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REVIEW
ARTICLEDrug-induced aseptic meningitis: a
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pierre.gillet@univ-lorraine.fr**ABSTRACT**

Aseptic meningitis associates a typical clinical picture of meningitis with the absence of bacterial or fungal material in the cerebrospinal fluid. Drug-induced aseptic meningitis (DIAM) may be due to two mechanisms: (i) a direct meningeal irritation caused by the intrathecal administration of drugs and (ii) an immunologic hypersensitivity reaction to a systemic administration. If the direct meningeal irritation allows a rather easy recognition, the immunologic hypersensitivity reaction is a source of challenging diagnostics. DIAM linked to a systemic treatment exerts typically an early onset, usually within a week. This period can be shortened to a few hours in case of drug rechallenge. The fast and spontaneous regression of clinical symptoms is usual after stopping the suspected drug. Apart from these chronological aspects, no specific clinical or biological parameters are pathognomonic. CSF analysis usually shows pleiocytosis. The proteinorachia is increased while glycorachia remains normal. Underlying pathologies can stimulate the occurrence of DIAM. Thus, systemic lupus erythematosus appears to promote DIAM during NSAID therapy, especially ibuprofen-based one. Similarly, some patients with chronic migraine are prone to intravenous immunoglobulin-induced aseptic meningitis. DIAM will be mainly evoked on chronological criteria such as rapid occurrence after initiation, rapid regression after discontinuation, and recurrence after rechallenge of the suspected drug. When occurring, positive rechallenge may be very useful in the absence of initial diagnosis. Finally, DIAM remains a diagnosis of elimination. It should be suggested only after all infectious causes have been ruled out.

INTRODUCTION

Drug-induced aseptic meningitis (DIAM) is an issue first raised in the 1980s–1990s with nonsteroidal anti-inflammatory drugs (NSAIDs) [1] and trimethoprim-sulfamethoxazole [2]. Since then, additional cases have been reported with various drugs. This mini-review aims to make an update about DIAM, providing clarification on the definition, predisposing factors, diagnosis, and management, discussing about potential mechanisms of action and listing the main causative pharmacological agents. To perform this mini-review, we searched for articles published up to

May 30, 2017, in PubMed, with no start date restriction, with the keywords ‘drug-induced aseptic meningitis’. About 62 references were found, and only 18 were selected based on their type (case reports, review) and relevance (study characteristics, quality, and accuracy). Secondly, a manual search of reference lists from selected articles was conducted, with the keywords ‘-steroidal anti-inflammatory AND aseptic meningitis’, ‘Ibuprofen AND aseptic meningitis’, ‘antimicrobial AND aseptic meningitis’, ‘Amoxicillin AND aseptic meningitis’, ‘Cotrimoxazole AND aseptic meningitis’, ‘Immunoglobulin AND aseptic meningitis’, ‘Monoclonal antibodies AND aseptic meningitis’, ‘Ipilimumab AND

aseptic meningitis' 'Intrathecal drugs AND aseptic meningitis', AND 'Vaccination AND aseptic meningitis'. Finally, 88 more references were added to perform the mini-review.

DEFINITION AND DIAGNOSIS OF DIAM

The meningitis is defined as inflammation of the meninges and is distinct from encephalitis, which is an inflammation of the brain tissue. The causes of meningitis are either infective or noninfective (called aseptic) including neoplasia, autoimmune, or auto-inflammatory systemic diseases (e.g., systemic lupus erythematosus (SLE), rheumatoid arthritis, Behçet's disease) and iatrogenic etiologies such as complications of a lumbar puncture or intrathecal drug adverse effects [3–7]. Few studies consider the aseptic meningitis as infectious disease of the central nervous system (CNS) negative for bacteria, thus, including viral and fungal meningitis [8–10].

The delay of onset of DIAM is variable, about days in some series [4], or from minutes to months in others [5]. The clinical features, often mimicking meningococcal meningitis, include fever, headache, photophobia, neck stiffness, nausea, vomiting, arthralgia, myalgia, rash, and abdominal pain [7]. The characterization of meningitis cannot be only ascertained by clinical symptoms. Indeed, the cerebral spinal fluid (CSF) analysis is required to measure typical pathological variables including but not limited to specific proteins, glucose levels, differential white cells counting, and microorganisms [3]. CSF analyzes in DIAM are considerably variable. However, there is usually a pleocytosis of a hundred to several thousand cells per microliter (mean 300/ μ L [7]). Although polymorphonuclear predominance is very common, lymphocytes and eosinophilic presence have also been reported. Moreover, the proteins level in CSF is usually elevated, whereas the concomitant glucose level in CSF remains normal [4,6]. Neuroimaging is usually noninformative [5,7], and CSF bacterial culture results are obviously negative.

Drug-induced aseptic meningitis (DIAM) should be differentiated from other CNS inflammatory diseases including infectious meningitis and noninfectious conditions such as intracranial hemorrhage, hemicrania, and flare of a systemic disease. A viral etiology is suggested when these criteria are met as follows: lymphocytic pleocytosis, normal CSF glucose, viral PCR evidences and serology, and the rapid spontaneous resolution of the symptoms (1–2 weeks). Meanwhile, a

bacterial etiology is challenging to distinguish due to the CSF neutrophil pleocytosis. Nevertheless, during DIAM, CSF glucose level is usually normal while it is decreased in bacterial meningitis. The predominance of neutrophils in the CSF favors consideration of bacterial meningitis, but normal CSF glucose and negative microbiological tests will exclude it. Moreover, inflammation markers, and especially C-reactive protein, are usually lower in DIAM than in bacterial meningitis. Several biomarkers of bacterial meningitis, as CSF lactates and procalcitonin, are proposed to argue in favor of DIAM diagnosis when their levels remain normal [11–13]. During infectious meningitis, recovery is usually obtained within 7–21 days of suitable antibiotic therapy (depending on the nature of the bacteria). In contrast, spontaneous recovery within few days after drug discontinuation suggests a DIAM diagnosis.

Drug-induced aseptic meningitis (DIAM) is a diagnosis of exclusion and depends on the establishment of a causal relationship with the drug concerned. Clinicians have to take into account the timing of administration, clinical features, compatible CSF findings, quick resolution after withdrawal of the implicated drug and when performed, often unintentionally, a confirmation by a positive rechallenge [3–5,14,15]. As sometimes DIAM may be initially confounded with viral meningitis or bacterial meningitis 'beheaded' by an antibiotic treatment, it is not rare for this diagnosis to be delayed. It will be finally established with several episodes of non-documented 'viral' meningitis occurrence. *Table 1* summarizes the main criteria suggesting a DIAM compared to the main infectious meningitis categories.

MANAGEMENT OF DIAM

A DIAM is managed with discontinuation of the causative drug and a symptomatic treatment. Symptoms and CSF abnormalities usually improve within 2–3 days. In cases when 'beheaded' bacterial meningitis could be potentially diagnosed, therapy with third-generation cephalosporins is recommended until normalization of CSF parameters is obtained [3]. Thus, the complete and rapid resolution of the clinical and CSF abnormalities, despite a very short course of antibiotics, further excluded bacterial meningitis. In typical cases of intravenous immunoglobulin (IVIg)-related DIAMs, patients have been hydrated and treated with analgesics [16]. Others were treated with systemic corticosteroids [17,18], but there was no obvious difference in the clinical courses between patients treated or not.

Table 1 Main criteria for differential diagnosis of DIAM compared to main infectious meningitis.

	Physiological conditions	Bacterial meningitis	Viral meningitis	Drug-induced aseptic meningitis
CSF Appearance	Cristal clear	Cloudy	Clear	Clear
Leukocytes/mm ³	<5	>200–1000	100–1000	100–2000
Main leukocytes type	Lymphocytes	Neutrophils	Lymphocytes	Lymphocytes
CSF protein level	0.15–0.45 g/L	Increased	N or slightly increased	Increased
CSF glucose level [6]	2/3 of blood level	Decreased	Normal	Normal
Procalcitonin blood level [12]	<0.15 ng/mL-	>20 ng/mL	≈0.3 ng/mL	–
CSF lactates [11,13]	<3.5 mM	>3.5 mM	<3.5 mM	<3.5 mM
Other criteria	Sterile	Bacteria in CSF	Positive PCR/serology	Sterile
Management	–	Antibiotic drugs	±Antiviral drugs	Drug discontinuation Symptomatic treatment
Time to regression [4]	–	7–21 days	7–15 days	Within 2–3 days

Finally, systemic steroid administration is not systematically beneficial [19]. Anti-TNF drugs have been also proposed in severe cases [20]. Interestingly, IVIG also has been used to manage immunotherapy-induced meningo-radiculo-nevritis [21].

PATHOPHYSIOLOGY OF DIAM

Two main mechanisms are thought to be involved in DIAM. First one is a direct toxicity of the administered drug. Using intrathecal route [22–24] increases the risk of meningitis, depending on the concentration of drug, the size of its particles, or its ability to cross lipidic brain barriers. The second mechanism suggested is an immunological hypersensitivity reaction that may be further subdivided into type I to type IV hypersensitivity [25–27].

- The type I is a classical allergic IgE-mediated reaction associated with release of the mast cell and basophil inflammatory mediators. It exerts a rapid onset accompanied by urticaria, wheezing, fall in blood pressure, and other symptoms of an allergic reaction is not often observed in the settings of DIAM.
- The type II hypersensitivity occurs when antibodies bind to a cellular target and complement is activated. This would happen only if the drug or a breakdown product was displayed on the cell surface and if the cell is localized in the meninges.
- The types III and IV hypersensitivity are more likely mechanisms involved in DIAM. In such reactions, antibodies combine to form complexes with the drug (or one of its metabolites) in the serum, activating complement (type III), or T cells reactive to the drug recruited to a site of

inflammation (type IV). Type III hypersensitivity is a plausible mechanism, particularly in the setting of systemic lupus erythematosus (SLE), which is an archetypal immune complex-mediated disease. This mechanism would be supported by the demonstration of specific binding between IgG antibodies to the drug and its metabolites in the CSF. Up to 60% of patients with SLE are estimated to have CNS symptoms associated with inflammation at some stage of their disease thus be predisposing them to DIAM.

The immunologic patterns of SLE- and DIAM patients have not been studied in detail; however, the number of reports associating autoimmune conditions, mainly SLE, with DIAM is noticeable [3,28]. Regarding type IV hypersensitivity, it involves T helper cells and takes place over 24–48 h after previous sensitization, requiring presentation of peptides to the T cells by antigen-presenting cells. Finally, there may be multiple underlying mechanisms in DIAM. It is important to note the rate of onset of symptoms and their resolution, as well as using the tests available (skin prick and patch tests, assays for specific IgG against drugs, or metabolites) were clinically appropriate, to further define the pathogenesis and allow more rational treatment [3].

IDENTIFICATION OF CAUSATIVE AGENTS INVOLVED IN DIAM

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs represent the main therapeutic class involved in DIAM (mainly ibuprofen but also naproxen, diclofenac, and sulindac [29,30]). Ibuprofen-induced symptoms (fever, chills,

headache, vomiting, arthralgia, generalized myalgia, skin rash, neck stiffness, abdominal pain, and confusion) usually occur several hours after drug ingestion [31,32]. Interestingly, there seems to be an additional risk of developing a NSAIDs-induced aseptic meningitis in patients with autoimmune disease such as SLE [33,34], Sjögren syndrome [35], or mixed connective tissue disease [36,37]. As a matter of fact, autoimmune diseases are predisposing factors for aseptic meningitis. On the other hand, arthritic patients are commonly treated with NSAIDs, themselves providers of DIAM.

Intravenous immunoglobulin (IVIG)

Immunoglobulin therapy is widely used for a broad range of diseases including immunodeficiency disorders, inflammatory, and autoimmune diseases such as Kawasaki disease [18,38]. This therapy is available for intravenous (IV) and subcutaneous (SC) administrations. Generally, immunoglobulin infusions are well tolerated. However, some well-known adverse reactions can occur, ranging from mild to severe. The most common adverse reactions include headache, nausea, vomiting, diarrhea, chills, fever, chest discomfort, dyspnea, skin and face flushing, anaphylactic reactions, myalgia, back pain, changes in blood pressure, and tachycardia. Such symptoms may occur immediately during the infusion or after (1–2 days, see thereafter) and may involve about 1%–15% of patients. They are usually mild and resolve soon after the interruption of the IV infusion or the reduction in its flow rate. More serious adverse effects, including aseptic meningitis, usually occur with a delayed onset [19,38].

The first case of aseptic meningitis following IVIG was reported in 1988 [39]. Some IVIG brands are more likely to cause aseptic meningitis for unknown reasons, probably related to the IgA concentration in each brand. Indeed, in patients with serum anti-IgA, administration of IVIG containing IgA may lead to dramatic clinical reactions [40]. Another reason could be the use of each brand in various labeled conditions, thus, with various dosage regimen and route of administration. As a matter of fact, adverse drug reactions, including DIAM, are less frequent with SCIG and low administrated doses [19,20]. Most of the patients who have developed aseptic meningitis did so during the first cycle of IVIG therapy or within 24–48 h after completing an infusion [17,18,41]. However, the delay could vary from a few minutes to 4 months after initiation of therapy [38]. According to Jain et al. [16], IVIG-associated transient DIAM is an uncommon

phenomenon occurring in 1% of patients. It has been suggested that patients with a history of migraine headaches, hypertensive diseases, and dehydration present higher risk to DIAM-associated IVIG therapy [17,20,38]. Furthermore, several cases of IVIG-associated DIAM have been reported in patients usually treated with high doses IVIG (2 g/kg/cycle), suggesting a correlation between high doses of IVIG and aseptic meningitis [17,20,38]. Such patients are treated so for an autoimmune disease (Kawasaki disease [18,42], myasthenia gravis [43], idiopathic thrombocytopenic purpura [17,38]) which may be a predisposing factor. Interestingly, no case of aseptic meningitis with standard replacement dose of IVIG for a congenital immunodeficiency has been reported.

The pathogenic mechanism of IVIG-induced DIAM remains unclear. The various postulated mechanisms include (i) a direct toxic effect, (ii) an immunological drug hypersensitive reaction with activation of the complement system triggered by immunoglobulin macro aggregates or interaction of immunoglobulin with some antigenic determinants in the endothelium of meningeal vessels, (iii) an allogenic immune reaction, and (iv) a hypersensitivity reaction to various stabilizing agents with subsequent release of inflammatory cytokines [16,38]. Neither neurological sequela nor death has been reported from aseptic meningitis associated with IVIG therapy [17,18,38]. Note that recurrence of symptoms can occur with reinfusion [17]. To avoid this, some reports suggest that IVIG brand should be switched, given in smaller quantities and with slower rates [20]. However, some authors note that these alternatives may not be beneficial for patients with a history of migraine. In such patients, analgesics and antimigraine medications may be used as prophylaxis before an IVIG infusion [17,44]. Another premedication can be considered as follows: prehydration and good fluid intake throughout treatment and antihistamines. If all preventive measures fail to control the aseptic meningitis with IVIG, switching to subcutaneous (SC) injection could be considered, given the very rare occurrence of aseptic meningitis with SCIG [19]. Nevertheless, these preventative measures are controversial, and research is lacking, as most patients are not reinfused [44].

Antimicrobial drugs

Several authors highlighted that trimethoprim-sulfamethoxazole (TMP-SMX) is the most common antimicrobial drug prone to cause aseptic meningitis [45–47].

Interestingly, TMP alone can lead to an aseptic meningitis [48] possibly mediated by interleukin 6 [49]. In addition to classical neurological symptoms, other symptoms such as hemolytic anemia, hepatitis, orthostatic hypotension, or maculopapular rash have been described in a man with glucose-6-phosphate dehydrogenase deficiency [50]. Please note that in the 42 published studies about TMP \pm SMZ-induced DIAMs (1996–2015), 26% had an autoimmune disease and 12% had HIV [48,51]. Other antimicrobial drugs have been implicated in drug-induced aseptic meningitis [5], for example. amoxicillin [14,52,53], cephalosporins [26,54], rifampicin [28], valacyclovir [55], and ornidazole [56].

Monoclonal antibodies

OKT3 (muromonab), a murine anti-CD3 antibody, was the first monoclonal antibody (mAb) used for therapeutic applications but also the first implicated in a drug-induced aseptic meningitis [57,58]. Chimeric mAb, such as cetuximab [59–62] or infliximab [63,64], but also humanized mAb such as efalizumab [65] and adalimumab [66,67] have already been involved in DIAM. Ipilimumab (anti CTLA-4), nivolumab, or pembrolizumab (two anti PD-1) are immune checkpoint inhibitors (ICIs) used in metastatic melanoma and usually associated with ancillary immune-related adverse effects (irAEs). The most common irAEs are skin-, gastrointestinal-, hepatic-, and endocrine-related. However, these drugs, especially ipilimumab (3 mg/kg, on day 1 of each 21-day cycle), have also been rarely associated with neurologic irAEs such as Guillain Barré's syndrome, myasthenia gravis, encephalitis, DIAM [68–71] meningoencephalitis [72], and meningo-radiculo-nevritis [21]. In simple or complex meningeal lesions, clinical symptoms reported were usually mild and classical (headache, cervicgia, vomiting) but could also be severe (fever, hallucinations). In these case reports, the time of onset was few days after the first or after the third or fourth injection. Biochemical and microbiological examinations of the CSF, as well as brain MRI and dural biopsy (when performed), ruled out any infectious or neoplastic etiology and were thus consistent with DIAM.

Management usually consisted in systemic steroid therapy leading in most cases to a prompt clinical improvement as well as a normalization of the CSF within a few days. Nevertheless, concerning the patient with meningo-radiculo-nevritis [21], this delay was longer, needing about 3 weeks for CSF normalization

and at least 4 months for a clinical improvement. This could be explained by the severity of the initial sensitive-motor damage (tingling, dysarthria, ataxia, gait disorders, tetraplegia). Moreover, corticosteroids alone were not effective, and management had to be completed with a 5-day course of IVIG. Some authors suggested that the mechanism of ipilimumab-induced meningitis is mediated by direct Th17 lymphocyte activation [21,73] and perhaps the altered 'immune-privileged' status of the brain secondary to inflammation (like for eyes and sympathetic ophthalmia).

Anticonvulsants

Among all anticonvulsants, only lamotrigine and carbamazepine have been reported as causative agents for aseptic meningitis. Indeed, more than 30 cases have been described with lamotrigine [5,74,75] and 4 cases with carbamazepine [5].

Vaccines

Several papers refer to postvaccine aseptic meningitis, mainly measles-mumps-rubella (MMR) [76–80]. Cases with hepatitis B vaccine [81] and diphtheria toxin [82] have also been reported. Authors often considered MMR-related DIAMs as 'infectious' disease of the CNS negative for bacteria, probably related to 'viral meningitis' [8–10]. Among the available strains, the rates of vaccine-associated DIAM vary, with an elevated risk estimate found for the Leningrad-Zagreb and Urabe mumps strains [83]. Indeed, in various cases reported with postvaccine DIAM related to mumps monovalent or MMR trivalent vaccines, the mumps virus has been isolated from the CSF [79]. Clinical findings did not differ from natural mumps meningitis, and the course was uncomplicated [78,79]. Symptoms were observed within 10–35 days of MMR immunization [84]. In some cases, DIAMs occur up to 6 weeks days after administration of MMR [85]. Besides, a Japanese prospective cohort study, including 21 465 children receiving the first dose of a mumps monovalent vaccine, showed that the cumulative incidence of aseptic meningitis increased with age. Accordingly, it has been suggested that this primovaccination should be administered in children <3 years of age to lower the risk of DIAM after immunization [80].

Miscellaneous

Numerous other molecules have been suspected of being responsible for DIAMs, such as allopurinol [86,87], azathioprine [88], cytarabine [89,90],

salazopyrine [91,92], and intramuscular methotrexate [93]. Chemical meningitis is a particular entity described after the intrathecal injection of a large number of molecules such as radiographic agents [30], corticosteroids [94–99], aminoglycosides [100], bupivacain [101–103], morphine [23], interferon (IFN) [24], and baclofene [22,104]. Three categories could be suspected [105] as follows: infection, chemical irritation, and patient-specific reaction(s). Infection is out of this topic and occurs when the drug-solution or the catheter/pump is contaminated [106]. Noninfectious collection of inflammatory cells, which is the most likely, is a direct irritation of the meninges (difference in lipid solubility, ionization, particle size, pH) sometimes leading to granulomas (e.g., intrathecal opioids). Besides, individual idiosyncratic drug related-meningitis depends on the drug administered in the CSF. Sequential IFN α/β was directly administered into the ventricular pulp cavity via a reservoir placed in the ventricle. Without excluding an immune mechanism, the authors strongly suggested a direct stimulus of the meninges to explain the five episodes of DIAM, leading to subacute sclerosing panencephalitis [24] contrasting with the good prognostic of classical DIAMs. Site-specific phlogistic properties have also been reported after intrathecal injection of baclofene, although oral administrations were safe, but ineffective, in the same patients [22,104], thus, questioning if a history of chemical meningitis constitutes a contraindication to baclofene pump indication.

CONCLUSION

Recognizing DIAM remains a big challenge for physicians as it remains a diagnosis of exclusion. The pathophysiological history of the patient must also be taken into account, especially in case of autoimmune disease or migraine history, as these conditions may promote DIAMs. This uncommon meningitis has been reported with numerous drugs, mainly NSAIDs, intravenous immunoglobulins, and antimicrobials, but also with monoclonal antibodies, anticonvulsants, intrathecal agents, and other miscellaneous drugs. The management of DIAM consists in stopping the suspected drug and administering a symptomatic treatment. Currently, the mechanism of DIAM is not clearly elucidated. Further research is thus needed to better characterize it with specific biomarkers and propose suitable management algorithms.

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ABBREVIATIONS

CNS – central nervous system
 CSF – cerebrospinal fluid
 DIAM – dug-induced aseptic meningitis
 IVIG – intravenous immunoglobulin
 MMR – measles-mumps-rubella
 SLE – systemic lupus erythematosus

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