Shrinking lung syndrome—a diagnostic dilemma: a case report

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic inflammatory connective tissue disorder with multi-organ involvement. A rare complication of SLE is shrinking lung syndrome (SLS), characterized by progressive exertional dyspnoea, reduced lung volumes, and diaphragmatic elevation.

Case Presentation: We report a case of SLS secondary to SLE, who required an extensive work up to exclude other more common causes of lung involvement in such a condition. This case report highlights the disease burden of SLS in a once active, independent young lady requiring nocturnal non-invasive ventilation (NIV) to relieve shortness of breath in a recumbent position. This patient had the triad of hypoxia at rest, type 2 respiratory failure, and diaphragmatic palsy. Several different immunomodulators were used initially with little success and it was not until she received six cycles of intravenous cyclophosphamide, that she no longer required NIV support, displayed improvements in pulmonary function tests and diaphragmatic motility and attained a normal lifestyle.

Conclusion: The use of immunomodulators appeared to be particularly effective in restoring normal functional capacity in shrinking lung syndrome. However, the pathophysiology of this condition requires further studies.

Keywords: Systemic lupus erythematosus (SLE), dyspnoea, diaphragmatic elevation, shrinking lung syndrome (SLS), immunomodulators, cyclophosphophomide, case report, hydroxychloroquine (HCQ), mycofenolate mofetil (MMF).

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Background

Systemic lupus erythematosus (SLE) is a chronic inflammatory connective tissue disorder with multi-organ involvement. A rare complication of SLE is shrinking lung syndrome (SLS), characterized by the triad of progressive exertional dyspnoea, reduced lung volumes, and diaphragmatic elevation [1]. We report a case of SLS secondary to SLE which required extensive work up and which highlights the disease burden of such a condition.

Case Report

This case report focuses on a young, Maltese, Caucasian female, who at 20 years of age presented to the rheumatologists with a 6 months history of fatigue, bilateral wrist swelling, and generalized arthralgias with early morning stiffness. Initially, the patient denied fever, rashes, mouth ulcers, alopecia, shortness of breath, and limb weakness. She had no other comorbidities and was on no regular treatment. She was a non smoker and she had a managerial post in a family run business. The patient's hand examination confirmed the presence of bilateral symmetrical synovitis at the metacarpophalangeal and proximal interphalangeal joints. The rest of the joints were normal with normal range of movement, there was no obvious facial rash, neither alopecia nor her chest and cardiovascular examinations were unremarkable. Her vital signs were normal. The patient's biochemical work up showed a positive anti-nuclear (1/640; homogenous uptake), anti-smith (>150 U/ml) and anti-double stranded DNA antibodies (>300 IU/ml) along with an elevated erythrocyte sedimentation rate (>100 mm/hour) and hypocomplimentemia (Complement 3 < 0.8 g/l; Complement 4 < 0.16 g/l)). A diagnosis of SLE was made given that the American College of Rheumatology / European League Against Rheumatisim criteria for SLE were met: >10 out 22 points were present. Her symptoms were well controlled with 200 mg of twice daily hydroxychloroquine (HCQ) for 8 years, until right after her first pregnancy. The patient developed pre-eclampsia with severe proteinuria. Three months post-partum, the proteinuria did not resolve. Hence, a renal biopsy was performed confirming lupus nephritis. mycophenolate mofetil (MMF) was added as an immunosuppressive agent as is recommended in addition to HCQ and high-dose steroids. Her lupus nephritis stabilized but 2 years after giving birth, and therefore 10 years since SLE

was initially diagnosed, she presented with dyspnoea. Her shortness of breath was progressive; it was worse on moderate exertion (classified as New York Heart Association stage 2) and lying down. She was previously energetic but now she could not keep up with her activities of daily living. She also complained of a dry cough but denied lower limb edema, weight loss, wheeze, and fever. Her examination was unremarkable, and a chest radiograph revealed the presence of a raised right hemidiaphragm. Pulmonary function tests (PFTs) and a trans-thoracic echocardiogram were performed showing a restrictive lung pattern (Figure 1) along with mild degrees of mitral regurgitation and tricuspid regurgitation, a mildly dilated left atrium and a preserved ejection fraction of >55%.

A high-resolution computed tomography (HRCT) scan showed no apparent interstitial lung disease. A fluoroscopic sniff test, also known as diaphragm fluoroscopy, was done to assess diaphragmatic motor function; this showed shallow movements of both hemidiaphragms with the presence of paradoxical motion. These findings, along with the absence of parenchymal disease were suggestive of SLS secondary to this lady's SLE.

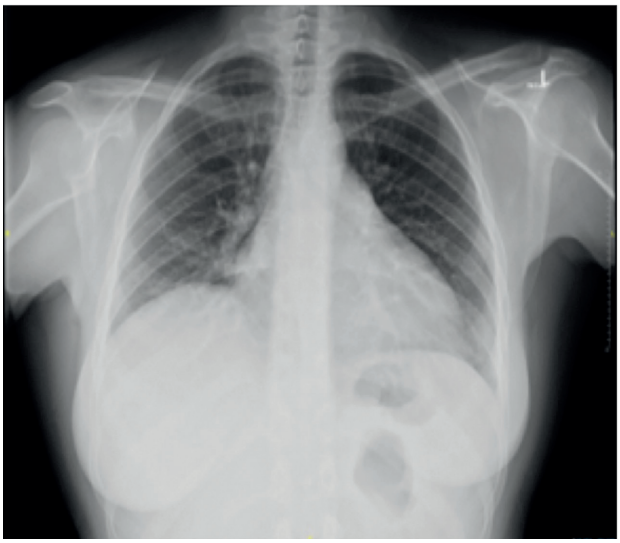

Figure 1. *Chest radiograph in 2014—showing raised right hemidiaphragm.*

The patient required hospitalization in view of worsening symptoms and was noted to have saturations of 90% on room air on pulse oximetry and was confirmed to have type 2 respiratory failure, with a low partial pressure of oxygen (65 mmHg) and a high partial pressure of carbon dioxide (> 60 mmHg) on arterial blood gases requiring a bi-level positive airway pressure (BiPAP) support. Her BiPAP settings were adjusted to an inspiratory airway pressure of 12 and an expiratory positive airway pressure of 5. She was started on rituximab immunosuppressive therapy at the dose of 1000mg intravenously, of which she was able to receive two doses only, in view of an allergic reaction despite the administration of hydrocortisone and chlorpheniramine as pre-medications. She was kept on high doses of steroids with nocturnal BiPAP for respiratory support. She was then given cyclophosphamide 1 g intravenously with Mesna to prevent hemorrhagic cystitis. Following six doses of cyclophosphamide, a repeat PFT showed drastic improvement in forced expiratory volume in 1 second (FEV1) with decreased dependency on non-invasive ventilation (NIV) (Figure 2). In 2018, the patient was able to undergo a mitral valve replacement as she developed severe mitral regurgitation secondary to Libman-Sacks endocarditis. The procedure was done under general anesthesia without any respiratory complications and was weaned off BiPAP. Since then, she has not required any ventilator support or inpatient treatment to date and has a near normal restoration of lung function, with an improvement reported on both chest radiographs and fluoroscopic studies (Figure 3).

Discussion

SLE is a chronic inflammatory connective tissue disorder with multi-organ involvement [1]. A rare complication of SLE is SLS, which is characterized by progressive exertional dyspnoea, reduced lung volumes, and diaphragmatic elevation. SLS can manifest at any point during the disease course, including patients with inactive disease or without previous/concomitant organ involvement [2]. Data reports show a low prevalence of SLS of 0.5%–1.1%

IMMUNOSUPPRESSANT TREATMENT	PREDICTED VALUES	FEBRUARY 2018 STEROIDS HCQ + MMF	APRIL 2016 STEROIDS HCQ + MMF CYCLOPHOSPHOMIDE	DECEMBER 2015 STEROIDS HCQ + MMF RITUXIMAB	NOVEMBER 2014 STEROIDS HCQ + MMF
FEV1 (litres)	2.33	1.79	1.28	1.26	1.30
FEV1 (%pred)		62	43	43	44
FVC (litres)	2.70	2.04	1.37	1.39	1.50
FVC (%pred)		61	40	41	44
FEV1/FVC (%)	83	88	93	91	87
PEF (litres/min)	407	383	324	325	466
PEF (%pred)		95	80	80	68

Figure 2. *Course of lung function tests over time.*

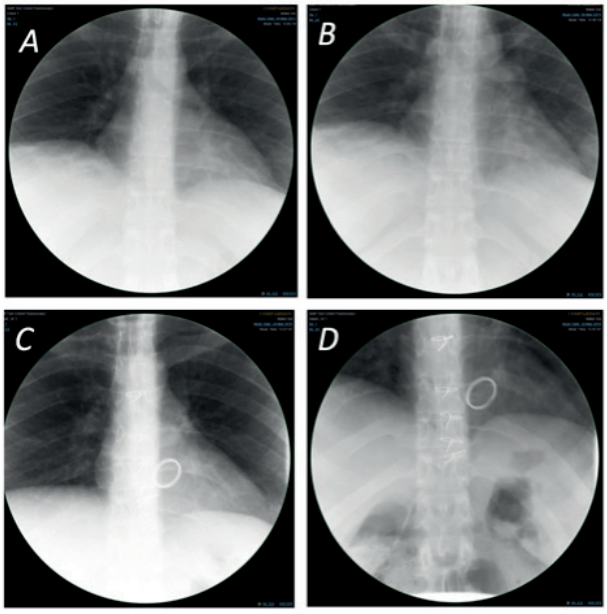

Figure 3. *Comparison in chest fluoroscopy (sniff test) 2014 versus 2018.* ***(A)*** *The position of the diaphragms at maximal inspiration and* ***(B)*** *The position of the diaphragms at maximal expiration. This study in 2014 showed only shallow movements of both hemidiaphragms with presence of paradoxical motion, confirming diaphragmatic involvement secondary to shrinking lung syndrome associated with SLE.* ***(C)*** *The position of the diaphragms at maximal inspiration and* ***(D)*** *The position of the diaphragms at maximal expiration in 2018. This study in 2018 showed a mitral valve prosthesis together with decreased migration of the diaphragms during respiratory movements. As compared to the previous study in 2014, there was an improvement in the diaphragm migration while paradoxic movements were not seen.*

in the SLE population, with a female to male ratio of 17:1 [3].

SLS represents a diagnostic dilemma in SLE patients presenting with dyspnoea and pleuritic chest pain. Distinctive pathognomonic findings include diaphragmatic elevation, with reduced lung volumes (TLC) and a restrictive ventilatory defect on PFTs in the absence of parenchymal lung disease or vascular pathology [4]. The pathophysiology of SLS remains controversial, as Borrell et al. [5] have shown, that it has been attributed to surfactant deficiency, myopathy, chest wall dysfunction, neuropathy, and pleural adhesions.

There are no guidelines regarding the management of SLS. Several reports describe the use of high dose steroids either alone or in combination with immunosuppressive therapy, such as azathioprine, rituximab, methotrexate, or cyclophosphamide [6]. Reports show that rituximab is often the first line immunosuppressant used [7]. Cyclophosphamide is many times reserved as a second line agent due to potential complications surrounding its use [8]. According to Oud et al. [9], its use in SLS is based on the hypothesis of phrenic nerve neuropathy secondary to vasculitis of the vasa nervorum. Reports have also suggested that concomittant use of rituximab and cyclophosphamide makes B cells more susceptible to lysis, achieving a better response [10].

The use of rituximab together with cyclophosphamide appeared to be particularly effective in restoring normal functional capacity after 6 months of treatment [11–13].

Conclusion

From this case report, we have evidence showing that combination immunosuppressant therapy is effective in the treatment of SLS. Further studies regarding the pathophysiology and treatment of this condition are needed to formulate management guidelines in these patients.

What is new?

This case report describes the diagnostic dilemma and the extensive work up in a patient with SLE presenting with exertional dyspnoea. Shrinking lung syndrome is an underdiagnosed and uncommon complication of SLE, of which the pathophysiology and treatment still merits further studies.

List of Abbreviations

BiPAP	Bi-level positive airway pressure
FEV1	Forced expiratory volume in 1 second
HCQ	Hydroxychloroquine
HRCT	high-resolution computed tomography
MMF	Mycophenolate mofetil
NIV	Non-invasive ventilation
PFTs	Pulmonary function tests
SLE	Systemic lupus erythematosus
SLS	Shrinking lung syndrome

Consent for publication

Written Informed consent was obtained from the patient for publication of this case report and any accompanying images.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Female, 20
2	**Final diagnosis**	Shrinking Lung Syndrome
3	**Symptoms**	Exertional dyspnoea
4	**Medications**	Hydroxychloroquine, mycophenolate mofetil, corticosteroids, rituximab, cyclophosphamide, mesna
5	**Clinical procedure**	Chext xray, HRCT, echocardiogram chest fluoroscopy, non-invasive ventilation, mitral valve replacement
6	**Specialty**	Rheumatology, Respiratory