Case Report

Intracranial lesions found in autoimmune hepatitis

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A case report of reversible intracranial lesions after long-term Azathioprine therapy in an autoimmune hepatitis patient

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Abstract

This study is written to report a case of 67-year-old female with known autoimmune hepatitis (AIH) who developed balance and walking difficulties. Clinical and imaging investigations were more suggestive of AIH suffering from lymphoproliferative disease. To identify the underlying suspected lymphoproliferative disease, series of brain scans were performed, which showed multiple brain lesions. This is a report on a striking case of multiple contrast enhanced brain lesions discovered in an AIH patient that was resolved upon withdrawal of azathioprine. Many side effects of azathioprine are acknowledged around the world; however, to the very best of our knowledge, an article on azathioprine inducing suspected malignancy was never reported.

Keywords: Autoimmune hepatitis; azathioprine therapy; immunosuppressive drugs; reversible neural lesions.

Introduction

Azathioprine, a known purine analogue, is an immunosuppressant drug that is used in inflammatory bowel disease (IBD), autoimmune hepatitis (AIH), and other inflammatory conditions. The European Association for the Study of the Liver (EASL) clinical guidelines advice azathioprine monotherapy in the maintenance of AIH as it delivers high efficacy and is relatively safer to the alternatives such as steroids, Mycophenolate mofetil, tumor necrosis factor, and other immunosuppressive agents. While it is true, the EASL recommends the use of azathioprine for maintenance of remission in AIH; it certainly has also warned caution against the side-effects of the drug that is rare but common such as hepatotoxicity, non-melanoma skin cancer, cytopenia, and other malignancies. To the best of our knowledge, brain lesions associated with azathioprine use in AIH were not reported in any literature to the date. Here, this case aims to present a reversed-neural lesions suspected to be induced by azathioprine in an AIH patient.

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Clinical Presentation

A 67-year-old female with known AIH (for 12 years), hypertension, and diabetes mellitus came into the ear, nose, and throat (ENT) polyclinic in September 2018 with complaints of headache, nausea, and difficulty walking. The specialist found no pathology on the ENT examination and referred to radiology for a brain magnetic resonance imaging (MRI).

The brain MRI taken on October 03, 2018, showed multiple focal cortical/leptomeningeal focal contrast-enhanced lesions with surrounding vasogenic edema at cerebellar and cerebral hemispheres (Fig. 1). When compared to the MRI scan of brain taken in 2017 for other reasons, it was clear that these lesions were new findings. Upon these revelations, the cerebellar lesions were than suspected to be a metastasis from an unknown primary site. To investigate the primary source, a PET scan was ordered a few days after, and the results were inconclusive, i.e., no primary site was found. Upon these findings, radiology referred the patient to neurosurgery with recommendations for brain biopsy before neuroradiotherapy.

The patient was than seen by neurosurgery department on the October 30, 2018, where the lesions were suspected to be intracranial hemorrhagic lesions with suspicion of metastasis. The patient was recommended to continue her regular medication but was withdrawn from azathioprine as a caution to prevent any exacerbation to a suspected lymphoproliferative disorder. The patient was instructed to continue taking the following medication: pantoprazole 40 mg tab o.d., paracetamol 500 mg tab o.d., metformin 1000 mg tab b.i.d., dexamethasone 4 mg tab q.i.d., candesartan 16 mg o.d., Novorapid (insulin pen) 100 IU/mL 1 × 6 units but was asked to stop taking azathioprine 50 mg b.d. that she was taking over the past 10 years. She was then referred to the hematology department for further investigations and an additional MRI of head.

The brain MRI taken on November 13, 2018, showed regression of both focal enhancing lesions and surrounding edema. Hematology department suspected non-Hodgkin's lymphoma (NHL) in the next following months and performed laboratory test which were again to no avail. The laboratory results only showed thrombophilia and eosinopenia.

During this time, the patient had continued her regular follow-up visits to gastroenterology unit as an AIH patient under watchful wait. A hepatobiliary ultrasound performed on February 05, 2019, showed no obvious pathology, but around the portal hilum, some lymph nodes were noted. During the same day, liver enzymes were also tested, which showed no derangement. In the following month, February 06, 2019, liver enzymes that were ordered for regular follow-up

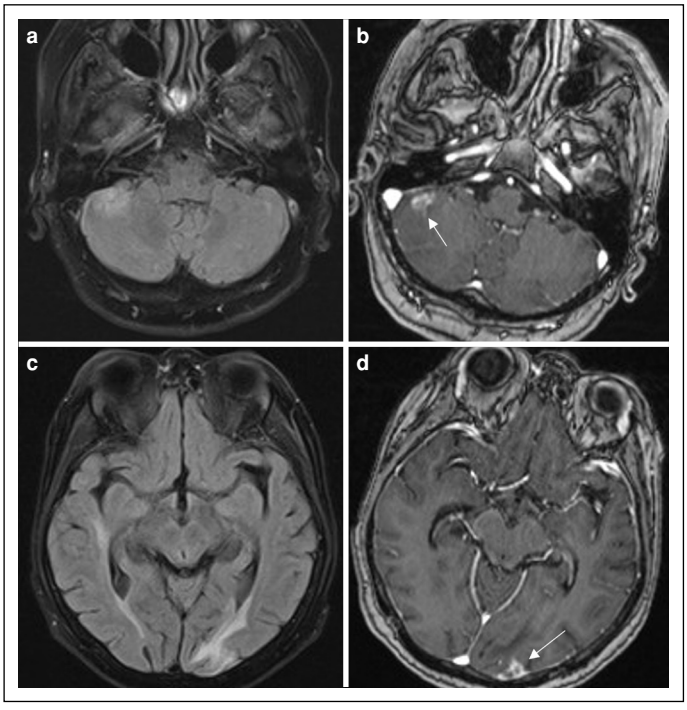

Figure 1. Brain MRI of the patient at the time of presentation with cranial symptoms. Fluid inversion recovery (FLAIR) images show focal right cerebellar **(a)** and left occipital **(c)** edematous hyperintensities which are due to patchy enhancing cortical lesions seen in post-contrast T1-weighted (w) images (arrows in **b** and **d**, respectively).

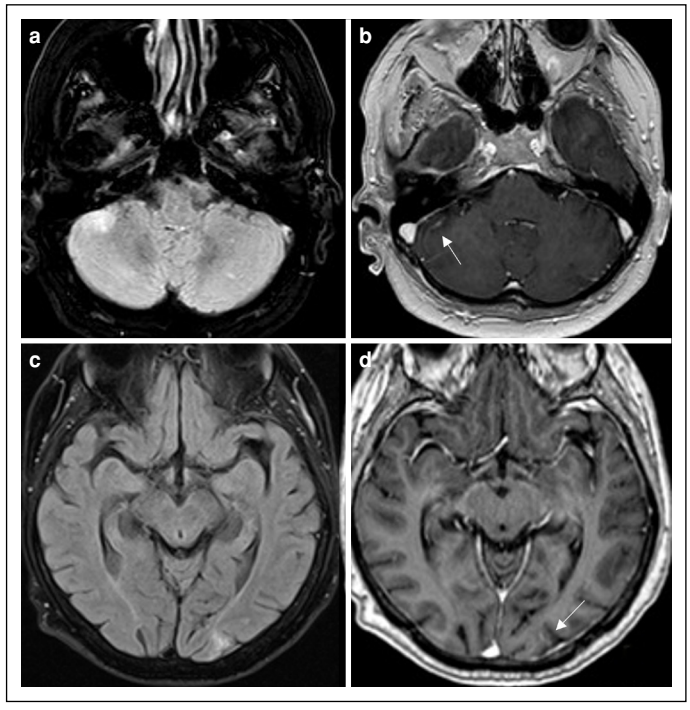

Figure 2. Follow-up brain MRI of the patient. FLAIR images (**a** and **c**) and post-contrast T1W images (**b** and **d**) show regression of both focal signal intensities and patchy enhancements (arrows).

showed that while alanine transaminase (ALT) had increased to 37 IU/L (normal value <35 IU/L), IgG was following a normal trajectory of 1550 mg/dL (normal value: 750–1560 mg/dL). The decision to continue close follow-up was taken. In the next coming 2 months (March-April), both ALT and IgG tests showed derangement with IgG reaching a peak of 1930 mg/dL (normal value: 750–1560 mg/dL) and ALT reaching 91 IU/L (normal value: <35 IU/L). Upon these values, budesonide induction therapy was initiated at a dose of 3 mg b.d.. Over the coming months, the ALT by June returned to normal value of 27 and IgG plateaued just above the normal range of 1700 mg/dL. Upon the satisfactory response to budesonide induction therapy, the patient's budesonide treatment was titrated down for maintenance dose of 3 mg o.d. by June 2019. Concurrently, the hepatobiliary ultrasound and abdominopelvic ultrasound performed over the time showed no obvious pathology.

As the patient was being seen by gastroenterology department, neurosurgery department was continuing their follow-up on the lesions seen in the brain MRI. Series of MRI taken during this particular interval with the last taken on April 18, 2019, showed near total regression of the lesions at the cerebellar hemisphere and the posterior left occipital lobe when compared with the first MRI report of 03/10/2018 (Fig. 2). The patient also reported no complaints of headache, nausea, or instability once azathioprine was withdrawn.

Over the course, due to COVID pandemic, the patient failed to attend the follow-up visits however adhered strictly to maintenance regimen initiated. Being on budesonide dose of 3 mg o.d. for 3 years, her ALT was recorded to be 19 and IgG was 1720 (March 16, 2022). The initial neurological complaints were no longer present, and a follow-up MRI ordered showed a clear regression of lesions.

Discussion and Conclusion

Admittedly, in the beginning of the case, the drug-related complication due to AIH in long-term use was very vague and the process of elimination was applied. Nevertheless, the use of azathioprine in AIH is wide due to its success rate and few cited side-effects as opposed to other drugs used in AIH.

There are at least 5 notes; we would like to make as the case is discussed, some of which are already established in the guidelines and journal entries. First, clinical practice guidelines for AIH published in European association[1] recommend the azathioprine use for long-term maintenance therapy over steroid therapy to simply avoid the cushingoid side-effects. It has been indicated that azathioprine successfully helps in maintaining remission and therefore is in fact the first line in maintenance therapy.

Second, the guidelines further reinstate that complications in azathioprine use maybe rare but common, and an eye must be kept on for hepatotoxicity, non-melanoma skin cancer, cytopenia, and other malignancies. Citing a case from the guideline "Up to 25% of patients with AIH develop side effects on azathioprine requiring withdrawal of the drug in about 10% of cases. Side effects are more common in cirrhotic patients. About 5% of patients develop a severe and early reaction with arthralgias, fever, skin rash, or pancreatitis within a few days or weeks which warrants its immediate discontinuation."[1] In addition, PubMed also has some journal entries cautioning about the other probable azathioprine long-term use side effects including hepatosplenic T-cell lymphoma, especially in IBD patients as well as post-transplant patients. Although the patient was not confirmed to have any of the above-mentioned specific complications, the brain lesions over the course of therapy were vigorously investigated and were seriously considered to be lymphoproliferative disorder with an unknown primary cancer site.

Third, to delve in and understand better, the drug azathioprine must be understood first, and unfortunately, the exact mechanism of action is unclear. However, it is understood that it is an immunosuppressor that acts on mercaptopurine resulting in inhibition of DNA, RNA, thionine synthesis, influences TPMT enzyme and has many more impacts on subsequent protein synthesis pathways. The reported effects of the drug range from nausea and vomiting to life-threatening complications. Among the complications listed in EASL clinical guide, it runs the risk of hepatic and extra-hepatic malignancy when kept on long-term therapy. In fact, in one study aiming at investigating disease control by azathioprine cited in the EASL "azathioprine monotherapy at a dose of 2 mg/kg/day, 5 of 72 patients (7%) developed malignancies over a median follow-up of 12 years;"[1] Which in this particular case, the patient had been on the drug for the past 12 years and developed neural lesions due to an unknown cause at the time.

Fourthly, with that being mentioned, azathioprine clearly played an instrumental role in this peculiar case since the lesions started to regress and the complaints of the patient ceased once the drug was promptly withdrawn. To be more specific, there was no direct treatment or intervention initiated for the brain lesions, the patient was only administered pre-procedural treatments for symptomatic relief. As the case came to a fold, wide research was undertaken to identify if any entry in PubMed or EASL was made. Upon research, there was no cited case in EASL announced; however, there were 2 reports indicating EBV-associated lymphoma after azathioprine use[2] and NHL[3] associated with chronic azathioprine use in AIH published in 2008. Nevertheless, the occurrence of cerebellar and cerebral lesions like in this case was never entered in PubMed. The occurrence of these lesions could be explained of 2-fold theories, in our opinion. The first fold is that it is likely that these lesions occurred due to the direct inhabitance of cytotoxic T-cell and natural killer cell function which in turn inhibits immunosurveillance facilitation leading to lymphoproliferative disorder. In other words, this weakened host immune system surveillance for tumor cells in long-term use led to uncontrolled proliferation of these malignancies. The second fold is relatively linked to the first fold which exacerbates the condition. TPMT an enzyme that assists in metabolizing the thiopurine-related immunosuppressant drug unfortunately shows variance among individuals and ethnicities. Hence, as mentioned in EASL clinical approach article, prior testing of TPMT is important as in the absence or lower level of TPMT enzyme leaves the patient prone to an increased risk of myelosuppression further adding insult to the injury in case of lymphoproliferative disorders. While admittedly, it is true that this patient was untested genotypically due to its unavailability in the hospital; this could be another factor adding on to the condition. Therefore, one of the many take away from this case would be to test for TPMT before initiating therapy, when possible. Taking aside all the theories of azathioprine's effects on different pathways, the only rational reason to explain why the brain lesions completely regressed without requiring any intervention but only the withdrawal of azathioprine is that the drug itself was likely to be responsible in the appearance of the lesions.

Finally, another point worth mentioning, besides the regression of lesions found in the brain MRI over the course of therapy is that during the biochemical relapse of the patient, the established partial success in the efficacy of budesonide monotherapy at induction (3 mg tds) and maintenance (3 mg o.d.). It goes without mentioning that the patient was revised pre-hand if she had developed cirrhosis before budesonide induction therapy. Upon this observation, our research showed that there were only handful entries in PubMed indicating the success of budesonide at induction. In fact, a journal entry from Germany in PubMed summarized that seven of the 12 patients (58%) reached complete remission; three patients (25%) had a partial response. Thus, 10/12 individuals (83.3%) responded to therapy.[4] Therapy was tolerated well in 10/12 cases (83.3%). Furthermore, EASL clinical approach had cited that in a prospective case trial conducted, although thought to be biased, indicated that budesonide use in induction therapy was effective in AIH.

Another point that ought to be argued that this case is unlikely to be caused due to AIH associated vasculitis. Initially, we believe that it is beneficial to acknowledge that AIH is strongly associated with vasculitis complications and was certainly kept in mind while the patient was being treated. Many journal entries can be found in PubMed supporting AIH associated vasculitis. Therefore, one may argue that 4 mg tab dexamethasone given as q.i.d for a week which was gradually discontinued within 5–7 days in this particular case essentially served its curative role. However, according to international protocols followed in the USA, Germany, and other developed countries, glucocorticoid therapy given in vasculitis should be in high dose to induce remission, specifically with an initial dose of prednisone 1 mg/kg/day that is increased to maximum of 80 mg/day for 26 weeks upon confirmation of vasculitis with biopsy. When converting the dose of dexamethasone given for cerebral edema to prednisone the measurement roughly marks up to 12 mg/day, but the days that the drugs must be given do not serve the curative purpose of central vasculitis.

In summary, this report is here to state that for the 1st time, a female belonging to Turkish ethnicity with chronic AIH presented with features of reversible brain lesions that were thought to be a case of metastatic disease early on. Findings conducted showed no evidence of primary metastatic condition. Upon case review in the follow-up plan by neurosurgery post-withdrawal of azathioprine revealed cerebral and cerebellar lesions to be regressing. Thus, it is detrimental that AIH patients on long-term azathioprine should be monitored closely for malignancies and immunosuppressant drugs should be immediately reviewed if any adverse symptom does occur.

Learning Objectives

A case report of reversible neural lesions induced by long-term azathioprine therapy in an AIH patient

1. To be able to have a differential diagnosis of azathioprine-induced cerebral and cerebellar lesions.
2. To understand the role of extra-hepatic disorders caused by azathioprine use.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – OK, AAH; Supervision – OK, EB; Materials – OK; Data Collection and/or Processing – OK, AAH, EB; Analysis and/or Interpretation – OK, AAH, EB; Literature Search – AAH; Writing – AAH; Critical Reviews – AAH.

Conflict of Interest: The authors have no conflict of interest to declare.

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References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol 2015;63(4):971-1004. Erratum in: J Hepatol 2015;63(6):1543-1544. [CrossRef]
2. Munz M, Pretscher D, Wilhelm M, Holzgrabe U, Sörgel F, Birkmann J. Azathioprine-induced reversible EBV-associated Hodgkin-like lymphoma after immunosuppressive therapy for autoimmune hepatitis . Int J Clin Pharmacol Ther 2018;56(3):142-147. [CrossRef]
3. Sawadogo A, Boursier J, Calès P, Oberti F, Schmidt A. Lymphome malin non hodgkinien au cours d'une hépatite chronique auto-immune traitée par azathioprine [Non hodgkin's lymphoma associated with chronic auto-immune hepatitis treated with azathioprine]. Gastroenterol Clin Biol 2008;32(2):143-145. [French] [CrossRef]
4. Wiegand J, Schüler A, Kanzler S, Lohse A, Beuers U, Kreisel W, et al. Budesonide in previously untreated autoimmune hepatitis. Liver Int 2005;25(5):927-934. [CrossRef]