Immune-related aseptic meningitis and strategies to manage immune checkpoint inhibitor therapy: a systematic review

Simon Nannini1 · Larysa Koshenkova1 · Seyyid Baloglu2 · Dominique Chaussemy3 · Georges Noël4 · Roland Schott1

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Abstract
Introduction  Immune checkpoint inhibitors (ICIs) can induce adverse neurological effects. Due to its rarity as an adverse effect, meningitis has been poorly described. Therefore, meningitis diagnosis and management can be challenging for specialists. Moreover, meningitis can be an obstacle to resuming immunotherapy. Given the lack of alternatives, the possibility of reintroducing immunotherapy should be discussed on an individual basis. Here, we present a comprehensive systematic review of meningitis related to ICIs.

Review  We performed a search for articles regarding immune-related meningitis published in PubMed up to November 2021 with the MeSH terms “meningitis” and “immune checkpoint” using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. We summarized the studies not only by category but also based on whether it was a primary article or case report to provide a systematic overview of the subject. We reviewed a total of 38 studies and herein report the clinical experiences, pharmacovigilance data and group knowledge from these studies.

Conclusion  This review summarizes the existing information on immune-related meningitis and the possibility of reintroducing immunotherapy after the development of central neurological side effects. To the best of our knowledge, there is little information in the literature to guide clinicians on decisions regarding whether immunotherapy should be continued after a neurological adverse event occurs, especially meningeal events. This review emphasizes the necessity of systematic examinations, steroid treatment (as a cornerstone of management) and the need for further exploratory studies to obtain a clearer understanding of how to better manage patients who experience these side effects. The findings summarized in this review can help provide guidance to practitioners who face this clinical situation.

Keywords  Immune-related adverse event · Immunotherapy · Reintroduction · Aseptic meningitis · Melanoma

Abbreviations
ASCO  American Society of Clinical Oncology
CNS  Central nervous system
CSF  Cerebrospinal fluid
CTLA-4  Cytotoxic T-lymphocyte-associated protein 4
EEG  Electroencephalography
ESMO  European Society of Medical Oncology
FDA  Food and Drug Association
ICI  Immune checkpoint inhibitor
IrAEs  Immune-related adverse events
MM  Metastatic melanoma
MRI  Magnetic resonance imaging
NCCN  National Comprehensive Cancer Network
NMDA  N-methyl-D-aspartate
NSCLC  Non-small-cell lung cancer
OS  Overall survival
PD(L)1  Programmed death (ligand) 1
PET-CT  Positron emission tomography-computed tomography
PFS  Progression-free survival

Roland Schott
r.schott@icans.eu

1 Department of Medical Oncology, Strasbourg-Europe Cancer Institute (ICANS), 67200 Strasbourg, France
2 Department of Radiology, Strasbourg University Hospital 67033, Strasbourg, France
3 Department of Neurosurgery, Strasbourg University Hospital 67033, Strasbourg, France
4 Department of Radiation Oncology, Strasbourg-Europe Cancer Institute (ICANS), 67200 Strasbourg, France
Introduction

Currently, immune checkpoint inhibitors (ICIs) have become the standard of care for numerous cancers. In 2011, ipilimumab was approved by the Food and Drug Administration (FDA) to treat metastatic melanoma (MM), with an improvement in progression-free survival (PFS) of 4 months [1]. In 2015, nivolumab, an inhibitor of programmed death ligand 1 (PDL1), improved the overall response of MM patients compared to dacarbazine [2]. In 2017, the combination of nivolumab and ipilimumab achieved a median overall survival (OS) of 60 months compared to the 36.9 months achieved with nivolumab alone for the treatment of MM [3]. Consequently, the nivolumab plus ipilimumab combination became the new standard of care for BRAF-negative MM.

However, ICIs induce unique side effects. Ipilimumab alone and its combination with nivolumab are associated with the highest rates of immune-related adverse effects (irAEs) among other immunotherapies, as 53% of patients treated with such regimens had grade 3–4 irAEs [4]. IrAEs can involve the central nervous system (CNS) and are often severe despite their rarity. Due to the difficulty in diagnosing neurological irAEs, the reported incidence of 1–5% is probably an underestimate [5]. In particular, immune-induced aseptic meningitis is associated with high rates of mortality and/or morbidity [7]. Systematic explorations with at least CNS imaging, lumbar puncture, viral screening and viral serology analysis are recommended by the European Society for Medical Oncology (ESMO) [8]. If meningeal irAEs cause sufficient concern, management typically features high-dose steroid administration for at least 4 to 6 weeks with decreasing doses [8].

Whether ICIs should be resumed thereafter is still debated. After some irAEs develop, because of the lack of an efficient alternative option for metastatic disease treatment, resuming ICIs can be the best choice. The current review attempted to summarize reported knowledge about the management of immune-related meningitis and the reintroduction of ICIs.

Methodology

We searched for articles related to immune-related meningitis published on PubMed with the MesH terms “meningitis” and “immune checkpoint” up to November 19, 2021, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method (Fig. 1.). We summarized primary articles and case reports to give a systematic overview of the subject.

Results

In 11 articles, 40 cases of immune-related meningitis or meningoencephalitis (with at least signs of meningitis on lumbar puncture) were reported [10–22] (Tables 1 and 2). An overview of the results is presented in Fig. 2. In our systematic review, 18 articles were reviews of neuronal irAEs. Their main points are summarized in the following sections in parallel with a description of the case series.

Population characteristics

Data from 40 patients, including 22 men and 16 women with a median age of 56 years, were collected [range 19–82 years]. Overall, 21 patients (52.5%), 10 patients (25.0%), six patients (15.0%), two patients and one patient presented with melanoma, lung cancer, renal cell carcinoma, Hodgkin lymphoma, and colorectal cancer with microsatellite instability, respectively. Four patients (10.0%) had brain metastasis, and surgery was performed on one patient, but no other data on local treatment were reported for the other patients.

Ipilimumab and nivolumab were the most frequently prescribed ICIs. The combination of both was used in 16 patients (40.0%), ipilimumab alone was used in seven patients (17.5%), and nivolumab alone was used in five patients (12.5%). Pembrolizumab was used in six patients (15.0%), atezolizumab was used in five patients, and spartalizumab was used in one patient.

Clinical outcomes

The most common symptoms were headache, fever, cognitive disturbance and gait instability. The symptoms began after a median of 2 cycles [range 1–14 cycles]. The clinical status of patients deteriorated quickly, occurring within a few days after the beginning of symptoms. All patients except three presented with cerebrospinal fluid (CSF) lymphocytosis. One patient refused lumbar puncture, and one did not have detectable cells in the CSF [11], and their last exam showed only a protein content over 6 g/L [14]. Data on the white blood cell count was available for 17 patients, with a median value of 25 cells/mm³ (0–320 cells/mm³). Proteinorachy was described for 16 patients, with a median value of 0.87 g/L (0.3–3.85 g/L). Cerebral imaging was performed by magnetic resonance imaging (MRI) for 38 patients, with diffuse leptomeningeal enhancement observed in 16 (42.1%). One patient had cerebral edema, which is a sign of encephalitis [19]. No specific signs were reported for 21 patients (55%). Some cases reported specific contrast enhancement of the basal ganglia, pituitary gland, corpus callosum or frontal lobe.
Identification of the studies obtained via databases and registers

Records identified from Medline using the following search terms: ((meningitis) AND (immunotherapy) OR (immune checkpoint))
Registers (n = 85)

Articles sought for retrieval (n = 42)

Reports assessed for eligibility (n = 38)

Articles included in the review (n = 38)

Records removed before screening (n = 43):
- Articles on another subject (n = 40)
- Records removed for other reasons (n = 3)

Records excluded after screening (n = 4):
- Articles reporting data from already included case-reports (n = 2)
- Articles on the physiopathology of carcinomatous meningitis and effects of immunotherapy (n = 2)

Record details (n = 38):
- Case reports (n = 11)
- Reviews of neuronal immune-related adverse effects (n = 18)
- Studies on pharmacovigilance (n = 3)
- Immunotherapy articles with data on immune-related meningitis (n = 6)

Fig. 1 PRISMA flow diagram of the literature search strategy

Treatment and evaluation

Proper tapering of high-dose corticosteroids is the cornerstone of treatment [70]. Unfortunately, 20% of patients did not improve with corticosteroids alone, and the addition of an immunosuppressive agent was required [71, 72]. Due to the potential residual benefit of ICIs, multidisciplinary discussions and decisions, particularly about the management of severe cases, are important, especially when the patient is in intensive care [73].

In our case series, the main treatment component was steroids. 30 patients received intravenous (IV) steroids (75.0%), and five received oral steroids (12.5%). The initial dose varied between 1 g/day and 1 mg/kg/day for 3 to 5 days, followed by a dose reduction over a median of 6 weeks after improvement. Katakura et al. reported a patient treated with 30 mg of oral steroids but did not specify the time to complete recovery.

In six patients (15.0%), symptoms did not improve after steroid treatment. IV immunoglobulins were administered to five patients, and infliximab was introduced to two patients. Garcia et al. reported a patient who improved after IV steroid administration but quickly relapsed at the end of the steroid decrease. Consequently, a combination of steroids and immunoglobulins was tried, but the outcome was unsatisfactory. The addition of infliximab finally induced a near complete recovery [23]. Thouvenin et al. reported the case of a 63-year-old man treated with nivolumab for renal cell carcinoma who developed immune-related meningoencephalitis with uncontrolled choreatic movements. Despite steroid and infliximab treatments, the patient deteriorated and died [19].
Table 1  Case reports on immune-related meningitis: patient characteristics and clinical and paraclinical signs

| References        | Sex | Age (years) | Tumor type          | ICI received | Time to 1st signs of meningitis | Symptoms                                                                 | Lumbar puncture results                           | MRI results                |
|-------------------|-----|-------------|---------------------|--------------|--------------------------------|--------------------------------------------------------------------------|----------------------------------------------------|---------------------------|
| Cuzzubbo S et al. [11] | M   | 71          | Stage IIIc melanoma | Nivo 3       | 6 days after the 1st cycle     | Fever, partial seizure and confusion                                    | Cyto: 40 cells/mm3 with 90% lymphocytes— protein content = 0.99 g/L | Nonspecific               |
|                   | F   | 29          | Stage IIIc melanoma | Ipi 1—Nivo 3  | 6 days after the 1st cycle     | Headache, nausea and photophobia                                        | Cyto: 8 cells/mm3 with 100% lymphocytes— protein content = 0.30 g/L | Nonspecific               |
|                   | F   | 51          | Stage IV melanoma   | Spartalizumab 400 mg | 95 days after the 1st cycle | Headache and pain in 4 limbs                                            | Cyto: 19 cells/mm3 with 90% lymphocytes— protein content = 0.39 g/L | Nonspecific               |
|                   | F   | 46          | Stage IV melanoma   | Ipi 1—Nivo 3  | 50 days after the 1st cycle    | Headache and vomiting                                                    | Cyto: 25 cells/mm3 with 90% lymphocytes— protein content = 0.43 g/L | Nonspecific               |
|                   | F   | 64          | Stage IIc melanoma  | Nivo 3        | 6 days after the 1st cycle     | Headache and vomiting                                                    | Cyto: 0 cells/mm3— protein content = 0.59 g/L          | Nonspecific               |
|                   | M   | 27          | Stage IIIc melanoma | Ipi 3 – Nivo 1 | 9 days after the 1st cycle     | Headache and fever                                                       | Cyto: 9 cells/mm3 with 90% lymphocytes— protein content = 0.54 g/L | Nonspecific               |
|                   | F   | 20          | Stage IV melanoma   | Ipi 3—Nivo 1  | 17 days after the 1st cycle    | Headache and fever                                                       | Cyto: 320 cells/mm3 with 90% lymphocytes— protein content < 0.45 g/L | Nonspecific               |
| Thouvenin L et al. [19] | F   | 46          | Stage IV uveal melanoma | Ipi 3       | 4 cycles after the reintroduction of ICI after the development of hypophysitis | Headache, hearing loss, nausea, asthenia, slightly elevated temperature, and cerebellar syndrome | Cyto: elevated cells/mm3 with 91% lymphocytes— elevated protein content | Regressive sequelae of hypophysitis |
|                   | M   | 70          | Stage IV renal cell carcinoma | Ipi 3—Nivo 1 | 5 days after the 1st cycle    | Neck pain, fever, gait disturbance, aphasia and confusion                | Cyto: elevated cells/mm3 with 66% lymphocytes— elevated protein content | Ventriculitis |
|                   | F   | 44          | Stage IV MSI colorectal carcinoma | Ipi 1—Nivo 3 | After 3 cycles                | Headache, fever, and photophobia                                        | Cyto: elevated cells/mm3 with 92% lymphocytes— elevated protein content | Nonspecific               |
| References | Sex | Age (years) | Tumor type | ICI received | Time to 1st signs of meningitis | Symptoms | Lumbar puncture results | MRI results |
|------------|-----|-------------|------------|--------------|-------------------------------|----------|------------------------|------------|
| M 82       | M   | 68          | Stage IV renal cell carcinoma | Pembrolizumab 200 mg | 10 days after the 1st cycle | Confusion, impaired speech, gait disturbance, and fever | Cytology: elevated cells/mm³ with 91% lymphocytes—elevated protein content | Multiple areas with contrast and leptomeningeal enhancement |
| M 68       | M   | 19          | Stage IV melanoma | Ipi 1—Nivo 3 | After 3 cycles of Ipi-Nivo and 1 cycle of Nivo alone | Fever, speech disturbance, confusion, and drowsiness | Cytology: elevated cells/mm³ with 99% lymphocytes—elevated protein content | Diffuse dural enhancements |
| F 70       | F   | 70          | Stage IV renal cell carcinoma | Ipi 1—Nivo 3 | After 2 cycles | Headache, nausea, and dizziness | Cytology: elevated cells/mm³ with 99% lymphocytes—elevated protein content | Nonspecific |
| M 56       | M   | 56          | Stage IV uveal melanoma | Ipi 3 | After 4 cycles | Nausea, asthenia, fever, gait imbalance, hallucinations, and myoclonic jerking | Cytology: elevated cells/mm³ with 96% lymphocytes—elevated protein content | Diffuse dural enhancements |
| M 55       | M   | 55          | Stage IV lung adenocarcinoma | Pembrolizumab 200 mg | After 11 cycles | Headache and photophobia | Cytology: elevated cells/mm³ with 30% lymphocytes—elevated protein content—high opening pressure | Nonspecific |
| F 53       | F   | 53          | Stage IV melanoma | Ipi 3—Nivo 1 | After 2 cycles | Fever, aphasia, dizziness, asthenia, and slurred speech | Cytology: elevated cells/mm³ with 86% lymphocytes—elevated protein content | Nonspecific |
| M 61       | M   | 61          | Stage IV melanoma | Ipi 3 – Nivo 1 | After 4 cycles of Ipi-Nivo and 1 cycle of Nivo alone | Altered mental status | Cytology: elevated cells/mm³—elevated protein content | Nonspecific |
| M 57       | M   | 57          | Stage IV melanoma | Nivo 3 follow by Ipi 3 | After 14 cycles of Nivo alone and 4 of Ipi alone | Headache and confusion | Cytology: elevated cells/mm³ (lymphocytosis)—elevated protein content | Nonspecific |
| UNK UNK    | UNK | UNK         | Stage IV melanoma | Ipi | After 2 cycles | Headache, nausea, vomiting, and drowsiness | Cytology: few lymphocytes | UNK |
| References | Sex | Age (years) | Tumor type                  | ICI received      | Time to 1st signs of meningitis | Symptoms                                                                 | Lumbar puncture results                                                                 | MRI results |
|------------|-----|-------------|-----------------------------|-------------------|-------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------|------------|
| UNK        | UNK | Stage IV melanoma | Ipi—Nivo                  | After 2 cycles     | Headache and nausea           | Cytology: reactive lymphocytes                                           | UNK                                                   |            |
| F 71       |     | Stage IV lung adenocarcinoma | Pembrolizumab          | After 6 cycles     | Diplopia, gait disturbance, and lower limb paresthesia | Cytology: elevated cells/mm³ (lymphocytosis)—elevated protein content—positive anti-Rib antibody | Nonspecific                                 |            |
| M 20       |     | Recurrent Hodgkin’s lymphoma | Nivo 3                  | After 3 cycles     | Headaches, diplopia, confusion, nausea, vomiting, ataxia, and dysmetria | Cytology: elevated cells/mm³ with 94% lymphocytes—elevated protein content | Cerebellar edema |            |
| M 63       |     | Stage IV renal cell carcinoma | Nivo 300 mg             | After 6 cycles     | Uncontrolled choreatic movements | Cytology: mild inflammation—positive anti-PNMA2 antibody—autopsy focal lymphocytic meningitis of the entire brain and cervical spinal cord | Pathological increased signal within the basal ganglia |            |
| M 51       |     | Stage IV squamous lung carcinoma | Pembrolizumab          | After 8 months     | Fever, headache, ataxia, and Kernig sign | Cytology: elevated cells/mm³ (lymphocytosis)—elevated protein content | Nonspecific |            |
| M 56       |     | Stage III melanoma        | Adjuvant Ipi 10         | After 4 cycles     | Dizziness, neck pain, headache, and severe gait ataxia | Cytology: elevated cells/mm³ with 99% lymphocytes—elevated protein content | Arachnoiditis |            |
| F 39       |     | Stage IIIA melanoma       | Adjuvant Ipi 10         | After 3 cycles     | Headache and flu-like symptoms | Cytology: elevated cells/mm³ (lymphocytosis)—elevated protein content—high opening pressure | Leptomeningeal enhancement and pituitary enlargement |            |
| M 51       |     | Stage IV melanoma         | Ipi 3                  | After the 1st cycle | Headache and fever            | Cytology: elevated cells/mm³—elevated protein content—high opening pressure | Nonspecific |            |
| References | Sex | Age (years) | Tumor type | ICI received | Time to 1st signs of meningitis | Symptoms | Lumbar puncture results | MRI results |
|------------|-----|-------------|------------|--------------|-------------------------------|----------|--------------------------|------------|
| Toyozawa R et al. — JTO Clin Res Rep. 2020 [22] | F   | 45          | Stage IV melanoma | Ipi 3 | After 3 cycles | Confusion, headache, nausea, and dysmetria | Cytology: elevated cells/mm³—elevated protein content—high opening pressure | Nonspecific |
| M           | 55          | Stage IV lung carcinoma | Atezolizumab (+ carboplatin + paclitaxel + bevacizumab) | 14 days after the 1st cycle | Fever and disturbance of consciousness | Cytology: normal cells/mm³—protein content = 1.36 g/L | Nonspecific |
| M           | 50          | Stage IV lung adenocarcinoma | Atezolizumab | 11 days after the 1st cycle | Fever and disturbance of consciousness | Cytology: normal cells/mm³—protein content = 1.30 g/L | Nonspecific |
| Ogawa K et al. [18] | M | 56          | Stage IV lung adenocarcinoma | Atezolizumab after 14 cycles of Nivo | 11 days after the 1st cycle | Fever, headache, asthenia, and dysarthria | Cytology: 25 cells/mm³—protein content = 1.34 g/L | Meningeal enhancement |
| Minami S et al. [17] | F  | 65          | Stage IV lung adenocarcinoma | Pembrolizumab | After 13 cycles (8 months) | Asthenia, chills, and fever | Cytology: 197 cells/mm³ (97% mononuclear cells)—elevated protein content=0.32 g/L | Nonspecific |
| Shields LBE et al. [16] | M  | 66          | Stage IV renal cell carcinoma | Nivo 240 mg | After 7 cycles | Bilateral lower extremity weakness, lethargy, fever, confusion, and coma | Cytology: 27 cells/mm³ (78% mononuclear cells)—elevated protein content | Diffuse leptomeningeal enhancements |
| Yonenobu Y et al. [15] | M  | 61          | Stage IV squamous lung carcinoma | Pembrolizumab | After 2 cycles | Consciousness disturbance | Cytology: 79 lymphocytes/mm³—protein content = 2.09 g/L | High signal intensity lesions in the left frontal lobe and pons |
| Laserna A et al. [14] | F  | 53          | Stage IV squamous lung carcinoma | Atezolizumab | 13 days after the 1st cycle | Altered mental status, headache, meningeal signs and coma | Cytology: 553 mcL (91% PNNs)—protein content > 6 g/L | Diffuse leptomeningeal enhancements |
| Bello-Chavolla OY et al. [13] | M  | 66          | Stage IV melanoma | Ipi 10 follow by Ipi 10—Nivo 3 | 3 days after the last cycle; after 9 cycles of Ipi alone and 4 cycles of Ipi-Nivo | Fever, generalized weakness, headache, and hyporexia | No lumbar puncture (patient refusal) | Not performed |
| Ohno N et al. [12] | M  | 76          | Stage IV renal cell carcinoma | Ipi 1—Nivo 3 | After 2 cycles | Consciousness disturbance, and fever | Cytology: 147 cells/mm³—protein content = 3.85 g/L | Diffuse meningeal enhancement |
After the initiation of the treatment, improvement usually occurred in a few days. However, Bompaire et al. reported a case of severe meningoneuritis that required IV steroids and immunoglobulin, which induced symptom improvement within only 1 month. The patient remained in complete remission after 24 months [24]. Sequelea-free complete recovery was observed in 35 patients (87.5%). Only three patients (7.5%) did not achieve complete symptom improvement. All of these patients had clinical signs more related to encephalitis (ataxia and diplopia) [25, 26] or polyradiculoneuropathy [12] than to meningitis. Kopecky et al. and Minami et al. reported two cases of death due to meningitis (4.9%). Both patients died quickly, 1 week after the beginning of deterioration, despite the start of high-dose steroids and/or infliximab [17, 27].

In five cases, the authors did not administer treatment because of low-grade meningitis. Spontaneous improvement was noted at a median time of 10 days (7–65 days) [11, 19].

## Follow-up and therapy reintroduction

After recovery, ICI reintroduction was proposed in 14 patients (35.0%). In four patients, the same ICI was prescribed. New irAEs were reported in three patients after reintroduction, all of whom had received the same ICI. One patient developed interstitial lung disease and meningitis relapse, and the other two developed adrenal insufficiency [11, 21, 28]. Takamasu et al. reported that a patient with stage IV renal cell carcinoma achieved a complete response owing to the combination of ipilimumab 1 mg/kg and nivolumab 3 mg/kg, despite irAE reoccurrence [28]. Six of the seven cases reported by Cuzzubbo et al. did not experience irAE reoccurrence, even after ICI continuation, with two of the six cases receiving dual ICI treatment with 1 mg/kg ipilimumab. The patient treated with spartalizumab was diagnosed with interstitial lung disease shortly after reintroduction of the same ICI [11]. Fellner et al. also reported successful outcomes after the reintroduction of ICIs, but only with nivolumab, as irAEs developed with the combination of ipilimumab and nivolumab [81].

Five patients who received therapy reintroduction (35.7%) demonstrated progressive disease, and three of these patients succumbed to disease-related death. Five patients (35.7%) had a complete or partial response, and one other had a dissociated response. No stable disease was reported in the therapy reintroduction population.

At the last follow-up after irAEs were reported, among the patients with reported data, the overall response rate was 51.9%. Five patients achieved a complete response (18.5%), and nine patients achieved a partial response (33.3%). Eight patients experienced disease progression (29.6%), and five patients had stable disease (18.5%). The disease control rate
| References                          | Treatment of irAEs                                                                 | Response                                                                 | Treatment reintroduction            | Reintroduced treatment | Best response after irAEs | Patient course |
|-----------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------------|------------------------|--------------------------|--------------------------|
| Cuzzubbo S et al. [11]            | Steroids 1 mg/kg/day for 7 days followed by 42 days of tapering                  | Complete recovery 2 days after steroid treatment and 18 days after the 1st signs | Yes—373 days after initial treatment | Ipi 1—Nivo 3 (0,5 mg/kg/J steroids) | PD                        | PD at 3 months and death from cancer progression |
| Steroids 1 mg/kg/day for 7 days followed by 42 days of tapering | Complete recovery 14 days after steroid treatment and 17 days after the 1st signs | Yes—54 days after initial treatment                                      | Ipi 1—Nivo 3                       | CR                     | CR at 32 months after reintroduction |
| No treatment                      | Complete recovery in 10 days                                                      | Yes—24 days after initial treatment                                      | Spartalizumab                      | PD                     | Grade 3 interstitial lung disease and PD 3 months after reintroduction |
| Steroids 1 mg/kg/day for 7 days followed by 42 days of tapering | Complete recovery 2 days after steroid treatment and 21 days from the 1st signs | Yes—118 days after initial treatment                                      | Nivo 3                             | PD                     | PD at 3 months and death from cancer progression |
| No treatment                      | Complete recovery in 65 days                                                      | Yes—4 days after initial treatment                                       | Nivo 3                             | PR                     | PR at 3 months, maintained at 6 months |
| Steroids 1 mg/kg/days for 14 days followed by 42 days of tapering | Complete recovery 14 days after steroid treatment and 49 days from the 1st signs | Yes—126 days after initial treatment                                      | Spartalizumab+ribociclib           | PD                     | PD at 3 months and death from cancer progression |
| No treatment                      | Complete recovery in 10 days                                                      | Yes—19 days after initial treatment                                      | Nivo 3                             | PR                     | PR at 3 months, maintained at 17 months—PR for 2 years—pembrolizumab given at disease progression without irAE—death 8 months after treatment with new ICI |
| Thouvenin L et al. [19]           | IV steroids 4 mg/kg/J for 6 days followed by 6 weeks of oral steroid tapering    | Improvement and relapse 1 week after steroid treatment> improvement and remission after treatment with 12 mg/day oral dexamethasone> tapering over 3 months | Yes—only after 2 years and disease progression | Pembrolizumab 2 mg/kg | PR                        |                          |
| IV steroids 1,8 mg/kg/J for 7 days followed by 6 weeks of oral steroid tapering | Improvement in a few days but long tapering because of several recurrences (total of 7 months) | No                                                                 | No                                 | PR                     | PR for 7 months and pazopanib administered after relapse |
| IV steroids 2 mg/kg/J for 3 days followed by 6 weeks oral steroid tapering | Complete recovery after 3 days of steroid treatment                             | Yes—shortly resumed after steroid discontinuation                        | Nivo 3                             | PR                     | Dissociated radiological response, no IrAE recurrence |
| IV steroids 1 mg/kg/J for 5 days followed by 3 months of oral steroid tapering | Complete recovery in a few days after steroid treatment                          | No                                                                     | No                                 | CR                     | CR without new treatment |
| Oral steroids for 7 days followed by 1 month of tapering | Complete recovery                                                               | No                                                                     | No                                 | SD                     | SD at 9 months |
| References | Treatment of irAEs | Response | Treatment reintroduction | Reintroduced treatment | Best response after irAEs | Patient course |
|------------|-------------------|----------|--------------------------|-----------------------|--------------------------|---------------|
| IV steroids for 8 days followed by 1 month of oral steroid tapering | Complete recovery | Yes—3 months after resolution | UNK | PD | PD |
| IV steroids 1 mg/kg/J and 1 month of oral steroid tapering | Complete recovery | Yes—3rd cycle at 10 mg/J steroids | Ipi 1—Nivo 3 | CR | Adrenal insufficiency, recurrence of meningitis and hepatitis after the 3rd cycle—no ICIs were administered, but CR was achieved |
| IV steroids followed by 4 months tapering | Improvement in 48 h | No | No | UNK | UNK |
| IV steroids followed by oral steroid tapering | Complete recovery in 1 day | No | No | CR | CR |
| IV steroids, but no tapering data | Complete recovery after 3 days of steroid treatment | Yes—after PD during treatment with dabrafenib-trametinib | Pembrolizumab | PD | PD without irAEs |
| IV steroids for a few days; the second treatment was combined with IG followed by oral steroid tapering | Complete recovery only after increased steroid and IG dose | No | No | PD | PD at 4 months |
| IV steroids followed by oral steroid tapering | Complete recovery in 6 days | No | No | PR | VGPR |
| No treatment | Complete recovery in 10 days | UNK | UNK | PD | PD at 6 months |
| No treatment | Complete recovery in 7 days | UNK | UNK | PR | PR for 16 months |
| Oral steroids for 12 weeks | Complete recovery at 8 weeks > relapse 3 weeks after steroid treatment; treated with rituximab and IV steroids > relapse under steroid treatment after 4 months; addition of cyclophosphamide | No | No | CR | CR |
| Steroids for 4 weeks | Recovery at days 6 except for diplopia | No | No | PR | PR |
| IV steroids with addition of infliximab at deterioration | Cognitive deterioration | No | No | UNK | Death due to irAE |
| References          | Treatment of irAEs                                                                 | Response                                                                 | Treatment reintroduction | Reintroduced treatment | Best response after irAEs | Patient course |
|---------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------|-------------------------|---------------------------|----------------|
| IV steroids with 10% tapering per week | Improvement in a few days except for ataxia                                      | No                                                                       | No                       | SD                      | SD at 1 year              |                |
| IV steroids for 3 days follow by IG for 5 days after the development of worsening neurological symptoms (ultimately resulting in tetraplegia), subsequent administration of oral steroids for 4 months | With IG and IV steroids, improvement over 1 month, but complete recovery only after 24 months | No                                                                       | No                       | UNK                     | UNK            |                |
| IV steroids and oral steroid tapering over 8 weeks; relapse treated with IV steroids, IG and infliximab with steroid tapering over 3 months | Rapid improvement of the first signs of disease; near complete recovery of relapse only after infliximab treatment | No                                                                       | No                       | UNK                     | UNK            |                |
| Oral steroids       | Complete recovery in a few days after steroid treatment                           | UNK                                                                      | UNK                      | SD                      | SD at 10 months           |                |
| Oral steroids, IV steroids after deterioration, and then IG       | Improvement only after IG treatment                                             | UNK                                                                      | UNK                      | UNK                     | UNK            |                |
| Toyozawa R et al.—JTO Clin Res Rep. 2020 [22]                          | IV steroids, but no tapering data                                               | Complete recovery                                                      | UNK                      | UNK                     | UNK            | UNK            |
|                     | IV steroids, but no tapering data                                               | Improvement after 2 days                                                 | UNK                      | UNK                     | UNK            | UNK            |
| Ogawa K et al. [18] | IV steroids, but no tapering data                                               | Complete recovery                                                        | UNK                      | UNK                     | UNK            | UNK            |
|                     | IV steroids 1 g/day for 3 days and 12 weeks of oral steroid tapering             | Improvement after 3 days                                                 | No                       | No                      | SD             | SD at 3 months |
| Minami S et al. [17] | IV steroids 1 g/body/day                                                        | Death after 5 days                                                       | No                       | No                      | UNK            | Death after 5 days |
| Shields LBE et al. [16] | Oral steroids 90 mg for 6 days follow by tapering                             | Complete recovery after 2 weeks                                          | No                       | No                      | SD             | SD after 40 months |
| Yonenobu Y et al. [15] | IV steroids 1 g twice for 3 days follow by oral steroid 1 mg/kg and IG         | Improvement in a few days                                                | UNK                      | UNK                     | UNK            | UNK            |
| Laserna A et al. [14] | IV steroids 15 days and tapering over 19 days                                  | Improvement after 15 days of IV steroid treatment                        | UNK                      | UNK                     | UNK            | UNK            |
|                     |                                                                                   |                                                                          |                          |                         |                |                |
was 70.4%, which is comparable to the rates reported in phase 3 studies of immunotherapy [3, 29].

**Pharmacovigilance studies**

Three articles analyzed pharmacovigilance data using disproportionality analysis, and the results revealed an association between ICI use and neurotoxicity [7, 30, 31]. Johnson et al. reported 18,518,994 neurological AEs, among which 48,653 were related to ICIs. The researchers concluded that the patients receiving ICIs had a higher incidence of myasthenia gravis (ROR = 16.5), encephalitis (ROR = 10.4), peripheral neuropathy and meningitis compared to those receiving other systemic treatments (ROR = 3.1). Meningitis (0.15% of patients in their cohort) was preferentially associated with the use of anti-CTLA-4 agents [7].

Sato et al. reported data from the Japanese Adverse Drug Event Report database. From a total of 7604 cases of irAEs, they identified 583 (7.67%) neurological AEs related to ICIs. The authors compared the incidences of AEs between nivolumab and other ICI subtypes. They concluded that the use of ipilimumab was associated with a higher incidence of meningitis. The time to the development of meningitis was shorter than the time to the development of other neurological irAEs [31]. In another study of 50,406 irAEs by Mikami et al., they used the FDA reporting system and identified 3619 neurological irAEs (7.2%). This number is similar to that reported by Sato et al., but Mikami et al. showed a higher incidence of neurological complications with the use of ICIs than non-ICI drugs. ICI combinations were associated with a higher incidence of neurological complications, mainly hypophysitis and hypopituitarism. The authors do not report any other risk factors associated with this higher incidence. Dual ICI therapy, older age, melanoma and non-small-cell lung cancer (NSCLC) seemed to be associated with a higher risk of fatal neurological irAEs, including meningeal irAEs [30].

**ICI efficacy in brain and leptomeningeal metastasis**

Of the studies retrieved by our literature search, five articles focused on the efficacy of ICIs in patients with central nervous system metastasis. Kuske et al. reviewed different treatments for melanoma brain metastasis and reported on phase 2 studies that evaluated ICIs in brain metastasis, which showed an intracranial response of approximately 42 to 55%. No difference in safety data was reported, except for slightly more headaches of any grade with dual ICI treatment [32].

Nguyen et al. focused on leptomeningeal metastasis and reported on the findings of different ongoing studies evaluating ICIs in this context. The researchers provided an interim analysis of the Brastianos et al. study, with 44% of patients alive at 3 months after pembrolizumab treatment for solid
The use of ICIs in this setting was also the topic of a review by Kondoh et al. [35]. For NSCLC, Gio et al. reported the efficacy of nivolumab in treating leptomeningeal metastasis and did not report any neurological irAEs [36]. Hendricks et al. reported an analysis of 19 patients with leptomeningeal metastases from NSCLC treated with ICIs. No safety data were reported, but the median overall survival was 3.7 months [37]. Nakashima et al. also reported the case of a 66-year-old woman with meningeval carcinomatosis from NSCLC treated with ICIs in combination with whole brain radiation. She achieved more than 23 months of survival without disease progression. This case introduced the idea of including radiotherapy in the treatment regimen. A higher irAE incidence with radiotherapy has not been reported [38–42].

These articles underline the importance of ICIs for the treatment of metastatic CNS tumors and confirm that there is no obvious increase in the incidence of irAEs after such treatment.
Discussion

Clinical signs and diagnosis

Neurological irAEs can present as various symptoms [43, 44]. In particular, CNS symptoms are easily underestimated because they manifest at a lower intensity than related symptoms. Usually, neurological irAEs are described in three categories: encephalitis, aseptic meningitis and multiple sclerosis. Non-specific isolated symptoms, such as headaches, are the most frequently reported symptoms (55%) and are usually low intensity [45].

Other than isolated symptoms, encephalitis and encephalopathy are the most frequently reported irAEs. Regardless, they occur in less than 1% of patients treated with ICIs [6]. Medical practitioners must be aware of these complications, especially due to the broad range of symptoms that can occur. Indeed, unexplained paucisymptomatic headache or focal weakness can be manifestations of grade 1 CNS irAEs [10]. Larkin et al. reported 6 cases of encephalitis, and most patients presented with mental disturbance, seizure and fatigue. Five of the six patients required prolonged hospitalization, and one of them died from complications [10]. Encephalitis leads to increased major morbidity and mortality, especially in cases of limbic encephalitis and cerebral inflammation, even with the administration high-dose steroids [46, 47]. Some pharmacovigilance databases have revealed a fatality rate of 19% when the brainstem is involved [48, 49]. The distinction between neurological irAEs and CNS infection can be challenging, particularly due to the lack of specific positive criteria and the presentation of flu-like symptoms in some cases of irAEs [50].

Infection can also probably induce neurological irAEs, as reported in some cases after herpes simplex infection or Epstein–Barr infection [49, 51]. Ultimately, the diagnosis should be based on a systematic approach with MRI, lumbar puncture, electroencephalography (EEG) if clinically indicated, and screening for typical autoimmune antibodies and/or infectious causes is necessary (Herpesviridae, enterovirus, varicella, and/or bacterial culture) [53, 54]. Non-specific inflammatory signs can be revealed on MRI and can be consistent with the presence of lymphocytic or neutrophilic pleocytosis, leading to the overlapping diagnosis of immune-induced meningoencephalitis. Of note, all of these tests can also yield normal results; ultimately, patient history and symptom resolution with corticosteroid therapy are factors indicative of a diagnosis of immune-related encephalitis [8].

The second most common CNS irAE described in the series was aseptic meningitis, which was more common with ICI combinations, especially combinations with ipilimumab. Immune-related aseptic meningitis occurred earlier than other neurological irAEs, with a median duration of two cycles and a delay of 9 days from the last injection of ICI to the manifestation of clinical signs [7, 45, 55, 56]. Immune-related aseptic meningitis occurs in less than 1% of cases and represents 6 to 15% of all neurological irAEs [5, 45, 57]. The clinical presentation varies from headache with photophobia to complete cranial hypertension with seizure. This variability in symptoms can make it difficult to distinguish aseptic meningitis from encephalitis. MRI results are often normal or reveal leptomeningeal inflammation. Lumbar puncture usually shows lymphocytosis with elevated protein, which is defined according to ESMO as a white blood cell count between 5 and 500/µL [7]. The CSF is sterile and negative for cytopathology. There are several overlapping diagnostic algorithms used to facilitate the differential diagnosis of immune-related meningitis [8, 58–60]. When testing for encephalitis, lumbar puncture and MRI with infectious disease screening (in particular, PCR for herpes simplex virus but also typical bacterial screening) are essential [61]. When peripheral symptoms are associated with central clinical signs, screening for thyroid dysfunction and/or vitamin B12/B9 deficiency is recommended [59].

Prevention of irAEs and survival outcomes

Because ICIs are almost universally accepted, the prevention of side effects is key to improving the benefit-risk ratio [65, 66]. The incidence of irAEs depends on the ICI, and different strategies have been explored to limit irAEs [67]. The Checkmate 511 study evaluated two combinations of nivolumab and ipilimumab, comparing treatment with nivolumab 1 mg/kg and ipilimumab 3 mg/kg and treatment with nivolumab 3 mg/kg and ipilimumab 1 mg/kg [68]. After 3 years, the number of grade 3–5 irAEs was significantly lower in the second group (48.3% versus 33.9%), without any difference in OS or PFS [68]. Only the irAEs that occurred in at least 10% of their population were actually reported, so specific data on meningitis are not available.

The prognostic value of irAEs has also been evaluated. Patients who developed side effects seemed to have better survival outcomes than those without any adverse effects [69]. Indini et al. showed improvements in both PFS and OS among patients with MM [9]. Shah et al. analyzed survival data from a cohort of patients who were readministered ICIs after irAEs occurred, and they reported the worst OS and PFS outcomes for patients with a shorter time to the development of initial or post-reintroduction irAEs. On the other hand, patients had a lower risk of disease progression if they completed more than 10 weeks of treatment after the resumption of ICIs.
Reintroduction of ICIs

The reintroduction of ICIs after the resolution of irAEs is still controversial. The National Comprehensive Cancer Network (NCCN), ESMO and the American Society of Clinical Oncology (ASCO) propose reintroducing ICIs only in cases of grade 1 or 2 irAEs [8, 70, 72]. Indeed, some reports have shown that half of the patients with severe irAEs will develop the same or distinct irAEs after the reintroduction of ICIs [74]. However, patients experiencing irAEs could have better OS and PFS outcomes after reintroduction than those who change treatment regimens [75]. A better understanding of the mechanisms of each irAE is clearly required [76–78].

The management and follow-up of patients with irAEs should be specific to the system affected. Indeed, patients with immune-related hepatitis as an irAE seem to be amenable to the reintroduction of ICIs, with more than 60% of patients avoiding recurrence of grade 2 or greater hepatitis in the study of Allouchery et al. [79]. In contrast, Simonaggio et al. reported that 55% of their patients experienced irAEs after reintroduction. In these patients, colic, pulmonary, joint and hematological toxicities were most likely to occur [74]. Dolladille et al. also explored the characteristics of irAEs after the reintroduction of ICIs, and the results showed that colitis and pneumonitis had higher recurrence rates than rarer irAEs, such as endocrine irAEs [80]. Although there are more than 400 reported irAEs, the rarity of CNS events complicates their analysis. The severity of irAEs, systems affected by irAEs, alternative therapeutic strategies and patient preference must be considered before the resumption of ICIs.

Regarding immune-related meningitis, case reports tend to show that reintroduction of ICIs is possible and can achieve good outcomes. Different strategies can be used, particularly for dual therapy. The reintroduction of ipilimumab has remained controversial because anti-CTLA4 agents are associated with a higher rate of meningitis and irAEs [7, 67]. Albandar et al. also studied survival outcomes after the reintroduction of ICIs, and they reported a median OS of 38.6 months among patients in whom treatment was reinitiated after interruption versus 24.9 months among patients in whom treatment was discontinued. However, this difference was not significantly different [82]. Only a few studies exploring the possibility of ICI reintroduction have been reported, so further studies are needed to help better understand and manage these meningeal irAEs.

Conclusion

With the emergence of ICIs, AEs have become a new challenge for specialists. In this review, we attempted to describe the variety of clinical signs and consequences of neurological irAEs. Due to their rarity, particularly meningitis, the guidelines recommend systematic biological and clinical examinations to avoid misdiagnosis. Steroids remain the principal treatment for neurological irAEs and successfully resolve the majority of cases. However, whether ICIs should be reintroduced remains to be determined. The answer seems to depend on the system involved, kinetics of improvement and clinical severity, but good outcomes have been achieved after reintroduction in some patients with immune-related meningitis. The collection of additional data in the near future will help to personalize the management strategy and follow-up schedule for patients with such irAEs. In conclusion, our review provides a comprehensive summary of the real-world knowledge on immune-related aseptic meningitis, which we hope will provide guidance for physicians who manage these patients.

Decalartions

Conflict of interest

None declared.

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Data availability All data analyzed during this study are included in this published article and its supplementary information files.

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