Pulmonary Manifestations of Connective Tissue Diseases

7

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7.1 Introduction

Pulmonary manifestations cause a huge burden for patients with connective tissue diseases (CTD). It has been associated with higher rates of mortality and morbidity.

There are six CTDs which have significant pulmonary manifestations:

- Systemic sclerosis (SSc) or scleroderma.
- Rheumatoid arthritis (RA).
- Systemic lupus erythematosus (SLE).
- Sjogren syndrome (SS).
- Mixed connective tissue disease (MCTD).
- Polymyositis/dermatomyositis (PM/DM).

7.2 Chapter Objectives

- To develop a practical approach to chronic and acute dyspnea and cough for the previously mentioned CTDs' patients.
- To know when and how to screen for the pulmonary diseases related to the CTDs.

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- To develop knowledge about most of the pulmonary manifestations of CTDs and how to diagnose them and treat them sufficiently.

7.3 About the Chapter

In the chapter, for every CTD, the pulmonary manifestations will be discussed according to the anatomical structure of the respiratory system as follows:

- Airways:
 - Upper airway.
 - Lower airway.
- Parenchyma:
 - Alveolar space.
 - Interstitium.
- Vasculature:
 - Pulmonary artery.
- Pleura:
 - Pleural space.
 - Pleura.
- Respiratory muscles:
 - Diaphragm.
 - Chest wall muscles.

7.4 To Get the Most of the Chapter

- In general, interstitial lung diseases (ILD) and pulmonary arterial hypertension (PAH) are the most common pulmonary manifestations of CTDs.

- The most common subtypes of ILD are non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP). Furthermore, for all CTDs except SSc, NSIP, which presents with ground glass opacities (GGO) on high resolution computed tomography (HRCT), has better prognosis than UIP, which presents as reticular opacities with or without honeycombing on HRCT. That's because GGO represents an ongoing inflammatory process, while reticular opacities and honeycombing represent fibrosis.

Due to the rarity of some CTDs or some of the pulmonary manifestations, there are few or lack of large randomized control trials (RCTs) to relay on in decision making, which makes the management not standardized.

7.5 Important Information about Pulmonary Manifestations of CTDs before Going through the Chapter

Most of the pulmonary manifestations could occur before, co-exist, or after the CTD itself being clinically manifested.

- The prevalence of each entity of pulmonary manifestations related to each CTD is presented in Table 7.1.

- Screening for pulmonary complications in CTD patients is not well established. However, the following model seems to be acceptable to be applied to all CTDs, while physicians should tailor it according to their patients and the clinical context (Fig. 7.1).
- CTD-related interstitial lung disease (CTD-ILD) subtypes are similar to those in idiopathic interstitial pneumonia (IIP). Each subtype has been named according to its histological and/or radiological pattern (Table 7.2).
- Classification of pulmonary hypertension (Fig. 7.2; Table 7.3).
- The decision of when to start treatment in CTD-ILD is considered a dilemma because some patients present with respiratory symptoms and others are asymptomatic but have physiological (i.e., pulmonary function test [PFT]) or radiological (i.e. HRCT) abnormalities related to ILD. Thus, a useful stepwise approach developed by the authors of the Scleroderma lung study could be used depending on the severity of the disease on HRCT. See text below (SSc-ILD treatment) and combine it with (Fig. 7.3). We think it's appropriate to apply it to the rest of the CTD-ILD.
- The approach to screening for CTD-related pulmonary hypertension (CTD-PAH) is illustrated in Fig. 7.4 [1].
- The approach to acute dyspnea in CTDs is presented in Fig. 7.5.
- The approach to chronic dyspnea in CTDs is presented in Fig. 7.6.

Table 7.1 Connective tissue diseases and pulmonary manifestations

CTDs and common pulmonary manifestations					
	ILD	Airways	Pleura	Vascular	DAH
Systemic sclerosis	+++	–	–	+++	–
Systemic sclerosis	++	++	++	+	–
Primary Sjogren’s syndrome	++	++	+	+	–
Mixed CTD	++	+	+	++	–
Polymyositis/dermatomyositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

Adopted from Aryeh Fischer, Prof [Roland du Bois](#). Interstitial lung disease in connective tissue disorders The Lancet, Volume 380, Issue 9842, Pages 689–698, 18 August 2012. The signs show prevalence of each manifestation (–, no prevalence; +, low prevalence; ++, medium prevalence; +++, high prevalence)
ILD interstitial lung disease, *DAH* diffuse alveolar hemorrhage, *CTD* connective tissue disease

Fig. 7.1 Screening of pulmonary complications of CTDs. *BNP* B-type natriuretic peptide, *CTD* Connective tissue disease, *ECG* Electrocardiogram, *Echo* Echocardiogram, *HRCT* High-resolution computed tomography, *Hx* History, *P/E* Physical examination, *PFT* Pulmonary function test

- Pleural fluid analysis for CTDs (except for PM/DM and MCTD, due to the lack of sufficient information about them) (Table 7.4).
- Although drug-induced lung injury is an uncommon complication (mostly reported in observational studies), treating physicians should consider it as one of the differential diagnoses of lung injuries. Furthermore, it's important to know the common and serious adverse events of the medications used in CTD-ILD, so it would be easier to monitor them and follow them up with patients. Once drug-induced lung injury is suspected, one

should take into consideration the duration between starting the drug and the development of pulmonary manifestation in addition to the dose of the drug. Eventually, there is no single test that could help in confirming this diagnosis. However, withdrawal of the offending drug appears to be best step to diagnose it besides other findings, which are presented in Table 7.5. Moreover, a useful website established by French pulmonologists from Dijon University has been launched to provide information about drugs causing lung toxicity (www.pneumotox.com). Of

Table 7.2 Radiological and histological patterns of idiopathic interstitial pneumonias

Radiological pattern	Histological pattern
IPF	UIP
NSIP	NSIP
OP	OP
LIP	LIP
RB-ILD	RB
AIP	DAD

Adopted from American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Resp Crit Care Med 2002; 165:277
IPF Idiopathic pulmonary fibrosis, *UIP* Usual interstitial pneumonia, *NSIP* Non-specific interstitial pneumonia, *OP* Organizing pneumonia, *LIP* Lymphocytic interstitial pneumonia, *RB-ILD* Respiratory Bronchiolitis interstitial lung disease, *RB* Respiratory Bronchiolitis, *AIP* Acute interstitial pneumonia, *DAD* Diffuse alveolar damage

note, doing bronchoalveolar lavage (BAL) is a must to rule out infections (bacterial, viral, fungal, mycobacterial).

7.6 Pulmonary Manifestations According to each CTD

7.6.1 Systemic Sclerosis or Scleroderma (SSc)

Systemic sclerosis (SSc) is a rare multisystem disease that involves skin and other body organs causing fibrosis and vascular complications. It is divided into local cutaneous systemic sclerosis (lcSSc), which is more commonly associated

Fig. 7.2 World health organization (WHO) classification of pulmonary hypertension. (Adopted from Simonneau G, Galie N, Rubin L, et al. Clinical classification of pulmo-

nary hypertension. J Am Coll Cardiol. 2004;43 Suppl 1:S5–12)

Table 7.3 World health organization functional classification of pulmonary hypertension

	WHO functional classification
I	Patients with pulmonary hypertension but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope
IV	Patients with pulmonary hypertension resulting in inability to carry on any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by physical activity

Adopted from: Rich, S. Primary hypertension: executive summary. Evian, France. World Health Organization, 1998

death in SSc patients [2]. Moreover, the most common pulmonary manifestations in SSc are ILD and PAH. While less common pulmonary involvements are pleural effusion, aspiration pneumonitis, spontaneous pneumothorax, bronchiectasis, drug-associated pneumonitis, and lung cancer.

7.6.1.1 Parenchymal Lung Diseases

SSc-associated interstitial lung disease (SSc-ILD), it occurs in about 40–52% of all SSc patients. However, the dcSSc type appears to be associated with higher risk to develop it compared with lcSSc. Risk factors are African American, gastroesophageal reflux disease (GERD), higher skin score, high level of C-reactive protein (CRP), hypothyroidism, cardiac involvement, Th/To ribonucleoprotein antibodies (anti-Th/To), and anti-topoisomerase I (Scl-70). On the other hand, anti-centromere antibody is considered protective against ILD in SSc. Of note, SSc-ILD is classified into limited versus extensive depending on HRCT finding and FVC (Fig. 7.3).

Fig. 7.3 A simple system to determine the extension of interstitial lung disease. *FVC* Forced vital capacity, *PFT* Pulmonary function test. (Adopted from Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008; 177: 1248–1254)

with the CREST syndrome, and diffuses systemic sclerosis (dcSSc) depending on skin involvement and distribution. Furthermore, lung involvement occurs in about 70% of SSc cases. Also, it is considered to be the leading cause of

Presentation

Usually patients present with dry cough, shortness of breath, decreased exercise intolerance, fine bibasilar crackles, and, infrequently, finger clubbing.

Diagnosis

The diagnosis is made collectively by symptoms, signs, PFT (which mostly shows restrictive pattern with low diffusion lung capacity of carbon monoxide [DLCO]) and imaging (chest radiograph may appear normal at the beginning but then progresses to irregular linear opacities and marked interstitial marking). However, in HRCT, it may show GGO without honeycombing in NSIP or reticular pattern with basilar honeycombing in UIP with/without traction bronchiectasis. Furthermore, the most common subtypes of SSc-ILD are NSIP followed by UIP. Although usually the subtypes of ILD may affect the outcome of CTD-ILD, in SSc it is not the case. For that, it is enough to diagnose it as SSc-ILD without specifying the subtype. While BAL is helpful

Fig. 7.4 The approach to screening for CTD-related pulmonary hypertension (CTD-PAH). *BNP* B-type natriuretic peptide, *CCBs* Calcium channel blockers, *DLCO* Diffusing capacity carbon monoxide, *ECG* Electrocardiogram, *ETRA* Endothelin receptor antagonist, *FVC* Forced expiratory vital capacity, *LcSSc* Limited cutaneous systemic sclerosis, *mPAP* mean pulmonary artery, *PDE-5 inhibitor* phosphodiesterase type 5 inhibi-

tor, *PE* pulmonary embolism, *PF* pulmonary fibrosis, *RV* right ventricular, *RVH* right ventricular hypertrophy, *TAPSE* Tricuspid annular plane systolic excursion, *TR* Tricuspid regurgitation, *V/Q* Ventilation/perfusion, *WHO* World health organization, *WU* Wood Units. (Adopted from Sweiss NJ, Hushaw L, Thenappan T, et al. Diagnosis and management of pulmonary hypertension in systemic sclerosis. *Curr Rheumatol Rep*)

in ruling out infection in the appropriate clinical context, lung biopsy is not usually required, unless such diagnosis is doubtful. Worth men-

tioning, the most serious complications of SSc-ILD are respiratory failure and pulmonary hypertension.

Fig. 7.5 Approach for acute dyspnea in systemic lupus erythematosus. Adopted from “Pulmonary manifestations of Systemic Lupus Erythematosus” (Chapter), Abdul Ghafoor Gari, Amr Telmesani, Raad Alwithenani, Systemic Lupus Erythematosus (Book), published by opentech. *ALP* Acute lupus pneumonitis, *BAL* bronchoalveolar lavage, *CXR* chest x-ray, *CT* computed tomography, *CTPA* computed tomography pulmonary angiogram, *DAH* diffuse alveolar hemorrhage, *GGO*’s ground-glass opacities, *V/Q Scan* ventilation/perfusion lung scan

Prognosis

ILD in SSc has poor outcome despite treatment. It's associated with higher mortality. The median survival for patients is 5–8 years.

Treatment

Many issues are involved in treating SSc-ILD, which are the decision of initiation of treatment, treatment modalities, the follow-up of treatment, duration of treatment, and assessment of success of treatment and promising drugs.

It is difficult to decide whether to initiate treatment or not since treatment has a minor effect on the outcome of SSc-ILD. Physicians should balance between the benefit of treatment and the

adverse drug reactions. Factors that favor starting treatment are the presence of respiratory symptoms, abnormal or declining lung functions (specially DLCO and forced vital capacity [FVC]), progressive disease, early intervention (within 12–24 months of the diagnosis of SSc-ILD), young age, GGO on HRCT, and no contraindications (such as active or suspected infection, neutropenia, history of cyclophosphamide hemorrhagic cystitis, pregnancy, and lactation) [3, 4].

When physician and patient agree to start treatment, there are three modalities available, which are drug therapy, lung transplantation, and hematopoietic stem cell transplantation. To start

Fig. 7.6 The approach to chronic dyspnea in CTDs. *CXR* Chest X-ray, *CTD* Connective tissue disease, *C-P* Costophrenic angle, *Dx* Diagnostic, *Rx* Therapeutic, *Bx* Biopsy, *GGO* Ground glass opacity, *HRCT* High resolution computed tomography, *PFT* Pulmonary function test, *ILD* Interstitial lung disease, *NSIP* Non-specific interstitial pneumonia, *OP* Organizing pneumonia, *UIP* Usual interstitial pneumonia, *OB* Obliterative bronchiolitis, *DLco* Diffusion Lung capacity for carbon monoxide, *DLVA* Diffusion per unit area of alveolar volume, *MIP* Maximum inspiratory pressure, *MEP* Maximum expiratory pressure,

VC Vital capacity, *FVC* Forced vital capacity, *EMG* Electromyogram, *SLS* Shrinking lung syndrome, *PASP* Pulmonary artery systolic pressure, *TR* Tricuspid regurge, *RHC* Right heart catheterization, *PAP* Pulmonary artery pressure, *PCWP* Pulmonary capillary wedge pressure, *R/o* Role out, *PH* Pulmonary hypertension, *PCP* Pneumocystis pneumonia, *CMV* Cytomegalovirus, *HSV* Herpes simplex virus, *TB* Tuberculosis, *LDH* Lactate dehydrogenase, *RF* Rheumatoid factor, *RBC* Red blood cell, Anti-nuclear antibody

Table 7.4 Pleural fluid analysis for rheumatic diseases

	RA	SLE	Sjogren
Appearance	Variable	Clear	N/A
WBC	<5000 cells/mm ³	<5000	High lymphocytes
Glucose	Low (<1.6 mmol/L)	Normal/low	Normal
Protein	High (>30 g/L)	Low	High
Cholesterol	>5.18 mmol/L	N/A	N/A
RBC	0	0	N/A
pH	Low (< 7.3)	N/A	Normal
Cytology	Positive tadpole cells	N/A	N/A
Complement	Low	Low	Low
RF	>240 IU/mL (titer >1:320)	None	N/A
ANA	+/-	Positive (titer >1:160 is more sensitive than specific)	N/A
LDH	High (> 700 IU/L)	High	N/A
Anti-Ro/anti-La antibodies	N/A	N/A	Positive
Immune complex	High	High	N/A

ANA Anti-nuclear anti-body, LDH Lactate dehydrogenase, RBC red blood cell, RF rheumatoid factor, N/A not applicable

with, there is no drug, up to date, considered as the gold standard treatment for SSc-ILD because of lacking of strong evidence to relay on. However, commonly used regimen is cyclophosphamide (CYC) (oral or intravenous) combined with low dose glucocorticoids (equal to or less than 10 mg/day equivalent to prednisone) for 12 months duration [5–10]. Then, physicians could stop the CYC and the steroids and start a maintenance therapy with azathioprine (AZA) for 18 months [11]. Although oral cyclophosphamide is superior to IV route, some clinicians prefer the IV route due to possible less side effects as a result of lower cumulative dose. An alternative regimen to CYC and steroids is AZA plus low-dose prednisone [12, 13]. This regimen is inferior to CYC and steroids but could be used if patient could not tolerate CYC. Steroids are used mostly as an adjuvant therapy to cyclophosphamide with low doses (equal to or less than 10 mg/day equivalent to prednisone). That's because moderate to high doses (>15 mg/day equivalent to prednisone) could expose patients to the risk of developing scleroderma renal crisis (SRC), which presents with acute kidney injury (AKI), hypertension (including hypertensive crisis), and mild proteinuria. Of note, there are some other prom-

ising drugs such as mycophenolate mofetil [14–20], rituximab [21, 22], and imatinib [23, 24], but more trials are needed to compare their efficacy to cyclophosphamide.

Monitoring usually consists of monthly follow-up to make sure there are no drug adverse events and, then, a visit every 6 months to check for respiratory symptoms, PFT, and HRCT. Clinicians should monitor patients for CYC drug toxicity by monitoring white blood cell (WBC) count, renal function, and urine analysis (specially for red blood cells [RBCs]) in urine to predict hemorrhagic cystitis and/or proteinuria [25].

Afterward, the treatment is considered successful if stabilization (no improvement nor deterioration) of respiratory symptoms and PFT is achieved. However, mild to moderate improvement could occur.

Cyclophosphamide is associated with high toxicity profile, which is a concern for both patients and physicians. The new preferred regimen is mycophenolate mofetil (MMF) (oral or intravenous) along with glucocorticoids. Both regimens showed significant reduction in loss of pulmonary function, but mycophenolate mofetil has safer profile with less side effects, better toleration, and the improvement last longer with (MMF) than (CYC).

Table 7.5 Drug-induced lung injury in CTD

	Type of lung disease occur	Duration of drug use until symptoms occur	Dose of the drug and other risk factors	Hx and P/E	Blood work	PFT	Imaging	BAL and Biopsy	Treatment	Notice
Gold	Interstitial pneumonia (NSIP, OP or eosinophilia pneumonia.)	1 week–84 months (typically >6 months)	– 30–3000 mg total accumulative dose (specially >500 mg) – Female	Hx: Acute or chronic cough, dyspnea and fever within P/E: Crackles but no clubbing	Non-specific): Leukocytes and eosinophilia. (rarely: Leucopenia, thrombocytopenia and hypogammaglobulinemia)	– Restrictive pattern with low DLCO	CXR: Upper zone opacity (unlike in CTD_ILD which occur in the lower zone) HRCT: Non-specific: GGO or diffuse or patchy opacities	– BAL: High lymphocyte no, CD4+/CD8+ <1, also, use it to r/o infection – Biopsy: NSIP, OP or eosinophilia pneumonia	Stop the drug and start systemic corticosteroid	BO, pulmonary-renal syndrome and DAH
D-Penicillamine	OB	3–14 months	375–1250 mg/day	Subacute dyspnea on exertion and cough	N/A	Obstructive pattern with no response to bronchodilator	CXR: Normal or hyperinflation. HRCT: Mosaic attenuation	Biopsy: Typical for OB	Stop the offending drug and start prednisolone 1–1.5 mg/kg/day Using other immunosuppressive therapy (e.g., CYC or AZA) may help	N/A

NSAIDs	Eosinophilia pneumonia	N/A	N/A	Hx: Fever, cough, dyspnea. P/E: Wheeze and crackles	Eosinophilia	N/A	Non-specific: Diffuse or patchy consolidations	Poorly defined granuloma + eosinophils infiltration	Stop the drug and in severe cases add systemic corticosteroid	N/A
MTX	ILD, acute lung injury (ALI) with DAD, pleurisy, pleural effusion, nodulosis, bronchitis, airway hyper-sensitivity and cough	12 weeks-18 years	<ul style="list-style-type: none"> – Minimum of <20 mg/week. – Age > 60 - rheumatoid pleuro-pulmonary involvement – Previous use of DMARD – Hypoalbuminemia – DM 	Dyspnea, dry cough, fever +/- chest pain	Eosinophilia	<ul style="list-style-type: none"> – Restrictive – Low DLCO – High A-a gradient 	Non-specific: Interstitial infiltrate	Cellular interstitial infiltrates, eosinophils, granuloma, DAD	Stop the drug and in severe cases add corticosteroid or other immunosuppressive therapy like CYC or AZA. Folinic acid may be used (not fully studied)	Reusing the medication after the treatment of its adverse event is not recommended
Leftunomide	Fatal exacerbation of previously diseased lung, diffuse nodulosis, pulmonary alveolar proteinosis and DAD	12 weeks	Previous lung disease or MTX pneumonitis	<ul style="list-style-type: none"> – Hx: Dyspnea, cough, fever P/E: Crackles. 	High C-reactive protein and KL-6	N/A	HRCT: GGO, reticular opacities and honey-combing or airspace disease	Bx: Pneumonitis with eosinophils, OP or DAD	Systemic steroids + Cholestyramine (8 g/day for 3 days)	Avoid using it when patients already have ILD. If new patients with no known ILD, screen by PFT and HRCT before starting the drug

(continued)

Table 7.5 (continued)

	Type of lung disease occur	Duration of drug use until symptoms occur	Dose of the drug and other risk factors	Hx and P/E	Blood work	PFT	Imaging	BAL and Biopsy	Treatment	Notice
TNF- α (etanercept, infliximab and adalimumab)	Exacerbation of ILD, UIP and OP	8 weeks	N/A	Dyspnea, cough and fever	N/A	N/A	Reticular opacities or airspace disease	Bx: Reticular opacities or airspace disease	Stop the drug and any DMARD added with it + systemic steroid (e.g., 40 mg/day)	N/A
CYC	NISP or fibrosis.	<ul style="list-style-type: none"> – Early onset: 1–6 months. – Late onset: >6 months 	<ul style="list-style-type: none"> – 150 mg–81 g – Risk factors: If used with other drugs cause lung toxicity, e.g., bleomycin, busulfan and amiodarone 	Dyspnea, cough +/- fever	N/A	<ul style="list-style-type: none"> – Restrictive pattern with low DLCO 	<ul style="list-style-type: none"> – Early onset: GGO on HRCT. – Late onset: Reticular opacities with honey-combing (in the mid to upper zone, unlike in CTD-ILD) 	Bx: Non-specific. But granuloma and hemosiderin could be present	<ul style="list-style-type: none"> – Early onset: Atop medication + systemic corticosteroids (prednisone 60 mg/day) – Late onset: Stop medication only. Steroid showed no effectiveness 	N/A
AZA	OP and UIP	1 week–1 month	Total dose of 2300–28,600 mg	Dyspnea, cough and fever	N/A	N/A	N/A	To r/o infections	Stop medication and start systemic steroid	It's very rare for AZA to cause lung toxicity especially in CTD population

Although the MMF duration in the last study was for 2 years, most of expertise recommend to continue the treatment for several years [26].

The second modality of treatment is lung transplantation. It is considered when drug therapy fails. The 1-year survival is 68–93% [27, 28]. Absence of GERD may play a great role in improving survival [27].

Last treatment modality is hematopoietic stem cell transplantation. It is still an experimental therapy. However, great improvement in FVC within 2 years occurred when using this method. Furthermore, it shows superiority to IV cyclophosphamide [29].

Aspiration Pneumonitis

A strong association between the degree of gastroesophageal reflux (GER) and the severity of ILD, which may raise the flag of micro-aspirations. However, it is still not clear whether the treatment of GER will improve or even prevent ILD [30, 31].

7.6.1.2 Vascular Diseases

SSc-associated pulmonary arterial hypertension (SSc-PAH).

Introduction

Pulmonary hypertension (PH) defined as mean pulmonary artery pressure (PAP) equals to or > 25 mmHg at rest. It can occur as a complication of SSc itself, which is SSc-PAH, or as a complication of ILD caused by SSc. Here, SSc-PAH is discussed.

It presents in 12–38% of SSc patients. Risk factors are increased number of telangiectases, lcSSc with anti-centromere antibody, dcSSc with ANA (dcSSc alone is less commonly associated with PAH), progressive decline in DLCO, and exercise-induced PAH on right heart catheterization.

Presentation

Patients usually present with exertional dyspnea, lethargy, and fatigue, which are the most common symptoms, and, less frequently, could be exertional angina, exertional syncope, symptoms of right ventricular failure (RVF) (due to Cor pulmo-

nale), cough, hemoptysis, and Ortner's syndrome (horsiness due left recurrent laryngeal nerve palsy caused by pulmonary artery compression or other cardiac cause). On physical examination, if there is no right ventricular hypertrophy (RVH), loud pulmonary component of second heart sound is heard. However, If right ventricular hypertrophy present, then, parasternal heave, forth heart sound, prominent A wave in jugular venous pressure (JVP) could be noticed. Moreover, ascites and lower limb edema may be present. Recent studies showed that combination therapy with phosphodiesterase type 5 inhibitors or combination between (ERA/PDE5I) is superior than endothelin receptor antagonist alone by decreasing deterioration time, recent European guidelines recommend combination initial therapy, But it still has not established yet in American guidelines [32].

Screening

In regard to screening for SSc-PAH, physicians could use the same screening method as any patient newly diagnosed with SSc (Fig. 7.1). Also, other indications for earlier echocardiography screening are when symptoms, signs, and PFT findings are suggestive of PAH are present, such as DLCO <70% predicted or FVC/DLCO >1.6 and echocardiography with Doppler study findings are suggestive of PAH such as RVH, right ventricular enlargement (the chamber itself), right atrial enlargement, tricuspid regurge (TR), mid-systolic notch on the pulmonary artery Doppler flow tracing and shifting of the interventricular septum toward the left ventricle, pulmonary artery systolic pressure (PASP) >50 and the maximum tricuspid regurgitant jet velocity (TVR) >3.4.

Diagnosis

The SSc-PAH diagnosis is confirmed by right heart catheterization when mean pulmonary arterial pressure equals to or > 25 mmHg at rest and mean pulmonary capillary wedge pressure (PCWP) <15 mmHg after excluding other causes of PH such as having normal ventilation/perfusion scan (V/Q scan) (to rule out chronic thromboembolic disease), negative HIV and hepatitis serology, normal or mild ILD findings on

HRCT (to rule out significant ILD), and normal sleep study in the appropriate clinical context.

Prognosis

Although the advancement of treatment during the past decade has improved the survival, it's still worse than that in idiopathic PAH (IPAH) [33]. The 3-year survival is estimated to be 64% [33]. Moreover, early detection has a good impact in survival [34]. On the other hand, SSc-PAH associated with ILD has worse prognosis than that of SSc-PAH alone. The 3-year survival for SSc-PAH with ILD is 47% [35].

Treatment

In general, therapy is usually directed to the underlying cause of PAH and to the PAH itself if it persisted. However, since there is no specific treatment for SSc, the therapy will be directed to PAH itself. Nevertheless, many issues are involved in the treatment of SSc-PAH such as the decision of initiation of treatment, treatment modalities, duration of treatment, and follow-up of therapy.

The decision of initiation of treatment is all symptomatic patients defined by the World Health Organization (WHO) functional classes of II or more (i.e., at minimum to have dyspnea when doing ordinary activity). This category should receive treatment.

Treatment modalities are PAH specific drug therapy, supportive therapy, and lung transplantation. To start with, for the PAH specific drug therapy, there is no single drug that has shown superiority for treatment in SSc or other CTDs in general.

However, the drug classes that have shown effect in CTD-PAH are endothelin-1 receptor antagonists (ERA), phosphodiesterase type 5 (PDE5) inhibitors, and prostanoids (PGI-2). All of them improved the 6-min walk test (6MWT) [36]. Clinicians should, most of the time, start with monotherapy then step up for a combination if no improvement is observed. Furthermore, the choice for PAH-specific drug therapy depends on physician expertise, patient preference, and cost-effectiveness.

Also, supportive therapy should be considered for most patients. It consists of supple-

mental oxygen for patients with hypoxemia, to keep oxygen saturation > 90%. In addition, diuretics could be given for patients with fluid overload. Moreover, anticoagulation might be considered for all patients based on non-randomized trials, especially those who receive IV prostaglandins (due to the risk of catheter related thrombosis) but also one should weigh risk of bleeding against benefits [37]. Furthermore, warfarin is the drug of choice to reach a therapeutic INR of 1.5–2.5 [37]. On top of that, exercise, with a special training program (bicycle ergometer at lower and higher workload for 15–30 min/day, dumbbell training [0.5–1 kg], and respiratory training) could be advised. However, heart rate should be monitored not to reach above 120 beat/min and the oxygen saturation not to fall <90% (if a supplemental oxygen is given). These exercises has been tested and showed improvement in 6-min walk test (6MWT) [38, 39]. Lastly, digoxin is not usually used in PAH because there are no enough data to support its effectiveness [37]. Nevertheless, it is usually used in patients with COPD and biventricular failure [40].

As a last resort, when drug therapy fails, lung transplantation should be considered, specially, in patients with severe symptoms. The 2-year survival reaches 71% [27].

7.6.1.3 Airway Disease

Bronchiectasis

It is a common finding on HRCT, but usually not clinically manifested, reaching 59% of SSc patients, and this may be attributed to the high number of GERD and aspirations [41]. Clinicians should pay attention to bronchiectasis when intended to start immunosuppressive therapy due to the risk of severe lower respiratory tract infections [42].

Pleural Involvement

Pleural Effusion

Occurs in about 7% of SSc patients. Usually asymptomatic and occasionally associated with pericardial effusion. It resolves spontaneously.

Spontaneous Pneumothorax

It's a rare complication of SSc. Patients present with shortness of breath and/or pleuritic chest pain. The management depends on cardiopulmonary status and pneumothorax size on CXR. Supplemental oxygen and air drainage by needle aspiration or chest tube insertion should be considered depending on the clinical context.

Respiratory Muscle Weakness

This could lead to respiratory failure with or without hypercapnia [43, 44].

7.6.1.4 Systemic Lupus Erythematosus (SLE)

Background

SLE is a multisystem autoimmune disease and affects mostly women in childbearing age. Pulmonary involvement, manifested clinically or radiologically, occurs in around 25% of all SLE patients. They usually happen later in the course of the disease. Furthermore, most common pulmonary diseases are pleuritis (78%) followed by bacterial infections (58%), alveolar hemorrhage (26%), distal airway alterations (21%), opportunistic infections (14%), and, lastly, acute or chronic pulmonary thromboembolism (8%).

Pulmonary Manifestations

Pleural Diseases

Pleuritis

- Presents as pleuritic chest pain, shortness of breath, and fever. On physical examination, pleuritic friction rub may be heard. It is a clinical diagnosis. However, pleural biopsy could be done but rarely needed. If so, it shows peculiar immunofluorescent pattern characterized by staining of nuclei with anti-IgG, anti-IgM, and anti-C3 [45]. Treatment usually consists of NSAIDs for mild cases and steroid for severe cases.

Pleural Effusion

Presentation

It tends to be bilateral and small to moderate in size; however, large effusion may occur. It usu-

ally presents with shortness of breath, cough, and/or chest pain. Nevertheless, sometimes, it could be asymptomatic. Physical examination may show dullness on percussion, decrease tactile fremitus, decrease intensity of breath sound, and decrease vocal resonance.

Diagnosis

Although the following investigations could lead to the diagnosis of pleural effusion to be secondary to SLE, physicians should always rule out other common/serious causes of pleural effusion such as heart failure, parapneumonic effusion, and pulmonary embolism if suspected.

Chest radiograph shows blunting of costophrenic angle. Furthermore, pleural fluid analysis is shown in Table 7.4.

Treatment

Small asymptomatic pleural effusion needs no treatment. It resolves spontaneously. On the other hand, mild symptomatic effusion usually responds to NSAIDs [46], while severe symptomatic effusion is treated with steroids. Also, if patient is currently on steroids, increasing the dose may be required [46]. In refractory cases, tetracycline or talc pleurodesis might be an alternative option [47–49].

7.6.1.5 Parenchymal Lung Disease

Acute Lupus Pneumonitis (ALP)

Introduction

It's an uncommon but serious complication of SLE, which occurs in 2–8% of patients. It affects younger and newly diagnosed SLE patients and also could manifest as a fulminant pattern in pregnant women.

Presentation

Acute-onset fever, cough, shortness of breath, pleuritic chest pain, and, occasionally, hemoptysis. Physical examination shows signs of hypoxia and bibasilar crackles.

Diagnosis

It's a diagnosis of exclusion (Fig. 7.5). However, BAL, with or without transbron-

chial biopsy, must be done to rule out infection. Blood tests may show high levels of anti-Ro (anti-SS-A), which are associated with more likelihood of ALP. Chest radiograph may show bilateral alveolar infiltrates with predominance in lower lung fields. Also, pleural effusion may occur in half of the cases. Rarely, chest radiograph could be normal or showing nodules. Chest CT may show diffuse ground glass opacities. BAL, when done, the sample should be sent for cell count and differential, bacterial, fungal, and viral cultures, cytology, pneumocystis pneumonia (PCP) stain, and acid-fast bacilli (AFB) smear, and culture in the appropriate clinical context. Transbronchial biopsy, when done, shows non-specific diffuse alveolar damage (DAD) with or without alveolar hemorrhage and capillaritis. Less common pathologic features are alveolar edema, hyaline membrane formation, and immunoglobulin and complement deposition.

Treatment

Usually starts with empiric broad-spectrum antibiotics for 3 days. If no response, then, pulse steroids (1 g methylprednisolone daily for 3 days) should be started. Furthermore, adding another immunosuppressive agents like cyclophosphamide (CYC) could be considered [50]. In refractory cases, intravenous immunoglobulin (IVIG), plasma exchange, or rituximab may help [51–53].

Prognosis

It has poor prognosis with mortality reaching 50% [54]. BAL showing eosinophilia and neutrophilia have worse prognosis than lymphocytosis.

7.6.1.6 Diffuse Alveolar Hemorrhage (DAH)

Introduction

The prevalence ranges from <2% to 5.4% and it tends to recur. Furthermore, it occurs more frequently in lupus nephritis patients and with high levels of serum anti-DNA antibody.

Presentation

Usually presents with acute shortness of breath, cough, fever, and hemoptysis, although absence of hemoptysis does not rule out DAH. The mean duration from onset of DAH to resolution of radiographic finding is 7.8 days. Physical examination reveals signs of respiratory distress and hypoxia.

Diagnosis

Blood tests may show acute drop in hemoglobin and low complement level. Chest radiograph may show bilateral alveolar infiltrates. But also could happen unilaterally in 18% of patients. Chest CT scan could show new bilateral ground glass opacities and consolidation. Moreover, magnetic resonance imaging (MRI) can suggest presence of blood. PFT show elevated DLCO (>130% predicted) due to excess hemoglobin in alveolar space. BAL is essential to rule out infection. Furthermore, bloody sample under microscope suggests DAH if hemosiderin-laden macrophages are present. Transbronchial biopsy could be done in stable patients. This may reveal bland hemorrhage (72%) or capillaritis (14%). Both of them are associated with intra-alveolar hemorrhage and hemosiderin-laden macrophages. Also, immunoglobulin G (IgG), complement 3 (C3), or immune complex deposition occurs in 50% of the cases. Thoracoscopic lung biopsy is rarely needed.

Treatment

Supportive therapy (i.e., mechanical ventilation) plays a major role since most patients are admitted to the intensive care unit (ICU) [55, 56]. However, if infection is ruled out or BAL suggest hemorrhage, physician should start pulse intravenous steroids (methylprednisolone 1 g/day for 3 days) followed by 60 mg/day of oral prednisone plus intravenous CYC every 4 weeks (the CYC could be started after discharge from hospital) [55, 56]. In refractory cases, plasmapheresis is an effective alternative, which improves survival. Also, rituximab has shown promising results [56–58].

Prognosis

DAH has a very poor outcome with mortality ranges between 50% and 90% [55, 58].

7.6.1.7 Chronic ILD

Introduction

Occurs in around 9% of SLE patients [59, 60]. Moreover, the most common ILD patterns are NSIP, UIP, and lymphocytic interstitial pneumonia (LIP).

Presentation

The initial presentation could be a dry cough. Other symptoms are shortness of breath and decreased exercise intolerance. Physical examination could reveal fine bibasilar crackles; however finger clubbing is rare.

Diagnosis

It is made by symptoms, signs, PFT, and HRCT collectively. Lung biopsy is not usually required unless such diagnosis is doubted. Chest radiograph may be normal at the beginning but then progresses to irregular linear opacities and marked interstitial markings. HRCT may show GGO without honeycombing in NSIP. On the other hand, reticular pattern with basilar honeycombing occurs in UIP with/without traction bronchiectasis. Moreover, 30% of asymptomatic patients could have abnormal HRCT findings. PFT may show restrictive pattern with low DLCO. Also, it does not correlate with the severity of ILD in HRCT. BAL is helpful in ruling out infection. While biopsy needed to confirm the subtype of ILD when HRCT is controversial.

Treatment

In mild cases, systemic corticosteroid (prednisone 60 mg/day for at least 4 weeks) could be used [56]. However, for moderate to severe cases, a combination therapy of oral glucocorticoids and AZA is a choice [60]. Furthermore, in severe cases, a combination of oral glucocorticoids and CYC could be considered [60].

Prognosis

ILD associated with SLE has better prognosis compared to the idiopathic forms [61].

7.6.1.8 Pulmonary Vascular Diseases

Thromboembolic Disease

Introduction

Venous thromboembolic (VTE) events are well-known manifestations of SLE specially when antiphospholipid (aPL) antibodies are present. This, in turn, will establish the diagnosis of antiphospholipid syndrome. Patients diagnosed with antiphospholipid syndrome are at risk of recurrent DVT, PE, chronic thromboembolic pulmonary hypertension (CTEPH), abortions, DAH, and acute respiratory distress syndrome (ARDS). Furthermore, when small vessel occlusion occurs in three or more organs, the condition is known as catastrophic antiphospholipid syndrome (CAPS). SLE patients are at risk of VTE events with a prevalence of 9%. This percent would become as high as 42% if SLE patients had aPL. Moreover, aPL present in up to two thirds of SLE patients [62].

Presentation

Patients could present with deep vein thrombosis (DVT) or pulmonary embolism (PE). DVT presents with calf pain (usually unilateral), swelling, and redness. On the other hand, pulmonary embolism (PE) presents with shortness of breath, pleuritic chest pain, cough, and/or hemoptysis. Furthermore, CTEPH manifested as progressive shortness of breath and exercise intolerance.

Diagnosis

DVT is diagnosed by Doppler ultrasound (US). PE is confirmed by chest CT angiogram. Moreover, CTEPH needs all diagnostic procedures needed to diagnose PAH.

Treatment

Long-term anticoagulation with warfarin is highly recommended with targeting INR of 2.0–3.0. High-intensity warfarin (targeting INR 3.0–

4.0) showed no superiority to moderate intensity [63]. Some clinicians use long-term low-dose aspirin as a primary prevention [64].

CAPS is usually treated by systemic glucocorticoids, immunosuppressants, plasmapheresis, and/or IVIg in addition to anticoagulation [56].

Prognosis

For CAPS, the mortality reaches 50% [65].

7.6.1.9 SLE-Associated Pulmonary Arterial Hypertension (SLE-PAH)

Background

For definition of PAH, please see SSc-PAH.

The duration of SLE, since diagnosis, does not correlate with the risk of development SLE-PAH. Its prevalence varies between 0.5% and 15% in SLE patients. Risk factors are Raynaud's phenomenon, which occurs in 75% of SLE-PAH [54]; antiphospholipid antibodies (aPL), which present in 83% of SLE-PAH; and anti-U1 ribonuclear protein (RNP), which presents in >25% of SLE-PAH.

Presentation

Please see SSc-PAH.

Screening

Due to the rarity of PAH in SLE, annual echocardiogram screening should be directed to women in childbearing age, pregnant ladies, patients with Reynaud's phenomenon, anticardiolipin antibody, and anti-U1 RNP antibody [66].

Treatment

All patients should receive supportive therapy as needed (See SSc-PAH). On the other hand, mild PAH patients should receive immunosuppressive therapy alone, while moderate to severe PAH patients should receive PAH-specific therapy with or without immunosuppressive therapy [56].

PAH-specific therapies are effective in SLE-associated PAH specially epoprostenol, bosentan, sildenafil, ambrisentan, and tadalafil. They improved the 6MWT and functional class [67–70]. Adding immunosuppressive therapy (e.g.,

IV CYC with or without oral glucocorticoids) showed improvement in 6MWT and lowered PAP [71–74].

Acute Reversible Hypoxia

It's a rare complication of lupus, and patients usually present with acute and unexplained hypoxia and hypercapnia. Blood investigation may show high C3 levels. Chest radiograph could be normal. V/Q scan should show no evidence of PE. Lastly, arterial blood gases (ABG) shows increase alveolar-arterial (A-a) PO₂ gradient. Furthermore, it responds quickly to high-dose systemic corticosteroids [75, 76].

7.6.1.10 Airway Disease

Upper Airway Involvement

Introduction

It occurs in around 30% of SLE patients. Also, it involves laryngeal mucosal inflammation or ulceration, cricoarytenoiditis, vocal cord paralysis, necrotizing vasculitis, and angioedema.

Presentation

Patients usually present with hoarseness and/or dyspnea. Moreover, they could develop angioedema symptoms such as lip and mouth swelling, dysphagia, odynophagia, and breathing difficulty.

Diagnosis

Chest radiograph and CT scan are usually normal. PFT may show flattening of the inspiratory or expiratory loop or both depending on the location of the obstruction. Furthermore, 3-D reconstructive images are needed to locate the site of obstruction. Fibro-optic laryngoscopy or bronchoscopy is needed for direct visualization of the vocal cord.

Treatment

Corticosteroids are of benefit in laryngeal mucosal inflammation or ulceration and vocal cord paralysis [77, 78]. However, in refractory cases, infectious causes should be considered (e.g., *Haemophilus influenzae* and *Streptococcus*.

Other rare pathogens are *Histoplasma*, *Coccidioides*, *Cryptococcus*, *Blastomycosis*, and *Candida*.

Lower Airway Involvement

Bronchiectasis

HRCT findings suggestive of bronchiectasis occur in around 21% of SLE patients. However, patients usually are asymptomatic [79].

Bronchiolitis Obliterans (BO)/Obliterative Bronchiolitis (OB)

It's a rare complication of SLE, which is characterized by severe airflow obstruction which is mostly irreversible. Patients usually present with progressive shortness of breath. Moreover, chest HRCT Shows mosaic attenuation pattern that gets accentuated in the expiratory images. PFT shows obstructive pattern. Biopsy is rarely required. Furthermore, anticholinergics were reported to have favorable outcome when compared to systemic steroids and immunosuppressive therapy [80, 81].

7.6.1.11 Muscle Involvement

Shrinking Lung Syndrome (SLS)

Introduction

It's an uncommon disorder, with a prevalence of 0.6–0.9% of SLE patients [80–82], characterized by unexplained dyspnea, decreased lung volumes, elevated diaphragm, and restrictive PFT pattern in the absence of parenchymal lung disease.

Presentation

Patients usually present with shortness of breath aggravated by being in supine position. Pleuritic chest pain is also reported. Physical examination reveals diminished breath sounds at the lung bases with or without crackles.

Diagnosis

Chest radiograph and HRCT show elevation of both diaphragms and basal atelectasis without evidence of parenchymal lung disease. PFT shows restrictive pattern with preservation of

DLCO when corrected for alveolar volume (DL/VA). Also, respiratory muscle assessment could show reduced maximal inspiratory pressure (MIP) and stable maximal expiratory pressure (MEP).

Treatment

Oral glucocorticoids with or without other immunosuppressive therapy showed to be effective [83, 84]. Other options are AZA, methotrexate (MTX), CYC, and rituximab [82–87].

Prognosis

SLS has good prognosis when treated. Moreover, respiratory failure rarely occurs [64, 88].

7.6.1.12 Associated Lung Disorders

Adult Respiratory Distress Syndrome (ARDS)

It occurs in 4–15% of SLE patients. The most common cause of ARDS in SLE is sepsis. Other causes are ALP, DAH, and CAPS. Furthermore, it occurs more frequently in younger age group and is more progressive than in non-SLE patients. ARDS-related mortality contributes to 30% off all lupus deaths. Furthermore, mortality could reach up to 70%. The treatment is mainly supportive care.

Infectious Complications

Most of the SLE infectious complications happen in patients who are on immunosuppressive therapy. It accounts for 30–50% of all SLE deaths. Furthermore, bacterial infections are the most common (75%) followed by mycobacterial (12%) then fungal infections (7%) and lastly viruses (5%). It could mimic ALP or DAH, so, careful diagnostic approach is recommended. The diagnosis is usually conducted by chest radiograph and HRCT and also BAL to differentiate infectious from non-infectious causes (Fig. 7.5).

Pneumocystis Pneumonia (PCP)

Prophylaxis

Since the incidence of PCP in SLE patients is very low (0.6%), it is not clear if all SLE patients

on immunosuppressants should receive prophylaxis. But, at least patients at highest-risk of PCP infection (e.g., who receive biologic agents or immunosuppressants in addition to high dose daily steroid) should do so. The prophylactic drug of choice is trimethoprim-sulfamethoxazole (TMP-SMX) [89].

Lung Cancer

SLE patients are at increased risk of developing lung cancer. Furthermore, histologically, adenocarcinoma is the most common type (similar to the general population). However, there is a tendency for uncommon thoracic malignancies like carcinoids and bronchoalveolar carcinoma.

Drug Reactions

Please refer to Table 7.5.

7.7 Rheumatoid Arthritis (RA)

7.7.1 Introduction

RA is an autoimmune disorder characterized by joint involvement in a chronic and symmetrical fashion. Pulmonary involvement considered one of the most frequent extraarticular manifestations together with the cutaneous involvement. Furthermore, around 10–20% of RA deaths are attributed to pulmonary causes. The most common pulmonary involvements are ILD, airway disease, rheumatoid nodule, and pleural effusion.

1. Pulmonary manifestations.
2. Parenchymal involvement.
3. Interstitial lung disease (ILD).

7.7.1.1 Introduction

It's the most common pulmonary manifestation of RA with a prevalence of 20–63% radiographically by HRCT. And up to 9.4% of the patients have clinically significant symptoms. Usually happens in a well-established RA disease. However, in around 20%, it could precede it. The most common patterns are UIP

followed by NSIP then desquamative interstitial pneumonia (DIP) and organizing pneumonia (OP). Also, risk factors for that are older age group, male gender, history of cigarette smoking, high titer of rheumatoid factor (RF), and anti-cyclic citrullinated peptides (anti-CCP) [90].

7.7.1.2 Presentation

Symptoms start to appear when lung function is greatly impaired. Moreover, pleuritic chest pain occasionally accompanied ILD symptoms. Please see SSc-ILD for more information.

7.7.1.3 Diagnosis

Chest radiograph might be normal in affected patients especially in early disease [91]. However, chest HRCT is the most important tool to diagnose early RA-ILD. UIP manifests as reticulation and honeycombing, while NSIP presents with GGO with/without bronchiectasis. The correlation between the radiographic and the histopathologic pattern is poor in NSIP [86]. Also, OP appears as diffuses patchy alveolar opacity and GGO. It's common to see different patterns simultaneously [90]. PFT may show restrictive pattern with declining of DLCO to be the earliest PFT sign [92, 93]. BAL might be utilized to rule out opportunistic infections, DAH, and/or drug reactions [86, 94, 95]. Biopsy is not recommended as a regular investigation unless the radiologic pattern is unclear and another treatment could make a difference [90].

7.7.1.4 Treatment

Patients with mildly progressive disease should receive high dose prednisone [96]. However, there are anecdotal reports of using daily oral CYC and corticosteroids in rapidly progressive extensive disease [97]. There is also another regimen of monthly IV CYC combined with corticosteroids. In refractory cases, physician could use rituximab, infliximab, or tocilizumab. The routine use of these agents has not been established yet due to the lack of strong evidence and the questionable safety, which is under investigation [98]. Of note, PCP prophylaxis should be given.

7.7.1.5 Prognosis

In general, RA-ILD has mild and slowly progressive nature. However, spontaneous resolution could happen [99].

When DLCO is <54%, it is suggestive of worse prognosis [99]. On the other hand, NSIP has better prognosis than UIP [100, 101].

7.7.2 Pleural Diseases

7.7.2.1 Pleural Effusion

Introduction

It's the second most common pulmonary involvement in RA (after ILD) with a prevalence ranges between 5% and 22%. It usually occurs unilaterally and small to moderate in size; however, large effusions may occur. Moreover, it is associated with RA flares. Risk factors are smoking, previous pleurisy, rupture of subpleural nodule, and high effusion protein levels (prevents resorption).

Presentation

Mostly asymptomatic, but if not, dyspnea, fever, and chest pain (if pleurisy) are the main manifestations [102].

Diagnosis

Chest radiograph shows blunting of costophrenic angles. Chest CT scan is more sensitive than chest radiograph. Furthermore, thoracentesis, if done, pleural fluid analysis could be diagnostic as following (Table 7.4). Pleural biopsy may be considered when TB or malignancy is suspected or when thoracentesis is not diagnostic. Also, the parietal pleura are the mainly involved part rather than the visceral one. When biopsy is done, it shows absence of the normal mesothelial cells covering the pleura, and they are replaced by pseudostratified layer of epithelioid cells with giant cells [103].

Treatment

If asymptomatic, mostly it will resolve spontaneously in up to 36 months. However, if symptomatic, for acute relief, a therapeutic thoracentesis

could be done. If no need for acute treatment, then start with NSAIDs. After that, if failed, moderate dose of oral glucocorticoids (10–20 mg prednisolone daily), intrapleural corticosteroids, fibrinolytics, or immunosuppressive could be given. In refractory cases, pleurodesis (mechanical or chemical) is an option.

Complications

The following complications may develop if pleural effusion is not treated. First of all, pleural fibrosis and lung entrapment, which could be treated by decortications. Moreover, bronchopleural fistula could develop, which intervention with video-assisted thoracoscopy (VATS) did not show effectiveness in RA. An open approach with thoracotomy and direct closure may be helpful. Lastly, empyema which can be treated with antibiotics (Usually it's polymicrobial infection) and drainage through chest tube. Worth mentioning, that bronchopleural fistula has been reported in the vast majority of the empyema cases in RA.

7.7.3 Pulmonary Vascular Diseases

7.7.3.1 PAH

It has lower prevalence than in other CTDs [104]. For presentation, diagnosis and treatment (see PAH in SSc).

7.7.3.2 DAH

It's a very rare complication of RA [105]. "Risk factors are treatment with infliximab, leflunomide, and rituximab [106–108]. For presentation, diagnosis, and treatment, please see DAH in SLE.

7.7.4 Airway Diseases: Upper Airway Diseases

7.7.4.1 Cricoarytenoid Arthritis

Introduction

The cricoarytenoid joint function is to abduct and adduct the vocal cord when a person speaks. Good history taking could reveal upper airway

symptoms in around two thirds of RA patients. The prevalence ranges between 26% and 55% with female predominance. Furthermore, joint abnormalities such as prominence, erosions, abnormal positioning of the vocal cord, and subluxation may occur [109].

Presentation

Patients usually presents with hoarseness of the voice (reaching 30%), dyspnea, sore throat, fullness sensation in the throat, shocking, stridor, dysphagia, and odynophagia.

Diagnosis

PFT shows fixed or variable upper airway obstruction. CT scan shows the abnormalities such as prominence, erosions, abnormal positioning of the vocal cord, and subluxation. Laryngoscopy may show vocal cord dysfunction.

Treatment

When patients presented with chronic symptoms, clinicians should start with medical treatment such as systemic or intra-articular steroid, which both have shown benefit. However, surgical options (e.g., tracheostomy, arytenoidectomy, arytenoidopexy) should be considered only if medical treatment failed [110].

On the other hand, patients may present with acute manifestations such as severe stridor and should get emergent tracheostomy [111].

Prognosis

Excellent results occur with aggressive therapy [112].

7.7.4.2 Vocal Cord Rheumatoid Nodule

Could mimic squamous cell carcinoma [111].

7.7.5 Airway Diseases: Lower Airway Diseases

7.7.5.1 Bronchiectasis

Prevalence ranges between 30% and 58% when elected by HRCT. However, only 1–5% of RA patients are symptomatic. Bronchiectasis usually

is a late manifestation of RA, but it can precede the articular involvement. Furthermore, presentation and management is like any other bronchiectasis without rheumatoid arthritis.

7.7.6 Airway Obstruction and Bronchial Hyperreactivity

It occurs in about 60% of RA patients when documented by spirometry. Recurrent airway infections and smoking could precipitate airway disease in RA. Patients usually present with wheeze and productive cough. Furthermore, PFT may shows obstructive pattern. However, HRCT is more sensitive than PFT in detecting the obstruction. It shows air trapping, attenuation in lung heterogeneity, and bronchiectasis. The treatments are mainly inhaled corticosteroids and bronchodilators.

7.7.6.1 Bronchiolitis Obliterans (BO)

Introduction

It's a clinically progressive small airway disease, which is characterized by narrowing, ulceration, and scarring of the respiratory and terminal bronchioles. The prevalence varies between 8% and 65%. Also, risk factors are female gender, long-standing RA, D-penicillamine, gold salt, and methotrexate use [113, 114].

Presentation

Progressive dyspnea and dry cough are the most common presentations, while physical examination reveals inspiratory crackles and squeaks.

Diagnosis

PFT shows progressive irreversible airflow obstruction. However, HRCT is more sensitive than PFT in detecting the disease. It may show air trapping (mosaic pattern of regions of low attenuation which get accentuated on expiratory images). BAL is done to rule out infections if suspected, while biopsy shows airway narrowing, ulceration, scarring, and lymphoplasmacytic infiltrate.

Treatment

Physicians should stop offending agent and may start oral prednisone, some studies suggested the use of IV CYC as well [115, 116] or stop offending agent and start low dose oral macrolide (erythromycin 400–600 mg/day, clarithromycin 200–400 mg/day or azithromycin) for 6 months may be used as improvement was shown in the treatment of diffuse panbronchiolitis [117, 118].

Prognosis

Usually carries poor prognosis specially when using corticosteroids only. Thus, adding CYC or trying macrolides may be beneficial.

7.7.6.2 Follicular Bronchiolitis

Introduction

The bronchioles are invaded by lymphocytic, plasmacytic, and hyperplastic lymphoid follicles, and reactive germinal cells infiltrates. It has some overlap with COP and BO [114].

Presentation

Patients usually present with dyspnea and also may present with fever and cough.

Diagnosis

Chest radiograph may show reticular or reticulonodular opacities. Furthermore, HRCT shows bilateral centrilobular and peribronchial nodules associated with areas of GGO.

Also, PFT may show obstructive, restrictive, or both patterns. DLCO is usually decreased. BAL is done to rule out infections. Biopsy shows bronchioles, which are invaded by lymphocytic, plasmacytic, hyperplastic lymphoid follicles, and reactive germinal cells infiltrates.

Treatment

May start with corticosteroid then after tapering starts oral macrolides (erythromycin, clarithromycin, or azithromycin) for up to 1 year [119].

Prognosis

Follicular bronchiolitis has relatively good prognosis when treated.

7.7.7 Rheumatoid Nodule and its Complications: (Necrobiotic Nodule)

7.7.7.1 Rheumatoid Nodule

Introduction

Up to 32% of rheumatoid nodule occurs in the lungs. Also, because the most common site in the respiratory system is subpleural or interlobular, it could present by many different ways such as pneumothorax, cavities, pleural effusion, empyema, and bronchopleural fistula. Furthermore, it could be solitary or multiple nodules. On the other hand, radiologically, it could mimic non-small cell lung cancer. So, physicians should be meticulous when approaching such patients specially when there is history of smoking. Also, histologically, it has a great overlap with granulomatous diseases. For that, biopsy should be interpreted very carefully [120]. Risk factors for rheumatoid nodule are with male gender, positive rheumatoid factor (RF), long-standing disease (but may precede the diagnosis of RA), and smoking.

Presentation

Mostly asymptomatic. However, if symptomatic, it depends on the complication, e.g., cavities present with hemoptysis, pneumothorax presents with dyspnea and chest pain, pleural effusion presents with dyspnea, empyema presents with dyspnea and fever, and bronchopleural fistula presents with productive cough, dyspnea, and fever occasionally.

Diagnosis

Chest radiograph may show nodule but always should compare with previous chest radiographs to notice any changes in size or shape. Also, HRCT will give better details and physician should look for size, shape, lymph nodes, and effusions. It could be solid or as a cavity.

Treatment

If no complications, spontaneous resolution is the usual natural history. Moreover, rituximab has shown effectiveness in its resolution.

However, if complicated, treat accordingly (e.g., if secondary pneumothorax happened, it's better to perform surgical intervention to prevent recurrence).

Rheumatoid Nodulosis

It is multiple rheumatoid nodules in different places. Risk factors are methotrexate, etanercept, and leflunomide use. Actually, it could lead to the same presentations the rheumatoid nodule does. Furthermore, the treatment is usually to stop the offending drug and start hydroxychloroquine, D-penicillamine, colchicine, or sulfasalazine.

7.7.7.2 Caplan Syndrome (Rheumatoid Pneumoconiosis)

Introduction

It occurs in RA patients who get exposed to coal, silica, asbestos, and ceramics industry and roof tiles products. Furthermore, it is characterized by rapid-onset lung nodules and could mimic TB or neoplasm. It occurs more commonly in Europe than in the United States. Also, it's more common in positive RF patients and in male.

Presentation

Most of the time patients are asymptomatic unless complicated by pneumothorax, pleural effusion, or progressive massive fibrosis, which is uncommon; they would present with dyspnea and/or chest pain. Also, rarely, patients may present with hemoptysis or *Aspergillus* colonization.

Diagnosis

Chest radiograph shows well-defined nodules starting from 0.5 cm in diameter and larger. Also, it could cavitate or calcify. Usually present in lung periphery [121]. HRCT may have a role in following up and detection of changes. Biopsy, since it could mimic TB or neoplasm, it is often done specially when there is high index of suspicion.

Treatment

There is no specific treatment, although some studies showed improvement when using corticosteroids when the lesions are compressive or rap-

idly progressive [122]. However, if complicated, treat accordingly.

Prognosis

It takes few weeks or months until nodules reach the final size. Usually, they remain at the final size for many years or may heal but leave behind an asteroid scar. Only 10% of the cavitations and the calcifications emerge.

7.7.8 Infections

7.7.8.1 Background

It's clear that lung infections are increased in RA patients since pneumonia is twice more common than in general population. However, it's very difficult to make sure if the risk of infection is due to RA itself or the immunosuppressive agents used to treat RA.

Immunosuppressive agents and risk of infection:

- **Corticosteroids:** It increases the risk of pneumonia by dose-dependent mechanism. For most of patients, a dose of more than 10 mg/day is sufficient to cause it [123–126].
- **MTX:** With or without corticosteroids, it makes patients at risk of developing opportunistic infections, e.g., PCP and disseminated histoplasmosis [124, 127]. Usually occurs in the first 2 years of initiation of MTX [124].
- **Anti-tumor necrosis factor-alpha (TNF-α):** Exposes patients to risk of many opportunistic infections, most importantly *Mycobacterium tuberculosis* (TB). Others like coccidioidomycosis, histoplasmosis, listeria, aspergillus, and nocardia have been reported [128].

7.7.8.2 Latent Tuberculosis Infection (LTBI) Screening [129]

Before initiating the treatment with any of the following biologic agents (adalimumab, certolizumab pegol, etanercept, infliximab, golimumab, abatacept, rituximab, or tocilizumab) a TB skin testing or interferon gamma release assay (IGRA) should be done to screen for latent TB infection (LTBI) regardless of the presence or absence of

TB risk factors. If negative results without presence of risk factors, then starting the treatment with the biologic agent is permissible. If negative results with the presence of TB risk factors, the physician should repeat the test in 1–3 weeks. If results are positive, CXR should be done. If negative CXR for TB signs, this is latent TB infection (LTBI), and referral to an infectious disease (ID) specialist should be undertaken. In this situation, the physician can initiate the treatment with the biologic agent after 1 month of starting the treatment of the LTBI. If positive CXR, then do sputum stain and culture for TB. If negative, it is LTBI. But if the sputum tested positive for TB, refer the patient to an ID specialist to start the treatment for active TB infection [129]. Of note, if patient is already on glucocorticoids, induration of 5 mm is considered positive [90].

For further reading, please see Infectious Disease Chap. 11.

7.7.8.3 Cancer

RA patients are at increased risk for developing lung cancer and lymphoma. The reason is not clear. But, a proposed theory could be due to RA itself, smoking, immunosuppressive therapy, or because RA is a middle age disease, which equals to the age at which cancers usually detected. Once mediastinal lymph node is detected, biopsy has to be undertaken as soon as possible.

7.7.8.4 Myopathy and Muscle Weakness

Introduction

Usually happens due to medication toxicity, rheumatoid vasculitis, and rheumatoid myositis. Physicians should suspect it when patients have progressive dyspnea with unclear cause and no improvement with treatment. Risk factors are the use of D-penicillamine and hydroxychloroquine.

Diagnosis

Blood tests show creatine-kinase (CK) within the normal limits. PFT show restrictive pattern. Also, FVC and VC in supine position is reduced by more than 10% than in upright. Furthermore, maximal inspiratory pressure (MIP) and maximal

expiratory pressure (MEP) are reduced. DLCO is normal unless another pathology present. Biopsy may be needed to confirm the diagnosis.

7.7.8.5 Fibrobullous Disease

It's a rare complication of rheumatoid arthritis and usually occurs in the apical part of the lung. It could be a complication of a rheumatoid nodule even in the absence of a radiological evidence.

7.7.8.6 Amyloidosis

Secondary amyloidosis, which involves lungs, has been reported. It could present as nodules, ILD, or tracheobronchomalacia.

7.8 Sjogren Syndrome (SS)

7.8.1 Background

It's an autoimmune disease characterized by involvement of exocrine glands through infiltration of lymphocytes. A clinically significant pulmonary manifestation occurs in around 9–24% of SS patients. Also, pulmonary involvements in asymptomatic SS patients who were detected by PFT, CT scan, or BAL reach 75% of patients. Also, pulmonary manifestations usually occur late in the disease course. Furthermore, if they were clinically significant, it could increase the risk of mortality by fourfold [130]. Risk factors for pulmonary involvement are positive rheumatoid factor, hypergammaglobulinemia, positive anti-Ro and anti-La, and decreased FVC and FVC1, smoking, elderly patients, and male sex. Overall, rituximab is a promising drug to treat SS and its extra-glandular manifestations (because it targets B lymphocytes), unlike anti-TNF drugs.

- Pulmonary manifestations.
- *Airway involvement.*
- Upper airway.
- Nasal crusting.

Around 18.5% of SS patients complain of nasal crusting. It is found in 50% during physical exam. The treatment usually consists of the use of room humidifiers and saline nasal spray as needed.

7.8.2 Epistaxis

It occurs in around 31.8% of patients with SS. The treatment is the same as for any patient with epistaxis.

7.8.3 Hoarseness of the Voice

This occurs in about 1/3 of SS patients. The diagnosis is done by laryngoscopy, which shows most commonly dryness or thick mucus covering the vocal cords. However, rarely, the presence of Bamboo node, which is a transverse yellow or white submucosal lesion, occurs in the vocal folds. Also, granulomatous and non-granulomatous nodules have been reported.

7.8.4 Xerotrachea and Xerobronchitis

Usually developed due to structural or functional disability of the mucociliary cells to clear the thickened secretions. It occurs in around 17% of SS patients. Those usually present almost always with dry cough. Chest radiograph, HRCT, and PFT are normal. On the other hand, recurrent bronchitis, bronchopneumonia, atelectasis, and peribronchial and peribronchiolar scarring and narrowing might occur as complications.

7.8.5 Lower Airway Disease

7.8.5.1 Follicular Bronchiolitis (FB)

Introduction

It's a benign lymphoproliferative disorder, characterized by hyperplastic lymphoid follicles distributed along the bronchioles and the peribronchiolar interstitium unlike the LIP, which involves the whole parenchyma. It is a histopathological diagnosis; however, it could be suspected by history, CT scan, and PFT results. It's a common manifestation of SS. Usually, patients present with cough, dyspnea, and sometimes fever.

Investigation

CT scan shows bilateral peribronchial and centrilobular nodules with size range between 1 and 3 mm but could reach up to 12 mm. Other findings are reticular opacities, GGO, and intrathoracic lymphadenopathy. Furthermore, PFT usually shows restrictive pattern but also could be obstructive pattern or both. Biopsy shows hyperplastic lymphoid follicles distributed along the bronchioles and the peribronchiolar interstitium.

Treatment

Primary treatment of SS could be enough. However, systemic corticosteroid is shown to be effective [131].

Prognosis

Has good prognosis when treated with corticosteroid.

7.8.6 Chronic Obstructive Pulmonary Disease (COPD)

It is found to be more prevalent in SS patients through their disease course, especially smokers, who have 5 times higher chance compared to non-smokers to develop COPD [132].

7.8.7 Lung Parenchyma

7.8.7.1 ILD

Introduction

It's the most common pulmonary manifestations of SS. Furthermore, the most common subtype are NSIP followed by lymphocytic interstitial pneumonia (LIP) then UIP and lastly OP. It is more common when patients have anti-Ro antibodies.

Subtypes

NSIP

It occurs in about 28–61%. Presentation is usually chronic dyspnea. Chest radiograph may show bilateral interstitial infiltrates. PFT shows restrictive pattern with decreased DLCO. HRCT

shows GGO (with subpleural and basilar predominance). Furthermore, reticular abnormalities with or without traction bronchiectasis could be found. Honeycombing happened with advanced disease. BAL is done to rule out infection when suspected. Biopsy shows uniform or homogenous pattern of cellular inflammation and/or fibrosis of the alveolar walls. Moreover, no need for treatment if patients are asymptomatic. However, if symptomatic with worsening symptoms, physician could give steroids (prednisone 1 mg/kg/day) [133]. Also, if refractory, immunosuppressive therapy (commonly AZA. Rarely CYC or cyclosporines) could be used [134–137]. The prognosis depends on the extent of fibrosis. The less fibrosis, the better prognosis [132].

Lymphocytic interstitial pneumonia (LIP)

It's one of the most common pulmonary manifestations of SS. It has potentials to progress into lymphoma. Thus, biopsy should always be considered if there is no response to standard therapy. The prevalence is 17% among SS patients who develop ILD [133] with female predominance [138]. Patients usually present with dyspnea and cough and, also, less commonly fever, weight loss and night sweat. Blood tests show polyclonal hypergammaglobulinemia (80% of cases). Chest radiograph may show bilateral reticular or reticulonodular opacities, more commonly in the lower zones. HRCT shows diffuse GGO and walled cysts (in 50% of cases). Also, interlobular septal thickening, centrilobular nodules, and bronchovascular bundle could be seen. PFT show restrictive pattern with low DLCO. BAL is done to rule out infection if suspected. Again, since it could progress to lymphoma, biopsy should always be considered if there is no response to standard therapy. Histopathology reveals infiltration of the interstitial septa and, sometimes, filling of the alveolar space by lymphocyte (B&T cells), plasma cells, and histiocytes. Patients usually treated with corticosteroids (start with prednisone 0.75–1.0 mg/kg/day then taper slowly for the following 3–6 months) [139–141]. Furthermore, initially, it responds well to corticosteroids. However, up to

1/3 of patients die due to progression of disease or due to the infectious complications resulted from the intensive immunosuppression therapy [142]. Rarely it could resolve spontaneously.

7.8.8 Pleural Involvement

7.8.8.1 Pleural Effusion

It's a very rare manifestation of SS. Therefore, when present, one should think of a secondary cause (i.e., in the setting of secondary SS), e.g., RA or SLE. Usually occurs bilaterally, but a unilateral presentation could happen. Pleural fluid analysis should be done for diagnosis (Table 7.4).

7.8.9 Pulmonary Vascular Disease

7.8.9.1 PAH

Introduction

It's a rare complication and usually occurs due to pulmonary artery vasculitis. Also, occasionally, it co-exists with Raynaud's phenomenon. Risk factors are Raynaud's phenomenon, ILD, skin vasculitis, hypergammaglobulinemia, positive anti-Ro, positive RF, and positive antiribonucleoprotein (anti-RNP) antibodies. Moreover, for presentation and diagnosis (see PAH in SSc). The mainstay of treatment is the use of PAH specific treatment (endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, or prostanoids) with/without immunosuppressive therapy [143].

7.8.10 Cancer

7.8.10.1 Lymphoma

Introduction

The risk of SS patients to develop lymphoma in general, not only pulmonary lymphoma, is 44 times compared with healthy population [144], while pulmonary lymphoma prevalence is 1–2% among SS patients [145]. Furthermore, SS patients could develop benign lymphocytic infiltration, like in LIP, and this in turn could progress

to lymphoma [145]. This benign lymphocytic infiltration is characterized by polyclonal B and T lymphocytes proliferation. Moreover, the most common type of lymphoma in SS patients is non-Hodgkin's lymphoma with a subtype of mucosa-associated lymphoid tissue (MALT) [145], while the most common pulmonary lymphoma is the low-grade extranodal marginal B-cell lymphoma of MALT type [145]. Risk factors are hypocomplementemia, cryoglobulinemia, vasculitis (palpable purpura), and severe exocrine involvement at time of diagnosis of SS [145].

Presentation

80% are asymptomatic at time of lymphoma diagnosis due to the incidental finding in radiological studies. If symptomatic: dyspnea, cough, weight loss, fatigue and sweat.

Diagnosis

Chest CT scan manifests as nodules (solitary or multiple), bilateral diffuse infiltrate, interstitial infiltration with slight lower zone predominance, mediastinal lymphadenopathy, and pleural effusion (usually do not occur alone rather happen with the parenchymal involvement). Furthermore, biopsy shows most commonly a non-Hodgkin's low-grade extranodal marginal B-cell lymphoma of MALT type [145]. Also, it has good prognosis with 5-year survival of more than 80% [146]. Of note, progression to high-grade lymphoma occasionally happens [145].

Pseudolymphoma

It's a rare and benign entity, also called pulmonary nodular lymphoid hyperplasia or bronchus-associated lymphoid tissue (BALT). It is characterized by infiltration of polyclonal lymphocyte and plasma cells. Usually it's asymptomatic but could present with dyspnea and cough. CT scan typically shows solitary nodule. However, less frequently, multiple nodules, which involve blood vessels, consolidation, mediastinal lymph node and/or pleural effusion, could be seen. Biopsy usually reveals bronchus-associated lymphoid tissue (BALT). Furthermore, corticosteroids or immunosuppressive therapy could be given [147]. It has good prognosis when

treated [147]. However, rarely transforms into lymphoma.

Amyloidosis

Its prevalence is around 0.6%, and patients' presentation depends on the location such as larynx, trachea, bronchi, interstitium, and/or mediastinum. CT scan shows micronodular lesions (could be calcified or cavitary) predominantly in the subpleural area and in the lower lobes, while biopsy shows positive amyloid staining. The prognosis is usually good [148, 149].

7.9 Mixed Connective Tissue Disease (MCTD)

7.9.1 Introduction

It was first described in 1972 and defined as a combination of SSc, SLE, and polymyositis/dermatomyositis (PM/DM) with positive anti-ribonucleoprotein (Anti-RNP). Yet, it's not clear if it's a separate entity of disease or not. Furthermore, pulmonary manifestations occur in up to 65% of MCTD patients. Worth mentioning, that patients with MCTD could present with any pulmonary manifestations related to SLE, SSc, or PM/DM [150].

7.9.2 Pulmonary Manifestations

7.9.2.1 Lung Parenchyma

Interstitial Lung Disease (ILD)

Introduction

It occurs in around 50–65% of MCTD patients [150]. Also, esophageal dilatation is a risk factor for developing ILD [151].

Presentations

Please see ILD in SSc.

Diagnosis

In early stages, PFT shows reduction in DLCO only. Then, in late stages, it shows restrictive pat-

tern with low DLCO. HRCT shows septal thickening, GGO, and non-septal linear opacities with predominance in the periphery or within the lower lobe. Also, in fact, no study encountered pathological findings, but thought to be NSIP and UIP.

Treatment

Physician should start corticosteroid (methylprednisolone 2 mg/kg/day) for 4–6 weeks then assess, if no improvement add CYC oral or IV to complete 6 months [152].

Prognosis

Good prognosis (in terms of preventing further progression of the disease) if treated during the acute inflammatory phase (GGO). Once signs of fibrosis on HRCT present, the response will be poor.

Alveolar Hemorrhage

It's an uncommon manifestation. Also, for presentation, diagnosis, and treatment refer to SLE-associated DAH.

Pulmonary Vascular Disease

PAH

Prevalence ranges between 3.4% and 27%. Furthermore, for presentation, diagnosis, screening and treatment, see SSc-PAH.

Pleural Diseases

Pleural Effusion

It's a common manifestation of MCTD with prevalence about 50% [153]. Pleural fluid analysis is usually exudative and with lymphocytic predominance. Moreover, it usually resolves spontaneously. However, if it persists, then a trial of corticosteroid could be effective.

7.10 Polymyositis (PM)/Dermatomyositis (DM)

7.10.1 Introduction

Pulmonary manifestations play big role in the mortality and morbidity of PM/DM patients.

Moreover, the main pulmonary complications are ILD, aspiration pneumonia, and hypoventilation due to muscle weakness.

7.10.2 Pulmonary Manifestations

7.10.2.1 Parenchymal Lung Disease

Interstitial Lung Disease (ILD)

Introduction

It's the most common pulmonary complication, which reaches up to 65% when screened by CXR, HRCT, or PFT. Furthermore, it can present as an acute, chronic, or asymptomatic with radiological findings only. When it is symptomatic, more than 60% of patients present with cough and dyspnea and normal radiograph, HRCT, or PFT. Also, it is more common in DM than in PM. However, recently, a new subtype of DM has been reported, the clinically amyopathic dermatomyositis (CADM), which is DM without muscle involvement. This subset, when associated with anti-CADM-140 antibodies, associated with higher prevalence of rapidly progressive ILD. Risk factors are positive antihistidyl tRNA synthetase antibody (anti-Jo-1), Krebs Von den Lungen-6 (KL-6), serum surfactant protein D, serum cytokeratin 19 fragment (CK-19), and anti-CADM-140 antibody (which associated with rapidly progressive ILD). All of them aren't present in every center as a routine test.

Presentations

Patients usually present with dyspnea and cough.

Diagnosis

PFT shows restrictive pattern with low DLCO. While HRCT could shows NSIP, UIP, OP, or DAD pattern. BAL to rule out infection or drug-induced pneumonitis. Biopsy is rarely needed because the HRCT findings correlate well with histopathology. Although transbronchial lung biopsy is inferior to open lung biopsy, it is a good choice if opportunistic infection or neoplasms are suspected because open lung biopsy associated with high mortality rate.

Treatment

Most commonly, corticosteroids with (CYC, AZA, cyclosporines) are given [154–161]. However, IVIG alone or with corticosteroids has shown good results in progressive disease [162, 163]. Also, tacrolimus and rituximab, individually, are promising drugs [164–166]. Anti-tumor necrosis factor- α (Anti-TNF- α) and MTX are less likely to be effective. In fact, they may induce irreversible lung fibrosis [167].

Prognosis

ILD in PM/DM increases mortality. A 5-year survival ranges between 60% and 86% [168, 169]. Also, worse prognosis is expected with DM compared to PM. Furthermore, when corticosteroids combined with other immunosuppressive therapy, approximately 1/3 of the patients will improve, 1/3 will remain the same, and 1/3 will deteriorate [154]. Moreover, rapidly progressive ILD has fatal outcome with 3-year survival of around 24% [170].

7.10.2.2 Aspiration Pneumonia

It occurs in around 17% [171] of PM/DM patients and is related to the dysfunction happens to the pharynx and esophagus muscles which lead to abnormal swallowing and frequent regurgitation. Risk factors are severe muscle disease [172]. Furthermore, investigations and treatment are like any other case of aspiration pneumonia.

7.10.2.3 Pulmonary Vascular Disease

PAH

Occasionally happens. For, presentation, diagnosis, and treatment, see SSc-PAH.

7.10.3 Pneumothorax (PNX) and Pneumomediastinum and Subcutaneous Emphysema

7.10.3.1 Introduction

They occur in two different clinical scenarios. The first one is vasculopathy with or without mild ILD (vasculopathy such as skin ulcers or

bronchial wall necrosis). The second one is severe ILD with or without vasculopathy. Whenever one of these complications (PNX, pneumomediastinum, or subcutaneous emphysema) happens, one should suspect pulmonary vasculitis. Diagnosis is made by chest radiograph and chest CT scan. Moreover, physicians should start corticosteroid and immunosuppressive therapy together at the beginning then taper the steroid gradually [173].

7.10.4 Respiratory Failure and Hypoventilation

7.10.4.1 Introduction

This happens due to severe respiratory muscle weakness with prevalence around 21.8% [171].

7.10.4.2 Diagnosis

PFT shows restrictive pattern. Furthermore, FVC and VC in supine position are reduced by more than 10% than in upright. Also, maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are reduced. DLCO is normal unless another pathology is present. Chest radiograph may show decreased lung volumes, elevated diaphragms, and basal atelectasis.

7.10.4.3 Complications

Atelectasis and recurrent pneumonia may develop due to mucus plugging because of reduced cough reflex secondary to respiratory muscle weakness.

7.10.4.4 Treatment

Physicians should start immunosuppressive therapy. However, if failed, home mechanical ventilation could be used which could save life and improves the quality of life.

7.10.4.5 Lung Cancer

There may be an association between lung cancer and myositis, especially DM.

Acknowledgments The Authors would like to thank Amr A. Telmesani, MD, for his contributions to this chapter in the previous edition.

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