18.14.3 Lymphocytic infiltrations of the lung 4241

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PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med, 348, 1201–14. Cottin V et al. (2016). Respiratory manifestations of eosinophilic granulo matosis with polyangiitis (Churg-Strauss). Eur Respir J, 48, 1429–41. De Giacomi F, et al. (2018). Acute eosinophilic pneumonia. Causes, diagnosis and management. Am J Respir Crit Care Med, 197, 728–36. DuMouchel W, et al. (2004). Association of asthma therapy and Churg-Strauss syndrome: an analysis of postmarketing surveillance data. Clin Therapeut, 26, 1092–1104. Guillevin L, Dunogue B, Pagnoux C (2011). Churg-Strauss syndrome. Eur Resp Mon, 54, 140–51. Kunst H, et al. (2011). Parasitic infections of the lung: a guide for the respiratory physician. Thorax, 66, 528–36. Marchand E, Cordier JF (2006). Idiopathic chronic eosinophilic pneu- monia. Semin Respir Crit Care Med, 27, 134–41. Patterson K, Strek ME (2010). Allergic bronchopulmonary aspergil- losis. Proc Am Thorac Soc, 7, 237–44. Simon HU, Plotz G, Dummer R, Blaser K (1999). Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. N Engl J Med, 341, 1112–20. Tefferi A, Gotlib J, Pardanani A (2010). Hypereosinophilic syndrome and clonal eosinophilia: point-of-care diagnostic algorithm and treatment update. Mayo Clinic Proceedings, 85, 158–64. 18.14.3 Lymphocytic infiltrations of the lung S. J. Bourke ESSENTIALS Lymphocytic infiltrations of the lung arise from the proliferation of bronchus-associated lymphoid tissue, resulting in a spectrum of rare conditions ranging from benign polyclonal lymphoid inter- stitial pneumonia to monoclonal primary malignant lymphomas of the lung. Lymphoid interstitial pneumonia is most commonly seen in Sjögren's syndrome or other connective tissue diseases, and in as- sociation with HIV infection, and is characterized by reticulonodular shadowing on CT imaging and (usually) a good response to corticosteroids. Primary pulmonary lymphomas fall into three categories: lymphomatoid granulomatosis, low-grade B-cell lymphoma, and high-grade B-cell lymphoma. The latter require treatment with cyto- toxic drugs and have a poor prognosis. Introduction Lymphoid tissue is usually inconspicuous or absent in normal lung tissue. Bronchus-associated lymphoid tissue develops as a reaction to exogenous stimuli such as smoking, infection, and antigen in- halation, or endogenous circulating antigens in autoimmune and connective tissue diseases. Reactive hyperplasia of this bronchus- associated lymphoid tissue occurs in conditions such as chronic infections, immune deficiency syndromes, obstructive pneumo- nias, and collagen vascular diseases. Both benign lymphoid infil- trations of the lung, such as lymphoid interstitial pneumonia (LIP), and neoplastic infiltrations in primary pulmonary lymphomas, are related to lymphoid hyperplasia of bronchus-associated lymphoid tissue (Box 18.14.3.1). Lymphoid interstitial pneumonia Lymphoid (lymphocytic) interstitial pneumonia (LIP) is a rare disease in which pulmonary lymphoid hyperplasia progresses to a diffuse polyclonal lymphoid cell infiltration, surrounding the air- ways as follicular bronchiolitis, and expanding the interstitium of the lung. In some cases it is idiopathic with no identifiable cause, but it is most commonly associated with collagen vascular dis- eases such as Sjögren's syndrome, systemic lupus erythematosus,

 rheumatoid disease, autoimmune diseases such as primary bil- iary cirrhosis, myasthenia gravis and Hashimoto's thyroiditis, and immune deficiency states such as common variable immunodefi- ciency and HIV infection. It has also been described in relation to drugs such as phenytoin and captopril. Epstein–Barr virus has been isolated in some cases. It most commonly presents in middle age and is more common in women. Symptoms usually include breathlessness, dry cough, and sometimes systemic symptoms of weight loss and malaise. Crackles may be audible. Features of an underlying autoimmune or systemic disease may be present, and should be sought. In HIV infection LIP is most common in children and is rare in adults. It may occur relatively early in the course of HIV infection, when the CD4+ T lymphocytes

count is still within the normal range. The chest radiograph shows nonspecific reticulonodular opacities, usually most apparent at the lung bases. CT imaging shows ground-glass attenuation with centrilobular nodules and thickened bronchovascular bundles and interlobular septa, sometimes with cysts. Lung function tests typically show restriction of lung volumes and impaired gas diffusion. Bronchoalveolar lavage shows lymphocytosis. Surgical biopsy is often required to confirm the diagnosis. The histology shows that the alveolar septa are extensively infiltrated by lymphocytes, plasma cells, and histiocytes with associated type II cell hyperplasia. The dif- ferential diagnosis includes nonspecific interstitial pneumonia, hypersensitivity pneumonitis, usual interstitial pneumonia, and pulmonary lymphoma. Careful immunohistochemistry and mo- lecular analysis are required to differentiate LIP from lymphoma. When a histological diagnosis of LIP has been established, investigations for associated diseases should be undertaken including HIV testing and auto-antibodies tests for connective tissue diseases. There is often polyclonal elevation of IgG and IgM but sometimes hypogammaglobulinaemia and monoclonal gammopathies. The clinical course of LIP is very variable and reflects also the course of the underlying disease. In many cases the disease is indolent, with little progression over many years, but about one-third of cases progress to pulmonary fibrosis. LIP is usually treated by corticosteroids, often with a good response. In HIV- associated LIP, antiretroviral treatment results in improvement. Lung transplant has been performed in very rare cases which have failed to respond to corticosteroids and progressed to end- stage fibrosis. Lymphoma The lung parenchyma may be involved in disseminated nodal lymphomas of all types but the clinical presentation of these sec- ondary lymphomas is usually dominated by disease at other sites (Chapter 22.4.3). Primary pulmonary lymphoma arises from bronchus-associated lymphoid tissue rather than lymph nodes, and is very rare, accounting for less than 0.5% of all primary lung neoplasms. Classification of primary pulmonary lymphomas is complex and different from nodal lymphomas, but generally falls into the categories of lymphomatoid granulomatosis (angiocentric lymphoma), low-grade B-cell lymphoma, and high-grade B-cell lymphoma. It seems that prolonged stimulation of bronchus- associated lymphoid tissue with a high turnover of B-cells in con- ditions such as Sjögren’s syndrome, autoimmune disease, and Epstein–Barr virus infection, may contribute to the development of lymphoma. Immunosuppression may also be an important factor, particularly in patients who have undergone organ transplantation, or in those with HIV infection. Additional neoplastic change seems to occur in prolonged lymphoid hyperplasia, with chromosomal translocations leading to constitutive activation of signalling path- ways progressing to lymphoproliferative change and lymphomatous transformation. Post-transplant lymphoproliferative disease may result from a decreased T-cell immune response to the Epstein–Barr virus induced by immunosuppression, and includes a spectrum of disease from lymphoid hyperplasia to high-grade lymphoma. The Epstein–Barr virus latent membrane protein has been shown to have oncogenic properties and may be a key factor in the development of some pulmonary lymphomas. Lymphomatoid granulomatosis (angiocentric lymphoma) Lymphomatoid granulomatosis is considered separately as a unique type of lymphoproliferative disorder with a propensity for blood vessel destruction, which particularly affects the lungs. It is now classified as an angiocentric, Epstein–Barr virus-associated B-cell lymphoma rather than a vasculitis. The lungs are the most com- monly involved site, but it is a multisystem disease which can also involve the skin, kidney, liver, and central and peripheral nervous systems. Although it is a lymphoproliferative disorder it is rare for it to involve the lymph nodes, spleen, or bone marrow. The disease is very uncommon in childhood but occurs through out adult life, particularly in middle age, with a slight predilection for males. Patients often present with prominent systemic symp- toms of fever, weight loss and general malaise, in addition to chest

symptoms such as cough, haemoptysis, and chest pain. About a quarter have neurological symptoms and half develop skin lesions. Lymphadenopathy is not usually present. The chest radiograph and CT imaging typically show multiple rounded masses, sometimes with cavitation, such that the disease mimics metastatic carcinoma, infection, or vasculitis (Fig. 18.14.3.1). Surgical biopsy of a lung lesion is usually necessary to establish the diagnosis. Histologically the disease is characterized by atypical B-cells infiltrating around the bronchovascular and perivascular Box 18.14.3.1 Lymphocytic infiltrations of the lung Reactive polyclonal lymphoid infiltration • Lymphoid interstitial pneumonia • Follicular bronchiolitis • Lymphoid hyperplasia Pulmonary lymphomas Secondary lymphoma involving the lung • Non-Hodgkin's lymphoma • Hodgkin's lymphoma Primary pulmonary lymphomas • Lymphomatoid granulomatosis (angiocentric lymphoma) • Bronchus-associated lymphoma (high/low grade) • HIV-related lymphoma • Post-transplantation lymphoproliferative disorder

 regions, with associated T-cells, plasma cells, and histiocytes. Immunocytochemistry and molecular analysis show that the B-cells are clonal and malignant, and evidence of Epstein–Barr virus infection may be present. Vascular infiltration is a prominent feature and patients may have haemoptysis and lung haemorrhage. Patients have sometimes been given corticosteroids because of a suspicion of a vasculitic or inflammatory disease, and temporary improvement in symptoms sometimes occurs from treatment with corticosteroids alone, but this is an aggressive malignant lymphoma with a high mortality and requires cytotoxic therapy. Chemotherapy usually involves drugs such as cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab, but regimens are not well established because of the rarity of the disease. The prognosis is gen- erally poor with a 5-year mortality of 50–70%. Low-grade B-cell lymphoma Low-grade B-cell non-Hodgkin's lymphomas account for about 80–90% of primary lymphomas affecting the lung parenchyma. They generally arise in middle aged or elderly adults from mucosa- associated lymphoid tissue of the bronchi, and may occur after a prolonged period of antigenic stimulation and high B-cell turn- over associated with Sjögren's syndrome, dysgammaglobulinaemia, amyloid deposition, collagen vascular disease, and HIV infection. Presentation is commonly as an incidental finding on a chest radio- graph, before symptoms have developed. When symptoms do occur, they include cough, haemoptysis, chest pain and (occasionally) breathlessness, and there may be systemic symptoms such as fever, malaise, and weight loss. The chest radiograph and CT imaging usu- ally shows multiple parenchymal nodules with diameters ranging up to a few centimetres. Sometimes spread outside the bronchi and pul- monary vessels, but within the bronchovascular bundles, may leave the airway patent and so produce air bronchograms within the tu- morous opacities. In a few cases there is a diffuse nodular infiltration. The clinical presentation and radiological features often cause confusion, hence biopsy is required to establish a diagnosis and to demonstrate a B-cell clone and the grade of activity of the lymphoma. These low-grade lymphomas can behave indolently and initial observation may be appropriate, before considering cytotoxic chemotherapy. The prognosis is generally good with an estimated 5- and 10-year survival rate of 90% and 72%, respectively. High-grade B-cell lymphoma High-grade B-cell non-Hodgkin's lymphomas account for 10–20% of primary lymphomas affecting the lung parenchyma. They par- ticularly occur in immunosuppressed patients in the context of HIV infection or after organ transplantation. The more aggressive nature of high-grade disease is reflected by the greater likelihood of respiratory and systemic symptoms. Multifocal involvement may cause cough, dyspnoea, haemoptysis, and chest pain, often with systemic symptoms of weight loss, fever, and malaise. Local infiltration by lymphomatous masses may pro- duce atelectasis of a segment or lobe of lung, sometimes with pleural effusions. The

prognosis of high-grade pulmonary lymphoma is much less favourable than that of low-grade disease. In post-transplant lymphoma associated with Epstein–Barr virus, a reduction in im- munosuppression and antiviral treatment, such as ganciclovir or valganciclovir, may be appropriate. Chemotherapeutic regimens for the treatment of pulmonary lymphoma are similar to those used in other lymphomas, including drugs such as rituximab, chlorambucil, cyclophosphamide, fludarabine, doxorubicin, and vincristine, ad- ministered under specialist oncology supervision. FURTHER READING Bae YA, et al. (2008). Marginal zone B-cell lymphoma of bronchus- associated lymphoid tissue: imaging findings in 21 patients. Chest, 133, 433–40. Borie R, et al. (2009). Clinical characteristics and prognostic factors of pulmonary MALT lymphoma. Eur Respir J, 34, 1408–16. Borie R, et al. (2017). Lymphoproliferative disorders of the lung. Respiration, 94, 157–75. Cha SI, et al. (2006). Lymphoid interstitial pneumonia: clinical fea- tures, associations and prognosis. Eur Respir J, 28, 364–9. Das S, Miller RF (2003). Lymphocytic interstitial pneumonitis in HIV infected adults. Sex Transm Infect, 79, 88–93. (a) (b) Fig. 18.14.3.1 CT of a patient with lymphomatoid granulomatosis showing (a) a cavitating mass in the left lower lobe (arrow) and (b) a further mass in the right lower lobe (arrow).

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