WHAT'S YOUR DIAGNOSIS?

Patient With Severe Headache After IV Immunoglobulin

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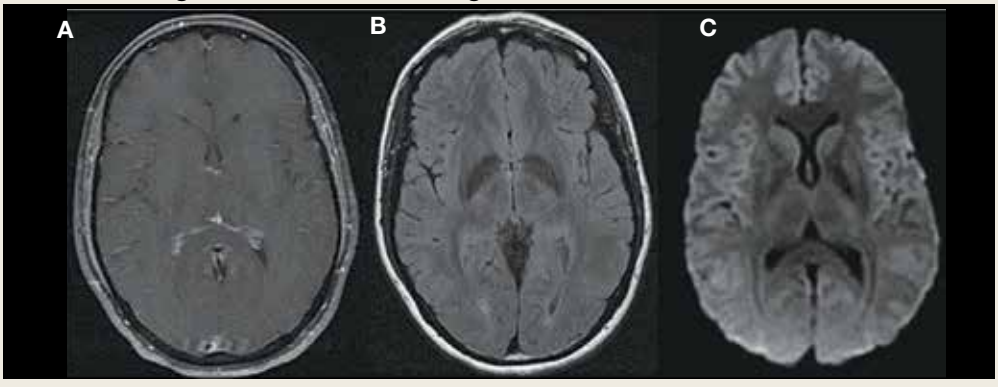
A 35-year-old woman with a history of hypothyroidism and idiopathic small fiber autonomic and sensory neuropathy presented to the emergency department (ED) 48 hours after IV immunoglobulin (IG) infusion with a severe headache, nausea, neck stiffness, photophobia, and episodes of intense positional eye pressure. The patient reported previous episodes of headaches post-IVIG infusion but not nearly as severe. On ED arrival, the patient was afebrile with vital signs within normal limits. Initial laboratory results were notable for levels within reference range parameters: 5.9×10^9/L white blood cell (WBC) count, 13.3 g/dL hemoglobin, 38.7% hematocrit, and 279×10^9/L platelet count; there were no abnormal urinalysis findings, and she was negative for human chorionic gonadotropin.

Due to the patient's symptoms concerning for an acute intracranial process, a brain computed tomography (CT) without contrast was ordered. The CT demonstrated no intracranial abnormalities, but the patient's symptoms continued to worsen. The patient was started on IV fluids and 1 g IV acetaminophen and underwent a lumbar puncture (LP). Her opening pressure was elevated at 29 cm H_2O (reference range, 6-20 cm), and the fluid was notably clear. During the LP, 25 mL of cerebrospinal fluid (CSF) was collected for laboratory analysis to include a polymerase chain reaction (PCR) panel and cultures, and a closing pressure of 12 cm H_2O was recorded at the end of the procedure with the patient reporting some relief of pressure. The patient was admitted to the medicine ward for further workup and observations.

The patient's meningitis/encephalitis PCR panel detected no pathogens in the CSF, but her WBC count was 84×10^9/L (reference range, 4-11) with 30 segmented neutrophils (reference range, 0-6) and red blood cell count of 24 (reference range, 0-1); her normal glucose at 60 mg/dL (reference range, 40-70) and protein of 33 mg/dL (reference range, 15-45) were within normal parameters. Brain magnetic resonance images with and without contrast was inconsistent with any acute intracranial pathology to include subarachnoid hemorrhage or central nervous system neoplasm (Figure 1). Bacterial and fungal cultures were negative.

- What is your diagnosis?
- How would you treat this patient?

FIGURE 1 Magnetic Resonance Images of the Brain



A, T1-weighted postcontrast; B, T2-weighted fluid-attenuated inversion recovery; C, Diffusion-weighted.

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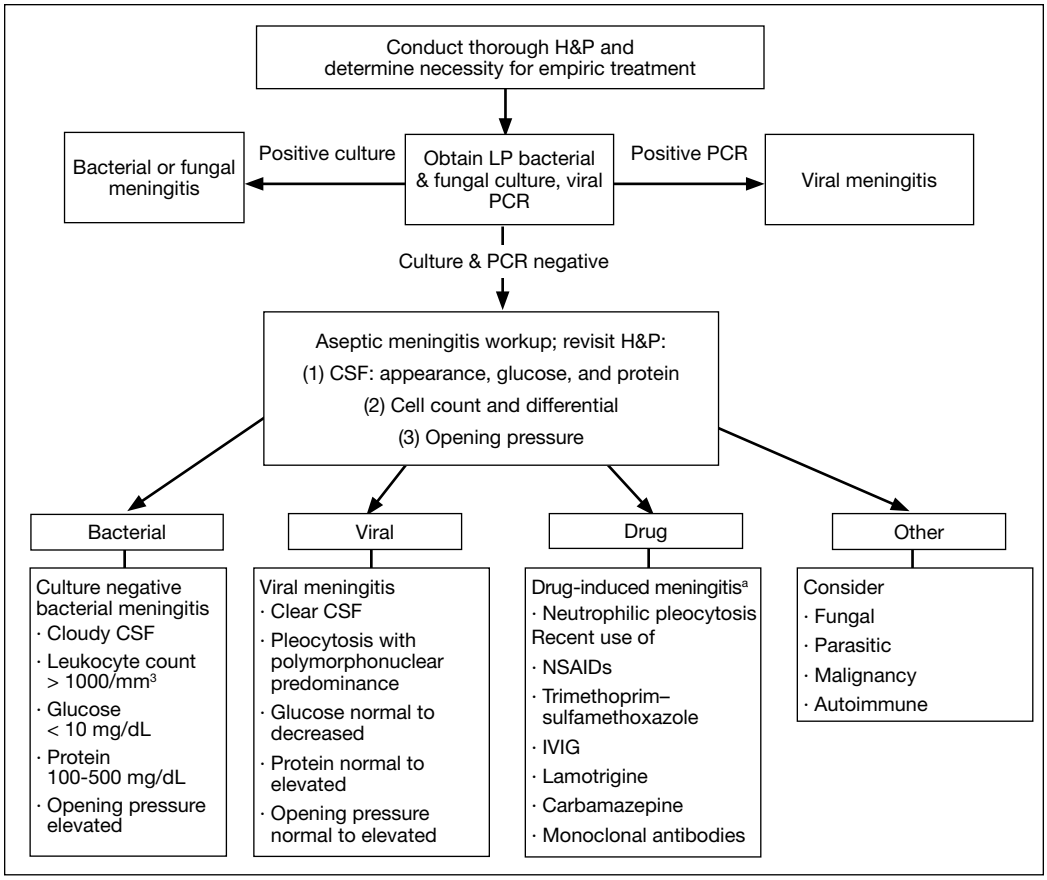
Fed Pract. 2022;39(12). Published online December 15. doi:10.12788/fp.0342

DISCUSSION

Aseptic meningitis presents with a typical clinical picture of meningitis to include headache, stiffened neck, and photophobia. In the event of negative CSF bacterial and fungal cultures and negative viral PCR, a diagnosis of aseptic meningitis is considered.[1] Though the differential for aseptic meningitis is broad, in the immunocompetent patient, the most common etiology of aseptic meningitis in the United States is by far viral, and specifically, enterovirus (50.9%). It is less commonly caused by herpes simplex virus (8.3%), varicella zoster virus, and finally, the mosquito-borne St. Louis encephalitis and West Nile viruses typically acquired in the summer or early fall months. Other infectious agents that can present with aseptic meningitis are spirochetes (Lyme disease and syphilis), tuberculous meningitis, fungal infections (cryptococcal meningitis), and other bacterial infections that have a negative culture. Once an infectious cause becomes low on the differential, the remaining 3.5% of cases can be attributed to a noninfectious aseptic etiology.[2] This includes neoplasia, autoimmune, auto-inflammatory, iatrogenic, and drug induced (the most common subtype of this category) as possible causes.

The patient's history, physical examination, vital signs, imaging, and lumbar puncture findings were most concerning for drug-induced aseptic meningitis (DIAM) secondary to her recent IVIG infusion. An algorithm can be used to work through the diagnostic approach (Figure 2).[3,4] Given the patient's absence of other etiology, her recent use of IVIG, and neutrophilic pleocytosis on LP (30% segmented neutrophils), a diagnosis of IVIG-induced aseptic meningitis was supported.[5] Other affirmative findings on LP include clear CSF and normal

FIGURE 2 Diagnostic Algorithm for Aseptic Meningitis



Abbreviations: CSF, cerebrospinal fluid; H&P, history and physical examination; IVIG, IV immunoglobulin; LP, lumbar puncture; NSAID, nonsteroidal anti-inflammatory; PCR, polymerse chain reaction.
[a]Considered a diagnosis of exclusion.

CSF glucose.[6] The patient's normal protein (33 mg/dL) is lower than most other case reports of DIAM, though, an elevated protein is not needed for diagnosis when other findings are consistent.[6,7]

Immediate and delayed adverse reactions to IVIG are known risks for IVIG therapy. About 1% to 15% of patients who receive IVIG will experience mild immediate reactions to the infusion.[6] These immediate reactions include fever (78.6%), acrocyanosis (71.4%), rash (64.3%), headache (57.1%), shortness of breath (42.8%), hypotension (35.7%), and chest pain (21.4%).[1] For a delayed adverse reaction, < 1% of patients are expected to experience IVIG-associated DIAM, though certain patient factors, such as patients with a history of migraines, hypertension, and dehydration are thought to increase this risk.[6]

IVIG is an increasingly used biologic pharmacologic agent used for a variety of medical conditions. This can be attributed to its multifaceted properties and ability to fight infection when given as replacement therapy and provide immunomodulation in conjunction with its more well-known anti-inflammatory properties.[8] The number of conditions that can potentially benefit from IVIG is so vast that the American Academy of Allergy, Asthma and Immunology had to divide the indication for IVIG therapy into definitely beneficial, probably beneficial, may provide benefit, and unlikely to provide benefit categories.[8] As the use of IVIG increases, more patients become susceptible to IVIG-associated DIAM, and it is important for clinicians to have the diagnosis on their differential.

For treatment of IVIG-associated DIAM, most cases are self-limiting and will resolve with supportive therapy within 2 to 3 days, which was the outcome in our patient's case.[6] Fluids should be given to assist with resolution of headache along with conservative pain control with acetaminophen. IVIG-associated DIAM is known to recur, and subsequent IVIG infusions should be monitored carefully. Slowing of subsequent IVIG infusion, ensuring hydration, pretreatment with acetaminophen, and use of antihistamines have been shown to be helpful for preventing subsequent episodes.[5,9] Our patient made a full recovery with supportive care and was discharged after 48 hours of observation.

CONCLUSIONS

We encourage heightened clinical suspicion of DIAM in patients who have recently undergone IVIG infusion and present with meningeal signs (stiff neck, headache, photophobia, and ear/eye pressure) without any evidence of infection on physical examination or laboratory results. With such, we hope to improve clinician suspicion, detection, as well as patient education and outcomes in cases of DIAM.

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The authors report no actual or potential conflicts of interest or outside sources of funding with regard to this article.

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Ethics and consent

Written informed consent was obtained from the patient reported in this case.

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