Case Report

Challenges in Diagnosing Lamotrigine-induced DRESS: A Unique Case of Acalculous Cholecystitis in Epilepsy

Safa Akeel Al-Hasan[1], Ali Abdulkareem Al-Fahham[2], Samih Akeel Al-hasan[3, 4], Baraa Akeel Al-Hasan[5, 6, 7], Fatma Akeel Al-Hasan[8], Ahmed Maki Radeef[9, 10, 11], Haider Abbas Hadi Al-Mhanaa[12], Ali Salah Wadday[13], Ghadeer Sabah Bustani[5*]

1. Department of Surgery, Faculty of Medicine, Kufa University, Kufa, Iraq.
2. Department of Ophthalmology, Najaf Teaching Hospital, Najaf, Iraq.
3. Department of Surgery, Faculty of Medicine, Jabir Ibn Hayyan Medical University, Najaf, Iraq.
4. Department of Anatomy, College of Medicine, University of Alkafeel, Najaf, Iraq.
5. Department of Medical Laboratory Technology, College of Medical Technology, The Islamic University, Najaf, Iraq.
6. Department of Laboratory, Al Najaf Veterinary Hospital, Najaf, Iraq.
7. Department of Veterinary Microbiology, College of Veterinary Medicine, University of Al-Qadisiyah, Diwaniyah, Iraq.
8. Department of pharmacy, Najaf Teaching Hospital, Najaf, Iraq.
9. Department of Anesthesia Techniques, College of Health and Medical Techniques, Al-Mustaqbal University, Babylon, Iraq.
10. Al-Furat Al-Awsat Hospital, Ministry of Health, Najaf, Iraq.
11. Intensive Care Unit, Department of Anesthesia, Health and Medical Technical College, Al-Furat Al-Awsat Technical University, Najaf, Iraq.
12. College of Nursing, Al-Mustaqbal University, Babylon, Iraq.
13. Department of Animal Husbandry, Faculty of Agricultural and Food Sciences and Environmental Management, University of Debrecen, Debrecen, Hungary.

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an infrequent yet severe idiosyncratic reaction to drugs, characterized by a diverse range of systemic manifestations and a mortality rate of 10% to 20%. Commonly associated with anticonvulsant drugs and sulfonamides, DRESS syndrome poses diagnostic challenges due to its variable presentation. This study presents a unique case of lamotrigine-induced DRESS associated with acalculous cholecystitis, an unprecedented manifestation. The patient, initially treated with levetiracetam and lamotrigine for generalized epilepsy, experienced a delayed onset of symptoms, with a European registry of severe cutaneous adverse reactions (RegiSCAR score of 7, confirming the diagnosis. Reactivation of *Epstein-Barr virus* was detected, suggesting a potential link between herpesvirus reactivation and DRESS pathogenesis. The case underscores the importance of careful monitoring and consideration of atypical organ involvement in DRESS diagnosis. Lamotrigine withdrawal resulted in rapid clinical resolution, allowing for a cautious transition to an alternative anti-epileptic medication which is valproate. This case contributes to the evolving understanding of DRESS syndrome, emphasizing the need for a comprehensive diagnostic approach in complex medication regimens.

Keywords: Acalculous cholecystitis, Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Herpesvirus reactivation, Lamotrigine

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*** Corresponding Author:**
Ghadeer Sabah Bustani, PhD.
Address: *Department of Medical Laboratory Technology, College of Medical Technology, The Islamic University, Najaf, Iraq.*
Phone: *964 (772) 8299090*
E-mail: *bustani@iunajaf.edu.iq*

Case History

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a fatal and complex hypersensitivity condition (Bocquet et al., 1996; González et al., 2024). In this syndrome, multiple organ systems, including the hematological, lymphatic, hepatic, and others, can be involved (Bonyadian & Kordi, 2020). Lamotrigine is an anti-epileptic medication that has an acceptable safety profile with mild central nervous system adverse effects (Richens, 1994; Vrhovski et al., 2022). Lamotrigine-associated skin rash occurs in 5% of patients but rarely requires hospitalization. DRESS is more common with other anticonvulsants, and levetiracetam is a rare cause of DRESS (Descamps et al., 2003; Seishima et al., 2006; Shiohara et al., 2007). To the best of our knowledge, acalculous cholecystitis in lamotrigine-induced DRESS has not yet been reported. In this study, we present a case of a patient on two anti-epileptic medications levetiracetam and lamotrigine that can cause DRESS syndrome. This was a great challenge to know the inciting drug, which was the second drug that introduced lamotrigine.

Clinical Presentation

A 29-year-old female was diagnosed with generalized epilepsy of myoclonus type and complex partial seizures. Initial treatment involved levetiracetam at a dosage of 500 mg, administered as half a tablet twice daily for the first week, followed by an escalation to 500 mg twice daily. Despite one month of continuous treatment, seizure control remained elusive. Subsequently, lamotrigine, a second anti-epileptic medication, was introduced into the therapeutic regimen (Komatsuda et al., 2008; Eshki et al., 2009; Brüning et al., 2024).

The initiation of lamotrigine involved a starting dose of 25 mg twice daily for 10 days, followed by an increment to 50 mg twice daily. Approximately, three weeks following the commencement of lamotrigine, the patient manifested symptoms, including low-grade fever (38-38.5 ˚C), painful enlargement of cervical and auricular lymph nodes, bone pain, headache, and a decrease in seizure control. This clinical state persisted for 10 days, during which the fever escalated to a high grade of 40-41 ˚C, accompanied by rigor and chills, partially responsive to antipyretic therapy.

Concurrently, the patient reported upper abdominal pain, nausea, vomiting, and decreased appetite. Physical examination revealed generalized lymphadenopathy, affecting cervical, auricular, axillary, inguinal, popliteal, and epitrochlear lymph nodes. The progression of symptoms included the development of an erythematous papillomacular rash on the arms, gradually extending to involve the abdomen, lower limbs, neck, and face. The rash was accompanied by severe pruritus.

Upon examination, the patient presented with a temperature of 40.5 ˚C, blood pressure of 110/60 mm Hg, oxygen saturation of 97%, a regular pulse rate of 118 beats per min with high volume, puffy face with jaundice, and non-pitting edema of the hands and feet. Comprehensive documentation of the rash on different parts of the body is provided in Figures 1, 2, 3 and 4. The abdominal examination revealed right upper quadrant tenderness with a positive Murphy sign.

Diagnostic Testing

Full laboratory investigations were done for the patient and the results are shown in Table 1. The blood film exhibited mild hypochromic red blood cells, with occasional oval cells and target cells; however, no malignant cells were identified. These findings were indicative of a presentation consistent with infectious mononucleosis. The blood culture demonstrated no bacterial growth.

Abdominal ultrasound revealed grade 1 fatty liver, with a gallbladder of normal size and shape, a thickened wall measuring 4 mm, and the absence of stones. The common bile duct appeared normal without the presence of stones, consistent with a diagnosis of acalculous cholecystitis, as illustrated in Figures 5 and 6.

Given the systemic manifestations, including a generalized erythematous rash emerging approximately three weeks after the initiation of lamotrigine (the second anti-epileptic medication in this case), suspicion arose regarding lamotrigine-induced DRESS (Shear & Spielberg, 1988; Fiszenson-Albala et al., 2003; Krivda et al., 2022). Immediate cessation of lamotrigine was instituted. The patient received an oral steroid regimen comprising prednisolone at 10 mg twice daily, along with silymarin which has an antioxidant property and is used as a protective drug in prophylaxis and treatment of drug-induced hepatotoxicity. To manage the rash and itching, desloratadine was used as needed, as clobetasol skin ointment, and as a skin lotion (Saltzstein & Ackerman, 1959; Doan et al., 2023).

The patient exhibited significant improvement in fever the day following lamotrigine discontinuation. Over the subsequent days, her overall condition, including the

Table 1. Laboratory data of the patient

Test	Results	Normal Range	Comment
White blood cell count	14.11	4-10×10^9/L	Normal count
Neutrophils (%)	20	40-60	
Lymphocytes (%)	60.9	20-40	Lymphocytosis with few reactive lymphocytes
Eosinophils (%)	12	0.5-5	Mild eosinophilia
Basophils (%)	0	0-1	
Monocytes (%)	8	3-12	
Platelets	137	150-400×10^9/L	Slightly reduced
Anti-EBV (VCA) IgG (IU/mL)	3	Up to 0.8	Consistent with old infection with EBV
Anti-EBV (VCA) IgG (IU/mL)	1.3	Up to 0.55	Consistent with new infection with EBV
RBG (mg/dL)	95	70- 139	Normal
Creatinine (mg/dL)	0.53	0.6-1.1	Normal
Urea (mg/dL)	13.7	15-45	Normal
Blood urea nitrogen (mg/dL)	6.4	6-26	
ALT (U/L)	770	14-54	Elevated more than 10 folds of upper limit
AST (U/L)	610	0-31	Elevated more than 10 folds of upper limit
Albumin (g/dL)	4	3.4-5.4	
Bilirubin (total) (mg/dL)	2.03	0.3-1	
AlkP (U/L)	269	0-115	Elevated
Total protein (mg/dL)	6.4	6.6-8.7	
HCV -Ab	Negative		
HBs- Ab	Negative		
PT (s)	14	11-14	
APTT (s)	25	24-35	
INR	1	0.9-1.3	
Anti-nuclear antibody	0.3	Negative <0.8	
AMA (IU/mL)	1.1	Negative <12	
Anti-DNA screen (U/mL)	4.6	Negative <20	
LKM Ab (U/mL)	1.7	Negative <12	
Anti-SLA (U/mL)	1.9	Negative <12	

Abbreviations: EBV: *Epstein–Barr virus*; VCA: Viral capsid antigen; IgG: Immunoglobulin G; ALT: Alanine transaminase; AST: Aspartate transferase; AlkP: Alkaline phosphatase; Ab: Antibody; HBs: hepatitis B; PT: Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; AMA: Antimitochondrial antibodies; LKM: Liver-kidney microsomal; SLA: Anti-soluble-liver-antigen; IU: International unit; RBG: Random blood glucose.

Table 2. Progression of liver function following lamotrigine-induced DRESS

Timing of Investigation	Tests	Results	Normal Range
Four days post-drug elimination	ALT (U/L)	773	0-40
	AST (U/L)	492	0-31
	Bilirubin (total) (mg/dL)	2.5	Up to 1
	Bilirubin (direct) (mg/dL)	2.1	0-0.25
	Bilirubin (indirect) (mg/dL)	0.4	0-0.75
	AlkP (U/L)	261	0-115
Eight days post-drug elimination	ALT (U/L)	308	0-40
	AST (U/L)	79	0-31
	Bilirubin (total) (mg/dL)	1.29	Up to 1
	Bilirubin (direct) (mg/dL)	0.56	0-0.25
	Bilirubin (indirect) (mg/dL)	0.73	0-0.75
	ALkP (U/L)	166	0-115
2 weeks of drug elimination	ALT (U/L)	78	0-40
	AST (U/L)	33	0-31
	Bilirubin (total) (mg/dL)	0.98	Up to 1
	Bilirubin (direct) (mg/dL)	0.42	0-0.25
	Bilirubin (indirect) (mg/dL)	0.56	0-0.75
	ALkP (U/L)	132	0-115
3 weeks post-drug elimination	ALT (U/L)	19	0-40
	AST (U/L)	23	0-31
	Bilirubin (total) (mg/dL)	0.8	Up to 1
	Bilirubin (direct) (mg/dL)	0.3	0-0.25
	Bilirubin (indirect) (mg/dL)	0.5	0-0.75
	AlkP (U/L)	68	0-115

Abbreviations: ALT: Alanine transaminase; AST: Aspartate transferase; AlkP: Alkaline phosphatase.

rash, edema, and lymphadenopathy, gradually resolved. Liver function showed progressive improvement, reaching complete recovery a few weeks after the onset, as detailed in Table 2.

Assessment

DRESS syndrome is a rare yet severe idiosyncratic drug reaction, with an estimated incidence ranging from 1 in 1000 to 1 in 10000 and a mortality rate of 10-20% (Chaabane et al., 2014; Mosallanejad et al., 2020). The spectrum of drugs capable of inducing DRESS is broad, with anticonvulsants and sulfonamides being the most commonly associated. This is particularly pertinent in the context of epileptic patients who may necessitate transitioning between medications following withdrawal of the causative drug (Vittorio & Muglia, 1995; Tas & Simonart, 2003; Kim et al., 2022).

Table 3. The RegiSCAR scoring system used in diagnosing DRESS syndrome

Features	No	Yes	Unknown
Fever >38.5 ℃	-1	0	-1
Enlarged lymph node >1 cm	0	1	0
Eosinophilia >700 or >10%/>1500 or >20%	0	1/2	0
Atypical lymphocytes	0	1	0
Skin rash >50% body surface area	0	1	0
At least two edema, infiltration, purpura, or scaling	-1	1	0
Biopsy suggesting DRESS syndrome	-1	0	0
Internal organ involvement 1, 2, or more	1	2	0
Resolution in over 15 days	-1		-1
At least three biological investigations were done to rule out an alternative diagnosis	0	1	0

Typically, the onset of DRESS occurs within two months of initiating the offending drug, with symptoms often manifesting between 2 to 6 weeks after its commencement. Thus, meticulous attention to the timing of drug administration and its correlation with symptom onset is critical, considering the variable susceptibility of different drugs to induce the syndrome (Sullivan & Shear, 2001; Eshki et al., 2009; Lin et al., 2021).

Clinical manifestations of DRESS encompass eosinophilia, skin rash, facial swelling, and lymphadenopathy, with the latter identified in nearly 75% of cases. Meanwhile, DRESS is characterized by the inflammation of visceral organs, notably the liver, kidneys, lungs, and heart (Naisbitt et al., 2003). Reactivation of herpesviruses, particularly human herpesvirus 6, has been frequently observed in DRESS cases, though cytomegalovirus, *Epstein–Barr virus*, and human herpesvirus 7 reactivation has been implicated in a minority of cases (Seishima et al., 2006; Shah et al., 2021). In this case, reactivation of EBV was noted.

A proposed hypothesis suggests that the reactivation of herpesviruses in DRESS may result from an allergic immune response to the triggering drug, stimulating latent T cells harboring the viruses. This immune stimulation leads to the reactivation of herpesviruses, a phenomenon potentially linked to the immunotropic properties of these viruses (Uetrecht, 1999).

Diagnosing DRESS poses challenges due to the heterogeneity of skin rashes and varied organ involvement among patients. In this case, the European registry of severe cutaneous adverse reactions (RegiSCAR) scoring system (Table 3) facilitated the diagnosis. RegiSCAR categorizes cases as "no," "possible," "probable," or "definite," with a score of 5 and above confirming the diagnosis (Knowles et al., 1999; Wang et al., 2024). Our patient's RegiSCAR score was 7, incorporating various criteria, such as generalized lymphadenopathy, eosinophilia >10%, skin rash covering over 50% of the body surface area, and visceral organ involvement (liver and gallbladder) (Descamps et al., 2001; Naveen et al., 2012).

Also, this case introduces a unique aspect, acalculous cholecystitis associated with lamotrigine-induced DRESS. To the best of our knowledge, this report is the first of its kind linking lamotrigine-induced DRESS with cholecystitis (Shiohara & Kano, 2007; Oriolo et al., 2016). The presence of levetiracetam in the patient's medication history posed a diagnostic challenge, but the gradual symptom development after three weeks from initiating lamotrigine strongly indicated lamotrigine as the inciting drug (Kano et al., 2010; Parsi & Daniel, 2020). Rapid improvement upon lamotrigine withdrawal, despite delayed normalization of laboratory results, further supported the diagnosis (Picard et al., 2010; Hamed et al., 2018; Al-Hasan et al., 2022).

With the patient's improvement aligned with expectations after lamotrigine cessation, a cautious wait-and-watch approach was adopted as per the patient's preference. Subsequently, she was initiated on valproate for epilepsy management, resulting in well-controlled seizures (Kardaun et al., 2013; Mansor et al., 2022). While

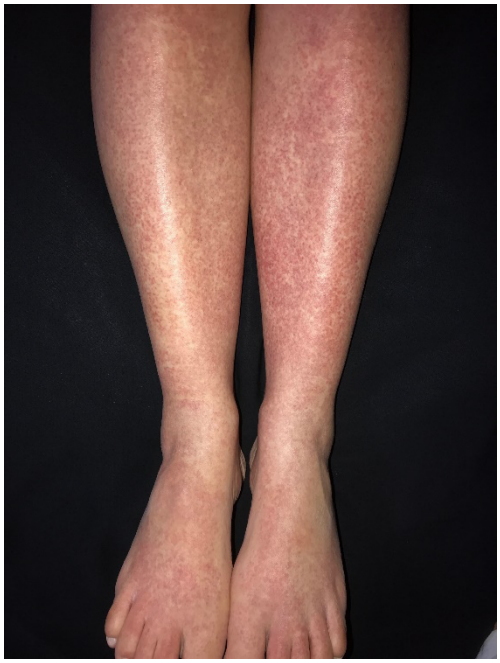

Figure 1. Papulomacular rash with non-pitting oedema on both legs

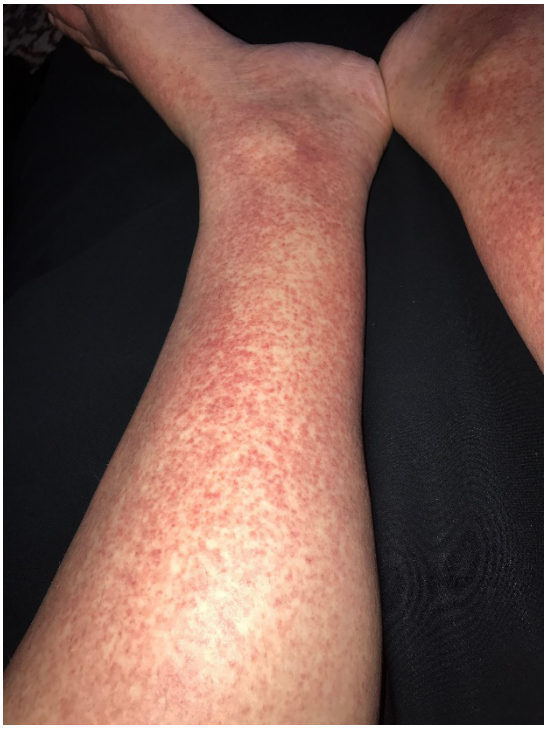

Figure 2. Maculopapular rash

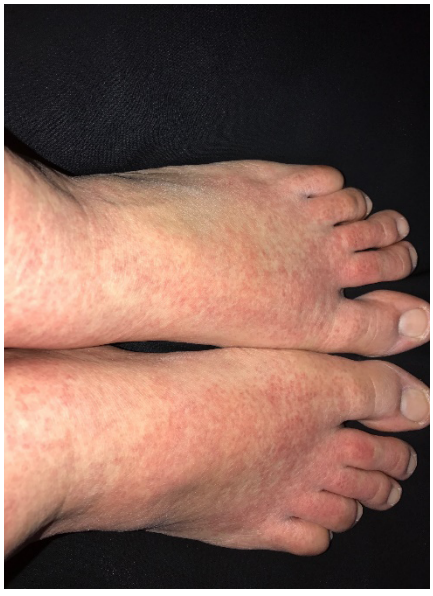

Figure 3. Maculopapular rash on the feet

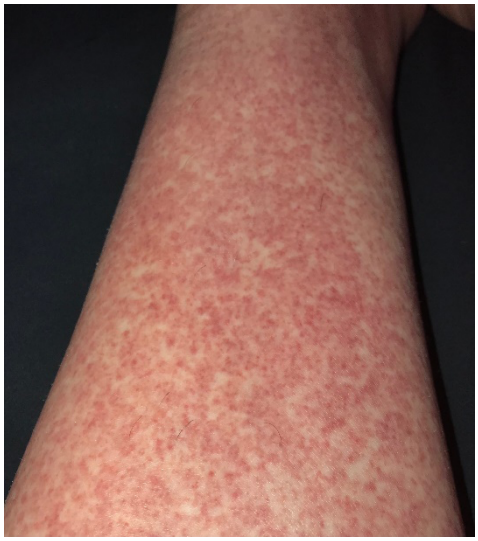

Figure 4. Maculopapular rash on the forearm

DRESS syndrome is a rare occurrence, its significant mortality rate of 10-20% underscores its severity. Linked to a diverse array of drugs, its clinical presentation can vary widely, posing diagnostic challenges that are amplified by atypical manifestations, such as acalculous cholecystitis. The utility of the RegiSCAR score is evident, aiding in the classification of cases into distinct categories, and guiding clinicians in their diagnostic approach. Prompt identification of the inciting drug and immediate discontinuation remain the cornerstone of management, ensuring a swift and comprehensive recovery for affected individuals.

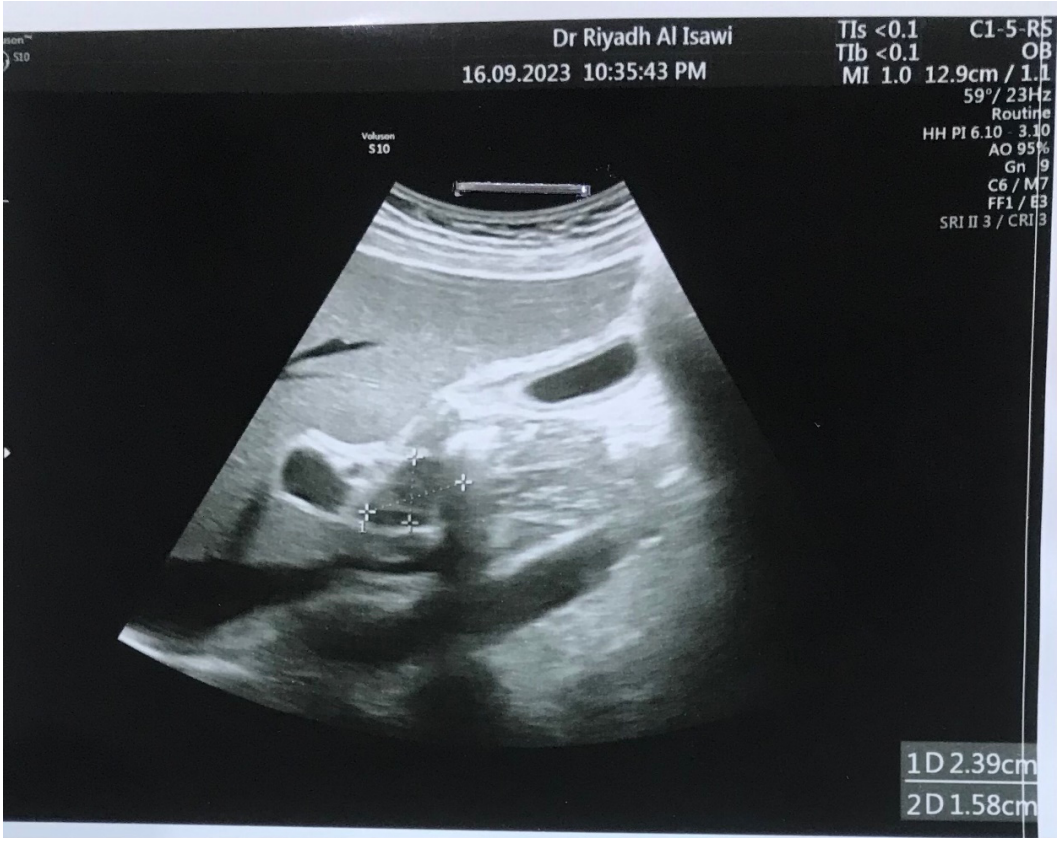

Figure 5. Trans-abdominal ultrasound showing acalculous cholecystitis with gallbladder dimensions of 2.39 cm and 1.58 cm and absence of stone

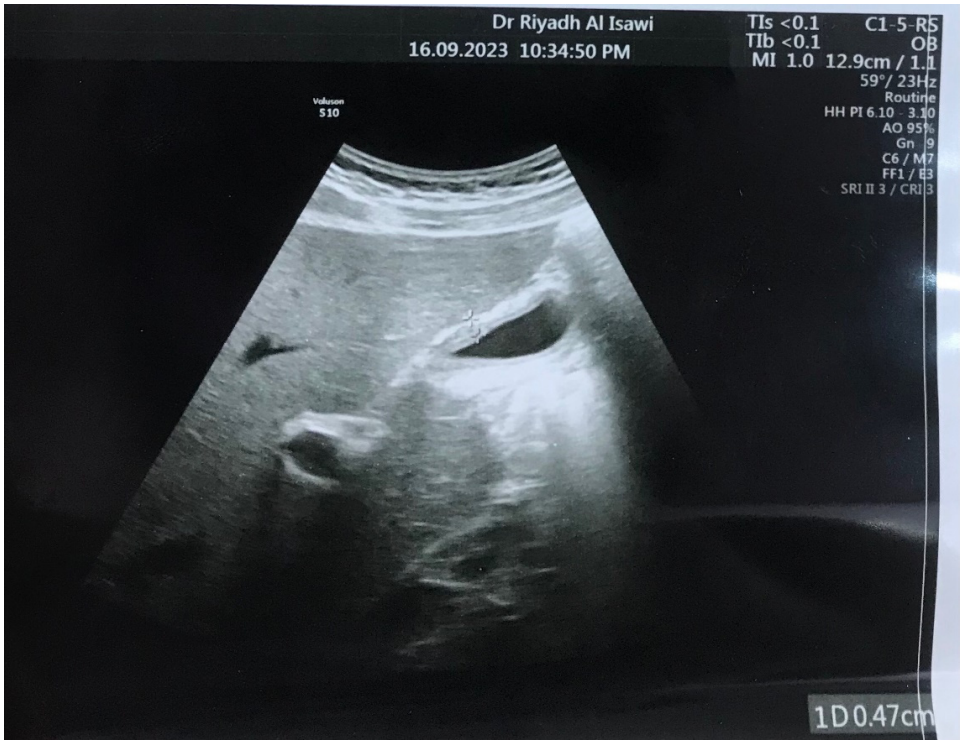

Figure 6. Trans-abdominal ultrasound showing acalculous cholecystitis with gallbladder wall thickness of 0.47 cm

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them. A written consent has been obtained from the subjects. Principles of the Helsinki Convention was also observed.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interpretation of the results, and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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References

Al-Hasan, B. A., Hameed, M. A., Bustani, G. S., & Al-Dhalimy, A. M. B. (2022). The first time, studying the behavior of foreign cats and comparing them with local cats in Iraq. *Revista Electronica de Veterinaria*, 69-76. [Link]

Bocquet, H., Bagot, M., & Roujeau, J. C. (1996). Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). *Seminars in Cutaneous Medicine and Surgery, 15*(4), 250-257. [DOI:10.1016/s1085-5629(96)80038-1] [PMID]

Brüning, K. K., Pelivan, E., Heinrich, M. C., Bufler, P., Kaindl, A., & Thumfart, J. (2024). Acute kidney injury in lamotrigine-induced DRESS syndrome. *Pediatric Nephrology (Berlin, Germany), 39*(11), 3213–3215. [DOI:10.1007/s00467-024-06397-3] [PMID]

Bonyadian, M., & Kordi, F. M. (2020). Comparison of yogurt test with commercial kit for detection of antibiotic residues in raw and pasteurized milk. *Iranian Journal of Veterinary Medicine, 14*(4), 394. [Link]

Chaabane, A., Ben Fadhel, N., Chadli, Z., Ben Fredj, N., Boughattas, N. A., & Aouam, K. (2014). Phenobarbital-Induced DRESS: A lichenoïd picture. *Iranian Journal of Allergy, Asthma, and Immunology, 13*(6), 453–455. [PMID]

Descamps, V., Mahe, E., Houhou, N., Abramowitz, L., Rozenberg, F., & Ranger-Rogez, S., et al. (2002). Drug-induced hypersensitivity syndrome associated with Epstein-Barr virus infection. *The British Journal of Dermatology, 148*(5), 1032–1034. [DOI:10.1046/j.1365-2133.2003.05330.x] [PMID]

Descamps, V., Valance, A., Edlinger, C., Fillet, A. M., Grossin, M., & Lebrun-Vignes, B., et al. (2001). Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Archives of Dermatology, 137*(3), 301-304. [PMID]

Doan, K. D., Akinsanya, A., Kuhar, M., & Mesa, H. (2023). Fatal eosinophilic myocarditis and submassive hepatic necrosis in lamotrigine induced DRESS syndrome. *Allergy, Asthma, and Clinical Immunology: Official Journal of the Canadian Society of Allergy and Clinical Immunology, 19*(1), 92. [DOI:10.1186/s13223-023-00848-6] [PMID]

Eshki, M., Allanore, L., Musette, P., Milpied, B., Grange, A., & Guillaume, J. C., et al. (2009). Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multiorgan failure. *Archives of Dermatology, 145*(1), 67–72. [DOI:10.1001/archderm.145.1.67] [PMID]

Fiszenson-Albala, F., Auzerie, V., Mahe, E., Farinotti, R., Durand-Stocco, C., & Crickx, B., et al. (2003). A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *The British Journal of Dermatology, 149*(5), 1018–1022. [DOI:10.1111/j.1365-2133.2003.05584.x] [PMID]

González, N. E. L., Rueda, M. A. A., Mosquera, E. M. D., & Cartelle, F. J. P. (2024). Case report: Lamotrigine-induced uncommon DRESS syndrome. *MOJ Clinical & Medical Case Reports, 14*(1), 19-20. [DOI:10.15406/mojcr.2024.14.00453]

Hamed, A., Hamed, A., & Lambert, K. (2018). Lamotrigine Induced DRESS Syndrome with multi-organ involvement including the pancreas: 1347. *American Journal of Gastroenterology, 113*, S771-S772. [DOI:10.14309/00000434-201810001-01347]

Kano, Y., Ishida, T., Hirahara, K., & Shiohara, T. (2010). Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. *The Medical Clinics of North America, 94*(4), 743-xi. [DOI:10.1016/j.mcna.2010.03.004] [PMID]

Kardaun, S. H., Sekula, P., Valeyrie-Allanore, L., Liss, Y., Chu, C. Y., & Creamer, D., et al. (2013). Drug reaction with eosinophilia and systemic symptoms (DRESS): An original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *The British Journal of Dermatology, 169*(5), 1071-1080. [DOI:10.1111/bjd.12501] [PMID]

Kim, H. N., Kim, S. Y., Kim, K. M., Chun, Y. H., Kim, H. H., & Kim, J. T. (2022). [DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome induced by lamotrigine in a child (Korean)]. *Allergy Asthma & Respiratory Disease, 10*(1), 66-70. [Link]

Knowles, S. R., Shapiro, L. E., & Shear, N. H. (1999). Anticonvulsant hypersensitivity syndrome: Incidence, prevention and management. *Drug Safety, 21*(6), 489-501. [DOI:10.2165/00002018-199921060-00005] [PMID]

Komatsuda, A., Okamoto, Y., Hatakeyama, T., Wakui, H., & Sawada, K. (2008). Sulfasalazine induced hypersensitivity syndrome and hemophagocytic syndrome associated with reactivation of Epstein-Barr virus. *Clinical Rheumatology, 27*(3), 395–397. [DOI:10.1007/s10067-007-0753-4] [PMID]

Krivda, L. K., Campagna, L. J., Mignano, M. S., & Cho, C. S. (2022). Prolonged drug-induced hypersensitivity Syndrome/ DRESS with Alopecia areata and autoimmune thyroiditis. *Federal Practitioner : For The Health Care Professionals of The VA, DoD, and PHS, 39*(8), 350–354. [DOI:10.12788/fp.0289] [PMID]

Lin, C. H., Lin, S. S., Hong, S. Y., Chen, C. H., & Chou, I. C. (2021). Lamotrigine induced DRESS syndrome in a child: A case report and literature review. *Children (Basel, Switzerland), 8*(11), 1063. [DOI:10.3390/children8111063] [PMID]

Mansor, M. R., Ali Hasan Kashkool, D., Safaa Abd Al-Ameer, S., Akeel Al-Hasan, B., & Almulla, A. F. (2022). Molecular detection of blaSHV-la gene in klebsiella pneumonia isolated from urinary tract infections, Najaf, Iraq. *Archives of Razi Institute, 77*(3), 1181-1184. [DOI:10.22092/ARI.2022.357617.2070] [PMID]

Mosallanejad, B., Jalali, M. R., Avizeh, R., & Pourmahdi, M. (2020). Evaluation of prophylactic and therapeutic effects of silymarin on phenobar- bital-induced hepatotoxicity in cats. *Iranian Journal of Veterinary Medicine, 14*(2), 205-214. [Link]

Naisbitt, D. J., Farrell, J., Wong, G., Depta, J. P., Dodd, C. C., & Hopkins, J. E., et al. (2003). Characterization of drug-specific T cells in lamotrigine hypersensitivity. *The Journal of Allergy and Clinical Immunology, 111*(6), 1393-1403. [DOI:10.1067/mai.2003.1507] [PMID]

Naveen, K. N., Ravindra, M. S., Pai, V. V., Rai, V., Athanikar, S. B., & Girish, M. (2012). Lamotrigine induced DRESS syndrome. *Indian Journal of Pharmacology, 44*(6), 798–800. [DOI:10.4103/0253-7613.103305] [PMID]

Oriolo, G., Brugués, A., Goikolea, J. M., & Pintor, L. (2016). Lamotrigine induced DRESS syndrome in bipolar disorder: Multiple snares behind a potentially life-threatening adverse reaction. *European Psychiatry, 33*(S1):S616-S616 [DOI:10.1016/j.eurpsy.2016.01.2304]

Parsi, M., & Daniel, C. (2020). Lamotrigine-induced DRESS Syndrome manifesting as 'eosinophilic colitis': An uncommon presentation of a very uncommon condition. *Cureus, 12*(4), e7570. [DOI:10.7759/cureus.7570] [PMID]

Picard, D., Janela, B., Descamps, V., D'Incan, M., Courville, P., & Jacquot, S., et al. (2010). Drug reaction with eosinophilia and systemic symptoms (DRESS): A multiorgan antiviral T cell response. *Science Translational Medicine, 2*(46), 46ra62. [DOI:10.1126/scitranslmed.3001116] [PMID]

Richens, A. (1994). Safety of lamotrigine. *Epilepsia, 35* (Suppl 5), S37–S40. [DOI:10.1111/j.1528-1157.1994.tb05965.x] [PMID]

Saltzstein, S. L., & Ackerman, L. V. (1959). Lymphadenopathy induced by anticonvulsant drugs and mimicking clinically pathologically malignant lymphomas. *Cancer, 12*(1), 164-182. [DOI:10.1002/1097-0142(195901/02)12:1<164::aid-cncr2820120122>3.0.co;2-y] [PMID]

Seishima, M., Yamanaka, S., Fujisawa, T., Tohyama, M., & Hashimoto, K. (2006). Reactivation of human herpesvirus (HHV) family members other than HHV-6 in drug-induced hypersensitivity syndrome. *The British Journal of Dermatology, 155*(2), 344-349. [DOI:10.1111/j.1365-2133.2006.07332.x] [PMID]

Shah, V., Patel, P., & Ullrich, K. (2021). Lamotrigine-Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) masquerading as a systemic autoimmune process. *Frontiers in Medical Case Reports, 2*, 1-07. [Link]

Shear, N. H., & Spielberg, S. P. (1988). Anticonvulsant hypersensitivity syndrome. In vitro assessment of risk.*The Journal of Clinical Investigation, 82*, 1826-1832. [DOI:10.1172/JCI113798]

Shiohara, T., Iijima, M., Ikezawa, Z., & Hashimoto, K. (2007). The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *The British Journal of Dermatology, 156*(5), 1083–1084. [DOI:10.1111/j.1365-2133.2007.07807.x] [PMID]

Shiohara, T., & Kano, Y. (2007). A complex interaction between drug allergy and viral infection. *Clinical Reviews in Allergy & Immunology, 33*(1-2), 124–133. [DOI:10.1007/s12016-007-8010-9] [PMID]

Sullivan, J. R., & Shear, N. H. (2001). The drug hypersensitivity syndrome: What is the pathogenesis? *Archives of Dermatology, 137*(3), 357-364. [PMID]

Tas, S., & Simonart, T. (2003). Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): An update. *Dermatology (Basel, Switzerland), 206*(4), 353-356. [DOI:10.1159/000069956] [PMID]

Uetrecht, J. P. (1999). New concepts in immunology relevant to idiosyncratic drug reactions: The "danger hypothesis" and innate immune system. *Chemical Research in Toxicology, 12*(5), 387-395. [DOI:10.1021/tx980249i] [PMID]

Vittorio, C. C., & Muglia, J. J. (1995). Anticonvulsant hypersensitivity syndrome. *Archives of Internal Medicine, 155*(21), 2285-2290. [DOI:10.1001/archinte.1995.00430210033005] [PMID]

Vrhovski, D., Ikić Matijašević, M., & Nesek Adam, V. (2022). Drug-induced hypersensitivity syndrome caused by lamotrigine, a case report. *Acta Clinica Croatica, 61*(Suppl 1), 88–92. [DOI:10.20471/acc.2022.61.s1.15] [PMID]

Wang, H., Peng, J., Zeng, W., & Pan, X. (2024). Lamotrigine-induced hemophagocytic lymphohistiocytosis with DRESS. *Clinical Laboratory, 70*(2), 10.7754/Clin.Lab.2023.230730. [DOI:10.7754/Clin.Lab.2023.230730] [PMID]

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