Acute Respiratory Events in Connective Tissue Disorders

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Key Words

Acute 'exacerbations' in fibrotic interstitial pneumonias · Diffuse alveolar hemorrhage syndromes · Acute pulmonary thromboembolism · Catastrophic antiphospholipid syndrome · Organizing pneumonia · Acute fibrinous organizing pneumonia · Acute hypercapnic respiratory failure · Myositis, ventilatory muscles · Pneumothorax · Pneumomediastinum · Aspiration pneumonitis · Pericarditis · Pleuropericarditis · Drug toxicity · Lung infections · Rheumatoid arthritis · Systemic lupus erythematosus · Systemic sclerosis · Dermatomyositis-polymyositis · Primary Sjögren's syndrome · Mixed connective tissue disease · Ankylosing spondylitis

Abstract

Subacute-acute, hyperacute, or even catastrophic and fulminant respiratory events occur in almost all classic connective tissue disorders (CTDs); they may share systemic life-threatening manifestations, may precipitously lead to respiratory failure requiring ventilatory support as well as a combination of specific therapeutic measures, and in most affected patients constitute the devastating end-of-life event. In CTDs, acute respiratory events may be related to any respiratory

compartment including the airways, lung parenchyma, alveolar capillaries, lung vessels, pleura, and ventilatory muscles. Acute respiratory events may also precipitate disease-specific extrapulmonary organ involvement such as aspiration pneumonia and lead to digestive tract involvement and heart-related respiratory events. Finally, antirheumatic drug-related acute respiratory toxicity as well as lung infections related to the rheumatic disease and/or to immunosuppression complete the spectrum of acute respiratory events. Overall, in CTDs the lungs significantly contribute to morbidity and mortality, since they constitute a common site of disease involvement; a major site of infections related to the

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'mater' disease; a major site of drug-related toxicity, and a common site of treatment-related infectious complications. The extreme spectrum of the abovementioned events, as well as the 'vicious' coexistence of most of the aforementioned manifestations, requires skills, specific diagnostic and therapeutic means, and most of all a multidisciplinary approach of adequately prepared and expert scientists. Avoiding lung disease might represent a major concern for future advancements in the treatment of autoimmune disorders.

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Introduction

Subacute-acute, hyperacute, or even catastrophic and fulminant respiratory events occur in the ambit of almost all classic connective tissue disorders (CTDs); they may share systemic life-threatening manifestations, may precipitously lead to respiratory failure – in most cases requiring ventilatory support – as well as a combination of specific therapeutic measures, and in most affected patients constitute the devastating end-of-life event [1–10].

In CTDs, acute respiratory events may be related to any respiratory compartment such as (a) the airways [e.g. acute infective exacerbations in bronchiectatic patients with rheumatoid arthritis (RA) [11]]; (b) the lung parenchyma [e.g. the development of diffuse alveolar damage (DAD) upon fibrotic interstitial lung disease (ILD), mainly usual interstitial pneumonia (UIP), but also fibrotic nonspecific interstitial pneumonia (f-NSIP) clinically manifesting as the development of acute respiratory distress syndrome (ARDS) upon chronic fibrotic ILD, or the development of organizing pneumonia (OP) or acute fibrinous OP (AFOP) [12]]; (c) the alveolar capillaries [e.g. diffuse alveolar hemorrhage (DAH), acute capillaritis, or bland hemorrhage related to systemic lupus erythematosus (SLE) [13]]; (d) the lung vessels [e.g. acute pulmonary thromboembolism or the development of a catastrophic antiphospholipid syndrome (CAPS) in SLE [14]]; (e) the pleura [e.g. pneumothorax and/or pneumomediastinum mostly in dermatomyositis-polymyositis (DM-PM) [15]], and (f) the ventilatory muscles (e.g. the development of acute hypercapnic respiratory failure related to acute ventilatory muscle myositis in DM-PM [16]). In addition, acute respiratory events may precipitate disease-specific extrapulmonary organ involvement such as aspiration pneumonia as well as the far less frequently occurring Mendelson syndrome with digestive tract involvement, mainly in scleroderma and DM-PM [17–19] as well as in acute heart-related respiratory events in

myocarditis or pericarditis with tamponade [20]. Last but not least, acute antirheumatic drug-related respiratory toxicity as well as acute lung infections related to the 'mater' disease, specific manifestations of rheumatic disease in the lung, and/or immunosuppressive treatment (including the widespread use of biological factors) complete the spectrum of acute respiratory events in CTDs (table 1) [4, 21–24].

Acute respiratory events rarely occur in early, undiagnosed, or undefined CTDs, facilitating the diagnostic approach and therapeutic decision-making, but the preexistence of other chronic lung manifestations of the mater disease, such as bronchiectasis or fibrotic ILD, clearly predisposes patients to the development of infective or drug-related lung events – especially those patients who need treatment according to any dosage schedule with steroids, cytotoxic agents, and the most recently developed biological factors (monoclonal antibodies, receptor analogs, and chimeric molecules) [25–28]. The common denominator upon which immunosuppression acts and precipitates respiratory infections is the existence of an altered and aggressive lung microbiome in chronically disrupted lungs [29]. Indeed, there is considerable concern regarding the initiation of treatment for RA with biological, disease-modifying factors in case of an already established lung disease, especially in the case of ILD and bronchiectasis; several experts advise 'careful counseling and patients' consent regarding the risks and benefits' [30]. The extreme spectrum of the abovementioned acute respiratory events, as well as the 'vicious' coexistence of most of the aforementioned manifestations where specific treatment for one disease manifestation may be deleterious with regard to a coexistent respiratory manifestation, requires skills, specific diagnostic and therapeutic means, and most of all a multidisciplinary approach of adequately prepared and expert scientists [31].

Acute 'Exacerbations' Developing upon Fibrotic ILDs

The superimposition of DAD of unknown etiology upon UIP histology has been described in idiopathic pulmonary fibrosis (IPF) by Kondoh and coworkers since 1993 and clinically represents the development of a devastating end-of-life ARDS [32, 33]. Kondoh et al. [33] were also the first to pose the fundamental question of whether the above-described condition represents an accelerated phase of the same disease or ARDS of any etiology developing upon disruption of the diseased lung, opting for the first hypothesis and suggesting steroids for its

Table 1. Acute respiratory events in CTDs

Manifestation	RA	SLE	SSc	DM-PM	pSS	MCTD	AS
ILD ‘acute exacerbation’	+	–	+	++	–	?	–
OP	+	+	+	++	–	+	–
AFOP	±	±	±	±	–	–	–
DAH	±	+	±	±	–	–	–
Venous thromboembolism	±	++	–	–	–	±	–
Catastrophic APS	–	+	–	–	–	–	–
Bronchiectasis exacerbation	++	–	–	–	±	–	–
PNX-pneumomediastinum	±	–	–	+	±	–	±
Aspiration pneumonia	–	–	++	++	–	±	–
Hypercapnic respiratory failure	–	±	–	++	–	–	–
Pericarditis	±	++	±	±	±	±	–
Pulmonary infections	+	+++	+	+	+	+	+
Drug toxicity	++	+++	++	++	+	++	+

SSc = Scleroderma; pSS = primary Sjögren’s syndrome; MCTD = mixed CTD; AS = ankylosing spondylitis; APS = antiphospholipid syndrome; PNX = pneumothorax.

management. A more recent consensus report fully adopted the above suggestion and named the whole condition ‘IPF acute “exacerbation”’, suggesting high-dose steroids for its management, a consensus also encountered in all subsequent guidelines on IPF [34, 35]. The suggestion to use high-dose steroids, as well as the poor response observed in most if not all cases, was interpreted by some clinicians as the necessity to push for an even more profound immunosuppression, and several cytotoxic agents were added on a case-by-case basis, again failing to prove any clear benefit [36–38]. The rising concern regarding the disappointing results of this therapeutic approach for so-called IPF acute ‘exacerbations’ and the necessity of an alternative approach have been voiced in the publications by our group of investigators since 2010; moreover, treatment of both stable and ‘exacerbated’ patients with steroids had been abandoned in our clinical practice more than a decade before that time [32, 39]. The more recent publication of the PANTER study on IPF – conducted under the auspices of the IPF Clinical Research Network (IPFnet) and proving for the first time that immunosuppression in IPF leads to infections, hospitalizations, ‘exacerbations’, and death – renders it inconceivable that even higher doses of steroids are used hoping for improvement in IPF patients already on treatment with steroids and cytotoxic drugs and developing ARDS [40]. Indeed, an even more recent study by Papiris et al. [41] showed that abolishing steroids in IPF patients developing ARDS may prove to be of benefit, and that a history of steroid use as the standard of care for these patients

before ARDS development abolishes this benefit and clearly predisposes to death.

After the first description of the development of DAD upon UIP in IPF, several reports have referred to the development of DAD upon other fibrotic ILDs, including idiopathic NSIP and fibrotic-phase established extrinsic allergic alveolitis, and also fibrotic ILDs of both the UIP type and the NSIP type in patients suffering from CTD (mainly RA, but also others), approaching a cumulative incidence of around 7% (fig. 1) [12, 42, 43]. In CTD-related fibrotic ILDs, an even greater matter of concern regarding the development of DAD in damaged fibrotic lungs arises, since most of the patients with such diseases not only are on treatment with combinations of steroids and cytotoxic drugs (synthetic disease-modifying drugs) such as azathioprine, methotrexate, cyclosporine, or others but also extensively use biological disease-modifying drugs such as TNF- α inhibitors (infliximab, etanercept, adalimumab, golimumab, or certolizumab pegol), an anti-IL-6 receptor monoclonal antibody (tocilizumab), T-cell signaling inhibitors (abatacept), an anti-CD20 monoclonal antibody (rituximab), or others [44]. Indeed, the extensive use of biological factors in CTDs over the past few years has been paralleled by an exponentially rising number of reports on the development of several types of lung toxicity, such as de novo development of chronic and/or acute ILD, ‘exacerbation’ of preexisting chronic fibrotic ILD, and finally significant infective lung and systemic toxicity [45–47]. On the other hand, similar types of lung toxicity have clearly been reported with the exten-

Fig. 1. HRCT images of the chest revealing subpleural interstitial thickening and areas of ground-glass attenuation together with some bronchial distortion and esophageal dilatation (**a, b**). The patient was a 62-year-old woman, a never-smoker with a long-standing history of scleroderma. After a few months, she experienced progressive dyspnea that led to severe hypoxemia; at that point, an HRCT of the chest demonstrated extensive areas of ground-glass attenuation, small focal areas of consolidation, irregular linear opacities, and traction bronchiectasis/bronchiolectasis in the lower lobes and particularly in the subpleural regions compatible with an acute ‘exacerbation’ upon the preexisting fibrotic ILD (**c, d**).

sive use of synthetic disease-modifying drugs, especially methotrexate [48, 49]. Therefore, the current common practice of combination treatment with both synthetic and biological disease-modifying drugs bears a considerable risk of acute drug toxicity, in particular if applied upon preexisting fibrotic ILD. Finally, the ineffectiveness or inadequacy of both synthetic and biological disease-modifying drugs in influencing the appearance or deterioration of preexistent CTD-related fibrotic ILDs becomes even more obvious since many patients were developing fibrotic ILDs even though they were already in treatment with the abovementioned drugs.

Actually, the pathogenesis and treatment of the development of DAD upon idiopathic fibrotic ILDs, and per extrapolation of ‘exacerbations’ upon CTD-related fibrotic ILDs, are reconsidered for several reasons including (a) the ineffectiveness and probably deteriorating effect of immunosuppressive treatment on ARDS, (b) the fact that an infective etiology for the development of ARDS upon fibrotic ILDs can never be excluded, (c) the fact that cur-

rent treatment of CTDs, as well as in many cases of the mater disease, predisposes to lung infections, and (d) the fact that damaged and disrupted lungs become hosts to an altered human microbiome. Therefore, a multidisciplinary approach should be warranted for any patient and at any level of therapeutic decision-making including (a) the initiation of treatment on preexisting ILDs and the obligatory ‘careful counseling and patients’ consent regarding the risks and benefits’ [30], (b) the diagnostic approach upon acute deterioration such as the development of ARDS upon fibrotic CTD-related ILDs, and (c) therapeutic decisions in a clinical context in which infections are difficult to detect and may never be excluded [50].

Acute Lung Infections in CTDs

Acute lung infections rank very high on the list of both common and detrimental acute respiratory events in CTDs, and they often constitute the most common etiol-

Fig. 2. **a** Posteroanterior chest radiograph showing reticulonodular opacities in the upper lung zones and areas of consolidation and atelectasis in the middle and lower lung zones. The patient was a 74-year-old woman with a history of long-standing RA in immunosuppressive treatment with corticosteroids. **b–d** HRCT images of the patient's chest demonstrating bilateral centrilobular nodular and branching opacities compatible with acute infectious bronchiolitis (**b, c**) upon preexisting lung bronchiectasis and cicatricial atelectasis of both the middle lobe and the lingula (**d**).

ogy leading to admissions of CTD patients to both hospitals and intensive care units; along with urinary tract infections, septic arthritis, septicemia, cellulites, aspiration pneumonia, and opportunistic infections in other sites, lung infections have a major impact on morbidity and mortality and are one of the three leading causes of premature death, the other two being cardiovascular events and irreparable damage to target organs [24, 25, 51–53].

Compared to the general population, the increased susceptibility of CTD patients to infections is related to three main parameters: (a) intrinsic immunological abnormalities associated with the mater CTD; (b) chronic specific CTD-related lung involvement such as bronchiectasis and fibrotic ILDs, both constituting hosts to an altered human microbiome, and (c) clinically significant immunological dysfunction induced by the use of synthetic and biological disease-modifying drugs [4, 29, 54–56]. Increased age and digestive tract involvement, predisposing to aspiration as in DM-PM and scleroderma, further aggravate the risk [25]. Of all CTDs, SLE presents a unique paradigm of disrupted immunity per se increasing the risk of infections attributable to the so-

called lupus paradox, that is, a state of severely impaired cellular and humoral immune responses in spite of B-lymphocyte hyperactivity and high levels of γ -globulins, including high antibody titers against viruses and other pathogens and a high ability to attack 'self-tissues' [26, 54, 57–59]. Recent data support an 'intrinsic' defective response to infectious agents also in RA and scleroderma [60, 61]. Bronchiectasis is known to result from and to perpetuate a 'vicious cycle' of chronic bacterial infection and dysregulated inflammation and is therefore considered a 'high-infection-risk' condition in RA patients (fig. 2) [56]. Furthermore, recent studies have shown that fibrotic ILD is characterized by an increased distal alveolar bacterial burden that might be responsible for both a rapidly deteriorating course of fibrotic disease and deadly 'exacerbations' [29]. The establishment via new DNA sequencing technologies of the long-time hypothetic theory that a disturbed lung microbiome could trigger and/or aggravate tissue injury in susceptible pulmonary fibrosis patients bears significant importance for CTD patients not only for its role in the development and maintenance of lung disease but also

Fig. 3. CT of the chest demonstrating a thick-walled cavity in the lingula together with extensive confluent alveolar infiltrates. Acid-fast bacilli were evident on microscopic sputum examination. The patient was an 83-year-old woman, a never-smoker who had long-standing RA treated with steroids and who had developed tuberculosis.

for its potential pathogenetic role in manifestations of the mater disease [62–64].

On top of the already described immune dysregulation and lung parenchymal structural changes, traditional and novel biological therapies – although indispensable for the management of systemic manifestations of several CTDs – further enhance the risk of infection by suppressing immune responses. Corticosteroids, for example, suppress both humoral and cellular immunity and have been shown to increase the infection rate by a factor of 2–4 at any dose, with doses of more than 20 mg prednisone per day having the most deleterious effect [54, 65]. The rest of the disease-modifying drugs, both synthetic and biological, are also implicated in the increased risk of common, mycobacterial, and opportunistic infections. More precisely, TNF- α inhibitors lead to blockade of a variety of immunological functions such as cell activation and proliferation, cytokine and chemokine production, and formation and maintenance of granulomas. This is the main reason why they are related to an increased risk of granulomatous infections, chiefly tuberculosis (fig. 3). Anti-CD20 antibodies, on the other hand, cause depletion of normal B lymphocytes lasting 2–6 months, which may be implicated in disseminated viral infections (*Parvovirus*, *Cytomegalovirus*, *Herpes simplex virus*, *Varicella zoster virus*) and severe pneumonias. Coadministration of biological factors or a combination of these therapies with high doses of corticosteroids multiplies the risk of

infection and should definitively be avoided, especially in elderly patients with lung comorbidities. On the other hand, upon a developed lung infection, discontinuation of immunosuppression does not lead to precipitous reconstitution of the immune system [55, 65–71]. All the above parameters significantly increase the risk of bacterial, mycobacterial, viral, and fungal pulmonary infections in CTD patients (fig. 4, 5) [23, 27, 51, 71–80].

DAH Syndromes

DAH – or, synonymously, intrapulmonary hemorrhage – designates diffuse bleeding from the pulmonary microcirculation (arterioles, alveolar capillaries, and venules) as a result of microvascular damage, leading to blood leakage into the alveolar spaces [81]. In most if not all cases, alveolar hemorrhage simultaneously affects multiple areas of both lungs, although in a minority of cases it may be less extensive at an early stage, involving one lobe or one lung, mimicking pneumonia (fig. 6, 7) [82]. Histologically, in the majority of patients alveolar hemorrhage is related to necrotizing capillaritis characterized by neutrophilic infiltration of the alveolar septa, which present expanded by both the inflammatory infiltrate and protein-rich edema. Alveolar spaces present filled with fresh blood, and in the following few days also with a high number of hemosiderin-laden macrophages (fig. 8). Occasionally, arteriolitis and venulitis may coexist [83]. In a minority of patients with pulmonary hemorrhage, capillaritis may be absent and defines a bland pulmonary hemorrhage [84, 85].

With regard to CTDs, alveolar hemorrhage occurs mainly in SLE (affecting 2–5% of lupus patients) and usually presents fulminant and catastrophic, occurring within hours or, in a minority of cases, in the space of a few days [57]. Clinically, it manifests as dyspnea, cough, and hemoptysis (may be absent in as much as 30% of patients) and usually coexists with lupus nephritis [13, 86]. In a significant proportion of patients, severe respiratory failure may develop, requiring ventilatory support and intensive care unit stay [87]. For a diagnosis of alveolar hemorrhage, the subsequent criteria should be fulfilled: (a) chest X-ray- or CT-proven bilateral and confluent alveolar shadows, (b) a new drop in hematocrit or hemoglobin levels (more than 1.5–2 g/dl), and (c) pink or red bronchoalveolar lavage fluid becoming increasingly red on successive aliquots (fig. 9) [84, 85]. An ‘active’ urinary sediment including the detection of dysmorphic (‘Mickey Mouse’) red cells strongly suggests the simultaneous oc-

Fig. 4. HRCT of the chest revealing extensive areas of consolidation with the presence of an air bronchogram in the right lung along with alveolar infiltrates in the left lung (**a, b**). The patient was an 80-year-old woman with long-standing RA in treatment with steroids who presented with purulent sputum, fever, and severe hypoxemia. The clinical and laboratory features were consistent with severe pneumonia complicated by septic shock.

Fig. 5. CT of the chest revealing pleural effusion with passive atelectasis of the right lower lobe associated with consolidation of the left lung and pleural calcifications. The patient was a 78-year-old man, an ex-smoker with long-standing RA treated with methotrexate and steroids who presented with purulent sputum, fever, agitation, and hypoxemia. Pleural fluid cultures grew *Listeria monocytogenes*.

currence of lupus nephritis [84, 85]. In the hands of a well-trained and expert physician, assessment of the above criteria does not need an excessive amount of time; this ensures a prompt diagnosis in order to provide appropriate treatment, both of which are of paramount importance for the achievement of a good outcome [87]. Indeed, early diagnosis and timely administration of treatment appear to have favorably influenced the prognosis of such patients; a few decades ago, the mortality rate had approached approximately 90% (fig. 10). In lupus patients, thrombocytopenia appears to be significant-

ly associated with the emergence of alveolar hemorrhage. Treatment consists of the administration of pulses of steroids and cyclophosphamide as early as possible [87]. In the past years, other therapeutic options have emerged, such as plasmapheresis, the administration of intravenous immunoglobulins, rituximab, mycophenolate mofetil, recombinant factor VII, and others, permitting a more individualized treatment according to the immunological status and general condition of the patient [88–94].

Pulmonary Thromboembolism and CAPS

As already stated, ‘pulmonary thromboembolism (PTE) is the third most characteristic respiratory manifestation in SLE patients appertaining to the spectrum of pulmonary manifestations of the lupus-associated antiphospholipid antibody syndrome (secondary) which also includes the chronic thromboembolic pulmonary arterial hypertension, the catastrophic antiphospholipid syndrome (CAPS) and ... others’ [59, 95]. Regarding acute pulmonary thromboembolism there exist several excellent reviews and guidelines to which the reader is directed to seek advice [96]. The antiphospholipid syndrome, the clinical expression of an acquired autoimmune dysregulation, may occur per se (primary) or be associated with other clinical autoimmune conditions (secondary), mainly CTDs, among which it is encountered in SLE and far less commonly in RA [97–99]. To ensure its diagnosis, it is necessary to ascertain the clinical detection of vascular thrombosis (venous, arterial, or microvascular) and/or pregnancy morbidity (one of the

Fig. 6. **a** Posteroanterior chest radiograph showing diffuse bilateral infiltrates with perihilar distribution, more prevalent in the middle and lower lung fields. The patient was a 52-year-old woman, a never-smoker who fulfilled the diagnostic criteria for SLE and developed DAH. **b** CT image of the chest (performed at the same time) showing extensive areas of ground-glass attenuation with relative sparing of the subpleural regions.

Fig. 7. **a** Posteroanterior radiograph of the chest revealing consolidation with an air bronchogram of the right upper lobe mimicking lobar pneumonia. The patient was a middle-aged woman with a history of fever and shortness of breath of several days' duration. **b, c** Extension of infiltrates in the right lung field despite antimicrobial treatment. **d** Remission of the initial infiltrate of the right upper lobe and development of new patchy infiltrates bilaterally in the right and left lower lung fields. The patient was submitted to bronchoalveolar lavage through bronchoscopy and lung biopsy which documented DAH.

above is enough) as well as one of the following laboratory seropositivities: (1) lupus anticoagulant, (2) IgG- or IgM-isotype anticardiolipin antibodies, or (3) IgG- or IgM-isotype anti- β_2 -glycoprotein I antibodies [100]. Pulmonary thromboembolism is the most common manifestation of venous system thrombosis, even though any

venous ramification (superficial or deep) may be involved. Arterial thrombosis mainly involves the cerebral arteries, but also others. Acute and extensive microvascular thrombosis, leading to multiorgan ischemia and failure, characterizes the rarely occurring and often lethal condition named CAPS. CAPS may present as idiopathic

Fig. 8. Histopathological examination of the lung biopsy of a patient with DAH demonstrating air spaces filled with both fresh blood and hemosiderin-laden macrophages, highlighting the acute-on-chronic character of the hemorrhage.

or secondary, the latter form mainly occurring in female lupus patients [14, 97, 98]. It commonly involves more than three organs (more frequently the kidneys, the lungs, the central nervous system, the heart, and the liver), always presents with antiphospholipid antibodies, occurs rapidly (within less than 1 week), and is histologically characterized by intravascular thrombosis (diagnostic criteria) [101, 102]. The pathogenesis of CAPS is chiefly related to the fact that antiphospholipid antibodies inappropriately activate platelets as well as endothelial and immune effector cells, inhibit anticoagulants, inhibit fibrinolysis, and activate complement, promoting a prothrombotic and proinflammatory vascular milieu leading to widespread and multiorgan thrombosis [103, 104]. A systemic inflammatory syndrome characterized by fever, tachycardia, tachypnea, and leukocytosis commonly coexists and is associated with the extensive ischemic tissue damage [105, 106]. Triggering factors identified in most patients include infections, surgery, obstetric complications, drugs or discontinuation of anticoagulants, and others [107, 108]. The clinical manifestations are related to the specifics of organ involvement and include severe hypertension, acute renal failure, proteinuria, and hematuria (kidneys); ARDS, pulmonary embolism, and DAH (lungs); hypertensive and/or ischemic encephalopathy and stroke (central nervous system); coronary artery thrombosis and valve lesions (heart), and livedo reticularis, acrocyanosis, purpura, and others (skin) [109, 110]. Prompt treatment with anticoagulants, immunosuppressants, intravenous immunoglobulins, plasmapheresis,

Fig. 9. Cytological bronchoalveolar lavage fluid stains showing hemosiderin-laden macrophages in a patient with DAH. **a** Giemsa stain. **b** Perl's stain. **c** Papanicolaou stain.

and antiplatelet agents – all of the above using antibiotic coverage as well as a multidisciplinary approach including intensivists – may favorably affect the outcome [111–113].

OP and AFOP

OP is a sort of subacute-acute lung injury occurring in a number of different settings such as infections, adverse drug reactions, inhalation of toxic gases and dusts, neoplasms, radiation exposure, aspiration, CTDs or even idiopathic diseases, and others [114–117]. It is synonymous with bronchiolitis obliterans OP and histologically represents a process in which distal bronchioles and the air space are filling with elongated fibroblasts and myofibroblasts intertwined with several inflammatory cells in a myxoid matrix forming plugs or polyps (Masson bodies or ‘bourgeons conjonctives’) [114, 118]. Occasionally, in surgical specimens, proteinaceous or fibrinous (fibrin ‘ball’) exudates may predominate, clinically characterizing a more severe condition named AFOP by some investigators and lying between OP and ARDS [119]. AFOP may occur in a number of clinical settings as OP, and the fact that on histological examination remnants of both acute and chronic inflammatory cells coexist, as well as that AFOP occurs in immunocompromised patients, may suggest an infectious etiology [119]. Both OP and AFOP share ultrastructural changes with DAD, which emphasizes similarities in their pathogenesis and their role in processes of acute lung injury, even though they show a different geographical extension in the lung and prognosis [119, 120]. In some patients, the overlapping of OP-AFOP and ARDS, as occurring in CTDs, may suggest a common immunological, infective, or other etiology [117, 119, 121, 122].

In CTDs, OP and AFOP may be the initial manifestation, set in simultaneously, or develop during clinical progression of the mater disease; in the last case, they may coexist with other forms of respiratory involvement or an already developed adverse drug reaction [59, 114, 117,

Fig. 10. **a** Radiograph of the chest of a patient with rapidly progressing DAH revealing extensive consolidation of both lungs. **b** Radiograph of the same patient a few hours later after endotracheal intubation and mechanical ventilation due to severe respiratory failure. **c** The patient underwent CT of the chest, demonstrating numerous poorly defined, confluent centrilobular opacities in both lungs, and deceased a few days later in the intensive care unit despite aggressive treatment.

Fig. 11. a, b HRCT scans of the chest showing areas of ground-glass attenuation together with focal areas of consolidation, principally in the lower lobes. The patient was a 72-year-old woman, a never-smoker with mixed connective tissue disease who had developed AFOP. **c** Histopathological examination of the lung biopsy of the same patient depicting AFOP with diffuse lung involvement. HE. $\times 4$. **d** Intra-alveolar spaces are filled with fibrin in the form of 'fibrin balls', whereas the intervening lung parenchyma shows minimal changes, mostly mild inflammatory infiltrates and minimal interstitial widening. HE. $\times 10$.

119–121, 123, 124]. OP and AFOP associated with various CTDs share clinical, radiographic, and histopathological features with idiopathic OP and AFOP (fig. 11) [121, 123]. CTD-related OP has been described in almost all CTDs, although more frequently in RA and DM-PM, and has a female predominance [121, 123]. In comparison to idiopathic OP, patients with CTD-OP present more commonly with autoantibodies and higher levels of inflammatory indices [121]. Occasionally, OP sets in during an episode of a CTD flare-up, suggesting an underlying, shared immunological mechanism [123]. The clinical outcome of CTD-OP has not been well defined, even though various studies have reported a worse prognosis, a lower complete recovery rate, and a tendency towards higher recurrence rates as compared to the idiopathic form [121, 123]. In RA, OP represents up to 10–15% of any ILD involvement and is often observed during the follow-up of joint-associated symptoms, but in rare cases it can predate the development of joint manifestations or serological conversion, which may lead to underdiagnosis and missing of the link between OP and underlying but early and undiagnosed RA [123, 125–127]. In DM-PM, OP is an even more common manifestation, with its reported prevalence approaching 20% [125, 128, 129]. In PM, OP commonly occurs in the ambit of the antisynthe-

tase syndrome and may coexist with an underlying and already established f-NSIP [125, 129]. Furthermore, in clinically amyopathic dermatomyositis (CADM), characterized by minimal or absent muscle involvement and anti-CADM-140 antibody seropositivity, OP has been described to occur as a more rapidly progressive respiratory disease often overlapping with DAD [59, 130–132]. In general, OP in DM-PM appears to carry a less favorable prognosis, and some clinicians advocate a more profound immunosuppressive treatment – although an infective etiology is impossible to exclude also in this setting [121, 123, 125]. OP is an unusual manifestation in SLE, and only few reports have been documented [123, 125].

AFOP has recently been recognized as a distinct pattern of lung injury, and two clinical forms have been described: an acute form, with fulminant presentation overlapping with ARDS, leading to death in most if not all patients, and a subacute form, with a more favorable outcome [119]. There are only single case reports of documented AFOP in DM-PM, ankylosing spondylitis, and mixed connective tissue disease [133–136]. As the assessment of AFOP is essentially histological, needing large biopsy specimens, surgical lung biopsy is essential for the diagnosis and the early institution of appropriate treatment [119].

Acute Hypercapnic Respiratory Failure Related to Acute Ventilatory Muscle Myositis

Inflammatory myopathy has been described in all of the CTDs [16]. However, when it occurs in diseases other than DM-PM and SLE (far less frequently), myositis tends to be mild and never predominates in the clinical expression [137]. Inflammatory myositis leads to muscle weakness, muscle tenderness, sometimes pain, and ultimately atrophy and fibrosis. In inflammatory myopathies, the proximal muscles of the legs are affected first, followed by the proximal arm muscles and the trunk [16]. Often, but characteristically in DM-PM, involvement of the thoracoabdominal ventilatory pump muscles may predominate or co-occur with generalized muscle involvement and leads to a more or less rapidly evolving hypercapnic respiratory failure necessitating ventilatory support [137–140]. In this clinical context, both inspiratory and expiratory muscles are involved – and usually to the same extent [141, 142]. The diagnosis requires a muscle biopsy, preferably an open one (because the characteristic lesions are spotty) from the quadriceps or the biceps brachii [16]. Prompt acquisition of the diagnosis is mandatory because of the precipitating or already precipitated hypercapnic respiratory failure and the necessity of obviating infections [16]. Infections are related to the coexistence of pharyngeal muscle involvement and weakness, predisposing to aspiration pneumonia and ineffectiveness of cough as well as reduced clearance of lung secretions associated with generalized thoracoabdominal muscle weakness [19, 143]. Treatment remains empirical and includes steroids and/or immunosuppressants, intravenous immunoglobulins, biological factors, and rituximab [16]. Diaphragmatic muscle involvement and related weakness may present as ‘shrinking lungs and high sluggish diaphragm with clear lung fields’ in lupus occurring mainly in patients without evidence of systemic myopathy [144–148]. In such a clinical context, hypercapnic respiratory failure has occasionally been reported [149]. The etiology remains unclear, although in some patients a diaphragmatic inflammatory myopathy has been documented histologically through biopsy [150–152]. The therapeutic approach includes steroids and immunosuppressants [146, 147, 153].

Pneumothorax-Pneumomediastinum

Air leak syndromes in the pleural cavity (i.e. pneumothorax) and/or in the mediastinum (i.e. pneumomediastinum) and/or in the subcutaneous loose tissues (i.e. sub-

cutaneous emphysema) constitute very rare acute respiratory events in CTDs and may occur simultaneously or in isolation. They have been described in the literature in a variety of case reports concerning each one of the major seven CTDs, and very scarcely do they represent spontaneous events or events at initial presentation of the disease [154–169]. Most of the times, they are secondary to a preexisting chronic lung disease such as ILD with subpleural cystic-honeycombing lesions, especially in RA, scleroderma, DM-PM, and mixed connective tissue disease; the presence of peripheral necrobiotic lung nodules in RA, cystic lung disease or lower respiratory tract infections in SLE and Sjögren’s syndrome, and fibrobullous disease of the lungs in ankylosing spondylitis further increases the risk of their development and aggravates their outcome. In DM, refractory pneumomediastinum is shown to develop more frequently in patients with rapidly progressing ILD, mainly CADM. Air leak syndromes should always be considered in case a CTD patient develops new respiratory symptoms or acute deterioration of dyspnea, chest pain, or facial and neck edema. Clinical behavior ranges from self-limited disease with a favorable outcome to refractory recurrent cases of pneumomediastinum or bilateral pneumothoraces leading to severe respiratory failure and death. Treatment of air leak syndromes in CTDs is not always effective and includes oxygen therapy, chest tube insertion, pleurodesis, or surgical interventions. Optimal therapy of the underlying CTD and any complication such as infection is indispensable for the ideal management of this rare respiratory manifestation in CTDs [170–181].

Acute Gastroesophageal Content Aspiration Pneumonitis

Aspiration pneumonia may develop as an acute or subacute respiratory event in any CTD patients, especially in older and debilitated ones [24, 182, 183]. However, scleroderma and DM-PM significantly surpass the other CTDs concerning this complication, due to the fact that both diseases are characterized by pathophysiologic mechanisms seriously predisposing to impaired function of swallowing and thus to overt acute aspiration or occult chronic microaspiration of oropharyngeal and/or gastropharyngeal contents [143, 184]. In scleroderma, the gastrointestinal tract is the internal system most commonly involved. Excessive and progressive fibrosis of the entire organ, starting from the pharyngoesophageal muscles, leads to dysmotility, dysphagia, and gastroesophageal re-

flux in the majority of patients, as well as to small intestinal bacterial overgrowth and chronic intestinal pseudo-obstruction [185, 186]. Poor oral hygiene, tooth loss, decreased saliva production, and periodontal disease are also frequently encountered in scleroderma patients, further aggravating the risk of aspiration pneumonia [187]. In DM-PM, on the other hand, dysphagia seems to be mostly related to impaired muscle contraction, reduced hyoid-laryngeal excursion, and/or failed upper esophageal sphincter relaxation [19, 143, 188].

Aspiration of oropharyngeal and/or gastropharyngeal contents may cause airway obstruction, lung abscess, lipoid pneumonia, ILD, and diffuse aspiration bronchiolitis, but much more frequently aspiration pneumonia, an acute infectious process related to the aspiration of material contaminated by common pathogens. More rarely, aspiration of sterile regurgitated acidic gastric material occurs, leading to a chemical pneumonitis known as the Mendelson syndrome. In this case, a severe inflammatory response results in acute lung injury or even ARDS, whereas a bacterial infection may be superimposed later on. Any aspiration event may easily become aggravated in any CTD patient due to the concurrent immunological dysfunction related to both the disease and its immunosuppressive treatment. Aspiration pneumonia should always be considered in CTD patients presenting with cough, wheezing, dyspnea, weight loss, and new pulmonary infiltrates. Appropriate antimicrobials and supportive measures should be initiated as soon as possible; in addition, early management of risk factors such as reflux and gastrointestinal tract dysmotility should always be adopted in a timely manner, since the development of aspiration pneumonia in CTD patients is a dramatic acute respiratory event often leading to increased rates of morbidity and mortality especially in scleroderma and DM-PM patients [182, 183, 189].

Acute Heart-Related Respiratory Events

Cardiovascular disease is increased in CTD patients compared to the general population and significantly contributes to morbidity and mortality [190, 191]. It may present as involvement of the coronary arteries (acute coronary syndromes and ischemic heart disease), myocardium (myocarditis, cardiomyopathy, rhythm and conduction disturbances, and heart failure), endocardium (valvular heart disease and thrombi), pericardium (pericarditis and pericardial effusion), and major vessels (aneurysm formation and arterial and venous thrombo-

sis) [190]. Atherosclerosis appears to be a major pathogenic mechanism in all major CTDs, which can be as accelerated, diffuse, and extensive as in patients with diabetes mellitus. The cardinal risk cofactor in all CTDs is chronic inflammation related to autoimmunity, which adversely interacts with genetic factors, smoking habit, age, gender, obesity, diabetes mellitus, dyslipidemia, and hypertension [192, 193]. Nonatherosclerotic mechanisms such as microvascular dysfunction, cardiac autonomic neuropathy, arrhythmias, and pericardial inflammation have also a contributing role in the development of cardiovascular disease. Ischemic heart disease with myocardial infarction occurs mainly in RA and SLE, whereas pericarditis presents in SLE, microvascular perfusion abnormalities of the myocardium are found in scleroderma, and valvular heart disease and conduction abnormalities occur more often in ankylosing spondylitis [194–198].

Whereas the majority of cardiovascular events are managed in a cardiology department setting, pulmonologists often diagnose and face acute events related to effusive pericarditis with or without tamponade and pleural effusion. Pericardial involvement may occur in as much as 50% of patients with scleroderma and SLE. However, with the exception of lupus, pericarditis usually presents as a ‘bystander’, and the occurrence of tamponade is rare. The pathogenesis of lupus-associated pericardial effusion may be related to the deposition of immune complexes and complement activation, leading to pericardial inflammation and effusion [199–201]. Depending on the speed of fluid accumulation, pericarditis may be asymptomatic or present as a life-threatening cardiac tamponade. Classic signs of tamponade include tachycardia, neck vein distension, elevated jugular venous pressure, diminished heart sounds, pulsus paradoxus, and dyspnea-tachypnea [202]. Early treatment of cardiac tamponade is of paramount importance as any delay may be life-threatening. Echocardiography should be performed in all patients with suspected pericardial effusion. It allows the estimation of effusion size and hemodynamic effects as well as pericardial thickening and intrapericardial adhesions. Cardiac magnetic resonance imaging should additionally be performed in cases where myocardial disease is also suspected [203]. Pericardiocentesis is important for management but may also improve diagnostic yield. When compared to surgical drainage, echocardiography-guided pericardiocentesis has been associated with lower morbidity and mortality rates, even though the placement of a pericardial drain or surgical pericardiectomy may become necessary [204]. Increased recognition of acute heart-related respiratory events leads to appropri-

Table 2. Acute respiratory events due to drugs

Drug	Pattern												
	OP	AFOP	AEP	DIP	AE-ILD	DAD (ARDS)	DAH	NCPE	pulmonary infections	broncho-spasm anaphylaxis	drug-induced lupus	VTE	vas-culitis
NSAIDs			+					+		+			
Steroids									++			+	
Azathioprine	+				+	+			++	+			
Methotrexate	+				+	+	+	+	++	+			
Leflunomide	+		+		+	+			++		+		
Mycophenolate mofetil						+	+		++				
Hydroxychloroquine			+			+			++	+			
Cyclosporine						+			++	+			
Cyclophosphamide	+				+	+	+	+	++	+			
Sirolimus/tacrolimus	+		+	+	+	+	+		++			+	+
Gold	+		+			+				+			
Anti-TNF													
Infliximab			+		+	+	+		++	+	+	+	
Etanercept	+		+		+	+	+		++	+	+	+	+
Rituximab	+				+	+	+	+	++	+			+
Anakinra					+				++				
Tocilizumab	+				+				++				
Abatacept		+							++				
Belimumab									++				
Golimumab									++				
Adalimumab					+	+			++	+	+		
Certolizumab pegol						+			++				
Epratuzumab									++				
Tofacitinib									++				
Immunoglobulins						+	+	+		+		+	

NSAIDs = Nonsteroidal anti-inflammatory drugs; AEP = acute eosinophilic pneumonia; DIP = desquamative interstitial pneumonia; AE-ILD = acute exacerbation ILD; NCPE = noncardiogenic pulmonary edema; VTE = venous thromboembolism.

ate management and prevention. Appropriate management of the underlying disease with optimal control of CTD activity, specific cardiovascular treatment, and prevention of traditional risk factors may decrease the prevalence of acute heart-related respiratory events, and most importantly the associated morbidity and mortality, in CTD patients [192, 193, 205–207].

Acute Antirheumatic Drug-Related Respiratory Toxicity

Several drugs, including the most recently introduced biological factors administered in CTDs, are clearly reported to be associated with acute and often severe respiratory toxicity on their own (not related to their immunosuppressive effect), adding significantly to the ‘vicious’

combination of acute respiratory events related to the disease itself, superimposed infections, and acute drug-related iatrogenic respiratory disease [208]. Most if not all of the previously described acute respiratory events – and several more not reported for reasons of space – may present as an acute adverse drug effect from the lungs, adding significantly to an already complicated diagnostic approach [209]. Acute drug-induced respiratory events in CTDs usually are not due to overdose and present in largely unpredictable, severe, and often life-threatening ways [209]. Regarding acute drug-induced iatrogenic respiratory toxicity there exist several excellent reviews, statements, and book chapters, including an Internet address (www.pneumotox.com), where the reader is directed to seek advice [210, 211]. Drugs commonly used in CTDs and the most common acute adverse events are reported in table 2 [22, 45, 212–226].

Conclusions

In CTDs, the lungs significantly contribute to morbidity and mortality, since they constitute a common site of disease involvement; a major site of infections related to the mater disease; a major site of drug-related toxicity, and a common site of treatment-related infectious complications. Avoiding lung disease might represent a major concern for future advancements in the treatment of autoimmune disorders.

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