lymphoid hyperplasia: evaluation of diagnostic criteria in 26 cases. *Am J Surg Pathol* 2002;26:76–81.
- 57 Fiche M, Caprons F, Berger F, Galateau F, Cordier JF, Loire R, Diebold J: Primary pulmonary non-Hodgkin's lymphomas. *Histopathology* 1995;26:529–537.
- 58 Turner RR, Colby TV, Doggett RS: Well-differentiated lymphocytic lymphoma. A study of 47 patients with primary manifestation in the lung. *Cancer* 1984;54:2088–2096.
- 59 Koss MN, Hochholzer L, Nichols PW, Wehunt WD, Lazarus AA: Primary non-Hodgkin's lymphoma and pseudolymphoma of lung: a study of 161 patients. *Hum Pathol* 1983;14:1024–1038.
- 60 Foulet A, Petrella T, Viard H, Jeannin L, Drouot F, Arnould L, Justrabo E, Michiels R: Lympho-epithelial lesions induced by plasma cells in a pulmonary MALT lymphoma (in French). *Ann Pathol* 1994;14:36–40.
- 61 Peterson H, Snider HL, Yam LT, Bowlds CF, Arnn EH, Li CY: Primary pulmonary lymphoma. A clinical and immunohistochemical study of six cases. *Cancer* 1985;56:805–813.
- 62 Abbondanzo SL, Rush W, Bijwaard KE, Koss MN: Nodular lymphoid hyperplasia of the lung: a clinicopathologic study of 14 cases. *Am J Surg Pathol* 2000;24:587–597.
- 63 Remstein ED, Dogan A, Einerson RR, Pateroster SF, Fink SR, Law M, Dewald GW, Kurtin PJ: The incidence and anatomic site specificity of chromosomal translocations in primary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in North America. *Am J Surg Pathol* 2006;30:1546–1553.

- 64 Farinha P, Gascoyne RD: Molecular pathogenesis of mucosa-associated lymphoid tissue lymphoma. *J Clin Oncol* 2005;23:6370–6378.
- 65 Streubel B, Simonitsch-Klupp I, Müllauer L, Lamprecht A, Huber D, Siebert R, Stolte M, Trautinger F, Lukas J, Puspök A, Formanek M, Assanasen T, Müller-Hermelink HK, Ceroni L, Raderer M, Chott A: Variable frequencies of MALT lymphoma-associated genetic aberrations in MALT lymphomas of different sites. *Leukemia* 2004;18:1722–1726.
- 66 Li Z, Wang H, Xue L, Shin DM, Roopenian D, Xu W, Qi CF, Sangster MY, Orihuela CJ, Tuomanen E, Rehng JE, Cui X, Zhang Q, Morse HC 3rd, Morris SW: Eμ-BCL10 mice exhibit constitutive activation of both canonical and noncanonical NF-κB pathways generating marginal zone (MZ) B-cell expansion as a precursor to splenic MZ lymphoma. *Blood* 2009;114:4158–4168.
- 67 Sagaert X, Theys T, De Wolf-Peeters C, Marynen P, Baens M: Splenic marginal zone lymphoma-like features in API2-MALT1 transgenic mice that are exposed to antigenic stimulation. *Haematologica* 2006;91:1693–1696.
- 68 Baens M, Fevery S, Sagaert X, Noels H, Hagens S, Broeckx V, Billiau AD, De Wolf-Peeters C, Marynen P: Selective expansion of marginal zone B cells in Eμ-API2-MALT1 mice is linked to enhanced IκB kinase γ polyubiquitination. *Cancer Res* 2006;66:5270–5277.
- 69 Dreyling M, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O, Kluin-Nelemans JC, Ladetto M, Le Gouill S, Iannitto E, Pileri S, Rodriguez J, Schmitz N, Wotherpoon A, Zinzani P, Zucca E: ESMO Consensus conferences: guidelines on malignant lymphoma. Part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. *Ann Oncol* 2013;24:857–877.
- 70 Zucca E, Stathis A, Bertoni F: The management of nongastric MALT lymphomas. *Oncology (Williston Park)* 2014;28:86–93.
- 71 Wöhrer S, Kiesewetter B, Fischbach J, Müllauer L, Troch M, Lukas J, Mayerhoefer ME, Raderer M: Retrospective comparison of the effectiveness of various treatment modalities of extragastric MALT lymphoma: a single-center analysis. *Ann Hematol* 2014;93:1287–1295.
- 72 Girinsky T, Paumier A, Ferme C, Hanna C, Ribrag V, Leroy-Ladurie F, Ghalibafian M: Low-dose radiation treatment in pulmonary mucosa-associated lymphoid tissue lymphoma: a plausible approach? A single-institution experience in 10 patients. *Int J Radiat Oncol Biol Phys* 2012;83:e385–e389.
- 73 Wang L, Xia ZJ, Zhang YJ, Huang HQ, Lin TY, Lu Y: Radical surgery may be not an optimal treatment approach for pulmonary MALT lymphoma. *Tumour Biol* 2015;36:6409–6416.
- 74 Nakamura S, Sugiyama T, Matsumoto T, Iijima K, Ono S, Tajika M, Tari A, Kitadai Y, Matsumoto H, Nagaya T, Kamoshida T, Watanabe N, Chiba T, Origasa H, Asaka M; JAPAN GAST Study Group: Long-term clinical outcome of gastric MALT lymphoma after eradication of *Helicobacter pylori*: a multicentre cohort follow-up study of 420 patients in Japan. *Gut* 2012;61:507–513.
- 75 Conconi A, Martinelli G, Thieblemont C, Ferreri AJ, Devizzi L, Peccatori F, Ponzoni M, Pedrinis E, Dell'Oro S, Pruneri G, Filipazzi V, Dietrich PY, Gianni AM, Coiffier B, Cavalli F, Zucca E: Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. *Blood* 2003;102:2741–2745.
- 76 Zucca E, Conconi A, Laszlo D, López-Guillermo A, Bouabdallah R, Coiffier B, Sebban C, Jardin F, Vitolo U, Morschhauser F, Pileri SA, Copie-Bergman C, Campo E, Jack A, Floriani I, Johnson P, Martelli M, Cavalli F, Martinelli G, Thieblemont C: Addition of rituximab to chlorambucil produces superior event-free survival in the treatment of patients with extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 randomized study. *J Clin Oncol* 2013;31:565–572.
- 77 Lévy M, Copie-Bergman C, Amiot A, Dupuis J, Baleur YL, Belhadj K, Hémerly F, Sobhani I, Delfau-Larue MH, Leroy K, Haioun C, Delchier JC: Rituximab and chlorambucil versus rituximab alone in gastric mucosa-associated lymphoid tissue lymphoma according to t(11;18) status: a monocentric non-randomized observational study. *Leuk Lymphoma* 2013;54:940–944.
- 78 Amiot A, Lévy M, Copie-Bergman C, Dupuis J, Szablewski V, Le Baleur Y, Baia M, Belhadj K, Sobhani I, Leroy K, Haioun C, Delchier JC: Rituximab, alkylating agents or combination therapy for gastric mucosa-associated lymphoid tissue lymphoma: a monocentric non-randomised observational study. *Aliment Pharmacol Ther* 2014;39:619–628.
- 79 Zinzani PL, Stefani V, Musuraca G, Tani M, Alinari L, Gabriele A, Marchi E, Pileri S, Bacarani M: Fludarabine-containing chemotherapy as frontline treatment of nongastrointestinal mucosa-associated lymphoid tissue lymphoma. *Cancer* 2004;100:2190–2194.
- 80 Wöhrer S, Drach J, Hejna M, Scheithauer W, Dirisamer A, Puspök A, Chott A, Raderer M: Treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) with mitoxantrone, chlorambucil and prednisone (MCP). *Ann Oncol* 2003;14:1758–1761.
- 81 Salar A, Domingo-Domenech E, Estany C, Canales MA, Gallardo F, Servitje O, Fraile G, Montalbán C: Combination therapy with rituximab and intravenous or oral fludarabine in the first-line, systemic treatment of patients with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type. *Cancer* 2009;115:5210–5217.
- 82 Salar A, Avivi I, Bittner B, Bouabdallah R, Brewster M, Catalani O, Follows G, Haynes A, Hourcade-Potelleret F, Janikova A, Larouche JF, McIntyre C, Pedersen M, Pereira J, Sayyed P, Shpilberg O, Tummyan G: Comparison of subcutaneous versus intravenous administration of rituximab as maintenance treatment for follicular lymphoma: results from a two-stage, phase IB study. *J Clin Oncol* 2014;32:1782–1791.
- 83 Troch M, Kiesewetter B, Willenbacher W, Willenbacher E, Zebisch A, Linkesch W, Fridrik M, Müllauer L, Greil R, Raderer M: Rituximab plus subcutaneous cladribine in patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue: a phase II study by the Arbeitsgemeinschaft Medikamentöse Tumortherapie. *Haematologica* 2013;98:264–268.
- 84 Troch M, Jonak C, Müllauer L, Puspök A, Formanek M, Hauff W, Zielinski CC, Chott A, Raderer M: A phase II study of bortezomib in patients with MALT lymphoma. *Haematologica* 2009;94:738–742.
- 85 Kiesewetter B, Troch M, Dolak W, Müllauer L, Lukas J, Zielinski CC, Raderer M: A phase II study of lenalidomide in patients with extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid tissue (MALT lymphoma). *Haematologica* 2013;98:353–356.
- 86 Jäger G, Höfler G, Linkesch W, Neumeister P: Occurrence of a myelodysplastic syndrome (MDS) during first-line 2-chloro-deoxyadenosine (2-CDA) treatment of a low-grade gastrointestinal MALT lymphoma. Case report and review of the literature. *Haematologica* 2004;89:ECR01.
- 87 Thieblemont C, Molina T, Davi F: Optimizing therapy for nodal marginal zone lymphoma. *Blood* 2016;127:2064–2071.
- 88 Stefanovic A, Morgensztern D, Fong T, Losos IS: Pulmonary marginal zone lymphoma: a single centre experience and review of the SEER database. *Leuk Lymphoma* 2008;49:1311–1320.
- 89 Zucca E, Conconi A, Pedrinis E, Cortelazzo S, Motta T, Gospodarowicz MK, Patterson BJ, Ferreri AJ, Ponzoni M, Devizzi L, Giardini R, Pinotti G, Capella C, Zinzani PL, Pileri S, López-Guillermo A, Campo E, Ambrosetti A, Baldini L, Cavalli F; International Extranodal Lymphoma Study Group: Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Blood* 2003;101:2489–2495.
- 90 Thieblemont C, Conconi A, Laszlo D, Tucci A, Vitolo U, Martelli M, Morschhauser F, Ghesquieres H, Pettengell R, Pinotti G, Devizzi L, Bouabdallah R, Lopez-Guillermo A, Ferreri AJ, Pileri S, Traverse-Glehen A, Jack A, Campo E, Mazzucchelli L, Cascione L, Johnson PW, Coiffier B, Martinelli G, Cavalli F, Zucca A: A simple and effective MALT lymphoma-specific prognostic index generated from the dataset of the IELSG-19 controlled clinical trial. *Hematol Oncol* 2015;33:167–168.

- 91 Hadjadj J, Malphettes M, Fieschi C, Oksenhendler E, Tazi A, Bergeron A: Lung disease in adult common variable immunodeficiency (in French). *Rev Mal Respir* 2015;32:991–1001.
- 92 Kawahara K, Shiraishi T, Okabayashi K, Iwasaki A, Hayashi K, Matsuo T, Mita S, Maekawa T, Shirakusa T, Kikuti M, Tashiro K: Nodular lymphoid hyperplasia in the lung. *Thorac Cardiovasc Surg* 1996;44:210–212.
- 93 Nakamura H, Miwa K, Haruki T, Adachi Y, Fujioka S, Taniguchi Y: Multifocal nodular lymphoid hyperplasia of the lung differently identified by ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET). *Thorac Cardiovasc Surg* 2009;57:439–440.
- 94 Saltzstein SL: Pulmonary malignant lymphomas and pseudolymphomas: classification, therapy, and prognosis. *Cancer* 1963;16:928–955.
- 95 Bois MC, Sekiguchi H, Ryu JH, Yi ES: No definite clinical features of IgG4-related disease in patients with pulmonary nodular lymphoid hyperplasia. *Hum Pathol* 2017;59:80–86.
- 96 Kajiwaras S, Sakai S, Soeda H, Takahashi N, Okafuji T, Yoshimitsu K, Yabuuchi H, Yoshino I, Honda H: Multifocal nodular lymphoid hyperplasia of the lung. *J Thorac Imaging* 2005;20:239–241.
- 97 Song JY, Pittaluga S, Dunleavy K, Grant N, White T, Jiang L, Davies-Hill T, Raffeld M, Wilson WH, Jaffe ES: Lymphomatoid granulomatosis – a single institute experience: pathologic findings and clinical correlations. *Am J Surg Pathol* 2015;39:141–156.
- 98 Thomas de Montpréville V, Le Pavéc J, Le Roy Ladurie F, Crutu A, Mussot S, Fabre D, Mercier O, Dorfmueller P, Ghigna MR, Fadel É: Lymphoproliferative disorders after lung transplantation: clinicopathological characterization of 16 cases with identification of very-late-onset forms. *Respiration* 2015;90:451–459.
- 99 Beaty MW, Toro J, Sorbara L, Stern JB, Pittaluga S, Raffeld M, Wilson WH, Jaffe ES: Cutaneous lymphomatoid granulomatosis: correlation of clinical and biologic features. *Am J Surg Pathol* 2001;25:1111–1120.
- 100 Katzenstein AL, Carrington CB, Liebow AA: Lymphomatoid granulomatosis: a clinicopathologic study of 152 cases. *Cancer* 1979;43:360–373.
- 101 James WD, Odom RB, Katzenstein AL: Cutaneous manifestations of lymphomatoid granulomatosis. Report of 44 cases and a review of the literature. *Arch Dermatol* 1981;117:196–202.
- 102 Katzenstein AL, Doxtader E, Narendra S: Lymphomatoid granulomatosis: insights gained over 4 decades. *Am J Surg Pathol* 2010;34:e35–e48.
- 103 Patsalides AD, Atac G, Hedge U, Janik J, Grant N, Jaffe ES, Dwyer A, Patronas NJ, Wilson WH: Lymphomatoid granulomatosis: abnormalities of the brain at MR imaging. *Radiology* 2005;237:265–273.
- 104 Gupta S, Gupta OP: Lymphomatoid granulomatosis of the oropharynx. *Ear Nose Throat J* 1980;59:152–154.
- 105 Hunter S, Samir A, Eisner B, Gervais D, Maher M, Hahn P, McGovern F, Mueller P: Diagnosis of renal lymphoma by percutaneous image guided biopsy: experience with 11 cases. *J Urol* 2006;176:1952–1956; discussion 1956.
- 106 Chung JH, Wu CC, Gilman MD, Palmer EL, Hasserjian RP, Shepard JA: Lymphomatoid granulomatosis: CT and FDG-PET findings. *Korean J Radiol* 2011;12:671–678.
- 107 Chavez JC, Sandoval-Sus J, Horna P, Dalia S, Bello C, Chevernick P, Sotomayor EM, Sokol L, Shah B: Lymphomatoid granulomatosis: a single institution experience and review of the literature. *Clin Lymphoma Myeloma Leuk* 2016;16(suppl):S170–S174.
- 108 Sabourin JC, Kanavaros P, Brière J, Lescs MC, Petrella T, Zafrani ES, Gaulard P: Epstein-Barr virus (EBV) genomes and EBV-encoded latent membrane protein (LMP) in pulmonary lymphomas occurring in non-immunocompromised patients. *Am J Surg Pathol* 1993;17:995–1002.
- 109 Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, ed 4. Geneva, WHO, 2008.
- 110 Petrella TM, Walker IR, Jones GW, Leber B: Radiotherapy to control CNS lymphomatoid granulomatosis: a case report and review of the literature. *Am J Hematol* 1999;62:239–241.
- 111 Jordan K, Grothey A, Grothe W, Kegel T, Wolf HH, Schmoll HJ: Successful treatment of mediastinal lymphomatoid granulomatosis with rituximab monotherapy. *Eur J Haematol* 2005;74:263–266.
- 112 Jaffe S, Jardin F, Dominique S, Duet E, Hubscher P, Genevois A, Corne F, Bota S, Nouvet G, Thiberville L: Fatal haemoptysis in a case of lymphomatoid granulomatosis treated with rituximab. *Eur Respir J* 2006;27:644–646.
- 113 Wilson WH, Kingma DW, Raffeld M, Wittes RE, Jaffe ES: Association of lymphomatoid granulomatosis with Epstein-Barr viral infection of B lymphocytes and response to interferon-alpha 2b. *Blood* 1996;87:4531–4537.
- 114 Johnston A, Coyle L, Nevell D: Prolonged remission of refractory lymphomatoid granulomatosis after autologous hemopoietic stem cell transplantation with post-transplantation maintenance interferon. *Leuk Lymphoma* 2006;47:323–328.
- 115 Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS: Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994;266:1865–1869.
- 116 Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P, d'Agay MF, Clauvel JP, Raphael M, Degos L, et al: Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castlemans's disease. *Blood* 1995;86:1276–1280.
- 117 Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM: Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *N Engl J Med* 1995;332:1186–1191.
- 118 Gantt S, Casper C: Human herpesvirus 8-associated neoplasms: the roles of viral replication and antiviral treatment. *Curr Opin Infect Dis* 2011;24:295–301.
- 119 Verma S, Nuovo GJ, Porcu P, Baiocchi RA, Crowson AN, Magro CM: Epstein-Barr virus- and human herpesvirus 8-associated primary cutaneous plasmablastic lymphoma in the setting of renal transplantation. *J Cutan Pathol* 2005;32:35–39.
- 120 Hiatt KM, Nelson AM, Lichy JH, Fanburg-Smith JC: Classic Kaposi sarcoma in the United States over the last two decades: a clinicopathologic and molecular study of 438 non-HIV-related Kaposi sarcoma patients with comparison to HIV-related Kaposi sarcoma. *Mod Pathol* 2008;21:572–582.
- 121 Marcelin AG, Motol J, Guihot A, Caumes E, Viard JP, Dussaix E, Cadranet J, Frances C, Carcelain G, Calvez V, Dupin N: Relationship between the quantity of Kaposi sarcoma-associated herpesvirus (KSHV) in peripheral blood and effusion fluid samples and KSHV-associated disease. *J Infect Dis* 2007;196:1163–1166.
- 122 Uldrick TS, Wang V, O'Mahony D, Aleman K, Wyvill KM, Marshall V, Steinberg SM, Pittaluga S, Maric I, Whitby D, Tosato G, Little RF, Yarchoan R: An interleukin-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without multicentric Castlemans disease. *Clin Infect Dis* 2010;51:350–358.
- 123 Yuzuriha A, Saitoh T, Koiso H, Mitsui T, Uchiyama H, Yokohama A, Handa H, Kojima M, Tsukamoto N, Karasawa M, Murakami H, Nojima Y: Successful treatment of autoimmune hemolytic anemia associated with multicentric Castlemans disease by anti-interleukin-6 receptor antibody (tocilizumab) therapy. *Acta Haematol* 2011;126:147–150.
- 124 Suthaus J, Stuhlmann-Laeisz C, Tompkins VS, Rosean TR, Klapper W, Tosato G, Janz S, Scheller J, Rose-John S: HHV-8-encoded viral IL-6 collaborates with mouse IL-6 in the development of multicentric Castlemans disease in mice. *Blood* 2012;119:5173–5181.
- 125 Schulz TF: The pleiotropic effects of Kaposi's sarcoma herpesvirus. *J Pathol* 2006;208:187–198.

- 126 Gao SJ, Kingsley L, Hoover DR, Spira TJ, Rinaldo CR, Saah A, Phair J, Detels R, Parry P, Chang Y, Moore PS: Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. *N Engl J Med* 1996;335:233–241.
- 127 Plancoulaine S, Abel L, van Beveren M, Tréguët DA, Joubert M, Tortevoe P, de Thé G, Gessain A: Human herpesvirus 8 transmission from mother to child and between siblings in an endemic population. *Lancet* 2000;356:1062–1065.
- 128 Pauk J, Huang ML, Brodie SJ, Wald A, Koelle DM, Schacker T, Celum C, Selke S, Corey L: Mucosal shedding of human herpesvirus 8 in men. *N Engl J Med* 2000;343:1369–1377.
- 129 Oksenhendler E, Cazals-Hatem D, Schulz TF, Barateau V, Grollet L, Sheldon J, Clauvel JP, Sigaux F, Agbalika F: Transient angiolymphoid hyperplasia and Kaposi's sarcoma after primary infection with human herpesvirus 8 in a patient with human immunodeficiency virus infection. *N Engl J Med* 1998;338:1585–1590.
- 130 Fajenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, Srkalovic G, Simpson D, Liu AY, Menke D, Chandrakasan S, Lechowicz MJ, Wong RS, Pierson S, Paessler M, Rossi JF, Ide M, Ruth J, Croglio M, Suarez A, Krymskaya V, Chadburn A, Colleoni G, Nasta S, Jayanthan R, Nabel CS, Casper C, Dispenzieri A, Fosså A, Kelleher D, Kurzrock R, Voorhees P, Dogan A, Yoshizaki K, van Rhee F, Oksenhendler E, Jaffe ES, Elenitoba-Johnson KS, Lim MS: International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. *Blood* 2017;129:1646–1657.
- 131 Oksenhendler E: Maladie(s) de Castleman; in Guillemin L, Meyer O, Sibilia J (eds): *Traité des Maladies et syndromes systémiques*, ed 5. Paris, Médecine-Sciences Flammarion, 2008, pp 917–927.
- 132 Oksenhendler E, Duarte M, Soulier J, Cacoub P, Welker Y, Cadranet J, Cazals-Hatem D, Autran B, Clauvel JP, Raphael M: Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. *AIDS* 1996;10:61–67.
- 133 Yeni P: *Prise en charge médicale des personnes infectées par le VIH*. Paris, Direction de l'information légale et administrative, 2010.
- 134 Mylona EE, Baraboutis IG, Lekakis LJ, Georgiou O, Papastamopoulos V, Skoutelis A: Multicentric Castleman's disease in HIV infection: a systematic review of the literature. *AIDS Rev* 2008;10:25–35.
- 135 Guihot A, Couderc LJ, Agbalika F, Galicier L, Bossi P, Rivaud E, Scherrer A, Zucman D, Katlama C, Oksenhendler E: Pulmonary manifestations of multicentric Castleman's disease in HIV infection: a clinical, biological and radiological study. *Eur Respir J* 2005;26:118–125.
- 136 Guihot A, Couderc LJ, Rivaud E, Galicier L, Bossi P, Oksenhendler E, Scherrer A: Thoracic radiographic and CT findings of multicentric Castleman disease in HIV-infected patients. *J Thorac Imaging* 2007;22:207–211.
- 137 Oksenhendler E, Carcelain G, Aoki Y, Boulanger E, Maillard A, Clauvel JP, Agbalika F: High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric Castleman disease in HIV-infected patients. *Blood* 2000;96:2069–2073.
- 138 El Karoui K, Vuiblet V, Dion D, Izzedine H, Guitard J, Frimat L, Delahousse M, Remy P, Boffa JJ, Pillebout E, Galicier L, Noel LH, Daugas E: Renal involvement in Castleman disease. *Nephrol Dial Transplant* 2011;26:599–609.
- 139 London J, Boutboul D, Agbalika F, Coppo P, Veyradier A, Gérard L, Oksenhendler E, Azoulay E, Galicier L: Autoimmune thrombotic thrombocytopenic purpura associated with HHV8-related multicentric Castleman disease. *Br J Haematol* 2016, Epub ahead of print.
- 140 Simonelli C, Tedeschi R, Gloghini A, Talamini R, Bortolin MT, Berretta M, Spina M, Morassut S, Vaccher E, De Paoli P, Carbone A, Tirelli U: Plasma HHV-8 viral load in HHV-8-related lymphoproliferative disorders associated with HIV infection. *J Med Virol* 2009;81:888–896.
- 141 Stebbing J, Adams C, Sanitt A, Mletzko S, Nelson M, Gazzard B, Newsom-Davis T, Bower M: Plasma HHV8 DNA predicts relapse in individuals with HIV-associated multicentric Castleman disease. *Blood* 2011;118:271–275.
- 142 Levi JE, Nascimento MC, Sumita LM, de Souza VA, Freire WS, Mayaud P, Pannuti CS: Non-detection of human herpesvirus 8 (HHV-8) DNA in HHV-8-seropositive blood donors from three Brazilian regions. *PLoS One* 2011;6:e23546.
- 143 Oksenhendler E: HIV-associated multicentric Castleman disease. *Curr Opin HIV AIDS* 2009;4:16–21.
- 144 Dupin N, Diss TL, Kellam P, Tulliez M, Du MQ, Sicard D, Weiss RA, Isaacson PG, Boshoff C: HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. *Blood* 2000;95:1406–1412.
- 145 Du MQ, Bacon CM, Isaacson PG: Kaposi sarcoma-associated herpesvirus/human herpesvirus 8 and lymphoproliferative disorders. *J Clin Pathol* 2007;60:1350–1357.
- 146 Naresh KN, Rice AJ, Bower M: Lymph nodes involved by multicentric Castleman disease among HIV-positive individuals are often involved by Kaposi sarcoma. *Am J Surg Pathol* 2008;32:1006–1012.
- 147 Du MQ, Liu H, Diss TC, Ye H, Hamoudi RA, Dupin N, Meignin V, Oksenhendler E, Boshoff C, Isaacson PG: Kaposi sarcoma-associated herpesvirus infects monotypic (IgM λ) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. *Blood* 2001;97:2130–2136.
- 148 Masaki Y, Kawabata H, Takai K, Kojima M, Tsukamoto N, Ishigaki Y, Kurose N, Ide M, Murakami J, Nara K, Yamamoto H, Ozawa Y, Takahashi H, Miura K, Miyauchi T, Yoshida S, Momoi A, Awano N, Ikushima S, Ohta Y, Furuta N, Fujimoto S, Kawanami H, Sakai T, Kawanami T, Fujita Y, Fukushima T, Nakamura S, Kinoshita T, Aoki S: Proposed diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome, 2015 version. *Int J Hematol* 2016;103:686–692.
- 149 Hoffmann C, Schmid H, Müller M, Teutsch C, van Lunzen J, Esser S, Wolf T, Wyen C, Sabranski M, Horst HA, Reuter S, Vogel M, Jäger H, Bogner J, Arasteh K: Improved outcome with rituximab in patients with HIV-associated multicentric Castleman disease. *Blood* 2011;118:3499–3503.
- 150 Oksenhendler E, Boulanger E, Galicier L, Du MQ, Dupin N, Diss TC, Hamoudi R, Daniel MT, Agbalika F, Boshoff C, Clauvel JP, Isaacson PG, Meignin V: High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood* 2002;99:2331–2336.
- 151 Gérard L, Michot JM, Burcheri S, Fieschi C, Longuet P, Delcey V, Meignin V, Agbalika F, Chevret S, Oksenhendler E, Galicier L: Rituximab decreases the risk of lymphoma in patients with HIV-associated multicentric Castleman disease. *Blood* 2012;119:2228–2233.
- 152 Bower M: How I treat HIV-associated multicentric Castleman disease. *Blood* 2010;116:4415–4421.
- 153 Bérezné A, Agbalika F, Oksenhendler E: Failure of cidofovir in HIV-associated multicentric Castleman disease. *Blood* 2004;103:4368–4369; author reply 4369.
- 154 Uldrick TS, Polizzotto MN, Aleman K, O'Mahony D, Wyvill KM, Wang V, Marshall V, Pittaluga S, Steinberg SM, Tosato G, Whitby D, Little RF, Yarchon R: High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: a pilot study of virus-activated cytotoxic therapy. *Blood* 2011;117:6977–6986.
- 155 Buyse S, Teixeira L, Galicier L, Mariotte E, Lemiale V, Séguin A, Bertheau P, Canet E, de Labarthe A, Darmon M, Rybojad M, Schlemmer B, Azoulay E: Critical care management of patients with hemophagocytic lymphohistiocytosis. *Intensive Care Med* 2010;36:1695–1702.
- 156 Boshoff C, Begent RH, Oliver RT, Rustin GJ, Newlands ES, Andrews R, Skelton M, Holden L, Ong J: Secondary tumours following etoposide containing therapy for germ cell cancer. *Ann Oncol* 1995;6:35–40.

- 157 Scott D, Cabral L, Harrington WJ Jr: Treatment of HIV-associated multicentric Castleman's disease with oral etoposide. *Am J Hematol* 2001;66:148–150.
- 158 Gérard L, Bérezné A, Galicier L, Meignin V, Obadia M, De Castro N, Jacomet C, Verdon R, Madelaine-Chambrin I, Boulanger E, Chevret S, Agbalika F, Oksenhendler E: Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemA Trial. *J Clin Oncol* 2007;25:3350–3356.
- 159 Bower M, Powles T, Williams S, Davis TN, Atkins M, Montoto S, Orkin C, Webb A, Fisher M, Nelson M, Gazzard B, Stebbing J, Kelleher P: Brief communication: rituximab in HIV-associated multicentric Castleman disease. *Ann Intern Med* 2007;147:836–839.
- 160 Buchler T, Dubash S, Lee V, Chilton D, Cartledge J, Isaacson P, Tedder RS, Lee SM: Rituximab failure in fulminant multicentric HIV/human herpesvirus 8-associated Castleman's disease with multiorgan failure: report of two cases. *AIDS* 2008;22:1685–1687.
- 161 Marcelin AG, Aaron L, Mateus C, Gyan E, Gorin I, Viard JP, Calvez V, Dupin N: Rituximab therapy for HIV-associated Castleman disease. *Blood* 2003;102:2786–2788.
- 162 Schmidt SM, Raible A, Kortüm F, Mayer F, Riessen R, Adam P, Gregor M, Bissinger AL: Successful treatment of multicentric Castleman's disease with combined immunochemotherapy in an AIDS patient with multiorgan failure. *Leukemia* 2008;22:1782–1785.
- 163 Bestawros A, Michel R, Séguin C, Routy JP: Multicentric Castleman's disease treated with combination chemotherapy and rituximab in four HIV-positive men: a case series. *Am J Hematol* 2008;83:508–511.
- 164 Boulanger E, Brière J, Gaulard P, Droz D, Oksenhendler E: HHV8-related non-Hodgkin's lymphoma of the spermatic cord in a patient with HIV-associated multicentric Castleman disease. *Am J Hematol* 2003;72:70–71.
- 165 Guillet S, Gérard L, Meignin V, Agbalika F, Cuccini W, Denis B, Katlama C, Galicier L, Oksenhendler E: Classic and extracavitary primary effusion lymphoma in 51 HIV-infected patients from a single institution. *Am J Hematol* 2016;91:233–237.
- 166 Carbone A, Gaidano G: HHV-8-positive body-cavity-based lymphoma: a novel lymphoma entity. *Br J Haematol* 1997;97:515–522.
- 167 Olszewski AJ, Fallah J, Castillo JJ: Human immunodeficiency virus-associated lymphomas in the antiretroviral therapy era: Analysis of the National Cancer Data Base. *Cancer* 2016;122:2689–2697.
- 168 Boulanger E, Agbalika F, Maarek O, Daniel MT, Grollet L, Molina JM, Sigaux F, Oksenhendler E: A clinical, molecular and cytogenetic study of 12 cases of human herpesvirus 8 associated primary effusion lymphoma in HIV-infected patients. *Hematol J* 2001;2:172–179.
- 169 Boulanger E, Gérard L, Gabarre J, Molina JM, Rapp C, Abino JF, Cadranet J, Chevret S, Oksenhendler E: Prognostic factors and outcome of human herpesvirus 8-associated primary effusion lymphoma in patients with AIDS. *J Clin Oncol* 2005;23:4372–4380.
- 170 Morassut S, Vaccher E, Balestreri L, Gloghini A, Gaidano G, Volpe R, Tirelli U, Carbone A: HIV-associated human herpesvirus 8-positive primary lymphomatous effusions: radiologic findings in six patients. *Radiology* 1997;205:459–463.
- 171 Carbone A, Gloghini A, Larocca LM, Capello D, Pierconti F, Canzonieri V, Tirelli U, Dalla-Favera R, Gaidano G: Expression profile of MUM1/IRF4, BCL-6, and CD138/syndecan-1 defines novel histogenetic subsets of human immunodeficiency virus-related lymphomas. *Blood* 2001;97:744–751.
- 172 Gaidano G, Carbone A: Primary effusion lymphoma: a liquid phase lymphoma of fluid-filled body cavities. *Adv Cancer Res* 2001;80:115–146.
- 173 Fais F, Gaidano G, Capello D, Gloghini A, Ghiotto F, Roncella S, Carbone A, Chiorazzi N, Ferrarini M: Immunoglobulin V region gene use and structure suggest antigen selection in AIDS-related primary effusion lymphomas. *Leukemia* 1999;13:1093–1099.
- 174 Luan SL, Boulanger E, Ye H, Chanudet E, Johnson N, Hamoudi RA, Bacon CM, Liu H, Huang Y, Said J, Chu P, Clemen CS, Cesarman E, Chadburn A, Isaacson PG, Du MQ: Primary effusion lymphoma: genomic profiling revealed amplification of SELPLG and CORO1C encoding for proteins important for cell migration. *J Pathol* 2010;222:166–179.
- 175 Carbone A, Gloghini A, Vaccher E, Zagonel V, Pastore C, Dalla Palma P, Branz F, Saglio G, Volpe R, Tirelli U, Gaidano G: Kaposi's sarcoma-associated herpesvirus DNA sequences in AIDS-related and AIDS-unrelated lymphomatous effusions. *Br J Haematol* 1996;94:533–543.
- 176 Galicier L, Fieschi C, Borie R, Meignin V, Daniel MT, Gérard L, Oksenhendler E: Intensive chemotherapy regimen (LMB86) for St Jude stage IV AIDS-related Burkitt lymphoma/leukemia: a prospective study. *Blood* 2007;110:2846–2854.
- 177 Oksenhendler E, Clauvel JP, Jouvessomme S, Davi F, Mansour G: Complete remission of a primary effusion lymphoma with antiretroviral therapy. *Am J Hematol* 1998;57:266.
- 178 Castillo JJ, Shum H, Lahijani M, Winer ES, Butera JN: Prognosis in primary effusion lymphoma is associated with the number of body cavities involved. *Leuk Lymphoma* 2012;53:2378–2382.
- 179 Gupta A, Sen S, Marley E, Chen W, Naina HV: Management and outcomes of HIV-associated primary effusion lymphoma: a single center experience. *Clin Lymphoma Myeloma Leuk* 2016;16(suppl):S175–S180.
- 180 Boulanger E, Daniel MT, Agbalika F, Oksenhendler E: Combined chemotherapy including high-dose methotrexate in KSHV/HHV8-associated primary effusion lymphoma. *Am J Hematol* 2003;73:143–148.
- 181 Boulanger E, Meignin V, Oksenhendler E: Bortezomib (PS-341) in patients with human herpesvirus 8-associated primary effusion lymphoma. *Br J Haematol* 2008;141:559–561.
- 182 Gasperini P, Tosato G: Targeting the mammalian target of rapamycin to inhibit VEGF and cytokines for the treatment of primary effusion lymphoma. *Leukemia* 2009;23:1867–1874.
- 183 Luppi M, Trovato R, Barozzi P, Vallisa D, Rossi G, Re A, Ravazzini L, Potenza L, Riva G, Morselli M, Longo G, Cavanna L, Roncaglia R, Torelli G: Treatment of herpesvirus associated primary effusion lymphoma with intracavity cidofovir. *Leukemia* 2005;19:473–476.
- 184 Birsan R, Boutboul D, Crestani B, Seguin-Givelet A, Fieschi C, Bertinchamp R, Giol M, Malphettes M, Oksenhendler E, Galicier L: Talc pleurodesis allows long-term remission in HIV-unrelated human herpesvirus 8-associated primary effusion lymphoma. *Leuk Lymphoma* 2017;58:1993–1998.