Case report

Meningitis due to non-steroidal anti-inflammatory drugs: an often-overlooked complication of a widely used medication

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SUMMARY

A 40-year-old man developed aseptic meningitis after ibuprofen consumption for tension-type headaches. After a thorough diagnostic workup and lack of improvement on empirical therapy for common aetiologies of meningitis (bacterial and viral infections), we suspected non-steroidal anti-inflammatory drug (NSAID) induced meningitis due to the temporal relationship between drug administration and symptom onset. Two days after NSAID suppression, the evolution was progressively favourable with complete resolution of fever and symptoms. On follow-up, symptoms did not recur and there was no neurological sequela. This article summarises the clinical picture and the complementary exams that led to the difficult-to-make diagnosis of NSAID-induced acute meningitis, in parallel with a brief review of the literature.

BACKGROUND

Non-steroidal anti-inflammatory drug (NSAID)-induced meningitis is a rare entity that presents with acute or recurrent symptoms and signs of aseptic meningitis. The term 'aseptic meningitis' refers to a clinical syndrome characterised by meningeal inflammation with negative cultures for common bacteria causing acute purulent meningitis. The main aetiologies of aseptic meningitis are viral infections, but it can also be caused by bacterial, fungal or parasitic infections, as well as non-infectious triggers, such as drugs, malignancies or autoimmune diseases, especially systemic lupus erythematosus (SLE) and rheumatoid arthritis.[1] The first drug-induced aseptic meningitis (DIAM) was described in 1978, in a patient with SLE who developed four episodes of meningitis after taking ibuprofen.[2] Since then, many offending drugs were described with NSAIDs and particularly ibuprofen being among the most frequently incriminated.

This clinical entity is worth attention. It is a rare complication of a widely used medication that can be easily missed. Indeed, diagnosis is difficult to make and usually leads to an extensive workup. In a recent UK multicentric prospective observational cohort of 638 patients with confirmed meningitis of any type, Mc Gill et al[3] found 16% (n=99) of bacterial meningitis and 36% of viral infections (n=231) mainly caused by enteroviruses, Herpes simplex viruses (HSV) and Varicella zoster virus (VZV) (n=225). The non-infectious causes that were

identified accounted for 3% of all cases (n=20). Interestingly, no DIAM was reported and there were still 42% (n=267) of meningitis of unknown cause, which is concordant with other studies.[4–6] It is reasonable to assume that at least some of these patients may have developed a DIAM.

We present a case report of an acute aseptic meningitis induced by ibuprofen with a brief overview of the literature.

CASE PRESENTATION

A 40-year-old Colombian man living in Switzerland for 11 years and working as a railway manufacturer was admitted to the emergency department (ED) for a 1-week history of persistent frontal headache. The pain started as a generalised throbbing headache without any other associated neurological symptoms. Given the progressive worsening of his symptoms despite taking over-the-counter painkillers (paracetamol and NSAID), he sought medical care.

His medical history is relevant for chronic lower back pain due to lumbar disc herniation for which he sometimes takes NSAID. He rarely suffers from headaches and has never had a migraine. Patient's social history revealed a 1-month trip to Colombia 6 months earlier, where he did not develop any symptoms. He did not recall bathing in fresh water during his trip and did not eat any unpasteurised dairy products. There was no known exposure to cattle, rodents or tick bites and the patient did not report any known contact with tuberculosis-infected people. He was vaccinated for yellow fever but could not confirm to have received the full vaccination plan in his childhood.

Neurological examination and laboratory work-up showed no abnormality. On admission, NSAIDs were suspended and opioid analgesics were administered resulting in a quick pain relief. The patient was finally discharged with the diagnosis of tension-type headache for which paracetamol, ibuprofen and tramadol were prescribed.

A few hours after taking all the above-mentioned drugs, the patient consulted again due to reappearance of a pulsatile, fronto-parietal headache with a fever sensation and an episode of diarrhoea. Physical examination revealed a temperature of 38.1°C (100.6°F) but no specific neurological findings. Nevertheless, the presence of headache with fever prompted a lumbar puncture for meningitis.

Table 1 Lumbar puncture results on days 1 and 5 after meningitis onset

	Normal values	Day 1	Day 5
Leukocytes (10^6/L)	0–4	90	741
Neutrophils (%)		52	13
Lymphocytes (%)		22	78
Erythrocytes (10^6/L)	0	<1	6
Proteins (mg/L)	150–450	915	1042
Glucose (mmol/L)	2.2–4.4	3.5	2.3
CSF/blood glucose ratio	>0.6	0.58	0.38

CSF, cerebrospinal fluid.

Indeed, cerebrospinal fluid (CSF) analysis revealed a neutrophilic meningitis with elevated protein levels and hypoglycorrhachia (table 1, Day 1). An empirical treatment of dexamethasone and ceftriaxone was initiated while microbiology results were pending. However, CSF bacterial culture and multiplex PCR assay for common infectious aetiologies (namely *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes*, *Haemophilus influenzae*, enteroviruses, HSV type 1 and 2 and VZV) yielded negative results. A contrast-enhanced computed brain tomography showed no anomaly. The empirical treatment for initial suspicion of bacterial meningitis was therefore rapidly discontinued. Again, ibuprofen and other prescribed analgesics were replaced by morphine due to pain severity thus allowing a rapid pain relief. Based on these results and the absence of headache recurrence after more than 24 hours observation, the patient was discharged with the diagnosis of aseptic meningitis of suspected viral aetiology, and paracetamol, ibuprofen and tramadol were reordered.

Two days later, the patient went to the ED for the third time with recurrent headaches. He stated that despite the preventive use of all the above-mentioned analgesics, the headaches reappeared together with fever and a gradual deterioration of the general condition. Moreover, the patient described new onset of neck pain, photophobia and phonophobia, loss of appetite and fatigue. At presentation this time, he was febrile at 38.6°C (101.48°F) with normal respiratory rate, pulse and blood pressure. On physical examination, the patient had a slight psychomotor deceleration without confusion. Neck stiffness was noted for the first time without any other neurological abnormality. The patient was hospitalised for further investigations and analgesia.

Investigations
At that time, a second lumbar puncture was performed (ie, 4 days after the first analysis) showing lymphocytic predominance (78%) with persistence of high protein levels and slightly lower blood glucose (table 1, Day 5). The patient was empirically treated with intravenous acyclovir, amoxicillin and ceftriaxone for suspected meningoencephalitis, but again, no common infectious aetiology was identified by CSF culture and multiplex PCR assay. At that time a thorough diagnostic workup was performed. Eubacterial and panfungal PCR were added in the CSF analysis and were both negative. We found a positive tuberculosis enzyme-linked immunospot assay for interferon-γ (TB-Spot) but CSF direct examination for acid-fast bacilli and CSF PCR for *Mycobacterium tuberculosis* complex were negative. Eventually, CSF mycobacterial culture was sterile after 8 weeks of incubation. A fourth-generation HIV test (antibodies and p24 antigen detection test) and a Syphilis screening (*Treponema*

pallidum Hemagglutination Assay) were negative. Despite no history of recent tick bite, endemic tick-borne associated infections were also considered. Tick-borne encephalitis serology showed a weakly positive IgG signal with negative IgM and *Borrelia burgdorferi* serology showed positive IgM with negative IgG on Enzyme Linked Fluorescent Assay but with a negative immunoblot test. PCR in the CSF for *B. burgdorferi* turned out negative. We completed the infectious diseases assessment with serologies for lymphocytic choriomeningitis (LCMV), West Nile and Toscana viruses which all came out negative. Mumps IgG serology was compatible with past immunisation.

Differential diagnosis
As defined above, the patient developed an aseptic meningitis (CSF pleocytosis of lymphocytic predominance with negative cultures and PCR for common aetiologies of acute purulent meningitis). CSF pleocytosis evolved from polymorphonuclear to lymphocytic predominance, which is described in cases where lumbar puncture is performed within the first 48 hours of disease progression. Thus, we believe that the meningitis process started shortly before the first lumbar puncture and that the first days of headache were linked to another condition (possibly tension-type headache as initially retained). In the workup, the patient had a negative two-tiered testing for *B. burgdorferi* as well as a negative CSF PCR. Although these tests have a low sensitivities for detecting early neuroborreliosis,[7] we considered them sufficient to exclude this diagnosis in the absence of obvious recent tick exposure. Although the CSF constellation together with the epidemiological context and the presence of a positive TB-spot rose up concern about possible meningeal tuberculosis, we stopped considering this diagnosis given the resolution of symptoms on NSAID interruption and without antituberculous treatment. Leptospirosis can occur as a biphasic illness and aseptic meningitis is a common finding. Diagnostic suspicion should be high in case of exposure to possible contaminated environmental sources, presence of haemorrhage, myalgia, bilateral enlarged kidneys, sterile pyuria, hypokalemia or thrombocytopenia.[8] None of the above was present in our case except a potential professional exposure to rodent's excrements. We did not formally exclude this infection, but we performed an eubacterial PCR (detection of bacterial ribosomal 16S DNA) in the CSF that would have detected leptospirosis if present. Research on enteroviruses, HSV type 1 and 2 and VZV by PCR in the CSF has also been negative. Aseptic meningitis can be directly caused by HIV-1 during acute infection and p24 antigen should be detected in the blood.[9] Thus, in absence of other signs for an acute HIV infection with negative p24 research, we did not retain this diagnosis. A second HIV test was performed 3 months later with negative results. Mumps can also cause an aseptic meningitis before parotid involvement[10] and because of an unknown vaccine history, we performed a serological test that reflected seropositivity with protective immunity. Concerning tick-borne encephalitis, we concluded that a cross-reaction with previous yellow fever vaccination explained the positive IgG results.[11] We also looked for LCMV infection but serology was negative. Our patient did not have any classical risk factors for invasive fungal infection, namely haematological malignancy, solid organ transplantation or intensive care unit stay.[12] Regarding endemic mycoses in Colombia, histoplasmosis, paracoccidiomycosis and coccidiomycosis can sometimes present as meningitis in immunocompetent patients.[13 14] Due to the clinical improvement of our patient without any specific treatment and thus a

low suspicion for this type of infections, we only performed a panfungal PCR (detection of fungal ribosomal DNA) that was negative.

Treatment

During the first days of hospitalisation, the patient remained febrile without improvement of headache despite paracetamol, ibuprofen and morphine administration. Based on an inconclusive infectious diseases workup and the lack of improvement with empirical therapy, we discontinued anti-infective therapies after 48 hours. Furthermore, we found a temporal relationship between ibuprofen use and symptom worsening: initial headaches worsened after the first ibuprofen dose, pain resolved when NSAIDs were replaced by morphine during the ED visits and symptoms of meningitis recurred after each NSAID restart on hospital discharge. As a result, we suspected ibuprofen-induced meningitis and this medication was immediately suspended.

OUTCOME AND FOLLOW-UP

The patient suffered from symptoms of meningeal syndrome for 8 days until ibuprofen was discontinued without any other intervention. The evolution was then progressively favourable with fever waning after 2 days and complete resolution of symptoms after 6 days of ibuprofen withdrawal. Further investigations, including research of auto-immune diseases, were suspended on patient's symptoms improvement. Nine months after the patient's initial presentation, he did not report any headache recurrence and he did not have any neurological sequela. Given the patient's favourable evolution after ibuprofen discontinuation and the absence of alternative diagnosis despite a thorough workup, we assumed that the patient developed a DIAM caused by ibuprofen as in most cases of NSAIDs induced meningitis.

DISCUSSION

While gastrointestinal and renal side effects of NSAIDs are widely described, central nervous system adverse events are less well appreciated and the true incidence of NSAID-associated meningitis remains difficult to define. The importance of neuropsychiatric disorders induced by NSAIDs was largely described in 1992, based on reports in New Zealand.[15] Other drugs have been described in DIAM including antibiotics such as trimethoprim with or without sulfamethoxazole, immunomodulating agents such as monoclonal antibody OKT3 and intravenous immunoglobulins, intrathecal agents and others.[16] DIAM is a rare condition with less than 200 cases reported in the literature until 2014.[17] DIAM involves all the typical symptoms of acute meningitis, most patients presenting with fever (88%), headaches (82%), meningeal signs (72%), altered consciousness (47%), and nausea or vomiting (49%). Some patients can develop generalised arthralgia/myalgia and cutaneous rashes or signs of meningoencephalitis with confusion and upgoing plantar reflexes.[18 19] CSF findings may vary but most described cases show elevated protein concentration with polymorphonuclear pleocytosis making it challenging to distinguish DIAM from acute bacterial meningitis. Occasionally, one might also find a significant percentage of lymphocytes and rarely eosinophils in CSF analysis.[20] Glucose levels are generally normal or slightly decreased.[21] To date, there is no laboratory test available to confirm drug-induced meningitis which remains a diagnosis of exclusion. However, a detailed medical history can reveal a temporal relationship between the offending drug and symptoms occurrence. Interval between drug intake and development of meningitis varies in the literature but signs and symptoms usually appear within 24–48 hours after drug ingestion.[21 22] Treatment of drug-induced aseptic meningitis consists of discontinuing the suspected medication and taking supportive measures. Use of corticosteroids has shown conflicting results.[23] Rapid resolution of symptoms after drug discontinuation is suggestive for the diagnosis and the clinical course, particularly with ibuprofen, is relatively short and benign. In general, a fairly rapid recovery is observed after 24–48 hours after drug discontinuation. A delayed resolution of symptoms for up to 5 days is also possible.[19] CSF findings may also take some time to return to normal.[20] Meningitis development might need repeated exposures to the offending drug, but it seems that once a drug has induced meningitis, symptoms will recur on each drug exposure.[19 20 22] Whether the symptom-free interval will be shorter after iterative exposures is still debated.[19 24]

Physiopathology mechanisms of DIAM remain poorly understood and insufficiently described. They may be different according to the eliciting drug and the condition of the patient. This is highlighted by the different types of pleocytosis described in CSF in this condition (neutrophils, lymphocytes or even eosinophils). Two types of mechanisms are commonly proposed for DIAM: a direct chemical irritation of the meninges or a hypersensitivity response.[18] The fact that the pathologic responses are confined to the meninges, and that some offending drugs, such as ibuprofen, only reach small concentrations in CSF make it difficult to understand and analyse these reactions.[25] However, it is striking that ibuprofen doses as low as 200 mg orally can elicit this adverse reaction.[18] Interestingly, a wide proportion of patients who develop DIAM have an underlying autoimmune pathology, mainly SLE. This is especially true for patients with ibuprofen-induced meningitis since the estimated prevalence of autoimmune connective tissue disorder is 61% in this group.[20] These patients have an immune system dysregulation which could make them more susceptible to inappropriate drug response, but at the same time they are also heavy NSAIDs consumers, which could lead to an overestimation of DIAM incidence in retrospectives analyses. Thus, it is not clear if an autoimmune workup should be warranted for all cases of DIAM. Our patient had no other complaint suggesting an autoimmune disease and we did not perform any autoantibodies screening.

For ibuprofen-induced meningitis, there is some evidence for type III or type IV hypersensitivity reactions.[25–27] To our knowledge, no study has demonstrated an IgE-mediated mechanism. The possibility of desensitisation or inducible tolerance in these patients is yet subject to clarification. Cross reactivity among

Learning points

- ► Ibuprofen-induced meningitis mimics infectious aetiologies and there is no specific marker for this adverse event, which makes it difficult to diagnose and suggests that its frequency is probably underestimated.
- ► Clinical course is benign and no long-term sequela has been described. However, avoidance of all NSAIDs is cautiously recommended after ibuprofen-induced meningitis, which excludes a drug class that is difficult to replace.
- ► A diagnosis confirmation with in-hospital drug challenge may be discussed in cases where NSAIDs are strongly needed to avoid inappropriate eviction or to test alternative NSAIDs.
- ► An infectious diseases workup is needed for any suspected case of DIAM which can be retained as a diagnosis after exclusion of other possibilities.

NSAIDs might be possible since recurrent episodes with different NSAIDs after an initial episode of ibuprofen-induced meningitis have been described.[18] Therefore, avoidance of all NSAIDs is cautiously recommended after ibuprofen-induced meningitis. A diagnosis confirmation with in-hospital drug challenge (or test of an alternative NSAID) may be discussed in cases where NSAIDs are essential for patient's management in order to avoid inappropriate eviction of the whole drug class.[28] In our case, the patient was young and had a chronic low back pain history for which he may benefit of NSAIDs in the future. Therefore, we considered a drug challenge that he eventually declined after enlightened explanations.

REFERENCES

1. Kumar R. Aseptic meningitis: diagnosis and management. *The Indian Journal of Pediatrics* 2005;72:57–63.
2. Widener HL, Littman BH. Ibuprofen-Induced meningitis in systemic lupus erythematosus. *JAMA: The Journal of the American Medical Association* 1978;239.
3. McGill F, Griffiths MJ, Bonnett LJ, et al. Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. *Lancet Infect Dis* 2018;18:992–1003.
4. Monticelli J, Geremia N, D'Agaro P, et al. Aseptic central nervous system infections in adults: what predictor for unknown etiological diagnosis? *Neurol Sci* 2018;39:863–70.
5. Jarrin I, Sellier P, Lopes A, et al. Etiologies and management of aseptic meningitis in patients admitted to an internal medicine department. *Medicine* 2016;95:e2372.
6. Kupila L, Vuorinen T, Vainionpää R, et al. Etiology of aseptic meningitis and encephalitis in an adult population. *Neurology* 2006;66:75–80.
7. Dessau RB, van Dam AP, Fingerle V, et al. To test or not to test? laboratory support for the diagnosis of Lyme borreliosis: a position paper of ESGBOR, the ESCMID Study Group for Lyme borreliosis. *Clin Microbiol Infect* 2018;24:118–24.
8. Yang H-Y, Hsu P-Y, Pan M-J, et al. Clinical distinction and evaluation of leptospirosis in Taiwan--a case-control study. *J Nephrol* 2005;18:45–53.
9. Siddiqi OK, Koralnik IJ. Neurologic Diseases Caused by Human Immunodeficiency Virus Type 1 and Opportunistic Infections. In: *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 1574. Elsevier Saunders, 2015.
10. Levitt LP, Rich TA, Kinde SW, et al. Central nervous system mumps a review of 64 cases. *Neurology* 1970;20:829–34.
11. Allwinn R, Doerr HW, Emmerich P, et al. Cross-Reactivity in flavivirus serology: new implications of an old finding? *Med Microbiol Immunol* 2002;190:199–202.
12. Pagano L, Mayor S. Invasive fungal infections in high-risk patients: report from TIMM-8 2017. *Future Sci OA* 2018;4.
13. Parish JM, Blair JE. Coccidioidomycosis. *Mayo Clin Proc* 2008;83:343–9. quiz 348–9.
14. Elias J, dos Santos AC, Carlotti CG, et al. Central nervous system paracoccidioidomycosis: diagnosis and treatment. *Surg Neurol* 2005;63 Suppl 1:S13–21.
15. Morgan A, Clark D. CNS Adverse Effects of Nonsteroidal Anti-Inflammatory Drugs : Therapeutic Implications. *CNS Drugs* 1998;9:281–90.
16. Cascella C, Nausheen S, Cunha B. A differential diagnosis of drug-induced aseptic meningitis. *Infect Med* 2008.
17. Morís G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis revisited. *JAMA Intern Med* 2014;174:1511–2.
18. Jolles S, Sewell WA, Leighton C. Drug-Induced aseptic meningitis: diagnosis and management. *Drug Saf* 2000;22:215–26.
19. Meier JE, Smith KP, Meningitis I-AA. Ibuprofen-Associated aseptic meningitis. *J Pharm Pract* 2006;19:113–23.
20. Rodríguez SC, Olguín AM, Miralles CP, et al. Characteristics of meningitis caused by ibuprofen: report of 2 cases with recurrent episodes and review of the literature. *Medicine* 2006;85:214–20.
21. Karmacharya P, Mainali NR, Aryal MR, et al. Recurrent case of ibuprofen-induced aseptic meningitis in mixed connective tissue disease. *Case Reports* 2013;2013.
22. Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis. *Arch Intern Med* 1999;159:1185–94.
23. Yelehe-Okouma M, Czmil-Garon J, Pape E, et al. Drug-Induced aseptic meningitis: a mini-review. *Fundam Clin Pharmacol* 2018;32:252–60.
24. Marinac JS, Drug-. Drug- and chemical-induced aseptic meningitis: a review of the literature. *Annals of Pharmacotherapy* 1992;26:813–22.
25. Chez M, Sila CA, Ransohoff RM, et al. Ibuprofen-Induced meningitis: detection of intrathecal IgG synthesis and immune complexes. *Neurology* 1989;39:1578–80.
26. Shoenfeld Y et al. Sensitization to ibuprofen in systemic lupus erythematosus. *JAMA* 1980;244:547–8.
27. Periard D, Mayor C, Aubert V, et al. Recurrent ibuprofen-induced aseptic meningitis: evidence against an antigen-specific immune response. *Neurology* 2006;67:539–40.
28. Moreno-Ancillo A, Gil-Adrados AC, Jurado-Palomo J. Ibuprofen-Induced aseptic meningoencephalitis confirmed by drug challenge. *J Investig Allergol Clin Immunol* 2011;21:484–7.