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CASE REPORT

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A case report and focused literature review of D-penicillamine and severe neutropenia: A serious toxicity from a seldom-used drug

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Key Clinical Message

Prescribing D-penicillamine for Wilson's disease must be accompanied by vigilant monitoring, including a complete blood cell count with differential. For most, this should occur once or twice weekly during the first month of therapy and during periods of dose escalation, then every two weeks for six additional months, then monthly.

KEYWORDS

neutropenia, penicillamine, Wilson's disease

1 | INTRODUCTION

A 29-year-old male with decompensated cirrhosis presented with fevers, oral mucositis, and severe neutropenia after introduction of D-penicillamine for the treatment of Wilson's disease. D-Penicillamine withdrawal, antibiotics, and supportive care resulted in hematologic and clinical recovery. Slow dose titration and close hematologic monitoring are essential with use of D-penicillamine.

The copper chelator D-penicillamine, originally isolated through hydrolysis of penicillin in 1943, was first applied to the treatment of Wilson's disease in 1956.[1,2] Although originally administered in its racemic form (D,L-penicillamine), only the D-enantiomer has been used clinically since 1960.[3] In the United States (US), D-penicillamine is Food and Drug Administration (FDA)-approved for Wilson's disease in adults, cystinuria in both pediatrics and adults, and severe active rheumatoid arthritis (RA) in adults that is nonresponsive to conventional therapy.[4] There are several reported non-FDA uses of the drug, including treatment of heavy metal poisonings.[5]

D-Penicillamine is associated with a variety of adverse drug effects affecting numerous organs, including the skin, kidneys, and nervous system.[6] However, some of the most serious adverse effects are hematologic, including severe neutropenia (absolute neutrophil count [ANC] < 500 mm^3).[7,8]

This report presents a case of severe neutropenia of probable association with D-penicillamine therapy in a patient with Wilson's disease and includes a focused literature review.

2 | PATIENT CASE

Our patient was a 29-year-old man with decompensated liver cirrhosis due to Wilson's disease. His family history

was unremarkable apart from a brother with a history of abnormal liver tests. The patient denied current use of recreational substances. Upon development of symptomatic ascites, splenomegaly, and thrombocytopenia, medical management of Wilson's disease was initiated at our institution and included the introduction of D-penicillamine and zinc. The initial prescribed dose of D-penicillamine was 250 mg orally twice daily, with instructions to titrate the dose to 750 mg twice daily over a period of 2 weeks.

After five weeks of D-penicillamine therapy, the patient presented with a one-week history of throat pain, odynophagia, and mouth ulcers and a three-day history of fevers (up to 39°C) and chills. Physical examination revealed severe oral mucositis, crackles over the lung fields bilaterally, and diffuse abdominal tenderness with ascites. Initial laboratory studies showed a white blood cell count (WBC) of 500/mm^3 (normal: 3.7-10.5 K/mm^3) with severe neutropenia (ANC of 40/mm^3), hemoglobin 13.9 g/dL (normal: 13.2-17.7 g/dL), and platelets 112 K/mm^3 (normal: 150-400 K/mm^3). The patient was promptly admitted and treated for febrile neutropenia with intravenous antibiotics and supportive measures, and D-penicillamine was discontinued. Diagnostic imaging was notable for signs of left lower lobe lung consolidation, moderate diffuse ascites, a nodular cirrhotic liver, and moderate splenomegaly without findings suggestive of abscess. Additional laboratory studies, including ascitic fluid analysis and further infectious workup for bacterial, viral, and fungal etiologies, were unremarkable.

On the second day of admission, the patient's ANC decreased to 0/mm^3 and remained at 0/mm^3 until the fourth day of admission. Over the next several days, the ANC increased slowly and reached a level of >500/mm^3 (645/mm^3) on the tenth day of admission. The patient's oral mucositis, abdominal pain, and left lower lung crackles also improved. He was discharged on the eleventh day of admission. D-Penicillamine was permanently discontinued. Trientine was initiated two weeks after discharge for the treatment of Wilson's disease.

Using the method described by Naranjo et al[9] to estimate the likelihood of an adverse drug reaction, we determined that our patient's severe neutropenia was a *probable* reaction to D-penicillamine. We considered other potential causes of severe neutropenia including the patient's other prior to admission medications and underlying hypersplenism, and the effects of copper deficiency.[10-12] Although no other apparent reason for his severe neutropenia was identified, we could not completely rule out the presence of another cause. Therefore, when coupled with the absence of rechallenging the patient with D-penicillamine, we could not categorize our case as a *definite* adverse drug reaction.

3 | DISCUSSION AND FOCUSED LITERATURE REVIEW

Due to its potential toxicity and the relative infrequency of its indications, D-penicillamine is uncommonly prescribed by current practitioners in most clinical settings. In the past, the drug was part of the treatment armamentarium for RA until newer, less-toxic medications became available. Indeed, much of the safety literature surrounding the use of D-penicillamine relates to its treatment of patients with RA in the 1970s-80s. The association between D-penicillamine and severe neutropenia, including case reports of patients diagnosed with aplastic anemia, has been extensively described in this population with fatalities reported.[8,13-20] In Wilson's disease, where the overall toxicity is purported to be less, the literature includes fewer descriptions of very low neutrophil counts.[21-25] Differences in the number of reports may be due to the smaller absolute number of patients taking D-penicillamine for Wilson's disease compared to those taking D-penicillamine for RA in the 1970s-80s or could represent a true difference in drug-induced toxicity in different patient populations.

The reported rate of leukopenia in RA patients receiving D-penicillamine varies from 0% to 7%.[26-29] However, the patient drop-out rate due to low WBC from D-penicillamine in RA clinical trials was 1%, while several other disease-modifying antirheumatic drugs (eg, methotrexate, sulfasalazine, gold, and azathioprine) were shown to have higher rates of discontinuation compared to D-penicillamine from WBC-lowering effects.[30,31] Examining hospital discharge records from 1973 to 1978 in the Stockholm County region, Arneborn et al[32] found D-penicillamine as the third most common cause of drug-induced neutropenia when adjusted for drug sales and excluding cytostatic agents. In 1985, the United Kingdom's Committee on Safety of Medicines determined that, when adjusted to ibuprofen, the index risk of fatality from blood dyscrasias due to D-penicillamine was 70:1.[7] The precise rate at which D-penicillamine leads to severe neutropenia is difficult to quantify, as reports often do not specify the exact neutrophil counts in patients with exposure to drug.

The dose of D-penicillamine varies by indication. When used for RA, maintenance doses averaged 500-750 mg/d, whereas for the treatment of Wilson's disease, maintenance doses for adults usually range from 750 to 1000 mg/d, starting with a low daily dose (ie, 125-250 mg/d) titrated up every 4-7 days in 250 mg increments to promote adequate urinary copper excretion and clinical improvement and to avoid medication-related adverse effects.[20,33,34] Larger daily doses of D-penicillamine appear to increase the risk of developing severe neutropenia in some cases but not all. Anecdotal reports describe a dose-dependent D-penicillamine-related neutropenia.[13,35] Frequently cited in the RA literature is Jaffe's

"go low, go very slow" dosing strategy to avoid the development of serious adverse reactions. Further, Jaffe advocated that a "very gradual rate of increase" in the dose of D-penicillamine during titration may be more important than the absolute maintenance dose in the prevention of serious D-penicillamine-associated adverse drug reactions.[36] However, in contrast to the proposed dose-dependent association of D-penicillamine with severe neutropenia, several cases describe severe neutropenia occurring in patients taking relatively low doses (ie, 125-250 mg/d).[16,37,38] Further hampering the predictability of D-penicillamine-induced severe neutropenia is the variability in timing of neutrophil depletion, as it has been documented to occur at any time during therapy.[30,39] Some of these chaotic doses and timing phenomena may be explained by Jaffe's categorization of D-penicillamine-induced neutropenia into two types: the first being an idiosyncratic, precipitous drop independent of dose usually occurring within the first year of therapy, and the second a more common gradual, dose-related decline in neutrophil count.[40]

The frequency of neutrophil monitoring for patients taking D-penicillamine is not well established. Reported complete blood cell count (CBC) monitoring rates in clinical trials of patients with RA were often every two weeks, at least initially.[18,19,28,41] For Wilson's disease, neither the European Association for the Study of the Liver (EASL) nor the American Association for the Study of Liver Diseases (AASLD) guidelines offer specific blood cell count monitoring recommendations for D-penicillamine, other than to obtain a "regular CBC."[33,34] The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends a once weekly blood count for pediatric patients taking D-penicillamine "at initiation of therapy, especially while increasing penicillamine dosages, every 1-3 months until remission and every 3-6 months afterward."[25] Adding discordance to monitoring recommendations, the FDA-approved prescribing information for both commercially available US D-penicillamine products (CUPRIMINE capsules and DEPEN tablets) had directed prescribers to obtain white and differential blood cell counts every two weeks for at least the first six months and monthly thereafter.[42,43] However, in 2003, prescribing information for CUPRIMINE was updated to instruct prescribers to now obtain white and differential blood cell counts *twice weekly* during the first month of therapy, every two weeks for the next five months and monthly thereafter.[44] The reason for the update is not publically available.[45] Taking the aforementioned recommendations into account, we suggest that for a majority of patients the responsible healthcare provider monitor a CBC and differential blood cell count once or twice weekly during the first month of D-penicillamine therapy and during any period of dose escalation, then every two weeks for six additional months, then monthly thereafter for as long as the patient is continued on the drug. Of note, US prescribing information for both products also states that "a confirmed reduction in WBC below 3500/mm^3 mandates discontinuance of penicillamine therapy…[and]…a progressive fall in… WBC in three successive determinations, even if values are still within the normal range, likewise requires at least temporary cessation."[43,44] However, because of the low baseline leukocyte counts due to hypersplenism in patients with Wilson's disease, the 3500/mm^3 cut point has been questioned, and it is posited that D-penicillamine may still be used with close monitoring in patients with Wilson's disease with a WBC <3500/mm^3.[46] Although routine and frequent monitoring will not prevent a sudden agranulocytosis, it may identify slow prodromal drops in the neutrophil count or prevent a mild cytopenia from becoming more severe. Patient and their caregivers can assist with monitoring by reporting any signs or symptoms of severe neutropenia such as fevers, sore throat, chills, or oral ulceration.[47]

If severe neutropenia is detected, D-penicillamine therapy should be suspended, at least temporarily, and in most cases permanently. Historically, treatment of D-penicillamine-induced severe neutropenia has subsequently involved supportive care, with antimicrobials and/or blood products when necessary. In some cases, various adjunct systemic steroid preparations have been administered.[13,48] The administration of colony stimulating factors has also been reported and recommended.[4,16,49,50]

Wilson's disease, unlike RA, is fatal without appropriate pharmacotherapy and therefore an alternative treatment strategy must be employed if severe neutropenia to D-penicillamine develops. A common strategy is to switch patients to the copper chelator, trientine, an alternative treatment option for Wilson's disease that was introduced in 1969 to specifically address safety and tolerability concerns related to D-penicillamine use. Alternatively, restarting D-penicillamine treatment at lower doses, with or without glucocorticoids, has been documented in cases of D-penicillamine-induced neutropenia for patients with Wilson's disease.[3,51] Although not specifically stated as a recommendation in the AASLD treatment guidelines, changing therapy from D-penicillamine to trientine in patients with Wilson's disease who are experiencing severe neutropenia and for whom continuation of a copper chelator is indicated would likely be the preferred approach in the overwhelming majority of patients, compared to D-penicillamine resumption strategies. Further support for this position comes from US prescribing information that states "patients with a history of penicillamine-related aplastic anemia or agranulocytosis should not be restarted on penicillamine."[43,44] While trientine has been suggested to have similar efficacy in terms of cupruresis compared to D-penicillamine and is much better tolerated, its use in clinical practice is primarily limited by its cost and insurance barriers.[52,53] Patients are often required by insurance carriers to demonstrate failure

or intolerability to D-penicillamine prior to being granted authorization to use trientine.

4 | CONCLUSION

Practitioners should exercise caution when considering the use of D-penicillamine. In the US, an FDA Boxed Warning states that "physicians planning to use penicillamine should thoroughly [be familiar] with its toxicity, special dosage considerations…[and] patients should remain under the close supervision of the physician."[42,43] Hematologic abnormalities such as severe neutropenia can be significant and lead to substantial morbidity and even mortality. In order to minimizes drug-related adverse effects and therefore maximize therapeutic benefit during dose escalation phases with D-penicillamine for patients with Wilson's disease, prescribers must start with low doses when initiating treatment, increase those doses in small increments, and leave an adequate amount of time between dose increases. Based on our literature review and case, we recommend all clinicians involved in the prescribing and monitoring of D-penicillamine for Wilson's disease closely monitor the CBC and differential count once or twice weekly during the first month of D-penicillamine therapy and during periods of dose escalation.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

TAB: conducted review of the patient´s medical record and contributed to drafting and critical revisions of the manuscript. JJA: contributed to drafting and critical revisions of the manuscript. TH: contributed to drafting and critical revisions of the manuscript. SKP: conceived the literature search strategy, conducted the literature search, reviewed the literature findings, and contributed to drafting and critical revisions of the manuscript. KAM: contributed to drafting and critical revisions of the manuscript.

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