Noninfectious Pulmonary Manifestation of GVHD: Bronchiolitis Obliterans Syndrome

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Clinical History

A 63-year-old man received a PBSCT from an HLA-matched sibling donor for acute myelogenous leukemia (FAB M2) in persistent relapse. Approximately 2 months post-transplant, biopsies confirmed GVHD in the skin and upper GI. The GVHD was treated with cyclosporine and high-dose prednisone which was tapered in 2 months. Approximately 3.5 months post-transplant, a lower endoscopy with biopsy noted zygomycete infection of the colon. Subsequent workup also noted splenic abscesses believed to have been caused by the fungal infection. The patient was treated with itraconazole and amphotericin B and placed on TPN for chronic malnutrition and hypoalbuminemia. Due to increased dyspnea upon exertion, at day 140 chest CT was performed which noted bilateral

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pulmonary opacities as well as pleural effusions. Blood cultures remained negative throughout. Pulmonary function testing (PFT) performed on day 144 showed a restrictive pattern with decreasing DLCO. Subsequent chest CTs showed increased opacities, pleural effusions, lymphadenopathy, and atelectasis. BAL contained no infectious organisms or other abnormalities. Video-assisted thoracoscopic surgery (VATS) was performed on day 169 with a lung biopsy confirming the diagnosis of cryptogenic organizing pneumonia (COP), formerly called bronchiolitis obliterans with organizing pneumonia (BOOP). This pathologic finding combined with the restrictive pattern PFT leads a clinicopathologic diagnosis to be consistent with pulmonary GVHD. He was treated with Solu-Medrol 2 mg/kg and an array of Levaquin, Zosyn, and Vancomycin while remaining on amphotericin B antifungal medication. On day 170 he developed acute renal failure and hyperbilirubinemia, so the amphotericin B was held. The patient also developed fever and septic shock in association to the infection and was intubated on day 172 for increased respiratory rate and decreased oxygenation ability. The patient passed away on day 173 from pulmonary decompensation. An autopsy was performed.

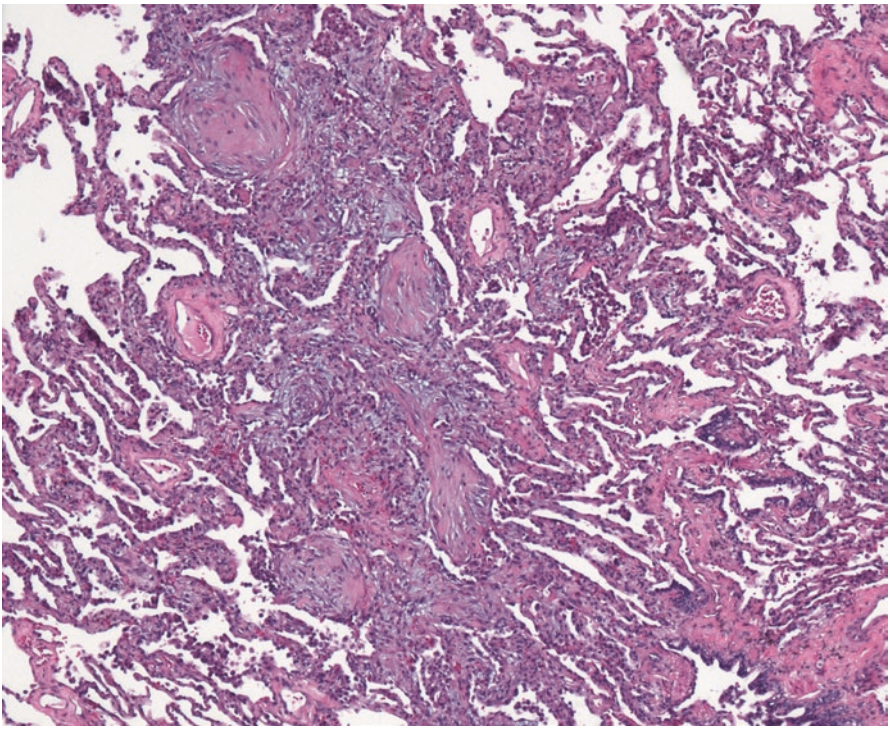

Fig. 18.1 Lung biopsy from day 169 demonstrating a segment of lung with a focal area of consolidation, in which there are numerous fibrous, onion skin-like Mason bodies obstructing the bronchioles and alveolar ducts

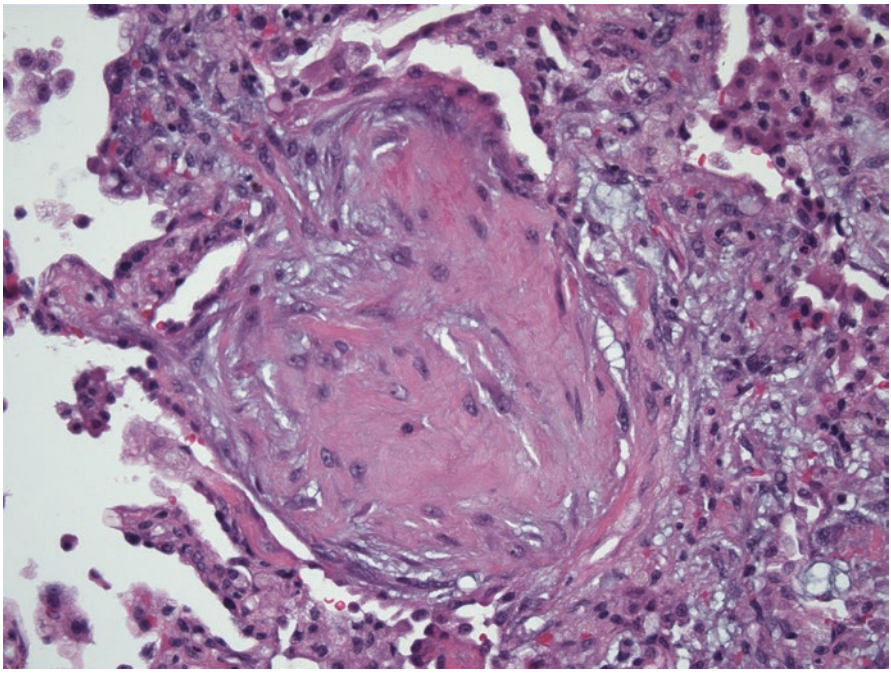

Fig. 18.2 A higher-power image of the same day 169 lung biopsy as in Fig. 18.1 shows a fibrotic foci obliterating a small airway

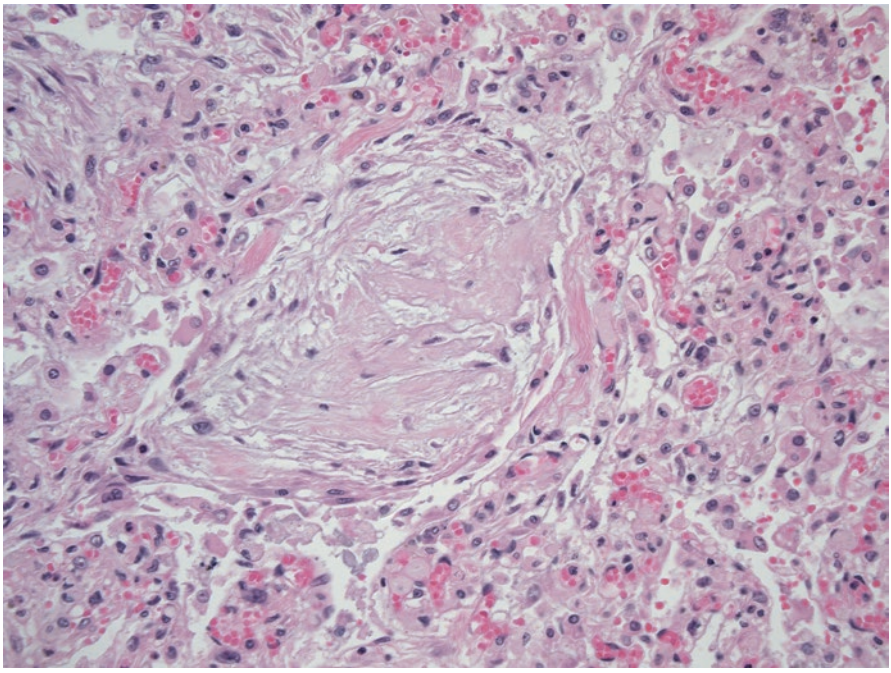

Fig. 18.3 This is a high-powered image of an obliterated small airway within a background of acute pneumonia of our patient at autopsy

Diagnosis

Cryptogenic organizing pneumonia (COP) with restrictive PFTs consistent with pulmonary graft-versus-host disease in the lung biopsy with acute organizing pneumonia superimposed at autopsy

Key Pathology Features

- The distribution of and degree of changes in obstructed bronchioles are correlated with the pulmonary function studies (PFTs).
- COP is characterized by patchy nodular consolidation which may be adjacent to uninvolved lung parenchyma. The consolidation foci consist of granulation tissue plugs that fill the lumens of the distal airways in a patchy distribution, extending into the alveolar ducts and alveolar sacs, and are associated with chronic interstitial inflammation.
- Lymphocytic bronchiolitis (LLB) describes chronic inflammation surrounding and infiltrating small bronchi and bronchioles.
- Constructive bronchiolitis obliterans (CBO) is characterized by dense fibrosis within the lumen of small bronchioles.

Differential Discussion

Our patient had a complex set of pulmonary findings including PFTs which showed a restrictive pattern and biopsy that showed COP, with CT studies which showed opacities, pleural effusions, and other findings concerning for an evolving infection. At autopsy, additional pulmonary findings were acute organizing pneumonia with zygomycete infection. We felt this case was a good example of complex borderline histopathology; when taken into consideration with the clinical context and additional PFTs, the diagnosis of pulmonary GVHD could be made. Pulmonary complications following HSCT can generally be categorized as infectious, noninfectious, or some combination of both etiologies. Bronchiolitis obliterans syndrome (BOS) encompasses the noninfectious clinical manifestations of pulmonary cGVHD which develop within several months to 2 years post-HSCT. In the NIH 2015 revised histopathologic diagnosis of GVHD, pathologic features of both LLB and CBO satisfy the criteria for diagnosis of BOS [1]. The 2015 NIH clinical criteria define BOS as an obstructive pulmonary disorder defined by PFTs of an FEV1/VC of <70% [2]. Based on the NIH clinical criteria, BOS is noted in 14% of patients with cGVHD. The mortality rates for BOS range from 25 to 50% (Table 18.1).

The histopathologic findings in CBO are classified as major diagnostic feature of cGVHD. The findings resemble those after rejection of a lung allograft. Other entities resembling CBO are systemic Castleman's disease, post-infectious scarring, chronic severe esophageal reflux, and toxic fume exposure. The characteristic findings in CBO

Table 18.1 Terms, acronyms, and definitions of the spectrum of histologic legions associated with pulmonary manifestations of acute and chronic GVHD

Terminology	Definition
Bronchiolitis obliterans syndrome (BOS)	The clinical manifestation from transplantation (lung or HSCT) where there is CBO or LLB.
Constrictive bronchiolitis obliterans (CBO)	A fibroproliferative process where there is progressive narrowing and eventual fibrous obliteration with loss of small airways. CBO is the late stage of BOS.
Lymphocytic bronchiolitis (LLB)	An early process in BOS where small airways are inflamed by a lymphocyte predominant infiltrate. It is a chronic inflammatory process that surround and infiltrate small bronchi and bronchioles. LLB can also be caused by a viral infection.
Pulmonary veno-occlusive disease (PVOD)	A rare manifestation of GVHD where intimal fibrosis narrows and occludes pulmonary veins of various sizes. Diagnosis requires combined clinical and radiographic evidence.
Restrictive lung disease (RLD)	A group of diseases characterized by increasing fibrosis on imaging studies and pleural pulmonary fibrosis. These are not currently considered diagnostic or distinctive of pulmonary cGVHD, although they encompass entities such as cryptogenic organizing pneumonia (COP) that may be associated with pulmonary GVHD.
Cryptogenic organizing pneumonia (COP)	Formerly known as bronchiolitis obliterans with organizing pneumonia (BOOP), this is an inflammatory process of the alveolar ducts, interstitium, and small bronchioles characterized by fibroblastic proliferation in the lumen of small airways. This process has been associated bacterial pneumonia, but often the inciting event is unknown.

are chronic inflammation with eventual fibrous obliteration of small bronchioles (Figs. 18.3 and 18.4). Special connective tissue stains, VVG, and trichrome allow distinction from pulmonary arteries and highlight the smooth muscle layer which surrounds bronchioles. Later secondary changes include distal mucostasis, aggregates of macrophages, and the late development of bronchiectasis. Early changes of BOS include LLB, whose major histologic features include small airways with subepithelial fibroproliferation and varying degrees of lymphocytic inflammation (Fig. 18.5). LLB has a multifactorial etiology including viral infections and hypersensitivity pneumonitis.

Workup of pulmonary dysfunction in the early post-transplant period must include microbiology studies, PFTs, X-rays, and CTs, which are necessary for identifying the presence of lobar, multilobar, or diffuse pulmonary infiltrates. A lung biopsy is only necessary when there are pulmonary symptoms suspicious for BOS and no other evidence of cGVHD can be diagnosed at other sites. A new diagnostic technique for BOS is currently under investigation, termed parametric response mapping. This technique involves a high-resolution (helical) CT of inspiration with a CT of expiration encouraged. This technique permits visual representation of the lung affected by BOS versus lung tissue with normal aeration or restrictive disease and may be a valuable noninvasive diagnostic tool in the future [3].

Williams describes the management of BOS and the variations in PFT profiles [4]. The pathologic spectrum of lesions encompassed within BOS is shown in the images from our index case and discussion images (Figs. 18.4, 18.5, and 18.6).

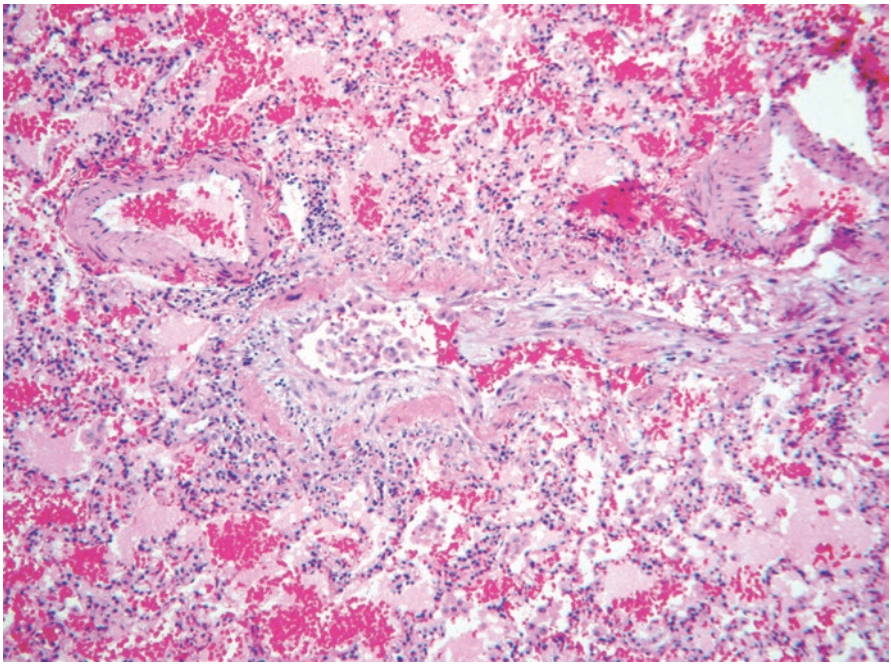

Fig. 18.4 This image demonstrates an evolving stage of BOS with incomplete obliteration of the airway. There is edema and lymphocytic infiltration beneath the ulcerated bronchiole epithelium. Image courtesy of Dr. Robert Hackman

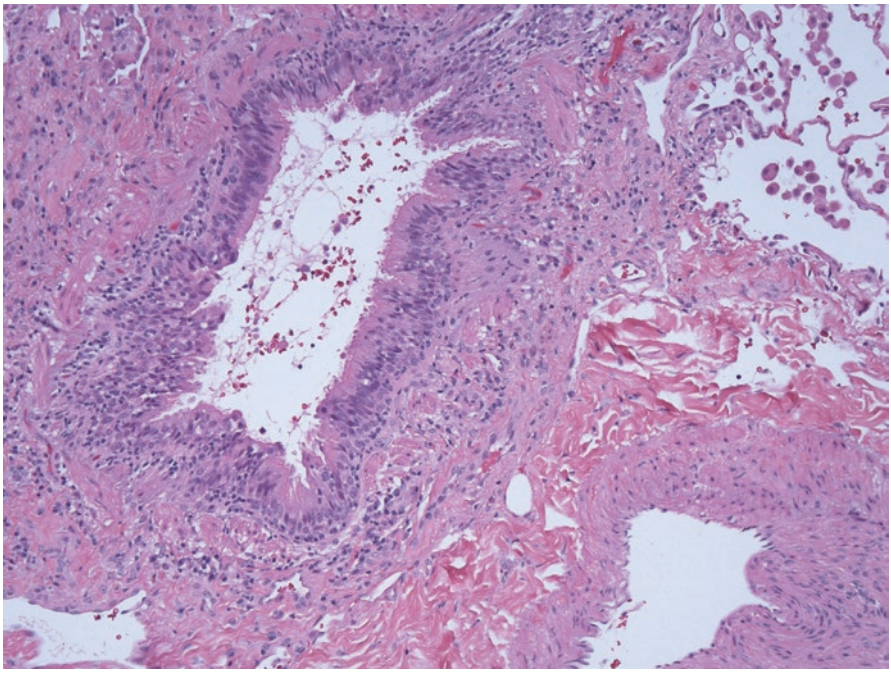

Fig. 18.5 This is an image of lymphocytic bronchiolitis featuring an airway with lymphocytic infiltration surrounding and infiltrating the bronchiole wall

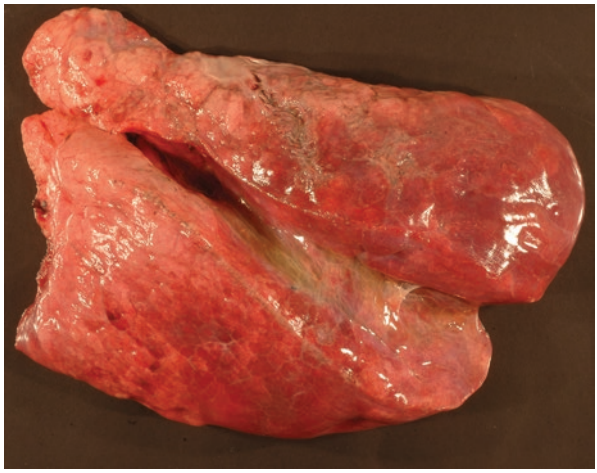

Fig. 18.6 This is a gross photo of a lung from an 18-year-old patient post-HLA-matched allo-HSCT with surface adhesions, widespread fibrosis, and inflammation who died of acute bronchopneumonia

They reflect the immune-mediated injury to small airways leading to fibrotic occlusion and obliteration. Both Chien et al. and Hildebrant et al. have found that genetic variation in the innate immune pathway influences the risk of developing CBO [5, 6]. Three studies have found that clinical syndrome of BOS included both LLB and CBO, which follow a final common pathway in the development ofsmall airway obstruction [7–10]. Gazourian has proposed that the unifying features may be PFT airflow disturbances [11]. The distinction between these entities has clinical relevance; patients with LLB had improved survival and response to treatment in comparison to patients with CBO [7].

The relationship of prior large airway inflammation, lymphocytic bronchitis (LB), to CBO has been studied. Greenland et al. evaluated endoscopic bronchial biopsies in lung allografts. Their findings suggested that LB in larger airways can predict the subsequent development of CBO (BOS) [12]. A 1978 study by Beschorner et al. done in the early era of HSCT found that LB was associated with the onset of aGVHD which in turn led to the development of bronchopneumonia caused by damage to the bronchial mucociliary apparatus [13]. O'Brien et al. conducted a large canine study of LB in allografted, autografted, and non-transplanted control dogs. They did not find any association between LB, aGVHD, or acute pneumonia and concluded that LB represents a nonspecific inflammation rather than a manifestation of pulmonary GVHD [14]. In summary, there is no clear evidence that LB is a step in the final common pathway leading to CBO.

Tracheobronchomalacia describes a rare clinical disease characterized by weakness of the trachea and bronchi due to softened supporting cartilage and hypotonic myoelastic fibers of the trachea and bronchus. It has been described after allo-HSCT as a potential mimic of BOS with similar abnormal PFTs to suggest obstructive airway disease [15].

Progressive restrictive lung disease (RLD) is manifested by increasing fibrosis on imaging studies and pleural pulmonary fibrosis. Though not currently considered diagnostic or distinctive of lung cGVHD, they are a topic of active investigation. The PFTs show a decrease in forced vital capacity (FVC) in conjunction with a lesser decline in FEV_1, reduction in total lung capacity, and decrease in diffusion

capacity for carbon monoxide. The most common RLD is COP. Clinical features of the disease include dyspnea, dry cough, shortness of breath, and rales. Imaging studies show diffuse peripheral fluffy infiltrates consistent with airspace consolidation. Histologically, COP displays patchy nodular consolidation with inflammation of bronchioles and surrounding lung tissue. A characteristic feature is plugs of fibroblasts filling alveolar ducts with an onion skin-like appearance, so-called Mason bodies (Figs. 18.1 and 18.7). COP has a strong statistical association with acute and chronic GVHD [16]. Key diagnostic features of COP include patchy fibrosis, granulation tissue within alveolar spaces, alveolar ducts, respiratory bronchioles, and absence of infectious organisms. However, in recent years due to better treatments and alternative testing strategies, the use of lung biopsies in the post-transplant setting is declining [17]. Differentiation between obstructive and restrictive lung diseases is important as CBO and COP differ in response to therapy. COP is quite responsive to corticosteroids and can resolve spontaneously, whereas CBO will not. Another differentiating characteristic is that RLD often has an earlier onset within the first 3 months, whereas obstructive lung disease will have later onset in 3–12 months.

Pulmonary veno-occlusive disease (PVOD) is a rare manifestation of GVHD featuring intimal fibrosis that narrows and occludes pulmonary veins of various sizes. Clinical diagnosis of PVOD requires radiographic evidence of pulmonary

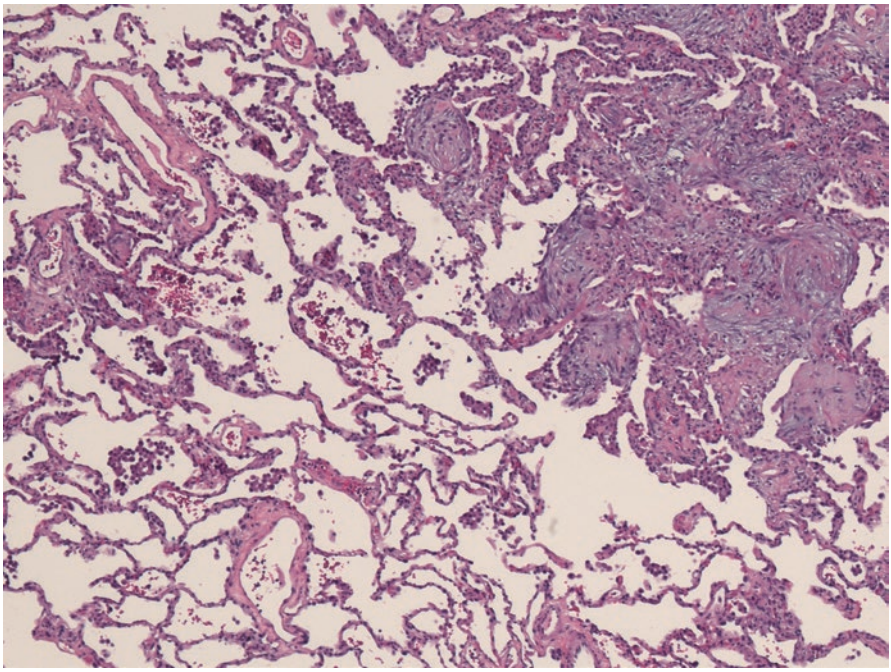

Fig. 18.7 This is an image of COP at low power. Note the patchy distribution with relatively normal alveoli adjacent to a segment of inflamed bronchioles with thickened walls

edema and a normal pulmonary artery wedge pressure. A study by Gazourian et al. found a spectrum of pulmonary pathologies in the lungs from 35 patients who survived at least 1 year after HSCT (80% had cGVHD). BOS was seen in 10 patients (including some who were asymptomatic), but PVOD was seen in 12 patients indicating PVOD may be more under-recognized in post-HSCT patients than previously anticipated [9].

Infections are a particular concern for immunocompromised patients in the HSCT setting who are often neutropenic and/or on IS treatment for GVHD, making these patients especially susceptible to a wide variety of infections. Bronchoscopy with bronchoalveolar lavage (BAL) fluid analysis can identify many infectious processes when complemented by a full panel of diagnostic testing such as bacterial and fungal cytologic stains, PCR, shell vial cultures, etc. The galactomannan test on serum or BAL fluid detects a heteropolysaccharide antigen that suggests or strongly points to invasive aspergillus [18] and may also detect other fungi. The panel of microbiology studies should include opportunistic organisms as well as unusual pathogens as immunocompromised patients are at increased risk for a wide variety of infectious agents [19–23]. Histopathology examination of the BAL cellular and background composition also provides critical information for other differentials commonly considered in post-HSCT patients including diffuse alveolar hemorrhage, pulmonary alveolar proteinosis, hypersensitivity pneumonitis, aspiration pneumonia, and involvement by relapse/persistent disease. Pulmonary alveolar proteinosis has a characteristic "milky" appearance in the BAL fluid due to high concentrations of surfactant, proteins, and lipids [24]. Microscopic examination of cytospin preparations will reveal many proteinaceous acellular fragments of densely PAS-positive material which is diastase resistant [25] (Fig. 18.8). Hypersensitivity pneumonitis is characterized by increased numbers of small lymphocytes in the BAL cellular composition, although mast cells, plasma cells, eosinophils, neutrophils, and rarely granulomas may also be seen [26].

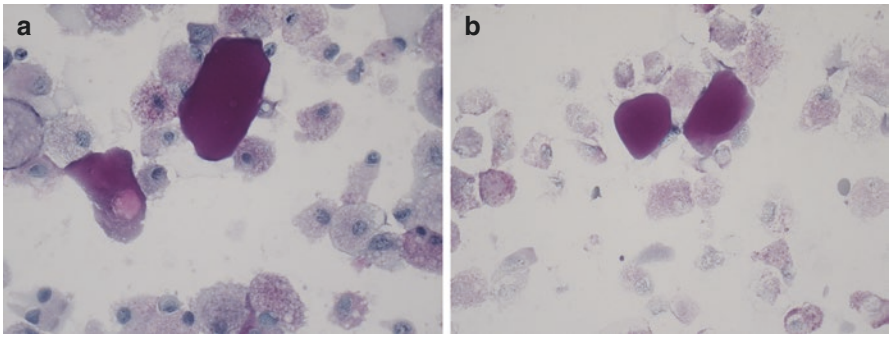

Fig. 18.8 Cytospin preparations are from a bronchoalveolar lavage from a patient with pulmonary alveolar proteinosis. Slide A contains two PAS-positive dense acellular lipoproteinaceous concretions. In slide B, similar dense concretions stained with PAS-diastase, have retained their positive staining

Teaching Points

- Bronchiolitis obliterans syndromes encompass LLB and CBO.
- LLB is considered a precursor lesion to CBO though the same changes may occur after viral bronchiolitis.
- CBO, the end stage of BOS, is characterized by dense fibrosis within the lumina of small bronchioles. These changes are best identified with VVG and trichrome stains which identify the outer smooth muscle layer surrounding the obstructed bronchiole.
- Lung biopsy is only indicated when there are abnormal obstructive pulmonary PFTs without other evidence of cGVHD in other sites.
- The diagnosis of BOS is based on PFT and imaging studies in a patient with other stigmata of cGVHD.
- Bronchoscopy with BAL is used to rule out infection.
- Differences in the PFTs, histology, and response to therapy distinguish obstructive from restrictive lung disorders. Restrictive lung disease presents earlier, often within the first 3 months, whereas obstructive lung disease presents later, between 3 months to two years post-transplant. COP is responsive to corticosteroids and can resolve sponteneously, whereas CBO is variable in its responsiveness to treatment [4].

Questions

1. Which entities produce symptoms and PFTs resembling BOS?
   A. Viral bronchiolitis
   B. Post-infectious scaring
   C. Tracheobronchomalacia
   D. Inhalation injury from toxic fumes
   E. All of the above
2. What is the main goal of treatment for lung injury in BOS?
   A. Kill infectious agent
   B. Reverse damages to obliterated airways
   C. Preserve lung function, decrease immune attack
   D. Prevent pulmonary hemorrhage
3. What tests should be performed on lung biopsy tissues?
   A. Cultures for bacteria on fresh tissue
   B. PCR for viruses including metapneumovirus in special media
   C. Special stains for bacteria including legionella with a modified Gimenez stain
   D. Special stains for VVF and trichrome stains to highlight the small bronchioles and any intraluminal fibrosis
   E. All of the above

Answers

1. Answer: E
2. Answer: C, since the changes caused by disease are often irreversible, the goal of treatment is to preserve whatever lung function that patient has left by decreasing the immune response and providing oxygen support.
3. Answer: E

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