Advances in Clinical Medicine 临床医学进展, 2023, 13(4), 6374-6383
Published Online April 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.134896

系统性红斑狼疮肺受累研究进展

杨真真[1]，李　健[2]

[1]济宁医学院临床医学院，山东　济宁
[2]济宁医学院附属医院，山东　济宁

收稿日期：2023年3月21日；录用日期：2023年4月17日；发布日期：2023年4月25日

摘　要

系统性红斑狼疮(Systemic Lupus Erythematosus)是一种累及多器官的自身免疫性疾病，包括肺受累。SLE肺受累的确切机制尚不清楚。SLE可以引起多种肺部疾病，包括狼疮性胸膜炎、胸腔积液、急性狼疮性肺炎、肺萎缩综合征、间质性肺病、弥漫性肺泡出血(DAH)、肺动脉高压和肺栓塞。SLE肺受累有许多诊断工具，包括胸部X线(CXR)、计算机断层扫描(CT)、肺功能检查(PFT)、支气管肺泡灌洗、活检、磁共振(MRI)、FDG-PET。治疗上一般采用皮质类固醇、环磷酰胺等免疫抑制疗法。本文就SLE肺受累的发病机制、诊断和治疗等方面的文献作一综述。

关键词

系统性红斑狼疮，胸膜肺，肺

Research Progress of Lung Involvement in Systemic Lupus Erythematosus

Zhenzhen Yang[1], Jian Li[2]

[1]The Clinical Medical College of Jining Medical University, Jining Shandong
[2]The Affiliated Hospital of Jining Medical University, Jining Shandong

Received: Mar. 21st, 2023; accepted: Apr. 17th, 2023; published: Apr. 25th, 2023

Abstract

Systemic lupus erythematosus is an autoimmune disease that involves multiple organs, including pulmonary involvement. The precise mechanism of lung involvement in SLE is unknown. SLE can cause various pulmonary diseases, including lupus pleuritis, pleural effusion, acute lupus pneumonitis, shrinking lung syndrome, interstitial lung disease, diffuse alveolar hemorrhage (DAH), pulmonary arterial hypertension, and pulmonary embolism. Pleuropulmonary involvement in SLE

文章引用: 杨真真, 李健. 系统性红斑狼疮肺受累研究进展[J]. 临床医学进展, 2023, 13(4): 6374-6383.
DOI: 10.12677/acm.2023.134896

requires many diagnostic tools, including chest X-ray (CXR), computed tomography (CT), pulmonary function tests (PFT), bronchoalveolar lavage, biopsy, MRI, FDG-PET. Immunosuppression therapies such as corticosteroids and cyclophosphamide are generally used in the treatment. This article reviews the literature on the pathogenesis, diagnosis and treatment of SLE lung involvement.

Keywords

Systemic Lupus Erythematosus, Pleuropulmonary, Lung

1. 引言

系统性红斑狼疮(SLE)是一种复杂的自身免疫性疾病，可能累及多器官，包括肺部受累、关节炎、光敏性皮疹、肾小球肾炎和细胞减少[1] [2]。SLE 是一种异质性极强的疾病，其病理生理学尚不清楚[3]。遗传、环境和激素的复杂相互作用导致免疫失调和对自身抗原的耐受性的破坏，导致自身抗体产生、炎症和终末器官的破坏[3]。SLE 患者的主要病理表现包括炎症、血管炎、免疫复合物沉积和血管病变。肺部表现，包括胸腔积液，在 SLE 中非常普遍[4]。50%~70%的 SLE 患者经历了从亚临床胸腔积液到危及生命的肺泡出血等肺部并发症，4%~5%的患者以肺部表现为症状[4]。儿童肺部表现较成人少，然而，它们可能是严重和致命的 SLE 并发症[5] [6]。与 SLE 相关的肺表现在儿童和成人 SLE 患者中有潜在的生命危险。深入了解 SLE 相关的肺部表现有助于早期诊断和阻碍病情进展。因此，本文就系统性红斑狼疮相关肺部疾病的发病机制、诊断和治疗进行综述。

2. 发病机制

SLE 是一种以产生针对细胞核成分的抗体为特征的自身免疫性疾病。SLE 患者的主要病理表现包括炎症、血管炎、免疫复合物沉积和血管病变。多疫耐受的丧失、抗原负荷的增加、T 细胞活性过剩、B 细胞抑制缺陷以及 Th1 向 Th2 免疫应答的转移导致细胞因子失衡、B 细胞过度活跃和致病性自身抗体的产生[7]。炎症和免疫反应失调是自身免疫性疾病肺部病理的重要驱动因素[8]。SLE 肺受累的确切机制尚不清楚，全身 1 型干扰素(IFN)、循环免疫复合物(IC)和中性粒细胞水平升高与 SLE 有关。SLE 和肺部受累的患者全身促炎细胞因子水平增加[9] [10]。在肺受累患者中，促炎性细胞因子如 IFN-γ、肿瘤坏死因子 α (TNF-α)、白细胞介素 6 (IL-6)、白细胞介素 8 (IL-8)和白细胞介素 12 的水平比非肺受累患者高 2~3 倍，IL-8/IL-10 的比值比限制性肺病患者高 3 倍[9] [10]。虽然炎症在肺纤维化进展中的作用尚不清楚，但细胞炎症，尤其是在疾病的早期阶段，与病理结果一致[9] [10]。作为最初炎症损伤(损伤、感染或抗体沉积)的影响，受损或激活的上皮或内皮细胞释放促炎细胞因子或趋化因子(如 TNF-a、IL-1 和 IL-8)，导致中性粒细胞的吸引和趋化，随后是单核细胞、巨噬细胞和 T、B 淋巴细胞[9] [10]。在 SLE 中，中性粒细胞在网状结构中释放 DNA 和组蛋白，从而进一步加剧炎症反应[11]。1 型 IFNs 还在推动中性粒细胞网状结构、自身抗体产生和打破肺部免疫耐受中发挥重要作用[12]。启动因子(IFNS、自身抗体、免疫复合物、感染性损伤或损伤)和下游反应(补体激活、中性粒细胞积累和激活)之间的相互作用可能在驱动 SLE 相关肺受累中发挥重要作用[12]。

3. 诊断

肺部受累的诊断是通过使用不同的影像学工具[13]做出的，包括胸片、CT、肺功能检查、活检、支气管肺泡灌洗(BAL)、MRI、FDG-PET 等。在慢性 ILD 和 SLS 的早期阶段，胸片图像可以显示正常的发现[14]。因此，胸片是评估 SLE 肺部受累最基本的影像学工具。利用高分辨率 CT (HRCT)可以实现 SLE 患者肺部受累的早期诊断。HRCT 有助于发现有症状和无症状 SLE 患者的早期肺受累。CT 对 SLE 患者的肺功能有较准确的预测，对肺部受累患者有一定的诊断价值。PFT 可作为 SLE 和亚临床肺疾病的有效诊断工具。PFT 可以早期发现肺部受累的 SLE 患者[15]。活检只有在诊断不确定和其他发现非特异性时才使用[16]。BAL 主要用于排除呼吸损害的其他原因。FDG-PET 可以评估 SLE-PAH 患者的肺内疾病活动标志[17]。MRI 可以证实 SLE 相关性肺萎缩综合征的胸膜炎。

4. 肺部受累类型

SLE 可引起多种肺部疾病，如胸腔积液/胸膜炎、肺萎缩综合征、急性肺炎、DAH、慢性 ILD 和肺动脉高压[14]。胸膜炎是 SLE 最常见的胸内疾病，表现为胸痛、咳嗽、呼吸困难和胸腔积液[18] [19]。ALP 和 DAH 是由肺泡－毛细血管单位受损引起的急性肺部疾病，而 ILD 是引起肺纤维化的慢性肺部疾病[19]。

4.1. 狼疮性胸膜炎

4.1.1. 临床表现

胸膜炎是胸膜组织的炎症，引起尖锐的胸痛(胸膜痛)，在呼吸时加重。胸膜炎伴或不伴胸腔积液是 SLE 急性肺受累最常见的特征[20]。它的特征是胸痛、呼吸困难、呼吸急促、咳嗽，可能还有发热。狼疮性胸膜炎患者还会出现血气胸；然而，自发性气胸并不常见[21]。纤维胸是一种罕见的并发症，可通过阻止肺扩张而导致呼吸困难和呼吸急促[22]。

4.1.2. 治疗

狼疮胸膜炎的治疗方案因症状的严重程度而异。轻度胸膜炎可用非甾体抗炎药治疗[23]，肾功能受损的患者应避免使用非甾体抗炎药。某些情况下可加用羟氯喹等抗疟药[24]。全身皮质类固醇是严重狼疮性胸膜炎患者的首选药物。如果胸腔积液较多，可能需要抽吸以减轻呼吸困难[22]。对皮质类固醇没有反应或伴有肾脏受累的患者应考虑使用环磷酰胺[23]。其他选择包括霉酚酸酯(MMF)和利妥昔单抗。静脉注射免疫球蛋白(IVIG)不是狼疮性胸膜炎的主要治疗方法；然而，迈斯纳等人报道 1 个月的 IVIG 治疗有效地减少了 SLE 和严重胸膜炎患者的胸腔积液[25]。谢勒等人同时报道 IVIG 和环孢素联合治疗可减轻大量胸腔积液[26]。这些报告提示 IVIG 在严重狼疮患者中的效用；但其临床有效性尚需进一步研究证实。罕见的难治性胸腔积液患者对免疫抑制剂没有反应时，可能需要进行胸膜切除术，有报道通过开放手术切除胸骨成功地治疗了这类患者[27]。

4.2. 胸腔积液

4.2.1. 临床表现

根据 EULAR/ACR_2019 标准，与肺受累相关的唯一标准是胸腔积液，该标准的定义由影像学技术证明：超声、X 线、CT 扫描和 MRI [28]。系统性红斑狼疮的胸腔积液可能是由自身免疫性胸膜炎引起的，但与其他原因如感染、心脏病和肺结核难以区分[3]。因此，应建立更详细的胸腔积液标准。

4.2.2. 治疗

通常，SLE 相关胸腔积液对皮质类固醇反应迅速[29]。然而，在某些情况下可出现持续性类固醇抵抗

性胸腔积液。治疗这些病例的方法多种多样。 四环素胸膜固定术成功地治疗了一些 SLE 相关的激素抵抗性胸腔积液[30] [31]。1 例系统性红斑狼疮相关难治性大量胸腔积液经胸膜切除术成功治疗[32]。

4.3. 急性狼疮性肺炎(ALP)

4.3.1. 临床表现

ALP 是 SLE 一种不常见的表现[33]。ALP 的临床表现与急性间质性肺炎相似，以急性发热、咳嗽和呼吸困难为特征[34]。有时，咯血时伴有呼吸急促、心动过速、吸气爆裂、体检时低氧血症等。半数 ALP 患者以肺炎作为 SLE 的初始表现[34]。组织病理学检查可发现弥漫性肺泡损害、肺泡水肿、透明膜形成、单个核细胞浸润。免疫球蛋白和补体沉积可能存在于毛细血管壁[35] [36]。也可以看到肺泡出血，而血管炎是不常见[35]。胸部 X 线片显示弥漫或斑片状混浊，主要发生在肺下段。需要与感染、组织性肺炎、肺栓塞、药物毒性、DAH、心力衰竭和恶性肿瘤相鉴别[36]。

4.3.2. 治疗

感染的发病率高，应立即给予经验广谱抗生素治疗[37]。在排除感染性病因后，必须启动积极的免疫抑制治疗。可以考虑大剂量静脉注射甲基强的松龙、口服皮质类固醇和静脉注射环磷酰胺[38]。此外，利妥昔单抗的成功治疗已有报道[39]。血浆置换和静脉注射免疫球蛋白已用于难治病例[40]。

4.4. 弥漫性肺泡出血

4.4.1. 临床表现

患有 DAH 的患者表现为呼吸困难、咳嗽、发烧、带血的痰，有时咯血，症状在几小时或几天内迅速发展[32]。典型的情况包括血红蛋白水平下降和弥漫性肺浸润在胸部 X 线或高分辨率胸部 CT 上可见[41]。感染可与 DAH 相关，应排除作为鉴别诊断[42]。当 BALF 中含有≥20%含铁血黄素的巨噬细胞时，BAL 可用于确认 DAH [32]。

4.4.2. 治疗

治疗方面，DAH 尚无具体的治疗指南；然而，经常使用大剂量甲基强的松龙[43]。环磷酰胺是另一种选择，但其有效性存在争议。一项研究中，血浆置换与环磷酰胺或甲基强的松龙联合使用；然而，其作为单一疗法的有效性尚未确立[44]。然而，最近的研究表明，对肺出血患者进行早期和积极的治疗可以提高存活率[45]，包括大剂量类固醇、IVIG 和环磷酰胺的治疗[46]。用适当的抗生素管理这些患者对降低死亡率非常重要[47]。此外，替代性和实验性治疗方法，如脐带来源的间充质干细胞移植，被证明可以改善结局[48] [49]。

4.5. 间质性肺病(ILD)

4.5.1. 临床表现

SLE 相关性间质性肺疾病(SLE-ILD)的真实患病率不明；然而，据报告流行率为 3%~9% [34] [38] [50]。非特异性间质性肺炎(NSIP)、机化性肺炎、淋巴细胞性间质性肺炎(LIP)、滤泡性毛细支气管炎、结节性淋巴样增生和普通间质性肺炎与 SLE 有关。其中 NSIP 最为常见[51]。SLE-ILD 患者在体检中通常表现为隐匿性慢性无生产力咳嗽、呼吸困难、运动耐受性下降和基底动脉爆裂，但有些患者没有症状[52]。

4.5.2. 治疗

SLE 相关性 ILD 的治疗主要基于专家意见[53]。最近的治疗算法建议单独使用皮质类固醇或环磷酰胺或 MMF 诱导治疗和硫唑嘌呤或 MMF 维持治疗。

4.6. 肺萎缩综合征

4.6.1. 临床表现

SLS 是一种罕见的 SLE 并发症。SLS 作为主要呼吸道 SLE 症状的出现是非常罕见的[54] [55]。所有 SLS 患者均有呼吸困难、咳嗽、胸膜性胸痛等呼吸道症状[56] [57]。SLS 的特点是 PFT 上肺体积进行性减少，胸部 CT 上没有间质性疾病或明显的胸膜疾病的证据[57] [58]。

4.6.2. 治疗

SLS 的治疗由于其罕见的发病率，目前尚无临床指南。然而，许多与 SLE 相关的 SLS 病例已被单独应用糖皮质激素或其他免疫抑制剂，如环磷酰胺、硫唑嘌呤、MTX 和霉酚酸酯[56] [59] [60]。茶碱和 β 激动剂可以帮助膈肌无力[61] [62] [63]。利妥昔单抗也被成功地用作单药治疗或与环磷酰胺和 β 激动剂联合使用，特别是在类固醇难治的病例中[59] [64] [65]。其他药物在类固醇失败后已成功使用；在 Robles-Perez 等人的一项回顾性研究中，6/18 名患者报告了利妥昔单抗的不良反应[66]。Belimumab 被批准用于非肾性 SLE，一个病例报告显示 SLS 症状改善；然而，还需要进一步的研究[67]。

4.7. 肺动脉高压

4.7.1. 临床表现

PAH 是一种罕见的并发症，它可能导致右心室或肺毛细血管的不可逆改变，造成 PAH 患者的高死亡率[68]。在大型队列研究中，大约 2%~5%的 SLE 患者被诊断为 PAH [69] [70]。SLE 和 PAH 之间的诊断延迟期约为 3~5 年[69] [71]。5 年生存率 70%~80% [69] [71]。系统性高血压、高纤维蛋白原水平、浆膜炎和血小板减少是SLE的临床危险因素，表明其他器官系统的并发症可能导致SLE的肺部表现[69] [70]。硬皮病样甲襞毛细血管形态和雷诺现象也是 SLE 患者 PAH 的重要危险因素，这与硬皮病和 PAH 之间的关系是一致的[71] [72]。许多研究发现，高水平的抗 SSA/SSB、抗心磷脂和抗 RNP 抗体预测 PAH 的发病率更高[71] [72] [73]。高水平的抗 U1-RNP 抗体也表明更长的生存期，尽管 PAH 患者的 SLE 发病率更高[71]。

4.7.2. 治疗

以静脉注射环磷酰胺为基础的免疫抑制疗法已经成功地用于几项研究。因此，静脉注射环磷酰胺和强的松龙可降低肺动脉压[74] [75]。除了免疫抑制疗法外，血管扩张剂也是有效的[76] [77]。多项研究表明，静脉应用前列醇(前列环素)可使肺动脉压恢复正常 。

4.8. 肺栓塞

4.8.1. 临床表现

肺栓塞(PE)是一种罕见但可能致命的系统性红斑狼疮肺部并发症，多项人群研究表明 SLE 患者明显更容易发生 PE 和相关临床表现，如深静脉血栓形成，这种关联与年龄、性别、种族和先前存在的患者共病无关[57] [78]。在 SLE 患者中，PE 的总患病率为 1%~5% [78] [79]。PE 的危险因素包括高体重指数、快速进展的 SLE、低白蛋白血症、抗磷脂抗体和高剂量的糖皮质激素[79]。

4.8.2. 治疗

对 SLE 相关性 PE 的治疗方面研究数量有限；以下建议一般适用于 PE。诊断或怀疑 PE 时应早期使用抗凝治疗，以降低其死亡率[80]。对于大量 PE 或持续性低血压(收缩压 < 90 mmHg)的患者，胸部指南推荐溶栓作为 2 级 B 推荐[81]。在大量 PE 患者中，溶栓的好处通常大于风险，除非有活动性、未控制的

出血[82]。此外，当单一抗凝治疗不能控制血栓形成时，可能需要皮质类固醇或免疫抑制剂的强化治疗[83]。

4.9. 药物毒性与系统性红斑狼疮肺损害

ILD 和 ALP 的药物毒性和肺受累可由多种药物引起，药物性肺部疾病应与 SLE 的肺受累相鉴别。一些肺部疾病是由治疗剂引起的基础疾病，如结缔组织病和癌症[84]。由于影像学研究可以区分这两种情况，在评估 SLE 肺部受累之前开始使用新药物的历史应该被考虑来诊断 ILD 和 ALP [85]。

5. 结论

SLE 患者中有很多肺部受累。胸膜炎、弥漫性肺泡出血、缩肺综合征、间质性肺病、肺动脉高压是肺部疾病的主要表现。一些患者出现严重并发症，如肺出血。因此，对 SLE 患者肺部受累的评估和治疗应及时进行。推荐 CXR、HRCT 和 PFT 作为诊断工具。临床医生和患者对 SLE 呼吸系统的影响认识较少。此外，SLE 肺部受累的确切诊断标准仍然难以确定。因此，应更多重视 SLE 肺部表现的积极监测和处理。

参考文献

[1] Bertsias, G.K., Pamfil, C., Fanouriakis, A. and Boumpas, D.T. (2013) Diagnostic Criteria for Systemic Lupus Erythematosus: Has the Time Come? *Nature Reviews Rheumatology*, **9**, 687-694. https://doi.org/10.1038/nrrheum.2013.103

[2] Stojan, G. and Petri, M. (2018) Epidemiology of Systemic Lupus Erythematosus: An Update. *Current Opinion in Rheumatology*, **30**, 144-150. https://doi.org/10.1097/BOR.0000000000000480

[3] Moulton, V.R., Suarez-Fueyo, A., Meidan, E., Li, H., Mizui, M. and Tsokos, G.C. (2017) Pathogenesis of Human Systemic Lupus Erythematosus: A Cellular Perspective. *Trends in Molecular Medicine*, **23**, 615-635. https://doi.org/10.1016/j.molmed.2017.05.006

[4] Hannah, J.R. and D'Cruz, D.P. (2019) Pulmonary Complications of Systemic Lupus Erythematosus. *Seminars in Respiratory and Critical Care Medicine*, **40**, 227-234. https://doi.org/10.1055/s-0039-1685537

[5] Çiftçi, E., Yalçinkaya, F., Ince, E., Ekim, M., Ileri, M., Örgerin, Z., Fitöz, S., Güriz, H., Aysev, A.D. and Dogru, Ü. (2004) Pulmonary Involvement in Childhood-Onset Systemic Lupus Erythematosus: A Report of Five Cases. *Rheumatology*, **43**, 587-591. https://doi.org/10.1093/rheumatology/keh120

[6] Rabinovich, C.E. (2012) Pulmonary Complications of Childhood Rheumatic Disease. *Paediatric Respiratory Reviews*, **13**, 29-36. https://doi.org/10.1016/j.prrv.2011.05.005

[7] Tsokos, G.C. (2011) Systemic Lupus Erythematosus. *The New England Journal of Medicine*, **365**, 2110-2121. https://doi.org/10.1056/NEJMra1100359

[8] Bertoli, A.M., Vila, L.M., Apte, M., Fessler, B.J., Bastian, H.M., Reveille, J.D. and Alarcon, G.S. (2007) Systemic Lupus Erythematosus in a Multiethnic US Cohort LUMINA XLVIII: Factors Predictive of Pulmonary Damage. *Lupus*, **16**, 410-417. https://doi.org/10.1177/0961203307079042

[9] Memet, B. and Ginzler, E.M. (2007) Pulmonary Manifestations of Systemic Lupus Erythematosus. *Seminars in Respiratory and Critical Care Medicine*, **28**, 441-450. https://doi.org/10.1055/s-2007-985665

[10] Kamen, D.L. and Strange, C. (2010) Pulmonary Manifestations of Systemic Lupus Erythematosus. *Clinics in Chest Medicine*, **31**, 479-488. https://doi.org/10.1016/j.ccm.2010.05.001

[11] Wallace, D.J. and Hahn, B. (2018) Dubois' Lupus Erythematosus and Related Syndromes. 9th Edition, Elsevier, Edinburgh.

[12] Lahita, R.G. (2010) Systemic Lupus Erythematosus. 5th Edition, Elsevier Academic Press, Amsterdam.

[13] Fenlon, H.M., Doran, M., Sant, S.M. and Breatnach, E. (1996) High-Resolution Chest CT in Systemic Lupus Erythematosus. *AJR American Journal of Roentgenology*, **166**, 301-307. https://doi.org/10.2214/ajr.166.2.8553934

[14] Aguilera-Pickens, G. and Abud-Mendoza, C. (2018) Pulmonary Manifestations in Systemic Lupus Erythematosus: Pleural Involvement, Acute Pneumonitis, Chronic Interstitial Lung Disease and Diffuse Alveolar Hemorrhage. *Reumatología Clínica*, **14**, 294-300. https://doi.org/10.1016/j.reumae.2018.03.001

[15] Nakano, M., Hasegawa, H., Takada, T., Ito, S., Muramatsu, Y., Satoh, M., Suzuki, E. and Gejyo, F. (2002) Pulmonary Diffusion Capacity in Patients with Systemic Lupus Erythematosus. *Respirology*, **7**, 45-49. https://doi.org/10.1046/j.1440-1843.2002.00361.x

[16] Keane, M.P. and Lynch, J.P. (2000) Pleuropulmonary Manifestations of Systemic Lupus Erythematosus. *Thorax*, **55**, 159-166. https://doi.org/10.1136/thorax.55.2.159

[17] Wang, L., Xiong, C., Li, M., Zeng, X., Wang, Q., Fang, W. and Zhao, L. (2020) Assessment of Lung Glucose Uptake in Patients with Systemic Lupus Erythematosus Pulmonary Arterial Hypertension: A Quantitative FDG-PET Imaging Study. *Annals of Nuclear Medicine*, **34**, 407-414. https://doi.org/10.1007/s12149-020-01461-y

[18] Crestani, B. (2005) The Respiratory System in Connective Tissue Disorders. *Allergy*, **60**, 715-734. https://doi.org/10.1111/j.1398-9995.2005.00761.x

[19] Torre, O. and Harari, S. (2011) Pleural and Pulmonary Involvement in Systemic Lupus Erythematosus. *La Presse Médicale*, **40**, e41-e51. https://doi.org/10.1016/j.lpm.2010.11.004

[20] Good, J.T., King, T.E., Antony, V.B. and Sahn, S.A. (1983) Lupus Pleuritis. Clinical Features and Pleural Fluid Characteristics with Special Reference to Pleural Fluid Antinuclear Antibodies. *Chest*, **84**, 714-718. https://doi.org/10.1378/chest.84.6.714

[21] King, T.E., Kim, E.J. and Kinder, B.W. (2011) Connective Tissue Diseases. In: Schwartz, M.I. and King, T.E., Eds., *Interstitial Lung Disease*, 5th Edition, People's Medical Publishing House, Shelton.

[22] Sharma, S., Smith, R. and Al-Hameed, F. (2002) Fibrothorax and Severe Lung Restriction Secondary to Lupus Pleuritis and Its Successful Treatment by Pleurectomy. *Canadian Respiratory Journal*, **9**, 335-337. https://doi.org/10.1155/2002/740878

[23] Wang, D.Y. (2002) Diagnosis and Management of Lupus Pleuritis. *Current Opinion in Pulmonary Medicine*, **8**, 312-316. https://doi.org/10.1097/00063198-200207000-00012

[24] Breuer, G.S., Deeb, M., Fisher, D. and Nesher, G. (2005) Therapeutic Options for Refractory Massive Pleural Effusion in Systemic Lupus Erythematosus: A Case Study and Review of the Literature. *Seminars in Arthritis and Rheumatism*, **34**, 744-749. https://doi.org/10.1016/j.semarthrit.2004.11.003

[25] Meissner, M., Sherer, Y., Levy, Y., Chwalinska-Sadowska, H., Langevitz, P. and Shoenfeld, Y. (2000) Intravenous Immunoglobulin Therapy in a Patient with Lupus Serositis and Nephritis. *Rheumatology International*, **19**, 199-201. https://doi.org/10.1007/s002960000053

[26] Sherer, Y., Langevitz, P., Levy, Y., Fabrizzi, F. and Shoenfeld, Y. (1999) Treatment of Chronic Bilateral Pleural Effusions with Intravenous Immunoglobulin and Cyclosporin. *Lupus*, **8**, 324-327. https://doi.org/10.1191/096120399678847759

[27] Kim, S., Park, H.-B., Cho, Y.K., Yi, S., Oh, K., Kim, D.K. and Yoo, B. (2017) Refractory Pleural Effusion in Systemic Lupus Erythematosus Treated by Pleurectomy. *Journal of Rheumatic Diseases*, **24**, 43-47. https://doi.org/10.4078/jrd.2017.24.1.43

[28] Aringer, M., Costenbader, K., Daikh, D., Brinks, R., Mosca, M., Ramsey-Goldman, R., Smolen, J.S., Wofsy, D., Boumpas, D.T., Kamen, D.L., *et al*. (2019) European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis & Rheumatology*, **71**, 1400-1412.

[29] Karkhanis, V.S. and Joshi, J.M. (2012) Pleural Effusion: Diagnosis, Treatment, and Management. *Open Access Emergency Medicine*, **4**, 31-52. https://doi.org/10.2147/OAEM.S29942

[30] Gilleece, M.H., Evans, C.C. and Bucknall, R.C. (1988) Steroid Resistant Pleural Effusion in Systemic Lupus Erythematosus Treated with Tetracycline Pleurodesis. *Annals of Rheumatic Diseases*, **47**, 1031-1032. https://doi.org/10.1136/ard.47.12.1031

[31] McKnight, K.M., Adair, N.E. and Agudelo, C.A. (1991) Successful Use of Tetracycline Pleurodesis to Treat Massive Pleural Effusion Secondary to Systemic Lupus Erythematosus. *Arthritis & Rheumatology*, **34**, 1483-1484. https://doi.org/10.1002/art.1780341121

[32] Elborn, J.S., Conn, P. and Roberts, S.D. (1987) Refractory Massive Pleural Effusion in Systemic Lupus Erythematosus Treated by Pleurectomy. *Annals of Rheumatic Diseases*, **46**, 77-80. https://doi.org/10.1136/ard.46.1.77

[33] Wiedemann, H.P. and Matthay, R.A. (1992) Pulmonary Manifestations of Systemic Lupus Erythematosus. *Journal of Thoracic Imaging*, **7**, 1-18. https://doi.org/10.1097/00005382-199203000-00003

[34] Matthay, R.A., Schwarz, M.I., Petty, T.L., Stanford, R.E., Gupta, R.C., Sahn, S.A. and Steigerwald, J.C. (1975) Pulmonary Manifestations of Systemic Lupus Erythematosus: Review of Twelve Cases of Acute Lupus Pneumonitis. *Medicine*, **54**, 397-409. https://doi.org/10.1097/00005792-197509000-00003

[35] Haupt, H.M., Moore, G.W. and Hutchins, G.M. (1981) The Lung in Systemic Lupus Erythematosus. Analysis of the Pathologic Changes in 120 Patients. *The American Journal of Medicine*, **71**, 791-798. https://doi.org/10.1016/0002-9343(81)90366-1

[36] Swigris, J.J., Fischer, A., Gillis, J., Meehan, R.T. and Brown, K.K. (2008) Pulmonary and Thrombotic Manifestations of Systemic Lupus Erythematosus. *Chest*, **133**, 271-280. https://doi.org/10.1378/chest.07-0079

[37] Gutsche, M., Rosen, G.D. and Swigris, J.J. (2012) Connective Tissue Disease-Associated Interstitial Lung Disease: A Review. *Current Respiratory Care Reports*, **1**, 224-232. https://doi.org/10.1007/s13665-012-0028-7

[38] Winslow, W.A., Ploss, L.N. and Loitman, B. (1958) Pleuritis in Systemic Lupus Erythmatosus: Importance as an Early Manifestation in Diagnosis. *Annals of Internal Medicine*, **49**, 70-88. https://doi.org/10.7326/0003-4819-49-1-70

[39] Todd, D.J. and Costenbader, K.H. (2009) Dyspnoea in a Young Woman with Active Systemic Lupus Erythematosus. *Lupus*, **18**, 777-784. https://doi.org/10.1177/0961203309104860

[40] Cervera, R., Khamashta, M.A., Font, J., Sebastiani, G.D., Gil, A., Lavilla, P., Aydintug, A.O., Jedryka-Goral, A., de Ramon, E., Fernandez-Nebro, A., *et al*. (1999) Morbidity and Mortality in Systemic Lupus Erythematosus during a 5-Year Period. A Multicenter Prospective Study of 1000 Patients. European Working Party on Systemic Lupus Erythematosus. *Medicine*, **78**, 167-175. https://doi.org/10.1097/00005792-199905000-00003

[41] Al-Adhoubi, N.K. and Bystrom, J. (2020) Systemic Lupus Erythematosus and Diffuse Alveolar Hemorrhage, Etiology and Novel Treatment Strategies. *Lupus*, **29**, 355-363. https://doi.org/10.1177/0961203320903798

[42] Amarnani, R., Yeoh, S.A., Denneny, E.K. and Wincup, C. (2020) Lupus and the Lungs: The Assessment and Management of Pulmonary Manifestations of Systemic Lupus Erythematosus. *Frontiers in Medicine*, **7**, Article ID: 610257. https://doi.org/10.3389/fmed.2020.610257

[43] Barile, L.A., Jara, L.J., Medina-Rodriguez, F., Garcia-Figueroa, J.L. and Miranda-Limon, J.M. (1997) Pulmonary Hemorrhage in Systemic Lupus Erythematosus. *Lupus*, **6**, 445-448. https://doi.org/10.1177/096120339700600506

[44] Martínez-Martínez, M.U. and Abud-Mendoza, C. (2014) Diffuse Alveolar Hemorrhage in Patients with Systemic Lupus Erythematosus. Clinical Manifestations, Treatment, and Prognosis. *Reumatología Clínica*, **10**, 248-253. https://doi.org/10.1016/j.reumae.2014.02.003

[45] Finucci Curi, P., Pierrestegui, M., Ortiz, A., Ceccato, F. and Paira, S. (2015) Pulmonary Hemorrhage in Patients with Systemic Lupus Erythematosus. Clinical Manifestations and Prognosis. *Medicina Clínica*, **145**, 375-379. https://doi.org/10.1016/j.medcle.2014.07.010

[46] Shen, M., Zeng, X., Tian, X., Zhang, F., Zeng, X., Zhang, X. and Xu, W. (2010) Diffuse Alveolar Hemorrhage in Systemic Lupus Erythematosus: A Retrospective Study in China. *Lupus*, **19**, 1326-1330. https://doi.org/10.1177/0961203310373106

[47] Rojas-Serrano, J., Pedroza, J., Regalado, J., Robledo, J., Reyes, E., Sifuentes-Osornio, J. and Flores-Suarez, L.F. (2008) High Prevalence of Infections in Patients with Systemic Lupus Erythematosus and Pulmonary Haemorrhage. *Lupus*, **17**, 295-299. https://doi.org/10.1177/0961203307086930

[48] Shi, D., Wang, D., Li, X., Zhang, H., Che, N., Lu, Z. and Sun, L. (2012) Allogeneic Transplantation of Umbilical Cord-Derived Mesenchymal Stem Cells for Diffuse Alveolar Hemorrhage in Systemic Lupus Erythematosus. *Clinical Rheumatology*, **31**, 841-846. https://doi.org/10.1007/s10067-012-1943-2

[49] Liu, G.-Y., Yang, H.-J., Tong, S.-Q., Li, Y.-J., Guo, A.-R. and Pang, H.-W. (2011) Value of Bronchoalveolar Lavage as a Rescue Measurement for Systemic Lupus Erythematosus Complicated with Diffuse Alveolar Hemorrhage. *Chinese Medical Journal*, **91**, 1917-1919.

[50] Weinrib, L., Sharma, O.P. and Quismorio, F.P. (1990) A Long-Term Study of Interstitial Lung Disease in Systemic Lupus Erythematosus. *Seminars in Arthritis and Rheumatism*, **20**, 48-56. https://doi.org/10.1016/0049-0172(90)90094-V

[51] Tansey, D., Wells, A.U., Colby, T.V., Ip, S., Nikolakoupolou, A., Du Bois, R.M., Hansell, D.M. and Nicholson, A.G. (2004) Variations in Histological Patterns of Interstitial Pneumonia between Connective Tissue Disorders and Their Relationship to Prognosis. *Histopathology*, **44**, 585-596. https://doi.org/10.1111/j.1365-2559.2004.01896.x

[52] Pope, J. (2008) An Update in Pulmonary Hypertension in Systemic Lupus Erythematosus—Do We Need to Know about It? *Lupus*, **17**, 274-277. https://doi.org/10.1177/0961203307087188

[53] Robles-Perez, A. and Molina-Molina, M. (2015) Treatment Considerations of Lung Involvement in Rheumatologic Disease. *Respiration*, **90**, 265-274. https://doi.org/10.1159/000441238

[54] Branger, S., Schleinitz, N., Gayet, S., Veit, V., Kaplanski, G., Badier, M., Magnan, A. and Harlé, J.R. (2004) Le syndrome des poumons rétractés et les maladies auto-immunes. *La Revue de Médecine Interne*, **25**, 83-90. https://doi.org/10.1016/j.revmed.2003.09.010

[55] Karim, M.Y., Miranda, L.C., Tench, C.M., Gordon, P.A., D'Cruz, D.P., Khamashta, M.A. and Hughes, G.R. (2002) Presentation and Prognosis of the Shrinking Lung Syndrome in Systemic Lupus Erythematosus. *Seminars in Arthritis and Rheumatism*, **31**, 289-298. https://doi.org/10.1053/sarh.2002.32555

[56] Duron, L., Cohen-Aubart, F., Diot, E., Borie, R., Abad, S., Richez, C., Banse, C., Vittecoq, O., Saadoun, D., Haroche, J., *et al*. (2016) Shrinking Lung Syndrome Associated with Systemic Lupus Erythematosus: A Multicenter Collaborative Study of 15 New Cases and a Review of the 155 Cases in the Literature Focusing on Treatment Response and Long-Term Outcomes. *Autoimmunity Reviews*, **15**, 994-1000. https://doi.org/10.1016/j.autrev.2016.07.021

[57] Hoffbrand, B.I. and Beck, E.R. (1965) “Unexplained” Dyspnoea and Shrinking Lungs in Systemic Lupus Erythematosus. *British Medical Journal*, **1**, 1273-1277. https://doi.org/10.1136/bmj.1.5445.1273

[58] Allen, D., Fischer, A., Bshouty, Z., Robinson, D.B., Peschken, C.A., Hitchon, C., El-Gabalawy, H., Meyers, M. and Mittoo, S. (2012) Evaluating Systemic Lupus Erythematosus Patients for Lung Involvement. *Lupus*, **21**, 1316-1325. https://doi.org/10.1177/0961203312454343

[59] Borrell, H., Narvaez, J., Alegre, J.J., Castellvi, I., Mitjavila, F., Aparicio, M., Armengol, E., Molina-Molina, M. and Nolla, J.M. (2016) Shrinking Lung Syndrome in Systemic Lupus Erythematosus: A Case Series and Review of the Literature. *Medicine*, **95**, e4626. https://doi.org/10.1097/MD.0000000000004626

[60] Langenskiöld, E., Bonetti, A., Fitting, J.W., Heinzer, R., Dudler, J., Spertini, F. and Lazor, R. (2012) Shrinking Lung Syndrome Successfully Treated with Rituximab and Cyclophosphamide. *Respiration*, **84**, 144-149. https://doi.org/10.1159/000334947

[61] Van Veen, S., Peeters, A.J., Sterk, P.J. and Breedveld, F.C. (1993) The “Shrinking Lung Syndrome” in SLE, Treatment with Theophylline. *Clinical Rheumatology*, **12**, 462-465. https://doi.org/10.1007/BF02231771

[62] Muñoz-Rodríguez, F., Font, J., Badia, J., Miret, C., Barberà, J., Cervera, R. and Ingelmo, M. (1997) Shrinking Lungs Syndrome in Systemic Lupus Erythematosus: Improvement with Inhaled Beta-Agonist Therapy. *Lupus*, **6**, 412-414. https://doi.org/10.1177/096120339700600413

[63] Guleria, V.S., Singh, P.K., Saxena, P. and Subramanian, S. (2014) Shrinking Lung Syndrome in Systemic Lupus Erythematosus-Scleroderma Overlap. *Lung India*, **31**, 407-409. https://doi.org/10.4103/0970-2113.142152

[64] Benham, H., Garske, L., Vecchio, P. and Eckert, B.W. (2010) Successful Treatment of Shrinking Lung Syndrome with Rituximab in a Patient with Systemic Lupus Erythematosus. *Journal of Clinical Rheumatology*, **16**, 68-70. https://doi.org/10.1097/RHU.0b013e3181d0757f

[65] Penacoba Toribio, P., Corica Albani, M.E., Mayos Perez, M. and Rodriguez de la Serna, A. (2014) Rituximab in the Treatment of Shrinking Lung Syndrome in Systemic Lupus Erythematosus. *Reumatología Clínica*, **10**, 325-327. https://doi.org/10.1016/j.reumae.2013.09.003

[66] Robles-Perez, A., Dorca, J., Castellvi, I., Nolla, J.M., Molina-Molina, M. and Narvaez, J. (2020) Rituximab Effect in Severe Progressive Connective Tissue Disease-Related Lung Disease: Preliminary Data. *Rheumatology International*, **40**, 719-726. https://doi.org/10.1007/s00296-020-04545-0

[67] Reyes, F. and Lazaro, D. (2016) Systemic Lupus Erythematosus Complicated by Shrinking Lung Syndrome Treated with Belimumab: A Case Report. *Chest*, **150**, 300A. https://doi.org/10.1016/j.chest.2016.08.313

[68] Shah, S.J. (2012) Pulmonary Hypertension. *JAMA*, **308**, 1366-1374. https://doi.org/10.1001/jama.2012.12347

[69] Chen, H.A., Hsu, T.C., Yang, S.C., Weng, C.T., Wu, C.H., Sun, C.Y. and Lin, C.Y. (2019) Incidence and Survival Impact of Pulmonary Arterial Hypertension among Patients with Systemic Lupus Erythematosus: A Nationwide Cohort Study. *Arthritis Research & Therapy*, **21**, 82. https://doi.org/10.1186/s13075-019-1868-0

[70] Xu, S.Z., Yan, L., Li, X.P., Li, X.M., Shuai, Z.W., Leng, R.X., Pan, H.F. and Ye, D.Q. (2018) Features Associated with Pulmonary Arterial Hypertension in Chinese Hospitalized Systemic Lupus Erythematosus Patients. *Clinical Rheumatology*, **37**, 1547-1553. https://doi.org/10.1007/s10067-018-4056-8

[71] Hachulla, E., Jais, X., Cinquetti, G., Clerson, P., Rottat, L., Launay, D., Cottin, V., Habib, G., Prevot, G., Chabanne, C., *et al*. (2018) Pulmonary Arterial Hypertension Associated with Systemic Lupus Erythematosus: Results from the French Pulmonary Hypertension Registry. *Chest*, **153**, 143-151. https://doi.org/10.1016/j.chest.2017.08.014

[72] Lian, F., Chen, D., Wang, Y., Ye, Y., Wang, X., Zhan, Z., Xu, H., Liang, L. and Yang, X. (2012) Clinical Features and Independent Predictors of Pulmonary Arterial Hypertension in Systemic Lupus Erythematosus. *Rheumatology International*, **32**, 1727-1731. https://doi.org/10.1007/s00296-011-1880-4

[73] Li, J., Leng, X., Li, Z., Ye, Z., Li, C., Li, X., Zhu, P., Wang, Z., Zheng, Y. and Li, X. (2014) Chinese SLE Treatment and Research Group Registry: III. Association of Autoantibodies with Clinical Manifestations in Chinese Patients with Systemic Lupus Erythematosus. *Journal of Immunology Research*, **2014**, Article ID: 809389. https://doi.org/10.1155/2014/809389

[74] Gonzalez-Lopez, L., Cardona-Muñoz, E.G., Celis, A., García-de la Torre, I., Orozco-Barocio, G., Salazar-Paramo, M., GarciaGonzalez, C., Garcia-Gonzalez, A., Sanchez-Ortiz, A., Trujillo-Hernandez, B., *et al*. (2004) Therapy with Intermittent Pulse Cyclophosphamide for Pulmonary Hypertension Associated with Systemic Lupus Erythematosus. *Lupus*, **13**, 105-112. https://doi.org/10.1191/0961203304lu509oa

[75] Sanchez, O., Sitbon, O., Jais, X., Simonneau, G. and Humbert, M. (2006) Immunosuppressive Therapy in Connective Tissue Diseases-Associated Pulmonary Arterial Hypertension. *Chest*, **130**, 182-189. https://doi.org/10.1378/chest.130.1.182

[76] Miyamichi-Yamamoto, S., Fukumoto, Y., Sugimura, K., Ishii, T., Satoh, K., Miura, Y., Tatebe, S., Nochioka, K., Aoki, T., Do, E.Z., *et al*. (2011) Intensive Immunosuppressive Therapy Improves Pulmonary Hemodynamics and Long-Term

Prognosis in Patients with Pulmonary Arterial Hypertension Associated with Connective Tissue Disease. *Circulation Journal*, **75**, 2668-2674. https://doi.org/10.1253/circj.CJ-11-0473

[77] Kommireddy, S., Bhyravavajhala, S., Kurimeti, K., Chennareddy, S., Kanchinadham, S., Rajendra Vara Prasad, I. and Rajasekhar, L. (2015) Pulmonary Arterial Hypertension in Systemic Lupus Erythematosus May Benefit by Addition of Immunosuppression to Vasodilator Therapy: An Observational Study. *Rheumatology*, **54**, 1673-1679. https://doi.org/10.1093/rheumatology/kev097

[78] Aviña-Zubieta, J.A., Lacaille, D., Sayre, E.C., Kopec, J., Choi, H.K. and Esdaile, J.M. (2012) Risk of Pulmonary Embolism and Deep Vein Thrombosis in Systemic Lupus Erythematosus: A Population-Based Cohort Study. *Arthritis Research & Therapy*, **14**, A53. https://doi.org/10.1186/ar3987

[79] You, H., Zhao, J., Wang, Q., Tian, X., Li, M. and Zeng, X. (2020) Characteristics and Risk Factors of Pulmonary Embolism in Patients with Systemic Lupus Erythematosus: A Case Control Study. *Clinical and Experimental Rheumatology*, **38**, 940-948. https://doi.org/10.1136/lupus-2020-eurolupus.39

[80] Smith, S.B., Geske, J.B., Maguire, J.M., Zane, N.A., Carter, R.E. and Morgenthaler, T.I. (2010) Early Anticoagulation Is Associated with Reduced Mortality for Acute Pulmonary Embolism. *Chest*, **137**, 1382-1390. https://doi.org/10.1378/chest.09-0959

[81] Kearon, C., Akl, E.A., Ornelas, J., Blaivas, A., Jimenez, D., Bounameaux, H., Huisman, M., King, C.S., Morris, T.A., Sood, N., *et al*. (2016) Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*, **149**, 315-352. https://doi.org/10.1016/j.chest.2015.11.026

[82] Meyer, G., Vieillard-Baron, A. and Planquette, B. (2016) Recent Advances in the Management of Pulmonary Embolism: Focus on the Critically Ill Patients. *Annals of Intensive Care*, **6**, 19. https://doi.org/10.1186/s13613-016-0122-z

[83] Orens, J.B., Martinez, F.J. and Lynch, J.P. (1994) Pleuropulmonary Manifestations of Systemic Lupus Erythematosus. *Rheumatic Disease Clinics of North America*, **20**, 159-193. https://doi.org/10.1016/S0889-857X(21)00230-1

[84] Skeoch, S., Weatherley, N., Swift, A.J., Oldroyd, A., Johns, C., Hayton, C., Giollo, A., Wild, J.M., Waterton, J.C., Buch, M., *et al*. (2018) Drug-Induced Interstitial Lung Disease: A Systematic Review. *Journal of Clinical Medicine*, **7**, 356. https://doi.org/10.3390/jcm7100356

[85] Spagnolo, P., Bonniaud, P., Rossi, G., Sverzellati, N. and Cottin, V. (2022) Drug-Induced Interstitial Lung Disease. *European Respiratory Journal*, **60**, Article ID: 2102776. https://doi.org/10.1183/13993003.02776-2021