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Atezolizumab Induced Neurotoxicity: A Systematic Review

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Abstract

Background: Traditionally, cytotoxic chemotherapy dominated cancer treatment, but in recent years, immunotherapies, mainly immune checkpoint inhibitors (ICIs), have revolutionized cancer therapy by enhancing T-cell responses. Despite their efficacy, ICIs can induce toxicities affecting various organs, including the nervous system. Although rare, neurological complications of ICIs can be severe, contributing significantly to treatment-related mortality. Atezolizumab, targeting programmed death ligand 1, is approved for various cancers, with a side effect profile akin to other ICIs. While neurological adverse events with atezolizumab are less frequent, serious cases have been documented. Diagnosing these events is challenging due to atypical symptoms and limited experience in managing them. This review aimed to characterize the clinical presentation of atezolizumab-induced neurotoxicity, including neurological symptoms, diagnostic approaches, and treatment outcomes.

Methods: A Medline search conducted on atezolizumab-induced neurotoxicity using PubMed, ScienceDirect, and Google Scholar databases until March 15, 2024.

The search strategy encompassed MeSH terms and free-text words, incorporating terms such as atezolizumab, PD-L1, neurotoxicity, and various neurological adverse events. Inclusion criteria comprised English language publications, all age groups, randomized clinical trials, observational studies, systematic reviews, case reports, and case series.

Results: Of the 56 citations identified, 39 (representing 45 patients' cases) were included. Atezolizumab-induced neurotoxicity exhibits various clinical presentations, with grades 1-2 neurotoxicities being common and typically nonspecific, while grades 3-4 syndromes are less frequent and more severe. These adverse events were documented across various cancer types, with patients who had a median age of 58 years. Symptoms typically appeared after the first cycle of atezolizumab therapy, with a median onset of two weeks after the last dose. Management typically involved steroid therapy, with a few patients requiring additional interventions such as intravenous immunoglobulin or plasmapheresis. Symptoms usually resolved within a median of 10 days after atezolizumab cessation, with partial or complete recovery in most cases. Fatal outcomes were observed in 10 cases, although causality was not definitively established in all instances.

Conclusions: Atezolizumab-induced neurotoxicity is challenging to recognize due to widely varying symptoms, emphasizing the need for a thorough safety assessment to determine the incidence and patient risk profiles. Continued research into this adverse event is crucial for understanding patient susceptibility and developing effective management strategies.

Keywords: Immune related adverse events, Central nervous system, Atezolizumab, Immune checkpoint inhibitors, Neurological complications, Encephalitis, Neuropathy, Coma, Seizures

Background

Traditional cytotoxic chemotherapy has historically been the primary approach for treating various malignant tumors. However, in recent years, remarkable advancements in cancer management strategies have emerged with the introduction of immunotherapies, signaling a new era in anti-neoplastic therapy [1]. Immune checkpoint inhibitors (ICIs), predominantly composed of programmed cell death protein 1, programmed cell death 1 ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen-4 monoclonal antibodies, constitute a class of immunotherapy that enhances antitumor

immune responses by upregulating T-cell activity [1-3]. While ICIs have demonstrated high response rates in patients with various advanced malignancies, they can also be associated with several toxicities affecting any organ system including the nervous system [4]. Neurotoxicity triggered by ICIs can impact various components of the nervous system, including the central nervous system (CNS), the peripheral nervous system (PNS), and the neuroendocrine system [1]. Although neurological toxicities of ICIs are rare accounting for approximately 2% to 4% of all adverse effects, they can exhibit increased severity compared to other complications and pose life-threatening risks if left undiagnosed or poorly managed [1,2]. Previous research has suggested that neurologic adverse effects have been implicated in nearly half of all deaths associated with ICIs [4]. Atezolizumab, an immune checkpoint inhibitor that selectively binds to PD-L1 [5], is approved for the treatment of non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), advanced triple-negative breast cancer, hepatocellular carcinoma (HCC) and urothelial carcinoma and is currently under study for the treatment of lymphoma, melanoma, gynecological and colorectal malignancies [6,7]. Atezolizumab exhibits a side effect profile comparable to other ICIs, commonly manifesting as fatigue, rash, and gastrointestinal symptoms [8,9].

The incidence of neurological adverse events associated with atezolizumab is relatively lower compared to other ICIs. However, several serious cases of nervous system toxicities have been reported following atezolizumab therapy [7]. Diagnosing neurological adverse events poses a significant challenge due to often atypical clinical symptoms and laboratory findings, coupled with limited practical experience in managing ICI-related toxicities. With the increasing use of ICIs in cancer therapy, there is an anticipated rise in the incidence of neurotoxicities. Delayed recognition of these adverse events as being drug-related can exacerbate patient vulnerability to further toxicity. Currently, the literature lacks a comprehensive characterization of the clinical course and specific symptoms linked to neurological manifestations associated with atezolizumab. Here, we review atezolizumab induced neurotoxicity, aiming to describe its clinical presentation, delay of onset and resolution of symptoms, diagnostic findings, treatment options, and patient outcomes.

Methods

Search strategy

A medline search on atezolizumab induced neurotoxicity using PubMed, Science Direct, and Google Scholar databases was performed and completed on March 15, 2024.

The search strategy included MeSH terms and free-text words. Search terms included: atezolizumab, PD-L1, neurotoxicity, neurological adverse events, neurological complications, neurological immune related side effects, central nervous system, encephalitis, encephalopathy, seizures, coma, myoclonus, confusion, aphasia, ataxia, and peripheral neuropathy. Duplicates were removed and the references of the included articles were cross-checked. Studies that discussed neurotoxicity associated with all immune checkpoint inhibitors without explicitly mentioning atezolizumab were excluded. Articles studying anti-PD-L1 agents without specifying atezolizumab were also excluded. Additionally, paraneoplastic neurological manifestations induced by atezolizumab were ruled out from our review.

These exclusion criteria were implemented to ensure that our literature review focused specifically on neurotoxicity attributed to atezolizumab therapy.

Study selection

We included English-language publications encompassing all age groups, randomized clinical trials, observational studies, systematic reviews, case reports, and case series. **Table 1** presents data from clinical trials and large scale retrospective studies identified in the literature. In **Table 2**, data from case studies and observational studies were compiled detailing patient demographics, cancer type, neurotoxic symptoms including onset and recovery timing, diagnostic procedures, co-administered chemotherapies, interventions, and clinical outcomes. Most case reports underwent thorough investigations to rule out infection, tumor progression, or other causes of neurotoxicity, attributing the majority of cases to atezolizumab. Variables were labeled as "unable to assess" if pertinent patient data were unavailable.

Results

A total of 56 articles were identified. Among these, 13 were clinical trials and only one was a prospective cohort study, while the remainder were retrospective data. This included 32 single-case reports, 1 case series, and 9 retrospective studies.

Controlled data from clinical trials and meta-analysis [10-22]

An analysis of data from controlled clinical trials shows that atezolizumab has a favorable safety profile. The most common adverse reactions (≥ 20%) included fatigue, nausea, urinary tract infection, fever, and constipation. The risk of adverse effects with atezolizumab is comparable to other chemotherapeutic agents and aligns with the incidence rates observed for other approved immune checkpoint inhibitors like pembrolizumab and nivolumab [12,18]. Immune-related adverse events (irAEs), including neurotoxicity, observed in patients treated with atezolizumab were predominantly low grade and manageable, with only a small number necessitating dose interruption or discontinuation alongside corticosteroid treatment. Both the POPLAR and OAK trials demonstrated favorable tolerability of atezolizumab compared to docetaxel, with a lower proportion of patients experiencing grade 3 or 4 treatment-related side effects [14,17]. Specifically, only

Table 1. Data on neurotoxicity described as an adverse drug reaction in clinical trials of atezolizumab and large scale retrospective studies (When delineating a particular type of neurotoxicity within the study, we indicate the percentage or number of cases. If this information is not specified, we mark as **'NS'** in the respective column).

First author	Type of study	Peripheral neuropathy/ Polyneuropathy	Guillain Barre syndrome	Myastenia gravis	Hypophysitis/ Pituitary disorders	Encephalitis/ Myelitis	Meningitis	Demyelinating disorders	Others
Mikami [23]	Retrospective study/ FAERS database	7.9%	10.8%	4.5%	2.5%	18.8%	11.3%	10.5%	Myositis: 6.9% Vasculitis: 11%
Kichendasse [10]	Analysis of OAK, POPLAR, BIRCH and FIR trials	84%/9%	7%	-	-	-		-	-
Shmid [11]	Randomised, double-blind, placebo-controlled phase 3 trial	Grade 1-2: 16% Grade 3: 6%	-	-	-	-		-	-
Johnson [24]	Retrospective study/ WHO VigiBase	-	4.69%	4.57%	-	10.58%	11.11%	-	-
Sato [25]	Retrospective study/ JADER database	3.09%	-	1.14%	0%	21.88%	37.04%	-	Myositis: 2.36%
Socinski [12]	Randomized controlled trial	Grade 1-2: 35.9% Grade 3-4: 2.8%	-	-	-	-	-	-	-
Hida [13]	Phase III OAK study	-	-	-	-	-	1 case (grade 4)	-	-
Rittmeyer [14]	Phase 3, open-label, multicentre randomised controlled trial	1%	-	-	-	-	-	-	-
Cortinovis [15]	Phase III OAK study	-	-	-	-	0.7%		-	-
Dermott [16]	Phase Ia study	Grade 1-2: 1% Grade 3-4: 0%	-	Grade 1-2: 1% Grade 3-4: 0%	-	-	-	-	Ataxia (3%) Tremor (1%) Somnolence (1%)
Fehrenbacher [17]	Multicentre, open-label, phase 2 randomised controlled trial (POPLAR)	NS	-	-	-	-	-	-	-
Ning [18]	FDA clinical trial	NS	-	-		×		×	Confusional state Seizure Paralysis Encephalopathy Aphasia

NS: percentage not specified

Table 2. Overview of all of the case reports and case series of atezolizumab induced neurotoxicity found in the literature and included in the present review.

Type of study, reference	First author, year (number of patients)	Sex	Age	Type of malignant tumor	Type of neurotoxicity	Grade of severity	Dosage (mg)/3 weeks	Duration	Number of cycles	Delay of onset (after last cycle)	Concurrent therapy	Clinical symptoms	Paraclinical investigations	Exclusion of other causes	Management options	Outcome (within)
Case report [27]	Mahjoubi, 2023 (1)	M	68	NSCLC	Seizures	Grade 3	1200	6 months	7th	21 days	None	sudden loss of consciousness with myoclonus of the right hemibody	MRI, EEG and CSF: No abnormalities	- Normal blood glucose and electrolytes levels -Negative bacterial culture -CSF cytology: no tumor cells -Viral serologies and immunological markers: negative	Leviteracetam	Recovery (7 days) Negative rechallenge
Case report [5]	Chao, 2023 (1)	M	76	HCC	Encephalitis	Grade 3	1200	2 weeks	1st	15 days	bevacizumab	altered consciousness, hypothermia, aphasia, dysarthria	CSF: elevated cell count, protein and albumin levels MRI: normal	Infectious, anatomical, endocrinal, and neoplastic etiologies were ruled out	methylpred-nisolone 3 mg/kg/day	Recovery (9 days)
Case report [28]	Prieto, 2023 (1)	UA	UA	Lung adenocarci-noma	NMO	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA
Case report [29]	Prasertpan, 2023 (1)	M	58	Bladder cancer	Striatal encephalitis	Grade 3	1200	NS	NS	2 years	None	Subacute progressive parkinsonism	MRI: diffuse hyperitense T2/FLAIR lesions with nodular and peripheral enhancement CSF: No abnormalities	Serum and CSF autoimmune and paraneoplastic antibodies: unremarkable CSF cytology and metastatic workup: normal	Two courses of IV pulse methyl prednisolone 600 mg of levodopa/carbidopa	Initial im-provement (1 month) Recurrence after 7-month period of remission
Case report [30]	Chen, 2023 (1)	M	46	SCLC	Cerebellar ataxia	Grade 2	1200	3 months	3rd	15 days	Platinum + etoposide	Dysarthria, multidirectional nystagmus, asymmetric dysmetria, slight wide-based gait	-CSF: No abnormalities -Electrophysiological examination: slight reduction in the sensory nerve action potential	-Serum: No antinuclear antigen antibodies -CSF: no autoantibodies associated with PNS or LE	methylpred-nisolone at 1g/day for 5 days, followed by oral prednisolone 80 mg/day for 2 weeks	Recovery (1 month)
Case report [31]	Kapagan, 2023 (1)	M	66	SCLC	Cerebellar ataxia	Grade 2	1200	3 months	3rd	UA	None	Cerebellar syndrome	MRI: leptomeningeal involvement	Blood tests and a lumbar puncture: no structural, biochemical, paraneoplastic, or infectious cause	High-dose steroid treatment	Recovery (20 days)

Case report [32]	Ibrahim, 2022 (1)	F	71	SCLC	Encephalitis	Grade 3	1200	4 months	4th	3 weeks	None	Impaired consciousness	CSF: high cell count, protein and glucose levels MRI: no acute pathology EEG: unremarkable	MRI: Brain metastasis CSF cultures: negative CSF cytology: no malignant cells	high-dose of systemic steroids	Recovery (10 days)
Case report [26]	Chen, 2022 (1)	F	65	Breast carcinoma	Encephalitis	Grade 5	1200	4 months	4th	10 days	paclitaxel	Coma Respiratory failure	MRI: T2 and DWI hyperintense signals in the bilateral cerebellar hemisphere, vermis of the cerebellum, bilateral frontal, temporal and parietal lobes and occipital cortex	Brain metastases and paraneoplastic neurological syndrome were not ruled out	Intravenous infusion of 10 ml dexamethasone	Death after few days due to respiratory failure
Case report [33]	Evin, 2022 (1)	M	64	SCLC	PRES	Grade 3	1200	1 day	1st	24 hours	Carboplatin + etoposide	Impaired consciousness, generalized seizure right hemiplegia, facial paralysis, pyramidal syndrome	EEG: absence of seizure MRI: multiple bilateral subcortical, parietal, temporal, occipital and cerebellar T2 FLAIR high signals, predominantly in the posterior region	CT: no evidence of stroke, bleeding or brain metastasis Autoimmune, infectious and vascular laboratory evaluation: no abnormalities	antihypertensive and antiepileptic treatment	Recovery (several days) Negative rechallenge
Case report [7]	Satake, 2022 (1)	F	42	HCC	Encephalitis	Grade 4	1200	12 days	1st	12 days	bevacizumab	High fever, peripheral sensory neuropathy, impaired consciousness, convulsion; right-sided paralysis, right hemispatial neglect, and aphasia	CSF: elevated cell count, protein and glucose levels MRI: MERS	influenza and SARS Cov 2 diagnostic tests: negative CSF cultures: negative Viral serologies: negative CSF cytology: no malignant cells CT: no signs of cerebral hemorrhaging MRI: no signs of cerebral infraction and no metastatic brain tumors PNS was not excluded	Propofol, methylprednisolone 1g/day for 3 days Levetiracetam	Initial improvement with remaining paralysis and aphasia (5 days) Death 109 days after starting ICI treatment due to tumor progression
Case report [34]	Foulser, 2022 (1)	F	56	Breast cancer	PRES	Grade 3	1200	6 months	4th	NS	Carboplatin	Cognitive impairment, behavioural changes, dysphasia, visual disturbance, severe hypertension	MRI: PRES-related changes	MRI: known cerebellar metastasis	antiviral+antibiotic therapies amlodipine	Recovery (21 days)
Case report [35]	Sebbag, 2022 (1)	UA	47	SCLC	Cerebellar ataxia	Grade 2	1200	4 omnths	4th	UA	UA	Kinetic and static cerebellar syndrome	UA	UA	UA	No clinical improvement

Case report [36]	Trontzas, 2021 (1)	UA	SCLC	Enteric plexus neuropathy	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA	UA
Case report [37]	Esechie, 2021 (1)	UA	UA	SCLC	LETM	Grade 3	1200	UA	UA	UA	UA	UA	acute paralysis of the lower extremity, sensory loss from chest down with overflow incontinence	MRI: enhancing lesions from C7–T7	COVID-19 vaccination one day prior to presenting symptoms	5-day course of pulsed methylprednisolone followed by therapeutic plasma exchange for 3 days	Minimal improvement
Case report [38]	Lu, 2021 (1)	M	45	LCNEC	MS flare	Grade 5	1200	3 weeks	1st	21 days	None	blurred vision, generalized weakness, confusion	MRI: numerous new enhancing lesions within the cerebrum, cerebellum, and brainstem, bilateral enhancements of the optic sheath complexes	CSF: oligoclonal bands without malignant cells. CSF antibodies: negative	high-dose glucocorticoids tapered in 3 weeks	Initial recovery Recurrence after 6-month period of remission Death 10 months after starting ICI treatment
Case report [39]	Nader, 2021 (1)	F	38	Breast cancer	Meningoencephalitis	Grade 3	1200	10 days	1st	10 days	None	Impaired consciousness, fever, tonico-clonic seizures	CSF: high cell counts and protein level, inflammatory cells MRI: diffuse leptomeningeal enhancement	Urine, and blood cultures: Negative Viral serologies: negative CT scan of the chest: no infiltrates or signs of infection CSF culture: negative CSF cytology: no malignant cells. PCR multiplex for viral infections on CSF: negative	high dose steroids with dexamethasone 24 mg daily	Partial improvement with remaining mild lower extremity weakness and numbness (2 weeks) Death 5 years after starting ICI treatment due to tumor progression
Case report [40]	Nishijima, 2021 (1)	F	72	NSCLC	Encephalitis	Grade 3	1200	9 months	7th	3 months	None	Gait disturbance, mild disturbance of consciousness	CSF: normal cytology MRI: symmetrical high signal in the thalamus bilaterally	Imaging: no cancer recurrence or Metastases Serum autoimmune antibodies: absent CSF: high immunoglobulin G index and positive oligoclonal bands CSF culture: negative	steroids and IV immunoglobulin	Partial improvement

Case report [41]	Wada, 2021 (1)	M	46	NSCLC	Limbic encephalitis	Grade 3	1200	8 months	8th	2 months	None	Depressive symptoms, dyskinesia, decreased spontaneous speech, disorientation, impairment in memory	CSF: high cell count MRI: high signal intensity in the limbic system	MRI: no brain metastasis CSF examination: positive for anti-Hu and anti-CV2 antibodies, increased interleukin 2 level EEG: no paroxysmal discharge Low TSH and FT3 levels but no signs of inflammation regard to the pituitary gland Endocrine tests: unremarkable CSF cytology: no tumor cells CSF work-up: no signs of an infectious, autoimmune or paraneoplastic inflammation	steroid pulse therapy and IV immunoglobulin	Partial improvement
Case report [42]	Ozdirik, 2021 (1)	F	70	HCC	Encephalitis	Grade 5	1200	10 days	1st	10 days	bevacizumab	Confusion, aphasia, emesis, dyspnea, fever, adynamia, respiratory failure	CSF: elevated cell counts and protein level EMG: motor neuropathy MRI: normal	MRI and CT-scan of the chest: no extrahepatic tumor manifestation No clinical or laboratory signs of hepatic encephalopathy were present Blood, urine, and sputum cultures: negative COVID 19 and influenza A and B: negative Cranial CT-scan: no signs of bleeding or ischemia Chest x-ray: normal	methylprednisolone 1 mg/kg/day then up to 2 mg/kg/day anti-infective therapy with ceftriaxone, amoxicillin, and acyclovir plasmapherisis	Initial recovery (21 days) Death 67 days after starting ICI treatment due to progressive tumor
Single center retrospective cohort [1]	Duong, 2021 (1)	M	46	NSCLC	MS flare	Grade 3	1200	NS	1st	NS	None	NS	CSF: OCB positive serology MRI: enhancing cerebral lesions and optic nerve enhancement	NS	IV methylprednisolone 1 g/day for 3 days, then prednisone taper over 1 month	Recovery

Prospective cohort [43]	Chang, 2020 (5)	F	37	Breast cancer	Encephalitis	Gradec3	1200	NS	NS	15 days	cobimetinib	Fever, altered mentality	CSF: Increased cell count and protein level MRI: Diffuse leptomeningeal enhancement EEG: not performed	NS	Steroid, immunoglobulin	Recovery (2 days)
		F	53	Bladder cancer	Encephalitis Guillain Barre syndrome	Grade 3	1200	NS	NS	18 days	None	Fever, seizure Limb weakness, facial palsy	CSF: Increased cell count and protein level MRI: T2 high signals in limbic and brainstem areas with leptomeningeal enhancement	NS	Steroid, immunoglobulin, rituximab, tocilizumab	Recovery (6 days)
		F	70	Bladder cancer	Encephalitis Guillain Barre syndrome Myelitis	Grade 3	1200	NS	NS	15 days	None	Fever, seizure, altered mentality Limb weakness, facial palsy Incontinence, saddle anesthesia	CSF: Increased cell count and protein level MRI: T2 high signals in white matter (right> left) and T6 ~ T9 spinal cord	NS	Steroid, immunoglobulin, rituximab	Recovery (4 days)
		M	42	Bladder cancer	Encephalitis	Grade 3	1200	NS	NS	15 days	cobimetinib	Fever, altered mentality	CSF: Increased cell count and protein level MRI: normal	NS	Steroid, IV immunoglobulin	Recovery (5 days)
		F	60	Breast cancer	Encephalitis	Grade 3	1200	NS	NS	16 days	Fulvestrant + ipataserib	Fever, altered mentality	CSF: increased cell count and protein level MRI: T2 high signals in the left medial frontal gyrus with leptomeningeal enhancement	NS	Steroid	Recovery (2 days)
Single center retrospective study [44]	Toyozawa, 2020 (3)	F	71	NSCLC	Aseptic meningitis	Grade 3	1200	14 days	1st	14 days	Carboplatin + paclitaxel + bevacizumab	Impaired consciousness, fever	CSF: high protein MRI: no abnormal findings	CSF: no malignant cells	Steroid pulse (1000 mg × 3/ day)	Recovery (18 days)
		M	50	Lung adenocarcinoma	Aseptic meningitis	Grade 3	1200	3 months	3rd	11 days	None	Impaired consciousness, fever	CSF: increased cell counts and protein level MRI: Multiple abnormal enhancements along the lines of the corpus callosum.	NS	Steroid pulse (1000 mg × 3/ day) Anti-epileptic drug (levetiracetam)	Recovery (4 days)
		M	55	Lung adenocarcinoma	Aseptic meningitis	Grade 3	1200	11 days	1st	11 days	None	Impaired consciousness, fever	CSF: high protein MRI: no abnormalities	NS	Steroid pulse (1000 mg × 3 day)	Recovery (18 days)

Case report [45]	Ogawa, 2020 (1)	M	56	NSCLC	Aseptic meningitis	Grade 3	1200	11 days	1st	11 days	None	Fever, headache, fatigue	CSF: increased cell counts and protein level MRI: meningeal enhancement	CSF: no cancer cells and non-specific inflammation suggestive of meningitis CSF cultures and serological tests: negative	IV methyl-prednisolone 1g/day for 3 days then prednisone taper over 12 weeks	Recovery (7 days)
Case report [8]	Kichloo, 2020 (1)	F	68	SCLC	Bell's palsy	Grade 2	1200	5 months	5th	15 days	None	right-sided facial droop and numbness	MRI: No abnormalities	No vesicular eruption consistent with HSV or VZV reactivation HIV testing: negative CT scan: no signs of bleeding Metabolic panel: no abnormalities Calcium, vitamin D, TSH and folate levels: normal limits CT-angiogram: no thrombotic occlusion Echocardiogram: normal	14-day tapering course of oral prednisone, starting at 60 mg	Recovery (1 month) Negative rechallenge
Case report [6]	Yamaguchi, 2020 (1)	M	56	Lung adenocarci-noma	Encephalitis	Grade 3	1200	17 days	1st	17 days	Carboplatin + nab-paclitaxel	Disturbance of consciousness, high fever, motor aphasia	CSF: high cell count, and protein level MRI: normal	CSF: increased interleukin 6 level CSF bacterial culture: negatvie PCR for HSV 1 and 2 and CMV: negative Serum antibody tests for paraneoplastic neurological syndrome: negative	steroid pulse with 1g/day of methylpred-nisolone for 3 days then oral administration of prednisolone 0.5 mg/kg/day	Recovery (16 days)
Case report [46]	Robert, 2020 (1)	F	48	Lung adenocarci-noma	Encephalitis	Gradde 3	1200	13 days	1st	13 days	None	Fever, psychomotor slow-down, memory impairment, aphasia	CSF: increased cell count, protein and glucose levels MRI: Pachy- and leptomeningeal enhancement	CSF: no malignant cells	Methylpredinis-olone 1 g/day for 3 days, then 1 mg/kg/dayy for 1 month fol-lowed by grad-ual decrease	Recovery (11 months) Negative rechallenge with pem-brolizumab
Single center ret-rospective cohort [47]	Vogrig, 2020 (1)	NS	NS	SCLC	Cerebellar ataxia	Grade 3	1200	NS	NS	NS	NS	gait ataxia, rotatory nystagmus, nausea	No abnormalities	NS	NS	Partial clini-cal improve-ment

Single center retrospective case series [48]	Francis, 2020 (1)	F	73	RCC	Optic neuritis	Grade 2	1200	NS	95th	21 days	None	"Big" Floaters optic nerve edema	MRI: No abnormalities	NS	prednisone 80 mg/day for 1 week taper over 2 months	NS
Case report [49]	Samanci, 2020 (1)	M	53	Lung adenocarcinoma	Optic neuritis	Grade 3	1200	20 days	1st	20 days	None	blurred vision, double vision, headache, and general fatigue,	Fundus examination: optic disc edema BCVA: 20/80 in left eye and 20/40 in right eye	MRI: brain metastasis/ no abnormalities in the pituitary body HSV types 1 and 2 and VZV serology: negative ACTH, TSH, free T4, and cortisol levels: normal	IV methylprednisolone 2 mg/kg followed by oral methylprednisolone	Partial recovery (2 months)
Case report [50]	Thakolwiboon, 2019 (1)	M	87	Urothelial carcinoma	MG	Grade 5	1200	NS	2nd	NS	NS	diplopia, ptosis, proximal muscle weakness and nasal voice	ECG: new right bundle branch block and left anterior fascicular block	MRI: no stroke or brain metastasis CT of the chest: no thymoma Antinuclear antibody, rheumatoid factor, cyclic citrulline peptide, SS-A, SS-B, proteinase-3, and myeloperoxidase antibodies: negative Myositis antibodies: undetectable	Prednisone 60 mg daily for 1 week, IV immunoglobulin 0.4 g/kg daily pyridostigmine	Death due to cardiac arrest
Single center retrospective study [51]	Yuen, 2019 (1)	M	65	Urothelial carcinoma	Facial palsy + neuropathy	Grade 2	1200	3 weeks	NS	15 days	None	Peripheral right facial palsy Weakness, burning pain, tringling sensation in the legs and hands	MRI: normal CSF: No abnormalities EMG: Cervical and lumbar polyradiculopathy	NS	prednisone 60 mg per day and then tapered	Recovery with remaining mild residual tingling in the toes (1 week)
Case report [52]	Kim, 2019 (1)	M	49	Bladder cancer	Encephalitis	Grade 5	1200	14 days	1st	14 days	None	Impaired consciousness, stupor, generalized tonic-clonic seizures	CSF: Increased cell count MRI: Diffuse leptomeningeal enhancement	CSF: no malignant cells, paraneoplastic antibodies, bacterial culture, fungus culture, tuberculous PCR, and viral PCR: negative EEG: no epileptiform discharge	Dexamethasone, IV immunoglobulin	Death 98 days after starting ICI treatment due to septic shock

Retrospective study/ FAERS database [53]	Garcia, 2019 (1)	F	49	Colon adenocarcinoma	MS flare	NS	1200	2 weeks	1st	15 days	cobimetinib	Fever, progressive confusion	MRI: nonspecific T2 hyperintense lesions within the subcortical, deep, and periventricular white matter	NS	high-dose corticosteroids	Death 1 month after starting ICI treatment due to progressive disease
Case report [54]	Chae, 2018 (1)	F	67	Lung adenocarcinoma	MG relapse	Grade 4	1200	6 weeks	2nd	Several days	None	Dyspnea, dysphagia, weakness, hypercapnic respiratory failure	NS	NS	Prednisone, pyridostigmine, VNI, plasmapherisis	Recovery
Case report [55]	Tan, 2018 (1)	M	66	Lung adenocarcinoma	Cerebellar ataxia	Grade 2	1200	8 months	NS	6 months	Carboplatin + pemetrexed	ataxic wide-based gait	CSF: acellular with normal proteinand glucose levels MRI: small vessel disease only	CT head with contrast: normal Blood tests: normal Paraneoplastic screen: negative CSF culture and viral PCR: negative	Prednisolone 1mg/kg	Initial improvement (1 week) Death 5 months due to progressive metastatic disease
Case report [56]	Mori, 2018 (1)	M	64	NSCLC	Optic neuritis+ hypopituitarism	Grade 2	1200	12 months	NS	NS	None	Sudden visual loss, optic disc edema, venous congestion, weakened direct reaction of light reflex	BCVA: 0.01 Fluorescein angiography: dye leakage MRI: high-intensity lesion in the optic nerve	Anti-aquaporin-4 antibodies: absent Pituitary body: no abnormalities HSV and VZV antibody titers: not elevated CSF: no signs of infectious or demelinating diseases ACTH, free T4, and cortisol, TSH, GH levels: normal FSh and prolactin levels: elevated	methylprednisolone 1 g/ day for 3 days followed by 30 mg oral prednisolone	Recovery (24 months)
Case report [57]	Laserna, 2018 (1)	F	53	CSCC	Encephalitis	Grade 3	1200	13 days	1st	13 days	Bevacizumab	Headache, meningeal signs, impaired cnsciousness	CSF: high cell count, protein and glucose levels EEG: non-convulsive status epilepticus MRI: Diffuse leptomeningeal enhancement	Head CT scan: no abnormalities CSF culture and viral serology: negative Paraneoplastic antibodies: negative	High-dose steroids	Recovery with remaining weakness (15 days)

Case report [58]	Arakawa, 2018 (1)	M	78	Lung adenocarci-noma	Encephalitis	Grade 3	1200	13 days	1st	13 days	None	Confusion, fever	CSF: high cell counts and protein level MRI: normal	CSF culture and viral serology: negative Paraneoplastic antibodies: negative	steroid pulse	Recovery (58 days)
Case report [9]	Levine, 2017 (1)	F	59	Bladder cancer	Encephalitis	Grade 3	1200	12 days	1st	12 days	None	Confusion, fatigue, spastic tremors, vomiting	CSF: normal MRI: isolated frontal metastasis	CSF culture and viral serology: negative Paraneoplastic antibodies: negative Blood and urine cultures: negative	dexametha-sone 10mg IV every 6 hours. methylprednis-olone 1 mg/kg/ day with taper over 4-6 weeks	Partial Reovery with remaining upper extremety weakness (5 days) Death 1 month after discharge due to progressive disease

NSCLC: Non-Small Cell Lung Cancer; HCC: Hepatocellular Carcinoma; CSF: Cerebrospinal Fuid; MRI: Magnetic Resonance Imaging; UA: Unable To Access; NMO: Neuromyelitis Optica; NS: Not Specified; IV: Intravenous; SCLC: Small Cell Lung Cancer; PNS: Paraneoplastic Neurological Syndrome; LE: Limbic Encephalitis; PRES: Posterior Reversible Encephalopathy Syndrome; CT: Computed Tomography; MERS: Mild Encephalitis/Encephalopathy with a Reversible Splenial Lesion; SARS Cov 2: Severe Acute Respiratory Syndrome Coronavirus 2; ICI: Immune Checkpoint Inhibitor; LETM: Longitudinal Extensive Transverse Myelitis; LCNEC: Large Cell Neuroendocrine Carcinoma of the Lung; MS: Multiple Sclerosis; PCR: Polymerase Chain Reaction; EMG: Electromyogram; FAERS: Food and Drug Administration Adverse Event Reporting System; OCB: Oligoclonal Bands; HSV: Herpes Simplex Virus; VZV: Varicella Zoster Virus; CMV: Cytomegalovirus; BCVA: Best-Corrected Visual Acuity; ACTH: Adrenocorticotropic Hormone; TSH: Thyroid-Stimulating Hormone; GH: Growth Hormone; FSH: Follicle-Stimulating Hormone; CSCC: Cervical Squamous Cell Carcinoma; MG: Myasthenia Gravis; ECG: Electrocardiogram; NIV: Non Invasive Ventilation

2.1% of irAEs in the atezolizumab group required treatment discontinuation [15]. Another Japanese patient study also revealed comparable rates of all-grade treatment-related adverse events between atezolizumab and docetaxel groups, albeit with fewer grade 3-4 events in the atezolizumab cohort [13]. Notably, neurological immune-related adverse events (irAEs), particularly neuropathy, have emerged as significant concerns in most previous clinical trials [10]. Peripheral neuropathy occurred approximately in 7% of patients in the atezolizumab group vs 1% in the placebo group [11,12,14]. Conversely, in the Japanese study, no cases of peripheral sensory neuropathy were reported, while serious neurological adverse effects such as meningoencephalitis and Guillain-Barre syndrome occurred in the atezolizumab group but were absent in the docetaxel group [13]. Notably, encephalitis was not reported as an irAE in earlier phases of POPLAR trials [17] but occurred at a low rate in subsequent studies, 0.8% and 0.3% in the OAK trial and the Impower 150 study, respectively [12,14]. Mikami's analysis indicates that meningoencephalitis was the most common neurological complication associated with atezolizumab, occurring in 30.3% of cases, followed by Guillain-Barre syndrome and demyelinating disorders, each accounting for about 10.5% of cases. The least frequent complication was hypophysitis, occurring in 2.5% of cases [23]. Overall, the controlled data from these trials indicate a manageable safety profile for atezolizumab, with distinct advantages over traditional chemotherapy agents.

Overall incidence and severity of atezolizumab-induced neurotoxicities

Neurological adverse events associated with atezolizumab exhibit diverse clinical presentations affecting various parts of the nervous system (**Figure 1**). The most frequently reported manifestations are grades 1-2 neurotoxicities, often presenting as nonspecific symptoms, such as asthenia, headaches, dizziness, paresthesias, or dysgeusia [26]. Grades 3-4 neurological syndromes are less commonly reported and encompass severe conditions such as encephalitis, encephalopathy, aseptic meningitis, myelitis, neuropathy, Guillain-Barre syndrome, myasthenia gravis, and demyelinating disorders [7,26].

Epidemiological and clinical characteristics of patient cases of atezolizumab-induced neurotoxicities reported in literature

Table 1 documented 39 studies detailing grade 3 and 4 neurotoxicities induced by atezolizumab, involving a total of 45 patients [1,5-9,26-58]. Conclusions regarding clinical characteristics can be drawn from the data provided for these patients. The demographic profile of patients experiencing atezolizumab-induced neurotoxicity revealed a male predominance (46.7%) with a median age of 58 years (range 37–87). The primary tumor localizations varied with lung being the most common (n=26) followed by bladder (n=9), breast (n=4), liver (n=3), kidney (n=1), colon (n=1) and cervix (n=1). Atezolizumab dosage was consistent across cases, administered at 1200 mg every three weeks. Symptoms of neurological toxicity typically manifested after the first cycle of atezolizumab therapy (37.8% of cases), with a median onset occuring 2 weeks after the last dose (range: 1day-1year). Six documented cases had a history of neurological disorders, including three with brain metastases [9,32,49], and four with preexisting demyelinating diseases [1,36,53,54]. Co-administration of chemotherapeutic drugs, notably bevacizumab, carboplatin, paclitaxel, and cobimetinib, was common in nearly half of the cases. Atezolizumab was discontinued in all published cases and treatment of neurotoxicities varied, including corticosteroids, antiepileptic drugs, empiric antimicrobial therapy, intravenous immunoglobulin, and plasmapherisis. Symptoms typically resolved within a median of 10 days after cessation of atezolizumab (range: 2days-2years) with partial or complete recovery noted in the majority of cases (82.6%). Atezolizumab rechallenge was successful in three cases [8,27,33] while one case reported negative rechallenge with pembrolizumab [46]. Recurrence of symptoms despite withdrawal of atezolizumab after a period of remission occurred in two cases [29,38]. Fatal outcomes were observed in 10 cases [7,9,26,38,39,42,50,52,53,55], however, definitively attributing neurotoxicities as the cause of death was challenging due to initial symptom improvement upon drug discontinuation and incomplete exclusion of disease progression in some cases. The neurotoxicities underlying fatal outcomes included encephalitis (n=6), multiple sclerosis (n=2), and single cases of myasthenia gravis and cerebellar ataxia.

Published cases of atezolizumab induced neurotoxicity **(Table 1)** encompassed various neurological manifestations, with encephalitis being the most common (39.6%), followed by cerebellar ataxia (10.4%), meningitis (8.3%), optic neuritis (6.3%), multiple sclerosis flare (6.3%), posterior reversible encephalopathy syndrome (4.2%), peripheral neuropathy (4.2%), Guillain-Barre syndrome (4.2%), myasthenia gravis relapse (4.2%), myelitis (4.2%), facial palsy (4.2%) and neuromyelitis optica (2.1%). Additionally, other neurological adverse events were reported in clinical trials and large-scale retrospective pharmacovigilance studies, including aphasia, hypophisitis, and paralysis.

Types of neurological adverse effects associated with atezolizumab

Encephalitis: Among CNS neurotoxicities associated with atezolizumab, encephalitis stands out as a rare yet potentially fatal adverse reaction [7]. The incidence rate of encephalitis following atezolizumab therapy, as reported in the OAK trial, was only 0.8% in patients with NSCLC [5].

At the time of this article, our review included 19 published cases of encephalitis following atezolizumab therapy (**Table 1**), with a few additional cases mentioned in clinical trials and large scae retrospective studies (**Table 2**). The presentation of

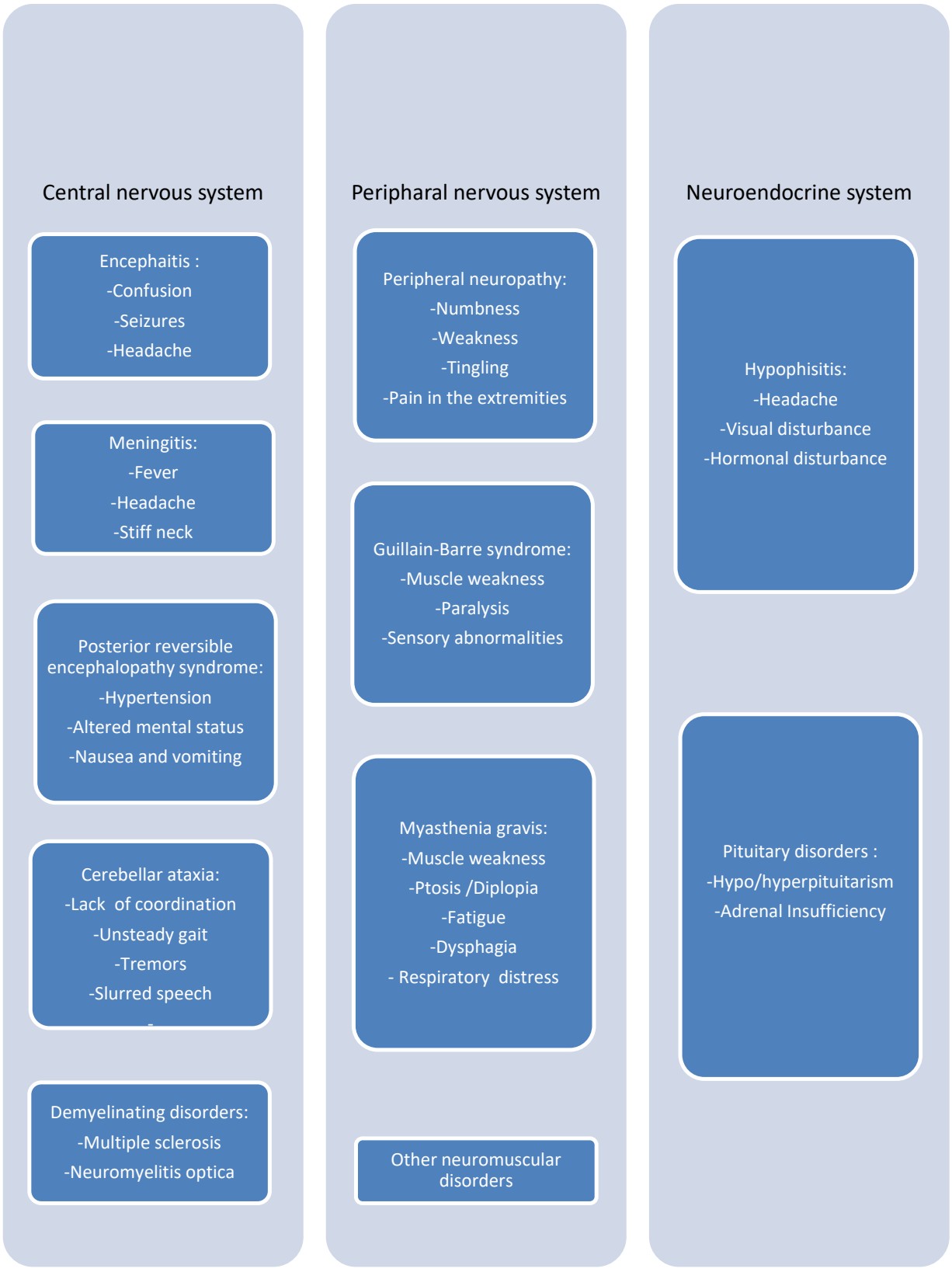

Figure 1. Summary of neurological manifestations induced by atezolizumab.

atezolizumab-induced encephalitis revealed typical features but was also demonstrated heterogeneity, encompassing symptoms such as fever, headache, confusion, gait instability, seizures, and in rare instances, meningeal signs. The onset of symptoms varied; with most cases occuring between 10 and 21 days after atezolizumab administration, though some cases presented much later, such as nine months post-administration [40]. Common CSF features include pleocytosis and elevated protein levels while MRI findings often revealed leptomeningeal enhancement or brain parenchymal lesions although pathological findings in imaging were absent in some cases. Management of encephalitis linked to ICI treatment remains uncertain; however favorable responses to steroid therapy were observed in 14 of our cases. Only a small number of patients required intravenous immunoglobulin [40,41,43,50,52] or plasmapheresis [42]. It's worth noting that in 2022, we documented a case involving a patient with SCLC who experienced recurrent seizures 21 days after completing the seventh cycle of atezolizumab treatment. Extensive investigations ruled out the diagnosis of encephalitis and the patient's symptoms were successfully managed with leviteracetam, leading to complete recovery within a week. Atezolizumab was subsequently reintroduced after a one-month period of remission without any recurring neurological symptoms [27].

Aseptic meningitis: Aseptic meningitis occurs in approximately 0.1–0.2% of patients treated with ICIs. Within our review, we identified four cases of aseptic meningitis induced by atezolizumab [44,45]. Additionally, two other studies have reported cases of meningitis associated with atezolizumab. Aseptic meningitis typically manifested between 11 to 14 days following the initial administration of atezolizumab in three cases, while in the fourth case, it occurred 11 days after the third dose. Fever could signal the onset of meningitis. Other common symptoms included altered consciousness and headache. CSF analysis revealed lymphocytic meningitis and high protein level accompanied by meningeal enhancement observed on MRI scans. All documented cases of aseptic meningitis are fully resolved with the administration of steroids and cessation of atezolizumab treatment.

Encephalopathy: Two cases of posterior reversible encephalopathy syndrome (PRES) occurring in patients receiving atezolizumab have been documented in the literature [33,34]. Symptoms manifested differently in each case: one patient experienced symptoms 24 hours after the first dose, while the other developed symptoms 6 months after the fourth cycle. Neurological manifestations included altered consciousness, visual disturbances, focal neurological deficits, seizures, and typical imaging alterations primarily affecting the posterior parietal and occipital lobes on MRI. Notably, both patients were presented with elevated blood pressure at the time of PRES diagnosis: 206/108 mmHg in a patient undergoing atezolizumab treatment for small cell lung cancer [33] and 169/81 mmHg in another patient treated for breast cancer [34]. In both case reports, there was marked neurological improvement following antihypertensive therapy in the subsequent days.

Cereballar ataxia: In our review, we identified five cases of acute cerebellar ataxia induced by atezolizumab. Furthermore, ataxia was previously reported in a phase 2 clinical trial [16]. The time lapse between the initiation of atezolizumab and the onset of ataxia was unspecified in most cases, except for one instance where ataxia appeared two weeks after starting atezolizumab. Symptoms of cerebellar syndrome observed in the documented cases included gait disturbances, ataxia, dysarthria, nystagmus, and nausea. Treatment typically involved corticosteroids, leading to complete recovery in two cases, partial improvement in one case and initial improvement within one week followed by eventual death due to metastatic disease in another case [55]. Unfortunately, no clinical improvement was observed in the remaining case [35].

Peripheral neuropathy: Peripheral neuropathy is a prominent aspect of the literature concerning ICI-associated neurotoxicity, although it has been described as a complication of atezolizumab primarily in clinical settings. Both sensory and motor peripheral neuropathies have been documented, presenting in acute or chronic forms. Within our review, we encountered a case report highlighting enteric plexus neuropathy; however, patient characteristics were inaccessible [36]. In another instance, a patient developed peripheral neuropathy associated with facial palsy two weeks after completing the last cycle of atezolizumab. Symptoms resolved within seven days, but residual paresthesia persisted in the toes [51].

Guillain Barre syndrome (GBS): GBS induced by ICI is a rare occurence, with only a few reported cases in the literature. In a prospective cohort study, two cases of Guillain-Barré syndrome induced by atezolizumab were documented [43]. The presentation was typical, characterized by limb weakness and facial palsy. Symptoms appeared 15 and 18 days, respectively, after receiving atezolizumab treatment. Both patients were treated with intravenous immunoglobulin and corticosteroids. Atezolizumab was discontinued in both instances, and complete recovery was achieved within a few days of initiating steroid therapy.

Paralysis: Our review identified two cases of paralysis induced by atezolizumab [8,51]. In both instances, patients developed peripheral facial palsy after two weeks of atezolizumab therapy. Symptoms resolved in both patients after discontinuation of atezolizumab. Interestingly, in one case, there was no recurrence of symptoms upon rechallenge. Additionally, two other patients with Guillain-Barre syndrome experienced cranial nerve palsy [43]. Paralysis was also observed in a previous clinical trial [18].

Multiple sclerosis (MS): In our review, we identified three MS patients who experienced relapse while undergoing treatment with atezolizumab. The history of MS was confirmed in all instances. Among these cases, two patients developed encephalopathic symptoms during their relapse [1,53], accompanied by blurred vision and weakness in one case [38]. The median onset of symptoms was 15 days. Imaging results were consistent with typical MS manifestations in all patients. Corticosteroids were administered in every case. Unfortunately, a fatal outcome was observed in two patients, while the remaining case achieved complete recovery.

Optic neuritis (ON): In the literature, ON has been reported following atezolizumab treatment. Three cases were included in our review. The onset of symptoms occurred three weeks after treatment initiation in two cases [48,49], while in the remaining case, ON manifested after 12 months [56]. Optic neuritis tended to be bilateral in most cases. MRI findings showed optic nerve enhancement abnormalities in only one case. Corticosteroids were administered to all three patients. Resolution of symptoms was observed in two cases, while the outcome of the remaining patient was not specified.

Myasthenia gravis (MG): The most frequently reported neuromuscular disorder associated with ICIs is MG. It can manifest either as *de novo* or as an exacerbation of pre-existing myasthenia. However, only two case reports of atezolizumab induced MG were found in the literature. Chae *et al.* reported a case of MG exacerbation emerging six weeks after initiating atezolizumab [54]. The progression was further complicated by hypercapnic respiratory failure, requiring intubation. However, stability was achieved following five sessions of plasmapheresis. Additionally, Thakolwiboon *et al.* documented a case of new onset MG following atezolizumab therapy, which resulted in fatal outcome due to cardiac arrest [50]. In addition to the neurotoxicities mentioned earlier, our review revealed one case each of longitudinal extensive transverse myelitis [37] and neuromyelitis optica [28].

Discussion

Clinical understanding of the toxic effects of ICIs remains relatively limited [1]. Due to the relatively low occurrence of ICI-related neurologic adverse events, there is limited data available, with most of these adverse effects documented in case reports. The majority of published reviews and large-scale studies have examined immune checkpoint inhibitors collectively, rather than focusing solely on any particular agent. This systematic review is the first to describe various types of neurotoxicities induced by atezolizumab and detail the range of symptoms, diagnosis features, and timing of onset and resolution.

Characteristics of atezolizumab-induced neurotoxicity

Encephalitis emerges as the most extensively studied neurotoxicity associated with atezolizumab therapy [4]. However, findings from clinical trials indicate that peripheral neuropathies are the most prevalent among observed neurological adverse events. In patients receiving atezolizumab, neurologic irAEs were most commonly observed in those with lung cancer [23]. In our review, the mean age of patients who developed atezolizumab-related multiple sclerosis (MS) flare-ups and ataxia were the youngest (46.7 and 56.25 years, respectively), while patients with myasthenia gravis and encephalitis were the oldest (77 and 60 years, respectively) [23]. Symptoms of atezolizumab associated neurotoxicity often exhibit a delayed onset, typically appearing around 15 days after drug initiation. However, in some instances, neurological toxicities occur much later, with rare cases emerging beyond 2 months after the start of atezolizumab treatment. Nearly all cases occur shortly after the first dose, with no instances reported following drug cessation. Atezolizumab-related multiple sclerosis or meningitis occurred significantly earlier (median of 15 days) compared to other neurologic irAEs. The broad range of onset times for neurological toxicity may compound clinicians' challenges in identifying and diagnosing atezolizumab-related neurotoxicity. MRI abnormalities are observed in almost all patients; however, certain findings lack specificity and could potentially signify alternative underlying causes. Neurological events are progressive unless drug discontinuation or interruption is initiated. Management of severe neurological events involves temporary immunosuppression utilizing steroids or alternative agents such as intravenous immunoglobulins, plasmapheresis, or in some cases, rituximab. These interventions lead to clinical resolution or improvement of symptoms in the majority of cases.

Comparison of neurological adverse effects between atezolizumab and other immune checkpoint inhibitors

The reported incidence and time course of irAEs in clinical trials have varied depending on the type of ICIs used. A recent meta-analysis identified atezolizumab as having the best safety profile [10,20,39]. Other studies reported an incidence of neurologic irAEs up to 5% with PD-1/PD-L1 inhibitors, and 12.7% with CTLA-4 inhibitors [23]. Moreover, anti-CTLA-4 agents have been associated with higher severity of irAEs. Clinical trials and meta-analyses report grade 3 or 4 neurologic adverse events occurring in 0.3–0.8% of patients under anti-CTLA-4 (ipilimumab) therapy, 0.2–0.4% under anti-PD-1 (nivolumab or pembrolizumab) treatment, and 0.1–1% under anti-PDL-1 (atezolizumab) treatment. Combined ipilimumab and nivolumab treatment increases the incidence of grade 3 and 4 neurologic adverse events to 0.7%. Anti-PD-1/L1 therapy is more frequently associated with myasthenic syndromes and less common in meningitis and cranial neuropathies, while anti-CTLA-4 therapy is more frequent in meningitis and less common in encephalitis and myositis [59]. In patients on anti-PD-1 or anti-PD-L1 monotherapies, neurologic AEs were most commonly observed in those with non-small cell lung cancer. In contrast, in patients on anti-CTLA-4, neurologic AEs were most

commonly observed in those with melanoma [23]. Notably, no cases of melanoma were found in our review. Anti-PD-L1 monotherapy, predominantly atezolizumab, was associated with an earlier onset of neurologic adverse events compared to anti-PD-1, anti-CTLA-4, and combination therapies [23]. Concerning ICI dosage, there is no clear relationship between the incidence of neurologic adverse events and drug dosage with anti-CTLA-4 antibodies. However, findings are inconsistent for anti-PD-1 agents, with increased neurological adverse events at 10 mg/kg nivolumab compared to lower doses, but the reverse observed with pembrolizumab [60]. Studies regarding anti-PDL1 inhibitors are lacking, with no available data on the correlation between atezolizumab and treatment dosage or schedule. Interestingly, age, sex, and metastatic status were not significant risk factors for overall neurologic ICI-related AEs [23].

Possible mechanisms of immune checkpoint inhibitors-induced neurotoxicity

The exact pathophysiology of ICI-associated neurotoxicity remains unclear, with multiple proposed mechanisms. First, increased T-cell activity against antigens shared by cancerous and healthy tissues potentially leads to an exaggerated inflammatory response and autoimmune neurologic damage due to unregulated T-cell activation against nerves [8]. Second, immunotherapeutic agents may elevate levels of inflammatory cytokines and trigger augmented complement-mediated inflammation by binding antibodies against PD1 and CTLA-4 expressed in normal tissue. Notably, studies have shown correlations between the presence of autoantibodies, particularly antineuronal antibodies, and improved survival but increased neurological toxicity in patients treated with checkpoint inhibitors [46]. Third, genetic susceptibility was suggested by a cohort study where the HLA-B27:05 genotype was over-represented in patients who developed autoimmune encephalitis after receiving atezolizumab [32].

Strengths: This study highlights uncommon but serious irAEs arising from immune checkpoint inhibitors (ICIs). It represents the largest review of patients who developed neurological irAEs from an anti-PD-L1 inhibitor; atezolizumab. This review provides a comprehensive analysis of atezolizumab-induced neurotoxicity by meticulously compiling epidemiological and clinical characteristics from case reports and retrospective studies. It covers the spectrum of neurological adverse effects, their time course, diagnostic investigations, management options, and outcomes. Additionally, it includes a comparative analysis of the safety profiles between atezolizumab and other immune checkpoint inhibitors, as well as discussions on potential mechanisms. The strength of this review lies in its thoroughness and the novel insights it offers, particularly in identifying patterns and providing a detailed comparison of adverse effects. This information is crucial for clinicians to better understand, anticipate, and manage neurotoxic effects in patients treated with atezolizumab.

Limitations: Several limiting features of this review deserve comment. With the exception of one prospective cohort study, published data available are limited to case series, single-case reports, and retrospective pharmacovigilance studies. The characteristics of these studies restrict our systematic review to descriptive reporting and preclude an examination of risk factors. The observational design of reports describing treatment for atezolizumab neurotoxicity precludes any statement about the efficacy of any specific strategy. Distinguishing atezolizumab-induced neurotoxicity from many conditions present in critically ill patients remains clinically challenging, and concurrent diagnoses may confound its identification. In fact, cancer patients commonly exhibit neurological complications such as brain metastasis, paraneoplastic syndrome and cerebrovascular disorders. Adding to this complexity, chemotherapeutic agents and radiation therapy may also be risk factors for neurotoxicity. Many questions remain regarding the true incidence and scope of atezolizumab-associated neurotoxicity. Further research evaluating atezolizumab adverse effects may provide vital information to determine key trends. Prospective evaluations with more standard and rigorous datasets are needed.

Recommendations: While our systematic review provides valuable insights into the neurotoxicity associated with atezolizumab, it is evident that further research is needed to address several important recommendations. Prospective registries collecting standardized clinical data, controlled trials comparing neurotoxicity profiles among different checkpoint inhibitors, and deeper investigations into the pathophysiology of neurotoxic syndromes are crucial steps to better understand and manage these adverse effects. Additionally, future case reports should aim to include severity grading of events and rigorously exclude alternative causes to strengthen causal conclusions. Larger retrospective analyses pooling detailed clinical data internationally could further elucidate risk factors and outcomes associated with specific treatment strategies. Embracing these recommendations will undoubtedly contribute to a more comprehensive understanding of this serious adverse drug reaction.

Conclusion

Given that case reports have documented atezolizumab-induced neurotoxicity across diverse cancer types, it is imperative to establish a comprehensive safety profile for this agent. Further investigations could enhance our understanding of which patients are at risk and how we can safely manage this serious adverse reaction.

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