Comprehensive Understanding of Airway Disease in Rheumatoid Arthritis

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Abstract

Although the high prevalence of airway diseases in patients with rheumatoid arthritis (RA) has been recognized for decades, their clinical significance and treatment strategies have not been well discussed. With the introduction of potent disease-modifying treatments for RA, respiratory complications have emerged as the most important obstacle impeding the safe implementation of these therapies and improvement of patient prognosis. Along with interstitial lung disease, airway diseases are now regarded as one of the major risk factors of these lung complications and also result in their own problems such as airway obstruction and lung destruction. Bronchiectasis (BE) and bronchiolitis are well-known airway diseases that often develop concurrently. They are found in more than 10–30% of RA subjects and are thought to be caused by persistent inflammation of the airway attributed to the dysregulated immune response in RA. Not infrequently, airway inflammation may provoke destruction of the peripheral airway and lung parenchyma, leading to the formation of a honeycomb-like structure mimicking interstitial lung disease. Control of this inflammation is an urgent issue that needs to be addressed in the future.

Keywords

Rheumatoid arthritis • Airway disease • Bronchiectasis • Bronchiolitis • Respiratory infection

2.1 Introduction

The recent introduction of potent disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX) and biologics, has revolutionized the treatment of rheumatoid arthritis (RA) and now allows almost complete control of joint inflammation in more than half of patients. However, we have yet to conclusively prove that they also improve patient prognosis.

A large-scale Japanese cohort survey in 2006 found that together with malignant tumors, respiratory diseases comprising pneumonia and interstitial lung disease (ILD) were the major causes of death in RA patients [1]. These data are derived from the prebiologics era (in Japan, biologics first became available in 2003). With the introduction of biologics, adverse events associated with these drugs were carefully studied in detail through clinical trials and postmarketing surveillance [2]. These studies elucidated that infections, specifically respiratory infections, were the most prominent issue among the various complications. Recently, a prospective, multicenter study was conducted in Japan to determine the prognosis of RA patients undergoing biologics therapy. Although treatment with biologics did not have a negative effect on overall outcomes, many fatalities occurred during this therapy, and in nearly 50% of the cases, death was attributed to respiratory diseases such as respiratory infections and ILD [3]. This means that one of the most vital challenges in current RA treatment,

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particularly with biologics, is the control of respiratory complications and especially respiratory infections.

Until recently, the high incidence of respiratory infections in RA patients was attributed to the use of immunosuppressants such as corticosteroids [4]. However, this is not necessarily true under biologics therapy. For example, many autoinflammatory diseases are treated with biologics, but respiratory infections are only observed in RA at a high frequency, whereas they are not nearly as prevalent in inflammatory bowel disease. This suggests that factors unique to RA exist in the etiology of these infections. Attention is increasingly directed to underlying lung diseases, i.e., airway disease and ILD, as the major risk factors [5, 6].

In the past, studies on chronic lung complications of RA have focused primarily on ILD [7], and airway diseases have not been investigated nearly as thoroughly. However, within recent years, knowledge has been compiled on their incidence, pathogenesis, and effect on prognosis in RA patients [8–10].

Airway diseases are traditionally handled in two distinct entity, large airway disease and small airway disease. Large airway disease presents as bronchiectasis (BE), whereas small airway disease comprises various forms of bronchiolitis. Furthermore, we advocate here that bronchiolar dilatation should be added to this discussion as another peripheral type of airway disease (described below). These airway diseases all occur far more frequently in RA patients than in the general population, the fact of which urges us to assume that their etiology is closely related to the pathophysiology of RA [8, 11].

2.2 Bronchiectasis (BE)

2.2.1 Epidemiology

The frequency of BE in RA patients has been assessed in many studies using high-resolution computed tomography (HRCT) over the past two decades. Most of these studies report prevalence between 30 and 40% (Table 2.1) [12–19]. Early studies were retrospective and subject to selection bias, whereas the more recent studies are prospective and consecutively enrolled all RA patients who presented to a medical facility during a specified period. Given the large subject size of these studies, the results are highly reliable. Rheumatologists who have used chest radiography alone to assess their patients may find these figures as unacceptable. In a review of BE coexistence in RA patients, Wilczynska and colleagues pointed out that RA patients rarely complain of respiratory symptoms and also that chest radiographs lack the requisite sensitivity, declaring HRCT to be essential to provide an accurate assessment of BE [8]. Figure 2.1 illustrates a case in which chest radiography showed no remarkable findings, while an HRCT scan revealed widespread BE. There is no room for argument that HRCT scans are required in the diagnosis of BE.

There do not appear to be any national or racial differences in this frequency, nor does treatment history appear to be relevant. Mori and colleagues performed HRCT scans in 126 consecutive RA patients on their first visit, of which 41% had signs of BE [18]. This was observed not only in

Table 2.1 Reported prevalence of bronchiectasis in RA patients, literature review

Author	Country	Study type	*n*	Mean age (y)	Mean duration of RA (y)	Prevalence of bronchiectasis (%)	References
Perez T et al.	France	Prospective	50	57.8 ± 1.5	14.4 ± 1.3	30	Am J Resp Crit Care Med 1994 [12]
Cortet et al.	France	Prospective	68	58.8 ± 10.6	12 ± 9.2	31	Ann Rheum Dis 1997 [43]
Despaux et al.	France	Prospective	46	60.1 (30–85)	10.1(1–32)	41	Rev Rhum Engl Ed 1998 [13]
Mori et al.	Japan	Prospective	126	60.0 ± 12.4	0 or 11.8 ± 9.7[a]	41	J Rheumatol 2008 [18]
Wilsher et al.	New Zealand	Prospective	60	54 (26–76)	0.6(0–1)	35	Resp Med 2012 [17]
Remy-Jardin et al.	France	Retrospective	84	57 ± 9	12 ± 8	24	Radiology 1994 [12]
Tsuchiya et al.	Japan	Retrospective	144	65.2 ± 9.8	9.7 ± 12.0	22	Eur Respir J 2011 [19]
Akira M et al.	Japan	Retrospective	29	59 ± 11	n.a.	52	J Comput Assist Tomogr 1999 [15]
Terasaki H et al.	Japan	Prospective	34[b]	61(41–80)	12(0–39)	62	Radiat Med 2004 [16]

[a]Within 1 year in 65 patients and longer duration in 61 patients
[b]Subjects are limited to those with respiratory symptoms

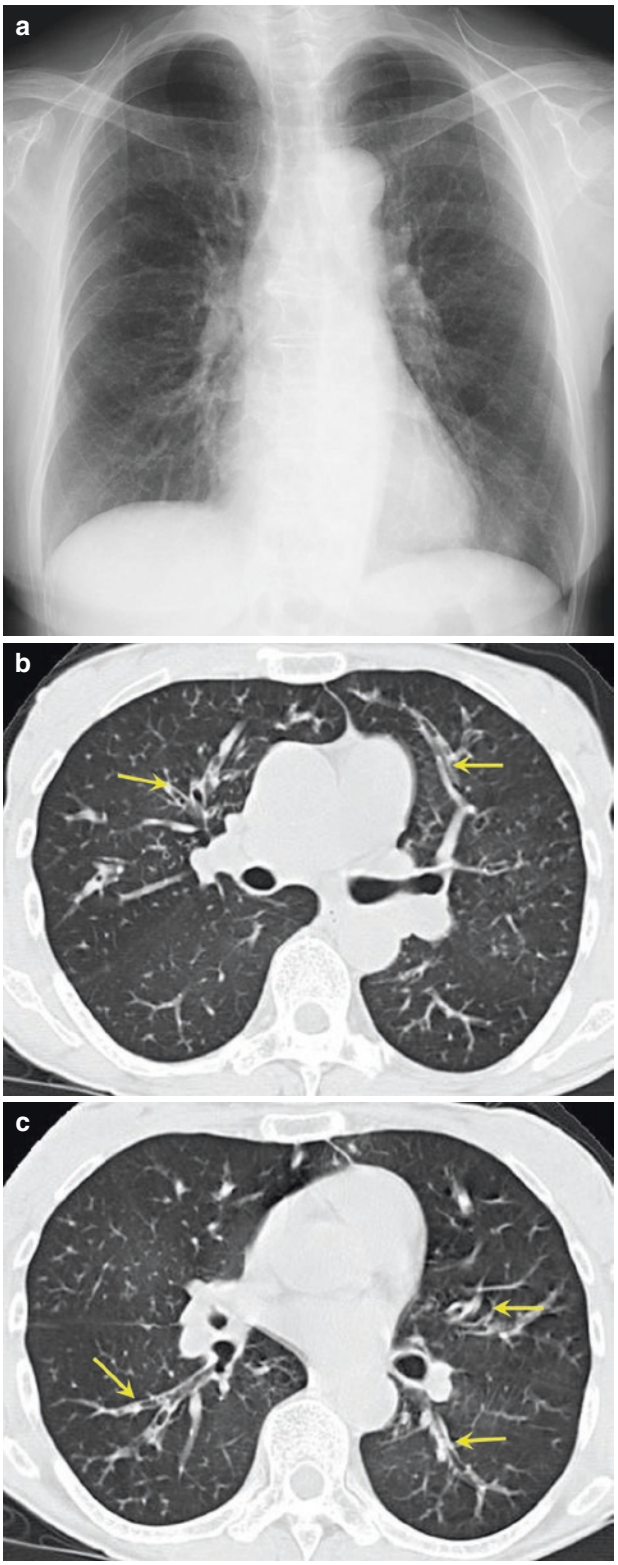

Fig. 2.1 Chest radiography is often powerless for detecting airway disease. (**a**) Chest radiograph in a 65-year-old woman with RA for 2 years. She complained of cough and sputum for several years. We cannot find any abnormality on this image. (**b**, **c**) HRCT reveals bronchiectasis with bronchial wall thickening distributed in every lobe (arrows), and also small nodules are scattered around. In this case, only HRCT can demonstrate these anatomic changes of the airway

patients with long-standing RA (49%) but also in 34% of patients with early RA. This high prevalence cannot be explained by the conventional hypothesis that BE is a result of repeated infection caused by immunosuppressive therapy. It is 10- to 20-fold higher than the prevalence in the general population [20], and it should be considered to be directly associated with RA itself.

2.2.2 Mechanism of Development

In non-RA subjects, BE is often attributed to a previous medical history of pneumonia or other infections during childhood or later years. This is, however, not true in those with RA. Detailed interviews prove that the majority had no history of major infectious episodes, whereas disease is often widespread with involvement of two or more pulmonary lobes at presentation.

In the general population, BE is considered to evolve through the following process (Fig. 2.2). Chronic neutrophilic inflammation in the airway persists and injures the supportive structure of the airway, that is, cartilage, elastic fibers and smooth muscle, causing fragility of the airway structure. There, negative pressure held inside the lungs causes airway dilatation. Edema of the submucosal layer, cellular infiltration, collagen deposition, and increases in bronchial glands then lead to thickening of the bronchial wall [21].

Recently, in addition to these morphological studies, immunological researches have been compiled and clarified the following scenario: macrophages and airway epithelial cells respond to the colonized bacteria such as *Streptococcus* or *Pseudomonas* and release cytokines such as IL-17, IL-8, and TNF-alpha, which drive neutrophils into action in the airway wall. Activation enzymes released from these neutrophils, such as elastase and matrix metalloproteinases, damage and destroy the supporting tissue of the bronchial wall as mentioned above (Fig. 2.3) [22–24].

In RA patients, it may be postulated that similar and more intense inflammation occurs in the airway, leading to the development of BE [11]. Unfortunately no studies have yet analyzed the inflammatory dynamics of the airway in patients with RA.

2.2.2.1 BE Appearing after RA Onset

BE may be observed to develop de novo in the course of RA. Figure 2.4 shows a case in which BE appeared in only a few years. This is a woman in her 60s with a 6-year history of RA. A CT scan performed 3 years ago for a mild productive cough revealed only a fibrotic scar in the middle lobe (Fig. 2.4a, b). Thereafter, she sometimes presented with a productive cough without any febrile episodes. At her presentation to our respiratory department, she complained of a

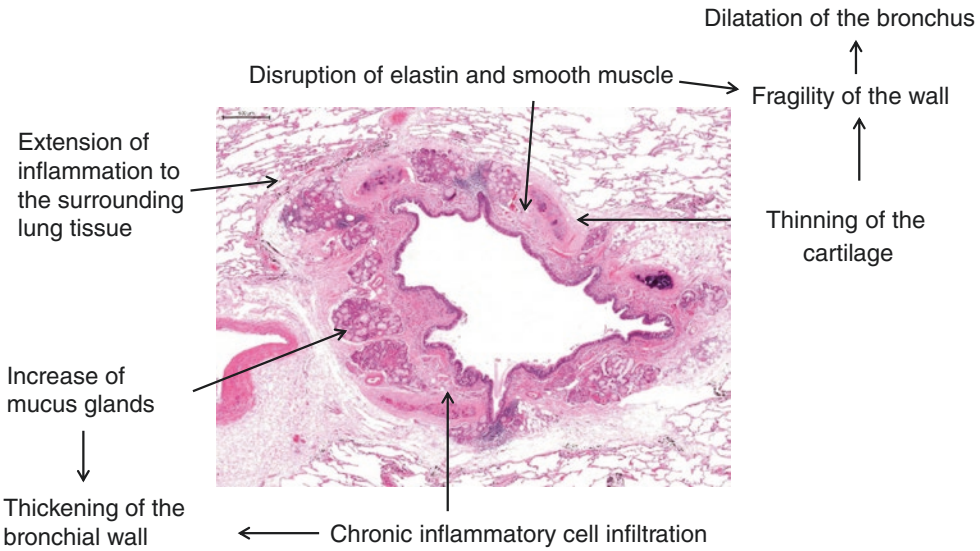

Fig. 2.2 Pathogenesis of bronchiectasis on a morphological basis. Chronic neutrophilic inflammation in the airway disrupts elastin, smooth muscle, and cartilage of the bronchial wall, leading to structural fragility and then dilatation of the bronchus. Thickening of the bronchial wall is also brought about by this chronic inflammation. Photomicrograph courtesy of Dr. T. Takemura

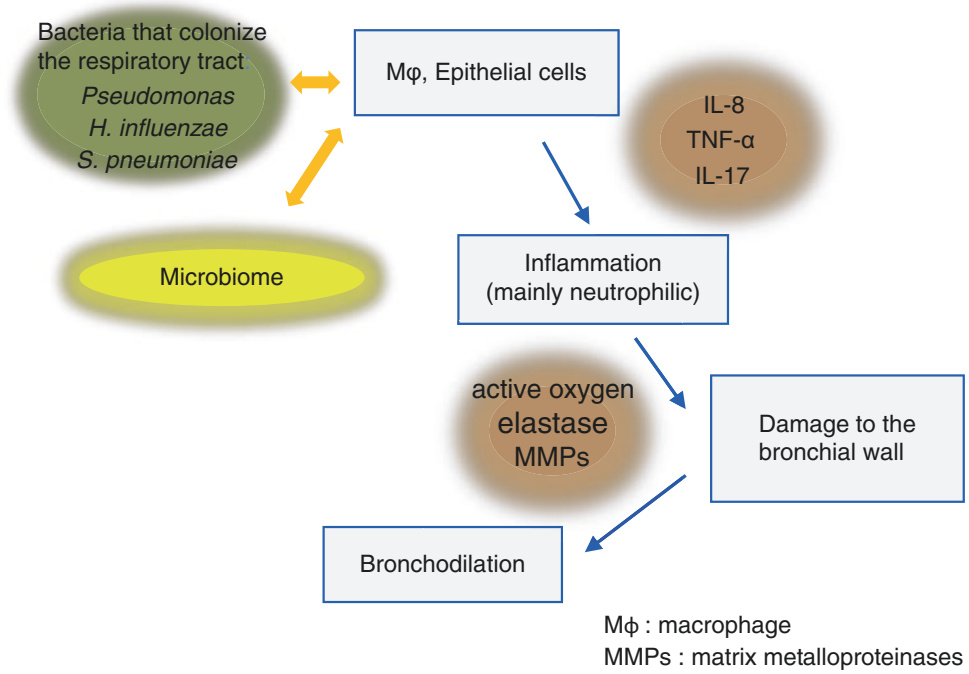

Fig. 2.3 Putative immunological pathogenesis of bronchiectasis in RA elucidated by clinical immunological studies over the recent decades. With the recognition of colonized bacteria, macrophages and epithelial cells release inflammatory cytokines such as IL-8, TNF-α, and IL-17, which induce persistent neutrophilic inflammation that leads to destruction of the bronchial wall. It has recently been postulated that this inflammatory process may be caused by dysbiosis of the microbiome in the airways and/or dysregulation of the host immune response, a subject that has attracted much attention in this decade

mild productive cough for 1 month and weight loss of 2 kg, and a CT scan was performed (Fig. 2.4c, d). BE has now become apparent in the right middle lobe over these 3 years. Fluoroquinolones were highly effective against symptoms in this patient and prevented further aggravation thereafter. This case clearly shows that BE may appear de novo during the course of RA. Importantly, in such cases, the signs or symptoms may be subtle or often absent. Physicians must be alert to this possibility.

BE also develops in patients with autoimmune diseases other than RA such as ulcerative colitis. How should we interpret this phenomenon? Boyton and colleagues, one of the leading investigators of the immunology of BE, postulate that in those patients with autoimmune diseases, an excessive and dysregulated immune response is the key concept [11, 25]. Recent advances in genome sequencing technology revealed that the respiratory tract, which was thought to be sterile until several years ago, harbors microorganisms that are not detected by standard culture techniques, forming a unique lung microbiome. In those autoimmune diseases, dysbiosis of this microbiome or dysregulation of the host immune response may evoke an exuberant immune response in the airway, leading to persistent inflammation and the development of BE (Fig. 2.3). Further research is awaited in this field.

2.2.2.2 BE Preceding RA Onset

As mentioned above, Mori and colleagues [18] found that 30% of patients showed signs of BE in HRCT during the

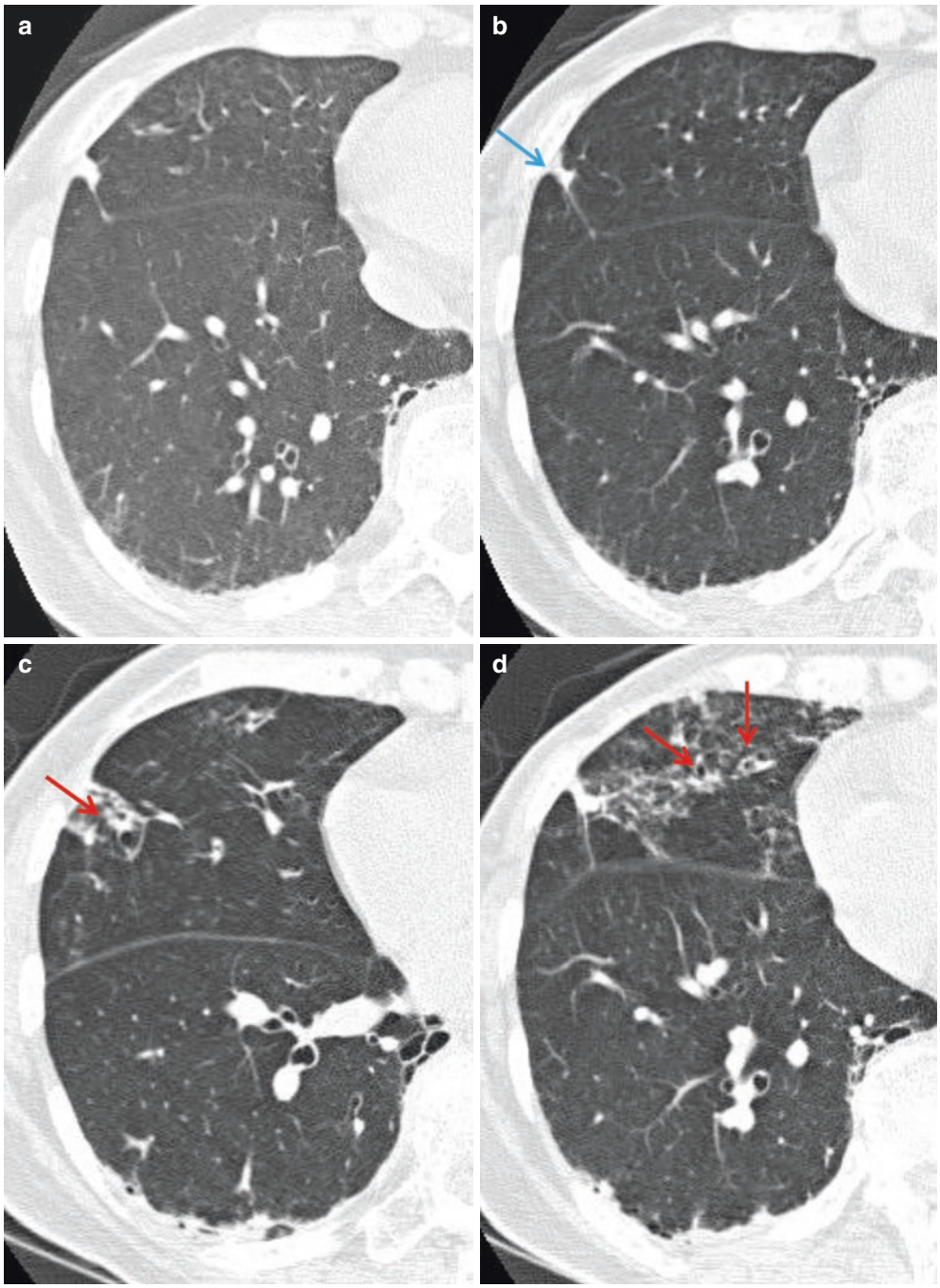

Fig. 2.4 A case of bronchiectasis in which its development was observed during the clinical course of RA. HRCT of a 67-year-old woman with RA of 6-year duration. (**a**, **b**) HRCT 3 years ago shows only fibrotic scarring in the right S^4 (blue arrow). No dilatation of the bronchi is visible. (**c**, **d**) Three years later, she complained cough, sputum, and weight loss. HRCT revealed newly developed bronchiectasis (red arrows) and micronodules surrounding these areas

early period of RA, suggesting the possibility of BE as concurrent or preceding disorder. In clinical experience, BE certainly precedes the onset of RA in a certain proportion of cases. We show a typical case of such a sequence in Fig. 2.5. A 55-year-old man who was diagnosed as RA 4 months earlier presented with a recurrent and prolonged productive cough. He had been diagnosed as having BE at his young age. In this patient, it is apparent clinically that BE preceded RA. CT scans revealed advanced BE in his middle and lower lobes. In the surrounding area, widespread micronodules are observed indicating bronchiolitis (Fig. 2.5a, b).

This sequence may have some relationship with the pathogenesis of RA. Demoruelle and colleagues examined HRCT findings in 42 subjects positive for RA-related autoantibody but who did not have inflammatory arthritis and found airway changes such as BE and bronchiolitis in 76% of them. Furthermore, five of those subjects later developed RA. They considered that an immune response at the mucosal site of the respiratory tract forms RA-related autoantibodies, particularly anti-CCP antibodies, which then reach the joints via the bloodstream and contribute to the development of RA. They postulated that the preclinical stage of RA

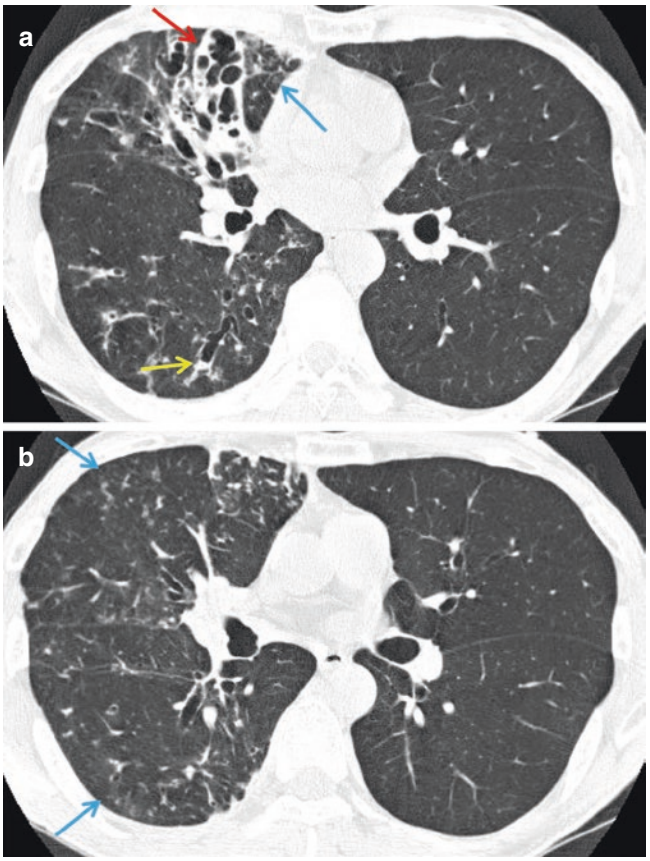

Fig. 2.5 A case of bronchiectasis that preceded the onset of RA. HRCT in a 55-year-old man with RA of 4-month duration. (**a**) Bronchiectasis with consolidation is conspicuous in the middle lobe (red arrow). (**b**) Bronchiectasis is also seen in the lower lobe (yellow arrow), and micronodules are scattered throughout the entire right lung (blue arrows). He was diagnosed as having BE at a younger age, that is, his airway disease preceded the onset of RA

may be chronic inflammation of the airway where interaction between the immune system and the altered microbiome may generate autoimmunity [26].

2.2.3 Imaging Findings

The diagnosis of BE on HRCT scans is detailed in Chap. 4. The criteria summarized and proposed by leading radiologist Naidich are easy to apply and are widely accepted [27].

The distribution of BE in RA patients is not necessarily limited to a single lobe. In nearly half of the patients, BE is found over two or more lobes and often in the entire lung including the upper lobes. Shrinkage of the affected lobe is common, which is thought to be a result of repeated bouts of inflammation. Findings indicating bronchiolitis such as centrilobular micronodules and branching opacities are often noted peripherally (Figs. 2.6 and 2.7).

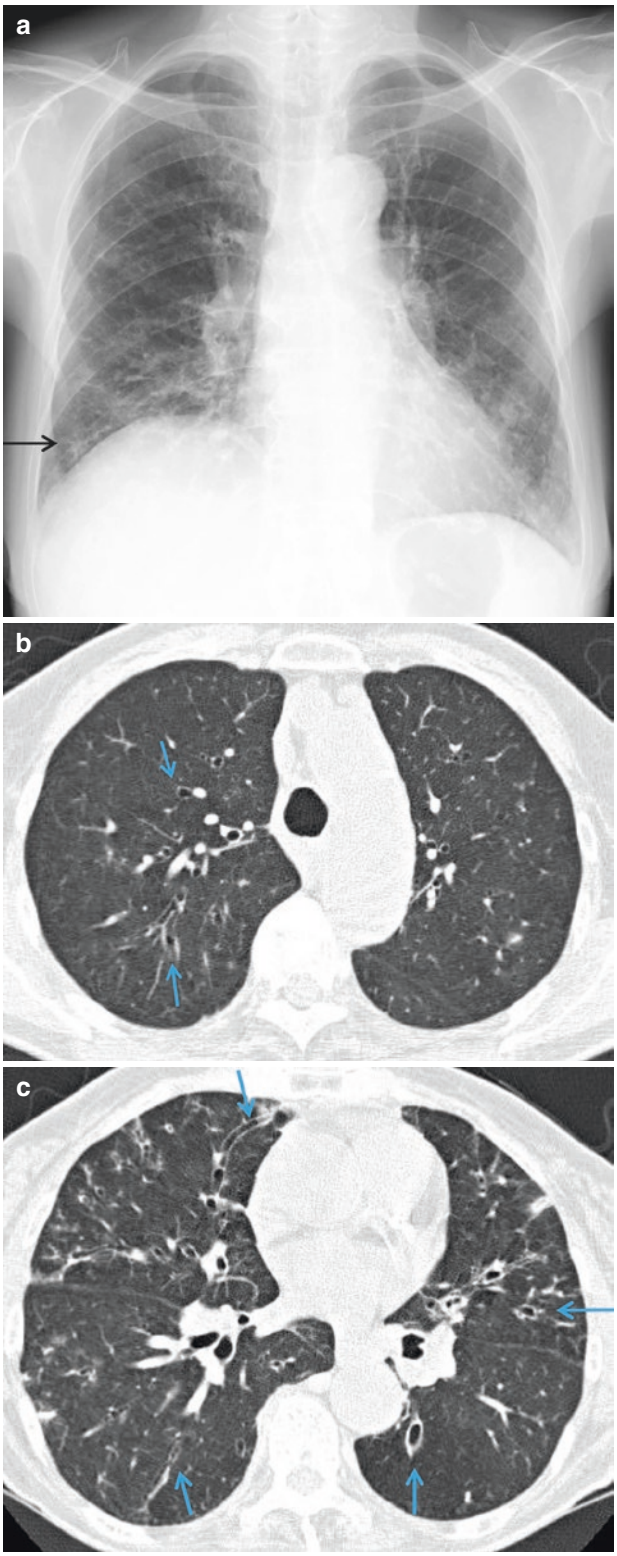

Fig. 2.6 Bronchiectasis distributed mainly in the lower lung field. (**a**) Chest radiograph in a 73-year-old woman with RA for 12 years. She had complained of a persistent productive cough for 2 years, with a weight loss of 4 kg. Reticular opacities are visible in the bilateral lung bases (arrow). In addition, shrinkage of the right lower lung is noted. (**b**) HRCT of the upper lung zone reveals mild bronchiectasis (blue arrows). (**c**) In the lower zone, diffuse bronchiectasis is visible with scattered micronodules in the surrounding area (blue arrows)

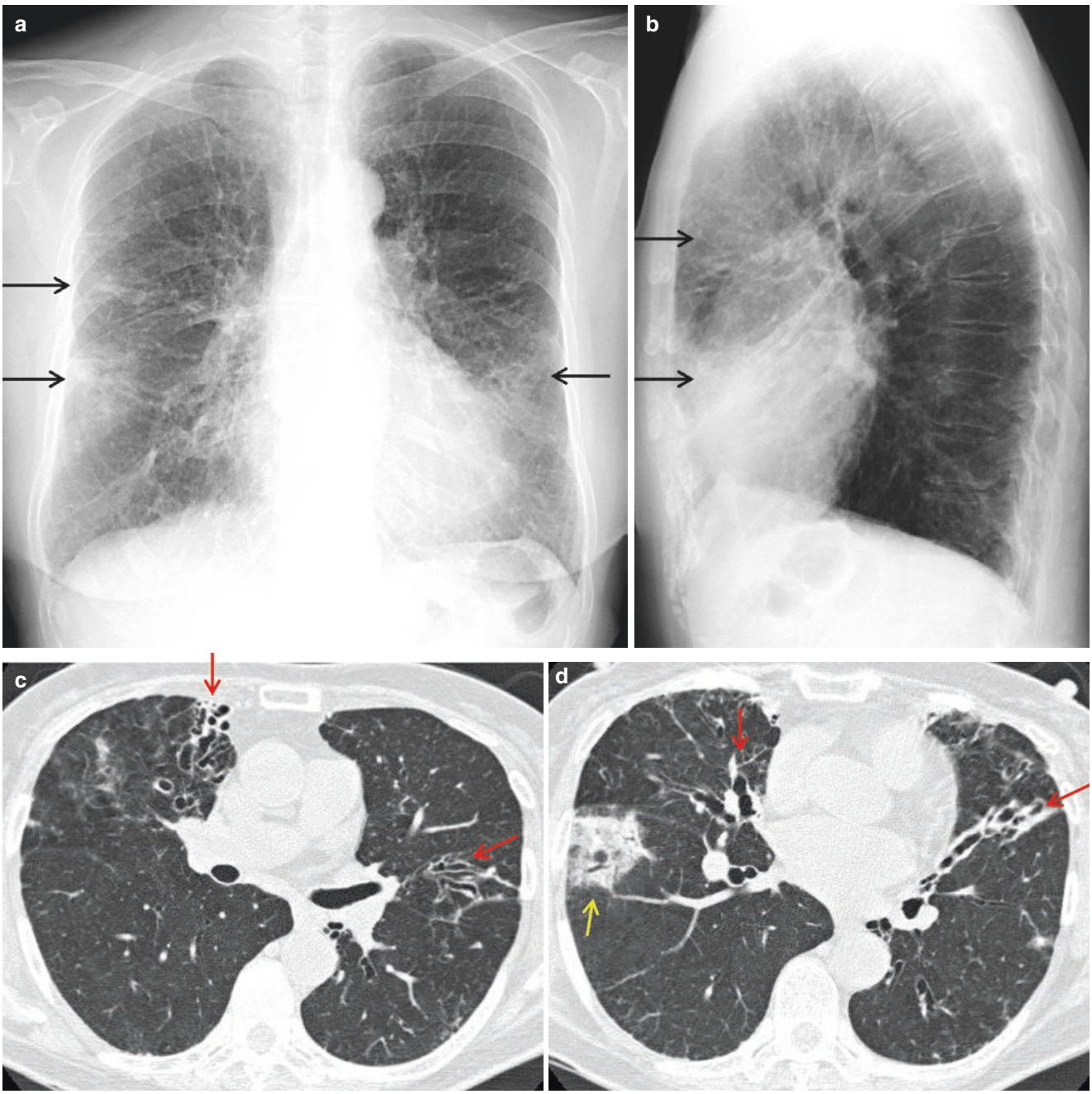

Fig. 2.7 Bronchiectasis with upper and middle lobe predominance. Chest radiograph of a 71-year-old woman. (**a**) In the posteroanterior radiograph, reticular shadows are visible in the middle and lower lung fields that mimic lung fibrosis (arrows). (**b**) In the lateral view, however, the shadows are extended to the ventral area in a segmental manner (arrow), suggesting upper and middle lobe distribution. (**c**, **d**) HRCT shows bronchiectasis distributed throughout the entire lung (red arrows). A focus of consolidation is seen in the right lower lobe (yellow arrow), indicating pneumonia

The primary clinical concern in BE is the risk of bacterial pneumonia [28, 29]. We show a case of pneumonia in Fig. 2.8. On the chest radiograph, a pneumonia shadow is visible in the right lower lung, and on HRCT, we recognize BE within the pneumonia and its adjacent area, indicating that BE is the predisposing factor for this pneumonia (Fig. 2.8b). RA patients with complications of BE are reported to have a poor prognosis because of repeated infection [30, 31]. This issue is detailed in Chap. 5.

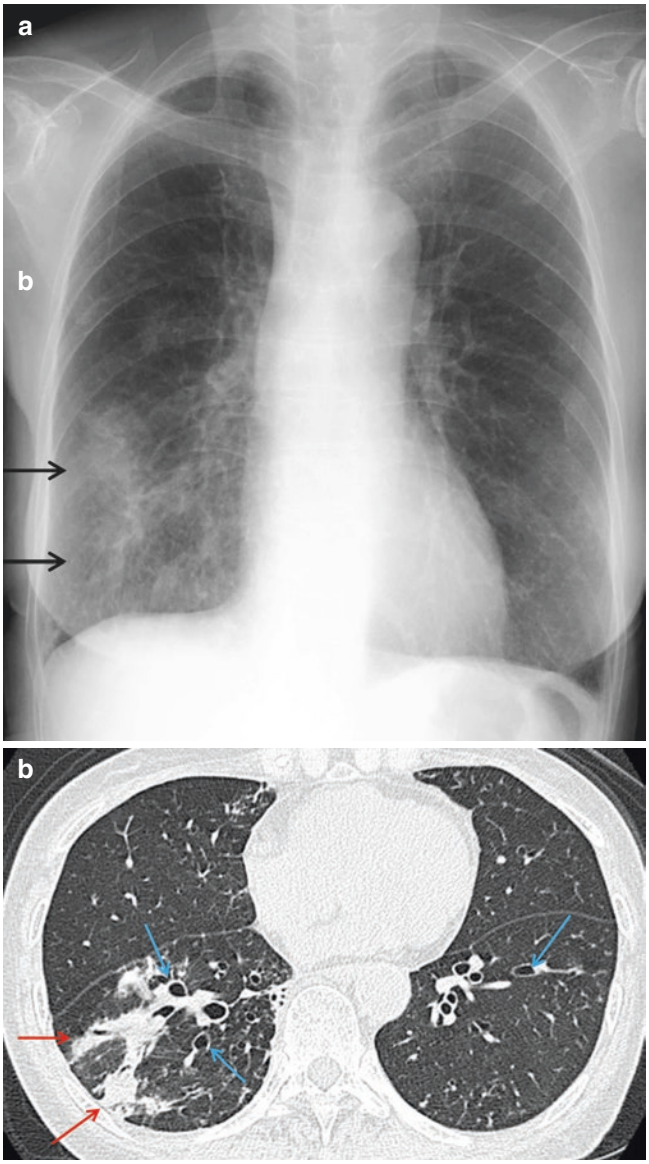

Fig. 2.8 Bronchiectasis complicated with pneumonia in a 72-year-old woman. She complained low-grade fever, cough, and sputum for several days. (**a**) This radiograph shows an infiltrative shadow in the right lower lung field (arrows). (**b**) HRCT shows an infiltrative shadow in the right lower lobe (red arrows). Bronchiectasis of a marked degree (blue arrows) is visible adjacent to those infiltrative shadow, suggesting that pneumonia has occurred at the base of bronchiectasis

2.3 Peripheral Airway Disease: Bronchiolitis

A great number of studies have been accumulated on the morphology and pathophysiology of bronchiolitis. They are detailed in Chap. 3. Here, we shall have a glance at these issues and consider their clinical significance.

2.3.1 Pathology of Bronchiolitis

Bronchiolitis in RA has been classified into several histopathological types [32] including (1) cellular bronchiolitis, (2) follicular bronchiolitis (FB), and (3) bronchiolitis obliterans (BO). We provide a simple overview below.

FB is observed in particular diseases such as RA or Sjögren's syndrome (Fig. 2.9b). FB is characterized by inducible bronchus-associated lymphoid tissue (iBALT) comprising mature B lymphocytes and plasma cells formed in the submucosal layer and outside the bronchial walls. In 2006, Rangel-Moleno and colleagues used modern immunohistological techniques to study the roles of these lymph systems and discovered that they produce various cytokines, chemokines, and anti-CCP antibodies that play major roles in the pathogenesis of RA. Of note, iBALT plays a harmful role to the surrounding lung tissue through these processes [33].

Agreement cannot be reached on the pathology of BO in RA [32]. BO is also often observed after transplantations, and there is controversy about whether BO in RA differs from post-transplant BO. In Japan, Homma and colleagues examined three BO patients with RA and described unique characteristics of these diffuse panbronchiolitis-like cases [34]. Hebisawa and colleagues reviewed many cases of BO and divided them into two categories. In one subtype, the structure of the airway wall is reserved, but the lumen is narrowed and obstructed by granulation tissue; they termed this "endobronchiolitis obliterans." This subtype is often found in patients after transplantation and is considered to be the same entity as conventional constrictive bronchiolitis. In the other subtype, inflammation extends to the entire airway wall, causing destruction and ultimate fibrosis of the wall that leads to constriction and obstruction of the lumen. They named the latter subtype "cellular and destructive bronchiolitis" (Fig. 2.9c). It is often seen in autoimmune diseases such as RA and Sjögren's syndrome and is accompanied by thickening and dilatation of the large airways [35]. These characteristics well match the clinical and radiological features of BO in RA [36].

In RA patients, two or more of these pathological types may coexist within the same patient's lungs [37]. A certain pattern may be prevailing at the biopsied site, but another pattern may prevail at another site; thence a diagnosis should not be based on this finding alone. Particularly in FB, several clinical and pathological reports handle this type as a distinct category [38]. Yet, on the basis of the above-mentioned reason, and because those reports failed to present distinct clinical features, the term "FB" should be used as a term for a pathological finding rather than an distinct clinicopathological entity.

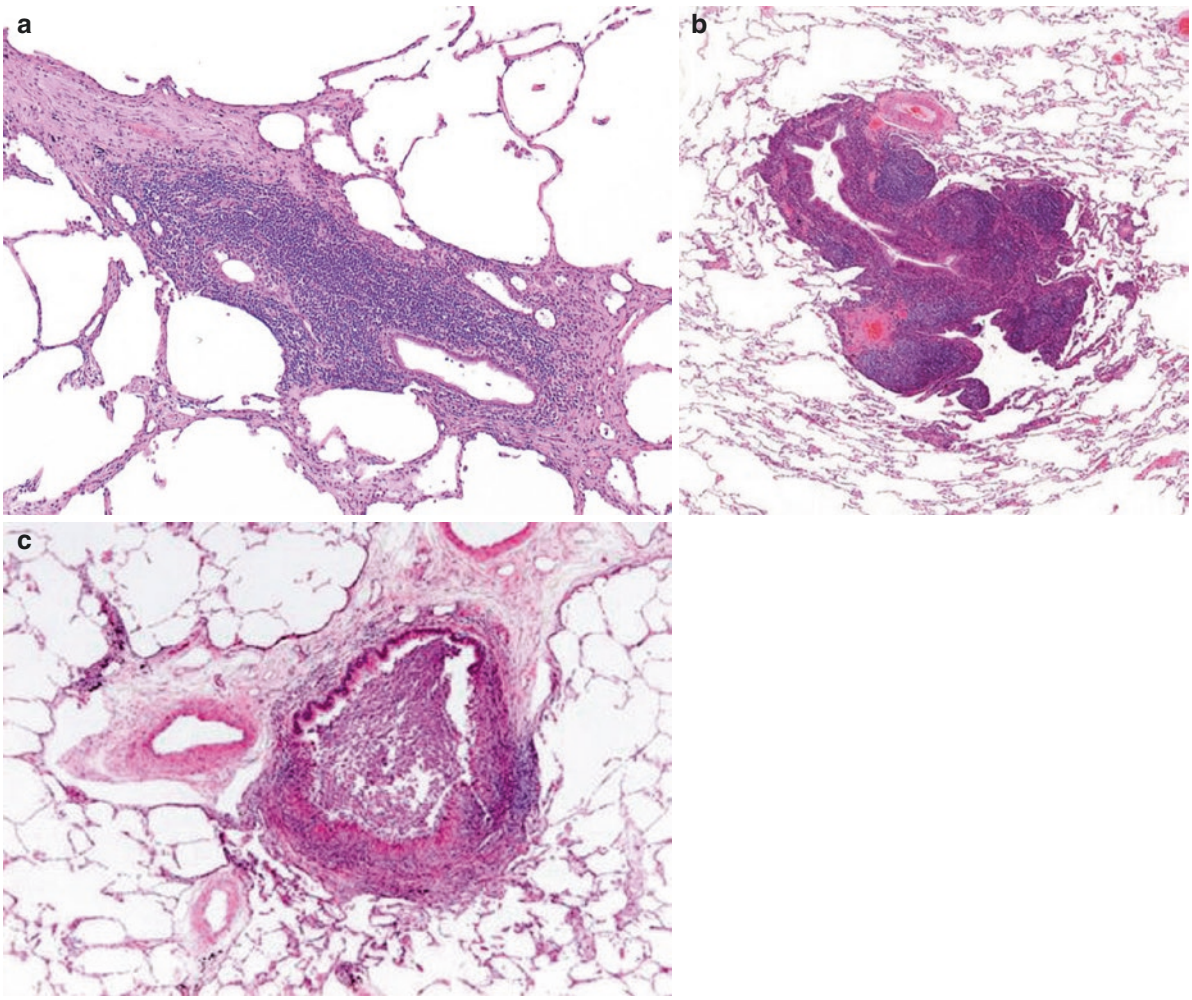

Fig. 2.9 Histological variations of bronchiolitis in RA. (**a**) Cellular bronchiolitis, (**b**) follicular bronchiolitis, and (**c**) cellular and destructive bronchiolitis (Photomicrograph in [**a**, **b**] courtesy of Dr. T. Takemura and that in [**c**] courtesy of Dr. A. Hebisawa)

How do the early stages of bronchiolitis look like? Figure 2.10 shows the histological findings of a surgical lung biopsy (SLB) specimen from an 18-year-old woman who developed RA 1 year ago. SLB was performed for suspicion of ILD. Cellular interstitial pneumonia was noted widely. At the site shown in this figure, a respiratory bronchiole is seen on a background of nearly normal lung. The walls are thickened due to inflammatory cell infiltration and collagen depo-

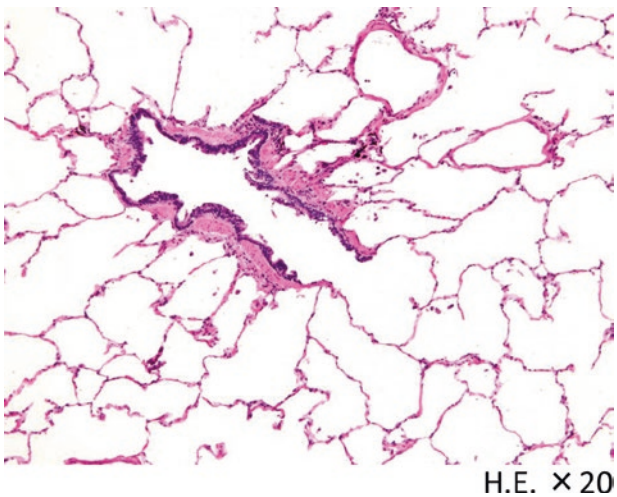

Fig. 2.10 Early stage of bronchiolitis in an 18-year-old woman with RA. Surgical lung biopsy was done for suspicion of interstitial pneumonia. In this almost normal lung, we see a respiratory bronchiole whose wall is thickened with inflammatory cell infiltration and collagen deposition. This patient has no respiratory symptoms (Photomicrograph courtesy of Drs. T. Takemura and H. Sugimoto)

sition and show the very early stages of bronchiolitis. This patient did not complain of any respiratory symptoms, indicating that bronchiolitis can develop from a very early stage in RA patients insidiously.

2.3.2 Epidemiology

The frequency of bronchiolitis among RA patients was investigated in various studies using HRCT, and a prevalence from 8 to 18% was reported [39, 40]. Takemura reported a prevalence of 61% in autopsied cases [41].

2.3.3 Imaging Findings

Centrilobular micronodules and branching opacities are thought to represent bronchiolitis on HRCT scans [37, 42]. The distribution is sometimes regional and sometimes diffuse. In BO, instead of the micronodular patterns, mosaic patterns may prevail in the lung field, which is shown more demonstrably in an expiratory CT scan. The details are discussed in Chap. 4.

2.3.4 How and When Does Bronchiolitis Appear and How Does It Progress in RA Patients?

No previous reports have tried to answer these questions. Below, we present some cases and discuss how and when bronchiolitis appears and how it persists or disappears in RA patients.

A case in which we fortunately witnessed the onset of bronchiolitis on sequential CT scans is shown in Fig. 2.11. The CT scan in Fig. 2.11a shows the first episode of pneumonia in a 49-year-old woman with RA of 15-year duration. The left lower lobe was consolidated with a marked loss of volume, inside of which dilated bronchi are visible. This was a case of pneumonia at the base of BE, which had progressed to organized pneumonia. This patient did not respond to antibiotics and required corticosteroids. At this point, there were no signs of abnormalities in the right lung.

Thereafter, MTX was restarted, and 4 months later, the patient had another episode of pneumonia. Along with the pneumonia in the left lower lobe, a chest radiograph revealed a newly developed granular opacity in the right lower lung (Fig. 2.11b), and HRCT scans confirmed a diagnosis of bronchiolitis (Fig. 2.11c). Thereafter, the patient suffered multiple recurrences of pneumonia, but each time, they were controlled with prompt administration of fluoroquinolones. Pharmacotherapy with MTX and biologics, essential to control her RA activity, was continued throughout the course of these episodes. Thanks to this persistence, the RA symptoms were stabilized, and she did not suffer recurrences of pneumonia thereafter. However, on the HRCT scan, micronodular opacities remained even after the successful disease course (Fig. 2.11d). A mild productive cough also persists. In this case, we observed the appearance of bronchiolitis, which was presumably formed through the spread of microorganisms from the left side during the second episode of pneumonia. We also learned through this case that once established, bronchiolitis would not disappear by any means.

A mild case of bronchiolitis in a woman in her 50s with RA for 10 years is shown in Fig. 2.12. Abnormal findings had been noted on chest radiography over the past 3 years (Fig. 2.12a). On HRCT, regional bronchiolitis is visible in the right upper lobe, and BE is noted in the left lingular division (Fig. 2.12b, c). During this period, the patient had suffered several episodes of mild respiratory tract infections. It was assumed that bronchiolitis had been formed through bacterial aspiration from the BE in the left side. Mycobacterial disease was ruled out with bronchoscopy. Over the next few years, this condition continued to wax and wane with aggravation and disappearance of the granular opacities on the images, which paralleled RA disease activity (Fig. 2.12d, e). A mild, productive cough was also noted during the periods of aggravation. This case shows that bronchiolitis, which began as an infectious type, may persist and fluctuate in parallel with RA disease activity in a patient with a mild disease course.

A 75-year-old woman with a chronic productive cough of a several years' duration and a 20-year history of RA is shown in Fig. 2.13. In chest images, widespread BE and bronchiolar disease were noted throughout the entire lung. Long-term therapy with macrolides had proven ineffective. Despite restrictive and occlusive mixed lung function impairment, the patients did not complain of dyspnea, presumably because of her low daily activity. This type of widespread broncho-bronchiolar disease is not infrequently seen in RA patients in clinical practice. Occasionally, this can be confused with diffuse panbronchiolitis in East Asia, but the distinct clinical course and the lack of response to macrolide therapy reveal a completely different disease profile.

Common to these cases presented here is the coexistence of BE at central side and bronchiolitis at peripheral side. Many CT studies report this coexistence, and also many studies using both HRCT and PFT have revealed a high prevalence of obstructive impairment in subjects with BE [17, 42, 43]. Airway inflammation in RA patients is not limited either to the central or peripheral airways, but it often involves the entire airway.

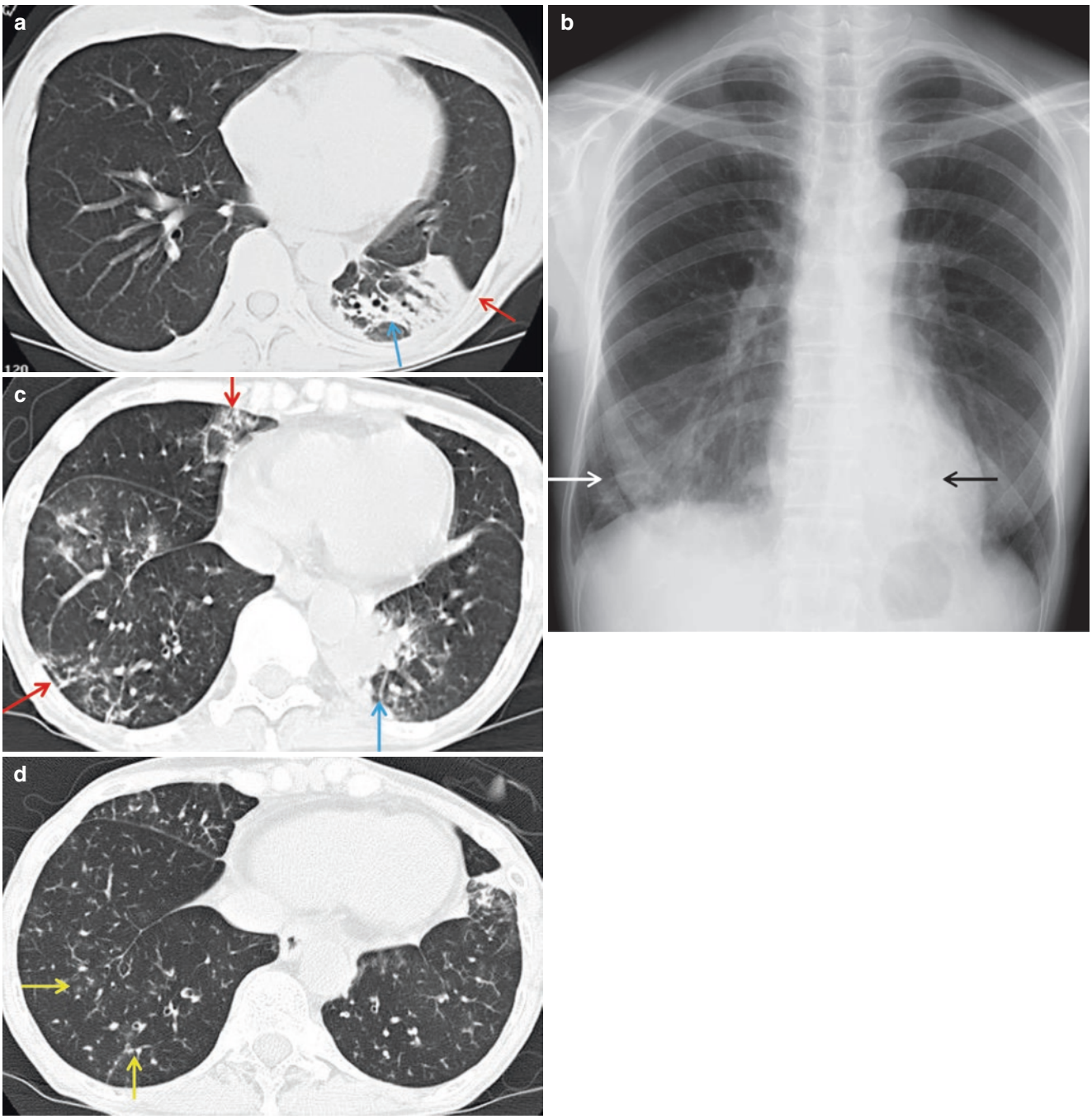

Fig. 2.11 Development of bronchiolitis observed in a 49-year-old woman with RA of 15-year duration. (**a**) HRCT at her first presentation for protracted pneumonia. The left lower lobe is collapsed and consolidated (red arrow), and dilated bronchial lumens are visible within it (blue arrow). This is the organized stage of pneumonia, which occurred at the base of bronchiectasis. Note that there are no abnormalities in the right lung. (**b**) The second episode of pneumonia after 4-month treatment of RA with MTX. The chest radiograph shows pneumonia in the left lower lung that obliterates the contour of the descending aorta (arrow). Disseminated granular shadows appear in the right lower lung field (white arrow). (**c**) HRCT scan shows pneumonia at S^{10} of the left lower lobe (blue arrow). Many micronodules are present in the right lower lobe and middle lobe (red arrows). (**d**) HRCT scan 4 years later shows micronodules and bronchiectasis remaining in the right lower lung field (yellow arrows). During this period, she suffered from several episodes of pneumonia, all of which were successfully controlled with the prompt use of fluoroquinolones. In the successive 5 years until now, she has not been troubled by pneumonia in accordance with good control of her RA disease activity. She still complains of cough and sputum, but it is tolerable

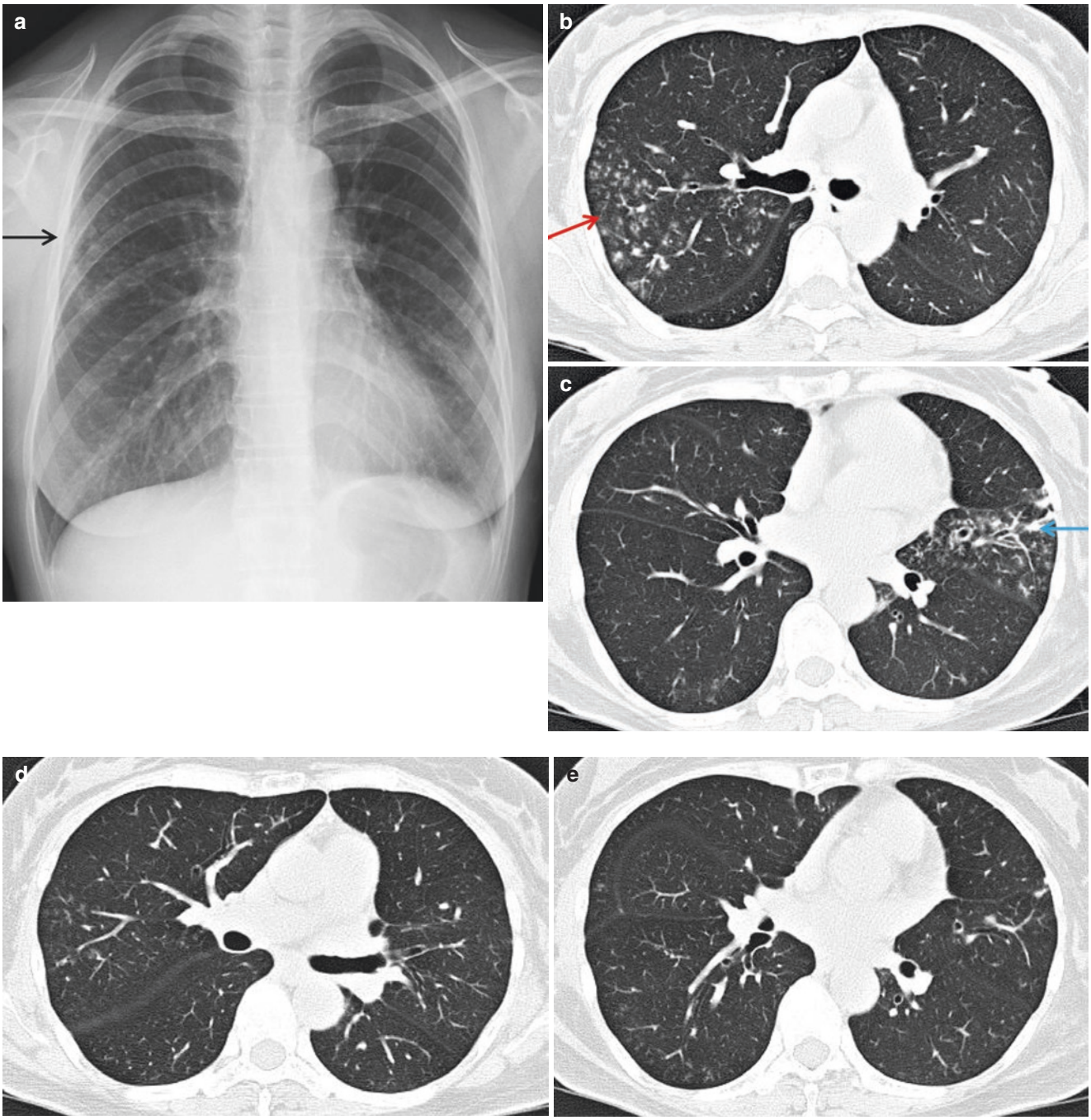

Fig. 2.12 Bronchiolitis in segmental distribution observed in a 57-year-old woman with RA for 10 years. (**a**) Chest radiograph shows a granular shadow in the right lung field (arrow), which had been pointed out for 3 years. Her RA disease activity is relatively low. (**b**) HRCT reveals centrilobular micronodules in S^2 of the right upper lobe (red arrow). (**c**) Bronchiectasis accompanied by micronodules is seen in the left lingular division (blue arrow), which is thought to be the origin of bacterial dissemination. This condition persisted for 3 years, with subtle respiratory symptoms. (**d**, **e**) Three years later, the micronodules have disappeared spontaneously without any specific therapy for this disorder. RA treatment was successfully conducted during this period

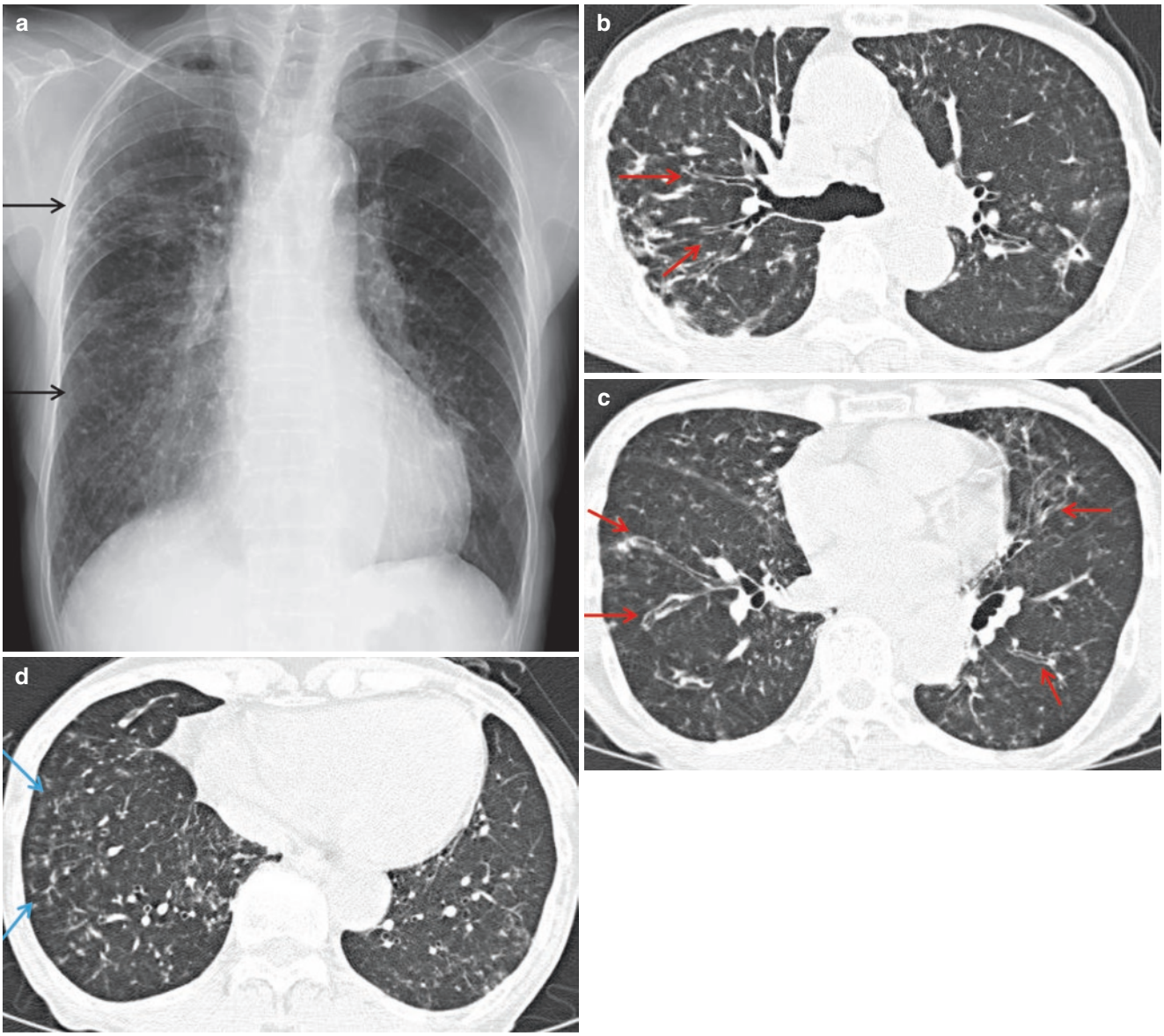

Fig. 2.13 Bronchiectasis and bronchiolitis diffusely distributed in the entire lung. (**a**) Chest radiograph of a 73-year-old woman with RA for 20 years shows a diffuse granular shadow (arrows). She complained of cough and sputum for several years, for which macrolides were prescribed with no effect. HRCT reveals prominent bronchiectasis in the upper lobes (**b**, red arrows) and also in the lower lobes (**c**, red arrows) with numerous centrilobular micronodules (**d**, blue arrows). These imaging findings closely resemble nontuberculous mycobacterial disease. However, the mycobacterium was not detected with repeated sputum examinations and with bronchoscopy. Thus, this condition was diagnosed as an advanced stage of RA-specific airway disease

2.4 Peripheral Airway Disease: Cystic Bronchiolectasis and Honeycomb-Like Structural Remodeling

As widely acknowledged, inflammation at the bronchiolar level leads to thickening of the bronchiolar walls and narrowing of the lumen; thereby, CT images show signs of centrilobular micronodular and branching opacities. Conversely, although relatively rare, the inflammatory process can destroy the bronchiolar wall and surrounding lung tissue, resulting in dilation of the bronchioles in patients with RA. In such cases, multiple cystic structures are formed along the stem bronchi or in subpleural region, revealing morphology similar to the honeycombing seen in chronic fibrotic interstitial pneumonia. These findings have never been described before and, in diagnostic imaging, have been most likely diagnosed as interstitial pneumonia, particularly ILD with usual interstitial pneumonia (UIP) pattern. We believe that this type of lung lesion is not rare in RA patients, and we would like to present our findings. Detailed pathological descriptions are provided in Chap. 7.

Case 1 (Fig. 2.14) A 75-year-old woman had a 30-year history of RA. She suffered from a chronic cough for several years, and reticular opacities are noted on her chest radiograph at the base of both lungs (Fig. 2.14a). Her coughing had worsened over the past 3 months, and because aggravation of ILD was suspected, she was referred to our respiratory department. Her main laboratory results were KL-6 813 IU/mL, ACPA 2530 U/mL, and RF 341 IU/mL. Arterial blood gas analysis showed mild oxygenation impairment. Bronchoscopy was performed, and bronchoalveolar lavage fluid revealed an increase in lymphocyte-predominant cells. On HRCT, we could see cysts of various sizes distributed in a segmental manner (Fig. 2.14b), which indicated a close relation to the airway. Lower lung slices showed clusters of cysts ranging from 5 to 10 mm in size arrayed contiguously in the subpleural area (Fig. 2.14c, d). These findings closely resemble the honeycombing seen in ILD with UIP pattern. In the pathological examination of the SLB specimen, a cystic structure is observed that involves an entire lobule (Fig. 2.14e, f). The walls of the cysts are made up of inflamed and disrupted bronchiolar walls. The surrounding alveolar tissue is also destroyed by inflammation and has disappeared. Histopathologically, these cysts are judged to be the result of inflammatory destruction and dilation of bronchioles. Notably, these changes were not accompanied by large airway disease in this case. When CT images in RA reveal clustered cysts in the subpleural area, radiologists commonly make a diagnosis of honeycombing, that is, ILD with UIP pattern. However, clinicians should note that similar findings might be produced by dilatation of bronchioles through intense inflammation owing to the RA.

Case 2 (Fig. 2.15) An 80-year-old woman was diagnosed as RA 4 years ago. On the same occasion, she was judged to have ILD based on CT findings. RA was treated with prednisolone and tacrolimus. She had no respiratory symptoms such as cough, sputum, or shortness of breath or any history of past pneumonia. The patient presented with a productive cough for 2 months, and a chest radiograph revealed a bilateral hilar infiltrative opacity that had expanded compared to previous films, and the patient was referred to our respiratory department. Her CRP was 2.5 mg/dL, KL-6 550 IU/mL, anti-CCP antibodies 362 U/mL, and results of PFT were within normal limits. She was diagnosed as having pneumonia at the base of BE, but antibiotics therapy failed to improve her condition. It was assumed the disease had developed into organized pneumonia, and she was started on 40 mg of prednisolone for 3 weeks, leading to successful resolution clinically and radiologically.

Chest radiographs showed a reticular opacity that predominated in the upper lobe with segmental distribution, indicative of bronchial origin, not ILD (Fig. 2.15a, b). HRCT scans showed dilation of the segmental bronchi with consolidation of the surrounding area containing countless dilated bronchi and cyst clusters (Fig. 2.15c, d). Consolidation in the surrounding areas showed a panlobular distribution, suggesting its airway origin. In the right lung, from S^2 to S^9, cyst clusters are formed along the segmental bronchi (Fig. 2.15e). Areas around these lesions showed the absence of reticular opacity, the sign of ILD, denying the possibility of traction bronchiectasis. These findings clearly ruled out ILD and led to the conclusion that all of these changes arose from an inflammatory process in the airway. Although lung biopsies were not conducted in this patient, the pathological findings of Case 1 help to imagine how these cyst clusters evolved (Fig. 2.15f, g). In inflamed lung tissue, respiratory bronchi arising from terminal bronchioles just adjacent to the membranous bronchioles are destroyed with the surrounding lung parenchyma. Inflammatory cell infiltration and fibrosis are also observed. From these findings, in such situation, we can postulate that small bronchi or bronchioles that branch off from the stem bronchus (so-called daughter branches) may form cysts, leading to the propagation of cysts such as is shown in Fig. 2.15c–e.

In summary, this is an example of extensive airway disease, not ILD, which has progressed insidiously. There were most likely several incidents of focal pneumonia that left organization after each episode, which ultimately created the consolidation around the bronchi. Concurrently, destruction and dilatation of the bronchi and bronchioles led to the formation of multiple cysts. These types of findings are relatively rare among RA patients, but they do occur and are the result of the intense inflammation of the airway characteristic in RA patients.

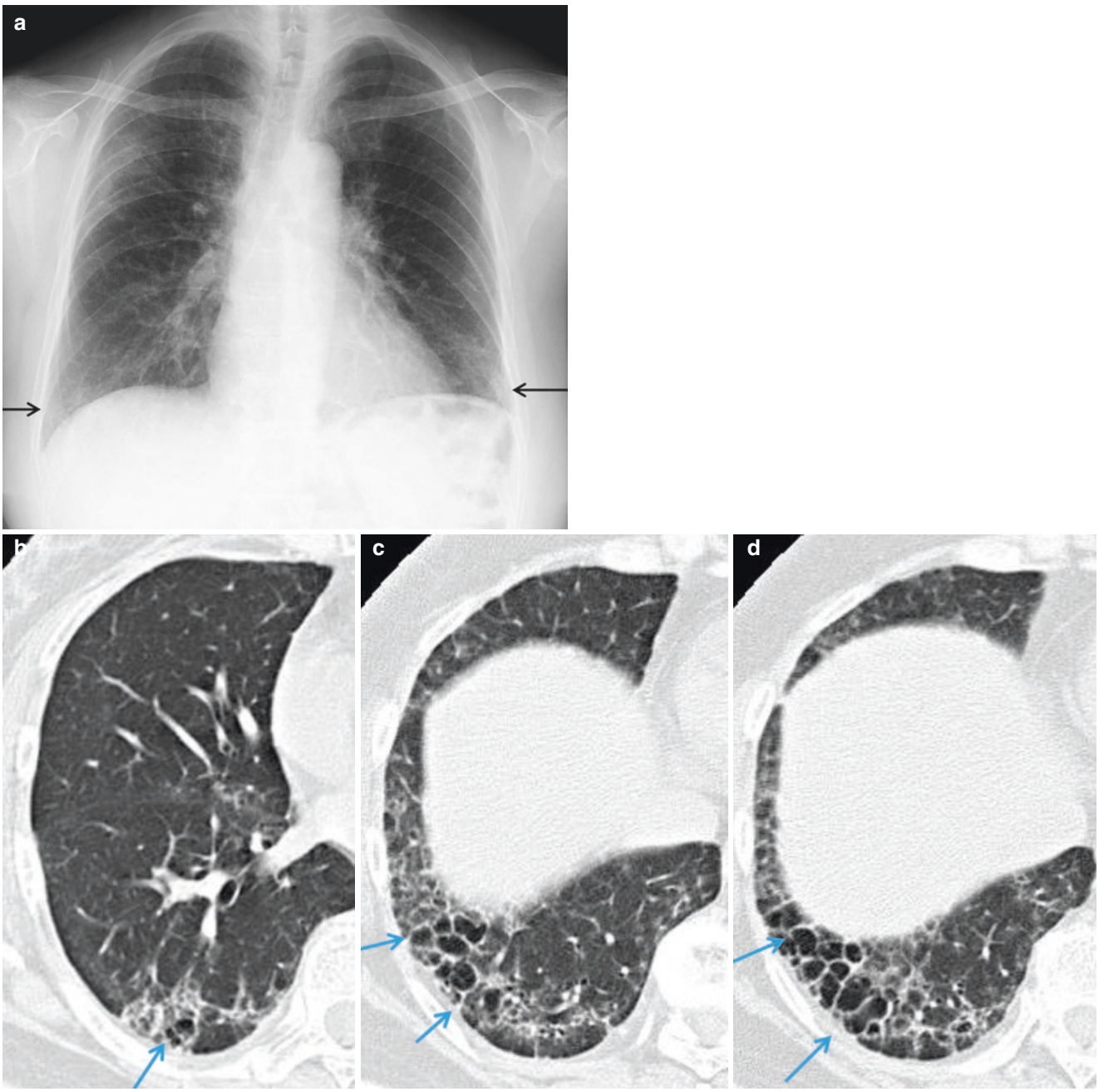

Fig. 2.14 Cystic bronchiolectasis mimicking honeycombing. (**a**) Chest radiograph of a 75-year-old woman with RA for 30 years. She complained of cough for 2 years, which had worsened over the recent 3 months. Tocilizumab had been given for 3 years. Reticular shadows are seen in the bilateral lung bases. (**b**) HRCT shows multiple cysts of various sizes distributed in a segmental manner (blue arrows). (**c**, **d**) Larger cysts are arrayed contiguously near the pleura that mimic a usual interstitial pneumonia (UIP) pattern (blue arrows). These cysts were proven to be dilated bronchioles histologically. Cystic bronchiolectasis was observed in the SLB specimen. (**e**) Panoramic view shows a cyst involving an entire lobule located slightly apart from the pleura (arrow). The cyst consisted of the destroyed and dilated bronchiole. (**f**) Cystic dilatation of bronchioles is visible in the inflammatory lesion (arrows). The wall of the cyst is composed of destroyed bronchiolar wall and the alveolar tissue around it, due to inflammatory destruction (Photomicrograph courtesy of Dr. T. Takemura)

These two cases share several clinical features. (1) KL-6, an important serum marker for ILD activity, was only slightly elevated, which is not compatible with ILD. KL-6 is also produced by the bronchiolar epithelium, making its slight elevation in these cases explicable [44]. (2) The symptoms were chronic cough and sputum presenting as of airway origin. (3) These airway symptoms were easily controlled with short-term fluoroquinolone therapy. These characteristics are all unlikely to occur in ILD. The details are described in Chap. 5.

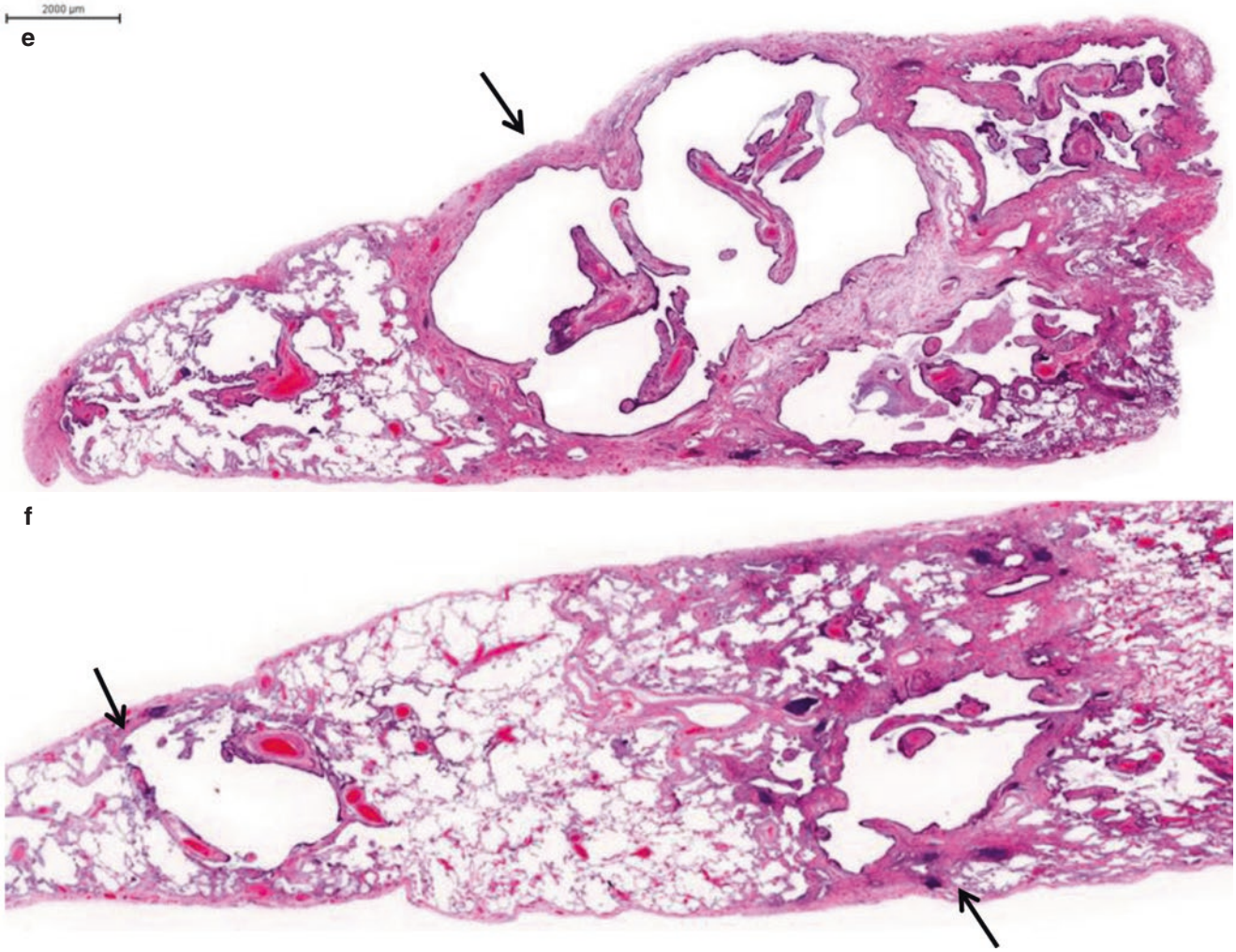

Fig. 2.14 (continued)

Case 3 In Fig. 2.16, we present a case with normal lungs at first in whom BE gradually developed and eventually progressed to honeycomb-like structures over 7 years of observation. At the time of first presentation, the patient was 50 years of age, with RA for 4 years, an ex-smoker (until age 30), and an office worker. Over the first 5 years, he experienced several episodes of pneumonia with hospitalization, and each time, antibiotics alone were not enough to cure, and he required additional corticosteroids. Over this period, BE emerged from an almost normal lung in the bilateral lower lobes (Fig. 2.16b–d). This emergence of BE can be attributed to the intense inflammation of the airway with repeated aggravation. Despite all treatment efforts over the next 2 years including biologics, his RA activity was difficult to control, and symptoms of chronic respiratory tract inflammation including productive cough also persisted. Two years later, a CT scan taken 7 years after the initial presentation revealed a new finding, the appearance of a honeycomb-like structure in the lingular division and lower lobes (Fig. 2.16e–h). Pathological studies on SLB specimens revealed that these cystic structures are formed through a destructive inflammatory process. The walls of the cysts are composed of the remaining bronchiolar wall and surrounding alveolar tissue that was destroyed by inflammation (Fig. 2.16i, j). In other words, although the findings appear similar to the honeycombing observed in ILD with UIP pattern (which is caused not by inflammation but by fibrosis), a completely different mechanism has created this structural remodeling, as shown in these sequences of CT images and the pathological findings. However, radiologists who interpret the last CT would likely make a diagnosis of ILD with honeycombing. We suspect that a certain proportion of RA patients diagnosed as having ILD of UIP pattern may in fact have airway disease formed through the process like this. RA patients with ILD with UIP pattern are reported to have poor prognosis. However, if a fair percentage of those were in fact airway diseases, then the treatment strategy would be entirely different. This is an important issue that should be addressed in the future.

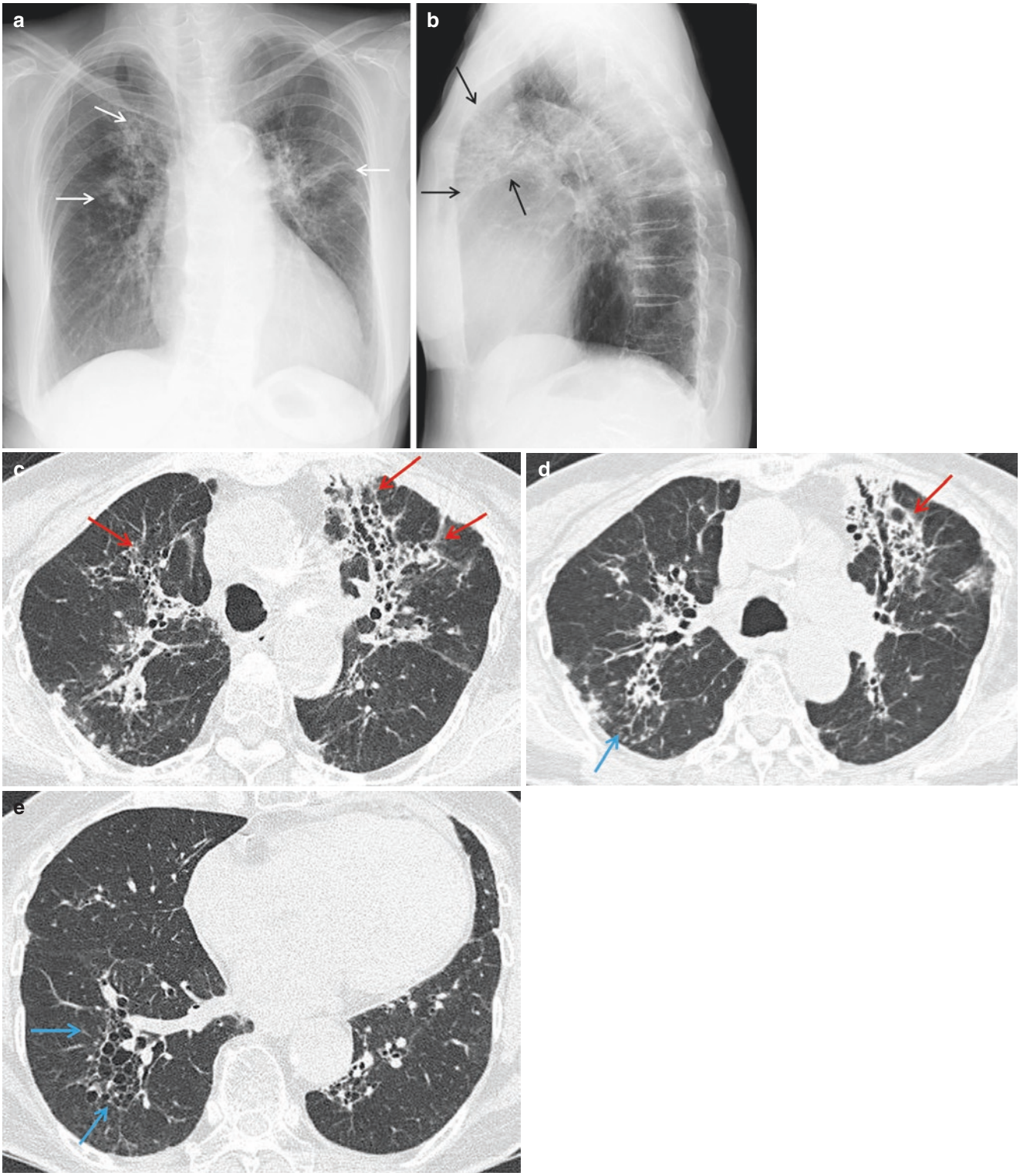

Fig. 2.15 (**a**) Posteroanterior chest radiograph in an 80-year-old woman with RA of 4-year duration. Infiltrative or reticular shadows are present in the bilateral hilar area (white arrows). (**b**) Lateral view shows segmental distribution of the reticular shadows (arrows). This pattern strongly suggests that the shadows are formed via the airway. (**c**, **d**) HRCT reveals multiple cystic lesions within the consolidated area around the dilated segmental-subsegmental bronchi (red arrows). (**e**) Clustered cysts are visible around B^9 and around B^2 (**d**) of the right lung (blue arrows). (**f**) Panoramic view of the SLB specimen of Case 1 and (**g**) a schema drawn by the inspecting pathologist would help to illustrate how all these abnormalities evolved. Both show structural remodeling in a lobule. Adjacent to the membranous bronchiole (red circle), cystic transformation of respiratory bronchioles arises from a terminal bronchiole, destroying the lung parenchyma in the vicinity. Chronic inflammatory cell infiltration and fibrosis are also noted. *Br* bronchiole (Photomicrograph and schema courtesy of Dr. T. Takemura)

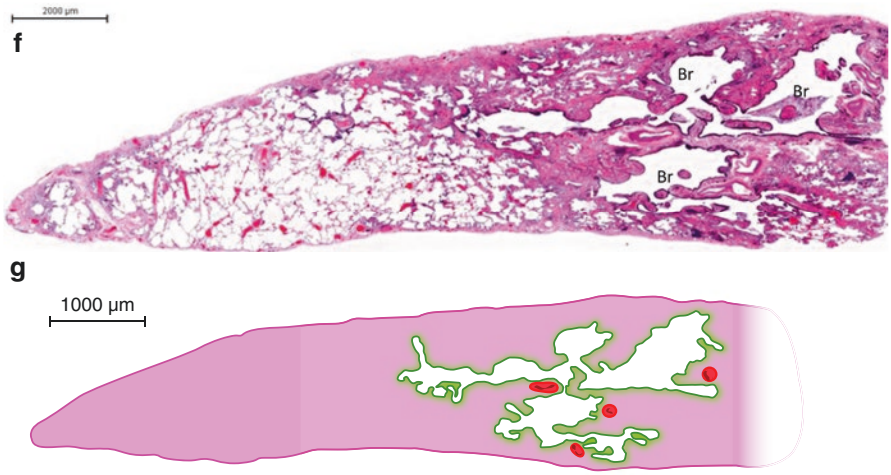

Fig. 2.15 (continued)

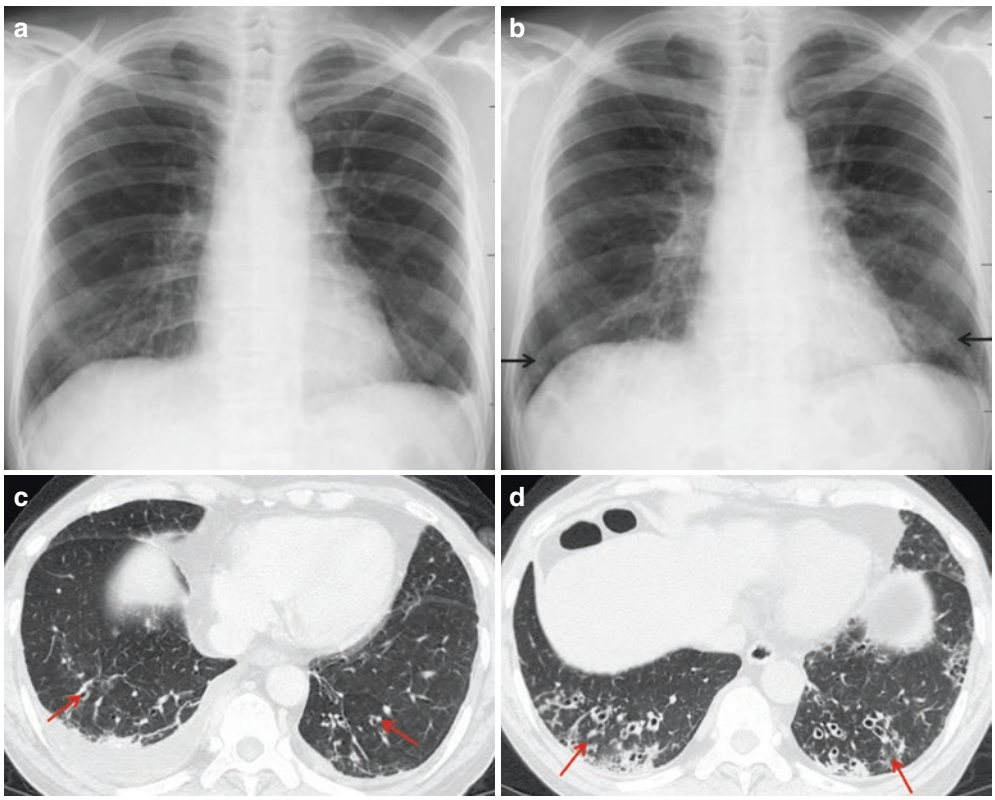

Fig. 2.16 (**a**) A case of uncontrollable airway disease observed for 7 years. Chest radiograph from a 50-year-old man with RA of 4-year duration at his first presentation to our respiratory department. The findings are almost normal except for pleural adhesion in the left costal phrenic angle. (**b**) Chest radiograph 5 years later. He had suffered from four recurrent episodes of pneumonia, all of which took a prolonged course that finally necessitated corticosteroid therapy. Reticular shadows appeared at the bilateral lung bases. (**c**) HRCT at the first presentation shows a small amount of pleural effusion, resolving pneumonia, and only a slight change in the bronchi (arrows). (**d**) HRCT 5 years later shows the emergence of many dilated bronchi with thickened walls in the bilateral lung base (arrows). These bronchial changes (bronchiectasis) are assumed to develop through repeated inflammation of the respiratory tract. Persistent inflammation of the airway ultimately caused bronchiolar destruction. (**e**) Chest radiograph 2 years later shows a reticular opacity at the left lung base (arrow), which has worsened compared with that in (**b**). (**f–h**) HRCT reveals multiple cyst formation along segmental and subsegmental bronchi (blue arrows) and a honeycomb-like appearance in the subpleural area (red arrows). This clinical course strongly suggests that the cysts are caused by persistent inflammation in the airway associated with RA. Histological findings in the SLB specimen. Panoramic view. (**i**) In addition to bronchiolar dilatation (red arrow), multiple cyst formation is visible (blue arrows).These cystic changes correspond to the honeycomb-like appearance found on HRCT. Infiltration of inflammatory cells is prominent around the cysts. (**j**) Magnified view of the box in (**i**). The walls of the cysts are composed of the remaining bronchiolar wall and surrounding alveolar tissue that was destroyed by inflammation. Although mimicking the honeycombing of ILD with UIP pattern, the pathogenesis of cyst formation is entirely different (Photomicrographs courtesy of Dr. T. Takemura)

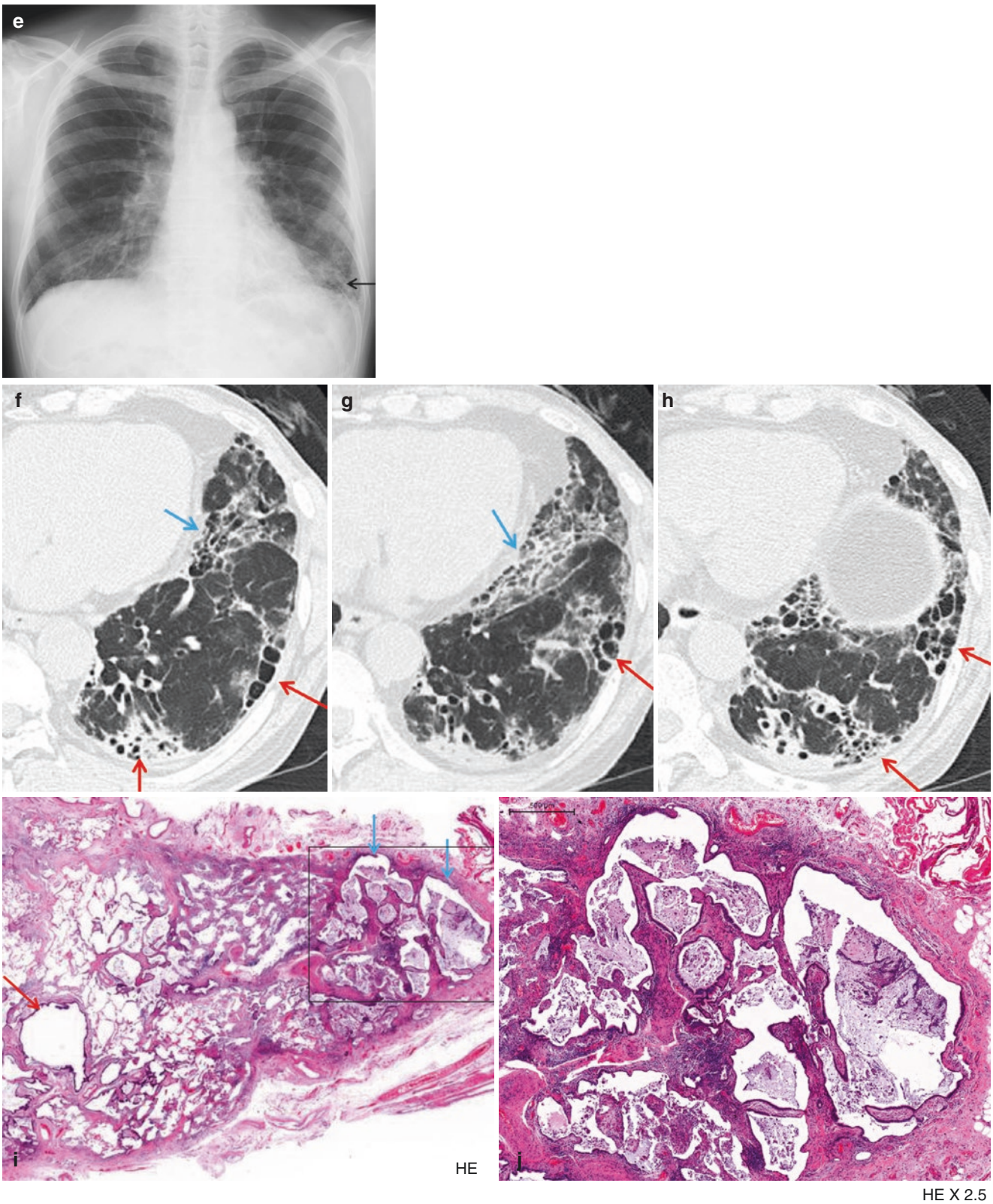

Fig. 2.16 (continued)

2.5 How to Understand and Confront Airway Diseases of RA Patients

We have discussed the high prevalence of airway diseases in RA patients and their significance in clinical settings of RA. Yet, questions remain: why are airway disorders formed so frequently, and how should we confront them?

Regarding the risk factors of airway disease in RA, Mori and colleagues have listed the clinical stage of RA and high titers of anti-CCP antibody and rheumatoid factor, whereas Nannini and colleagues have pointed out disease severity of RA (erythrocyte sedimentation rate, rheumatoid factor, necessity of DMARDs) [45, 46], both of which stress the importance of host factors.

From another viewpoint, the airway is an interface between the host and the external environment. It has a proper immune system in the submucosal zone in which an active immunological response is continuously in process with the microbiota, invading microorganisms, or inhaled particles (such as those of tobacco). It is hypothesized that in RA subjects, dysregulated and exuberant responses of this immune system occur, causing airway disorders [11, 46]. From this perspective, airway diseases of RA should be considered to be one of the extra-articular manifestations (EAM), pulmonary EAM. ILD, small airway disease, pleuritis, and rheumatoid nodules have been listed as pulmonary EAM [47], but the latter two are relatively rare and do not affect patient prognosis. Currently, airway diseases

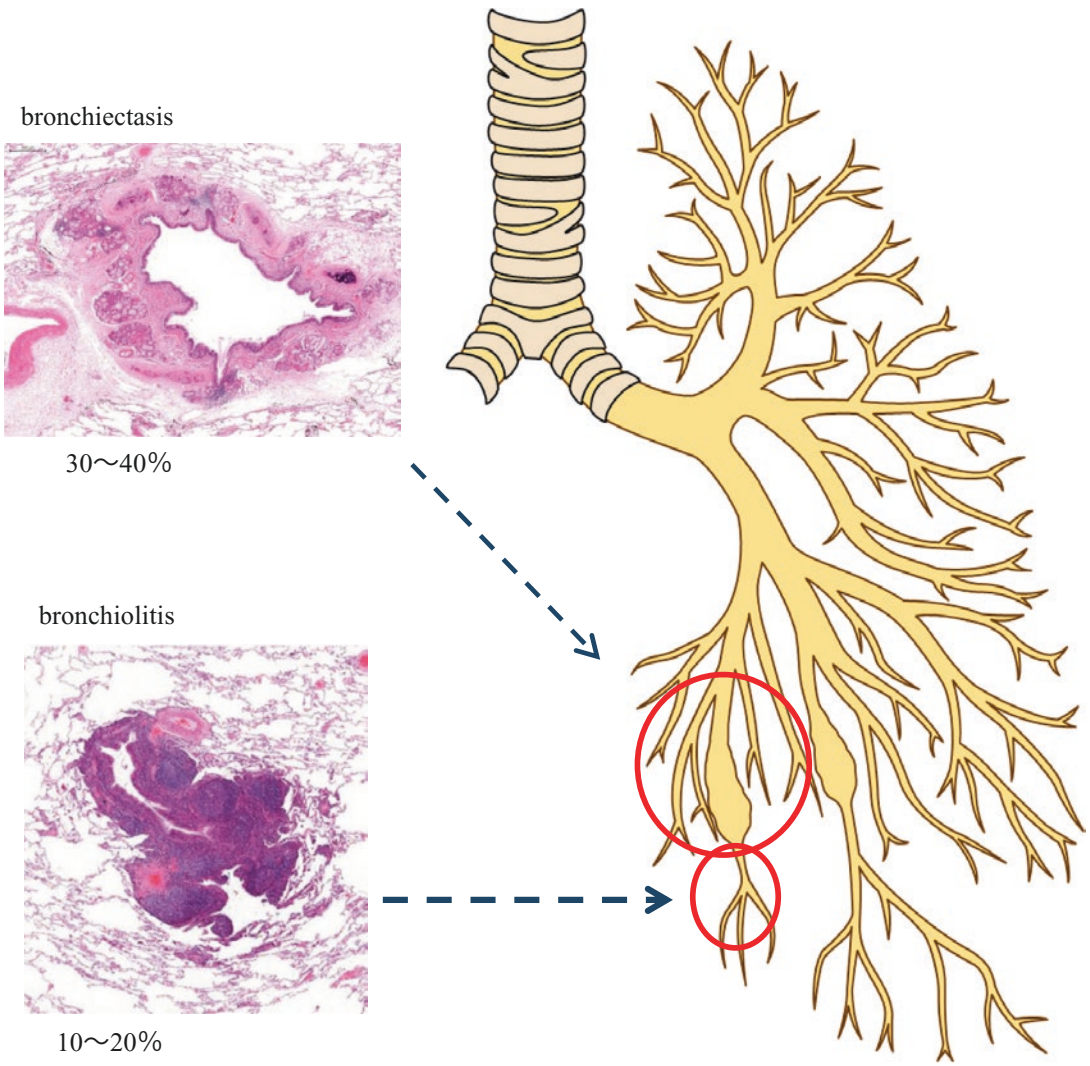

Fig. 2.17 How to understand airway diseases in RA patients? The airway is an interface between the host and the external environment. Various microorganisms may invade or colonize there, and inhaled particles such as those of tobacco could reach them. In RA patients, an exuberant host immune reaction might occur against these microorganisms and particles, leading to persistent inflammation and the formation of various airway disorders. Thus, these disorders should be considered as extra-articular manifestations of RA

including BE and ILD are considered to be the major pulmonary EAM [9, 46] (Fig. 2.17).

It is well acknowledged that the presence of EAM is associated with poor survival in RA patients [47, 48]. A recent epidemiological study of EAM conducted in the USA has revealed a steady, major decrease in vasculitis, carditis, and Felty's syndrome. These improvements are thought to be caused by the new disease-modifying RA treatments. The only exceptions are respiratory complications, which have conversely increased and threaten the lives of RA patients [49]. This tendency could be interpreted as follows: organs such as the heart, kidneys, and vasculature are closed systems and are benefitted by new-generation DMARDs without intervening factors. However, the lungs are exposed to the environment, and thereby, inhibition of the immune process with immune modulators would enhance vulnerability to infections or worsening of ILD. This could result in the destruction of lung structures, which would further aggravate the lung conditions, leading to a vicious cycle.

Taking these perspectives into consideration, we must manage to conquer lung complications, especially those originating from airway disorders, to successfully accomplish the control of RA and improve patient prognosis.

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