Delayed Presentation of Anticonvulsant Hypersensitivity Syndrome Secondary to Lamotrigine

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Abstract

Anticonvulsant hypersensitivity syndrome (AHS) is a rare condition that needs to be seriously recognized and diagnosed. However, it is difficult to diagnose it since its clinical manifestation mimics other common infectious and neoplastic diseases. AHS manifests as skin rash that is preceded by fever accompanying internal organ involvement, with the liver being mostly affected. AHS is a condition that develops secondary to anticonvulsant exposure like phenytoin, phenobarbitone, carbamazepine, and lamotrigine. A defect in epoxide hydroxylase leading to the accumulation of toxic metabolites of aromatic anticonvulsant is hypothesized to play a role in developing AHS. This report presents a case of a 49-year-old epileptic Asian female, who complained of persistent high-grade fever followed by generalized maculopapular rash, high liver enzymes, and pancytopenia. The patient had unremarkable past history and systematic review. The patient went through various investigations to rule out infections and systematic diseases and all investigations were normal. After excluding every possible cause, the patient was diagnosed with AHS secondary to lamotrigine usage for one month.

Introduction

Anticonvulsant hypersensitivity syndrome (AHS) is a rare condition that needs to be seriously recognized and diagnosed. However, it is difficult to diagnose it since its clinical manifestation mimics other common infectious and neoplastic diseases. AHS manifests as skin rash that is preceded by fever accompanying internal organ involvement, with the liver being mostly affected. AHS is a condition that develops secondary to anticonvulsant exposure like phenytoin, phenobarbitone, carbamazepine, and lamotrigine. A defect in epoxide hydroxylase leading to the accumulation of toxic metabolites of aromatic anticonvulsant is hypothesized to play a role in developing AHS. This report presents a case of a 49-year-old epileptic Asian female, who complained of persistent high-grade fever followed by generalized maculopapular rash, high liver enzymes, and pancytopenia. The patient had unremarkable past history and systematic review. The patient went through various investigations to rule out infections and systematic diseases and all investigations were normal. After excluding every possible cause, the patient was diagnosed with AHS secondary to lamotrigine usage for one month.
The patient was diagnosed with AHS after one month of phenytoin usage as seizure prophylaxis due to a previous head injury [4]. Additionally, exposure to sulfonamides, sulfones, allopurinol, and non-steroidal anti-inflammatory medication can cause a similar reaction to AHS, so this reaction has also been referred to as drug-induced hypersensitivity syndrome (DIHS) or drug-related rash with eosinophilia and systemic symptoms (DRESS) syndrome [3]. AHS is frequently undetected due to the failure of many physicians to recognize and treat AHS [1]. Since most AHS cases are underreported, the true incidence of this condition is still unknown [2]. Therefore, in this case report, we present an interesting case of a 49-year-old female patient who experienced AHS symptoms after approximately one month of lamotrigine exposure to treat her seizure disorder.

Case Presentation

A 49-year-old Asian female who was newly diagnosed with epilepsy on lamotrigine presented for the first time to the Employee Health Clinic with a complaint of a high-grade fever of 41°C for two days along with a sore throat. The high-grade fever was spiking despite taking antipyretics to treat the fever. The systematic review was unremarkable as there were no skin lesions, and neurological, respiratory, gastrointestinal, urinary tract, or musculoskeletal symptoms. The patient had undergone gastric bypass surgery five years ago. Also, she has been diagnosed with epilepsy four months ago and was well controlled on levetiracetam 750 mg BID. However, the patient could not tolerate levetiracetam, so it was switched to lamotrigine 50 mg BID. The patient started to use lamotrigine for one month before her first presentation to the clinic. The patient was a physician herself and had no close contact with any sick patients with similar symptoms. The travel history was negative and there were no reported insect or mosquito bites, contact with animals, ingestion of raw milk, or ingestion of raw meat. Additionally, the patient was not a smoker and did not use alcohol or illicit drugs. On examination, she was vitally stable apart from a fever of 41°C. She looked pale and dehydrated with injected throat but no exudates. The systemic examinations were normal. The lab showed mild raised C-reactive protein (CRP), normal procalcitonin, low white blood cell (WBC) count and lymphocytes 0.72 × 10^9/L, normal neutrophils, and normal platelets. Lab results are shown in Table 1.

| Exam                    | Result         | Reference     |
|-------------------------|----------------|---------------|
| C-reactive protein (CRP) | 6.4 mg/L       | 0-5 mg/L      |
| Procalcitonin           | 0.11 ug/L      | <0.25 ug/L    |
| White blood cells (WBC) | 3.6 × 10^9/L   | 5.9-19.5 × 10^9/L |
| Lymphocytes             | 0.72 × 10^9/L  | 2.1-13.8 × 10^9/L |
| Neutrophils             | 2.13 × 10^9/L  | 0.8-6.8 × 10^9/L |
| Platelets               | 155 × 10^9/L   | 150-450 × 10^9/L |

TABLE 1: Lab work on the day of the presentation

She was arranged to have the following tests: malaria smear, Brucella antibodies, PCR swab for COVID-19, influenza A and B, Middle East respiratory syndrome coronavirus (MERS-COV), parainfluenza viruses 1-2-3-4, respiratory syncytial virus, *Mycoplasma pneumoniae, Chlamydia pneumoniae, Bordetella pertussis*, coronaviruses 229E, HKU1, NL63, and OC43, *Human metapneumovirus*, adenovirus, human rhinovirus/enterovirus.

The next day, the patient was following up with the Employee Health Clinic. She reported a generalized maculopapular rash with few pustular lesions and all of the above investigations came back as undetected/normal. Given that all the above initial workup was negative with persistent fever and now rash, she was treated empirically with oral cefuroxime.

On day 3 of her presentation, the patient continued to have fever (39-40°C) and rash showed no improvement despite 48 hours of cefuroxime. Hence, she had labs repeated, which showed raised CRP, normal procalcitonin, high creatinine, low WBC, low lymphocyte, dropped platelets, low hemoglobin, and low sodium. Lab results are shown in Table 2.
Therefore, she was admitted and the examination findings were unremarkable except for small palpable tender bilateral occipital lymph nodes, dehydration signs, and pallor. Investigations to rule out EBV, CMV, TB, and dengue were ordered in addition to a chest x-ray (CXR), and discharged to be followed up after administration of IV acetaminophen and IV normal saline. The results of dengue, CMV, EBV serology, CXR, and urine culture were all reported as normal but she continued to spike fever of 40°C with generalized persistent rash but was otherwise hemodynamically well.

Five days after discharge, she had lab work repeated, which showed raised CRP, normal procalcitonin, high alanine aminotransferase (ALT), high aspartate aminotransferase (AST), low lymphocyte, low WBC, low neutrophils, low platelet, low hemoglobin, low sodium, and low chloride. Lab results are shown in Table 3.

The patient was readmitted as case of fever of unknown origin with generalized rash, pancytopenia, and abnormal liver profile. Differential diagnosis involved acute viral illness, drug reaction, malignancy, and autoimmune disease. Lab workup was repeated and the results showed low platelet, low hemoglobin, low mean corpuscular volume, low mean corpuscular hemoglobin, critically low WBC, low lymphocyte, low neutrophils, low eosinophil, low monocyte, high lactate dehydrogenase, high ALT, high AST, high CRP, high erythrocyte sedimentation rate, normal procalcitonin, and normal rheumatology markers. Lab results are shown in Table 4.

| Exam                        | Result     | Reference     |
|-----------------------------|------------|---------------|
| C-reactive protein (CRP)    | 0.7 mg/L   | 0-5 mg/L      |
| Procalcitonin               | 0.19 ug/L  | <0.25 ug/L    |
| Creatinine                  | 75 umol/L  | 28-47 umol/L  |
| White blood cells (WBC)     | 3.4 × 10⁹/L| 5-19.5 × 10⁹/L|
| Lymphocytes                 | 0.66 × 10⁹/L| 2.1-13.8 × 10⁹/L|
| Platelets                   | 137 × 10⁹/L| 150-450 × 10⁹/L|
| Hemoglobin                  | 9.5 g/dL   | 10-14 g/dL    |
| Sodium                      | 134 mmol/L | 135-144 mmol/L|

| Exam                          | Result         | Reference      |
|-------------------------------|----------------|----------------|
| C-reactive protein (CRP)      | 18.7 mg/L      | 0-5 mg/L       |
| Procalcitonin                 | 0.19 ug/L      | <0.25 ug/L     |
| Alanine aminotransferase (ALT)| 140 IU/L      | 6-28 IU/L      |
| Aspartate aminotransferase (AST)| 254 IU/L | 5-34 IU/L |
| Lymphocytes                   | 0.63 × 10⁹/L   | 2.1-13.8 × 10⁹/L |
| White blood cells (WBC)       | 2.3 × 10⁹/L    | 5-19.5 × 10⁹/L |
| Neutrophils                   | 1.12 × 10⁹/L   | 0.8-6.8 × 10⁹/L |
| Platelets                     | 140 × 10⁹/L    | 150-450 × 10⁹/L |
| Hemoglobin                    | 9.6 g/dL       | 10-14 g/dL     |
| Sodium                        | 132 mmol/L     | 135-144 mmol/L |
| Chloride                      | 99 mmol/L      | 101-111 mmol/L |
TABLE 4: Readmission lab work

| Exam                          | Result       | Reference    |
|-------------------------------|--------------|--------------|
| Platelets                     | $144 \times 10^9/L$ | $150-450 \times 10^9/L$ |
| Hemoglobin                    | 8.9 g/dL     | 10-14 g/dL   |
| Mean corpuscular volume (MCV) | 70.2 fL      | 76-96 fL     |
| Mean corpuscular hemoglobin (MCH) | 23.9 pg   | 27-32 pg     |
| White blood cells (WBC)       | $1.3 \times 10^9/L$ | $5-19.5 \times 10^9/L$ |
| Lymphocytes                   | $0.36 \times 10^9/L$ | $2.1-13.8 \times 10^9/L$ |
| Neutrophils                   | $0.69 \times 10^9/L$ | $0.8-6.8 \times 10^9/L$ |
| Eosinophils                   | $0.06 \times 10^9/L$ | $0.1-1.6 \times 10^9/L$ |
| Monocytes                     | $0.19 \times 10^9/L$ | $0.2-0.8 \times 10^9/L$ |
| Lactate dehydrogenase (LDH)  | 362 U/L      | 100-217 U/L  |
| Alanine aminotransferase (ALT)| 140 U/L      | 6-28 U/L     |
| Aspartate aminotransferase (AST)| 254 IU/L   | 5-34 IU/L    |
| C-reactive protein (CRP)      | 17.8 mg/L    | 0-5 mg/L     |
| Erythrocyte sedimentation rate (ESR) | 77 mm/h  | 0-20 mm/h    |
| Procalcitonin                 | 0.19 ug/L    | <0.25 ug/L   |
| Rheumatology markers          | Normal       | Normal       |

Then, additional labs were ordered to further investigate the pancytopenia to rule out viral infections including hepatitis A, B, C, parvovirus, and HIV, which all came back as negative for acute infections. Chest CT, and abdomen and pelvis CT were ordered and they showed unremarkable results.

Finally, lamotrigine-related drug reaction was confirmed by the triad of AHS including fever, rash, and high liver function test (LFT) with pancytopenia suggesting that internal organ involvement was present while all other differentials were ruled out. Thus, lamotrigine was tapered off to 25 mg twice per day with the addition of lacosamide 50 mg twice per day. Three days after discharge, lamotrigine was stopped. Finally, two weeks after discharge, the patient followed up in the outpatient clinic, the fever had subsided, the rash resolved, and lab normalized following stoppage of lamotrigine. Lab results are shown in Table 5.
### Exam

|                  | Results          | Reference        |
|------------------|------------------|------------------|
| Platelets        | 171 × 10⁹/L      | 150-450 × 10⁹/L  |
| Hemoglobin       | 12.7 g/dL        | 10-14 g/dL       |
| Mean corpuscular volume (MCV) | 88 fL            | 76-96 fL         |
| White blood cells (WBC) | 5.9 × 10⁹/L      | 5-19.5 × 10⁹/L   |
| Lymphocytes      | 1.76 × 10⁹/L     | 2.1-13.8 × 10⁹/L |
| Neutrophils      | 3.54 × 10⁹/L     | 0.8-6.8 × 10⁹/L  |
| Eosinophils      | 0.10 × 10⁹/L     | 0.1-1.6 × 10⁹/L  |
| Monocytes        | 0.52 × 10⁹/L     | 0.2-0.8 × 10⁹/L  |
| Alanine aminotransferase (ALT) | 10 U/L          | 6-28 U/L         |
| Aspartate aminotransferase (AST) | 13 IU/L         | 5-34 IU/L        |

**TABLE 5: Lab work after lamotrigine termination**

### Discussion

AHS was first discovered in 1950 [2]. However, in recent days, there have been some efforts to reclassify AHS under the broader term "drug-induced hypersensitivity syndrome (DIHS)" [2]. AHS is characterized by fever, rash, and internal organ involvement [4]. The AHS criteria include fever, lymphadenopathy, maculopapular rash starting after three weeks of treatment, clinical symptoms that last for two weeks after the suspected drug was retired, abnormal liver profile, leukocytosis, atypical lymphocytes, or eosinophilia [1]. Frequently, the rash that is caused by AHS is preceded by fever and malaise [2]. Skin rash manifests in 90% of the patients with AHS, and the rash is mostly maculopapular eruption in character with subsequent desquamation during resolution [4]. The skin eruption can range from morbilliform eruption to toxic epidermal necrolysis [2]. It has been noticed that carbamazepine has a higher incidence of skin manifestation compared to both lamotrigine and phenytoin [4]. In contrast, topiramate and valproic acid have a rare incidence of skin reaction [4]. In AHS, internal organ involvement is the major cause of morbidity and mortality [1]. In 50%-60% of the cases, the liver is the mostly affected internal organ followed by Clara cell in the lungs and tubular cells in the kidney [4]. Hepatic involvement is presented with high levels of liver enzymes that can reach up to fulminant hepatic failure levels [4]. The hematological alteration that occurs with AHS includes leukocytosis >11 × 10⁹/L, at least 5% of atypical lymphocytes, or eosinophilia >1.5 × 10⁹/L [1].

What makes our case unique is that the 49-year-old female patient presented with symptoms of AHS accompanying pancytopenia and low levels of eosinophils. According to different reports that discussed this adverse event, leukopenia can come along with hyponatremia which was present in our case. Moreover, according to the literature, there are other possible problems that can occur with AHS, such as thrombocytopenia, hemolytic anemia, carditis, pneumonitis, conjunctivitis, and splenomegaly [4]. In the case we are presenting, thrombocytopenia was present in addition to microcytic anemia. The diagnosis of AHS was difficult because the clinical manifestation and lab results could mimic infectious and neoplastic disorders, so many laboratory investigations were ordered to rule out other common causes. Therefore, AHS is still a diagnosis of exclusion [1].

The treatment of AHS is mainly supportive [2]. The discontinuation of the offending agent is the primary management [2]. The administration of systematic corticosteroids is frequently used even though there have been no clinical trials conducted to prove systematic corticosteroids' efficacy [2]. The patient in our case was managed by suspension of lamotrigine after being gradually tapered off and followed up with both internal medicine and neurology. After a few weeks of follow-up, the patient’s condition including fever and rash has improved along with her lab results.

### Conclusions

AHS is a rare condition that can be fatal if not treated early. It is characterized by fever, rash, and involvement of internal organs. The cause of AHS is still poorly understood. However, it is mostly hypothesized to be due to a defect in the metabolism of aromatic anticonvulsants. The diagnosis of AHS is considered difficult due to its great similarity to other more common conditions. It is mainly managed by
discontinuation of the offending drug.

**Additional Information**

**Disclosures**

**Human subjects:** Consent was obtained or waived by all participants in this study. King Abdullah International Medical Research Center issued approval IRB/2631/21. This case report was approved by King Abdullah International Medical Research Center after submitting the proposal. However, the case report was not sponsored by any institution. In addition, a consent from the patient and hospital was obtained to use the medical record (BestCare system) and other needed documents for the case report publication. Confidentiality has been completely protected and no personal or identifiable aspects including names, MRNs, or others have been disclosed. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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