Opportunistic infections in systemic lupus erythematosus

Opportunistic infections (OIs) are not frequently seen in systemic lupus erythematosus (SLE). However, when present they are very dangerous, being potentially fatal in the majority of cases. Immunosuppressive therapy is the strongest risk factor for OI and correlates with death during infective episodes, but there are other factors predisposing to infection in SLE patients, such as several defects of the immune system that are intrinsic to the disease. The diagnosis of OI in SLE may be overlooked, owing to the fact that SLE flares may mimic infection with fever and inflammatory syndrome, and needs special attention in patients at risk. Finally, we have to consider that OIs could be a trigger of SLE too.

KEYWORDS: apoptosis ▪ glucocorticoids ▪ immunosuppressive therapy ▪ infection ▪ microRNA ▪ opportunistic infection ▪ systemic lupus erythematosus

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As we know from the literature [1], infections are the second leading cause of death in systemic lupus erythematosus (SLE) patients (25%), immediately after the complications related to disease activity (26%). Infections are an important cause of hospitalization too, mostly if there are some concomitant conditions, such as an active disease with a high SLE disease activity index score, extensive use of immunosuppressants, long disease duration and protracted permanence in hospital. Thus, infection continues to be a critical problem in the clinical management of SLE, and clinicians should be aware of its possible occurrence especially when the patient presents with fever of unknown origin, often mimicking a SLE flare. In this special report, we discuss the major risk factors for infections, major microorganisms involved and the relationships between autoimmunity and infection. We have not attempted to perform complete analysis of the microorganisms responsible for SLE infections; instead, we aim to discuss some interesting aspects of opportunistic infections (OIs) in SLE.

Risk factors for infection in SLE patients

The susceptibility to infections in SLE patients may be explained by several intrinsic and acquired defects in the immune system, related to the disease itself or to immunosuppressive therapies. According to Navarro Zarza *et al.*, the most important factors suggesting community-acquired infections in SLE patients are immunosuppressive therapy (intravenous methylprednisolone and intravenous cyclophosphamide), while antimalarials seem to have a protective effect; fever at admission; active renal/mucocutaneous disease; leukopenia; lymphopenia; and a hospital permanence of more than 7 days [2]. Factors associated with nosocomial infections are prednisone, intravenous cyclophosphamide, azathioprine, involvement of the CNS, fever at admission, active disease at admission and a hospital stay of more than 7 days [2]. There are risk factors associated with all infections: duration of disease, number of days in hospital and organ involvement (renal, neurological, hematological and mucocutaneous involvement) [2]. OIs are those infections due to a microorganism ubiquitous in the environment that does not cause a disease in immunocompetent people, while representing the cause for an infectious disease in immunocompromised patients, such as autoimmune disease patients. Hellmann *et al.* found an OI in 34% of cases in a study on fatal infections in SLE and 66% of such OIs were fatal; immunosuppressive therapy was the strongest risk factor correlated with death during infection and there was no correlation between the occurrence of infection and total white bood cell count [3]. In our experience in 301 SLE patients admitted to our rheumatologic unit for various reasons in the last 10 years, all patients presenting with infection had been treated with glucocorticoid therapy and 89.5% of them had received immunosuppressive agents before infection developed. In our series, infection was the cause of hospitalization in 24 cases (8%), while an additional 14 cases acquired the infection during hospitalization. Other factors that predispose SLE patients to infection are reported

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in Box 1. All these factors represent abnormalities of the immune system that have been described in SLE, possibly contributing to the increased susceptibility to infection of SLE patients. In Table 1 we summarize the frequency of those microorganisms involved in the infections discussed in this work.

Bacterial & mycobacterial infections

In a study of infections in SLE performed by Ruiz-Irastorza *et al.*, *Escherichia coli* was the most frequent microorganism isolated (16%), followed by *Staphyloccocus aureus* (14%), *Mycobacterium tuberculosis* (14%) and *Streptococcus pneumoniae* (12%) [4]. Eighty three patients (29%) suffered from at least one major infection. Fifty five patients (66%) had one infection, 22 patients (27%) had two infections, five patients (6%) had three infections and one patient had nine major infections. Eleven of these 83 infections (13%) were nosocomial. Eight patients died as a consequence of infection: pneumonia was the cause of death in four cases, septic shock in three cases and peritonitis in one case. Erdozain *et al.* studied the incidence of tuberculosis (TB) infection in SLE patients [5]. The annual incidence of TB infection in the authors' area was 30 out of 100,000 individuals in a 10-year study period. The annual incidence of TB among SLE patients varied between 150 out of 100,000 patients in Turkey and 2450 out of 100,000 patients in India. TB was more frequent in SLE patients than expected in the general population but Erdozain's data compare favorably in terms of incidence, severity and outcome with those from highly endemic areas. In particular they found three clinically manifested cases of TB infection in 1603 patients (two cases of pulmonary TB and a case of tuberculous pleuritis). The authors did not see any case of disseminated infection and all patients had a good response to treatment. According to our experience, there is a low incidence of TB cases in SLE, so we would discourage an antimycobacterial prophylaxis with isoniazid in SLE patients. Nontuberculous mycobacteria are ubiquitous microorganisms in the environment and their infections have been described in patients affected by autoimmune diseases. *Mycobacterium chelonae*, *Mycobacterium avium–Mycobacterium intracellulare* complex, *Mycobacterium fortuitum* and *Mycobacterium haemophilum* are the most common mycobacteria involved in SLE patient infections with a frequency of 1.5% in a series of 725 SLE patients [6] and they tend to occur more chronically and heavily than *M. tuberculosis* infections, determining skin nodules, abscesses and cutaneous ulcers above all.

Box 1. Factors predisposing systemic lupus erythematosus patients to infection.

- Reduced $CD4^+$ T cells (due to disease and/or to corticosteroids)
- Reduced $CD25^+$ regulatory T cells
- Abnormal T-cell-mediated cytotoxicity
- Impaired chemotaxis and phagocytosis of macrophages and PMNs
- Complement deficiency
- Decreased expression of cellular complement receptors (CR1, CR2, CR3)
- Mannose-binding lectin deficiency
- Low levels of soluble Fc-γ receptor III
- Chronic inflammation and tissue damage

PMN: Polymorphonucleate.

Fungal infections

Fungal infections are not frequent in SLE. Chen *et al.* reported 15 cases (0.64%) during a 26-year period, in a retrospective study on a series of 2344 northern Taiwanese SLE patients [7]. In a series from southern Taiwan, *Cryptococcus neoformans*, *Candida albicans*, *Allescheria boydii*, *Aspergillus niger* and *Nocardia* were the fungal infective agents most frequently involved. The identified risk factors for these fungal infections were the use of cytotoxic drug therapy, heroin addiction, surgery, cardiac prostheses, antibiotic use, hemolytic anemia, active SLE (SLEDAI >7) and high doses of glucocorticoids (more than 1000 mg/month) [8]. Each fungal agent prefers a typical site, for example *C. neoformans* usually affects the CNS with meningitis, while less common sites are the lung and skin [9]. *Pneumocystis carinii*, nowadays known as *Pneumocystis jirovecii*, causes pneumonia in immunosuppressed transplant patients as well as autoimmune disease patients. It is an uncommon but often fatal infection in the case reports that we can find in the literature. Galeazzi *et al.* described a case of *P. carinii* infection where the pathogenesis of infection was related to a selective depletion of $CD4^+$ T lymphocytes due to high doses of steroids [10], as shown in other cases [11,12] or to the presence of anti-$CD4^+$ lymphocyte antibodies, already evidenced in SLE patients [13]. The frequency of *P. carinii* infection is quite variable in different autoimmune diseases, with higher numbers in Wegener's patients. Ward *et al.* evidenced a frequency of 89 out of 10,000 hospitalizations/year in patients affected by Wegener's granulomatosis and a frequency of 12 cases out of 10,000 hospitalizations/year in rheumatoid arthritis patients [14]. The authors evidenced that clinicians with a prior experience in dealing with

patients with *P. carinii* infection are facilitated in recognizing this infection in patients affected by connective tissue disease.

Viral infections

Among viral infections, the poliomavirus JC produces a latent infection in the general population; its reactivation is responsible for lytic infection of myelin-producing oligodendrocytes, which leads to progressive multifocal leukoencephalopaty (PML). PML is described in immunosuppressed patients, including chronic inflammatory diseases, in which immunosuppressive drugs, such as mycophenolate and rituximab, are the risk factors, even if less commonly than other immunosuppressive conditions (e.g., HIV). Particularly, SLE patients seem to have a greater predisposition to develop PML than patients with other rheumatic diseases (two-thirds of the cases of PML as yet described among rheumatic disease patients have been in SLE patents), even if the reason for this is not known (0.44% compared with a rate of PML in the background population of 0.2 out of 100,000 discharges) [15]. Many SLE patients affected by PML have been treated with only a modest level of immunosuppressives, suggesting that SLE itself could be a risk factor. A second risk factor could be the use of some biological therapeutic agents such as rituximab [16]. In patients with SLE, it is sometimes difficult to distinguish between PML and the neurological involvement of the disease itself, so PML is often underdiagnosed. PML must therefore be considered in the differential diagnosis when a SLE patient presents with unexplained neurologic symptoms or signs; moreover, negative PCR analysis on cerebrospinal fluid does not exclude the diagnosis of PML, so a biopsy should be considered in these cases.

Table 1. Prevalence of some microorganisms involved in systemic lupus erythematosus infections.

Type of infection	Microorganism	Frequency of total infections (%)
Bacterial	*Escherichia coli*	16
	Staphyloccocus aureus	14
	Mycobacterium tuberculosis	14
	Streptococcus pneumoniae	12
Fungal	*Cryptococcus neoformans*	0.6
	Candida albicans	
	Allescheria boydii	
	Aspergillus niger	
	Nocardia	
Viral	*Polyomavirus JC*	0.44

Data taken from [4,7,15].

Can infection induce SLE?

At the same time, OIs may act as a 'trigger' of SLE. Possible mechanisms are 'molecular mimicry'; increased apoptosis, with the delivery of previously masked autoantigens; mannose-binding lectin (MBL) deficiency; dysregulation of the miRNA control of gene expression. 'Molecular mimicry' mechanisms determine a cross-reactivity between antigens of infectious viruses and self-proteins; Epstein–Barr virus (EBV) is a human herpesvirus that persists in the memory B cells of the majority of the world population in a latent form. Primary EBV infection is asymptomatic or causes a self-limiting disease, infectious mononucleosis. Virus latency is associated with a wide variety of neoplasms, some occurring in immune-suppressed individuals. In immune suppressed and infectious mononucleosis patients, an increased viral load can be detected in the blood. Enhanced lytic replication may result in new infection – and transformation – events and this is a risk factor for both malignant transformation and the development of an autoimmune disease. An increased viral load or a variation in the presentation of a subset of lytic or latent EBV proteins that cross-react with cellular antigens may trigger pathogenic processes through molecular mimicry that result in SLE [17]. Increased apoptosis, due to infections or drugs, causes increased exposure of the target antigens and subsequent production of the corresponding autoantibodies. Under certain conditions, increased phagocytosis of nuclear material may be found in a subgroup of patients with SLE. Clearance deficiency leads to the accumulation of apoptotic cells and could break self-tolerance. Furthermore, enhanced uptake of nuclear immune complexes may maintain chronic autoimmunity in patients with SLE [18]. MBL, a calcium-dependent serum lectin secreted by the liver as an acute-phase protein, is structurally homologous to C1q, so a low serum MBL, as demonstrated in some gene polymorphisms of SLE, can cause defective activation of the complement system and this fact leads to impaired complement-mediated clearance of immune complexes suggesting that MBL deficiency not only increases infection risk, but might predispose to the development of immune complex disease such as SLE [19]. miRNAs are noncoding RNAs that control gene expression by directing their mRNA for degradation

and/or translation repression. miRNAs are mediators of the so-called mechanism of RNA interference (RNAi), which is involved in post-transcriptional regulation or gene expression in many eukaryotes; they are important regulators for cell differentiation, proliferation, growth, mobility and apoptosis, so we can understand how dysregulation of miRNA function may lead to cancer, cardiovascular disease, immune dysfunction and metabolic diseases. Among autoimmune diseases, in rheumatoid arthritis there is an abnormal expression of miRNA 146, 155 and 223; in SLE there are 16 miRNAs differentially expressed compared with normal controls. Dysregulation of miRNAs due to viral infections, such as EBV or HCV, may promote the development of autoimmunity through their association with components of the RNAi pathway [20].

On the other hand, some infections could protect against SLE. As discussed at the 7th Autoimmunity Congress in Ljubljana, Slovenia, there is a high prevalence of SLE in African descendents living in North America or Europe compared to western Africa. A possible explanation for the low prevalence in Africa could be that malaria and parasitic infections alter the immune response in a such a way as to protect against SLE [21]. In conclusion, as Kivity and coworkers state, autoimmunity can be triggered by many environmental factors, among which infectious agents are pivotal [22]. An autoimmune disease can be induced or triggered by infectious agents, which can also determine its clinical manifestations. Most infectious agents, such as viruses, bacteria and parasites, can induce autoimmunity via different mechanisms. In many cases, it is not a single infection but rather the 'burden of infections' from childhood that is responsible for the induction of autoimmunity. The development of an autoimmune disease after infection tends to occur in genetically susceptible individuals. By contrast, some infections can protect individuals from specific autoimmune diseases (i.e., there is an association between parasitic load and the degree of autoimmunity) [23].

Management of SLE infections

According to the European League Against Rheumatism (EULAR), every SLE patient should be screened for HIV, HCV, HBV and CMV infection before undergoing immunosuppressive therapy, including glucocorticoids. Furthermore, *M. tuberculosis* infection should be searched for in endemic areas [24]. In addition, we have to observe that SLE flares may mimic infection with fever, inflammatory syndrome and chills and this fact can make it difficult to differentiate between infection and SLE itself. Elevated serum procalcitonin (PCT) levels have been reported to be predictive of bacterial infection but this is not true for SLE patients. In a retrospective study on 53 hospitalized SLE women and seven hospitalized SLE men, five patients had systemic infection. Only one patient had increased PCT levels suggesting that PCT levels are in normal range both in infected and noninfected SLE patients [25]. C-reactive protein (CRP) levels are claimed not to be increased during SLE flares [26]. However, CRP levels may also be increased in SLE patients with no correlation with disease activity [27]. In a retrospective series of 124 SLE patients without infection, Williams *et al.* reported that only 30% of patients had normal CRP levels during the course of the disease, with a mean CRP level as high as 53 ± 76 ng/ml. Half of the 30% of SLE patients without elevated serum CRP were considered not to present clinically active SLE. One of the authors' explanations for the absence of CRP elevation in some patients was a defect of the IL-1 and IL-2 signaling pathways in SLE [28]. This suggests that CRP is not a reliable marker for inflammation and/or infection in SLE patients, and that further studies are necessary to individuate sensitive and specific markers able to differentiate infection from disease activity in SLE.

Future perspective

SLE flares may mimic infection with fever and inflammatory syndrome; this makes differential diagnosis difficult. Further studies are

Executive summary

- Opportunistic infections represent approximately one-third of all cases of infections in systemic lupus erythematosus (SLE) patients and most of them are potentially fatal.
- The susceptibility to infection in SLE patients may be explained by several risk factors, above all, defects in immune system caused by SLE and immunosuppressive therapies.
- Opportunistic infections could be a trigger of SLE through 'molecular mimicry', increased apoptosis, mannose-binding lectin deficiency and dysregulation of miRNAs.

necessary to individuate sensitive and specific markers able to differentiate infection from disease activity in SLE.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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