EDITORIAL

Late-onset systemic lupus erythematosus: clinical manifestations, course, and prognosis

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Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disease with a wide spectrum of clinical and laboratory manifestations involving almost all organs and tissues. Both genetic and environmental factors are suspected to play a role in its etiology. SLE affects women 9 times more frequently than men, mainly at a child-bearing age. Moreover, it has diverse presentation, course, severity, and response to treatment. Therefore, it has been suggested that it represents a syndrome rather that a single disease. During its course, periods of flares are intercepted by periods of remission inevitably leading to damage caused by disease and immunosuppressive therapy.[1]

Differences in the course and prognosis of SLE have been ascribed to ethnicity, sex, and age of onset. Predominance of young women and frequent exacerbations during pregnancy suggest a role of estrogens as a precipitating factor. However, the levels of estradiol and progesterone are lower in the second and third trimesters in pregnant SLE patients compared with healthy pregnant women.[1] In about 3% to 18% of cases, the disease is diagnosed later in life, over the age of 50 years, and is called late-onset SLE.[2] The development of new immunological tests as well as the introduction of new, revised diagnostic criteria enabled to diagnose some of the atypical, benign cases, particularly in elderly patients.[3] It is generally believed that in this form of SLE the onset is more insidious and it has a more benign course with a lower incidence of malar rash, photosensitivity, purpura, alopecia, Raynaud phenomenon, nephritis, and central nervous system involvement, but a higher prevalence of pleuritis and pericarditis, pulmonary involvement, Sjögren syndrome, and arthritis.[1,4] There are contradictory data as to whether late-onset SLE is associated with a better prognosis than an early-onset disease.[5,6] Recent studies have shown that older age at onset has a negative impact on morbidity and mortality owing to a higher frequency of comorbid conditions and organ damage, as well as coexisting classic vascular risk factors.[6,7]

In the current issue of this journal, Jeleniewicz et al.[8] described 20 patients with late-onset SLE (diagnosed at the age of 50 years or later), identified among a larger group of 230 consecutive SLE patients treated at the University Medical Centre in Poland between 2004 and 2014. The authors conducted a retrospective analysis of clinical manifestations of late-onset SLE, including comorbidities and the treatment of SLE. The incidence of clinical features and immunological abnormalities was then compared with the group of 108 SLE patients with an early-onset of the disease. The authors showed that malar rash, photosensitivity, and other skin manifestations as well as nephropathy, vasculitis, and central nervous system involvement were significantly less common among patients with the late-onset SLE compared to its early form. No differences were found regarding the incidence of arthritis, serositis, and general symptoms, Raynaud phenomenon, and cytopenias. The most common SLE manifestations in the late-onset group were arthritis, rash, nephropathy, photosensitivity, mouth ulcerations, fever, leukopenia, and thrombocytopenia. Delay in diagnosis in the late-onset group was on average 31.7 months. Among immunological findings, anti-Smith antigen antibodies, antibodies against ribonucleoprotein, and hypocomplementemia were more frequently observed in early-onset SLE. In women, late-onset SLE was characterized by a milder course of the disease. The 4 male patients with late-onset SLE had a severe course of the disease with an acute onset. All of the above findings are mostly in line with the literature data[5-7,9] with only minor differences, mainly due to a relatively small size of the Polish late-onset SLE group.[8]

An interesting issue brought up by some authors is the effect of the age at onset of SLE on survival. Merola et al.[9] showed that the overall 10-year survival was slightly higher among younger patients. A similar observation was made in the

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TABLE 1 Comparison of epidemiological and clinical features, laboratory findings, treatment, and prognosis of late- and early-onset systemic lupus erythematosus

	Late-onset SLE (≥50 years)	Early-onset SLE (<50 years)
frequency, % of all SLE cases[a]	3–18	82–97
female/male ratio[a]	lower (2.5–9)	higher (9–14.4)
clinical manifestations	more frequently: arthritis, pleuritis, pericarditis, myositis, pulmonary fibrosis, associated Sjögren's syndrome	more frequently: malar rash, photosensitivity, purpura, vasculitis, Raynaud phenomenon, lymphadenopathy, neuropsychiatric lupus, lupus nephritis
serological abnormalities	more frequently RF, less frequent hypocomplementemia	more frequently anti-dsDNA, anti-RNP, anti-SM antibodies, more frequent hypocomplementemia
disease onset	usually insidious	usually overt
delay to diagnosis, mo	9.6 (4.8–24)[b] 37.1 (0–144)[c]	6 (2.4–12)[b] –
disease course	usually benign	more severe with acute flares and shorter periods of remission
treatment	according to manifestation usually: NSAIDs, antimalarial drugs, low to moderate doses of corticosteroids, azathioprine, methotrexate rarely: cyclophosphamide and mycophenolate mofetil	according to manifestation usually: antimalarial drugs, moderate-to-high doses of corticosteroids, cyclophosphamide, and mycophenolate mofetil biological therapy (rituximab, belimumab)
concomitant diseases	cardiovascular, infections, diabetes, malignancies	rare
survival[a], %	5-year: 84 10-year: 71 15-year: 59	5-year: 95 10-year: 95 15-year: 92
most frequent death causes[9,12,15]	infections, cardiovascular disorders, malignancies, drug-induced complications	mostly SLE and treatment-related: lupus nephritis, infections (sepsis)

a data from Arnaud et al.[12]
b data from Alonso et al.[6]; median (interquartile range)
c data from Jeleniewicz et al.[8]; mean value and range

Abbreviations: anti-dsDNA, anti-double-stranded DNA antibodies; anti-RNP, antibodies against ribonucleoprotein; anti-SM, anti-Smith antigen antibodies; NSAIDs, nonsteroidal anti-inflammatory drugs; RF, rheumatoid factor; SLE, systemic lupus erythematosus

Chinese population with SLE.[10] This, however, did not seem to be associated with the disease activity and damage scores. The most prominent cause of death in this group compared with patients with juvenile-onset (<18 years) and early-onset (< 45 years) SLE was infection, even though they were not intensively treated. In another series of late-onset SLE in women from Taiwan, Chen et al.[11] showed a higher mortality risk due to cardiovascular diseases, malignancies, and infections. SLE is an independent risk factor for myocardial infarction, after adjusting for other cardiovascular risk factors.[12] Recent data have demonstrated that ischemic heart disease was the leading cause of death among SLE patients, and age (among other factors) was an independent predictor of cardiovascular disease-related mortality in SLE.[13]

SLE tends to have a milder course in the older age while the prognosis seems to be worse. It is therefore interesting to see whether the milder severity of the disease justifies a less intensive treatment in the late-onset group of patients. According to literature data, fewer late-onset patients require cytotoxic drugs, such as cyclophosphamide and mycophenolate mofetil, or high doses of corticosteroids.[2,12] Treating SLE in older patients is a challenge, with possible drug interactions in patients with concomitant diseases and decreased renal clearance. The management of the disease, like in younger patients, depends on the type and severity of SLE manifestations. Antimalarial drugs (chloroquine or, preferably, hydroxychloroquine) should be used in all SLE patients, if not contraindicated. Contraindications include hypersensitivity or any type of retinopathy including age-related macular degeneration.[14] Therefore, ophthalmological examinations should be performed more frequently in older SLE patients receiving antimalarial drugs. As shown by Jeleniewicz et al.[8] arthritis is the most prominent manifestation in the late-onset group, and nonsteroidal anti-inflammatory drugs are usually the first treatment choice. They should be used with caution in older patients owing to decreased renal function and possible interactions with other drugs. Gastroprotective treatment should always be given to older patients.[12] Patients with late-onset SLE usually require low to moderate doses of corticosteroids. Still, side effects of these drugs in the elderly may cause substantial morbidity. Calcium, vitamin D, and bisphosphonates should be always considered. Of note, vitamin D levels should be checked in all patients, as deficiency of this vitamin is also observed among late-onset SLE patients.[8] If doses higher than 10 mg of prednisone are required, corticosteroid-sparing drugs, such as azathioprine and methotrexate, should be considered. Intensive treatment

with cytotoxic drugs is usually required in severe forms of lupus nephritis, which is relatively rare among patients with late-onset SLE. In the past 10 years, new biological agents targeting B-lymphocytes have been introduced to SLE treatment. Despite the promising results of the recent trials, they excluded the oldest patients, so there are no data regarding the efficacy and safety of these agents in this patient group.[12]

In conclusion, the paper by Jeleniewicz et al.[8] provides further data on the differences between late- and early-onset SLE. These are also summarized in the **TABLE 1**. They also provide evidence that in the elderly a delay in establishing diagnosis is unacceptably long. It is important as prognosis and survival are usually worse in patients with late-onset SLE.

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