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LATE ONSET OF SLE IN MALES: A MISDIAGNOSED DISEASE - Case report

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by the production of antibodies to components of the cell nucleus in association with a diverse array of clinical manifestations. When the immune system attacks its own tissues, it causes widespread inflammation and tissue damage in the affected organs. It can affect the joints, skin, brain, lungs, kidneys, and blood vessels. The primary pathological findings in patients with SLE are those of inflammation, vasculitis, immune complex deposition, and vasculopathy.

Late-onset SLE represents a specific subgroup of SLE and is often initially missed leading to a significant delay in diagnosis. Elderly patients frequently present to hospital with nonspecific symptoms such as fatigue, recurrent fever of an unknown cause, weight loss, serositis (pleural and/or pericardial effusions), and acute kidney injury.

We are describing a case of late onset SLE in a male patient that has been previously only syptomaticaly treated for the complications of the disease itself, whilst it took a longer period for physicians to think of SLE and make further investigations about it, because of the age and sex of the patient.

***Keywords*:** systemic lupus erythematosus, male, late onset, pleural effusion, myocarditis.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by production of antibodies to components of the cell nucleus in association with a diverse array of clinical manifestations [1].

When the immune system attacks its own tissues, it causes widespread inflammation and tissue damage to the affected organs. It can affect the joints, skin, brain, lungs, kidneys, and blood vessels. The primary pathological findings in patients with SLE are those of immune complex deposition with sequential inflammation and vasculopathy [1,2].

The exact etiology of SLE is unknown [1-3]. Multiple genes contribute to disease susceptibility. SLE shows a strong familial aggregation, with a much higher frequency among the first degree relatives of patients. Moreover, in extended families, SLE may coexist with other organ specific autoimmune diseases, such as hemolytic anemia, immune thrombocytopenic purpura, and thyroiditis [3].

The interaction of sex, hormonal milieu, and the hypothalamo–pituitary–adrenal axis modify this susceptibility and the clinical expression of the disease [1].

Defective immune regulatory mechanisms, such as the clearance of apoptotic cells and immune complexes, are important contributors to the development of SLE. The loss of immune tolerance, increased antigenic load, excess helper T cells, defective B cell suppression, and the shifting of T helper 1 (Th1) to T helper 2 (Th2) immune responses lead to B cell hyperactivity and to production of pathogenic autoantibodies [1-3]. Finally, certain environmental factors are probably required to trigger the disease [1].

Late-onset systemic lupus erythematosus represents a specific subgroup of SLE and is often initially misleading to a significant delay in diagnosis [4].

Elderly patients frequently present to hospital with nonspecific symptoms, such as fatigue, recurrent fever of an unknown cause, weight loss, serositis (pleural and/or pericardial effusions), and acute kidney injury [4,5].

In this case report, we present a 71-year-old male with late-onset systemic lupus erythematosus in order to highlight some commonly associated symptoms and serological markers and to aid other clinicians in the early diagnosis of this condition.

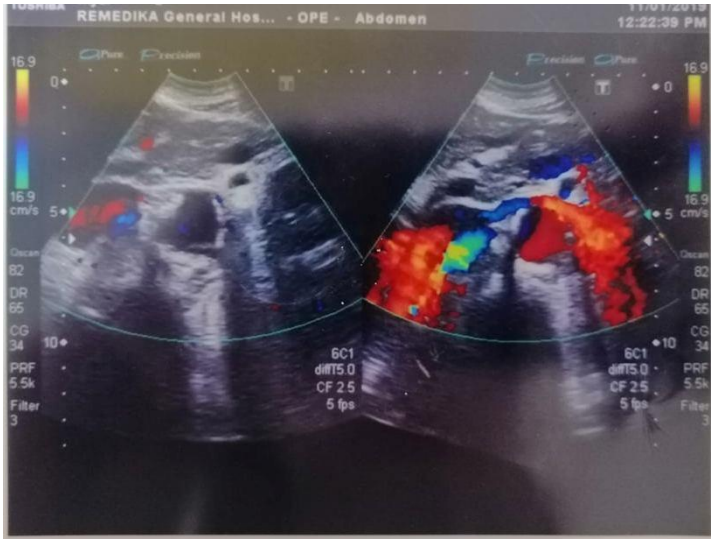
Case report

A 66-year-old male dentist presented with a 2-month history of swelling in the right parotid region which was not accompanied by pain, nor by any other symptoms in 2017. The biopsy of the parotid gland showed nonspecific pathological markings, except for hyperplasia and hypertrophy of the gland cells. Nevertheless, the patient underwent gland extraction at the local maxillofacial surgical department. He wasn't admitted for further laboratory examinations considering the origin of the painless enlargement of the gland.

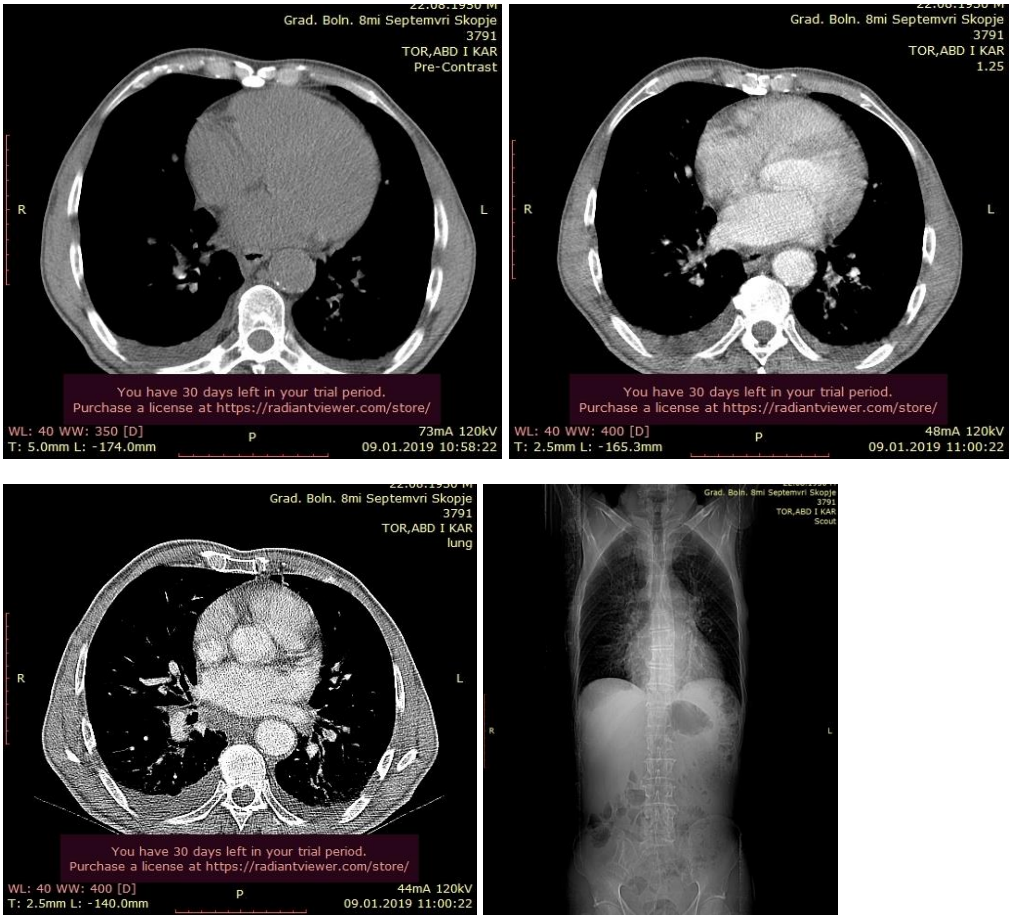
Two years later, in 2019, the patient presented with malaise, dry cough with severe dyspnea, evening sweats and general weakness. He underwent laboratory examinations which showed ESR 25 (normal range <15) , RBC 4.1 (normal range >4.5) , Hgb 136 (normal range >140) , Hct 38.1 (normal range >40) , AST 120 (normal range <37) , ALT 203.65 (normal range <41) , GGT 185.2 (normal range <60) , AP 188.9 (normal range <130), glucose 7.67 (normal range <6) , CRP 31.09 (normal range <3.5), total protein 64.2 (low reference value 66). The ultrasonography of the abdomen (Appendix 1) showed enlarged congestive liver with dilated hepatic veins (right hepatic vein with a diameter of up to 15 mm) and widened VCI of up to 25 mm during inspirium. There was a detectable pleural effusion in the right f-c sinus.

The later performed CT of the chest and abdomen (Appendix 2) showed bilateral pleural effusion, pericardial effusion, mediastinal reactive lymphadenopathy, low range ascites and an enlarged diameter of the portal vein which all lead to misdiagnosed right heart weakness. The ultrasound of the heart chambers and the 12 lead ECG during the first cardiologic check-up on 9th January 2019 showed non-specific myocarditis with sinus bradycardia (53/min). The patient was given an antibiotic, ACE inhibitor and a diuretic. During the check-up 2 days later (11th January 2019), the patient had worsening of the initial symptoms and the ECG showed an AV block of II degree (Mobitz II) (Appendix 3). He was admitted to the cardiologic department and underwent a PCI implantation procedure. The cardiologist prescribed 100 mg Acetylsalicylic acid (1x1), 10 mg Atorvastatin (1x1), 4 mg Perindopril, 500 mg Ciprofloxacin (2x1). The PCI technical activity was regularly checked up afterwards and there was no significant disease activity.

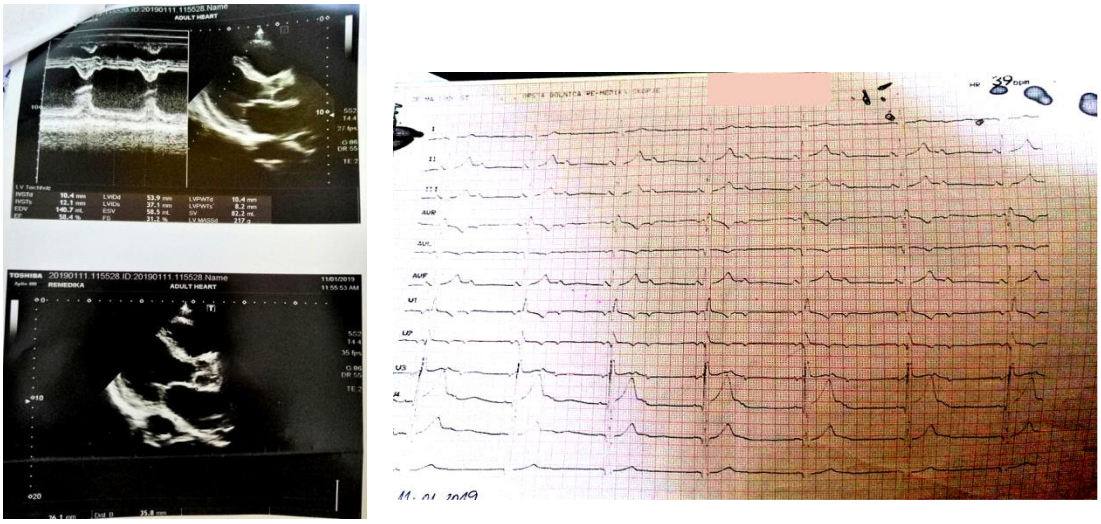
Appendix 1. The ultrasonography of the abdomen.



Appendix 2. CT of the chest and abdomen.



Appendix 3. ECG showed an AV block of II degree (Mobitz II).

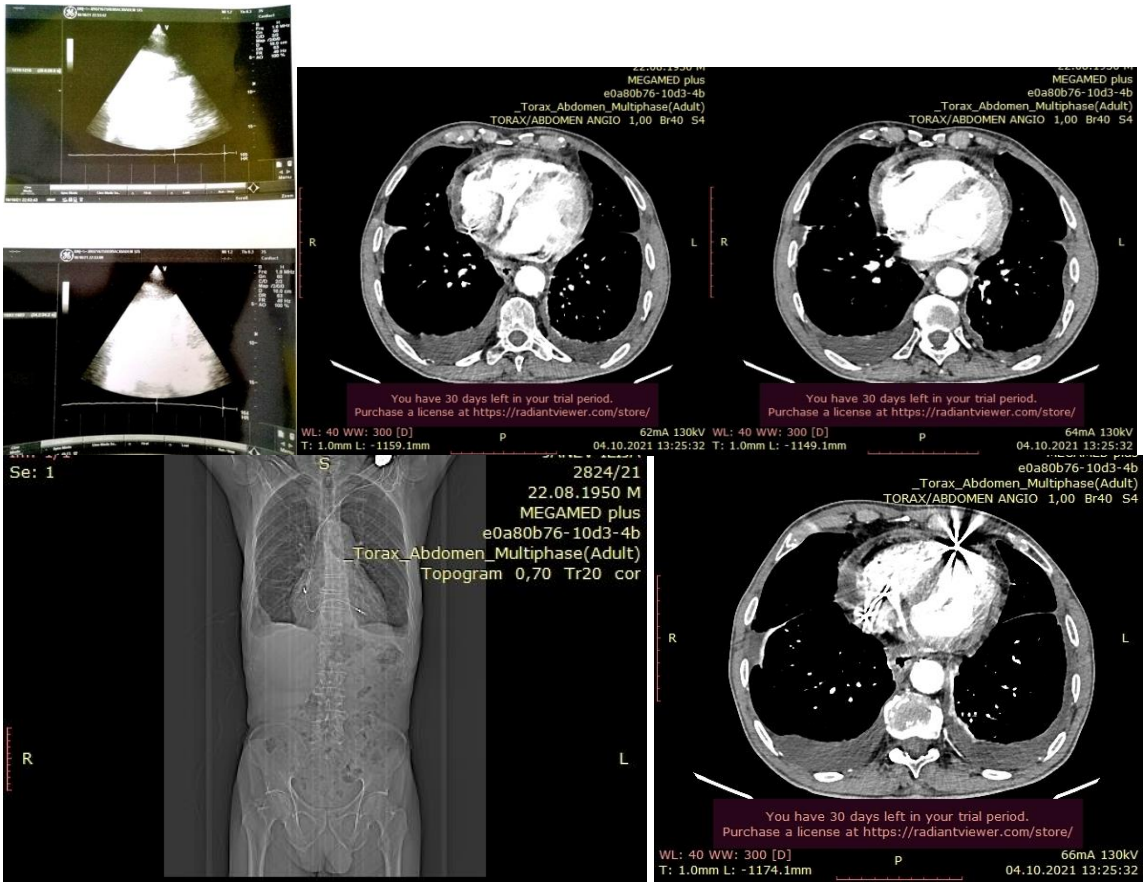


In 2021, the patient presented with a low-grade fever (37.4 C) that lasted for 2 days, extreme muscle weakness, inability to walk more than 100 m at a slow pace without taking a rest, muscle and joint pains, headache and dry cough. He was PCR tested twice for Sars Cov 2 and came out negative. The serological IgM and IgG three weeks after the prodromal symptoms were also below range (negative). The laboratory examinations performed were as follows: CRP 126.2 (normal range <3.0), Ddimers 7240 (normal range <500), ESR 55 (normal range <20), PLT 412 (normal range <400), Hgb 115 (normal range >120), Hct 32.0 (normal range >35), Serum Iron 4.5 (normal range >7.6), AST 52.2 (normal range <37), ALT 88.0 (normal range <63). The CT and the ultrasound of the chest organs again showed bilateral effusions with right side predominance and thereby it was suggested that he should undergo pleural evacuation and that the evacuated liquid should be tested for pathological and/or microbiological abnormalities ([Appendix 4]).

There was also a significant pericardial effusion present on the performed ultrasound of the heart at a later stage. He was additionally given diuretics (40 mg Furosemide (1x1), 25 mg Spironolactone (1x1)) and a double dose of antibiotics (500 mg Clarythromycin (2x1), 400 mg Cefixime (1x1)) and an antithrombotic therapy of LWH (0.6 ml Nadroparin 1x1 s.c. 20 days). The laboratory parameters of the patient showed a slight improvement (inflammatory markers were lower) at the 7-day follow-up but the patient literally still felt ill.

Then, he was admitted to a rheumatology department in order to be tested for an autoimmune underlying disease, and he tested positive for Anti SSA 53, Anti SSB 46, Anti Ds DNA 286, ANA +++, which according to the previous clinical manifestations and laboratory markers met the criteria from 2019 for Systemic Lupus Erythematosus with a Secondary Sjogren diagnosis. He was given Azathioprine 50 mg (2x1), Hydroxychloroquine 200 mg (1x1), Prednisolon 5 mg (1x1), Vitamin D3 2000IE (1x1) in addition to the patient's regular cardiologic therapy.

Appendix 4. The CT and the ultrasound of the chest organs.



Discussion

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease with well-documented female predominance especially during the reproductive age [5].

According to literature, SLE is 8 to 15 times more common in childbearing women compared to age-matched men, but sex disparities are much lower before puberty and after menopause [6].

Because of predominance in women, SLE is commonly overlooked in men thus leading to delayed diagnosis and late initiation of treatment. As a result, the time from symptoms onset to diagnosis might be as high as 60 months for men with late-onset SLE which leads to higher rates of disease flares and frequent hospitalization [4,7].

Various hypotheses have been proposed as an explanation for sex discrepancies in SLE. There are numerous reports associated with the use of estrogen-containing oral contraceptives and rapid sex-hormonal changes during pregnancy and post-partum with exacerbations of SLE [5].

Furthermore, it is believed that estrogens cause enhanced autoimmune reactivity (T helper-2 cells predominant) that creates immune milieu prone to SLE, while male hormones have the opposite effect [6]. However, most men with lupus have normal gonadal function with normal levels of sex-hormones [5].

Sex chromosome hypothesis is another potential explanation for the role of sex chromosomes in disease susceptibility. The fundamental standpoints of this theory are based on observations that showed a

10-fold higher lupus risk in females (46,XX) or men with Klinefelter's syndrome (46, XXY) compared to men with euploidy (46,XY) [8]. In addition, skewed X-chromosome inactivation in thymus may lead to a loss of T cell tolerance and predisposition to SLE development in women [9].

It can be concluded that sex factors are insufficient, and probably some other more complex genetic mechanisms influence the sex discrepancy of lupus.

Based on an analysis of more than 1000 cases of SLE in men, *Lu L.J. et al* concluded that male patients have some distinct frequencies of major organ involvement compared to females with SLE [6]. Renal involvement was more frequent among male SLE patients of all age groups and diffuse proliferative glomerulonephritis was the dominant histologic finding on renal biopsy in males [6,10-13]. In a retrospective analysis of 21 male and 82 female patients with SLE, *Specker C. et al* noted that renal involvement occurred in 16 male (76%) as opposed to 26 female patients (32%; $p < 0.05$) and end-stage renal disease (ESRD) was far more common in men (24% of men and only 7% of women with SLE developed ESRD) [14].

However, participants in both above-mentioned studies were men of all ages, so data cannot be simply extrapolated to older men with lupus. During the analysis of patients with late-onset SLE (men and women), *Kutky et al* noted that although these patients have a higher incidence of decreased creatinine clearance (CrCl), nephritis and nephropathy were less likely in this subgroup and baseline renal function (probably deteriorated by other comorbidities) did not correlate with new renal damage as a consequence of SLE [7].

In an analysis of 121 patients with late-onset SLE, *Stefanidou S. et al* also observed less frequent renal involvement while lung involvement, pericarditis and sicca syndrome were more common. In addition, older patients with SLE had a higher incidence of hypertension, diabetes mellitus and osteoporosis [15].

We did not find in the literature any data about frequency and pattern of renal involvement specifically in older men with lupus. In our case renal biopsy was not done, but we assume that additional comorbidities (hypertension, cardiovascular damage) are a more acceptable explanation for decrease creatinine clearance than lupus itself.

Affection of the skin in the form of discoid and/or subacute skin lesions was found to be more prevalent in men with SLE [6].

However, in older men classical skin manifestations, such as malar rush, mucosal ulcers and photosensitivity were rarely present, non-specific and frequently overlooked [6,16].

Regardless of the slight variation between the studies, several other clinical features such as serositis, neurological involvement, hepatosplenomegaly, fever, weight loss, hypertension and vasculitis have been found to be more common among males with SLE, especially in those with older mean age at diagnosis [6,17].

In addition, *Specker C. et al* reported a significantly higher frequency of thromboembolic complications in male SLE-patients (57% of males VS 6% of females, $p < 0.0001$) accompanied with persisting elevated IgG-anti-cardiolipin antibodies (48% of male and only 16% of female patients, $p < 0.05$) [14].

Mohnaty R. et al. also presented a case of a 26-year old male with neuropsychiatric findings as a first manifestation of SLE, emphasizing the importance of considering the diagnosis of SLE in male patients of all age groups [18].

In our case, the patient's symptoms were non-specific which accompanied by lack of suspicion for SLE in older males resulted in delayed diagnosis and exposed the patient to some unnecessary procedures. Consistently with the studies, serositis (pleuritis and pericarditis) was also the most prominent finding in our patient. Hypertension, cardiovascular damage (myocarditis with AV block), decreased creatinine clearance and prothrombotic state (high D-dimer), which are considered to be part of phenotype of male lupus, were present in our patient. *Kutky M et al* [7] noted that patients with late-onset SLE, due to an unknown reason, have an increased overlap with Sjögrens syndrome with a higher incidence of anti-Ro and anti-La positivity, which was also true for our case patient. Anti-dsDNA and anti-Sm antibodies, as serologic hallmarks of SLE, were found to be more prevalent in male lupus, but their value in older males

is unclear and has yet to be established. Anti-cardiolipin antibodies and lupus anticoagulant tested positive more often in males which may lead to thrombogenesis and a major cardiovascular manifestation [5].

SLE in males has a more complex clinical course with higher one-year mortality compared to women, caused by disease activity and/or complications of the treatment over time [5].

Male sex, followed by the age of 50 plus and low C3 levels might increase the risk of fatal outcome in patients with SLE [7].

Based on the results obtained from LUpus in MInorities, NAture versus nurture multiethnic cohort (LUMINA) study group, the male sex was independently associated with higher early damage scores (quantified by SLICC), and an increased risk of developing organ damage over the course of the disease [19]. On the basis of the data collected with a retrospective analysis of 2144 male patients with SLE, *Prete et al.* found that males with SLE have a more severe disease course characterized by more hospitalizations, longer hospital stays and poorer survival compared to women [20].

However, it is known that older SLE-patients are more likely to die due to complications related to treatment with immunosuppressants. Many authors believe that older SLE-patients do not require immunosuppression as frequently as younger ones, because of a lower incidence of lupus nephritis [19].

Based on the afore-mentioned studies, the male sex is associated with more severe organ damage, but on the other hand, SLE in older patients (men and women) has a more indolent course [7,19,20].

Therefore, according to us, it is reasonable to use an individual assessment of the patient based on the disease activity and present comorbidities during the initiation of an immunosuppression therapy.

Conclusion

The late-onset lupus has a different profile of clinical manifestations and high clinical awareness is necessary in order to diagnose it timely in older male patients. The clinicians need to be more attentive for the presence of comorbidities, such as cardiac ischemia and neoplasms in those patients, which seriously burdens the disease prognosis and treatment options.

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