

Chapter 2

Sarcoidosis of the Upper and Lower Airways

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Introduction

Sarcoidosis granulomas have a predilection for the submucosa of the entire respiratory tract. As a result, sarcoidosis may cause a variety of airway-based clinical syndromes, which can be the dominant clinical feature in some patients. Respiratory symptoms referable to airway disease are often similar to more common illnesses, such as rhinitis, sinusitis, and asthma, not infrequently leading to delayed diagnosis [1–4]. Moreover, the pathologic features of sarcoidosis can be confused with other inflammatory disorders, including granulomatosis with polyangiitis and tuberculosis [5].

Including patients with pulmonary function abnormalities, radiologic abnormalities, and symptoms, the reported prevalence of airway involvement in sarcoidosis ranges from 40 to 60 % [5]. Advanced parenchymal disease, especially fibrotic sarcoidosis, increases the risk of lower respiratory tract airway involvement [6], whereas the presence of lupus pernio is associated with a higher risk for sinonasal sarcoidosis [7]. When lower respiratory tract airways are affected, morbidity and mortality are both elevated [8]; upper respiratory tract involvement is strongly associated with a high risk for non-resolving sarcoidosis [9]. The frequency of involvement and the prognostic implications both imply that the presence of airway sarcoidosis should be actively sought and factored into management decisions when it is found.

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Upper Respiratory Tract

Presentation and Diagnosis

Sarcoidosis of the upper respiratory tract (SURT) occurs in 2–6 % of individuals with sarcoidosis [7, 10]. It occurs more commonly in black patients and in females [3, 11, 12]. Any structure from the nares to the vocal cords may be affected. The most commonly affected areas are the nasal mucosa and sinuses [7], but the larynx, epiglottis, pharynx, and oral mucosa may also be involved.

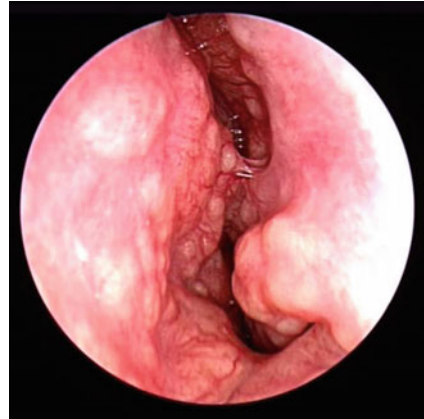
SURT typically presents with sinonasal congestion, crusting, nasal drainage, and variable degrees of hyposmia. Sometimes, sinonasal sarcoidosis may lead to sinus headache pain, epistaxis, watery eyes (from nasolacrimal duct obstruction), otitis media, and even destruction of nasal cartilage resulting in saddle nose deformity or septal perforation (Fig. 2.1). Glottic or supraglottic sarcoidosis symptoms may be due to exuberant granulomatous inflammation, or to strictures. Dyspnea, cough, stridor, obstructive sleep apnea, dysphagia, and dysphonia may be the presenting manifestations of laryngeal or pharyngeal sarcoidosis.

Nasal mucosal sarcoidosis is usually diagnosed by examination. Nodular pale white to yellow papular lesions, or exuberant inflammation with mucus crusting are the findings most typically observed with direct examination of the anterior nares, or by fiberoptic examination (Fig. 2.2) [4, 12]. Biopsy of the lesions should

Fig. 2.1 Collapse of anterior nasal cartilage from severe sinonasal sarcoidosis. There is also a substantial fleshy protuberance of the tip of the nose from granulomatous inflammation



Fig. 2.2 Cobblestoning of nasal mucosa. The nodular lesions are typically pale *white yellow*; there may be associated hyperemia and crusting [Courtesy of Martin Citardi, MD.]



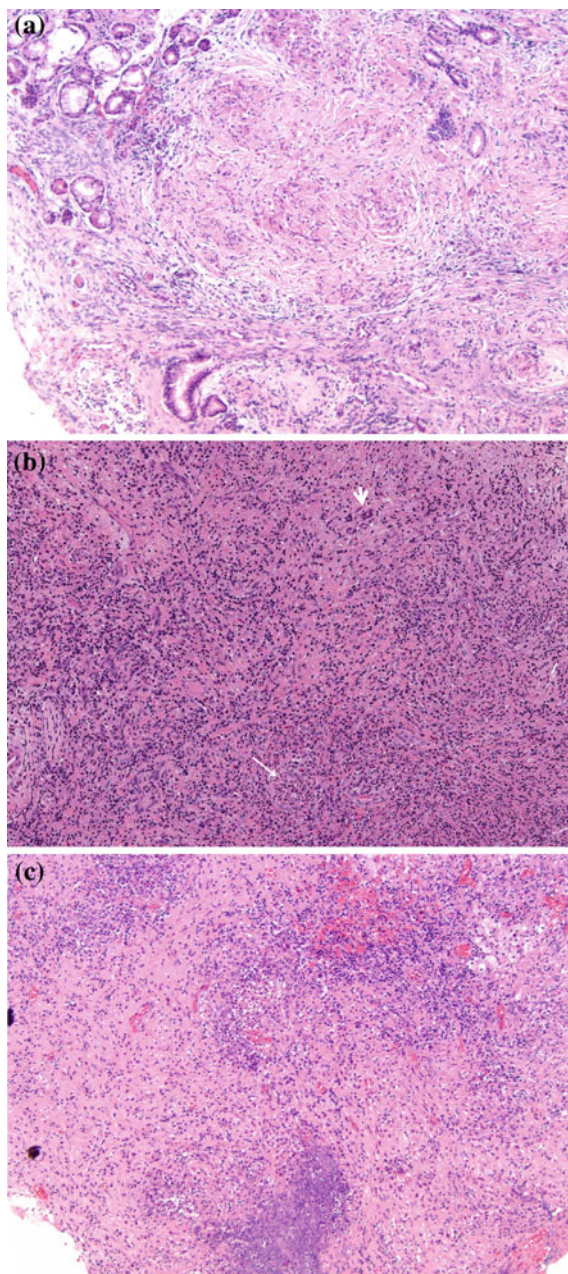
document predominantly well-formed non-necrotizing granulomas, with no evidence of infectious agents. Occasionally, the inflammatory lesions of granulomatosis with polyangiitis (GPA) may be difficult to distinguish from sarcoidosis [13]. Evidence of either disease outside of the upper respiratory tract is usually sufficient to confirm the diagnosis. In contradistinction to the well-formed discrete non-necrotizing granulomas of sarcoidosis, the “granulomas” of GPA show central geographic basophilic necrosis with palisading histiocytes and multinucleated giant cells and can be associated with vasculitis and neutrophilic microabscesses (Fig. 2.3a–c).

The prevalence of supraglottic and glottic involvement is approximately 1–2 % [3, 14]. It may occur in isolation, or in combination with sinonasal sarcoidosis. Fiberoptic examination findings include epiglottic thickening, masses, and granular infiltration of the aryepiglottic folds, false vocal cords, or surrounding tissues (Fig. 2.4a–b). Severe disease may lead to respiratory distress or respiratory failure, occasionally requiring tracheostomy [15]. Physical examination and inspection of the flow-volume curves are helpful adjunctive diagnostic tests when symptoms suggest the possibility of laryngeal sarcoidosis.

Management of Upper Respiratory Tract Sarcoidosis

The presence of SURT portends a low likelihood of spontaneous remission and also relative treatment resistance compared to many other organs [3, 16]. When the symptoms are relatively modest, topical therapy with corticosteroids and saline nasal washes may be adequate [12, 17, 18]. However, most patients with symptomatic SURT require systemic therapy [16]. In one center, emergence of SURT in patients with preexisting sarcoidosis led to a greater-than-four-fold escalation in the

Fig. 2.3 Well-formed granulomas are typical in sinonasal sarcoidosis (**a**), where clustered histiocytes are tightly arranged, and there is no substantial necrosis. The histiocytic inflammation seen in granulomatosis with polyangiitis, in contrast, is usually less tightly organized and may consist only of clusters of multinucleated giant cells with microabscesses (**b**). Other features (**c**) include clusters of foamy histiocytes, and histiocytes palisading adjacent to basophilic geographic necrosis [Courtesy of Andrea Arrossi, MD.]



mean daily prednisone dose in an attempt to control the disease (4 mg/d to 18.6 mg/d) [3]. Despite the increased corticosteroid dose, intralesional steroid injections, and surgical interventions, only 40 % of the patients had significant symptomatic improvement [3].

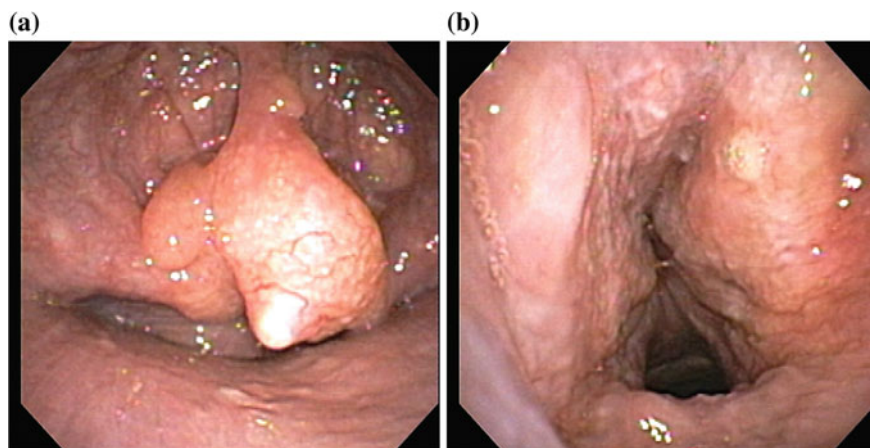


Fig. 2.4 Severe laryngeal sarcoidosis requiring debulking surgery. There is exuberant mass-like polypoid granulomatous inflammation of the epiglottis and aryepiglottic folds (a) leading to subtotal obstruction. The subglottic airway (b) is circumferentially infiltrated and narrowed by active granulomas and associated inflammation

Other immunosuppressive agents may be useful for SURT, but the data are sparse. In several series, the antimalarial agent hydroxychloroquine demonstrated modest efficacy, especially for milder cases [16, 19]. Cytotoxic agents, including methotrexate, azathioprine, and leflunomide were reportedly beneficial in small case series and case reports [13, 16, 19, 20]. Tumor necrosis factor antagonists, such as infliximab and adalimumab, are useful for treatment of sarcoidosis, but there are few data about their effectiveness for SURT. In a double-blind placebo-controlled trial of infliximab for pulmonary sarcoidosis, there was a trend ($p = 0.236$) for improvement of sinonasal sarcoidosis among the 7 patients who received infliximab, compared to four placebo-treated patients [21]. Obviously, this post hoc analysis was underpowered to provide meaningful information regarding infliximab for SURT.

Intralesional corticosteroid injections may be useful for isolated granulomatous masses. For sinonasal disease, their effectiveness appears to be relatively modest—in the series reported by Panselinas et al., only 2 of the 11 patients had improvement of symptoms at the end of the follow-up period [3]. For glottic and supraglottic lesions, several case reports have suggested that intralesional injections may be useful [18, 22–25]. Although intralesional injection may provide only temporary relief of severe airway obstruction, the resultant improvement of symptoms may allow sufficient time for slower-acting medications to effect longer term improvements [5]. Less commonly employed approaches to laryngeal sarcoidosis include laser ablation and external beam radiation [26, 27].

Sinus surgery may be necessary when there is severe sinus obstruction or suspected infection. Sinus surgery may provide temporary relief, but its benefits are usually not durable [3], and it may lead to nasal septal perforation and disease

recurrence [7, 28]. It is usually reserved for severe SURT refractory to medical therapy, or when there is life-threatening upper airway obstruction.

Lower Respiratory Tract

Presentation and Diagnosis

Sarcoidosis can affect any part of the tracheobronchial tree. The manifestations may be subdivided according to whether they are mainly due to airway luminal (intrinsic) involvement, or to extraluminal (extrinsic) compression or distortion by sarcoidosis inflammation or fibrosis occurring in the peribronchial lung parenchyma. A second distinction may be drawn between those manifestations that are due to active granulomatous inflammation versus those due to fibrosis (Table 2.1). This section will be organized using this categorization, but it should be recognized that many patients have more than one mechanism responsible for symptoms and physiologic abnormalities. Obviously, lower respiratory tract sarcoidosis due to granulomatous inflammation may require inhaled or systemic immunosuppressive medications for treatment. The general principles for treatment of pulmonary sarcoidosis apply to these patients, but are beyond the scope of this chapter.

Lower respiratory tract sarcoidosis, regardless of the mechanism, commonly causes cough, wheezing or dyspnea. Although airway mucosa is often very friable, hemoptysis is rare and should prompt evaluation for other problems, such as mycetomas, infections, or concomitant malignancies [29]. Pulmonary function testing may demonstrate obstruction in 11–57 % of individuals with pulmonary sarcoidosis [10, 30, 31]. In African American cohorts, the prevalence of airflow limitation is even higher; in a study of 123 consecutive non-smoking patients, 63 % were found to have an FEV1/FVC ratio less than 0.75 [32]. On the other hand, obstruction appears to be unusual in Japanese patients—in one prospective study of 228 subjects, only 9 % exhibited reduced airflow [33]. One possible explanation for the higher frequency of airflow obstruction in African American patients may be a

Table 2.1 Mechanisms of tracheobronchial sarcoidosis

| | Granulomatous | Non-granulomatous |
|-----------|---|---|
| Intrinsic | Granulomatous tracheobronchitis Hyper-reactive airways ^a | Endoluminal stenosis Bronchiectasis Hyper-reactive airways ^a |
| Extrinsic | Extraluminal inflammation (masses or bronchovascular bundle thickening) Lymph node enlargement | Bronchial distortion Traction bronchiectasis |

^aContribution of granulomas to hyper-reactivity is unclear but associated with physiologic hyper-reactivity

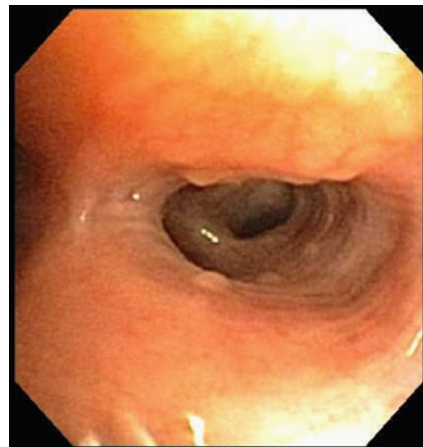
higher granuloma density compared Caucasians [34, 35]. Measurements of small airway dysfunction, such as frequency dependence of dynamic compliance and closing volume to vital capacity ratio, confirm that airway disease occurs in more than 50 % of Scadding stage 1–2 patients and should be assessed when dyspnea is unexplained [36]. As a rule, however, obstruction tends to be more evident and more severe with advancing parenchymal lung involvement [33].

Intrinsic/Granulomatous

As mentioned previously, granulomas are very common in mucosal and submucosal airways. In up to 55 % of patients with pulmonary sarcoidosis, direct examination of the airways will reveal abnormalities [34]. Common features include erythema, edema, mucosal granularity, cobblestoning, and plaques (Fig. 2.5). The mucosa may be extremely friable, but overt hemoptysis is rare [29]. The endoluminal nodules seen in sarcoidosis are typically wax or pearly, whitish to yellowish, and when present in a non-contiguous distribution, resemble cobblestones. However, this appearance is not specific, so a biopsy is mandatory if the diagnosis has not been established previously.

Endobronchial forceps biopsy is a low-risk modality for securing histologic evidence of sarcoidosis. In patients with abnormal mucosa, the yield of directed endobronchial biopsy has ranged from 45 to 91 %, with most series in the 50–60 % range [37–41]. However, endobronchial biopsy may still be useful in suspected sarcoidosis when there is no visible mucosal abnormality, where performing 2–4 random mucosal biopsies results in 20–37 % sensitivity for granulomas [37, 39, 41]. In a retrospective review of 154 patients, the yield of endobronchial biopsy was 85 % for African American patients, versus 38 % for Caucasians [34]. These data

Fig. 2.5 Cobblestone appearance of tracheobronchial sarcoidosis at the main carina. The lesions tend to be more discrete in the trachea and mainstem bronchi and more like to coalesce into diffusely irregular mucosal inflammation in the lobar and segmental airways



suggest that careful airway inspection and directed endobronchial biopsy is a useful part of bronchoscopic diagnosis, especially in African American patients.

Chest CT scan may be useful to identify patients with endobronchial involvement; in a series of 60 patients, CT scan revealed bronchial involvement in 65 % of the cases [42]. An additional CT feature that suggests small airway involvement is the presence of air trapping on expiratory scans. In one series, air trapping was found in 19 of 20 evaluated patients; its presence correlated with reduced mid-expiratory flow rate and increased residual volume, but not with other spirometric parameters [43]. It is unknown whether all air trapping in sarcoidosis is due to granulomatous inflammation or to other mechanisms.

Bronchial hyper-reactivity is common in sarcoidosis. It may be extremely difficult to distinguish from asthma, since extrinsic triggers like fumes, smoke, or pollen may precipitate exacerbations. As a result, misdiagnosis of asthma is not uncommon in sarcoidosis cohorts, resulting in delayed sarcoidosis diagnosis [44]. Bronchial provocation testing is abnormal in approximately 20 % of patients [45–47]. Bronchial hyper-reactivity appears to be more frequent patients with lower baseline FEV1 [46] and occurred solely in those with positive endobronchial biopsies in the study performed by Shorr et al. [45]. These observations raise the possibility that the presence of abnormal bronchial provocation responses may be due to intrinsic small airway disease with smaller baseline airway diameter, which could potentially lead to false-positive FEV1 declines. As further evidence that there may be no pathophysiologic association between asthma and sarcoidosis, a recent case–control study examined the likelihood of atopic eczema, asthma, or hay fever in a series of 225 sarcoidosis patients and 177 controls [48]. The prevalence of all three features was similar in sarcoidosis and control patients, raising the likelihood that the apparent relationship between asthma and sarcoidosis may be coincidental rather than pathologic.

Intrinsic/Non-granulomatous

Significant endoluminal stenosis is very rare, occurring in only 18 of 2500 (0.7 %) patients seen in a French institution from 1980 to 2000 [49]. Most of the lesions occur in the upper lobes or middle lobe and involve more than one lobar or segmental bronchus [49–51]. Occasionally, the stenosis may be diffuse [52]. Bronchoscopically, the lesions typically appear as webs or concentric narrowing by bland fibrotic tissue (Fig. 2.6a). However, in some patients, there may be a granulomatous component (Fig. 2.6b), so that endobronchial forceps biopsy and consideration of immunosuppressive therapy may be useful.

The presence of endoluminal stenosis may be suspected when there is cough, dyspnea, or wheezing; physical examination is extremely important as it may demonstrate focal prolongation of the expiratory phase or even wheezing. The flow-volume loop may likewise reveal variable emptying of large airways, sometimes visible as a notch on the expiratory limb. Endoluminal stenosis should be

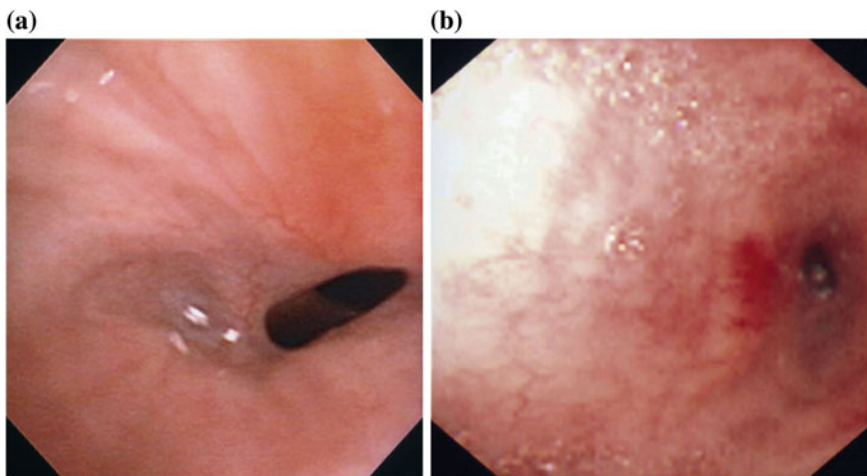


Fig. 2.6 Airway stenosis due to sarcoidosis. Isolated or multiple fibrotic webs may be found, usually in the segmental or subsegmental airways. **a** Depicts subtotal obstruction of the entire left lower lobe, with the anteromedial basal and lateral basal subsegments still visible. **b** There is extensive fibrogranulomatous proliferation at the level of the right mainstem bronchus leading to ventilation of the right lung through a pin-hole-size orifice

suspected in patients with dyspnea that is out of proportion to chest imaging findings, especially when airflow obstruction is present [53]. However, it may occur even in patients with normal pulmonary spirometry [49].

When active granulomatous disease is present, treatment should include immunosuppressive therapy, such as corticosteroids [49, 53]. In patients for whom immunosuppressive therapy is not helpful, mechanical dilatation via balloon bronchoplasty can be considered (Fig. 2.7). Bronchoplasty can be performed via rigid or flexible bronchoscopy [54, 55]. Repeat bronchoscopic evaluation is usually necessary since the stenosis may recur, requiring more than one session of dilatation before the airways remain fully patent. Although spirometry is often unchanged after bronchoplasty, it is not uncommon that dyspnea is alleviated [54]. For refractory cases, endobronchial stenting is an option, but it may lead to exuberant granulation tissue in sarcoidosis patients. Therefore, stenting should be reserved for as a last resort and performed only centers with substantial experience.

Extrinsic/Granulomatous

Sarcoidosis tends to involve the peribronchial lung parenchyma in the mid-to-upper lung zones. Sometimes, the sarcoidosis lesions coalesce in a perihilar distribution to form conglomerate inflammatory masses (Fig. 2.8). The perihilar conglomerate mass-like lesions are typically difficult to distinguish from enlarged lymph nodes

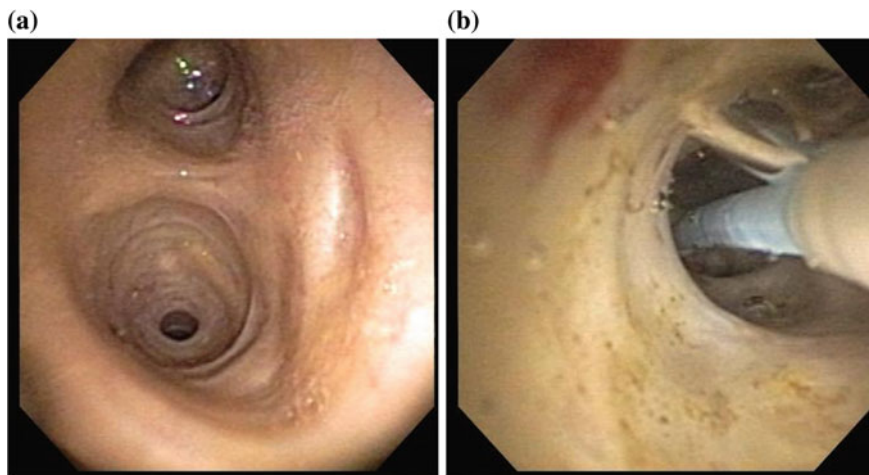
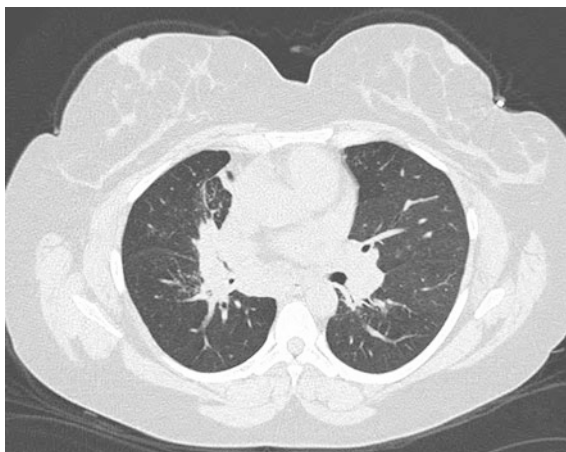


Fig. 2.7 Web-like stenosis of the airways (a) treated by advancing a balloon catheter into the obstructed segments (b) to perform bronchoplasty. The procedure requires that the operator is able to pass the catheter through the stenotic lesion. We routinely perform circumferential methylprednisolone injections at the level of the stenosis after dilatation [Courtesy of Thomas R. Gildea, MD.]

Fig. 2.8 Conglomerate perihilar inflammatory mass-like inflammation leading to compression of the right upper lobe, bronchus intermedius, and left lower lobe superior segment airways



and usually occur in advanced or long-standing disease [56, 57]. Although the lesions may already have been treated with corticosteroids and other therapies, the emergence of fludeoxyglucose positron emission tomography (FDG-PET) scanning has shown that many of these lesions previously thought to be fibrotic actually harbor active granulomatous inflammation [58]. The intensity of FDG uptake correlates positively with the magnitude of response to therapy [59]. Therefore, in

patients with extrinsic airway compression from conglomerate parenchymal sarcoidosis, assessment of disease activity and trials of therapy should be attempted. In some patients, aggressive immunosuppressants, such as infliximab, are necessary to alleviate the impact on the airways [59].

Lymph node enlargement is a very rare cause of airway compression. In the French series of 2500 patients, only 2 patients had substantial main carina enlargement [49]. Lobar obstruction due to lymph node enlargement has been reported [60–62]. In a series of 42 patients with airflow obstruction, only one had obstruction solely due to compression from enlarged lymph nodes, but another 10 (36 %) had some contribution from lymph node enlargement [56]. Taken together, these data suggest that there are several granulomatous mechanisms of extrinsic airway obstruction in sarcoidosis; in the absence of failed treatment trials and negative FDG-PET scanning, the presumption should be that aggressive therapy has the potential to improve symptoms and physiologic indices.

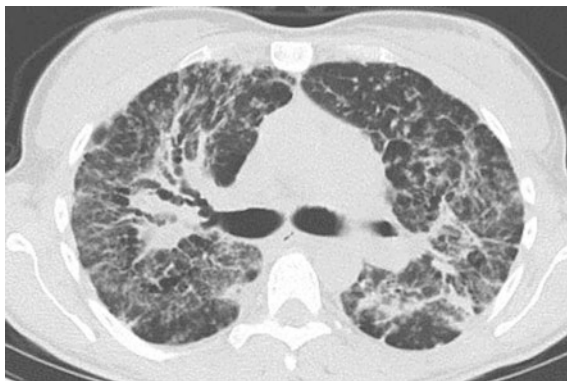
Extrinsic/Non-granulomatous

Sequelae of granulomatous inflammation may lead to irreversible airflow obstruction when the airways get caught up in the peribronchial fibrotic response. The response may include parenchymal architectural distortion, leading to loss of airway patency, bullous disease, honeycombing, and traction bronchiectasis [57]. These radiologic features may all be present in Scadding stage IV chest radiographs and are all associated with physiologic and symptomatic airway obstruction [63]. The most common manifestation is bronchial distortion, which tends to occur in the mid-to-upper lung zones [56, 57] (Fig. 2.9).

Bronchiectasis from sarcoidosis can be localized, but it is usually diffuse. Diffuse cystic bronchiectasis occurs in two situations: due to traction from honeycombing or other parenchymal fibrosis, or from direct damage to the airways from granulomatous inflammation. In cases with localized bronchiectasis, long-standing endobronchial sarcoidosis or focal lymph node compression is usually the culprit [64]. Using chest CT, bronchiectasis has been found on 18–40 % of patients with a stage 4 chest radiograph [57, 65]. The rate of bronchiectasis may approach 100 % in patients who require lung transplantation [66].

Hemoptysis and substantial sputum production are unusual when bronchiectasis occurs in sarcoidosis, and their presence should prompt evaluation for other morbidities such as infections. However, in a minority of patients with bronchiectasis, the clinical course may be dominated by classical bronchiectasis features. In that situation, there may be a high rate of clubbing, crackles, and recurrent exacerbations requiring hospitalization [65]. Management of recurrent infectious exacerbations may be more useful than escalating corticosteroid doses. In a small series, the mortality rate in this situation was high (4 of 7) [65].

Fig. 2.9 Severe right upper lobe bronchus architectural distortion from parenchymal fibrosis. The airway is curved by the surrounding fibrotic process in a pattern that is nearly pathognomonic for sarcoidosis. Endoluminal irregularity is typically visible as well, as in this example



Conclusion

Airway involvement from sarcoidosis is common but under-recognized. Its presence implies a low likelihood of spontaneous remission and the need for more aggressive immunosuppression when treatment is indicated. Therefore, a treatment strategy that considers long-term tolerability and effectiveness should be initiated in those patients with significant airway disease. It is important to distinguish active granulomatous inflammation from fibrotic sequelae of sarcoidosis when formulating a treatment strategy, using imaging findings, response to therapeutic trials, biopsies, and FDG-PET scanning to assess activity.

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