



Infections in systemic connective tissue diseases: systemic lupus erythematosus, scleroderma, and polymyositis/dermatomyositis

Marcela Juárez, MD^a, Richard Misischia, DO^b,
Graciela S. Alarcón, MD, MPH^{a,b,*}

^a*Department of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru*

^b*Division of Clinical Immunology and Rheumatology, Department of Medicine, The University of Alabama at Birmingham, Birmingham, AL, USA*

Systemic lupus erythematosus (SLE), scleroderma, and polymyositis/dermatomyositis (PM/DM) are autoimmune diseases with high morbidity and mortality. The important role infections play in these diseases has been documented in the literature over the years [1–16]. This article reviews the role of infections in these three disorders, emphasizing in each (1) the predisposing factors for the development of infections, (2) the effect of infections on mortality, and (3) the most common microorganisms involved in these infectious processes.

Infections in systemic lupus erythematosus

Infections are responsible for 30% to 50% of the morbidity and mortality in patients with SLE [1,2,4,10–12,16–19]. These infectious processes usually result from common microorganisms [1,10,13,15,16,19–21], but opportunistic infections may also occur and are important causes of death in patients who receive corticosteroid and immunosuppressive therapy [8,17–20,22].

Supported (GSA) by a grant from the National Institute of Arthritis and Musculoskeletal and Skin Disorders # R01-AR42503

* Corresponding author. Jane Knight Lowe Chair of Medicine in Rheumatology, 830 FOT, 510 20th Street, The University of Alabama at Birmingham Birmingham, AL 35294-3408.

E-mail address: graciela.alarcon@ccc.uab.edu (G.S. Alarcón).

Predisposing factors

Genetic predisposition to immune dysfunction

Systemic lupus erythematosus patients with inherited complement deficiencies may present abnormalities of all complement proteins, particularly those of the early classic pathway [23]. Systemic lupus erythematosus patients with early complement deficiencies have a higher risk of infections caused mainly by *Streptococcus pneumoniae*, whereas SLE patients with late complement deficiencies show a greater susceptibility to infections by *Neisseria meningitidis* and *Neisseria gonorrhoea* [23,24].

Variant alleles in the coding portion of the mannose binding lectin (*MBL*) gene have been associated with lower levels of MBL, a protein that plays an important role in the phagocytosis of microorganisms and has a similar function to C1q [25]. Systemic lupus erythematosus patients homozygous for *MBL* variant alleles also have a significantly higher risk of developing infections such as pneumonia by *S pneumoniae*. It has been demonstrated, for example, that the annual incidence of infections requiring hospitalization is four times higher in these SLE patients than in those heterozygous for the variant allele or homozygous for the normal allele [25,26].

Abnormalities in the immune system

Patients with SLE have lower levels of complement proteins as well as a reduced number of cellular complement receptors (CR1, CR2, CR3) [27,28]; this is particularly the case for B cells and polymorphonuclear leukocytes (PMNs) [29]. These abnormalities may increase the risk of infections [24]. Petri et al [12] described lower C3 levels 1 year later among lupus patients who required hospitalization for infection, and Kim et al [30] reported reduced complement levels among those patients who died of infection.

Systemic lupus erythematosus can affect a variety of cell functions, and PMNs show many abnormalities. Chemotaxis, recognition of microorganisms, phagocytosis, and oxidative metabolism are usually altered [27,28]. Also, in active SLE, a decreased production of interleukin 8 (IL-8) by PMNs resulting in an altered acute inflammatory response has been described [31]. These PMN abnormalities predispose SLE patients to the development of infections [27,28,31].

Several macrophage and monocyte functions, including phagocytosis and oxidative metabolism, are also impaired in patients with SLE, thus increasing the risk of infections [28]. These abnormalities result from the presence of autoantibodies directed against all three types of Fc gamma receptors (Fc γ R) [28,32] as well as from a decrease in the production of tumor necrosis factor alpha (TNF α) [28,33].

During exacerbations of SLE, patients present with decreased levels of T cells as well as diminished activity of T-helper cells against viral antigens, toxoids, and alloantigens [28,34]. Prolonged corticosteroid therapy also impairs T-cell immunity producing redistribution of T cells, lymphopenia, and inhibition of T-cell

activation and proliferation [35]. These T-cell abnormalities result in a higher risk of infections particularly by intracellular microorganisms [18,34–36]. The spleen, through its system of macrophages, is involved in the clearance of microorganisms, thus preventing them from dissemination [36]. When splenic function is impaired, as it is in some SLE patients, the risk of developing severe infections caused by encapsulated microorganisms such as *S pneumoniae*, *N meningitidis*, and *N gonorrhoeae* increases [24,36].

Disease activity

Disease activity (quantified by validated activity scores) has been found to be an independent risk factor for the occurrence of infections [11,12,16,37–39]. Immune abnormalities, such as decreased complement levels and dysfunction of PMNs, macrophages, monocytes, and T cells, seem to be more pronounced during periods of SLE activity [27,28,31,34]. Duffy et al [37] found that disease activity (quantified by the SLE disease activity index or SLEDAI) is associated with infections independent of the duration of SLE and the dose of prednisone used. Petri et al [12] demonstrated that SLE activity (quantified by the lupus activity index and the SLEDAI) is a predictive factor for hospitalization because of infections, even after carrying out statistical adjustment for corticosteroid use [12]. There are, however, studies that dispute this association [21,40] and others in which disease activity has not been found to be a risk factor for the occurrence of infections after carrying out adequate multivariate analyses [4,10,22].

Corticosteroids and other immunosuppressive drugs

The use of corticosteroids has been associated with increased occurrence of infections in patients with SLE [4,10,12,18,22,37–39]; it is not clear, however, whether this risk relates to doses larger than 10 mg per day [12], incremental doses of corticosteroids [22], or the use of the intravenous route [11,12]. Probable reasons underlying this risk include decreased production of cytokines by suppression of nuclear factor kappa B (NF κ B) [41] and the inhibition of different PMN, monocyte, and T-lymphocyte functions [35].

Cyclophosphamide is now commonly used for the treatment of diffuse proliferative glomerulonephritis, as well as other serious manifestations of SLE otherwise unresponsive to high doses of corticosteroids [42]. Unfortunately, the use of cyclophosphamide increases the risk of severe infections in SLE patients [10,43]. Risk factors strongly associated with infections in SLE patients who receive cyclophosphamide are the sequential use of intravenous and oral cyclophosphamide and a leukocyte count below 3000 cells/mL³ [43]. These patients have an increased risk of developing fatal opportunistic infections [18,43]. This risk is greater when patients are also receiving high doses of corticosteroids [43].

Procedures

Certain procedures have been associated with increased risk of infections in patients with SLE. Patients who receive both plasmapheresis and pulses of cyclophosphamide are at greater risk of developing severe and fatal bacterial

Table 1
Mortality from infections in patients with SLE

Author/year	Study characteristics ^a	Place	Total patients			Deaths (all causes)			Deaths (infection)		Causal microorganism, %		5-Year survival %
			<i>n</i>	Ethnicity	%	<i>n</i>	%	%	Common/ unidentified	Opportunistic			
Hellmann/ 1987 [18]	Chart review (1969–1985 ^b) (deceased patients)	USA	44 (33 autopsies)	Caucasian Black Other	57 14 29	44	100	30	53	47	NA		
de Luis/1990 [17]	Chart review (1979–1987)	Spain	96	White ^c	100	12	13	50	50	50	NA		
Massardo/ 1991 [8]	Chart review (1978–1990)	Chile	159	Hispanic ^c	100	30	19	63	89	11	NA		
Ward/1995 [15,126]	Cohort (1969–1983) Follow up: ~ 11 years	USA	408	White ^d African American ^d	51 49	144	35	22	75	25	82 ^d		
Huicochea/ 1996 [50]	Chart review (1970–1993)	Mexico	65 (2–18 years of age)	Hispanic ^c	100	14	22	29	NA	NA	60 ^c		
Kim/1999 [30]	Chart review (1993–1997)	Korea	544	Asian ^c	100	43	8	33	69	31	94		
Cervera/ 1999 [2]	Multinational cohort (1990) Follow up: 5 years	Europe	1000	White Black Other	97 2 1	45	5	29	85	15	95		
Jacobsen/ 1999 [55]	Cohort (1975–1995) Follow up: ~ 8 years	Denmark	513	Caucasian ^c	100	122	24	21	88	12	91		

Mok/2000 [52]	Cohort (1992–1999) Follow up: variable	China (Hong Kong)	186	Asian ^c	100	9	5	67	50	50	93
Bellomio/ 2000 [47]	Chart review (1990–1998)	Argentina	366	Hispanic ^c	100	44	12	54	100	0	91
Jindal/2000 [51]	Chart review (1984–1998) (deceased patients)	India	25 (all autopsies)	Asian (Indian) ^c	100	25	100	40	67	33	NA
Rodriguez/ 2000 [53]	Chart review (1960–1994)	Puerto Rico	662	Hispanic ^c	100	161	24	27	82	18	95 ^f
Hernandez-Cruz/ 2001 [49]	Case control autopsy study (1958–1994)	Mexico	152	Hispanic ^c	100	76 (all autopsies)	50	42	59	41	NA
Alarcón/2001 [1]	Cohort (1993–1999) Follow up: variable	USA	288	Hispanic African American White	28 41 31	34	12	32	NA	NA	86
Iriya/2001 [19,124]	Chart review (1981–1994) (deceased patients)	Brazil	113 (all autopsies)	Multiethnic ^c	100	113	100	58	77	23	NA
Nöel/2001 [10]	Chart review (1960–1997)	France	87	White ^c	100	10	12	20	100	0	NA

Abbreviations: SLE, systemic lupus erythematosus; NA, not available or not applicable.

^a Length of follow up noted only for cohort studies.

^b Closing date inferred.

^c Inferred based on country origin.

^d Inferred based on characteristics of cohort.

^e At 5–10 years.

^f Patients without renal involvement.

and viral infections than patients with comparable clinical features receiving cyclophosphamide alone [44]. The risk is increased because the levels of B cells, T cells, and immunoglobulins, and consequently their functions, are markedly decreased as a result of plasmapheresis, particularly when this therapy is combined with immunosuppressive therapy [44]. Systemic lupus erythematosus patients receiving chronic peritoneal dialysis have a greater risk of peritonitis or catheter-related infections than non-SLE (and nondiabetic) patients with comparable clinical characteristics [45]. Immunoablation, with or without autologous stem cell transplantation, has emerged as an alternative treatment for patients with SLE not responding to other treatment modalities [46]. Data are scarce, and follow up is still short, but some severe infections such as herpes zoster (HZ), herpes simplex, and *Pneumocystis carinii* pneumonia (PCP) have been reported in these patients, most likely resulting from profound immunosuppression [46].

Infections as a cause of death

Infection is the primary cause of death in SLE patients in developing countries [19,47–54]. In a Chinese cohort of SLE patients followed from 1992 to 1996, 66% of deaths were caused by infections [52]. In a series of autopsies performed in SLE patients from Brazil, infections were responsible for 58% of all deaths; 34% of deaths were attributed to active SLE [19]. In developed countries, infection is also one of the most important causes of death among SLE patients and is considered the first or second most common cause of mortality in several studies [1,2,10,15,17,18,30,55,56]. In the multicenter European study of 1000 patients followed for more than 5 years, infections and disease activity were found to be responsible for over half of all deaths [2]. Similar data come from a study performed in France between 1960 and 1997; in this study active SLE and infections were responsible for 28% and 20% of deaths, respectively [10]. This high rate of mortality from infections is probably the result of the more aggressive use of corticosteroids, immunosuppressive drugs, and support therapy (including dialysis and critical care) in controlling the activity and complications of SLE.

Opportunistic infections are emerging as important causes of death in patients with SLE in both developed and developing countries. These infections are frequently associated with the increased use of high doses of corticosteroids and immunosuppressants and are often diagnosed only post mortem [8,17–19,43]. Table 1 summarizes the published data regarding infections as a cause of death in SLE; however, the different studies summarized in this table are not directly comparable, because as their methodologies vary significantly.

Types of infections occurring in systemic lupus erythematosus

Infections cause 25% to 50% of morbidity in SLE patients, and major infections are important causes of hospitalization. These infections have been described in different studies that are summarized in Table 2. The most frequent

Table 2
Morbidity from infections in patients with SLE

Author/year	Study characteristics ^a	Country	Patients <i>n</i>	Ethnicity	%	Patients infected %	Episodes of infections <i>n</i>
De Luis/1990 [17]	Chart review (1979–1987)	Spain	96	White ^b	100	55	102
Massardo/1991 [8]	Chart review (1972–1990)	Chile	159	Hispanic ^c	100	49	155
Petri/1992 [12,127]	Cohort (1989–1990) Follow up: 2 years	USA	261 ^d	African American ^c	51	14 ^d	51
				White	48		
				Other	1		
Oh/1993 [21]	Chart review (1988–1989)	Singapore	28	Asian (Chinese)	78	100	38
				Asian (Malay)	11		
				Asian (Indian or other)	11		
Shyam/1996 [54]	Chart review (1989–1994)	India	309	Asian (Indian) ^b	100	27	NA
Paton/1996 [11]	Chart review (1978–1993)	Malaysia	102	Asian (Chinese)	47	NA	240
				Asian (Malay)	46		
				Asian (Indian)	7		
Cervera/1999 [2]	Multinational cohort (1990) Follow up: 5 years	Europe	1000	White	97	27	389
				Black	2		
				Other	1		
Zonana-Nacach/2001 [16]	Cohort (1990–1996) Follow up: ~2 years	Mexico	200	Hispanic ^b	100	32	65
Al-Mayouf/2001 [40]	Chart review (1990–1998)	Saudi-Arabia	70 (children)	Arab ^b	100	41	NA
Nöel/2001 [10]	Chart review (1960–1997)	France	87	White ^b	100	40	57
Gladman/2002 [4,125]	Cohort (1987–1992) Follow up: 5 years	Canada	363	White ^c	86	26	148
				African American	7		
				Asian	6		
				Other	1		

Abbreviations: SLE, systemic lupus erythematosus; NA, not available.

^a Length of follow up noted only for cohort studies.

^b Inferred based on country of origin.

^c Inferred based on characteristics of cohort.

^d 354 Hospitalizations (number used as denominator).

infection sites and most common microorganisms affecting SLE patients are presented in Table 3. Like the studies summarized in Table 1, the studies presented in these tables are not directly comparable, because their methodologies vary substantially.

Bacterial infections

Common bacteria are responsible for most infections in SLE patients [2,4, 8–10,12,15,16,19,30,40,43]. The most frequently described bacteria are gram-negative bacilli [4,8,16,17,30] and gram-positive cocci [4,9,15]. Among the gram-positive bacteria, *Staphylococcus aureus* is a common pathogen that often gains entry through injured skin [9,10]. Infections with *S aureus* may be localized to the integument [9], but severe and fatal infections such as bacteremia [15,17,18,43,], pneumonia [13], and catheter-related infections [10] may also occur.

S pneumoniae in SLE patients typically causes pneumonia [10,15,16]; however, meningitis [15] and sepsis [15,43] also occur. The more severe presentations occur in those patients who either have associated inherited deficiencies of the early complement pathway or splenic dysfunction [23,24,28,36].

Table 3
Sites of infection and infectious organisms in patients with SLE

Author/year	Sites of infections (%)						Causal microorganisms			
	Respiratory	Skin	Urinary tract	CNS	Blood	Other	Bacteria	Virus	Fungus	Parasites
de Luis/ 1990 [17]	26	18	31	0	17	8	90 ^a	9	1	0
Massardo/ 1991 [8]	30	17	23	1	NA	29	74 ^a	8	15	3
Petri/1992 [12]	NA	NA	NA	NA	NA	NA	88 ^a	4 ^a	8 ^a	0
Oh/1993 [21]	29	32	8	0	13	18	86 ^a	11	3	0
Shyam/ 1996 [54]	54	5	17	0	0	24	82 ^{a,b}	7	11	0
Paton/ 1996 [11]	28	19	10	2	13	28	97 ^{a,c}	0 ^c	3 ^c	0 ^c
Cervera/ 1999 [2]	19	20	29	1	6	25	NA	NA	NA	NA
Zonana-Nacach/ 2001 [16]	12	23	26	0	0	39	71 ^a	13	16	0
Al-Mayouf/ 2001 [40]	NA	NA	28	NA	14	NA	NA	NA	NA	NA
Nöel/2001 [10]	40	NA	NA	NA	29	NA	82	16	2	0
Gladman/ 2002 [4]	29	23	18	3	5	22	65 ^a	27	6	2

Abbreviations: SLE, systemic lupus erythematosus; NA, not available.

^a Inferred from data presented; includes patients in whom no pathogen was isolated but who responded to antibiotic treatment.

^b *Mycobacterium tuberculosis* the most frequent isolate.

^c Only major infections included.

Infections with *Listeria monocytogenes* are rare, but meningitis and sepsis have been reported in patients receiving high doses of corticosteroids or immunosuppressive therapy [43,57] and in those with active SLE [57]. Therefore, listeriosis should be ruled out in critically ill SLE patients who present with infections of the CNS [57].

Gram-negative bacilli (*Escherichia coli*, *Klebsiella* spp, *Pseudomona* spp, among others) are often the cause of urinary tract infections [16,17,43], lower respiratory tract infections [15,16,43], and severe and lethal bacteremias [15,17,18, 30,43].

Infections by *Salmonella* occur mainly in SLE patients with lower levels of complement, splenic dysfunction, receiving immunosuppressive therapy, or ingesting desiccated rattlesnake [58–61]. The typical presentation is bacteremia [10,17,58,59], and the most commonly isolated species are *S choleraesuis*, *S enteritidis*, and *S arizona* [58–60]. In fact, SLE is the most frequent underlying disease in patients who present with salmonella bacteremia [58,59]. Infections with encapsulated organisms such as *N gonorrhoeae* and *N meningitidis* are infrequent in SLE patients unless there is an underlying complement deficiency or splenic dysfunction [23,24].

Other less common bacteria also result in infection in SLE patients. Nocardiosis is a rare and fatal opportunistic infection that involves mainly the lungs and the CNS [43,62,63]. The mortality rate in nocardial infections is 35%, but that rate doubles when there is CNS involvement [63].

Mycobacterial infections, mainly *M tuberculosis*, are important opportunistic infections in these patients, particularly in developing countries [19,54,64]. It is thus important to suspect and rule out tuberculosis in patients with SLE living in or coming from areas of the world where tuberculosis is endemic. Pulmonary tuberculosis is the most common presentation [10,15,17,64], but cases of miliary, urinary, osteoarticular, soft tissue, and CNS tuberculosis have also been described [16,64].

Infections caused by atypical mycobacteria have been reported in SLE patients receiving immunosuppressive therapy [43]. These infections are usually insidious rather than acute and are often localized in the musculoskeletal system [65,66]. The authors recently have had the opportunity to diagnose and treat two SLE patients with atypical mycobacterial infections. The first patient developed osteomyelitis of the thoracic vertebrae but presented only with mild pleuritic chest pain (thought to be related to lupus activity); chest and thoracic spine radiographs were not informative at that time. A few months later she was found to have *Mycobacterium avium intracellulare* on biopsy material obtained when thoracic spine radiographs (Fig. 1), and MR imaging studies clearly demonstrated vertebral and disc space involvement (Fig. 2). The second patient presented with an extremely large and deep cutaneous ulceration of the left lower extremity, initially thought to be related to active disease; deep tissue biopsies were taken from which *Mycobacteria chelonae* was isolated. These cases illustrate the difficulties usually encountered in diagnosing infections in the immunocompromised SLE patient.



Fig. 1. Lateral radiograph of the thoracic spine. There is loss of intervertebral disc space at T7-8 with loss of the endplate cortex anteriorly and little reactive bone formation. (Courtesy of Dr. Robert López-Ben, Division of Diagnostic Radiology, Department of Radiology, The University of Alabama at Birmingham, Birmingham, Alabama).

Viral infections

Herpes zoster is the most frequent viral infection [4,10,12,16,43,44,], occurring mainly in SLE patients with previous histories of nephritis, hemolytic anemia, thrombocytopenia, and previous use of cyclophosphamide [67]. Localized HZ is the most common clinical presentation and generally occurs during periods of disease quiescence and in patients receiving 20 mg or less of prednisone/day [67]. Disseminated HZ and bacterial superinfection may also occur and are usually related to the use of high doses of corticosteroids (prednisone \geq 60 mg/day) or immunosuppressants [43,67].

Cytomegalovirus (CMV) is another opportunistic infection occurring in SLE patients, especially in those receiving cyclophosphamide or high doses of corticosteroids [15,17,43] or in patients receiving plasmapheresis [44]. Pneumonia and encephalitis produced by CMV are fatal in most cases [15,18]. Risk behaviors leading to infection by retroviruses are not increased in SLE patients [68]; thus, retroviral infections have not been described with increased frequency.



Fig. 2. Magnetic resonance image of the thoracic spine. (A) Sagittal T1-weighted MR image of the thoracic spine. There is marked marrow edema in T7 and T8 vertebral bodies. An epidural mass bulges the posterior longitudinal ligament and compresses the spinal cord at this level. (B) Sagittal T1-weighted MR image of the thoracic spine with fat suppression after intravenous administration of gadolinium contrast. There is marked contrast enhancement of the vertebral bodies of T7 and T8. There is rim enhancement of the epidural mass and the contiguous posterior disc space is better appreciated. (Courtesy of Dr. Robert López-Ben, Division of Diagnostic Radiology, Department of Radiology, The University of Alabama at Birmingham, Birmingham, Alabama)

Nevertheless, infections with the human immunodeficiency virus need to be distinguished from SLE, because the illnesses share some clinical characteristics and some of the same autoantibodies [69].

Human parvovirus B19 DNA has been detected in patients with SLE, but its clinical relevance is unclear to date [70].

Fungal infections

Fungal infections can occur frequently in SLE patients receiving high doses of corticosteroids or immunosuppressive therapy [15,18,43]. The most common fungal infections are produced by *P carinii* and *Candida* spp. The risk factors for developing PCP are the use of high doses of corticosteroids or of immunosuppressive drugs as well as lymphopenia [43,71–75]. Even though PCP occurs infrequently, it has a high mortality rate [18,43,72,73]; therefore, PCP prophylaxis may be indicated in SLE patients who have these risk factors. Infections by *Candida* spp (mainly *Candida albicans*) are common in SLE patients [10,16,18,19,43]. The clinical spectrum includes oral and esophageal

mucosa infections as well as infections of the genitourinary tract [16]. Disseminated candidiasis, which is frequently fatal, occurs less often [15,17–19,43].

Disease flares, immunosuppressive therapy, leukopenia, and associated bacterial infections are risk factors for the development of aspergillosis in SLE patients [76]. There are only a few reported cases of aspergillosis; however, most of them have been lethal [15,76].

Parasitic infections

Disseminated strongyloidiasis with massive pulmonary hemorrhage was reported in a patient with SLE from Japan [77]. Visceral leishmaniasis was reported in a German patient [78]. Encephalitis caused by *Toxoplasma gondii* has been described in SLE patients [79]. The cases of strongyloidiasis and leishmaniasis did not occur in areas where these infections are endemic, and it is unclear how these patients became infected with these pathogens. It is important to take appropriate diagnostic measures, because these parasitic infections can simulate clinical presentations of active SLE when they include neurologic, pulmonary, and gastrointestinal manifestations.

Infections in scleroderma

Predisposing factors

Risk factors associated with infections in scleroderma patients include esophageal and pulmonary involvement, severe Raynaud's phenomenon, severe calcinosis, and the use of specific treatments for the management of the disease. Scleroderma patients with smooth muscle involvement of the esophagus are at increased risk of aspiration pneumonia, because these patients usually have lower esophageal sphincter dysfunction and severe gastroesophageal reflux [13,80–82]. To avoid postoperative infections, esophageal involvement should be considered and ruled out in patients with scleroderma lung selected to receive lung transplants [81,83]. Pneumonia has been described in scleroderma patients with pulmonary involvement, particularly in those with interstitial lung disease [5], suggesting that pulmonary fibrosis may be a predisposing factor for the development of pulmonary infections.

In scleroderma patients, severe Raynaud's phenomenon with digital ischemia and ulcerations increases the risk of localized superinfections, which may be complicated by gangrene [81]. Severe calcinosis has also been associated with bacterial infections, especially in the soft tissues around the calcific lesions [84]. Although there are no large studies from which to draw conclusive data, some reported cases show that the risk of infection relates to specific treatments. For example, the aggressive use of immunosuppression and autologous stem cell transplantation resulted in a lethal infection in a neutropenic scleroderma patient [85]. Pneumonia has been reported with cyclophosphamide and corticosteroid

use [86], and local infections have been reported in 10% of patients receiving subcutaneous relaxin [87].

Infections as a cause of death

In scleroderma patients, pulmonary complications cause 17% to 24% of the mortality [88,89]. Pneumonia has been described in scleroderma patients who died of pulmonary involvement [5]. In the Swedish scleroderma cohort studied by Hesselstrand et al [5], approximately 12% of deaths were caused by pneumonia and severe lung fibrosis occurring simultaneously. Aspiration pneumonia has also been described as a cause of death in scleroderma patients with esophageal involvement, often producing adult respiratory distress syndrome [13,82]. Unlike SLE, however, there are no conclusive data regarding infections as a predictive factor of mortality in scleroderma [5,88–91].

Types of infections occurring in scleroderma

Bacterial infections

Data about common bacterial infections in patients with scleroderma are limited to case reports. Group G streptococcus pyomyositis was described in a patient with scleroderma who was receiving chlorambucil [92], and soft tissue *S aureus* infection around multiple calcific lesions was reported in a patient with scleroderma and a long history of Raynaud's phenomenon [84]. Another scleroderma patient with lower gastrointestinal tract involvement was reported to have developed bacterial peritonitis secondary to colon perforation [93].

M avium intracellulare, an opportunistic infection, was the cause of septic arthritis in a scleroderma patient; he did not respond to medical treatment, refused surgical intervention, and went on to develop osteomyelitis and subsequently Charcot's arthropathy [94]. An ocular infection secondary to nocardia was described in a scleroderma patient receiving a moderate dose of corticosteroids [95].

A report from Japan describes an increased frequency of *Helicobacter pylori* infection in patients with scleroderma; a possible role of this infection in esophageal dysfunction has been suggested but remains unproven for now [96].

Viral and fungal infections

There are no reported cases of viral infections complicating the course of scleroderma. Nevertheless, Epstein-Barr virus and CMV have been described as triggering the onset of scleroderma, particularly in pediatric patients [97,98], and parvovirus B19 DNA has been detected in patients with scleroderma, but the clinical correlate of this finding is unclear at the present [99]. *P carinii* pneumonia has been reported in some patients with scleroderma. This infection is rare but has a rapid and usually fatal course. Therefore, an early diagnosis in patients with respiratory failure is important if the survival rate is to be improved [100].

Esophageal fungal infections have been described with the same frequency in scleroderma patients with and without esophageal involvement [101]; treatment

of these fungal infections, however, is not followed by improvement of esophageal motility.

Infections in polymyositis/dermatomyositis

Predisposing factors

Patients with PM/DM have a host of predisposing factors placing them at risk for developing infections. These factors include upper esophageal involvement, thoracic muscle myopathy, calcinosis cutis, and the use of immunosuppressive drugs.

Some patients with PM/DM have involvement of the striated muscle of the hypopharynx and the upper third of the esophagus resulting in altered swallowing, gastroesophageal reflux, and aspiration and a greater risk of developing aspiration pneumonia [6,7,13,80,102,103]. Likewise, the myopathy affecting the thoracic muscles, present in less than 5% to 10% of PM/DM patients, creates difficulty in handling bronchial secretions [6,7,102]. This difficulty may lead to the development of atelectasis and ventilatory insufficiency [7,103]. This ventilatory compromise can worsen the course of aspiration pneumonia, thereby increasing the risk of death from this complication [7,103].

Calcinosis cutis, frequently described in patients with juvenile dermatomyositis [6,102], is a known risk factor for the development of staphylococcal soft tissue and dermal infections around calcinotic lesions [104–106]. This risk probably results from the decreased granulocyte chemotaxis to *S aureus* that has been described in these patients [106]. These infections may cause severe growth retardation of the extremities and significant functional impairment, thus worsening the course of the disease [105].

To date, there are no large-scale studies comparing the use of immunosuppressive drugs and the incidence of infections. Reported case studies, however, suggest that the simultaneous use of corticosteroids and immunosuppressive drugs in the treatment of PM/DM could increase the risk of infections [107]. For example, a PM/DM patient treated with methotrexate (22.5 mg/week) and prednisone (50 mg/day) developed PCP [107], and a pediatric patient with severe dermatomyositis treated with methotrexate (25 mg/week) and prednisone (150 mg/day) developed disseminated nocardiosis [108].

Infections as a cause of death

Malignancy [6,7,102,109] and pulmonary complications [6,7,102,109,110] are the main causes of death among patients with PM/DM. Aspiration pneumonia is one of the most common pulmonary complications [6,7,13,102,103,109,110] and causes of death in PM/DM patients [7,103]. In the study published by Marie et al [7], aspiration pneumonia was reported in 17% of all PM/DM patients and was responsible for 30% of the mortality. Aspiration pneumonia has emerged as an independent predictive factor for PM/DM deterioration and as a risk factor for

death in PM/DM patients. Therefore, patients with esophageal and respiratory compromise should be diagnosed and treated early to decrease the probability of a fatal outcome [6,7,13,80,102,103].

Types of infections occurring in polymyositis/dermatomyositis

Bacterial infections

Aspiration pneumonia, produced by Gram-positive and anaerobic bacteria, is the most common infection, occurring in 15% to 20% of PM/DM patients [7,103].

S aureus infections involving the soft tissue and skin around calcinotic lesions are frequently described in patients with juvenile dermatomyositis and calcinosis cutis [104,106]. Other bacterial infections in dermatomyositis constitute only isolated reported cases. For example *Streptococcus pyogenes* myositis has been described in patients with juvenile and adult DM with or without calcinosis; in these patients the myopathy probably favored the bacterial colonization of muscle from bacteremia originating in dermal lesions [111,112].

Among the opportunistic infections, disseminated *Nocardia brasiliensis* involving the skin and the lungs was reported in a pediatric patient receiving immunosuppressive therapy with methotrexate and prednisone for severe dermatomyositis [108], and extra pulmonary infections produced by *Mycobacterium tuberculosis* and generalized *M avium intracellulare* have been described in patients with PM/DM [113,114]. Although opportunistic infections in these patients are uncommon, early diagnosis and adequate treatment are essential to improve survival.

Viral infections

Herpes zoster is a common viral infection in patients with PM/DM and usually occurs during periods of disease inactivity [115]. Cytomegalovirus is an uncommon opportunistic viral infection in patients with PM/DM; however, some cases of severe and fatal infection, such as interstitial pneumonia, have been noted in patients receiving corticosteroid or immunosuppressive therapy [116,117]. Some studies have demonstrated a temporal relationship between coxsackie virus, parvovirus B19, hepatitis C, and other enterovirus infections and the onset of PM/DM; however, the role of these pathogens in the etiology of PM/DM remains speculative [118–120].

Fungal infections

Pneumocystis carinii pneumonia is frequently fatal in patients with PM/DM. This infection has a rapid and severe course, and most patients require critical care support [71,121]. Known risk factors for the development of PCP are interstitial pulmonary disease [72], lymphopenia [71,72,121], and the use of corticosteroids [71,121] and immunosuppressive drugs [71]. Based on the often fatal course of PCP, patients with these risk factors can benefit from the initiation of PCP prophylaxis although there are no definite published guidelines.

Candidiasis is another fungal infection occurring in patients with dermatomyositis. In a very large study of more than 40,000 patients with various skin disorders, the frequency of mucocutaneous candidiasis was three times higher in patients with dermatomyositis, bullous pemphigous, tinea inguinalis, or condylomata acuminata than in the general population, suggesting that pre-existing dermal involvement may increase the susceptibility of patients with dermatomyositis to this infection [122].

Finally, disseminated histoplasmosis involving the muscles and fascia has been reported in a patient with dermatomyositis being treated with corticosteroids and methotrexate who was initially thought to have a disease flare [123].

Summary

In SLE, scleroderma, and PM/DM, infections are important causes of morbidity and mortality. This increased risk of developing infections is the result of immune abnormalities and of organ system manifestations associated with these diseases and their treatments. Common bacteria are responsible for most mild and lethal infections; however, opportunistic microorganisms cause death in some patients, particularly in those receiving high doses of corticosteroid and immunosuppressive therapy. Various viral and fungal infections also contribute to the morbidity and mortality associated with these diseases. Regardless of the cause of infections, adequate and prompt recognition and proper treatment of the infected patient are imperative. Thus, patients with these diseases, especially when receiving high doses of corticosteroids and immunosuppressive therapy, need to be monitored closely for these infections. This care and concern is necessary to ensure optimal patient outcomes, both in terms of morbidity and mortality.

References

- [1] Alarcón GS, McGwin Jr G, Bastian HM, et al. Systemic lupus erythematosus in three ethnic group VII. Predictors of early mortality in the LUMINA cohort. *Arthritis Rheum* 2001;45:191–202.
- [2] Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 5-year period. A multicenter prospective study of 1,000 patients. European Working Party on Systemic Lupus Erythematosus. *Medicine (Baltimore)* 1999;78:167–75.
- [3] Fessler BJ. Infectious diseases in systemic lupus erythematosus: risk factors, management and prophylaxis. *Bailliere's Best Pract Res Clin Rheumatol* 2002;16:281–91.
- [4] Gladman DD, Hussian F, Ibanez D, et al. The nature and outcome of infection in systemic lupus erythematosus. *Lupus* 2002;11:234–9.
- [5] Hesselstrand R, Scheja A, Akesson A. Mortality and causes of death in a Swedish series of systemic sclerosis patients. *Ann Rheum Dis* 1998;57:682–6.
- [6] Koler RA, Motemarano A. Dermatomyositis. *Am Fam Physician* 2001;64:1565–72.
- [7] Marie I, Hachulla E, Hatron PY, et al. Polymyositis and dermatomyositis: short term and long term outcome, and predictive factors of prognosis. *J Rheumatol* 2001;28:2230–7.
- [8] Massardo L, Martinez ME, Baro M, et al. Infections in systemic lupus erythematosus. [Infecciones en lupus eritematoso sistémico]. *Rev Med Chil* 1991;119:1115–22 [in Spanish].

- [9] Nived O, Sturfelt G, Wollheim F. Systemic lupus erythematosus and infection: a controlled and prospective study including an epidemiological group. *QJM* 1985;55:271–87.
- [10] Noel V, Lortholary O, Casassus P, et al. Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. *Ann Rheum Dis* 2001;60:1141–4.
- [11] Paton NI, Cheong IK, Kong NC, et al. Risk factors for infection in Malaysian patients with systemic lupus erythematosus. *QJM* 1996;89:531–8.
- [12] Petri M, Genovese M. Incidence of and risk factors for hospitalizations in systemic lupus erythematosus: a prospective study of the Hopkins lupus cohort. *J Rheumatol* 1992;19:1559–65.
- [13] Prakash UBS. Thoracic manifestations of the systemic autoimmune diseases. Respiratory complications in mixed connective tissue disease. *Clin Chest Med* 1998;19:733–46.
- [14] Rahman P, Gladman DD, Urowitz MB, et al. Early damage as measured by the SLICC/ACR damage index is a predictor of mortality in systemic lupus erythematosus. *Lupus* 2001;10:93–6.
- [15] Ward MM, Pyun E, Studenski S. Causes of death in systemic lupus erythematosus: long-term followup of an inception cohort. *Arthritis Rheum* 1995;38:1492–9.
- [16] Zonana-Nacach A, Camargo-Coronel A, Yañez P, et al. Infections in outpatients with systemic lupus erythematosus: a prospective study. *Lupus* 2001;10:505–10.
- [17] de Luis A, Pigrau C, Pahissa A, et al. Infections in 96 cases of systemic lupus erythematosus. [Infecciones en 96 casos de lupus eritematoso sistémico]. *Med Clin (Barc)* 1990;94:607–10 [in Spanish].
- [18] Hellmann DB, Petri M, Whiting-O’Keefe QE. Fatal infections in systemic lupus erythematosus: the role of opportunistic organisms. *Medicine (Baltimore)* 1987;66:341–8.
- [19] Iriya SM, Capelozzi VL, Calich I, et al. Causes of death in patients with systemic lupus erythematosus in Sao Paulo, Brazil: a study of 113 autopsies. *Arch Intern Med* 2001;161:1557–61.
- [20] Le Moing V, Leport C. Infections et lupus. [Infections and lupus]. *Rev Prat* 1998;48:637–42 [in French].
- [21] Oh HM, Chng HH, Boey ML, et al. Infections in systemic lupus erythematosus. *Singapore Med J* 1993;34:406–8.
- [22] Ginzler E, Diamond H, Kaplan D, et al. Computer analysis of factors influencing frequency of infection in systemic lupus erythematosus. *Arthritis Rheum* 1978;21:37–44.
- [23] Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. *Medicine (Baltimore)* 1984;63:243–73.
- [24] Mitchell SR, Nguyen PQ, Katz P. Increased risk of neisserial infections in systemic lupus erythematosus. *Semin Arthritis Rheum* 1990;20:174–84.
- [25] Garred P, Madsen HO, Halberg P, et al. Mannose-binding lectin polymorphisms and susceptibility to infection in systemic lupus erythematosus. *Arthritis Rheum* 1999;42:2145–52.
- [26] Garred P, Voss A, Madsen HO, et al. Association of mannose-binding lectin gene variation with disease severity and infections in a population-based cohort of systemic lupus erythematosus patients. *Genes Immun* 2001;2:442–50.
- [27] Bouza E, Moya JG, Munoz P. Infections in systemic lupus erythematosus and rheumatoid arthritis. *Infect Dis Clin North Am* 2001;15:335–61.
- [28] Petri M. Infection in systemic lupus erythematosus. *Rheum Dis Clin North Am* 1998;24:424–56.
- [29] Wilson JG, Ratnoff WD, Schur PH, et al. Decreased expression of the C3b/C4b receptor (CR1) and the C3d receptor (CR2) on B lymphocytes and of CR1 on neutrophils of patients with systemic lupus erythematosus. *Arthritis Rheum* 1986;29:739–47.
- [30] Kim WU, Min JK, Lee SH, et al. Causes of death in Korean patients with systemic lupus erythematosus: a single center retrospective study. *Clin Exp Rheumatol* 1999;17:539–45.
- [31] Hsieh SC, Tsai CY, Sun KH, et al. Decreased spontaneous and lipopolysaccharide stimulated production of interleukin 8 by polymorphonuclear neutrophils of patients with active systemic lupus erythematosus. *Clin Exp Rheumatol* 1994;12:627–33.

- [32] Boros P, Muryoi T, Spiera H, et al. Autoantibodies directed against different classes of Fc gamma R are found in sera of autoimmune patients. *J Immunol* 1993;150:2018–24.
- [33] Yu CL, Chang KL, Chiu CC, et al. Defective phagocytosis, decreased tumour necrosis factor-alpha production, and lymphocyte hyporesponsiveness predispose patients with systemic lupus erythematosus to infections. *Scand J Rheumatol* 1989;18:97–105.
- [34] Bernas BL, Petri M, Goldman D, et al. T helper cell dysfunction in systemic lupus erythematosus (SLE). Relation to disease activity. *J Clin Immunol* 1994;14:169–77.
- [35] Boumpas DT, Chrousos GP, Wilder RL, et al. Glucocorticoid therapy for immune-mediated disease: basic and clinical correlates. *Ann Intern Med* 1993;119:1198–208.
- [36] Cunha BA. Infections in nonleukopenic compromised hosts (diabetes mellitus, SLE, steroids, and asplenia) in critical care. *Crit Care Clin* 1998;14:264–82.
- [37] Duffy KN, Duffy CM, Gladman DD. Infection and disease activity in systemic lupus erythematosus: a review of hospitalized patients. *J Rheumatol* 1991;18:1180–4.
- [38] Iliopoulos AG, Tsokos GC. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. *Semin Arthritis Rheum* 1996;25:318–36.
- [39] Suh C-H, Jeong Y-S, Park H-C, et al. Risk factors for infection and role of C-reactive protein in Korean patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 2001;19:191–4.
- [40] Al-Mayouf SM, Al-Jumaah S, Bahabri S, et al. Infections associated with juvenile systemic lupus erythematosus. *Clin Exp Rheumatol* 2001;19:748–50.
- [41] Auphan N, DiDonato JA, Rosette C, et al. Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis. *Science* 1995;270:286–90.
- [42] Ortmann RA, Klippel JH. Update on cyclophosphamide for systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000;26:363–75.
- [43] Pryor BD, Bologna SB, Kahl LE. Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:1475–82.
- [44] Aringer M, Smolen JS, Graninger WB. Severe infections in plasmapheresis-treated systemic lupus erythematosus. *Arthritis Rheum* 1998;41:414–20.
- [45] Huang JW, Hung KY, Yen CJ, et al. Systemic lupus erythematosus and peritoneal dialysis: outcomes and infectious complications. *Perit Dial Int* 2001;21:143–7.
- [46] Traynor AE, Schroeder J, Rosa RM, et al. Treatment of severe systemic lupus erythematosus with high-dose chemotherapy and haemopoietic stem-cell transplantation: a phase I study. *Lancet* 2000;356:701–7.
- [47] Bellomio V, Spindler A, Lucero E, et al. Systemic lupus erythematosus: mortality and survival in Argentina. A multicenter study. *Lupus* 2000;9:377–81.
- [48] Harris EN, Williams E, Shah DJ, et al. Mortality of Jamaican patients with systemic lupus erythematosus. *Br J Rheumatol* 1989;28:113–7.
- [49] Hernández-Cruz B, Tapia N, Villa-Romero AR, et al. Risk factors associated with mortality in systemic lupus erythematosus. A case-control study in a tertiary care center in Mexico City. *Clin Exp Rheumatol* 2001;19:395–400.
- [50] Huicochea Grobet ZL, Berron R, Ortega Martell JA, et al. Survival up to 5 and 10 years of Mexican pediatric patients with systemic lupus erythematosus. Overhaul of 23 years experience. *Allergol Immunopathol (Madrid)* 1996;24:36–8.
- [51] Jindal B, Joshi K, Radotra BD, et al. Fatal complications of systemic lupus erythematosus—an autopsy study from North India. *Indian J Pathol Microbiol* 2000;43:311–7.
- [52] Mok CC, Lee KW, Ho CT, et al. A prospective study of survival and prognostic indicators of systemic lupus erythematosus in a southern Chinese population. *Rheumatology* 2000;39:399–406.
- [53] Rodríguez VE, González-Parés EN. Mortality study in Puerto Ricans with systemic lupus erythematosus. *P R Health Sc J* 2000;19:335–9.
- [54] Shyam C, Malaviya AN. Infection-related morbidity in systemic lupus erythematosus: a clinico-epidemiological study from northern India. *Rheumatol Int* 1996;16:1–3.

- [55] Jacobsen S, Petersen J, Ullman S, et al. Mortality and causes of death of 513 Danish patients with systemic lupus erythematosus. *Scand J Rheumatol* 1999;28:75–80.
- [56] Rosner S, Ginzler E, Diamond HS, et al. A multicenter study of outcome in systemic lupus erythematosus II. Cause of death. *Arthritis Rheum* 1982;25:612–7.
- [57] Kraus A, Cabral AR, Sifuentes-Osornio J, et al. Listeriosis in patients with connective tissue diseases. *J Rheumatol* 1994;21:635–8.
- [58] Abramson S, Kramer SB, Radin A, et al. Salmonella bacteremia in systemic lupus erythematosus. Eight year experience at a municipal hospital. *Arthritis Rheum* 1985;28: 75–9.
- [59] Chen YH, Chen TP, Lu PL, et al. Salmonella choleraesuis bacteremia in southern Taiwan. *Kaohsiung J Med Sci* 1999;15:202–8.
- [60] Kraus A, Guerra-Bautista G, Alarcón-Segovia D. Salmonella arizona arthritis and septicemia associated with rattlesnake ingestion by patients with connective tissue diseases. A dangerous complication of folk medicine. *J Rheumatol* 1991;18:1328–31.
- [61] Lim E, Koh W-H, Loh S-F, et al. Non-thyphoidal salmonellosis in patients with systemic lupus erythematosus. A study of fifty patients and a review of the literature. *Lupus* 2001;10:87–92.
- [62] Mc-Nab P, Fuentealba C, Ballesteros F, et al. Nocardia asteroides infection in a patient with systemic lupus erythematosus. [Infección por Nocardia asteroides en un paciente con lupus eritematoso sistémico]. *Rev Med Chil* 2000;128:526–8 [in Spanish].
- [63] Mok CC, Yuen KY, Lau CS. Nocardiosis in systemic lupus erythematosus. *Semin Arthritis Rheum* 1997;26:675–83.
- [64] Victorio-Navarra ST, Dy EE, Arroyo CG, et al. Tuberculosis among Filipino patients with systemic lupus erythematosus. *Semin Arthritis Rheum* 1996;26:628–34.
- [65] Hoffman GS, Myers RL, Stark FR, et al. Septic arthritis associated with mycobacterium avium: a case report and literature review. *J Rheumatol* 1978;5:199–209.
- [66] Zvetina JR, Demos TC, Rubinstein H. Mycobacterium intracellulare infection of the shoulder and spine in a patient with steroid-treated systemic lupus erythematosus. *Skeletal Radiol* 1982; 8:111–3.
- [67] Kahl LE. Herpes zoster infections in systemic lupus erythematosus: risk factors and outcome. *J Rheumatol* 1994;21:84–6.
- [68] Drevlow BE, Schilling EM, Khabbaz RF, et al. Retroviral risk factors in patients with autoimmune disease. *J Rheumatol* 1996;23:428–31.
- [69] Kopelman RG, Zolla-Pazner S. Association of human immunodeficiency virus infection and autoimmune phenomena. *Am J Med* 1988;84:82–8.
- [70] Hsu T-C, Tsay GJ. Human parvovirus B19 infection in patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 2001;40:152–7.
- [71] Godeau B, Coutant-Perronne V, Le Thi Huong D, et al. Pneumocystis carinii pneumonia in the course of connective tissue disease: report of 34 cases. *J Rheumatology* 1994;21:246–51.
- [72] Kadoya A, Okada J, Iikuni Y, et al. Risk factors for *Pneumocystis carinii* pneumonia in patients with polymyositis/dermatomyositis or systemic lupus erythematosus. *J Rheumatol* 1996;23: 1186–8.
- [73] Liam CK, Wang F. *Pneumocystis carinii* pneumonia in patients with systemic lupus erythematosus. *Lupus* 1992;1:379–85.
- [74] Porges AJ, Beattie SL, Ritchlin C, et al. Patients with systemic lupus erythematosus at risk for *Pneumocystis carinii* pneumonia. *J Rheumatol* 1992;19:1191–4.
- [75] Wainstein E, Neira O, Guzman L. Lupus erythematosus disseminatus and *Pneumocystis carinii* pneumonia. [Lupus eritematoso diseminado y neumonía a *Pneumocystis carinii*]. *Rev Med Chil* 1993;121:1422–5 [in Spanish].
- [76] Katz A, Ehrenfeld M, Livneh A, et al. Aspergillosis in systemic lupus erythematosus. *Semin Arthritis Rheum* 1996;26:635–40.
- [77] Setoyama M, Fukumaru S, Takasaki T, et al. SLE with death from acute massive pulmonary hemorrhage cause by disseminated strongyloidiasis. *Scan J Rheumatol* 1997;26:389–91.
- [78] Braun J, Sieper J, Schulte KL, et al. Visceral leishmaniasis mimicking a flare of systemic lupus erythematosus. *Clin Rheumatol* 1991;10:445–8.

- [79] Deleze M, Mintz G, del Carmen Mejia M. *Toxoplasma gondii* encephalitis in systemic lupus erythematosus. A neglected cause of treatable nervous system infection. *J Rheumatol* 1985;12:994–6.
- [80] Domenech E, Kelly J. Swallowing disorders. *Med Clin North Am* 1999;83:97–113.
- [81] Mitchell H, Bolster MB, Leroy EC. Scleroderma and related conditions. *Med Clin North Am* 1997;81:129–49.
- [82] Rajapakse CN, Bancewicz J, Jones CJ, et al. Pharyngo-oesophageal dysphagia in systemic sclerosis. *Ann Rheum Dis* 1981;40:612–4.
- [83] Rosas V, Conte JV, Yang SC, et al. Lung transplantation and systemic sclerosis. *Ann Transplant* 2000;5:38–43.
- [84] Pando J, Nashel DJ. Clinical images: progressive calcifications and draining lesions following staphylococcal infection in a patient with limited scleroderma. *Arthritis Rheum* 1998;41:373.
- [85] Binks M, Passweg JR, Furst D, et al. Phase I/II trial of autologous stem cell transplantation in systemic sclerosis: procedure related mortality and impact on skin disease. *Ann Rheum Dis* 2001;60:577–84.
- [86] Silver RM, Warrick JH, Kinsella MB, et al. Cyclophosphamide and low-dose prednisone therapy in patients with systemic sclerosis (scleroderma) with interstitial lung disease. *J Rheumatol* 1993;20:838–44.
- [87] Seibold JR, Korn JH, Simms R, et al. Recombinant human relaxin in the treatment of scleroderma. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000;132:871–9.
- [88] Ferri C, Valentini G, Cozzi F, et al. Systemic sclerosis. Demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine (Baltimore)* 2002;81:139–53.
- [89] Scussel-Lonzetti L, Joyal F, Raynauld JP, et al. Predicting mortality in systemic sclerosis. Analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. *Medicine (Baltimore)* 2002;81:154–67.
- [90] Jacobsen S, Halberg P, Ullman S. Mortality and causes of death of 344 Danish patients with systemic sclerosis (scleroderma). *British Journal of Radiology* 1998;37:750–5.
- [91] Nishioka K, Katayama I, Kondo H, et al. Epidemiological analysis of prognosis of 496 Japanese patients with progressive systemic sclerosis (SSc). Scleroderma Research Committee Japan. *J Dermatol* 1996;23:677–82.
- [92] Minor Jr RL, Baum S, Schulze-Delrieu KS. Pyomyositis in a patient with progressive systemic sclerosis. Case report and review of the literature. *Arch Intern Med* 1988;148:1453–5.
- [93] Pialoux G, Mouly F, Cadranel JF, et al. Infection of ascitic fluid by perforation of a sclerodermic colon. [Infection d'ascite par perforation sur colon sclerodermique]. *Gastroenterol Clin Biol* 1992;16:705–7 [in French].
- [94] Walz BH, Crosby LA. *Mycobacterium avium*-intracellulare infection of the knee joint. Case report. *Am J Knee Surg* 1995;8:35–7.
- [95] Ferry AP, Font RL, Weinberg RS, et al. Nocardial endophthalmitis: report of two cases studied histopathologically. *Br J Ophthalmol* 1988;72:55–61.
- [96] Yazawa N, Fujimoto M, Kikuchi K, et al. High seroprevalence of *Helicobacter pylori* infection in patients with systemic sclerosis: association with esophageal involvement. *J Rheumatology* 2000;27:1568–9.
- [97] Kahaleh MB, Leroy EC. Autoimmunity and vascular involvement in systemic sclerosis (SSc). *Autoimmunity* 1999;31:195–214.
- [98] Longo F, Saletta S, Lepore L, et al. Localized scleroderma after infection with Epstein-Barr virus. *Clin Exp Rheumatol* 1993;11:681–3.
- [99] Ferri C, Zakrzewska K, Longombardo G, et al. Parvovirus B19 infection of bone marrow in systemic sclerosis patients. *Clin Exp Rheumatol* 1999;17:718–20.
- [100] Ward MM, Donald F. *Pneumocystis carinii* pneumonia in patients with connective tissue diseases: the role of hospital experience in diagnosis and mortality. *Arthritis Rheum* 1999;42:780–9.
- [101] Zamost BJ, Hirschberg J, Ippoliti AF, et al. Esophagitis in scleroderma. Prevalence and risk factors. *Gastroenterol* 1987;92:421–8.
- [102] Kovacs SO, Kovacs SC. Dermatomyositis. *J Am Acad Dermatol* 1998;39:899–921.

- [103] Schwarz MI. Thoracic manifestations of the systemic autoimmune diseases. The lung in polymyositis. *Clin Chest Med* 1998;19:701–12.
- [104] Bahner D, Meller J, Stiefel M, et al. Juvenile dermatomyositis—acute recidivism or sepsis. [Juvenile dermatomyositis—akutes Rezidiv oder Sepsis]. *Nervenarzt* 1999;70:547–51 [in German].
- [105] Eisenstein D, Paller AS, Pachman LM. Juvenile dermatomyositis presenting with rash alone. *Pediatrics* 1997;100:391–2.
- [106] Moore EC, Cohen F, Douglas SD, et al. Staphylococcal infections in childhood dermatomyositis—association with the development of calcinosis, raised IgE concentrations and granulocyte chemotactic defect. *Ann Rheum Dis* 1992;51:378–83.
- [107] Kanik KS, Cash JM. Methotrexate. Does methotrexate increase the risk of infection or malignancy? *Rheum Dis Clin North Am* 1997;23:955–67.
- [108] Klein-Gitelman MS, Szer IS. Disseminated nocardia brasiliensis infection: an unusual complication of immunosuppressive treatment for childhood dermatomyositis. *J Rheumatol* 1991;18:1243–6.
- [109] Xue L, Chen X, Chen S. Prognostic factors of dermatomyositis: analysis of 119 cases. *Zhonghua Nei Ke Za Zhi* 1997;36:32–5 [in Chinese].
- [110] Amano K, Maruyama H, Mori S, et al. [Respiratory failure in polymyositis and dermatomyositis: differential diagnosis between pulmonary infection and interstitial pneumonitis]. *Kansenshogaku Zasshi* 1998;72:517–25 [in Japanese].
- [111] Casademont J, Roger N, Pedrol E, et al. Streptococcal myositis as a complication of juvenile dermatomyositis. *Neuromuscul Disord* 1991;1:375–7.
- [112] Soriano ER, Barcan L, Clara L, et al. Streptococcus pyomyositis occurring in a patient with dermatomyositis in a country with temperate climate. *J Rheumatol* 1992;19:1305–7.
- [113] Hernández-Cruz B, Sifuentes-Osornio J, Ponce de Leon RS, et al. Mycobacterium tuberculosis infection in patients with systemic rheumatic diseases. A case-series. *Clin Exper Rheumatol* 1999;17:289–96.
- [114] Schaller M, Korting HC, Meurer M, et al. Generalized mycobacterium avium-intracellulare infection due to immunosuppressive therapy of paraneoplastic dermatomyositis. [Generalisierte mycobacterium avium-intracellulare infektion immun suppressiver therapie einer paraneoplastischer dermatomyositis]. *Hautarzt* 1997;48:118–121 [in German].
- [115] Nagaoka S, Tani K, Ishigatsubo Y, et al. [Herpes zoster in patients with polymyositis and dermatomyositis]. *Kansenshogaku Zasshi* 1990;64:1394–9 [in Japanese].
- [116] Nishi K, Myoh S, Bandoh T, et al. [An autopsy case of dermatomyositis associated with interstitial pneumonia probably due to cytomegalovirus infection]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1992;30:1975–80 [in Japanese].
- [117] Yoshihara S, Fukuma N, Masago R. [Cytomegalovirus infection associated with immunosuppressive therapy in collagen vascular diseases]. *Ryumachi* 1999;39:740–8 [in Japanese].
- [118] Crowson AN, Magro CM, Dawood MR. A causal role for parvovirus B19 infection in adult dermatomyositis and other autoimmune syndromes. *J Cutan Pathol* 2000;27:505–15.
- [119] Fiore G, Giacovazzo F, Giacovazzo M. HCV and dermatomyositis: report of 5 cases of dermatomyositis in patients with HCV infection. *Riv Eur Sci Med Farmacol* 1996;18:197–201.
- [120] Lewkonja RM, Horne D, Dawood MR. Juvenile dermatomyositis in a child infected with human parvovirus B19. *Clin Infect Dis* 1995;21:430–2.
- [121] Bachelez H, Schremmer B, Cadranet J, et al. Fulminant *Pneumocystis carinii* pneumonia in 4 patients with dermatomyositis [clinical observation]. *Arch Intern Med* 1997;157:1501–3.
- [122] Henseler T. [Mucocutaneous candidiasis in patients with skin diseases]. *Mycoses* 1995;1:7–13 [in German].
- [123] Voloshin DK, Lacomis D, McMahon D. Disseminated histoplasmosis presenting as myositis and fasciitis in a patient with dermatomyositis. *Muscle Nerve* 1995;18:531–5.
- [124] Jacobsen S, Petersen J, Ullman S, et al. A multicentre study of 513 Danish patients with systemic lupus erythematosus. I. Disease manifestations and analyses of clinical subsets. *Clin Rheumatol* 1998;17:468–77.

- [125] Abu-Shakra M, Urowitz MB, Gladman DD, et al. Mortality studies in systemic lupus erythematosus. Results from a single center I. Causes of death. *J Rheumatol* 1995;22:1259–64.
- [126] Ward MM, Pyun E, Studenski S. Long-term survival in systemic lupus erythematosus. Patient characteristics associated with poorer outcomes. *Arthritis Rheum* 1995;38:274–83.
- [127] Petri M. Musculoskeletal complications of systemic lupus erythematosus in the Hopkins lupus cohort: an update. *Arthritis Rheum (Arthritis Care Res)* 1995;8:137–45.