CLINICAL VIGNETTE

Lamotrigine Induced Neutropenia

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Case Presentation

A 22-year-old female, recently diagnosed with epilepsy, managed with lamotrigine presents with three days of right eye pain, fevers, fatigue, headaches, anterior and posterior cervical lymphadenopathy. She initially was evaluated in urgent care had tested negative for COVID-19 infection and was taking ibuprofen.

She was not vaccinated against COVID-19 and had a recent symptomatic infection and started to have seizures one month later. She was assessed by Neurology and started on topiramate ER 200 mg daily. She transferred care to another neurologist who switched her to Lamotrigine due to breakthrough seizures. Lamotrigine was started at 25 mg daily and titrated to 50 mg in the morning and 25 mg in the evening.

Physical examination was significant for right eye pain discomfort medial gaze. She had palpable left cervical, right posterior neck and right periauricular lymphadenopathy Brudzinski's sign was absent. Laboratory tests were significant for neutropenia, WBC 1.53 x10e3/uL, ANC 900) and mild thrombocytopenia with platelet count of 116 x10E3/uL. Chart review of outside Neurology records noted baseline WBC of 3.9x10e3/uL when she initiated on lamotrigine. She was referred to the emergency room for neutropenic fevers with unclear etiology.

Patient was admitted from the ER, with Hematology/Oncology consultation. Her neutropenic fevers, lymphadenopathy and mild thrombocytopenia were suspected to be due to viral syndrome. HIV, COVID-19, EBV, CMV, ANA, hepatitis panels and bacterial cultures were negative.CBC with peripheral smear were unremarkable. Influenza swab returned positive. She was not started on oseltamivir as she was outside the treatment window. Neck ultrasound confirmed multiple prominent lymph nodes and CT chest, abdomen and pelvis were negative. Neurology was consulted for seizure management. Given the recent initiation of lamotrigine prior to her neutropenia, Neurology recommended holding lamotrigine and topiramate was started. Symptoms improved and she was discharged home.

At outpatient follow up, she reported resolution of the neck pain and lymphadenopathy, and improvement in fatigue. Her white blood cell count had improved and returned to normal on follow up testing.

Discussion

Neutrophils are the most abundant WBCs in peripheral blood, typically 40-70%. Neutropenia is defined as an ANC <1500 cells/microL in an adult. The World Health Organization uses ≤1800 cells/microL. Neutropenia can be categorized as Mild: ANC ≥1000 and <1500 cells/microL, Moderate: ANC ≥500 and <1000 cells/microL, and Severe – ANC <500 cells/microL.[1] Our patient's ANC was 900, in the moderate range.

Antibiotics cause nearly half of drug related neutropenia. These include ß-lactams and cotrimoxazole; other drugs include antithyroid drugs (16.7%); neuroleptic and anti-epileptic agents (11.8%); antiviral agents (7.9%); and platelet aggregation inhibitors (ticlopidine and acid acetylsalicylic) (6.9%). The primary clinical manifestations during hospitalization include: isolated fever (26.3%); septicemia (13.9%); documented pneumonia (13.4%); sore throat and acute tonsillitis (9.3%); and septic shock (6.7%).[2]

Lamotrigine is an antiseizure drug approved by the FDA in 1994 to treat focal (partial) seizures, primary generalized tonic–clonic seizures, and generalized seizures of Lennox–Gastaut Syndrome in both children and adults. It was also evaluated for mood disorders and later approved for maintenance of adult bipolar disorder.[3] Common reported side effects include dizziness, diplopia, blurred vision, headache, ataxia, rhinitis and somnolence.[4] Lamotrigine-induced neutropenia has been reported often within a few days after initiation or dose increase. Some cases of life-threatening rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have occurred with lamotrigine use. Risk of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include: co-administration with valproate, exceeding recommended initial dose, and exceeding recommended dose escalation.[5] Lamotrigine-induced severe neutropenia has been reported following initial intensive dosing, especially when concomitant with phenytoin.[6]

Neutropenic patients have high rates of influenza complications.[6,7] While lymphopenia is a well-defined risk factor for severe influenza, the effect of neutropenia is unknown. Changes in blood composition could be attributed to several suggested mechanisms, including inhibition of dihydrofolate reductase, or due to the spectrum of drug hypersensitivity syndrome (DHS). DHS is an iatrogenic condition believed to be triggered by a metabolite of lamotrigine known as Lamotrigine-arene-oxide intermediate, which is processed through a less significant

pathway involving cytochrome P450. This condition can manifest as skin reactions, liver problems, and abnormalities in blood composition. Importantly, lamotrigine-induced DHS seems to be more strongly associated with sudden high exposure or increases rather than the actual dose administered. Therefore, gradual increases in lamotrigine dosage are recommended labeling aims. This promotes adaptive changes in metabolism, detoxification, and immune responses, facilitating desensitization.[6]

Conclusion

This case is a valuable reminder for clinicians to consider medication-induced side effects and to thoroughly evaluate patients with new symptoms, especially those presenting with neutropenic fevers and lymphadenopathy. The interdisciplinary approach highlights the importance of collaborative communication and emphasizes the value of multidisciplinary team approach.

REFERENCES

1. **Berliner N**. Approach to the adult with unexplained neutropenia. In: *UpToDate*, Post TW (Ed), Wolters Kluwer. Accessed 15 May 2024.
2. **Andrès E, Mourot-Cottet R, Maloisel F, Séverac F, Keller O, Vogel T, Tebacher M, Weber JC, Kaltenbach G, Gottenberg JE, Goichot B, Sibilia J, Korganow AS, Herbrecht R**. Idiosyncratic drug-induced neutropenia & agranulocytosis. *QJM*. 2017 May;110(5):299-305. doi: 10.1093/qjmed/hcw220. Epub 2017 Jan 9. PMID: 28069912.
3. **Mitra-Ghosh T, Callisto SP, Lamba JK, Remmel RP, Birnbaum AK, Barbarino JM, Klein TE, Altman RB**. PharmGKB summary: lamotrigine pathway, pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics*. 2020 Jun;30(4):81-90. doi: 10.1097/FPC.0000000000000397. PMID: 32187155; PMCID: PMC10258870.
4. **Błaszczyk B, Czuczwar SJ**. Efficacy, safety, and potential of extended-release lamotrigine in the treatment of epileptic patients. *Neuropsychiatr Dis Treat*. 2010 May 6;6:145-50. doi: 10.2147/ndt.s6515. PMID: 20505846; PMCID: PMC2874338.
5. **Edinoff AN, Nguyen LH, Fitz-Gerald MJ, Crane E, Lewis K, Pierre SS, Kaye AD, Kaye AM, Kaye JS, Kaye RJ, Gennuso SA, Varrassi G, Viswanath O, Urits I**. Lamotrigine and Stevens-Johnson Syndrome Prevention. *Psychopharmacol Bull*. 2021 Mar 16;51(2):96-114. PMID: 34092825; PMCID: PMC8146560.
6. **Salem M, El-Bardissy A**. Lamotrigine-induced neutropenia after high-dose concomitant initiation with phenytoin. *Clin Case Rep*. 2021 Nov 22;9(11):e05136. doi: 10.1002/ccr3.5136. PMID: 34849233; PMCID: PMC8607801.
7. **Durani U, Dioverti Prono MV, Tosh PK, Patnaik M, Barreto JN, Tande AJ**. Influenza infection in neutropenic adults. *Infect Dis (Lond)*. 2017 Feb;49(2):141-146. doi: 10.1080/23744235.2016.1231418. Epub 2016 Sep 16. PMID: 27636702.