Late-onset lupus: facts and fiction

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As the world population ages, it is not uncommon to encounter patients who develop systemic lupus erythematosus (SLE) late in life. However, not much is known about SLE in this age group, but it clearly differs from younger onset disease in its epidemiologic, clinical and serological features; moreover, it is often misdiagnosed as drug-induced SLE or another rheumatic disease. As a result, a significant delay in its diagnosis is commonly observed. The choice of therapeutic agents in patients from this age group must also be very carefully considered. Immunosenescence, the development of $CD8^+$ T-cell oligoclonal expansion and an abnormal apoptosis signaling pathway are some of the possible biologic mechanisms underlying late-onset SLE. Some misconceptions (fiction) are not uncommon in this subset of patients; they are gradually being replaced by facts as new data emerge.

Systemic lupus erythematosus (SLE) is associated with substantial morbidity and increased mortality. The reported prevalence of SLE in the USA is 6–241 cases per 100,000 inhabitants [1,2], whereas the incidence is 1–7.6 [3,4]. Due to improved detection of milder forms of the disease, the incidence has nearly tripled in the last 40 years [5]. SLE predominantly affects women, particularly during their childbearing years [6]. However, life expectancy increased substantially in the second half of the 20th century with the diagnosis of SLE among older individuals increasing in parallel; in fact, lupus late in life may occur in up to 25% of all patients [7]. As the age at onset has been recognized as having a modifying effect on the clinical manifestations of SLE, late-onset disease is considered a specific SLE patient subset; however, relatively few studies have focused on this patient subgroup. As new studies emerge, some misconceptions (fictions) are being replaced by facts. We are now summarizing the available literature data regarding this SLE patient subset.

Epidemiology of late-onset SLE

The majority of studies have arbitrarily defined SLE as late onset if it is diagnosed at age 50 or beyond [6,8,9]. However, in recent studies a cut-off age of 65 years or even greater has been proposed [10–12], given the increased life expectancy of the general population [101].

The frequency of late-onset SLE among published series ranges from 4 to 25% [7,9,13–16]. This wide range is probably due to the different cut-off ages used in various studies; however, the possible underestimation of the disease in this patient subgroup needs to be considered, as it may be diagnosed as drug-induced SLE, rheumatoid arthritis, polymyalgia rheumatica or vasculitis.

Striking differences between late- and adult-onset SLE have been reported. First, and as noted in Table 1, the female:male sex ratio declines from a 10–11:1 ratio in the younger adult to a 4:1 ratio in the older adult [6,7,10,13,16–30]; however, this has not been uniformly reported in all studies [8,12,31–34]. This drastic reduction has been attributed to the absence of the effect of sex hormones, which is present in the younger patients [35]. Second, a Caucasian predominance has been reported in late-onset lupus in studies involving multi-ethnic groups [17,26,36]. It is not clear why this is, although data from the Lupus in Minorities: Nature versus Nurture (LUMINA) study [Unpublished Observ., May, 2008], PROFILE (genotype determining the phenotype) and other studies, suggest that African–Americans and Hispanics develop lupus earlier in life because their genetic load in terms of susceptibility to lupus is, overall, of greater magnitude than it is in the Caucasian patients [17,26,27,37].

Clinical features & diagnosis of late-onset SLE

Of interest, the clinical manifestations of late-onset SLE have been found to be comparable in patients with late-onset disease, independent of the cut-off age chosen to define it [13]. In contrast to patients with early-onset disease, late-onset lupus, particularly at the beginning of its course, is characterized by the presence of nonspecific symptoms such as weight loss, arthralgias, myalgias, weakness, fatigue, pyrexia and cognitive or affective dysfunction [12,33,38,39]. More specific clinical manifestations may occur later; the most frequent ones being serositis, lung involvement (particularly interstitial lung disease), sicca and cytopenias [9,12,17,20,33,40]. In addition, an increased frequency of neurologic manifestations such as headache,

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Table 1. Female:male ratio in systemic lupus erythematosus patients with early and late onset.

Study	Number of patients studied		Study type	F:M ratio		Risk reduction F:M	Ref.
	Early	Late		Early	Late		
Boddaert *et al.* (2004)*	4700*	714*	Medical records review	10.6	4.4	2.4	[6]
Boddaert *et al.* (2004)	114	47	Medical records review	13.3	2.6	5.1	[6]
Mok *et al.* (2005)	213	22	Longitudinal cohort	13	6	2.2	[64]
Gomez *et al.* (2006)	259	91	Medical records review	11	3	3.7	[7]
Karoubi *et al.* (2007)	11	11	Longitudinal cohort	6.3	5.5	1.2	[41]
Padovan *et al.* (2007)	163	62	Longitudinal cohort	11	5	2.2	[13]
LUMINA† database (2008)	542	93	Longitudinal cohort	9.6	5.6	1.7	

**Pooled data analysis from 22 studies.*

†*Lupus in minorities: nature versus nurture* [Unpublished Observ., May 2008].

neurocognitive impairment and peripheral neuropathy have been reported [13,27]. On the other hand, seizures, psychosis [8,16,21,34], renal involvement [7,18,27,40], integument manifestations [6,7,18,40] and arthritis [12,18,33] occur less frequently in these patients than in adult-onset SLE. These data are summarized in Box 1. Although renal involvement is not frequent, the long-term renal prognosis in these patients is not necessarily better, since they tend to accrue more renal damage and experience a decreased overall survival [11].

In contrast to patients with younger-onset SLE who tend to develop the disease in a relatively short time period, the so-called acute-onset lupus [36], older patients are more likely to have an insidious presentation, which implies that certain time elapses from the first manifestation or ACR criterion until the diagnosis is made or four ACR criteria are met [13]; this interval has been reported to vary from 5 to 60 months [10,13,17–19,21,24,41]. Thus, late-onset lupus patients have a fewer number of ACR criteria for the classification of SLE than the younger-onset patients at presentation. Atypical presentations, nonspecific manifestations, concurrent disease and the fact that SLE is thought not to occur in this age group may contribute to a delayed diagnosis, while true insidious presentation is also more likely to occur in these patients.

Box 1. Clinical manifestations of systemic lupus erythematosus in patients with late-onset disease.

Infrequent

- Seizures
- Psychosis
- Renal involvement
- Integument manifestations
- Arthritis

Common

- Nonspecific symptoms (fatigue, weakness etc.)
- Serositis
- Lung involvement
- Sjögren's syndrome
- Cytopenias
- Cognitive dysfunction

Patients with late-onset lupus may exhibit a different autoantibody profile to patients with younger-onset disease; however, significant variability exists among the different published studies. For example, a lower frequency of anti-dsDNA antibodies has been reported in some studies [6,19,32,40], whereas levels similar to the ones occurring in younger patients have been reported in others [10,24,26,39]; likewise, some, but not all, studies have reported a lower frequency of hypocomplementemia [16,24,26,32,33,38,39,42]. Anti-RNP [6,12,33] and anti-Sm [27,34] antibodies probably occur at a lower frequency, but other autoantibodies have been reported at higher frequency in these late-onset patients, but not consistently [39]; they include rheumatoid factor [13,21,40] and anti-Ro and anti-La antibodies [11,12,16], which correlate with the increased frequency of Sjögren's syndrome seen in these patients. Patient selection and the total number of patients studied may explain the differences in the frequencies of autoantibodies reported by different investigators in late-onset SLE [39].

Differential diagnosis

Although we have emphasized in this review the importance of considering the diagnosis of SLE in elderly individuals presenting with nonspecific complaints, it is important to point out that other diagnoses need to be considered under these circumstances. Of particular importance will be the diagnosis of disorders that will require a totally different therapeutic approach, such as occult malignancies and infectious processes.

Treatment of late-onset SLE

The basic principles on which therapeutic strategies rest are the same regardless of age at disease onset. However, as elderly patients may be on multiple other medications, it is necessary to consider that the pharmacokinetics of the drugs commonly used for lupus may be significantly altered (absorption, distribution, metabolism and excretion) [43].

Antimalarial agents, such as hydroxychloroquine, should be prescribed to all patients whether or not they are receiving other medications such as glucocorticoids and immunosuppressants, as they have been associated with a decreased frequency of flares, less damage accrual and improved survival [44–49].

NSAIDs, non-narcotic analgesics and/or low doses of glucocorticoids can be used; however, the diminished renal reserve commonly observed in older individuals should be taken into account, particularly with regards to NSAIDs; moreover, the increased risk these older patients have of developing osteoporosis and atherosclerosis should also be considered [50,51].

The involvement of main organs such as the kidneys, lungs, blood or the CNS may require high doses of glucocorticoids and the use of immunosuppressant drugs such as cyclophosphamide, azathioprine and mycophenolate mofetil. These drugs should be used with great caution.

Immunosenescence & late-onset SLE

Aging is associated with a decline in immune competence or immunosenescence. The thymus gradually becomes smaller as we age, but some thymic function remains; however, the overall output of T cells emigrating from the thymus is decreased. This results in a severely limited immune response [52–55]. The diversity of T-cell receptors repertoire diminishes, and extensive oligoclonal expansion often develops, particularly of $CD8^+$ T cells [56–59]; this is likely a consequence of age-related abnormal apoptosis signaling. T-cell senescence has been associated with defects in genes involved in cell-cycle arrest, such as p21; in turn, p 21-deficient animals develop a lupus-like disease [60].

Aging is also associated with diminished B-cell lymphopoiesis, which contributes to the peripheral accumulation of self-reactive B cells and antigen-experienced B cells (marginal zone, $CD5^+$ b1-like and memory) [61]. A shift from a Th1 to Th2 cytokine profile has been postulated to account for the increased production of some autoantibodies in the elderly, as seen in patients with late-onset lupus (RF, anti-Ro and anti-La antibodies) [60].

Changes in the cytokine profile, particularly in the pro-inflammatory cytokines IL-6 and tumor necrosis factor-α, may in part explain the development of autoimmune disease in elderly individuals. Likewise, a decreased production of IL-2 (with the consequent reduction in the activation of T regulatory cells) has been shown with aging [54].

In conclusion, the abnormalities observed in aging individuals in terms of their T-cell and B-cell function and cytokine profile (immunosenescence) may predispose them to the occurrence of autoimmune disease.

Outcome

Despite the fact that, overall, patients with late-onset lupus exhibit a milder disease with less major organ involvement and lower levels of disease activity [13,27,32], they do not have a better outcome than patients with disease beginning earlier in life. In fact, older-onset patients tend to accrue more damage than patients with disease onset at a younger age [27,62,63]. This is probably due to the negative impact of age and associated comorbidities, and the specific effect of lupus in these patients. In addition, higher mortality rates have been observed in this patient subset than in patients with younger-onset disease [6,10,27,64].

Future perspective

As awareness that SLE can occur for the first time in older individuals permeates to the general medical community, bringing down the old dogma that lupus is a disease of younger individuals, we should expect a less pronounced delay in the diagnosis of SLE among patients in this age group. Ongoing and future studies of large cohorts will certainly advance our knowledge about this SLE subset, including the possible identification of specific genetic markers, as well as the development of better therapeutic alternatives.

A summary of the points discussed in this paper is presented in Table 2.

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Table 2. Facts and fiction in late-onset systemic lupus erythematosus.

Fiction	Facts
Lupus occurs only in young women	Lupus may occur at any age and in both genders; it does occur in the elderly, in whom the F:M ratio is less pronounced
The ethnic distribution of late-onset lupus is the same as that in younger-onset SLE	There is a predominance of Caucasians in this SLE subset
Older-onset SLE patients exhibit the same clinical manifestations that those with younger-onset disease	Late-onset lupus has a distinct clinical profile: increased occurrence of nonspecific symptoms, serositis, lung involvement, Sjogren's syndrome, cytopenias, cognitive dysfunction, and decreased occurrence of seizures, psychosis, renal involvement, integument manifestations and arthritis
The frequency of antibodies is the same than in younger-onset patients	The autoantibody profile of late-onset lupus is characterized by a lower frequency of anti-RNP and anti-Sm antibodies, a variable frequency of anti-dsDNA antibodies and hypocomplementemia and a higher frequency of RF and of anti-Ro and anti-La antibodies
Patients with late-onset disease exhibit lower disease activity and have a better outcome in terms of damage and survival	Despite the fact that late-onset lupus patients exhibit a milder disease, they tend to accrue damage faster and to have higher mortality rates than patients with younger-onset disease
Treatment is the same as in younger-onset disease	Treatment must consider the altered pharmacokinetics associated with age; the medications must be used with great caution
Patients have a disminished production of auto-antibodies due to immunosenescence	Immunosenescence is associated with immune dysregulation, resulting in severely limited immune response and increased production of some auto-antibodies

RF: Rheumatoid factor; SLE: Systemic lupus erythematosus.

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