ACADEMIC

Pathogenesis and predisposing factors in drug-induced aseptic meningitis: A case study

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Case Presentation

A 61-year-old European man was admitted with two days of progressive high-grade fevers, neck stiffness, and headache. He started taking ibuprofen 400 mg three times a day for an ankle sprain 24 hours prior to his symptoms. He was screened for genitourinary, gastro-intestinal, and cardiorespiratory causes for his symptoms, which were negative.

Collateral history revealed previous admissions with meningitis but suggested his current presentation was more severe than the previous admissions in 2012 and 2016, neither of which yielded identifiable pathogens on lumbar puncture, despite showing neutrophilic pleocytosis. He had also taken non-steroidal anti-inflammatories (NSAIDs) prior to those admissions.

The patient had no other significant medical history and took no regular medications. He was a non-drinker, an ex-smoker (5 pack-years), and normally independent in his activities of daily living.

On examination, the patient was tremulous and flushed. His temperature was 38.2°C. Kernig's and Brudzinski's signs were positive, and he complained of moderate photophobia in a well-lit room. No focal neurological signs were noted, and apart from his ankle, all systems examinations were unremarkable.

Blood tests revealed mildly elevated inflammatory changes (C-reactive protein 8 mg/L and white cell count (WCC) 15.1×10^3/μL). Liver, thyroid, and renal function tests were normal, as were electrolytes, B12, folate, creatine kinase, and lipase. Blood cultures, human immunodeficiency virus (HIV), and Treponemal serology were negative. Head imaging with computed tomography (CT) and magnetic resonance imaging (MRI) was normal, and a lumbar puncture showed a neutrophilic pleocytosis (WCC 67×10^6/L; 54% neutrophils) with raised protein (820 mg/L) and normal glucose (2.8 mmol/L). Cerebrospinal fluid (CSF) cultures were sterile, and a polymerase chain reaction (PCR) panel was negative for herpes simplex virus 1 and 2, varicella zoster virus, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and enterovirus. There were no other sources of infection found through either a CT chest or echocardiogram.

PROBLEM LIST

1. Recurrent Aseptic Meningitis
   a. Neutrophilic Pleocytosis
   b. PCR-negative
   c. Temporal association with NSAIDs
2. Right Ankle sprain

The patient was commenced empirically on ceftriaxone, benzylpenicillin, acyclovir, and dexamethasone for meningitis. Based on his unexplained neutrophilic pleocytosis and the temporal relationship of his recurrent admissions with NSAIDs, a provisional diagnosis of drug-induced aseptic meningitis (DIAM) was made — likely NSAID-induced. Ibuprofen was discontinued, and antibiotics were ceased within three days. His symptoms improved markedly over the course of his admission.

The patient was discharged after five days. He was followed up in clinic two weeks later with fully resolved symptoms and no further complaints. He was advised to avoid NSAIDs and prescribed alternative pain relief for his ankle.

Discussion

Aseptic meningitis is the inflammation of the meningeal membranes in the absence of an identifiable pathogen. While viruses are the most common culprit, bacteria, fungi, rheumatological conditions, and neoplastic processes are also known causes.[1] It is also an uncommon, yet increasingly reported, adverse effect of certain drugs. Due to its recurrent nature, association with a specific medication, and resolution upon drug withdrawal, DIAM is an important diagnosis of exclusion in prevention and management.

DIAGNOSIS

Most often presenting clinically with the classical signs of meningitis or meningoencephalitis — fever, headache, meningism, and sometimes rash — DIAM is difficult to distinguish from infectious meningitis.[2] Recent research comparing the clinical and biological characteristics of DIAM and viral encephalitis suggests DIAM CSF generally shows neutrophilic pleocytosis, normal-to-low glucose, and increased protein,[3] as was the case with this patient. While neutrophilic pleocytosis is indicative of DIAM, partially treated bacterial meningitis and fungal meningitis must be excluded. Neuroimaging is typically normal, although cases of diffuse cerebral oedema or contrast enhancement have been reported. If, alongside these findings, symptoms arise and resolve within days of commencing and ceasing the causative agent, DIAM should be considered. While only a drug re-challenge would be confirmatory, it would be unethical, given the risk of a recurrence of unknown severity.

RISK FACTORS

An updated literature review of 192 case studies identified four drug groups consistently associated with DIAM.[4] NSAIDs, especially ibuprofen, were the commonest, followed by antibiotics, anti-epileptics, and immunosuppressive-immunomodulatory therapies. Prior exposure to the causative agent was present in 26–35% of cases, and time to onset post-administration ranged from minutes to months. There was no evidence suggesting developing DIAM was dose-dependent for any drug class.

Specific drugs implicated in DIAM include:[4,5]

- NSAIDs
  Ibuprofen, naproxen, diclofenac, celecoxib
- Antibiotics
  Trimethoprim-sulfamethoxazole, trimethoprim, amoxicillin, sulfamethoxazole, ciprofloxacin, valacyclovir, isoniazid, penicillin, metronidazole, cephalosporins, pyrazinamide
- Immunosuppressive-immunomodulatory therapies
  Intravenous immunoglobulin (IVIG), cetuximab, infliximab, methotrexate, sulfasalazine, leflunomide, etanercept, adalimumab
- Anti-epileptics
  Lamotrigine, carbamazepine

Recurrence in DIAM is not uncommon, especially in the presence of underlying conditions.[3,4] Systemic Lupus Erythematosus (SLE) is the most frequently reported underlying association with DIAM, with up to 59% of recurrent DIAM cases having SLE, even if subclinical. Other auto-inflammatory conditions are also associated with DIAM.[4] Female sex is a risk factor, although this may be confounded by the female predominance of SLE. Although reported in previously healthy individuals too, screening and follow-up for auto-inflammatory conditions in these patients may be indicated, as case reviews indicate subsequent development of these conditions can occur months after DIAM episodes.[6]

PATHOGENESIS

The pathogenesis of DIAM is not yet fully understood. However, evidence suggests mechanisms may differ between drug groups.[7] Immune hypersensitivity reactions are postulated in systemic NSAID, antibiotic, and IVIG-related cases. However, local cytokine-mediated release through direct meningeal irritation from intrathecal drug administration has also been reported.

Numerous theories have been posited in the development of NSAID-induced aseptic meningitis. Although the majority are ibuprofen-induced, most patients have tolerated different NSAIDs before and after developing meningitis, suggesting no link to inhibition of the cyclooxygenase pathway.[7] A delayed hypersensitivity reaction theory is supported by data through the common temporal association with intake and symptoms, resolution upon withdrawal of the offending agent, and allergic symptoms (rash in 22%, facial oedema and conjunctivitis in 22%). Specifically, T-cell mediated hypersensitivity has been observed in confirmed DIAM through a positive lymphocyte transformation test (LTT).[8] Thus, *in vitro* blood or CSF testing through LTT or enzyme-linked immunospot (ELISpot) assays may be useful in distinguishing DIAM from infective causes based on cytokine release and drug-specific cell activation and hypersensitivity. Confirmation of this theory may establish safer diagnostic methods for excluding infective processes than a drug re-challenge. However, latency is not always shorter upon re-exposure, and symptoms are not always more severe.

Alternatively, it has been suggested that causative drugs may interact with hapten-like CSF or meningeal proteins, stimulating an antibody-mediated inflammatory response.[9] However, given the lack of drug dose-dependence of DIAM and the limited CSF uptake of ibuprofen, this theory is not fully explanatory.

Trials demonstrated that patients with SLE have increased sensitivity to ibuprofen through specific cell-mediated immunity, despite some never being exposed to it previously.[10] This possibly occurs through a cross-reactivity process between ibuprofen and naturally occurring antibodies or immune complexes and would explain individual sensitivities and the predisposition of DIAM for those with or without auto-inflammatory conditions.[7] However, aseptic meningitis is a known neurological manifestation of many of these conditions. This may be due to abnormal inflammasome activity shifting the balance of the innate immune system to a proinflammatory state.[11] This results in greater cytokine production and plays an important role in chronic inflammatory processes, although the role of inflammasomes in DIAM has not yet been investigated. The pathogenesis of this case of DIAM is unclear, although the increased severity of his current symptoms, temporal association with intake, and resolution upon withdrawal of ibuprofen may fit a hypersensitivity picture.

CLINICAL RELEVANCE

DIAM presents a clinical challenge for diagnosticians, as symptoms and CSF findings are often insufficient to differentiate it from infectious meningitis. Furthermore, DIAM risk with certain antibiotics introduces the differentials of DIAM versus inadequately treated bacterial or fungal meningitis. However, third-generation cephalosporins like ceftriaxone, which this patient was started on, very rarely cause DIAM.[12]

While DIAM is more common in patients with underlying systemic conditions, it is important to differentiate true DIAM from complications of the other condition(s). Immunosuppressive conditions and drugs may cause susceptibility to atypical infections, while SLE is a cause of lupus aseptic meningitis, although it produces a more typically lymphocytic pleocytosis.[7]

This patient's symptoms had resolved fully at follow-up two weeks following his discharge. He was advised to avoid NSAIDs and keep careful track of the medications he takes, including over-the-counter ones. With no literature reviews or trials demonstrating the likelihood or time course of previously healthy individuals developing an autoimmune condition following DIAM, this patient should have antibody screening for conditions like SLE now and in subsequent months. Given his rapid resolution, avoidance of ibuprofen alone will likely prevent further recurrence, although care should be taken with NSAIDs in general. DIAM research consists primarily of case reports and literature reviews, primarily focusing on patients with underlying disorders. Future research may involve investigating the potential role of *in vitro* investigations as diagnostic testing for DIAM.

CONCLUSION

Overall, DIAM is a rare, yet important, cause of aseptic meningitis. A comprehensive medication history is important, with emphasis on non-prescription drugs, given the increasing accessibility of over-the-counter medications. While it presents similarly to bacterial meningitis, DIAM is an important diagnosis of exclusion when evidence of recurrent meningitis or underlying rheumatological disorders is present.

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