Scientific Research Publishing

Case Reports in Clinical Medicine, 2025, 14(11), 599-606
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Hypersensitivity Reaction to Lamotrigine with Rash and Cervical Adenopathies: A Case Report

Flávia Fundora Ramos, Catarina Pinto Silva, Flávia Freitas, Laura Caine

Internal Medicine Department of Hospital Santa Maria Maior, Unidade Local de Saúde Barcelos/Esposende, Braga, Portugal
Email: flaviafundoraramos@gmail.com

How to cite this paper: Ramos, F.F., Silva, C.P., Freitas, F. and Caine, L. (2025) Hypersensitivity Reaction to Lamotrigine with Rash and Cervical Adenopathies: A Case Report. *Case Reports in Clinical Medicine*, **14**, 599-606.
https://doi.org/10.4236/crcm.2025.1411077

Received: September 25, 2025
Accepted: November 3, 2025
Published: November 6, 2025

Abstract

Introduction: Lamotrigine is an anticonvulsant widely used in the treatment of epilepsy and affective disorders. Despite its favorable safety profile, potentially serious hypersensitivity reactions can occur. **Case Report:** A female patient in her early thirties developed a lupus-like maculopapular rash and painful cervical adenopathy after three weeks of treatment with lamotrigine. Laboratory tests revealed initial lymphopenia and slightly increased IgG. Serology for hepatotropic viruses, HIV, CMV, and EBV (IgM) was negative. Computed tomography revealed bilateral level II cervical adenopathy and a thin layer of pericardial effusion. The condition was interpreted as a hypersensitivity reaction to lamotrigine, which resolved after discontinuation of the drug and oral corticosteroid therapy. **Conclusion:** Rash associated with adenopathy in the first weeks of lamotrigine use should raise suspicion of a serious adverse reaction and justify immediate discontinuation of the drug.

Keywords

Lamotrigine, Adverse Drug Reaction, Hypersensitivity, Drug-Induced Rash, Cervical Adenopathy

1. Introduction

Lamotrigine is an antiepileptic medication that functions primarily as a voltage-gated sodium channel blocker. It has become widely used not only in the management of epilepsy but also in the treatment of affective disorders, most notably bipolar disorder. In addition to these well-established therapeutic roles, lamotrigine is sometimes prescribed for several off-label indications, reflecting its broad clinical utility across different patient populations.

Although lamotrigine is generally considered to be well tolerated and safe for most individuals, adverse cutaneous reactions remain a significant clinical concern. It is estimated that around ten percent of patients receiving lamotrigine therapy will develop some form of skin reaction. While the majority of these rashes are mild and self-limiting, a small but clinically important proportion (approximately 0.1% to 0.3%) will progress to severe and potentially life-threatening conditions. These include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and the drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome [1] [2].

Several factors have been identified as increasing the risk of developing lamotrigine-induced rashes. Among the most important are initiating treatment with a high starting dose, a rapid or sudden escalation in dosage, and concomitant use of valproic acid, which interferes with lamotrigine metabolism. Additional risk factors include a history of previous hypersensitivity or cutaneous reactions to other antiepileptic medications, as well as younger age, particularly in children under the age of thirteen [3].

The time of onset for lamotrigine-associated rashes is also clinically relevant. Most eruptions typically occur between the second and eighth week after treatment initiation, but cases have been documented as late as six months into therapy. This variability highlights the need for careful and continuous monitoring of patients, especially during the early months of treatment. Importantly, the appearance or extent of the rash alone does not reliably distinguish between benign self-limited reactions and those that may progress to severe, life-threatening syndromes. For this reason, current clinical recommendations emphasize that lamotrigine should be discontinued at the first clear sign of a drug-related rash, unless there is strong evidence that the skin manifestation is unrelated to medication exposure.

Finally, early recognition and prompt discontinuation of lamotrigine remain the cornerstone of preventing progression to severe cutaneous adverse reactions. Nevertheless, clinicians must be aware that immediate withdrawal does not fully guarantee that the rash will not evolve into a more dangerous condition. Thus, early diagnosis, careful patient education, and vigilant follow-up are essential components of safe lamotrigine therapy.

2. Case Report

A female patient in her early thirties, with no significant past medical history apart from a diagnosis of plantar fasciitis and a probable family history suggestive of psoriasis, was started on lamotrigine for the management of an anxiety disorder. The initiation of therapy followed the standard titration protocol. During the first week, she received lamotrigine at a dose of 25 mg once daily. In the second week, the regimen was adjusted to 25 mg administered twice a day. The following week, the dosage was increased further to 25 mg in the morning and 50 mg in the evening. By the fourth week, the planned maintenance dose reached 50 mg twice daily.

Approximately three days before the final dose escalation, the patient noticed

generalized muscle pain accompanied by odynophagia. At that time, she did not report fever, malaise, or any other systemic symptoms. Soon after the increase in dose, however, she developed a widespread maculopapular rash that involved multiple areas of the body. This cutaneous eruption was associated with the presence of numerous tender and mobile cervical lymph nodes. Notably, there was no enlargement of the axillary or inguinal lymph nodes.

Despite the cutaneous and lymphatic manifestations, the patient did not develop fever, chills, or other systemic warning signs. The patient was not taking any other medications, had no known allergies, and had a body weight of 60 kg, ruling out other drug interactions or dose adjustments based on body weight. When she presented to the emergency department for the first time, she was hemodynamically stable, afebrile, and in no acute distress. Physical examination confirmed the diffuse rash, as illustrated in the figures below (**Figures 1-3**), along with palpable but mobile cervical lymphadenopathy. Importantly, abdominal examination did not reveal hepatomegaly or splenomegaly, and no other organ involvement was detected at this initial assessment.

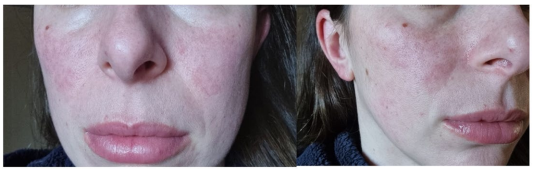

Figure 1. Lupus-like malar rash.

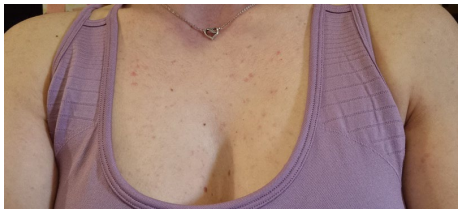

Figure 2. Difusse maculopapular rash (chest).

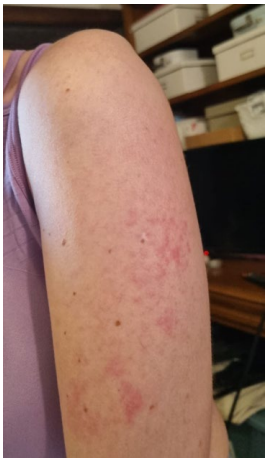

Figure 3. Difusse maculopapular rash (arm).

Detailed Timeline

Day 0: Initiated lamotrigine 25 mg/day;
Day 7: Adjusted to 25 mg twice daily;
Day 14: 25 mg morning, 50 mg evening;
Day 21: Planned increase to 50 mg twice daily;
Day 18: Onset of myalgia and odynophagia;
Day 22: Developed extensive maculopapular rash, cervical lymphadenopathy;
Day 22: Attended emergency services.

3. Laboratory Tests Carried out

The laboratory investigations carried out during the initial evaluation revealed only subtle abnormalities. Hematological analysis demonstrated mild neutrophilia accompanied by lymphopenia, while hemoglobin levels and platelet counts remained within the expected normal range, thereby excluding clinically significant anemia or thrombocytopenia at that stage. The inflammatory profile showed an erythrocyte sedimentation rate (ESR) of 20 mm/h, which is only mildly elevated, and a C-reactive protein (CRP) value below 0.5 mg/dL, indicating the absence of marked systemic inflammation.

Assessment of renal and metabolic function, including serum electrolytes, total protein, creatine kinase, myoglobin, and lactate dehydrogenase, revealed no abnormalities, suggesting preserved organ function and no evidence of muscle or tissue breakdown. Immunological studies showed that both immunoglobulin A (IgA) and immunoglobulin M (IgM) were within reference limits, while immunoglobulin G (IgG) was slightly elevated, a finding that may reflect either a nonspecific immune activation or prior antigenic exposure. Serum protein electrophoresis did not demonstrate any clinically relevant alterations.

Viral serology testing was performed to exclude infectious etiologies. Results showed positivity for Epstein-Barr virus (EBV) IgG antibodies with negative IgM, consistent with past infection rather than acute disease. Cytomegalovirus (CMV) serology revealed low IgG titers with negative IgM, also excluding acute infection. Screening for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) was negative, ruling out these potential viral cofactors.

Finally, the autoimmune profile was explored to exclude systemic autoimmune or connective tissue disorders that might explain the clinical presentation. Both antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA) tested negative, making autoimmune disease an unlikely contributor to the patient's symptoms.

4. Computed Tomography

The cervical tomodensitometry study performed did not identify any structural or dimensional changes in the parotid or submandibular glands bilaterally. Level II adenopathies were identified bilaterally, the largest on the right, with a hetero-

geneous structure, measuring 15 × 20 mm in the longest axial axes, and a nonspecific appearance. There were some other laterocervical lymph nodes bilaterally, but without criteria for adenopathy. There were also no supraclavicular, axillary, or mediastinal-hilar adenopathies. A thin layer of pericardial effusion and incidental hepatic hemangioma were identified. The remainder of the evaluation was unremarkable.

5. Diagnosis and Treatment

A diagnosis of probable hypersensitivity reaction to lamotrigine was established. After exhaustive study, no other possible cause was identified for the clinical picture presented. The drug was immediately discontinued, and oral corticosteroid therapy was started with Prednisolone 40 mg/day (approximately 0.5 - 1 mg/kg/day) for 5 days, and a slow tapering scheme, guided by the general response of the patient and resolution of the symptoms. After the first 2 weeks of treatment, complete resolution of the rash was observed, and after one month, no palpable lymphadenopathy remained. At that time, corticosteroid therapy was discontinued and follow-up laboratory studies showed normalization of lymphocyte counts and inflammatory markers. Cervical ultrasound confirmed the disappearance of lymphadenopathies. There was no clinical relapse with corticosteroid tapering, and after 2 months without treatment (3 months after symptom onset), the patient was discharged from follow-up.

6. Discussion

This clinical case illustrates a hypersensitivity reaction to lamotrigine, manifested primarily through the appearance of a diffuse rash accompanied by cervical lymphadenopathy. These findings are characteristic of an immune-mediated systemic response to the drug. The laboratory data provided further support for this interpretation: the presence of initial lymphopenia suggested immune system activation and redistribution of lymphocyte populations, while the detection of a mild pericardial effusion also pointed toward systemic involvement. Taken together, these elements reinforce the diagnosis of a drug-induced hypersensitivity reaction. Nevertheless, the absence of peripheral eosinophilia, along with the lack of significant hepatic, renal, or hematologic compromise, indicates that the reaction belonged to a milder spectrum and did not fully meet the criteria for DRESS syndrome [4] [5].

One of the key challenges faced by clinicians is the distinction between relatively benign exanthematous eruptions, which are often self-limited, and more severe cutaneous adverse drug reactions that can progress to life-threatening complications. Clinical warning signs that should heighten suspicion of a severe reaction include the development of high-grade fever, generalized lymphadenopathy involving multiple nodal regions, biochemical or clinical evidence of liver or kidney injury, marked hematological abnormalities such as eosinophilia or cytopenias, and the presence of systemic constitutional symptoms [6]. When such features are present, a diagnosis

of a severe hypersensitivity syndrome becomes more likely.

In suspected cases of lamotrigine hypersensitivity, immediate discontinuation of the medication is imperative. Delay in withdrawal increases the risk of progression toward more dangerous entities such as SJS, TEN, or DRESS, which are associated with significant morbidity and mortality [7]. Even after cessation of therapy, patients must be closely monitored, since the immune-mediated reaction may continue to evolve despite the absence of ongoing exposure to the drug. Careful clinical observation, repeated laboratory assessments, and timely supportive interventions are therefore essential to ensure patient safety.

This case also highlights an important consideration for prescribing practices. Although lamotrigine has well-established efficacy in epilepsy and bipolar disorder, its use in off-label contexts, such as anxiety disorders, requires careful reflection. Given the non-negligible incidence of hypersensitivity reactions and the potential for severe outcomes, clinicians should weigh the risks and benefits judiciously. In situations where other medications with a safer profile and formal regulatory approval are available, these agents should be prioritized over lamotrigine, particularly when treating conditions for which the drug is not officially indicated. Such caution may help minimize avoidable harm while preserving lamotrigine's therapeutic role in conditions where its efficacy is well supported by evidence.

The manufacturer's recommended lamotrigine titration schedule for adults who are not taking valproate or enzyme-inducing drugs is as follows [8]:

1) Weeks 1 and 2: 25 mg once daily.

2) Weeks 3 and 4: 50 mg once daily.

3) After Week 4: Increase the daily dose by up to 50 mg every 1 - 2 weeks, according to response and tolerability.

4) Usual maintenance dose: 100 - 200 mg per day, divided into one or two doses.

This gradual titration is designed to reduce the risk of serious skin reactions. Therefore, the regimen applied to the patient exceeded the recommendation by advancing the weekly increases in both dose and timing, constituting a possible risk factor for cutaneous adverse reactions.

The lymph node manifestation, without fever or multiorgan dysfunction, in this case, resembles the profile of moderate to severe cases reported in recent reviews. A 2023 report describes a similar progression, with rash and cervical lymphadenopathy without systemic involvement, also following relatively accelerated titration; clinical resolution occurred after drug discontinuation and corticosteroid treatment. Another case from 2024 presented with cutaneous rash and submandibular adenomegaly but progressed to toxic epidermal necrolysis and systemic inflammation, highlighting the severity spectrum and the importance of early diagnosis and management [9] [10].

7. Conclusion

This case emphasizes the crucial importance of careful clinical monitoring during the initial weeks of lamotrigine therapy, a period in which most hypersensitivity

reactions are known to occur. The appearance of a rash, particularly when accompanied by lymphadenopathy, should not be underestimated and must be regarded as an early warning sign of a potentially serious adverse drug reaction. In such circumstances, immediate discontinuation of lamotrigine is justified to prevent further progression toward more severe or life-threatening complications. Furthermore, the involvement of a multidisciplinary team—including dermatology, internal medicine, immunology, and, when appropriate, cardiology—ensures a comprehensive evaluation of the patient's condition and facilitates timely therapeutic decisions. This integrative approach underscores the balance that must always be maintained between the therapeutic benefits of lamotrigine and the vigilance required to mitigate its risks.

Acknowledgements

The authors are grateful to the patient who allowed to report her clinical manifestations in this report for her valuable contribution.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Hirsch, L.J., Weintraub, D.B., Buchhalter, J.R., *et al.* (2021) Lamotrigine-Induced Rash: Risk/Benefit Considerations in Adults and Children. *Epilepsia*, **62**, 748-760.

[2] Bloom, R. and Amber, K.T. (2017) Identifying the Incidence of Rash, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Patients Taking Lamotrigine: A Systematic Review of 122 Randomized Controlled Trials. *Anais Brasileiros de Dermatologia*, **92**, 139-141. https://doi.org/10.1590/abd1806-4841.20175070

[3] Jokubaitė, J., Martinėlė, L., Joskaudaitė, G. and Raudonis, T. (2023) Lamotrigine-Related Skin Rash. *Neurologijos Seminarai*, **27**, 223-234. https://doi.org/10.15388/ns.2023.27.98.3

[4] Kardaun, S.H., Sidoroff, A., Valeyrie-Allanore, L., Halevy, S., Davidovici, B.B., Mockenhaupt, M., *et al.* (2007) Variability in the Clinical Pattern of Cutaneous Side-Effects of Drugs with Systemic Symptoms: Does a Dress Syndrome Really Exist? *British Journal of Dermatology*, **156**, 609-611. https://doi.org/10.1111/j.1365-2133.2006.07704.x

[5] Chen, Y., Cho, Y., Chang, C. and Chu, C. (2013) Drug Reaction with Eosinophilia and Systemic Symptoms: A Drug-Induced Hypersensitivity Syndrome with Variable Clinical Features. *Dermatologica Sinica*, **31**, 196-204. https://doi.org/10.1016/j.dsi.2013.09.006

[6] Roujeau, J.C. and Stern, R.S. (1994) Severe Adverse Cutaneous Reactions to Drugs. *New England Journal of Medicine*, **331**, 1272-1285. https://doi.org/10.1056/nejm199411103311906

[7] Mockenhaupt, M. (2011) The Current Understanding of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. *Expert Review of Clinical Immunology*, **7**, 803-815. https://doi.org/10.1586/eci.11.66

[8] Nakamura, T., Tomita, M., Hirota, S., Matsunaga, T. and Uchimura, N. (2022) Impact of Selected Initial Titration Schedules on Safety and Long-Term Effectiveness of Lamotrigine for the Treatment of Mood Disorders. *Journal of Clinical Psychophar-*

macology, **42**, 350-356. https://doi.org/10.1097/jcp.0000000000001557

[9] Duan, Y., Qiu, F., Zhou, J., Liu, S., Zhao, D. and Qiu, C. (2023) Case Report: Progressive Skin Rash and Lymphadenopathy Associated with Lamotrigine-Valproic Acid Combination in a Bipolar Adolescent. *Frontiers in Pharmacology*, **14**, Article 1106423. https://doi.org/10.3389/fphar.2023.1106423

[10] Zhang, L., Yang, P., Zhu, Y., Liu, K. and Sun, Z. (2025) Toxic Epidermal Necrolysis Following Lamotrigine Replacement Therapy in a Woman Planning Pregnancy: A Case Report and Literature Review. *BMC Women's Health*, **25**, Article No. 371. https://doi.org/10.1186/s12905-025-03796-y