Lung Lesions

14

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14.1 Introductory Remarks

A variety of pulmonary lesions have been reported in IgG4-RD in the past several years, but many uncertainties remain regarding their pathophysiology and diagnosis. Such lung lesions had originally been reconized as interstinal pneumonia and inflammatory pseudotumor in patients with autoimmune pancreatitis or "Mikulicz's disease" [1–7]. Knowledge of the wide spectrum of the pulmonary phenotype in IgG4-RD continues to expand [8]. The radiologic features of IgG4-related lung disease rival the clinical findings in their diversity.

At least two factors contributed to the delay in recognition of IgG4-related lung disease in the past. First, mucosal lesions in the lung appear to be uncommon. And second, approaches to the diagnosis based upon transbronchial lung biopsy (TBLB) have a low yield. Histopathological diagnosis from lung tissue is essential when no other organ involvement is evident. In some cases, a definite diagnosis can be obtained only via a video-assisted thoracoscopy (VATS) procedure.

IgG4-RD occurs principally in middle-aged and elderly men across the full spectrum of organ involvement. Most cases are associated with elevated serum IgG4 concentrations and good responses to glucocorticoid therapy. Lesions show lymphoplasmacytic cell infiltration and fibrosis, and the infiltrating plasma cells demonstrate disproportionate staining for IgG4. Clinicians from every specialty must become familiar with the clinical and imaging findings specific not only to their individual organ of interest but also of the features that are common to the broader disease as a whole. In this chapter, we outline the lung lesions of IgG4-RD. Our focus is primarily on the imaging findings of IgG4-related lung disease, but where appropriate we also indicate other conditions in the differential diagnosis that must be excluded before settling upon the diagnosis of IgG4-RD.

14.2 What Lesions Occur Where?

Following careful radiopathologic correlation of surgical biopsies, we observed that four major types of IgG4-related lung disease are readily apparent. These types include (1) solid, nodular lesions; (2) rounded ground-glass opacities (GGO); (3) alveolar-interstitial infiltrates; and (4) a bronchovascular pattern [9]. We also have observed that the inflammatory cell infiltration and fibrosis occur mainly within the connective tissues of the lung—i.e., the interstitium—namely, the bronchovascular bundle, interlobular septa, and the alveolar interstitium [9, 10].

The distribution of disease along the bronchovascular bundle coincides generally with the intrapulmonary distribution of the lymphatic system. The bronchial mucosal surface is typically spared, despite the fact that severe lesions can develop within the bronchovascular bundle interstitium, bronchus-associated glands, interlobular septa, and alveolar

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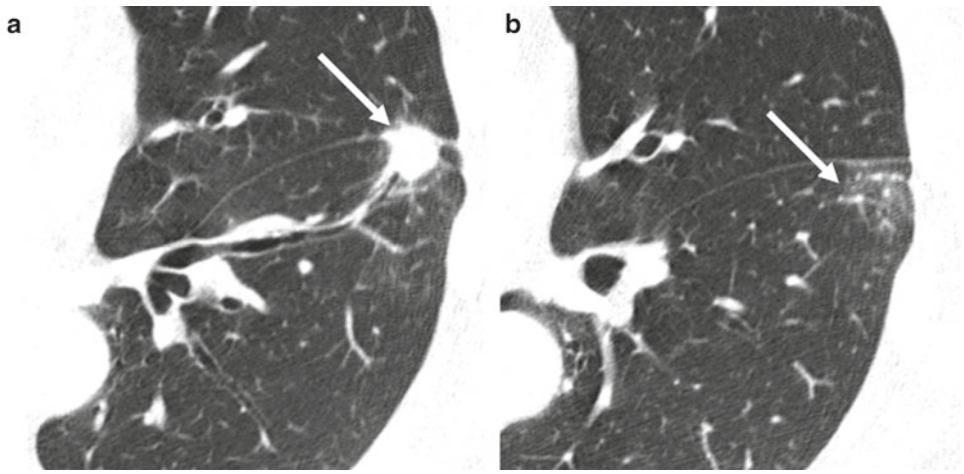

Fig. 14.1 In the left lower lobe, a spiculated nodule is demonstrated (**a**: *arrow*). Perinodularly patchy ground-glass opacities are seen (**b**: *arrow*)

interstitium. The CT correlates of this pathology are ground-glass opacities and thickening of the bronchovascular bundles and interlobular septa. Lesions occurring around the distal bronchi are sometimes recognized as small, centrilobular nodules.

The alveolar lumen can also be affected by the characteristic inflammatory cell infiltrates and fibrosis, and mass lesions develop in some cases. Lesions extending into the alveolar lumen are recognized on CT as a mass or infiltrative shadow. In about one half of cases, mediastinal lymph node swelling is observed, but central necrosis and fusion of lymph nodes are both atypical of IgG4-RD.

Most patients with pulmonary IgG4-RD present with a mixture of these findings, but it is possible to classify them according to the most prominent of these into one of these four major types. Below, we outline the clinical and radiologic features of each type and also discuss the differential diagnosis of each category.

14.2.1 Solid Nodular Type

Solid, nodular lesions are not limited to the lung interstitium, and when marked cell infiltration and fibrosis occur in the alveolar lumen, a large nodule or mass is recognized on CT. This corresponds to the "inflammatory pseudotumor" often reported in the literature. In some cases, these nodules are accompanied by inflammatory cell infiltration and fibrosis along the edge of the alveolar interstitium. On CT, these appear spicule-like and require differentiation from primary lung cancer (Figs.14.1a and 14.7a). In the surrounding tissues, bronchovascular bundle swelling and patchy ground-glass opacities are sometimes observed, marking features that are atypical of lung cancer (Fig. 14.1b). Although the presence of bronchovascular bundle thickening and ground-glass opacities is helpful in raising the possibility of IgG4-RD, cases generally require histopathological confirmation.

14.2.2 Rounded GGO Type

Ground-glass opacities are a common CT finding in IgG4-RD. These are typically focal and have a rounded shape (Fig. 14.2). Distinction of this lesion from well-differentiated adenocarcinoma and bronchial alveolar epithelial cancer by diagnostic imaging alone is not possible with certainty, and histological diagnosis via a VATS procedure is usually required.

14.2.3 Alveolar-Interstitial Type

"Interstitial pneumonia" was once recognized as an extrapancreatic complication of autoimmune pancreatitis [1]. In fact, such lesions were simply the pulmonary manifestations of IgG4-RD that is now referred to as the alveolar-interstitial type. Such lesions are characterized by ground-glass opacities on CT, but these lesions differ radiologically from the rounded ground-glass opacities described above and may be distributed widely. Fibrotic changes that ensue can lead to cyst-like dilatation of the alveolar lumen. These cysts are recognized on imaging as thick, ringlike structures that resemble honeycomb lung, but the lesions generally comprise a less severe form of honeycombing than that which accompanies usual interstitial pneumonia/idiopathic pulmonary fibrosis. Some cases show bronchovascular bundle thickening and bronchial dilatation due to tractive changes. On CT, findings of nonspecific interstitial pneumonia are frequently shown (Fig. 14.3).

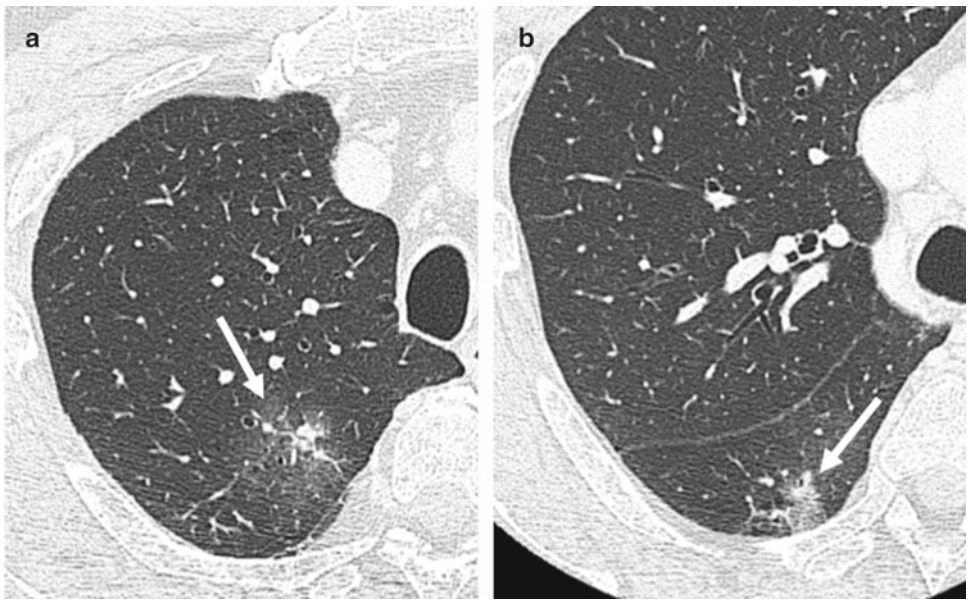

Fig. 14.2 In the right lung field, multiple round, localized ground-glass opacities are present (**a**, **b**: *arrow*)

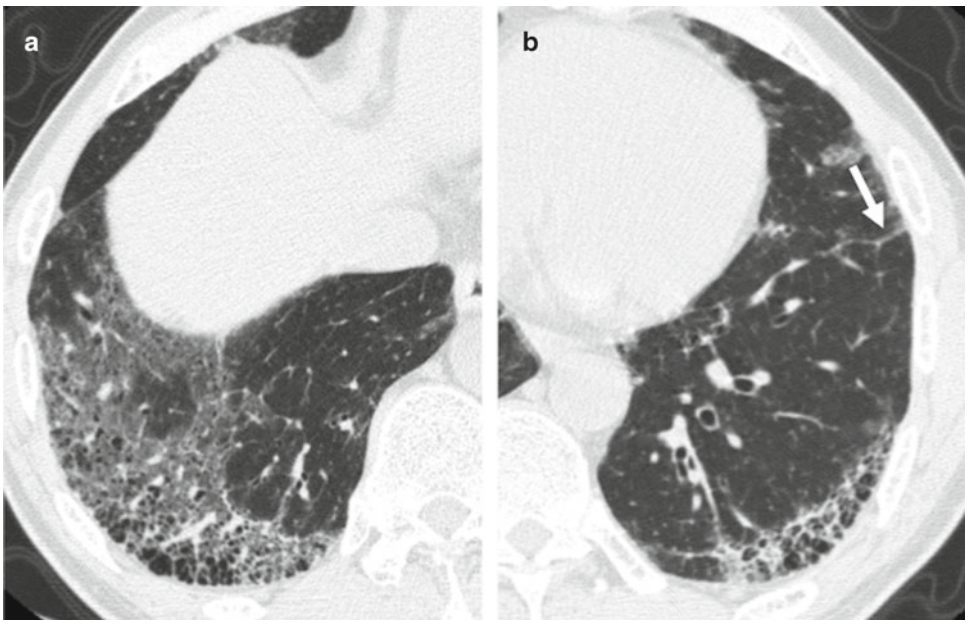

Fig. 14.3 In the bilateral lower lobe subpleura, a cluster of ringlike shadows is found. Also in the right lung field, patchy ground-glass opacities are seen. The interlobular septal wall is also thickened in parts (**b**: *arrow*)

14.2.4 Bronchovascular Type

The most typical picture of IgG4-related lung disease is perhaps the bronchovascular type. Its major CT findings are thickening of the bronchovascular bundle and interlobular septa, which reflects cellular infiltration and fibrosis (Figs. 14.4 and 14.5). Ground-glass opacities and small nodules are sometimes intermingled with these changes to varying degrees. The presence of small nodules reflects inflammatory cell infiltration around the distal bronchioles. These nodules usually have a centrilobular distribution. Cyst formation and pleural effusions are rare.

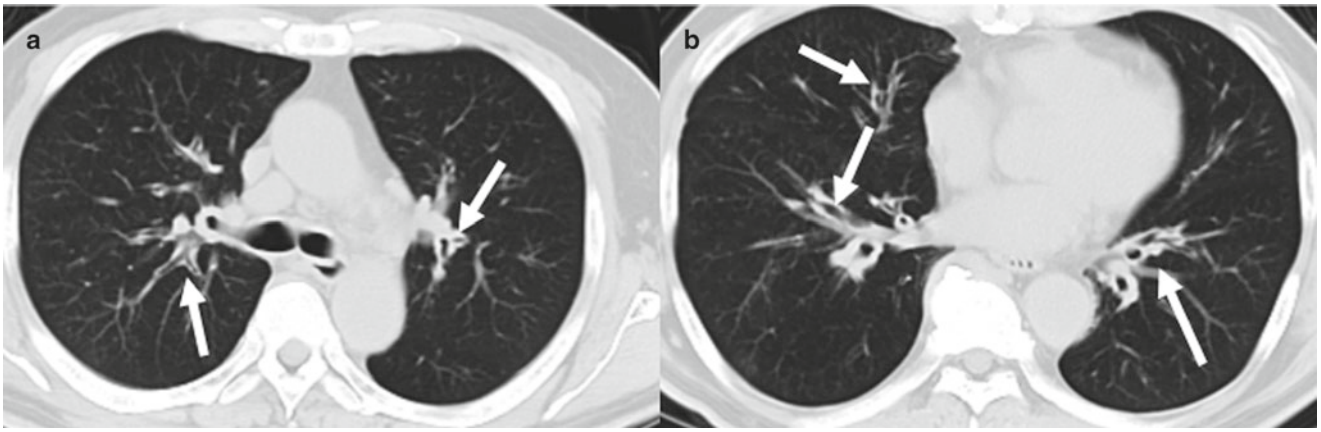

Fig. 14.4 Bilateral bronchovascular bundle swelling is found

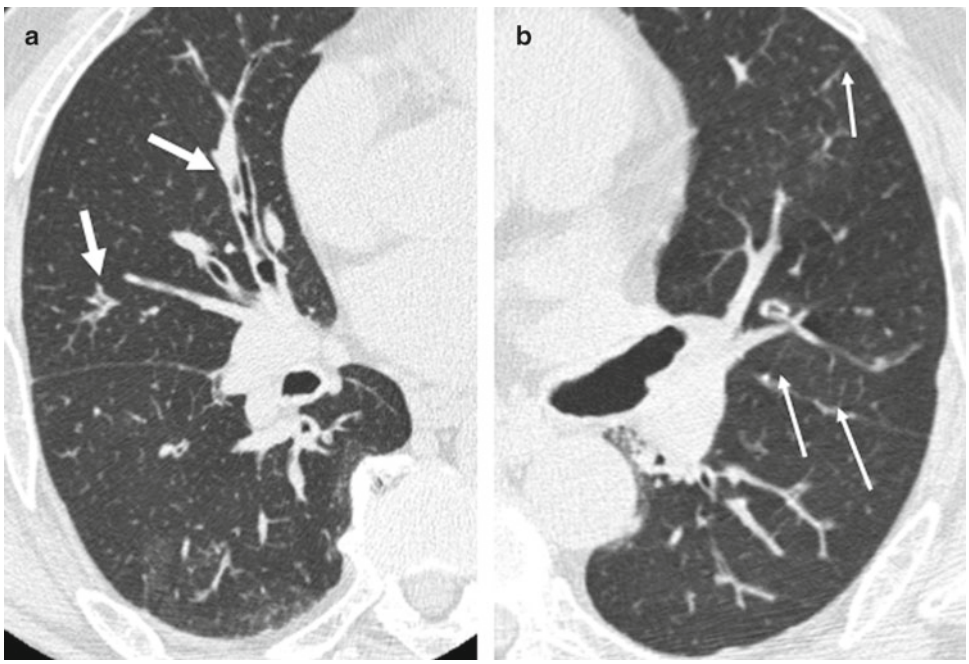

Fig. 14.5 Bronchovascular bundle swelling is found (**a**: *arrows*). Interlobular septal thickening is also seen (**b**: *arrows*)

The bronchovascular type of IgG4-related pulmonary disease must be distinguished from multicentric Castleman disease (MCD), lymphomatoid granulomatosis, lymphangiosis carcinomatosa, and sarcoidosis.

14.3 What Other Lesions Occur?

Cases with radiologic findings that suggest organizing pneumonia have been reported [6, 7]. These consist of dense, relatively well-defined shadows associated with ground-glass opacities (Fig. 14.6). In these lesions, a marked inflammatory cell infiltrate affects not only the lung interstitium but also extends to the alveolar lumen. These lesions have also been reported to form in the pleura [10]. Clinicians must be aware that this may be reflected as pleural thickening on imaging (Fig. 14.7).

14.4 Diagnosing IgG4-Related Lung Lesions

We have outlined the imaging findings of IgG4-related lung lesions in this chapter, but in clinical practice these lesions are frequently more difficult to diagnose than those in other organs. We surmise that the main reasons for this are:

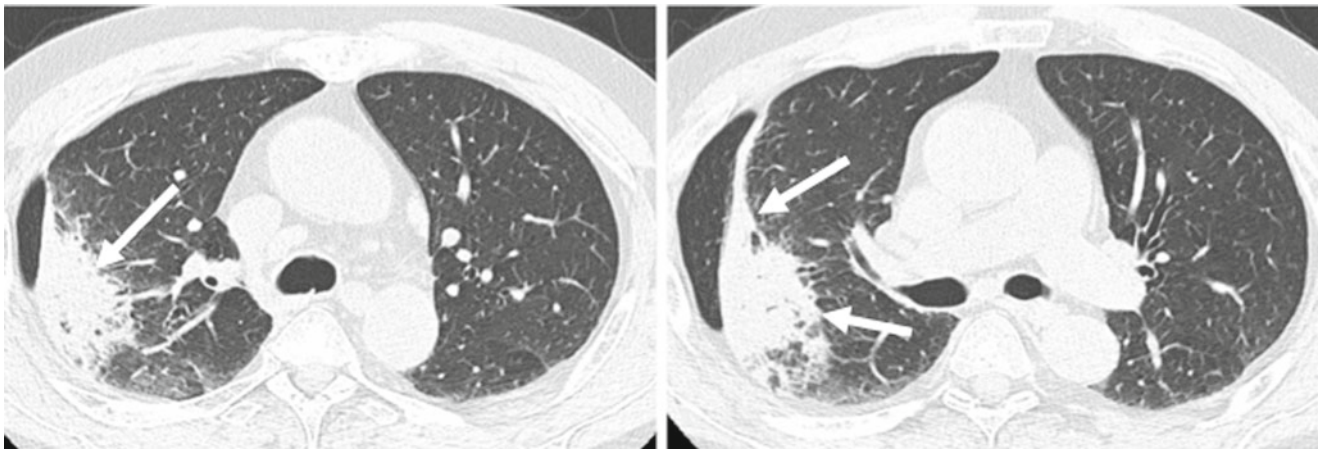

Fig. 14.6 A dense shadow is found in the right upper lobe around which patchy ground-glass opacities are seen

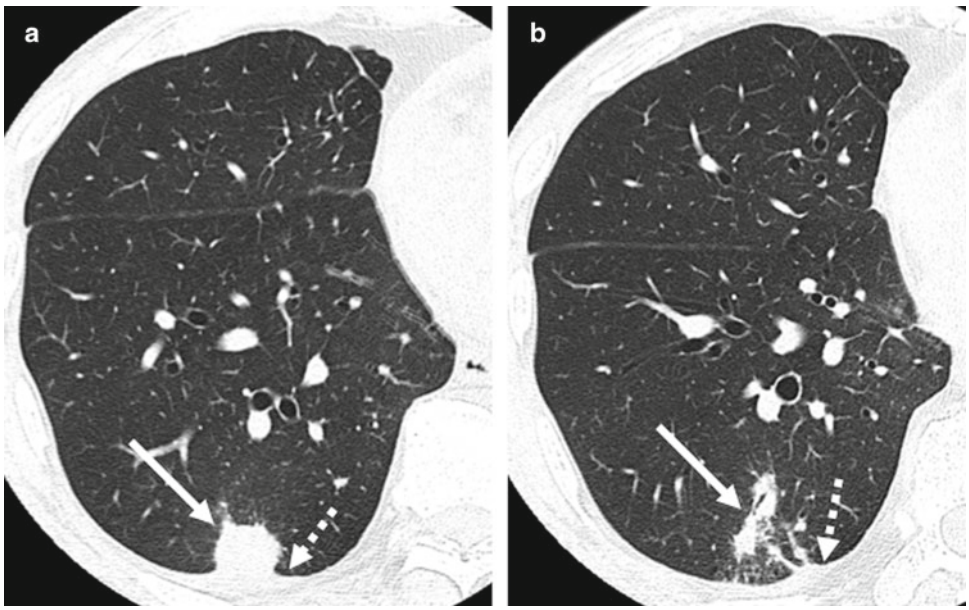

Fig. 14.7 A spiculated nodule is noted in the right lower lobe (**a**: *arrow*). Bronchovascular bundle swelling is also seen (**b**: *arrow*), associated with bilateral pleural thickening (**a**: *broken line*)

(1) the clinical spectrum is wide, with signs of respiratory distress like cough and breathlessness prominent in some cases, while others are asymptomatic when detected; (2) the imaging findings are similarly diverse; and (3) adequate amounts of tissue are difficult to procure by TBLB.

In cases associated with IgG4-RD in other organs, one can reasonably suspect IgG4-RD on the basis of guilt by association, and to diagnose lung disease it is important that appropriate investigations be undertaken to determine the presence/absence of multiorgan lesions. The majority of cases of IgG4-related lung disease have extra-pulmonary lesions. In cases with pathology limited to the lung, most of the lesions are of the solid nodular type and are diagnosed incidentally following a diagnostic evaluation for suspected cancer. Further refinement of the diagnostic approach to cases with lung lesions alone is required.

At present, it is thought possible to suspect alveolar-interstitial-type and bronchovascular-type lesions from the imaging findings, but in these cases as well, as already noted, some other diseases require differentiation, and a

comprehensive diagnosis must be made taking into consideration current serum IgG4 concentration, determination retrospectively of the presence/absence of other organ involvement, and histology.

To facilitate collection of adequate samples for a tissue diagnosis, multiple biopsies from the same sites by TBLB or biopsy by VATS is frequently necessary. In the setting of solid nodular lesions and rounded ground-glass opacities, IgG4-RD should not be diagnosed hastily even when the presence of lesions can be confirmed in other organs, and it is absolutely necessary to exclude malignancy by histological diagnosis beforehand. Other investigators and we have encountered cases in which autoimmune pancreatitis or IgG4-related lung lesions were complicated by lung cancer [10]. Whenever IgG4-RD is suspected, particular care must be given to the exclusion of cancer in the diagnostic process.

14.5 Concluding Remarks

We have outlined the lung lesions of IgG4-related disease, focusing mainly on their radiologic aspects. Recently IgG4-RD has attracted increasing interest, and conversely the number of cases difficult to diagnose has also been rising. We consider that IgG4-related lung lesions occur mainly along the distribution of the lung connective tissue (lymph tract). And even though the imaging findings of lung lesions are diverse, this does not mean that any lesion can be attributed to an IgG4-related cause.

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