Ukrainian Journal of Nephrology and Dialysis
Scientific and Practical, Medical Journal

Founder:
- National Kidney Foundation of Ukraine

ISSN 2304-0238;
eISSN 2616-7352

Journal homepage: https://ukrjnd.com.ua

Case Reporte

doi: 10.31450/ukrjnd.3(83).2024.02

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The scarcity dilemma in lupus nephritis: A rare case of diffuse alveolar hemorrhage and its multitargeted management

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Citation: Badrinath TA, Pathak N, Thampan SJ, Gunasekaran I. The scarcity dilemma in lupus nephritis: A rare case of diffuse alveolar hemorrhage and its multitargeted management. Ukr J Nephrol Dial. 2024;3(83): 8-13. doi: 10.31450/ukrjnd.3(83).2024.02.

Abstract. *Systemic lupus erythematosus (SLE) is an autoimmune disease that often involves lupus nephritis, affecting the kidneys. A severe and rare complication of SLE is diffuse alveolar hemorrhage. When both conditions occur together in a young male, the prognosis is generally poor. Managing SLE effectively requires strong immunosuppression, but despite the availability of new immunosuppressive agents, treating lupus nephritis remains challenging. Many patients do not achieve complete remission with conventional treatments, highlighting the need for better therapeutic strategies. Research indicates that targeting multiple components of the immune system can be more effective for patients who do not respond to standard treatments, leading to the adoption of multitarget therapy in lupus nephritis.*

We present a case report of a young male with biopsy-proven Class IV lupus nephritis and diffuse alveolar hemorrhage who did not respond well to conventional treatments but showed improvement with a multitargeted treatment regimen.

Key words: *lupus nephritis, diffuse alveolar hemorrhage, multitarget therapy, tacrolimus, mycophenolate mofetil.*

Article history:
Received May 2, 2024
Received in revised form July 8, 2024
Accepted July 12, 2024

Conflict of interest. The author declares no conflict of interest.

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УДК 616.5-002.525.2+616.611-002.524]:616.61-005.1-07-08

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Дилема вовчакового нефриту: рідкісний випадок дифузного альвеолярного крововиливу та його мультитаргетного лікування

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Резюме. *Системний червоний вовчак (СЧВ) – це аутоімунне захворювання, яке часто супроводжується ураженням нирок. Дифузний альвеолярний крововилив є важким та рідкісним респіраторним ускладненням СЧВ. У разі розвитку дифузного альвеолярного крововиливу у пацієнта з вовчаковим нефритом чоловічої статі, прогноз, як правило, негативний. Лікування СЧВ вимагає ефективної імуносупресії, але, незважаючи на прогрес в імуносупресії, лікування вовчакового нефриту залишається складним. Багато пацієнтів не досягають повної ремісії за допомогою існуючих методів лікування, що вимагає кращих терапевтичних стратегій. Останні дослідження демонструють ефективність мультитаргетної терапії у пацієнтів, які не відповідають на стандартне лікування.*

Ця робота демонструє клінічний випадок дифузного альвеолярного крововиливу у чоловіка з вовчаковим нефритом IV класу, підтвердженого біопсією нирки, який не відповів належним чином на стандартне лікування, але продемонстрував покращення за застосування мультитаргетної схеми лікування.

Ключові слова: *вовчаковий нефрит, дифузний альвеолярний крововилив, мультитаргетна терапія, такролімус, мікофенолату мофетил.*

Introduction. Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect multiple organ systems, most commonly presenting as lupus nephritis (LN) in the kidneys [1]. Diffuse alveolar hemorrhage (DAH) is a rare and serious complication of SLE, predominantly affecting females [2]. Conventional treatments for SLE with LN include glucocorticoids combined with mycophenolate mofetil (MMF) or cyclophosphamide [3]. However, some patients do not respond to these standard treatments and are considered refractory. Due to the essential role of immunosuppression in managing the disease, multitarget therapy with tacrolimus has shown clinical improvement in patients who do not respond adequately to conventional immunosuppressive therapy [4].

We present a rare case of a young male with Class IV LN and DAH who exhibited a heterogeneous response to immunosuppression across different organ systems. Achieving disease remission required a multitarget regimen with tacrolimus, MMF, and high-dose glucocorticoids.

Case report. A 22-year-old male was admitted with a gradual onset of oliguria, shortness of breath, and coughing up blood, which worsened over the course of a week. Initial arterial blood gas analysis indicated hypoxemia. Chest imaging at presentation showed bilateral ground-glass opacities with thickening of the interlobar septa, consistent with diffuse alveolar hemorrhage (DAH) (Fig. 1).

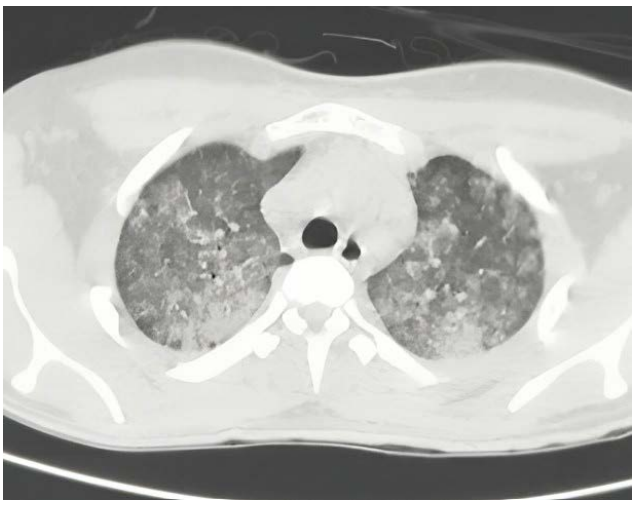

Fig. 1. High-resolution computed tomography (HRCT) of the thorax, performed in the supine position, showing bilateral diffuse and scattered areas of ground-glass opacities predominantly in the dependent lung fields, with areas of interlobar septal thickening suggestive of diffuse alveolar hemorrhage.

Laboratory investigations revealed normocytic normochromic anemia, deranged kidney function tests, proteinuria, and microscopic hematuria. The progress of important parameters on the day of admission and during the course of treatment is shown in Table 1.

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Table 1

Laboratory data during the disease course

LAB PARAMETERS	DAY – 0*	DAY – 14**	DAY – 22***	DAY – 90****
Haemoglobin (g/dL)	9.8	9.6	9.0	9.2
MCH (pg)	28.5	29	27.9	30.2
MCHC (g/dL)	32.5	33	34.6	33.5
Urine protein to creatinine ratio	2.34	1.24	0.96	0.42
Creatinine (mg/dL)	2.8	1.3	1.0	0.6
Blood Urea (mg/dL)	98	54	45	22
eGFR (mL/min/1.73 m^2)	32	80	109	140

* *On the day of hospital admission. ** Day 14 – During the course of MMF and steroids. *** Day 22 – During relapse of symptoms of DAH requiring hospital re-admission. **** Day 90 – During follow-up while the patient was on multitargeted therapy.*

Abbreviations: MCH - mean corpuscular hemoglobin; MCHC - mean corpuscular hemoglobin concentration; eGFR - estimated glomerular filtration rate.

The ANA test showed a speckled pattern of immunofluorescence. Both C-ANCA and P-ANCA were negative, making Wegener's granulomatosis an unlikely diagnosis. Therefore, a complete ANA profile was conducted, which was positive for mixed connective tissue disorder, as shown in Table 2.

Table 2

Complete ANA profile by immunoblot assay

Test description ANA studied	Observed value	Disease association
Mi – 2	negative	POLYMYOSITIS, DERMATOMYOSITIS
Ku	strong positive	SLE, SJOGREN'S SYNDROME, SCLERODERMA, MYOSITIS, MCTD
Sm / RNP	strong positive	MCTD, SHARP SYNDROME
Sm	strong positive	SLE
SSA	strong positive	SJOGREN'S SYNDROME
Ro 52kD	strong positive	SJOGREN'S SYNDROME
SSB	negative	SJOGREN'S SYNDROME, SLE
Scl – 70	strong positive	SYSTEMIC SCLEROSIS
PM Scl 100	negative	OVERLAP SYNDROME
Jo – 1	negative	POLYMYOSITIS
CENP – A/B	negative	CREST SYNDROME
PCNA	negative	SLE
dsDNA	negative	SLE
Nucleosome	negative	SLE
Histones	negative	DRUG INDUCED LUPUS, RHEUMATOID ARTHRITIS
Ribosome PO	strong positive	SLE
AMA M2	weak positive	PRIMARY BILIARY CIRRHOSIS

Abbreviations: Sm – smith; RNP – ribonucleoprotein; SSA - Sjogren's syndrome-related antigen A; SSB - Sjogren's syndrome-related antigen B; Scl -70 - scleroderma 70; PM-Scl - polymyositis scleroderma; CENP -A/B - centromere protein A and B; PCNA - proliferating cell nuclear antigen; dsDNA - double-stranded DNA; AMA - M2 anti mitochondrial antibody M2; SLE - systemic lupus erythematosus; MCTD - mixed connective tissue disorder.

Based on the findings, a kidney biopsy was performed, revealing 22 glomeruli. Out of these, 19 glomeruli exhibited endocapillary hypercellularity (in over 50% of the glomeruli) with neutrophilic infiltrate and karyorrhexis. Seven glomeruli had hyaline deposits, some showed mild mesangial expansion with or without mesangial proliferation, and the remaining three appeared histologically normal. There was also mild interstitial fibrosis and tubular atrophy affecting 20-24% of the sampled cortex. Direct immunofluorescence showed a full house pattern with granular positivity along the glomerular capillary wall and mesangium: IgG 3+, IgM 1-2+, IgA 1-2+, C3 2-3+, C1q 2-3+, Kappa light chain 2-3+, and Lambda light chain 3+. Histopathological, clinical, biochemical (low C3 and C4 levels), and serological findings suggest Class IV - diffuse lupus nephritis (Fig. 2).

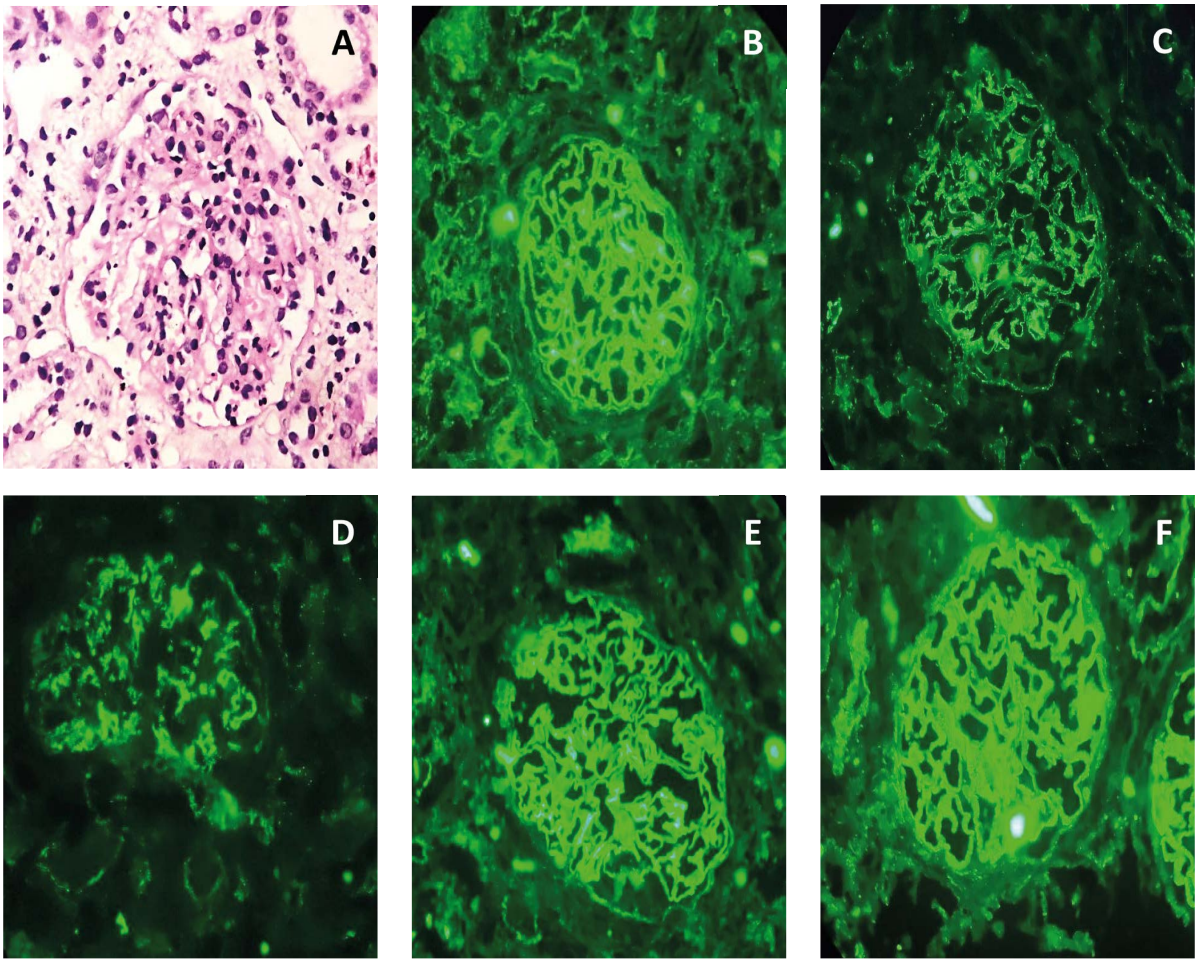

Fig. 2. Kidney biopsy results. A) H&E stain (400x) shows a glomerulus with endocapillary hypercellularity and neutrophilic infiltrate. B) IgG: 3+ C) C3: 2-3+ D) C1q: 2-3+ E) Kappa light chain: 2-3+ F) Lambda light chain: 3+

A diagnostic fibreoptic bronchoscopy was performed, and the bronchoalveolar lavage fluid cytology from both the right and left lungs showed similar findings. Both smears were cellular, consisting of increased alveolar macrophages, hemosiderin-laden macrophages, a few benign and reactive bronchial epithelial cells, occasional mature squamous epithelial cells, and a few acute and chronic inflammatory cells in a hemorrhagic background. Pearl stain showed 60%-65% hemosiderin-laden macrophages, suggestive of diffuse alveolar hemorrhage (Fig. 3).

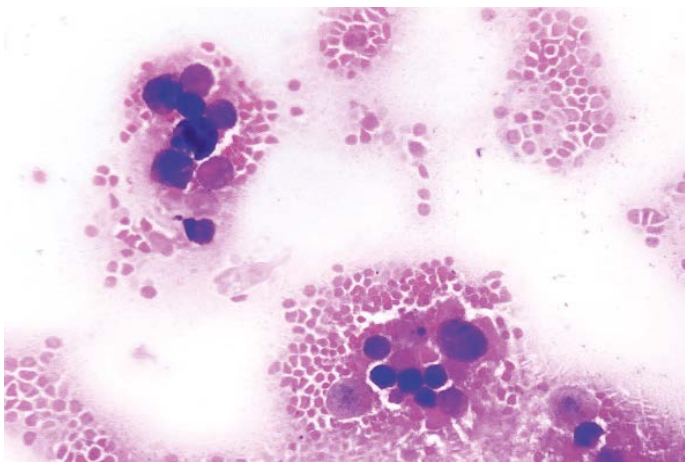

Fig. 3. Hemosiderin-laden macrophages observed in bronchoalveolar lavage fluid cytology (Pearl's stain, 400x).

Although the patient demonstrated strong serological evidence of a mixed connective tissue disorder (MCTD) on the ENA profile, he did not show typical clinical signs and symptoms of MCTD. This highlights the importance of regular follow-up to screen for potential future manifestations of MCTD. With a working diagnosis of Class IV lupus nephritis (LN) presenting with diffuse alveolar hemorrhage (DAH), the patient was started on pulse steroid therapy (500 mg IV once daily) for three days, followed by oral glucocorticoids (1 mg/kg). Mycophenolate mofetil (MMF, 720 mg twice daily) was then added to the treatment regimen. The patient improved symptomatically and was discharged after 14 days on MMF and oral prednisolone.

On Day 22 of follow-up post-discharge, while the patient was compliant with MMF and tapering doses of steroids, he developed hemoptysis, indicating a clinical and radiological worsening of DAH. He was readmitted and restarted on pulse steroid therapy and switched to oral glucocorticoids. Although there was a symptomatic improvement on pulse steroid therapy, symptoms of DAH relapsed within two days after switching to oral glucocorticoids. Despite adherence to conventional immunosuppressive treatment with MMF and oral steroids, the patient showed a heterogeneous response: worsening DAH but improved kidney function tests (see Table 2).

Given this, a diagnosis of Class IV LN with DAH not adequately responding to conventional treatments was confirmed. Consequently, the patient was started on a multitargeted therapy regimen, including tacrolimus (4 mg/day), MMF (720 mg twice daily), hydroxychloroquine (300 mg/day), and prednisolone (60 mg/day). Prednisolone was tapered by 10 mg/day every two weeks to a maintenance dose of 10 mg/day over three months. The patient had an uneventful follow-up at three months post-initiation of multitargeted therapy.

Discussion. SLE predominantly affects young women, with a male-to-female ratio of 1:9. LN has a mortality rate ranging from 30% to 50% [1]. Diffuse alveolar hemorrhage (DAH), although rare, has a mortality rate of 60% to 80% and occurs in 1% to 5% of SLE cases [2]. Characterized by blood in the alveoli, DAH can result from autoimmune disorders like SLE, vasculitides, infections, drug reactions, and lung injuries. Symptoms include hemoptysis, dyspnea, and hypoxemia, and diagnosis involves clinical evaluation, imaging, bronchoscopy, and histopathology [3].

A and T cell activation drives inflammation and cytokine production in SLE, highlighting the importance of immune suppression in patient management. Multitarget therapy, which combines steroids, mycophenolate mofetil (MMF), and tacrolimus, is recommended for refractory cases to enhance efficacy and minimize side effects [4]. Plasmapheresis may be considered for severe DAH that does not respond to high-dose steroid therapy in SLE.

In our study, DAH responded to high-dose methylprednisolone but remained unresponsive to conventional steroid doses. This may be attributed to increased expression of P-glycoprotein (P-gp) within lung inflammatory cells. P-gp, encoded by the multidrug resistance 1 (MDR-1) gene, mediates drug resistance and affects intracellular corticosteroid levels [5]. Research indicates that elevated P-gp expression in peripheral blood lymphocytes correlates with reduced corticosteroid responsiveness in SLE [5]. Inhibiting P-gp could enhance intracellular drug concentrations [5]. Tacrolimus, a calcineurin inhibitor, not only inhibits P-gp but also suppresses T cell activation and antibody production by inhibiting T cell-dependent B cell activation, contributing to its efficacy in autoimmune conditions [5, 6].

To the best of our knowledge, this is the first study to report differing responses to immunosuppression across two organ systems in SLE. Pulmonary involvement necessitated pulse steroid therapy and multitargeted immunosuppression, while kidney improvement was seen with glucocorticoids and MMF. This variability underscores the complex factors influencing drug efficacy. Despite our insights, limitations include the lack of data on P-gp expression and tacrolimus effects, which warrants further investigation into their mechanisms.

Conclusions. Our case report underscores the effectiveness of a multitargeted regimen in achieving remission for a patient with Class IV lupus nephritis complicated by diffuse alveolar hemorrhage, who exhibited varying responses to immunosuppression across different organ systems. Effective management requires consideration of organ-specific factors, patient variability, and careful monitoring of drug levels. The multitargeted treatment approach enables the selection of optimized immunosuppression for individuals who do not respond adequately to conventional therapies.

Ethics Committee approval. The Institute's ethics committee has approved this report for publication (RC/2024/12). We confirm that this work is original, has not been published elsewhere, and is not currently under consideration for publication elsewhere.

Author's contribution.

Thannushree Aritakulu Badrinath: contributed to data collection and design of case report, performed the literature search, and drafted the manuscript;

Nadabwip Pathak: contributed to the conceptualization of the case report, performed the literature search, provided critical revisions and final approval of the manuscript;

Sebin John Thampan: contributed to the data analysis, reviewed the case report, and provided valuable analysis on framing the case report;

Indira Gunasekaran: studied and provided data related to pathology in reference to our case report and provided valuable analysis on framing the case report.

Conflict of interest. The authors declare that there are no conflicts of interest related to this research.

Funding source. No financial support was sought for the completion of this study.

Acknowledgment. The authors would like to acknowledge our Institute for granting access to the medical record database, which was crucial for completing this research study.

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