Autopsy and Case Reports
E-ISSN: 2236-1960
autopsy.hu@gmail.com
Hospital Universitário da Universidade de São Paulo
Brasil

Alencar Pires Barbosa, Breno José; Malta Cardozo, Francisco Akira; Figueiredo Marcondes Ferraz, João Francisco; Rays, Jairo; Yoshie Kanegae, Márcia; Takayasu, Vilma

Severe cognitive dysfunction and shrinking lung syndrome in systemic lupus erythematous

Autopsy and Case Reports, vol. 4, núm. 4, octubre-diciembre, 2014, pp. 63-69
Hospital Universitário da Universidade de São Paulo
São Paulo, Brasil

Autopsy Case Reports

Article / Clinical Case Reports
Artigo / Relato de Caso Clínico

Severe cognitive dysfunction and shrinking lung syndrome in systemic lupus erythematous

Breno José Alencar Pires Barbosa[a], Francisco Akira Malta Cardozo[b], João Francisco Figueiredo Marcondes Ferraz[b], Jairo Rays[c], Márcia Yoshie Kanegae[c], Vilma Takayasu[c]

Barbosa BJAP, Cardozo FAM, Ferraz JFFM, Rays J, Kanegae MY, Takayasu V. Severe cognitive dysfunction and shrinking lung syndrome in systemic lupus erythematous. Autopsy Case Rep [Internet]. 2014;4(4): 63-9. http://dx.doi.org/10.4322/acr.2014.041

ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect any organ or system. Neuropsychiatric and pulmonary involvement can occur in 40 and 50% of patients respectively, and may occur in several different clinical forms. While the main neuropsychiatric manifestations are represented by cognitive impairment, organic cerebral syndromes, delirium, psychosis, seizures, and peripheral neuropathies, the main forms of pulmonary involvement are pleurisy with or without pleural effusion, pneumonitis, interstitial disease, pulmonary hypertension, and alveolar hemorrhage. The authors report the case of a 49-year-old woman whose first manifestation of SLE was represented by two rare manifestations: rapidly progressive cognitive impairment, which was associated with respiratory failure caused by the shrinking lung syndrome. The authors call attention to the under-diagnosis of lupus pulmonary complications and its association with severe cognitive impairment that often necessitates aggressive treatment.

Keywords
Lupus Erythematosus, Systemic; Lung Diseases; Cognition Disorders.

CASE REPORT

A 49-year-old woman, born and residing in the north of Brazil, was brought to medical attention by relatives who reported her rapid cognitive decline over the last 4 months. According to them, the patient had initially presented short-term memory loss followed by psychomotor retardation and diminished patient-environment interaction, ultimately becoming bedridden and fully dependent for basic daily activities. A short while after symptom onset, the patient sought medical attention and ischemic stroke was diagnosed, and she was discharged with the prescription of acetylsalicylic acid. She was reportedly alternating between periods of partial cognitive recovery and the worsening of symptoms. Dyspnea developed and worsened over a few weeks until it was present even at rest. Her past medical history included hypertension, insulin-dependent diabetes mellitus (DM), and dyslipidemia. She reported an episode of arthralgia (without arthritis) 5 years ago, which improved after the use of prednisone for a few months.

[a] Department of Neurology - Hospital das Clínicas - Faculdade de Medicina - Universidade de São Paulo, São Paulo/SP – Brazil.
[b] Department of Internal Medicine - Hospital das Clínicas - Faculdade de Medicina - Universidade de São Paulo, São Paulo/SP – Brazil.
[c] Department of Internal Medicine - Hospital Universitário - Universidade de São Paulo, São Paulo/SP - Brazil.

Physical examination showed a pale patient with a respiratory rate of 44 breaths per minute; the pulse rate was 144 beats per minute; blood pressure was 120/90 mmHg, and the axillary temperature was 36.4°C. The patient had alopecia without other noticeable skin lesions. There was a marked cognitive impairment without other neurological findings. The remaining examination was normal.

On a previous brain magnetic resonance imaging (MRI), there was hyperintense T2 signal on the periventricular white matter without signs of ischemia or previous strokes (Figure 1).

A chest x-ray (Figure 2) and thoracic computed tomography (CT) (Figure 3) revealed the elevation of diaphragm domes with minimal pleural effusion, and laminar atelectasis consistent with a reduced lung volume. Arterial blood gas: pH = 7.47, pO2 = 57 mmHg, HCO3 = 20 mEq/L, pCO2 = 28 mmHg, and SpO2 = 87% while breathing ambient air. Electrocardiography showed sinus tachycardia. The total blood cell count showed hemoglobin = 9.4 g/dL (reference value [RV]: 12.3-15.3 g/dL], leukocytes = 2,930/mm^3 (RV: 4.4-11.3 × 10^3/mm^3) (62% neutrophils, 7% lymphocytes) and 264,000 platelets/mm^3 (RV: 150-400 × 10^3/mm^3). The inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate were elevated.

Additional laboratory workup revealed: urinalysis with proteinuria (1300 mg/24 h (RV: 28-141 mg/24 h) with normal cell counts and without casts; urea = 35 mg/dL (RV: 5-25 mg/dL); creatinine = 0.46 mg/dL (RV: 0.4-1.3 mg/dL); blood glucose = 140 mg/dL (RV: 70-99 mg/dL); aspartate aminotransferase (AST) = 29 U/L (RV: 9-36 U/L); and alanine transaminase (ALT) = 32 U/L (RV: 10-31 U/L). Kidney ultrasonography was consistent with parenchymal disease because of the increased echogenicity of the cortex. The brain CT showed mild hypodense areas that were poorly delimitated at the periventricular white matter topography. The cerebral spinal fluid examination revealed 2 cells/mm^3, 14 red blood cells/mm^3, and protein of 72.8 mg/dL (RV: < 40 mg/dL). India ink and cultures were negative. Serologic tests were negative for HIV, syphilis, and hepatitis B and C. Testing for cryoglobulins was negative.

Since the patient's pulse and respiratory rates remained elevated over the following days, a pulmonary angiotomography was performed, which ruled out the diagnosis of pulmonary embolism and showed hypoinflated lungs and laminar atelectasis, predominantly in the lower lobes. Diaphragm domes were elevated, especially at the right side, where, along with a tiny pleural effusion, they caused partially restrictive atelectasis of the lower and

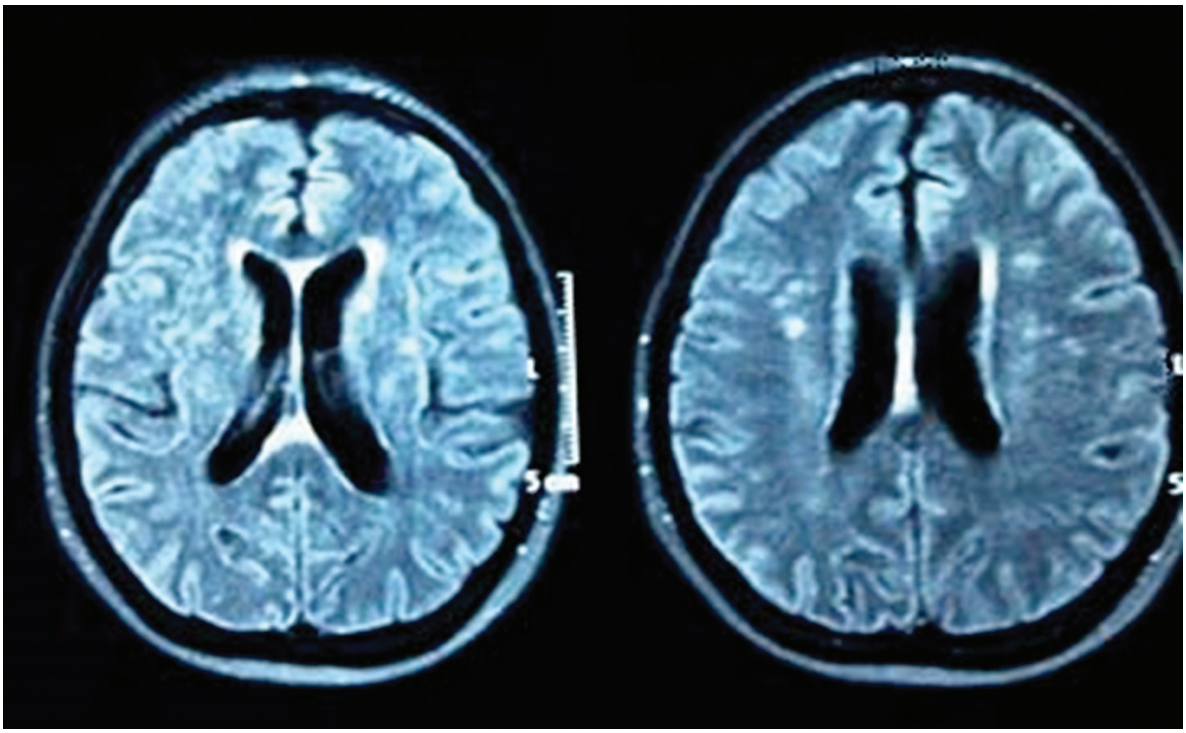

Figure 1. Brain MRI exam with hyperintense T2 signal on periventricular white matter.

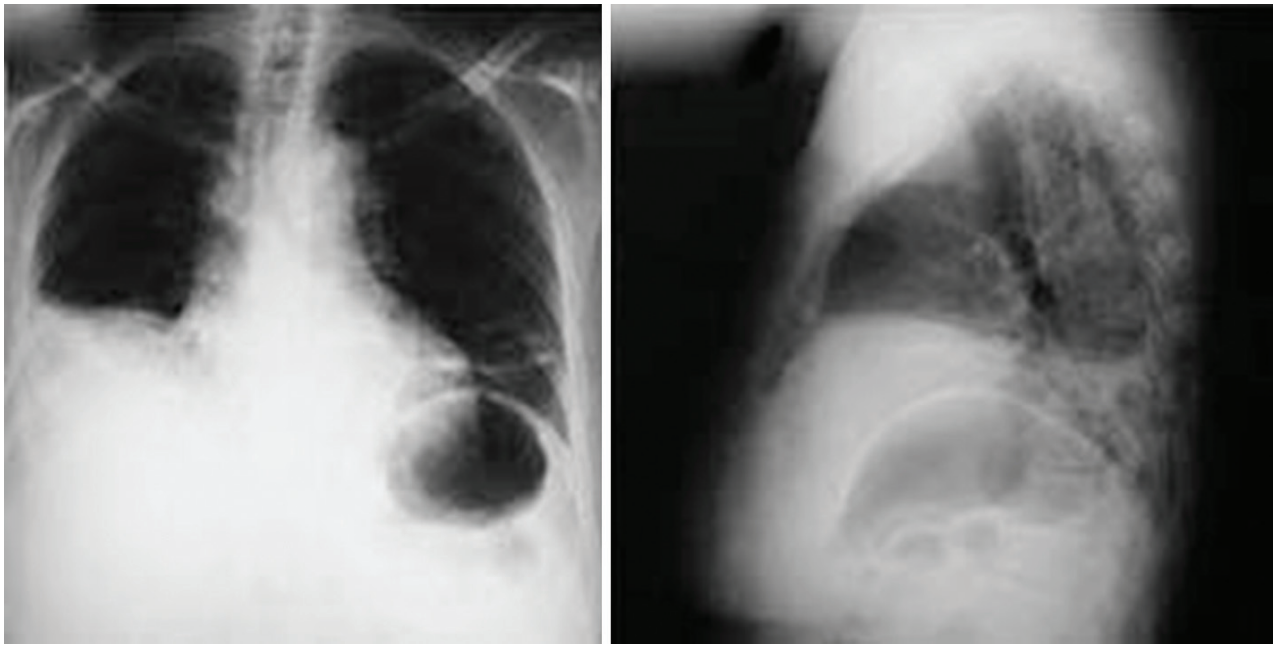

Figure 2. Chest X-ray showing reduced lung volume, elevation of diaphragm domes, and laminar atelectasis.

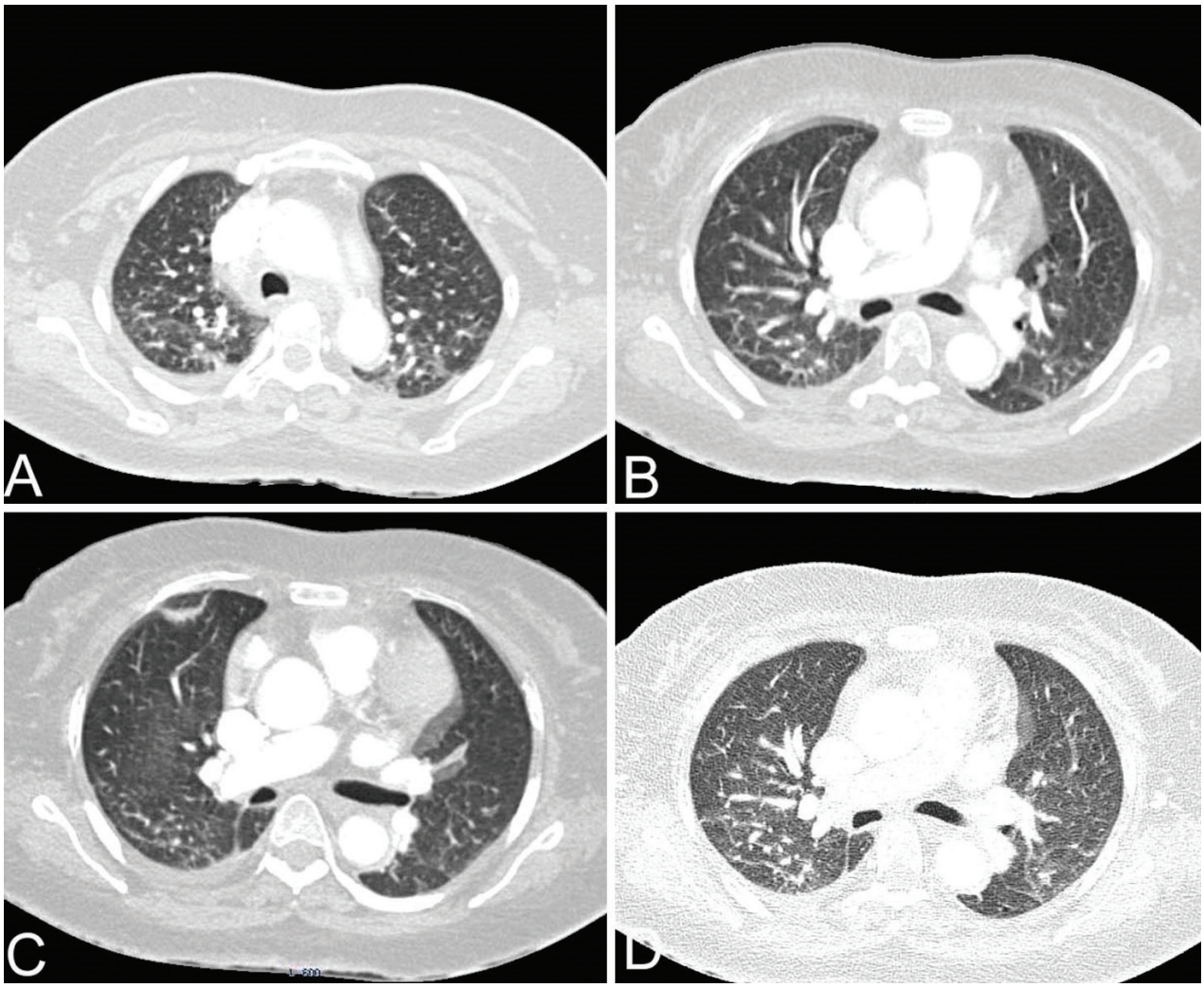

Figure 3. Axial thoracic CT revealed reduced lung volume, right tiny pleural effusion and laminar atelectasis. Note that no remarkable parenchymal lesion is observed.

middle lobes (Figure 3). Normal determination of creatine kinase fraction MB (CK-MB), troponin and creatine phosphokinase (CPK), an electrocardiogram and an echocardiogram ruled out the diagnosis of myocarditis. Thyroid hormones were also normal. The echocardiogram showed left atrium = 32 mm, ejection fraction = 66%, septum = 9 mm, and posterior wall = 9 mm. Left and right ventricle sizes were normal. The aortic valve was slightly thickened and presented a mild reflux. Anemia attributed to a chronic disease was confirmed after dosage of iron and vitamin B12.

Antinuclear antibody determination was 1:1280 showing a nuclear homogeneous pattern and anti-dsDNA was positive: ELISA > 200 IU/mL (RV: negative < 20 UI/mL), confirmed by *Crithidia luciliae* indirect immunofluorescence test. Anti-Sm, anti-Ro (SSA), and anti-La (SSB) were negative. (Anti-P, anti-cardiolipin, and lupus anticoagulant were not tested.) Complement levels were low (C3 = 39 mg/dL [RV: 90-180 mg/dL], C4 = 6 mg/dL [RV: 10-40 mg/dL]).

The patient was diagnosed with systemic lupus erythematosus (SLE) with pulmonary, hematologic, and neuropsychiatric involvement. Renal dysfunction could be either attributed to SLE or to the patient's associated conditions (DM and hypertension).

Pulse therapy with methylprednisolone was administered (1g/day for 3 days) and the patient was started on prednisone (60 mg/day) as well as hydroxychloroquine (400 mg/day) afterwards. Her cognitive impairment improved remarkably, but she still showed signs of psychomotor retardation. The respiratory rate improved (26/min without oxygen supplementation) and the white blood cells rose to normal levels. The patient was discharged and referred to a tertiary hospital for outpatient follow-up.

DISCUSSION

Neuropsychiatric and pulmonary involvement in SLE has been extensively described, presenting in up to 40% and 50% of patients, respectively.[1,2] It is also known that severe cognitive impairment and the shrinking lung syndrome (SLS) are rare manifestations of the disease even in patients with both neuropsychiatric and pulmonary involvement.

Several forms of lupus neuropsychiatric manifestations are observed, which are often associated with remarkable morbidity and mortality. Headache, humor disorders, anxiety, epilepsy, and cerebrovascular disease are the most common syndromes.[1,3] High titers of anti-phospholipid antibodies, previous or current episodes of major neuropsychiatric disorders, and elevated systemic activity of the disease are considered the main risk factors for the development of neuropsychiatric manifestations.[1] In this setting, syndromes are classified as primary (direct involvement of central nervous system [CNS]) or secondary (CNS complications related to SLE or its treatment).

Among primary lupus neuropsychiatric manifestations, cognitive impairment has been commonly reported (> 5%), while severe or rapidly progressive forms are uncommon (3-5%).[3] McLaurin and colleagues[4] reviewed 123 patients with SLE in a prospective study, identifying the presence of persistently elevated antiphospholipid antibodies, diabetes mellitus, depression, lower educational levels, and the continuous use of prednisone as the main predictors of cognitive impairment.

Mild cognitive disturbances are often subclinical, and include a deficit in attention, information processing, learning, memory, and executive functions.[5,6] These diagnoses become evident only with the aid of specific neuropsychological tests. Severe and rapidly progressive forms are less frequent and can present as disorientation, a reduced level of consciousness, and hallucinations. These forms seem to be associated with generalized involvement of the CNS.[5]

The physiopathology of neuropsychiatric disorders in SLE includes: neuronal and vascular damage secondary to intrathecal production of cytokines (interferon alpha, interleukins),[2,7,8] the rupture of the hematoencephalic barrier, and the action of autoantibodies (anti-DNA and anti-glutamate-receptor).[3] An antiphospholipid antibody also play an important role in the cognitive impairment of SLE, since it causes direct small vessel lesions and microangiopathy, which is often seen in imaging studies.[6] Neuroimaging findings include various degrees of cerebral atrophy, microinfarctions, and focal lesions with hyperintensity on T2-weighted imaging in white matter.[9] However, structural findings were nonspecific and none of the neuroimaging modalities has shown efficacy in predicting cognitive impairment.[6]

Secondary causes must always be ruled out in rapidly progressive demential processes, including medication use, exposure to toxic substances, abnormal findings in neurological exam, vitamin B12 deficiency or thyroid dysfunction.[3] Among associated medications, corticosteroids seem to be one of the main causes of the neuropsychiatric manifestations of SLE. Prednisone doses higher than 40mg/day and recent therapy are risk factors for the development of neuropsychiatric syndromes.[10]

After excluding secondary causes, treatment should be targeted at the presumed etiology of cognitive impairment. If it is associated with anti-phospholipid antibodies, anticoagulation should be considered. In the case of antineuronal antibodies, a rapid course of corticosteroid (prednisone 0.5 mg/kg for a few weeks) can be beneficial.[11] Regular use of aspirin can prevent cognitive decline in elderly patients.[4] In severe cases, it might be necessary to administer a high dose of corticotherapy, immunosuppressive drugs (cyclophosphamide, azathioprine), and antipsychotic agents. Simultaneously, the patient's comorbidities should always be under control (cardiovascular risk factors and, especially, depression). Psycho-educational support is recommended for all patients.

The pulmonary involvement in SLE is common and includes pleuritis, interstitial lung disease, alveolar hemorrhage, thromboembolic disease, pulmonary hypertension, airways disease, and SLS.[2] The latter is considered a rare manifestation of SLE, occurring in 0.5% of patients and is characterized by unexplained dyspnea, episodes of pleuritic chest pain, a progressive decrease in lung volumes, a restrictive ventilatory defect on pulmonary function tests (PFTs), and no evidence of interstitial fibrosis or of significant pleural disease on chest CT.[2,7,12-14]

Dyspnea and restrictive lung disease, apparently without pulmonary parenchyma disease, appear to be underestimated, since up to 60% of lupus patients may have reduced forced vital capacity (FVC) in PFT.[2,15] Moreover, most of these patients do not meet the criteria for SLS diagnosis, which results in low prevalence in larger series.[16] In an important case-control study, Allen and colleagues[8] found that long-term SLE diagnosis, previous history of pleurisy, and positivity for anti–RNP antibodies were associated with the diagnosis of SLS. Possible mechanisms involved in the pathogenesis of SLS include myopathy of respiratory muscles, diaphragmatic paralysis, and pulmonary reorganization after several episodes of pleural inflammation.[7,13,14]

Currently, fewer than 100 cases of SLS in adults have been reported in the English literature.[17] The lack of clinical suspicion and the disincentive to report milder cases may explain the scarcity of these cases. Warrington and colleagues,[18] in a comprehensive review of literature between 1965 and 1997, found 49 case reports on SLS. In this review, the mean age was 40 years, the patients were predominantly females (female: male ratio was 5:1) and there was a previous history of pleurisy in almost half the patients (45%). A search in the SciELO database revealed three case reports of SLS published in the Portuguese language,[19-21] including one of the articles addressing the difficulties of mechanical ventilation in these patients during the perioperative care.[21] Another Brazilian group[22] reported a series of four cases with an SLS diagnosis, all of whom were females with some degree of systemic activity, including lupus nephritis. In this series, no patient had neuropsychiatric manifestations. The initial manifestation of SLE may be represented solely by SLS, challenging the diagnosis of SLE as reported by Pillai et al.[17]

Currently, there is still no consensus on the treatment for SLS related to SLE. Most commonly recommended therapies involve anti-inflammatories and immunosuppressive agents.[8,22,23] Oral corticosteroids are the most used agents, with doses ranging from 20 mg/day to 1 mg/kg/day of prednisone. In the absence of response to corticosteroids, immunosuppressive drugs (cyclophosphamide, azathioprine, and methotrexate) or biologic agents (rituximab) can be prescribed, with varying reported results. Adjuvant treatments with beta-agonists or theophylline may be associated as an attempt to improve diaphragmatic musculature strength.[23]

In most patients, dyspnea and thoracic pain tend to disappear in days to weeks after treatment.[17] Mortality related to SLS is low; however, full pulmonary recovery occurs in only 23% of patients, which runs into marked morbidity.[24]

Pulmonary involvement in the reported case was considered as SLS since it presented respiratory distress with hypoxemia and reduced lung volumes. Primary or secondary pulmonary hypertension was ruled out as

both the ECG and the echocardiogram did not show right heart dysfunction nor right QRS deviation in the horizontal leads. Thoracic angiotomography showed no signs of pulmonary embolism, alveolar disease, or interstitial lung disease. Neither was there any sign of pleural effusion, which could have justified the patient's shortness of breath and elevated respiratory rate. Unfortunately PFT was not undertaken due to the patient's impaired mental status. Neurologically, the patient presented a severe and rapidly progressive cognitive impairment associated with alterations in the cerebrospinal fluid, electroencephalogram and neuroimaging studies (CT and MRI); consistent with CNS lesions caused by immune mediated inflammatory process. After pulse corticotherapy, significant improvements of cognitive and respiratory functions were observed, allowing the continuous treatment schedule in the outpatient clinic.

The case reported herein illustrates a concomitance of two rare lupus manifestations. The presence of SLS is of paramount importance to be diagnosed, since proper and early treatment may restore normal lung capacity. Similarly, the neuropsychiatric disturbance may return to normal with immunosuppressive therapy. Although challenging, these manifestations should always be suspected when respiratory failure ensues without a recognized pulmonary lesion, and if dementia-like symptoms arise in a young patient.

REFERENCES

1. Fanouriakis A, Boumpas DT, Bertsias GK. Pathogenesis and treatment of CNS lupus. Curr Opin Rheumatol. 2013;25(5):577-83. http://dx.doi.org/10.1097/BOR.0b013e328363eaf1. PMid:23836074

2. Mittoo S, Fell CD. Pulmonary manifestations of systemic lupus erythematosus. Semin Respir Crit Care Med. 2014;35(2):249-54. http://dx.doi.org/10.1055/s-0034-1371537. PMid:24668539

3. Bertsias GK, Boumpas DT. Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations. Nat Rev Rheumatol. 2010;6(6):358-67. http://dx.doi.org/10.1038/nrrheum.2010.62. PMid:20458332

4. McLaurin EY, Holliday SL, Williams P, Brey RL. Predictors of cognitive dysfunction in patients with systemic lupus erythematosus. Neurology. 2005;64(2):297-303.

5. Fisk JD, Eastwood B, Sherwood G, Hanly JG. Patterns of cognitive impairment in patients with systemic lupus erythematosus. Br J Rheumatol. 1993;32(6):458-62. http://dx.doi.org/10.1093/rheumatology/32.6.458. PMid:8508281

6. Kozora E, Hanly JG, Lapteva L, Filley CM. Cognitive dysfunction in systemic lupus erythematosus: past, present, and future. Arthritis Rheum. 2008;58(11):3286-98. http://dx.doi.org/10.1002/art.23991. PMid:18975345

7. Henderson LA, Loring SH, Gill RR, et al. Shrinking lung syndrome as a manifestation of pleuritis: a new model based on pulmonary physiological studies. J Rheumatol. 2013;40(3):273-81. http://dx.doi.org/10.3899/jrheum.121048. PMid:23378468

8. Allen D, Fischer A, Bshouty Z, et al. Evaluating systemic lupus erythematosus patients for lung involvement. Lupus. 2012;21(12):1316-25. http://dx.doi.org/10.1177/0961203312454343. PMid:22813546

9. Tomietto P, Annese V, D'agostini S, et al. General and specific factors associated with severity of cognitive impairment in systemic lupus erythematosus. Arthritis Rheum. 2007;57(8):1461-72. http://dx.doi.org/10.1002/art.23098. PMid:18050188

10. Bhangle SD, Kramer N, Rosenstein ED. Corticosteroid-induced neuropsychiatric disorders: review and contrast with neuropsychiatric lupus. Rheumatol Int. 2013;33(8):1923-32. http://dx.doi.org/10.1007/s00296-013-2750-z. PMid:23588411

11. Denburg SD, Carbotte RM, Denburg JA. Corticosteroids and neuropsychological functioning in patients with systemic lupus erythematosus. Arthritis Rheum. 1994;37(9):1311-20. http://dx.doi.org/10.1002/art.1780370907. PMid:7945494

12. Hoffbrand BI, Beck ER. "Unexplained" dyspnoea and shrinking lungs in systemic lupus erythematosus. BMJ. 1965;1(5445):1273-7. http://dx.doi.org/10.1136/bmj.1.5445.1273. PMid:14278816

13. Rubin LA, Urowitz MB. Shrinking lung syndrome in SLE—a clinical pathologic study. J Rheumatol. 1983;10(6):973-6. PMid:6663599.

14. Hardy K, Herry I, Attali V, Cadranel J, Similowski T. Bilateral phrenic paralysis in a patient with systemic lupus erythematosus. Chest. 2001;119(4):1274-7. http://dx.doi.org/10.1378/chest.119.4.1274. PMid:11296200

15. Silberstein SL, Barland P, Grayzel AI, Koerner SK. Pulmonary dysfunction in systemic lupus erythematosus:prevalence classification and correlation with other organ involvement. J Rheumatol. 1980;7(2):187-95. PMid:7373620.

16. Bertoli AM, Vila LM, Apte M, et al. Systemic lupus erythematosus in a multiethnic US Cohort LUMINA XLVIII: factors predictive of pulmonary damage. Lupus. 2007;16(6):410-7. http://dx.doi.org/10.1177/0961203307079042. PMid:17664231

17. Pillai S, Mehta J, Levin T, Muzumdar H, Nandalike K. Shrinking lung syndrome presenting as an initial pulmonary manifestation of SLE. Lupus. 2014;23(11):1201-

3. http://dx.doi.org/10.1177/0961203314536248. PMid:24836585

18. Warrington KJ, Moder KG, Brutinel WM. The shrinking lungs syndrome in systemic lupus erythematosus. Mayo Clin Proc. 2000;75(5):467-72. http://dx.doi.org/10.1016/S0025-6196(11)64215-8. PMid:10807075

19. Costa CA, Castro DO Jr, Jezler S, Santiago M. Shrinking lung syndrome in systemic lupus erythematosus. J Bras Pneumol. 2004;30(3):261-3. http://dx.doi.org/10.1590/S1806-37132004000300012.

20. Santis M, Martins V, Moita J. Síndroma do pulmão encolhido: relato de um caso clínico e revisão da literatura. Rev Port Pneumol. 2010;16(4):687-91. Portuguese. PMid:20700566

21. Piccolo-Daher S, Magalhães E. Anesthesia in patient with shrinking lung syndrome: case report. Rev Bras Anestesiol. 2012;62(2):274-80. http://dx.doi.org/10.1016/S0034-7094(12)70126-5. PMid:22440383

22. Calderaro DC, Ferreira GA. Presentation and prognosis of shrinking lung syndrome in systemic lupus erythematosus: report of four cases. Rheumatol Int. 2012;32(5):1391-6. http://dx.doi.org/10.1007/s00296-011-1863-5. PMid:21431288

23. Toya SP, Tzelepis GE. Association of the shrinking lung syndrome in systemic lupus erythematosus with pleurisy: a systematic review. Semin Arthritis Rheum. 2009;39(1):30-7. http://dx.doi.org/10.1016/j.semarthrit.2008.04.003. PMid:18585760

24. Langenskiöld E, Bonetti A, Fitting JW, et al. Shrinking lung syndrome successfully treated with rituximab and cyclophosphamide. Respiration. 2012;84(2):144-9. http://dx.doi.org/10.1159/000334947. PMid:22301521

Conflict of interest: None

Submitted on: September 24, 2014
Accepted on: November 13, 2014

Correspondence
Divisão de Clínica Médica
Hospital Universitário da Universidade de São Paulo
Av. Prof. Lineu Prestes, 2565 – Cidade Universitária - São Paulo/SP – Brazil
CEP: 05508-000
Phone +55 (11) 3091-9200
E-mail vilmatakayasu@uol.com.br