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School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Review Article

Aseptic meningitis induced by monoclonal antibodies used in cancer treatment: a systematic review

Nasibeh Ghalandari[1,2], Sara Ataei[1,2], Fahime Nasr Esfahani[3], and Shahaboddin Emami[1,2,*]

[1]Pharmaceutical Sciences Research Center, Institute of Cancer, Avicenna Health Research Institute, Hamadan University of Medical Sciences, Hamadan, I.R. Iran. [2]Department of Clinical Pharmacy, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, I.R. Iran. [3]13Aban Pharmacotherapy Clinic, Tehran University of Medical Sciences (TUMS), Tehran, I.R. Iran.

Abstract

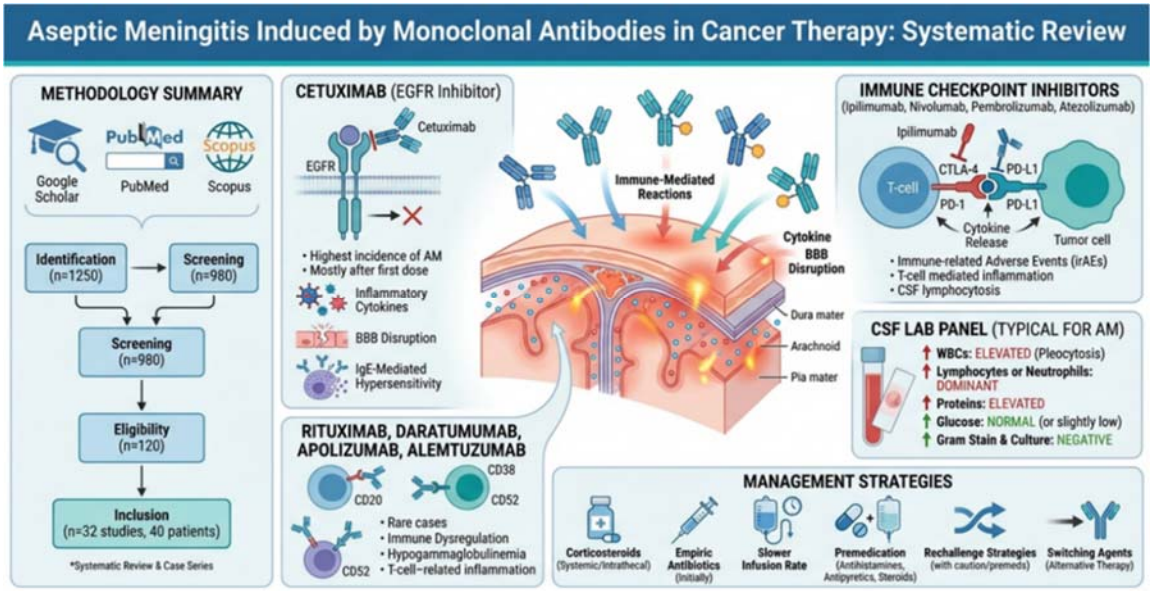
Background and purpose: Monoclonal antibodies (MAbs) have revolutionized cancer treatment but are associated with a spectrum of adverse events, including neurological complications. Understanding the mechanism and management of complications is crucial for optimizing patient care. The present systematic review aimed to identify case reports of MAbs used for cancer treatment that resulted in aseptic meningitis (AM).

Methods: Databases including Google Scholar, PubMed, and Scopus were searched for studies published until March 2024 (updated in May 2025). The Joanna Briggs Institute (JBI) critical appraisal checklist was used to assess the quality of case report studies, and the methodological quality of the included studies was considered acceptable.

Findings/Results: In total, 32 articles were analyzed in the present systematic review. Cetuximab had the highest reported incidence of AM, while rituximab, daratumumab, and apolizumab had the lowest prevalence. The quality of the studies was also acceptable.

Conclusion and implications: AM appears to occur more frequently with monoclonal antibodies than with conventional drug structures. Prompt recognition of the underlying mechanisms can help physicians manage these complications more effectively.

Keywords: Aseptic meningitis; Cancer immunotherapy; Drug-induced adverse effect; Monoclonal antibodies; Review.



*Corresponding author: S. Emami
Tel: +98-8138381675, Fax: +98-8138381591
Email: sh.emami@umsha.ac.ir

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1. INTRODUCTION

Aseptic meningitis (AM) is characterized by inflammation of the meninges and presents with symptoms such as severe headache, fever, neck stiffness, and photophobia. AM is a rare but serious adverse event associated with the use of monoclonal antibodies (MAbs) in cancer treatment. MAbs have revolutionized the field of oncology offering targeted therapy with fewer systemic side effects compared to traditional chemotherapy (1-3).

The development of AM in cancer patients receiving MAbs has been reported in the literature, with varying incidences depending on the specific MAbs used. The pathophysiology of AM induced by MAbs is not fully understood, but it is thought to be related to an immune-mediated response triggered by the antibodies (4-6).

Several MAbs have been implicated in the development of AM, including rituximab, an anti-CD20 antibody used in the treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL), and ipilimumab, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor used in the treatment of advanced melanoma (7). The incidence of AM associated with these agents varies, with reported rates ranging from 0.5% to 3% for rituximab and approximately 3% for ipilimumab. Other MAbs, such as nivolumab and pembrolizumab, which are immune checkpoint inhibitors used in the treatment of various solid tumors, have also been linked to AM, albeit rarely (8-10).

Given the expanding use of MAbs in cancer treatment, healthcare providers must be aware of the potential for AM as a rare but important adverse event. This article aimed to review the current literature on AM induced by MAbs used in cancer treatment, including incidence, clinical presentation, pathophysiology, diagnosis, and management. By increasing awareness and understanding of this complication, clinicians may optimize the safe and effective use of MAbs in the oncology setting.

2. METHODS

2.1. *Data sources*

The present systematic review aimed to identify and analyze AM induced by MAbs in cancer treatment. The report was prepared based on the Preferred Reporting Items for systematic reviews and meta-analyses (PRISMA) checklist. The databases, including Google Scholar, PubMed, and Scopus, were searched for studies published until March 2024. Each was updated in May 2025.

2.2. *Search strategy*

The keywords used in the PubMed database were the following: aseptic meningitis,

monoclonal antibody, cancer, and case report. The following MeSH terms were used: (aseptic meningitis) AND (monoclonal antibody OR antibody, monoclonal OR monoclonal antibodies) AND (tumors OR neoplasia OR neoplasias OR neoplasm OR tumor OR cancer OR cancers OR malignant neoplasm OR malignancy OR malignancies OR malignant neoplasms OR neoplasm, malignant OR neoplasms, malignant OR benign OR neoplasms OR neoplasms, benign OR neoplasm, benign OR benign neoplasm). In the Scopus database, the same keywords were utilized in the "article title, abstract, keywords" field. Moreover, the same keywords were used as a search query in the advanced search of Google Scholar.

2.3. *Eligibility criteria*

The inclusion criteria for this study were as follows: (a) case reports or case series, (b) reports addressing AM associated with the use of MAbs in cancer management, (c) availability of full text (except for two articles (11,12). Records were excluded if they were (a) non-English, (b) AM induced by traditional chemotherapy, and (c) review or meta-analysis studies, letters to the editor, clinical trials (except those mentioned in Table 1 as they contained individual information of affected patients), and qualitative studies.

2.4. *Data extraction*

Endnote® version 7 (Clarivate Analytics) was used to screen and extract data from the selected studies. Two researchers extracted data based on standard criteria, first based on the title and if not clear or in case of discrepancy, abstracts were searched. The chosen articles were reviewed by the remaining author. The extracted data were then used to complete the population, intervention, comparison, and outcome (PICO) table and analyzed for further information (e.g., proposed mechanisms and reported management).

2.5. *Quality of the studies*

The methodological quality of case report studies was evaluated using the Joanna Briggs Institute (JBI) critical appraisal checklist (13). This checklist comprises eight Likert questions that assess crucial aspects of case reports. These included the accurate presentation of patient demographic information, proper documentation of patient history, a comprehensive description of the current clinical conditions of patients, clear expression of diagnostic measures, thorough presentation of therapeutic measures, elucidation of patients' conditions post-therapeutic interventions, and identification and explanation of the causes of reported side effects. The assessment also encompassed an evaluation of the overall utility of the case reports, as detailed in Table 1.

3. RESULTS

A search in the mentioned databases, conducted up to March 25, 2024, resulted in 204 articles being selected, of which 108 duplicates were removed, leaving 96 articles that were independently examined by two researchers. Screening of titles and abstracts led to the removal of 60 more articles. Finally, the remaining articles were examined in full text, which resulted in the exclusion of 5 articles due to intervention method, language, type of drug, and adverse effect (Fig. 1). One article was added after the search was updated on May 5, 2025. Lastly, 32 articles were considered eligible, and the clinical details of 40 patients were recorded. The related studies were summarized in Table 2. Fourteen studies were published from the United States, followed by 7 studies recorded from Japanese patients, and the rest were conducted in European countries (France, Germany, Belgium, Switzerland, UK, *etc*.). Accordingly, 40 patients from 32 studies on 9 MAbs as monotherapy and 2 combination therapies were identified. Among the 40 patients, 13 were female, 23 were male, and the sex of the remaining patients was not reported.

3.1. *MAbs causing AM*

3.1.1. Cetuximab

Cetuximab, a MAb, inhibits the dimerization of the epidermal growth factor receptor (EGFR), thereby preventing the activation of downstream signaling pathways that promote tumor proliferation and survival (42). Some of the adverse effects of this drug include skin rashes, infusion reactions, gastrointestinal disorders, and headache (43). Although research on different neurological adverse effects of cetuximab has been limited, cases of seizure, polyneuropathy, headache, confusion, and delirium have been reported (44).

Table 1. JBI critical appraisal checklist for case reports.

Study	Were the patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Were the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Overall appraisal
Rogers *et al.* (14)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Feinstein *et al.* (15)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Nagovskiy *et al.* (16)	Y	Y	Y	Y	N	Y	Y	Y	Include
Givens *et al.* (17)	Y	Y	Y	Y	UC	N	Y	Y	Include
Emani and Zaiden (18)	Y	Y	Y	Y	Y	UC	Y	Y	Include
Prasanna *et al.* (19)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Ulrich *et al.* (20)	Y	Y	Y	Y	Y	UC	Y	Y	Include
Maritaz *et al.* (21)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Oishi *et al.* (22)	Y	Y	Y	Y	Y	N	Y	Y	Include
Reddy *et al.* (23)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Inui *et al.* (24)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Vulsteke *et al.* (25)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Rohrer *et al.* (26)	Y	Y	Y	UC	N	Y	Y	Y	Include
Jäger *et al.* (27)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Al-Khateeb *et al.* (28)	Y	Y	Y	Y	UC	Y	UC	Y	Include
Takamatsu *et al.* (29)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Bot *et al.* (30)	Y	Y	Y	Y	Y	UC	Y	Y	Include
Cordes *et al.* (31)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Lima *et al.* (32)	Y	UC	Y	Y	Y	Y	Y	Y	Include
Toyozawa *et al.* (33)	Y	N	Y	Y	Y	Y	Y	Y	Include
Kaur *et al.* (34)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Katakura *et al.* (35)	Y	Y	Y	Y	UC	N	Y	Y	Include
Tonk *et al.* (36)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Kuroda and Nakagawa (37)	Y	Y	Y	Y	Y	Y	Y	Y	Include
Kanawaka *et al.* (38)	Y	Y	Y	Y	Y	Y	Y	Y	Include

Y, Yes; N, no; UC, uncertain.

Table 2. Case reports of aseptic meningitis induced by anti-cancer monoclonal antibodies.

Drugs	Study	Type of cancer/medical history	Previous chemotherapy regimen	Timeline of occurrence	CSF analysis	Symptom duration/therapy	Cancer treatment	Demographic characteristics (year/gender)	Outcome
Cetuximab	Rogers *et al.* (14)	mCRC to liver	FOLFOX + bevacizumab	A few hours after the first dose	Elevated WBC, neutrophil ratio and protein	5 days/empiric antibiotics with supportive measures	Changed to panitumumab, then to FOLFIRI	42/F	Symptoms resolved
	Feinstein *et al.* (15)	Laryngeal SCC	Radiosurgery	A few hours after the first dose	Elevated WBC, neutrophil ratio and protein	4 days/empiric antibiotics	Re-challenged with adding dexamethasone to premedication	45/M	Symptoms resolved
		Tonsil SCC / History of Guillain-Barré syndrome	Radiation + Pemetrexed	About 8 h after the first dose	Elevated WBC, neutrophil ratio and protein	12 days/empiric antibiotics	Re-challenged with adding dexamethasone and famotidine premedication and a slower infusion rate	42/M	Symptoms resolved
	Nagovski *et al.* (16)	NSCLC/history of breast cancer	Radiotherapy	A few hours after the first dose	Elevated PML, neutrophil ratio and protein	NM/empiric antibiotics with supportive care	NM	78/F	Symptoms resolved
		NSCLC/Liver transplant and alcoholic cirrhosis	NM	A few hours after the first dose	Elevated nucleated cells, total protein and segmented cell	Several days/empiric antibiotics	NM	59/M	Symptoms resolved
	Emani *et al.* (18)	Metastatic squamous maxillary cancer	NM	A few hours after the first dose	Elevated WBC, neutrophil ratio and protein	NM/empiric antibiotics	Re-challenged, but symptoms occurred again	54/F	Symptoms resolved
	Prasana, *et al.* (19)	Tonsillar squamous cell cancer/HIV/HTN /dyslipidemia/CKD	NM	1 h after the first dose	Elevated WBC, neutrophil ratio and protein	4 days/empiric antibiotics with supportive measures	Re-challenged without again experiencing said symptoms	58/M	Symptoms resolved
	Ulrich *et al.* (20)	Advanced oropharyngeal SCC/ESRD	Carboplatin/paclitaxel	9 h after first dose	Elevated WBC, neutrophil ratio and protein	14 days/empiric antibiotics	Discontinued	67/M	Died after 6 weeks of discharge

	Maritaz *et al.* (21)	Advanced laryngeal squamous cell carcinoma/AF/HTN smoker	Docetaxel + cisplatin + 5FU	4 h after the first dose	Elevated WBC, neutrophil ratio and protein	2 days/empiric antibiotics	Reintroduced 28 days later with a slower rate and methylprednisolone premedication	66/F	Symptoms resolved
	Rohrer *et al.* (26)	Metastatic colon cancer/extended beta lactamase bacterial infection	Capecitabine	9 h after the twelfth dose	Elevated WBC, neutrophil ratio and protein	4 days/empiric antibiotics	Not re-challenged	43/F	Symptoms resolved
	Jäger *et al.* (27)	Metastatic rectum carcinoma	FOLFIRI	3 h after the first dose	Elevated WBC, neutrophil ratio	2 days/empiric antibiotics	Discontinued/naranjo scale:5	50/M	Symptoms resolved
	Vulstek *et al.* (25)	Squamous cell carcinoma/HTN/Depression/Hypercholesterolemia/GERD/Ex-smoker	Docetaxel + cisplatin + 5FU	A few hours after the first dose	Elevated WBC, neutrophil ratio	5 days/empiric antibiotics	Not re-challenged	53/M	Symptoms resolved
	Riggs (11)	HPV-positive squamous cell carcinoma/Tourette syndrome	NM	16 h after the first dose	Elevated WBC, neutrophil ratio and protein	2 days/empiric antibiotics	Changed to panitumumab	54/M	Symptoms resolved
	Kaur *et al.* (34)	Laryngeal cancer/COPD/Hepatitis C/Ex-smoker	Docetaxel + cisplatin + 5FU	6 h after first dose	Elevated WBC, neutrophil ratio and protein	3 days/empiric antibiotics	Re-challenged after 2 weeks with the addition of dexamethasone to premedication	65/F	Symptoms resolved
Rituximab	Givens *et al.* (17)	Follicular lymphoma	R-CHOP	NM, but at least after 6 cycles	Elevated WBC, lymphocyte ratio/PCR enterovirus	NM/IVIG	Discontinued	36/M	Symptom resolved
Ipilimumab	Voskens *et al.* (24)	Metastatic melanoma	Dacarbazine	3 weeks after the first infusion	lymphomonocytic (CD3-positive)	NM/empiric antibiotics	Permanently discontinued/changed to fotemustine	52/F	Symptoms resolved
	Yang *et al.* (12)	NM	Interleukin-2 therapy	After the fourth dose	Elevated WBC, lymphocyte ratio	NM/high-dose dexamethasone	NM	NM	Symptoms resolved
	Oishi *et al.* (22)	Metastatic melanoma	Dacarbazine	One week after the third cycle	Elevated WBC, lymphocyte ratio, and protein	NM/methylprednisolone then prednisolone	NM	59/M	Symptoms improved

	Bot *et al*. (30)	Metastatic melanoma	NM	After the first course	Elevated WBC, protein	2 days/dexamethasone	NM	51/M	Symptoms resolved
	Spain *et al*. (39)	Advanced melanoma/hypothyroidism	Cisplatin + dacarbazine + vincristine	After the second cycle	Lymphocyte	10 days/empiric antibiotics	Discontinued	NM	Symptoms resolved
		Advanced melanoma/hypertension/stroke	Dacarbazine	After second cycle	Normal	8 weeks/empiric antibiotics and prednisolone	Discontinued	NM	Symptoms resolved
Nivolumab	Tonk *et al*. (36)	Melanoma	Ipilimumab	92 days after	Elevated WBC, lymphocyte	NM/methylprednisolone	Discontinued	57/M	Complete resolution of symptoms
	Cordes *et al*. (31)	Urothelial carcinoma/HTN/hyperlipidemia/obesity/anxiety/depression/OSA/fatty liver disease	Gemcitabine + carboplatin/+ cabozantinib	After 24 doses	Elevated WBC, lymphocyte	72 h/methylprednisolone then oral dexamethasone	Discontinued	58/M	Symptoms resolved
	Al-Khateeb *et al*. (28)	Renal cell carcinoma	Monthly	4 years after initiation of therapy	Elevated WBC, mononuclear cell ratio, and protein	Not clear, but almost 3 weeks/observation	Re-challenged	60s/M	Symptoms resolved
Ipilimumab + nivolumab	Takamats *et al*. (29)	Metastatic renal cell carcinoma/HTN	Ipilimumab + nivolumab	14 days after the second cycle	Elevated WBC, lymphocyte ratio, and protein	NM/IV prednisolone then oral	Re-challenged after 50 days, but after 25 days, symptoms re-emerged	70/F	Symptoms resolved
	Spain *et al*. (39)	Advanced melanoma/cavernoma	NM	After the first cycle	Elevated WBC	7 weeks/observation	Re-challenged after 4 weeks	NM	Symptoms resolved
	Katakura *et al*. (35)	Melanoma	Nivolumab	4 weeks after the first dose	Elevated mononucleosis cell	NM/prednisolone	Changed to nivolumab monotherapy	25/M	NM
	Tonk *et al*. (36)	Melanoma	2 cycles	24 days after the second cycle	Elevated WBC, lymphocyte	NM/prednisolone	Discontinued	38/F	Complete resolution of symptoms
		Melanoma	2 cycles	32 days after the second cycle	Elevated WBC, lymphocyte	NM/prednisolone	Discontinued	55/M	Complete resolution of symptoms
Pembrolizumab	Inui *et al*. (24)	NSCLC	Pembelizumab/pemetrexed + carboplatin	Second- fifteenth days after first dose	Elevated WBC, lymphocyte	3 days/betamethasone to prednisolone	Discontinued	67/M	NM

	Lima *et al.* (32)	NSCLC/autoimmune hepatitis	11 cycles	3 weeks after the last dose	Elevated WBC, lymphocyte ratio and protein	1 day/dexamethasone IV then oral	Discontinued	55/M	Symptoms resolved
Daratumumab	Reddy *et al.* (23)	Progressive multiple myeloma	RVD/VDPACE/KRD	2 days after the first dose	Elevated WBC, neutrophil ratio, protein	NM/empiric antibiotics	After 1 month, it was resumed	46/F	Symptoms resolved/died
Atezolizumab	Kuroda *et al.* (36)	Squamous cell lung cancer	CBDCA + TS-1/VNR/DTX + RAM	10 days after the first dose	Elevated protein, monocyte ratio	4 days/IV methylprednisolone	Discontinued	46/M	Symptoms resolved
	Toyozawa *et al.* (32)	NSCLC	Carboplatin + paclitaxel + bevacizumab	14 days after the first cycle	Elevated protein	1 day/methylprednisolone	NM	71/F	Symptoms resolved
		Lung adenocarcinoma	NM first line	11 after the first cycle	Elevated protein	2 days/methylprednisolone	NM	55/F	Symptoms ameliorated
		Adenocarcinoma	NM first, second, and third lines	11 after the first cycle	Elevated protein, monocytes	4 days/methylprednisolone	Discontinued	50/M	Symptoms improved
Atezolizumab + Bevacizumab	Kawanaka *et al.* (38)	Hepatocellular carcinoma/HTN/dyslipidemia	First line	5 days after the 3rd course	Elevated protein	2 days/prednisolone	Discontinued	74/F	Symptoms resolved
Apolizumab	Lin *et al.* (40)	ALL or CLL	NM	After dose 7	Elevated protein, WBC, neutrophil ratio/apolizumab	7 days/empiric antibiotics	Discontinued	65/M	Symptoms resolved
Alemtuzumab	Kako *et al.* (41)	AML	Fludarabine + busulfan + TBI	After conditioning	Elevated WBC and mononuclear ratio	Increased dose of IV acyclovir	Discontinued	19/M	Symptoms resolved
		Follicular Lymphoma	Fludarabine + melphalan + TBI	After conditioning	Elevated WBC and mononuclear ratio/zoster	Increased dose of IV acyclovir	Discontinued	58/M	Symptoms resolved

M, Male; F, female; NM, not mentioned; WBC, white blood cell; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; IV, intravenous; HTN, hypertension; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; GERD, gastroesophageal reflux disease; AF, atrial fibrillation; OSA, obstructive sleep apnea; HIV, human immunodeficiency virus; HPV, human papillomavirus; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; mCRC, metastatic colorectal cancer; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; AML, acute myeloid leukemia; TBI, total body irradiation; FOLFOX, folinic acid (leucovorin) + fluorouracil + oxaliplatin; FOLFIRI, folinic acid (leucovorin) + fluorouracil + irinotecan; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; RVD, lenalidomide (revlimid) + bortezomib (velcade) + dexamethasone; VDPACE, bortezomib + dexamethasone + cisplatin + doxorubicin + cyclophosphamide + etoposide; KRD, carfilzomib + lenalidomide + dexamethasone; CBDCA, carboplatin; TS-1, tegafur/gimeracil/oteracil; VNR, vinorelbine; DTX, docetaxel; RAM, ramucirumab; IVIG, intravenous immunoglobulin; CD3, cluster of differentiation 3.

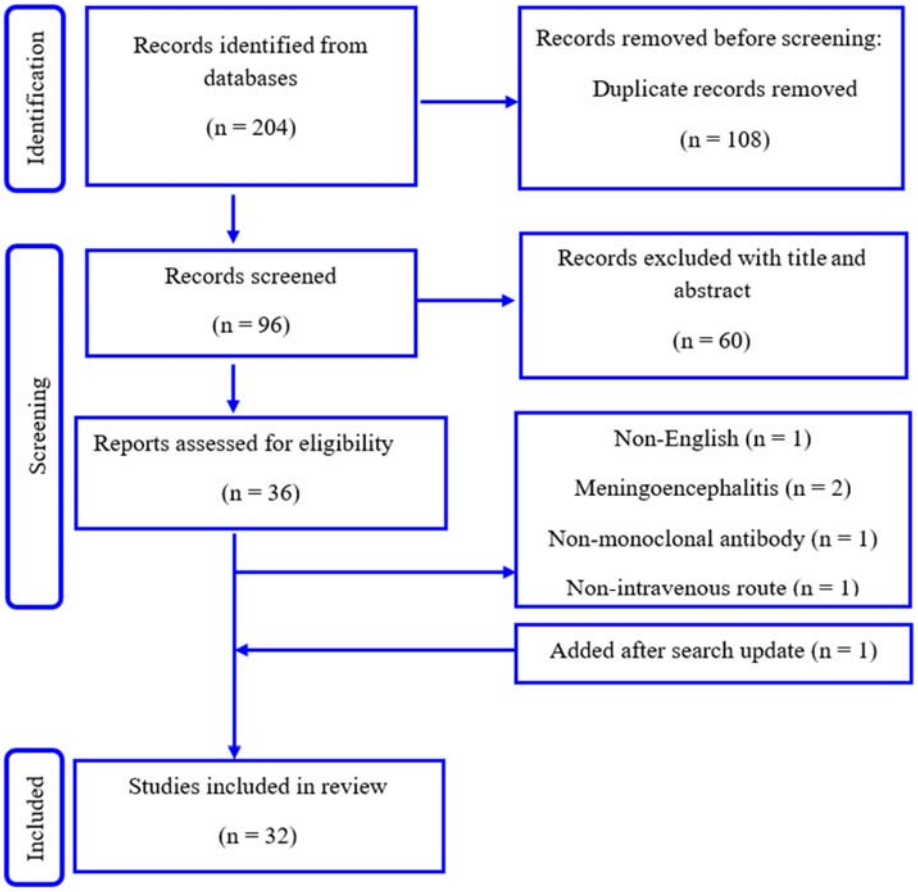

Fig. 1. Reporting items for the flowchart of systematic review of the included studies.

AM is a rare neurological adverse effect of cetuximab, which occurs in head and neck malignancies, and most commonly after the first dose. Symptoms are typical and last for a few days. Cerebrospinal fluid (CSF) shows increased white blood cell (WBC) count, elevated neutrophil proportion, and increased protein levels, which typically return to normal within a few days. Management has been documented with corticosteroids, empiric antibiotics, rechallenge with lower doses, heavier premedication, and slower infusion rate (43).

As shown in Table 2, cetuximab was the most reported suspect of reviewed case reports on AM. Of the fourteen patients in this group, 8 were male, 9 had head and neck malignancies, and 13 had received the first dose.

3.1.2. Rituximab

Rituximab is a chimeric MAb targeting CD20, used in the treatment of various conditions, including non-Hodgkin's lymphoma, rheumatoid arthritis, and CLL (45). Rituximab has some adverse effects, such as late-onset neutropenia, immune reconstitution defects, infections, progressive multifocal leukoencephalopathy, reactivation of hepatitis, intestinal perforation, and interstitial pneumonitis (46). In addition, rare neurological adverse effects of rituximab include seizure, cerebral infarction, and serotonin syndrome (47). Also, AM has been reported in patients with systemic lupus erythematosus and hypogammaglobulinemia secondary to rituximab (48).

During the review of literature, we encountered one case report of using this MAb as part of chemotherapy.

3.1.3. Ipilimumab

Ipilimumab, a MAb that targets the immune-inhibitory molecule CTLA-4, has shown promise in the treatment of advanced melanoma, with potential applications in

prostate and non-small cell lung cancers (49). These include potentially fatal conditions such as enterocolitis and ileitis, as well as less severe but still significant cutaneous effects (50-53). Some of the neurological adverse effects linked to ipilimumab therapy include inflammatory myopathy, AM, posterior reversible encephalopathy syndrome, Guillain-Barré syndrome, myasthenia gravis-like syndrome, sensorimotor neuropathy, and inflammatory enteric neuropathy (30,53).

The data presented in Table 2 reveal that melanoma was the most common malignancy type in patients, and it happened seemingly regardless of dose and time of administration. Six patients in 5 researches were evaluated. CSF analysis showed a rise in lymphocyte count, and patients were responsive to corticosteroid administration.

3.1.4. Nivolumab

Nivolumab, a programmed cell death protein 1 (PD-1) blocking antibody, has shown promising results in the treatment of advanced and metastatic renal cell carcinoma. It has also been used for unresectable malignant melanoma (54). Nivolumab adverse effects include rare events like adrenal insufficiency and autoimmune diabetes. Common side effects are pneumonitis, thyroiditis, hepatitis, pruritus, vitiligo, and diarrhea (54). Rare but potentially severe neurological adverse effects linked to nivolumab include inflammatory myopathy, AM, posterior reversible encephalopathy syndrome, Guillain-Barré syndrome, myasthenia gravis-like syndrome, and neuropathy (55).

Literature review revealed three reports of AM. All exhibited rose lymphocyte in CSF analysis. One was re-challenged without return of symptoms, and methylprednisolone was described as effective in its management.

3.1.5. Ipilimumab + nivolumab

The combination of ipilimumab and nivolumab is a first-line treatment for metastatic renal cell carcinoma (56). It has shown efficacy in patients with advanced melanoma and hepatocellular carcinoma receiving the combination of ipilimumab and nivolumab (57,58).

Ipilimumab and nivolumab combination has been associated with a higher risk of adverse effects than ipilimumab or nivolumab monotherapy. Common side effects include fatigue, diarrhea, pruritus, rash, and gastrointestinal disorders such as colitis and enterocolitis (59,60). In addition, there are some serious neurological side effects, such as myasthenia gravis, encephalitis, and toxic encephalopathy, in the administration of the combination (53).

The literature review results showed that the ipilimumab and nivolumab combination-induced AM was diagnosed in five patients from four studies. As expected, WBC counts presented in CSF rose supporting inflammatory mediation, and patients responded well to prednisolone therapy.

3.1.6. Pembrolizumab

Pembrolizumab is a PD-1 blocking antibody used in cancer immunotherapy to treat various types of cancer, such as non-small cell lung cancer (61). Pembrolizumab has serious adverse effects, including acute renal failure, severe neurological toxicity, myopathy, psychosis, and lichen planus. Also, the neurological immune-related adverse events include myasthenia gravis, encephalitis, myositis, and acute inflammatory demyelinating polyradiculoneuropathy (62).

Two patients, males of 67 and 55 years old, were recorded as having AM related to this medicine. CSF involvement, non-time dependence, and response to steroids were reported (Table 2).

3.1.7. Daratumumab

Daratumumab targets CD38, inducing apoptosis in $CD38^+$ multiple myeloma cells. It is generally well tolerated, but hematological reactions such as neutropenia, anemia, and thrombocytopenia are reported (63). Leukoencephalopathy has been reported as a neurological adverse effect of daratumumab (64).

3.1.8. Atezolizumab

Atezolizumab targets programmed death ligand 1 (PD-L1), enhancing T-cell activity against tumor cells by blocking the PD-L1/PD-1 immune checkpoint (65). Side effects with this drug range from autoimmune diabetes, encephalitis, and hemolytic anemia to gastrointestinal disorders (66). The neurological side effects include encephalitis, meningoencephalitis, neuropathy, acute

inflammatory demyelinating polyneuropathy, ataxia, seizure, and myopathy (67).

3.1.9. Apolizumab

Apolizumab targets the HLA-DR ß-chain on B cells, inducing complement-mediated cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and apoptosis of B cells (68). The neurological side effects, including global aphasia, seizure, motor weakness, diffuse cerebral edema, and coma, have been reported with this drug (69). According to the literature review results, apolizumab was detected in the patient's CSF (Table 2).

3.1.10. Alemtuzumab

Alemtuzumab, targeting CD52, is utilized in treating lymphoid malignancies like CLL and T-cell prolymphocytic leukemia (70). Alemtuzumab can increase the risk of stroke, both ischemic and hemorrhagic, as well as autoimmune-related secondary disorders such as Guillain-Barré syndrome (71).

4. DISCUSSION

This research aimed to investigate the underlying mechanisms of AM in patients undergoing chemotherapy with MAbs. The study sought to identify the at-risk patient population and to develop personalized treatment strategies that can improve the safety and efficacy of MAbs used in malignancy treatments.

AM of cetuximab has been expressed in many cases, and the mechanism behind this phenomenon has been hypothesized as immune-mediated against the drug molecule or a direct effect of the drug in meninges (21,26,27).

Intravenous immunoglobulin (IVIG) associated with AM is stated in many publications (21,72,73). It has been suggested that IgG crossing the blood-brain barrier (BBB) induces an inflammatory reaction in the meninges (33). Speculation of BBB cross of cetuximab has been shaded by its large molecule structure, although Prasanna *et al*. stated that EGFR inhibitors may result in the release of proinflammatory cytokines, which could potentially disrupt the BBB and allow entry into the CSF (19). Based on Maritaz's research, the release of histamine, serotonin, and prostaglandin as a result of inflammatory reaction could lead to meningeal microvasculature (21). Kaur *et al*. proposed that hypersensitivity reaction with steroid response, as other mechanism can empower this hypothesis (34). Chung *et al*. stated that an IgE-mediated reaction due to infusion of cetuximab can be another possible mechanism, and, as seen in some re-challenged cases, slow infusion and premedication with H_1 and H_2 antihistamines didn't lead to reappearance of symptoms (74). Dose-dependency has been suggested as a risk factor behind this side effect as high doses of cetuximab are administered in the first dose (27). However, in colorectal cancer, one of the most prevalent cancers, cetuximab is administered in high doses, and more frequently, many fewer reports have been recorded in colorectal cancer patients. Though in some reports, authors suggested that occurrence might not be dose-dependent and irrespective of dose, the first exposure to cetuximab may cause irritation of the meninges (18). Also, the half-life of cetuximab aligns with the onset and alleviation of symptoms. Premedication with glucocorticoid is effective in some cases after re-challenge (27). Inflammatory reaction of this drug has been connected to its chimeric structure, as panitumumab, a humanized MAb with the same mechanism, has not been reported causative of AM, thus changing to this agent has been used as a management in some cases reported (27). As most of the patients affected were suffering from head and neck malignancy may suggest a specific inflammatory mechanism. Interleukin-6 has been proposed to be involved in processes of squamous cell carcinomas of the head and neck associated with tumors. Therefore, it is conceivable that cytokine activation may be linked to cetuximab-associated AM (27).

The exact mechanism behind pembrolizumab-induced AM is not fully understood. However, it is believed to be related to the immunological response triggered by the immune checkpoint inhibitor (24,32). Steroids have been suggested as a management option, affecting the duration of response to immunotherapy (32).

The occurrence of ipilimumab-induced meningitis may be linked to the attraction of the drug to the cranial nervous system. It is believed that ipilimumab frequently triggers hypophysitis, an ailment thought to be caused by the expression of CTLA-4 in the anterior pituitary cells and resulting in a type II hypersensitivity reaction

(12,57). The potential involvement of a T helper 1 (Th1)/Th17-mediated autoimmune response may have been raised, as evidenced by the elevated presence of Th1 phenotype lymphocytes and a notable proportion of Th17 phenotype in the CSF (22). Immune-related adverse events (irAEs) with ipilimumab are prevalent in 14-77% of patients, apparently a high incidence since the action of this drug leads to T-cell proliferation and activation, which may respond to autoantigens (30).

The concurrent administration of anti-PD-1 and anti-CTLA-4 antibodies in combination therapy is anticipated to demonstrate a heightened efficacy. Nevertheless, it is noted that the incidence and intensity of irAEs may surpass therapy with each individual (35). If patients experience ipilimumab-induced irAEs, prompt steroid treatment can help to reduce the severity and duration of symptoms, even in cases where steroids are usually ineffective, such as Guillain-Barré syndrome or hypophysitis. Severity and frequency of irAEs appear to be dose-dependent, although immunotherapeutic do not show a dose-response in a linear curve manner as they depend on the immune system of the host to induce a response (38). Emerging evidence has established a relationship between irAEs and the effectiveness of immune checkpoint inhibitors (ICIs) in individuals diagnosed with solid tumors (31). According to a prior report, although steroid therapy was not effective, natalizumab, which inhibits lymphocytes from entering the BBB, was successful in treating autoimmune encephalitis as an irAE, which was triggered by the combination of ipilimumab and nivolumab (56).

Notably, the exact mechanism of nivolumab-induced AM is not fully elucidated. The mechanism of nivolumab-induced AM involves irAEs and is similar to other ICIs. These adverse effects are believed to be predominantly mediated by T cells, with some cases potentially involving other immune cells. In the context of immune-mediated encephalitis related to ICIs, antibodies against N-methyl-D-aspartate (NMDA) receptors have been implicated in the pathogenesis. These antibodies, found in patients with immune-mediated encephalitis, may cross-react with NMDA receptors in the brain, leading to encephalitis (75). Al-Khateeb *et al*. stated one possible explanation that is the suppression of an immune response targeting antigens common to both tumor and non-malignant tissues, potentially resulting in self-directed immunity (28). Additional research indicated that agents targeting CTLA-4 may induce the reduction of regulatory T-cells, influencing their function in inhibiting cell-mediated immune responses. Furthermore, it has been suggested that regulatory T-cells upregulate PDL1/PDL2 in the tumor microenvironment. The involvement of B-cells in the pathophysiology is also considered significant (76). Mizukami *et al*. reported that the concentration of interleukin-6 is proportional to the magnitude of the manifestation of meningoencephalitis (77).

The mechanism of rituximab-induced AM involves the impact of the drug on B cells and subsequent immune response. Rituximab leads to B cell depletion and hypogammaglobulinemia. This depletion affects the humoral immune response, potentially predisposing individuals to severe infections like AM caused by enteroviruses (17). Thus, IVIG seems a plausible treatment option used in the reported case.

The postulated mechanism behind daratumumab-induced AM involves immune hypersensitivity responses, likely related to T-cells, leading to meningeal inflammation (23).

Despite an extensive search of the literature, there was no specific mechanism related to alemtuzumab-induced AM. Nevertheless, it is notable that alemtuzumab can be involved in depleting lymphocytes, immune reconstitution syndrome, which can result in irAEs. The alemtuzumab effects seem to be dose-independent. The patients receiving the reduced doses of alemtuzumab revealed similar adverse immune-related events, whereas the high doses used in multiple sclerosis have not been reported to induce the same effects (41).

Japanese patients are believed to be more predisposed to atezolizumab-induced irAEs. Approximately 12% of Japanese cancer patients treated with atezolizumab displayed meningitis. Though the exact mechanism of this phenomenon is not explained, as atezolizumab is considered an ICI, the same mechanism explained for other members of this category can be proposed for atezolizumab (33).

There were some limitations in this study. Case reports and case series were frequently considered weak sources of evidence due to the high risk of bias. Also, language limitations hindered us from reviewing some of the articles.

5. CONCLUSION

AM is considered one of the bothersome complications of drug therapy. The emergence of new MAbs raises significant long-term safety concerns. Post-marketing surveillance reports of MAbs pose new challenges regarding the management of symptoms and replacement of offending agents. This study aimed to review and evaluate the published reports on cancer treatment and MAbs-associated AM to shed light on new insights and assist fellow healthcare providers in better managing patients and improving quality of life.

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Conflict of interest statement

The authors declared no conflict of interest in this study.

Authors' contributions

S. Emami contributed to the concept, design, and definition of the intellectual content; F. Nasr Esfahani performed the literature search; N. Ghalandari carried out data analysis and prepared the manuscript; S. Ataei was responsible for manuscript editing and review.

All authors have read and approved the finalized article. Each author has fulfilled the authorship criteria and affirmed that this article represents honest and original work.

AI declaration

During the preparation of this work, the authors used ChatGPT 4.0 to improve the text grammatically, readability, and language, but the drafting, idea structure, and data collection were carried out without any help from this tool. After using this tool, the authors reviewed and edited the content and take full responsibility for the content of the publication.

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