Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

International meeting of the French society of neurology & SPILF 2019

Aseptic meningitis

P. Tattevin [a,*], S. Tchamgoué [b], A. Belem [a], F. Bénézit [a], C. Pronier [c], M. Revest [a]

[a] Service de maladies infectieuses et réanimation médicale, CHU de Pontchaillou, rue Le Guilloux, 35033 Rennes Cedex, France
[b] Médecine interne, centre hospitalier, 33500 Libourne, France
[c] Virologie, CHU de Pontchaillou, 35033 Rennes Cedex, France

INFO ARTICLE

Article history:
Received 3 June 2019
Received in revised form
1st July 2019
Accepted 2 July 2019
Available online 30 July 2019

Keywords:
Aseptic meningitis
Drug-induced aseptic meningitis
Sarcoidosis
Behçet disease
Neoplastic meningitis

ABSTRACT

Aseptic meningitis is defined as meningeal inflammation – i.e. cerebrospinal fluid (CSF) pleocytosis ≥ 5 cells/mm^3 – not related to an infectious process. Etiologies of aseptic meningitis can be classified in three main groups: (i) systemic diseases with meningeal involvement, which include sarcoidosis, Behçet's disease, Sjögren's syndrome, systemic lupus erythematosus and granulomatosis with polyangiitis; (ii) drug-induced aseptic meningitis, mostly reported with non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics (sulfamides, penicillins), intravenous immunoglobulin, and monoclonal antibodies; (iii) neoplastic meningitis, either related to solid cancer metastasis (breast cancer, lung cancer, melanoma) or malignant hemopathy (lymphoma, leukemia). Most series in the literature included groups of meningitis that are not stricto sensu aseptic, but should rather be included in the differential diagnosis: (i) infectious meningitis related to virus, parasites, fungi, or fastidious bacteria that require specific diagnostic investigations; (ii) bacterial meningitis with sterile CSF due to previous antibiotic administration, and (iii) parameningeal infections associated with meningeal reaction. Despite progress in microbiological diagnosis (including PCR, and next generation sequencing), and identification of a growing panel of autoimmune or paraneoplastic neurological syndromes, up to two thirds of aseptic meningitis cases are of unknown etiology, finally labeled as 'idiopathic'. Description of new entities, such as the syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL) may decrease the proportion of idiopathic aseptic meningitis. This state-of-the-art review summarizes the characteristics of main causes of aseptic meningitis.

* Corresponding author at: Service de maladies infectieuses et réanimation médicale, CHU de Pontchaillou, rue Le Guilloux, 35033 Rennes Cedex, France.
E-mail address: pierre.tattevin@chu-rennes.fr (P. Tattevin).
https://doi.org/10.1016/j.neurol.2019.07.005

1. Introduction

The term 'aseptic' usually refers to a process free from contamination caused by harmful bacteria, viruses, fungi, or parasites. Aseptic meningitis may thus be defined as meningeal inflammation – i.e. cerebrospinal fluid (CSF) pleocytosis ≥ 5 cells/mm^3 – not related to an infectious process. Etiologies of aseptic meningitis can be classified in three main groups: (i) systemic diseases with meningeal involvement; (ii) drug-induced aseptic meningitis; (iii) neoplastic meningitis [1]. However, many series of so-called 'aseptic meningitis' in the literature included groups of meningitis that are not stricto sensu aseptic [1–6], and should rather be included in the differential diagnosis: (i) infectious meningitis related to virus, parasites, fungi, or fastidious bacteria, that require specific diagnostic investigations; (ii) bacterial meningitis with sterile CSF due to previous antibiotic administration, and (iii) parameningeal infections associated with meningeal reaction.

Over the last two decades, new tools have improved the yield of microbiological diagnosis, including polymerase chain reaction (PCR), single or multiplex, and next generation sequencing. In parallel, dramatic progress have been achieved in the characterization, and the diagnosis, of autoimmune or paraneoplastic neurological syndromes. However, up to two thirds of aseptic meningitis cases remain of unknown etiology, even in most recent series, despite comprehensive diagnostic work-out [4,6,7]. New entities have been recently described, such as the syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL) [8], and the meningitis-retention syndrome [9], which may decrease the proportion of idiopathic aseptic meningitis. This state-of-the-art review summarizes the characteristics of the main causes of aseptic meningitis. Encephalitis, and autoimmune or paraneoplastic neurological syndromes will not be detailed, as they are developed elsewhere in this issue of *Revue Neurologique*.

2. Systemic diseases with meningeal involvement

The main systemic diseases potentially associated with aseptic meningitis include sarcoidosis [10,11], Behçet's disease [12,13], Sjögren's syndrome [14], systemic lupus erythematosus [15], and granulomatosis with polyangiitis (formerly Wegener's granulomatosis) [16,17]. Their diagnosis is often delayed, and usually relies on a comprehensive diagnostic work-out, including anamnesis, physical examination, and additional investigations (immunological tests, imaging studies, ophthalmological consultation, etc.). The litterature review points out three major messages: (i) the context is of paramount importance (i.e. sex, age at first symptoms, anamnesis, family medical history, geographical origin); (ii) extraneurological signs are major clues; (iii) cytological and biochemical CSF findings may differ from one systemic disease to another (Table 1). For example, sarcoidosis and Behçet's disease are the two main systemic diseases to consider in patients with aseptic meningitis and CSF pleocytosis > 50 cells/mm^3. Aseptic meningitis with a predominance of neutrophils in CSF is suggestive of Behçet's disease, or drug-induced aseptic meningitis.

Investigations of higher yield for the diagnosis of systemic diseases with meningeal involvement include chest X-ray, proteinuria and urine cytology, and a panel of auto-antibodies: anti-nuclear, anti-SSA, anti-SSB, and anti-neutrophil cytoplasmic antibody (ANCA). A comprehensive ophthalmological examination including slit-lamp, fundoscopy, and Schirmer test should be performed. Accessory salivary glands biopsy may be diagnostic for sarcoidosis, and Sjögren's syndrome. Consultation with an internal medicine specialist, and/or multidisciplinary concertation, may be of high value for these complex diseases. Most systemic diseases with CNS lesions will require high-dose corticosteroids initially (e.g. oral prednisolone, 1 mg/kg/day, or pulse intravenous methylprednisolone, 1 g or 15 mg/kg/day for 3 days). Different immunosuppressant regimens are proposed in case of corticoresistance, or to prevent relapses, while allowing corticosteroid tapering, to avoid tolerability issues related to prolonged high-doses corticosteroids.

2.1. *Neurosarcoidosis*

Approximately 10% of patients with sarcoidosis will develop neurosarcoidosis, mostly as cranial nerve(s) palsy (50–75% of neurosarcoidosis), sub-acute or chronic meningitis, seizures, myelopathy, peripheral neuropathy, or neuropsychiatric symptoms [10]. When patients previously diagnosed with sarcoidosis develop neurological symptoms, the diagnosis is usually straightforward. However, in 50–70% of cases, neurosarcoidosis is part of the initial presentation of sarcoidosis [11]. In that situation, the diagnosis mostly relies on the combination of neurological, and extraneurological manifestations, including intrathoracic/lungs (88–94%), eyes (37–55%) and skin (30%).

The investigations with higher yield for the diagnosis of neurosarcoidosis include (i) demonstration of a granulomatous inflammation on tissue biopsy; (ii) documentation of leptomeningeal involvement, seen in the form of gadolinium-enhanced nodules or plaques on brain magnetic resonance imaging (MRI). Leptomeningeal involvement most frequently affects the suprasellar and frontal basal meninges. Other suggestive lesions on brain MRI include enhancement of cranial nerves, and non-enhancing lesions in the periventricular white matter; (iii) whole-body gallium (Ga)-67, or F-18 fluorodeoxyglucose positron emission tomography (PET) scanning are usually abnormal and document multisystem disease, but are not specific for sarcoidosis. These investigations may identify potential sites more accessible for biopsy than the CNS. The usefulness of CSF angiotensin converting enzyme (ACE) levels for the diagnosis of neurosarcoidosis is controversial, with low sensitivity (24–55%), but high specificity (95%): although it cannot replace a tissue biopsy for the diagnosis of neurosarcoidosis, its positive predictive value is high [11].

2.2. *Neuro-Behçet*

Behçet's disease mostly affects young adults, with first manifestations usually occurring between the ages of 20 and 35 years. Patients are almost always diagnosed before 50

Table 1 – Main systemic diseases associated with aseptic meningitis.

Etiology	Context	Clincial and paraclinical features	Cerebrospinal fluid (CSF)
Sarcoidosis	Female predominance Disease onset in young adults (20–40-year-old) Higher prevalence in people originating from sub-Saharan Africa and Caribbean islands	Neurological Often early in the disease course: (i) Cranial nerve(s) palsy (ii) Chronic meningitis Extraneurological Chest X-ray (enlarged mediastinal lymph nodes, nodules, infiltrates) Parotiditis, eye disorders (uveitis), skin lesions (erythema nodosum), arthritis Major diagnostic clue = Granuloma, on accessory salivary gland biopsy, or any other affected tissue (skin, etc.)	Lymphocytic meningitis, sometimes > 100 cells/mm^3 Hyperproteinorachia Normoglycorachia (useful for differential diagnosis with tuberculosis)
Behçet's disease	Male predominance (80%) Disease onset in young adults (20–35-year-old), always before 50 Higher prevalence in people originating from Mediterranean countries, Middle East, Japan	Neurological Usually after years of Behçet's disease: meningoencephalitis (rhombencephalitis common), cerebral vasculitis Extraneurological Bipolar aphtosis (genital and oral ulcers), skin lesions (erythema nodosum, folliculitis), thrombosis Eye disorders	Neutrophilic meningitis (90% of cases) Usually > 50 cells/mm^3
Sjögren's syndrome	Female predominance (90%) Disease onset typically after the age of 40	Neurological Combination of peripheral (polyneuropathy, cranial nerve palsy), and central nervous system lesions Extraneurological Sicca syndrome Antibodies anti-SSA (Ro), anti-SSB (La), characteristic features on accessory salivary gland biopsy	Lymphocytic meningitis, sometimes with plasma cells Usually <50 cells/mm^3
Systemic lupus erythematosus	Female predominance Disease onset before the age of 40 Individual or family history of autoimmune disorders	Neuropsychiatric (i) depression, psychosis (ii) convulsions Extraneurological Rheumatologic (80%), kidney (80%), and skin lesions (70%) Anti-nuclear antibodies	Meningitis unusual (20-50% of neuro-lupus), low level pleocytosis (<50 cells/mm^3), always lymphocytic
Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)	Sex ratio 1/1 Disease onset after the age of 50	Neurological (i) cerebral vasculitis (ii) *Pseudotumor cerebri* Extraneurological Upper and lower respiratory tract symptoms (epistaxis, pneumonia), Glomerulonephritis Anti-neutrophil cytoplasmic antibodies (c-ANCA), anti-PR3	Meningitis a rare event

years old. Males are at higher risk of Behçet's disease, and, among patients with Behçet's disease, at higher risk of neurological manifestations, representing 60–80% of neuro-Behçet's cases in most series [12,13]. The disease is much more common in countries which formed the ancient Silk Route, with a mean prevalence of 300/100,000 in Mediterranean countries (Turkey, Maghreb, Italy, Greece, Egypt), Middle East (Israel, Iran, Iraq), or Japan, as compared to 1/100,000 in Western Europe. There is a clear association with HLA-B51 in high-prevalence countries, but not in Europe [18].

Extraneurological manifestations include recurrent, multiple, painful oral aphthosis (> 95% of patients, the signature of the disease), and genital ulcers (60–90%), but may also affect the skin (pseudofolliculitis/erythema nodosum, 40–90%), the eyes (uveitis/retinal vasculitis, 45–90%), the gastrointestinal tract (diarrhea/hemorrhage/perforation/pain, 4–38%), with characteristic vascular tropism (venous/arterial thrombosis, aneurysm, 2.2–50%). As for neurosarcoidosis, the diagnosis of neuro-Behçet is much more complicated when neurological manifestations develop while patients have not yet been diagnosed with Behçet's disease, which occurs in approximately one-third of cases. Overall, 5–30% of patients with Behçet's disease will develop neuro-Behçet, categorized as either parenchymal (meningoencephalitis), or vascular (cerebral venous thrombosis, stroke, aneurysms) [12,13]. In patients with aseptic meningoencephalitis, the predominance of neutrophils, and the frequent involvement of brain stem (rhombencephalitis), are major clues (Fig. 1).

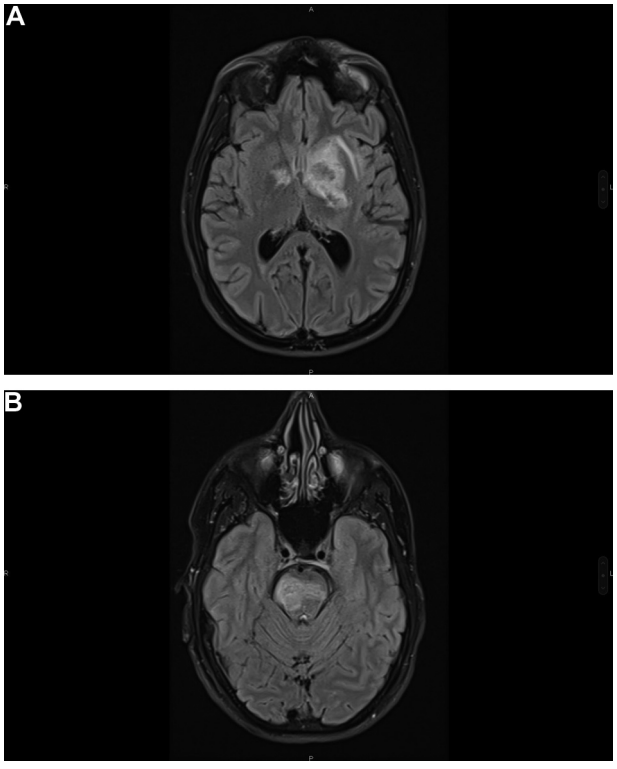

Fig. 1 – Rhombencephalitis in a 35-year-old man with neuro-Behçet (A&B).

2.3. *Other systemic diseases associated with aseptic meningitis*

Apart from neurosarcoidosis, and neuro-Behçet's, by far the two leaders [6,7], other systemic diseases may very rarely be associated with aseptic meningitis: The main characteristics and clues for the diagnosis of aseptic meningitis related to Sjögren syndrome [14], systemic lupus erythematosus [15], and granulomatosis with polyangeitis, are summarized in Table 1. Vogt-Koyanagi-Harada disease [19], cryoglobulinemia [20], Still disease [21], Kikuchi disease [22], Hashimoto encephalopathy [23], are even more seldomly reported in case series of aseptic meningitis.

3. Drug-induced aseptic meningitis

The diagnosis of drug-induced aseptic meningitis or meningoencephalitis is often puzzling, as may be inferred from the long diagnostic delay in many cases reported thus far (Table 2). Indeed, a significant proportion of cases are diagnosed only after several episodes of acute, self-resolving, undocumented meningitis have occurred [24]. The time elapsed between drug intake, and onset of neurological symptoms, may vary from a few minutes, to several months. Most common manifestations include fever (86%), headache (79%), meningeal signs (70%), and altered consciousness (50%). Localization signs (18%), and seizures (10%) are less common. Myalgia (54%) may be a clue [25].

CSF analysis usually reveals frank meningitis (median cell count, 300/mm^3), with a predominance of neutrophils (60–80% of cases), so that the main differential diagnosis is bacterial meningitis. However, biochemical abnormalities are usually limited, with normal glucose level and moderately elevetad protein level in CSF (1–1.5 g/l). Brain imaging is unremarkable in 95% of cases [26,27].

The four main categories of drugs that have been associated with aseptic meningitis are: (i) non-steroidal anti-inflammatory drugs (NSAIDs), especially ibuprofene, with an increased risk in patients with systemic lupus erythematosus; (ii) antibiotics (especially sulfamides, penicillins [24]); (iii) intravenous immunoglobulin (especially if infusion was administered over a too short time); and (iv) monoclonal antibodies. The prognosis of drug-induced aseptic meningitis is excellent, and most patients fully recover once the culprit drug is discontinued [28].

4. Neoplastic meningitis

Neoplastic meningitis complicate 3–8% of all neoplasia, and their incidence is increasing, due to the increased life expectancy of many cancers with medical progress (Table 3). More precisely, 4–15% of patients with solid cancer (carcinomatous meningitis) [29,30], and 5–15% of patients with hematological malignancy, will develop aseptic meningitis, either by the time of neoplasia diagnosis, or later during their disease progression. The three major solid cancers associated with neoplastic meningitis are breast cancers, lung cancers,

Table 2 – Drug-induced aseptic meningitis.

Etiology	Context	Clinical features	Cerebrospinal fluid (CSF) analysis
Non-steroidal anti-inflammatory drugs (NSAIDs) Antibiotics (sulfamides, penicillins) Intravenous immunoglobulin Monoclonal antibodies Miscellaneous (antiepileptic drugs)	NSAID-induced aseptic meningitis more common in young women, with systemic lupus erythematosus Time elapsed between drug intake, and meningitis, highly variable (from minutes to months)	Neurological signs headache (79%) meningeal signs (70%) altered consciousness (50%) Extraneurological signs fever (86%) myalgia (54%)	Neutrophilic meningitis (60–80%), with frank meningitis (median cells count, 300/mm^3) Moderate biochemical abnormalities: normal glucose level, protein level < 2 g/l

Table 3 – Neoplastic meningitis.

Etiology	Context	Clinical features	Cerebrospinal fluid (CSF) analysis
Solid cancer: carcinomatous meningitis (breast cancer, lung cancer, melanoma) Hematologic malignancies (leukemia, lymphoma)	Primary neoplasia already diagnosed, with treatment failure (70%) Primary neoplasia already diagnosed, considered on remission (meningitis reveals failure, 20%) Inaugural neoplastic meningitis (neoplasia previously unsuspected, 5–10%)	Rapidly progressive Multifocal neurological lesions Various motor and sensory deficit, including cranial nerves palsies Cognitive impairment Central and peripheral nervous sytem manifestations	Rapid transportation of an adequate volume (ideally, 10 ml) Experimented cytologist Repeated tests may increase the sensitivity, from 45% with a single analysis, to 80% if repeated on a second sample

and melanoma. Neoplastic meningitis is usually diagnosed in a patient already followed-up for the primary neoplasia, and considered as treatment failure (70% of cases), but sometimes considered as well-controlled before the diagnosis of neoplastic meningitis (20% of cases). Rarely, neoplastic meningitis is already present by the time neoplasia is diagnosed (5–10% of all neoplastic meningitis) [29,30].

Neoplastic meningitis is characterized by rapidly progressive, multifocal neurological lesions, various motor and sensory deficits, including cranial nerve palsies, cognitive impairment, with a combination of central and peripheral nervous sytem manifestations [31]. The diagnosis of neoplastic meningitis relies on the accuracy of CSF cytological analysis, which requires rapid transportation of an adequate volume of CSF (ideally, 10 ml) to an experimented cytologist. Repeated tests may increase the diagnostic yield, with a sensitivity increasing from 45% with a single CSF analysis, to 80% if the test is repeated on a second sample [31]. The prognosis used to be dismal, but improved with the advent of new treatments (check-point inhibitors, monoclonal antibodies, etc.).

5. Conclusion

Aseptic meningitis encompasses a broad range of systemic inflammatory, drug-induced, and neoplastic diseases. More than half of cases will be finally labeled as 'undocumented', which probably reflects both the sub-optimal diagnostic tools currently available for CNS diseases, and the remaining gaps in modern medicine, despite dramatic progress over the last two decades in microbiological diagnostic tools, and the discovery of a large panel of autoimmune and paraneoplastic neurological diseases. The final diagnosis may be obtained through rigorous diagnostic work-up, from careful collection of anamnesis and physical examination, to well-informed investigations, including, but not necessarily restricted to, CNS investigations (i.e. brain imaging and CSF analysis). Multidisciplinary concertation is a key component for timely and accurate diagnosis.

Funding

None.

Disclosure of interest

The authors declare that they have no competing interest.

REFERENCES

[1] Nigrovic LE. Aseptic meningitis. Handb Clin Neurol 2013;112:1153–6.
[2] Mount HR, Boyle SD. Aseptic and bacterial meningitis: evaluation, treatment, and prevention. Am Fam Physician 2017;96:314–22.
[3] Monticelli J, Geremia N, D'Agaro P, Petix V, Luzzati R. Aseptic central nervous system infections in adults: what predictor for unknown etiological diagnosis? Neurol Sci 2018;39:863–70.
[4] Shukla B, Aguilera EA, Salazar L, Wootton SH, Kaewpoowat Q, Hasbun R. Aseptic meningitis in adults and children: Diagnostic and management challenges. J Clin Virol 2017;94:110–4.
[5] Nowak DA, Boehmer R, Fuchs HH. A retrospective clinical, laboratory and outcome analysis in 43 cases of acute aseptic meningitis. Eur J Neurol 2003;10:271–80.
[6] Jarrin I, Sellier P, Lopes A, Morgand M, Makovec T, Delcey V, et al. Etiologies and management of aseptic meningitis in patients admitted to an internal medicine department. Fundam Clin Pharmacol 2016;95:e2372.
[7] de la Motte MB, Abbas R, Jouan F, van Gysel D, Chauveheid MP, Papo T, et al. Systemic inflammatory disorders in patients admitted for aseptic meningitis. Clin Med (Lond) 2018;18:132–7.
[8] Moavero R, Papetti L, Tarantino S, Battan B, Salfa I, Deodati A, et al. Syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocitosis should be considered in children presenting with acute confusional state. Headache 2018;58:438–42.
[9] Hiraga A, Kuwabara S. Meningitis-retention syndrome: Clinical features, frequency and prognosis. J Neurol Sci 2018;390:261–4.
[10] Fritz D, Voortman M, van de Beek D, Drent M, Brouwer MC. Many faces of neurosarcoidosis: from chronic meningitis to myelopathy. Curr Opin Pulm Med 2017;23:439–46.
[11] Ungprasert P, Crowson CS, Matteson EL. Characteristics and long-term outcome of neurosarcoidosis: A population-based study from 1976-2013. Neuroepidemiology 2017;48:87–94.
[12] Charca-Benavente LC, Gomez de la Torre R, Caminal-Montero L, Coto-Hernandez R, Colunga-Arguelles D.

Neuro-Behcet disease in the central university hospital of Asturias. Rheumatol Clin 2019.
[13] Noel N, Drier A, Wechsler B, Piette JC, De Paz R, Dormont D, et al. Neurological manifestations of Behcet's disease. Rev Med Interne 2014;35:112–20.
[14] Margaretten M. Neurologic Manifestations of Primary Sjogren Syndrome. Fundam Clin Pharmacol 2017;43:519–29.
[15] Bendorius M, Po C, Muller S. From Systemic Inflammation to Neuroinflammation: The Case of Neurolupus., 19. 2018.
[16] Onyeuku NE, Balakrishnan N, Cartwright MS. Granulomatosis with polyangiitis presenting with pachymeningitis. J Neurol Sci 2014;344:208–9.
[17] Jung YH, Lee MJ, Lee C, Cha J, Chung CS. Granulomatosis With Polyangiitis-Associated Hypertrophic Pachymeningitis Mimicking Spontaneous Intracranial Hypotension: A Case Report. Headache 2017;57:488–93.
[18] Davatchi F. Behcet's disease. Rheum Dis 2014;17:355–7.
[19] Street D, Sivaguru A, Sreekantam S, Mollan SP. Vogt-Koyanagi-Harada disease. Int J Mol Sci 2018;19.
[20] Feldman L, Dhamne M, Li Y. Neurologic manifestations associated with cryoglobulinemia: A single center experience. J Neurol Sci 2019;398:121–7.
[21] Akkara Veetil BM, Yee AH, Warrington KJ, Aksamit Jr AJ, Mason TG. Aseptic meningitis in adult onset Still's disease. Rheumatol Int 2012;32:4031–4.
[22] Komagamine T, Nagashima T, Kojima M, Kokubun N, Nakamura T, Hashimoto K, et al. Recurrent aseptic meningitis in association with Kikuchi-Fujimoto disease: case report and literature review. BMC Neurol 2012;12:112.
[23] Ferracci F, Carnevale A. The neurological disorder associated with thyroid autoimmunity. J Neurol 2006;253:975–84.
[24] Chu L, Eustace M. Recurrent amoxicillin-induced aseptic meningitis. Can J Neurol Sci 2018;45:701–2.
[25] Yelehe-Okouma M, Czmil-Garon J, Pape E, Petitpain N, Gillet P. Drug-induced aseptic meningitis: a mini-review. Fundam Clin Pharmacol 2018;32:252–60.
[26] Jolles S, Sewell WA, Leighton C. Drug-induced aseptic meningitis: diagnosis and management. Drug Saf 2000;22:215–26.
[27] Kepa L, Oczko-Grzesik B, Stolarz W, Sobala-Szczygiel B. Drug-induced aseptic meningitis in suspected central nervous system infections. J Clin Neurosci 2005;12:562–4.
[28] Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis. Arch Intern Med 1999;159:1185–94.
[29] Le Rhun E, Taillibert S, Chamberlain MC. Neoplastic meningitis due to lung, breast, and melanoma metastases. Cancer Control 2017;24:22–32.
[30] Lombardi G, Zustovich F, Farina P, Della Puppa A, Manara R, Cecchin D, et al. Neoplastic meningitis from solid tumors: New diagnostic and therapeutic approaches. Oncologist 2011;16:1175–88.
[31] Rigakos G, Liakou CI, Felipe N, Orkoulas-Razis D, Razis E. Clinical presentation, diagnosis, and radiological findings of neoplastic meningitis. Cancer Control 2017;24:9–21.