Characterization and management of neurological adverse events during immune-checkpoint inhibitors treatment: an Italian multicentric experience

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Abstract

Background Neurological immune-related adverse events (nirAEs) are rare toxicities of immune-checkpoint inhibitors (ICI). With the increase of ICI oncological indications, their incidence is growing. Their recognition and management remain nevertheless challenging.

Methods A national, web-based database was built to collect cases of neurological symptoms in patients receiving ICI and not attributable to other causes after an adequate workup.

Results We identified 27 patients who developed nirAEs (20 males, median age 69 years). Patients received anti-PD1/PDL1 (78%), anti-CTLA4 (4%), or both (19%). Most common cancers were melanoma (30%) and non-small cell lung cancer (26%). Peripheral nervous system was mostly affected (78%). Median time to onset was 43.5 days and was shorter for peripheral versus central nervous system toxicities (36 versus 144.5 days, $p=0.045$). Common manifestations were myositis (33%), inflammatory polyradiculoneuropathies (33%), and myasthenia gravis (19%), alone or in combination, but the spectrum of diagnoses was broad. Most patients received first-line glucocorticoids (85%) or IVIg (15%). Seven patients (26%) needed second-line treatments. At last follow-up, four (15%) patients were deceased (encephalitis, 1; myositis/myasthenia with concomitant myocarditis, 2; acute polyradiculoneuropathy, 1), while seven (26%) had a complete remission, eight (30%) partial improvement, and six (22%) stable/progressing symptoms. ICI treatment was discontinued in most patients (78%).

Conclusions Neurological irAEs are rare but potentially fatal. They primarily affect neuromuscular structures but encompass a broad range of presentations. A prompt recognition is mandatory to timely withheld immunotherapy and administrate glucocorticoids. In corticoresistant or severely affected patients, second-line treatments with IVIg or plasmapheresis may result in additional benefit.

Keywords Neurological immune-related adverse events · Neurotoxicity · Immune-checkpoint inhibitors · Myositis · Polyradiculoneuropathy

Introduction

Immune-checkpoint inhibitors (ICIs) have changed the scenario of antineoplastic treatments in recent years [1]. They are monoclonal antibodies that enhance host immune system response against tumour cells by blocking different T cell inhibitory pathways (CTLA-4, PD-1/PDL-1) [1]. ICIs can induce toxicities, called immune-related adverse events [irAEs], against any organ due to their intrinsic ability to modulate the immune system and cause the interruption of the tolerance to self-antigens [2]. Hence, irAEs often require ICI interruption and immunomodulatory treatments, limiting the therapeutic strategies for the underlying tumour [3].

Neurological irAEs [nirAEs] are rare and often misdiagnosed adverse events of ICIs, potentially resulting in severe disability, and sometimes life-threatening [4]. Their

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recognition is challenging due to the broad differential diagnosis of neurological symptoms in oncological patients [5]. Neurological irAEs typically resemble neurological syndromes of the peripheral nervous system [PNS] (i.e. inflammatory demyelinating polyradiculoneuropathies, myasthenia gravis [MG], inflammatory myopathies), and central nervous system [CNS] (i.e. encephalitis, myelitis, meningitis) [5–7]. Nonetheless, an overlap between syndromes and atypical presentations has been largely reported [6, 8–11]. Neurologists and oncologists are variously involved worldwide in the management of nirAEs, resulting in extremely heterogeneous diagnostic and therapeutic approaches. Consensus guidelines for the diagnosis [12] and the management [13, 14] of irAEs have been recently published. Nevertheless, the level of evidence regarding these rare toxicities remains scarce.

The aim of this study is to further define the clinical spectrum of nirAEs, collecting real-life data of oncological patients treated with ICIs, and diagnosed at specialized neurological centers referring to the Neuro-oncology Study Group of the Italian Neurological Society (SIN).

Methods

Patients

Inclusion criteria were (i) oncological patients, treated with at least one cycle of ICIs; (ii) new neurological symptoms, presenting no later than three months since the last ICI administration, attributed to ICI treatment by the treating neurologist after the exclusion of other causes (e.g. tumour progression, infection, metabolic derangement).

Data collection

A national, web-based database was created to collect the data. Centers referring to the Neuro-oncology Study Group of the Italian Neurological Society [SIN] were allowed to enter data. Seven centers took part in the survey in the period 01/02/2019–30/09/2020: IRCCS Mondino Foundation, Pavia ($n = 14$ cases included), Presidio Ospedaliero Santa Maria della Misericordia, Udine ($n = 4$), Ospedale San Giacomo, Novi Ligure ($n = 3$), Azienda Ospedale Università di Padova, Padua ($n = 2$), IRCCS Regina Elena National Cancer Institute, Rome ($n = 3$), University and City of Health and Science, Turin ($n = 1$), Ospedale Santa Chiara, Trento ($n = 1$).

Demographic (sex, age, previous autoimmune or neurological diseases), oncological (type of cancer, previous treatments, ICI type and number of cycles), clinical (neurological syndrome, presenting symptoms, time to onset, severity according to CTCAE grading v5.0), imaging (brain, spine, and muscle magnetic resonance imaging [MRI]), serological (antibodies profiling, creatine phosphokinase [CPK] levels), CSF (protein level, cell count, oligoclonal banding, antibodies profiling), neurophysiological (nerve conduction studies [NCS], needle EMG, repetitive nerve stimulation [RNS], single-fiber EMG [sfEMG]), treatment (first-line treatment, response to first-line treatment, further lines of treatment), and outcome (toxicity response and CTCAE grading at last follow up, discontinuation of ICI) data were recorded.

Neuronal surface antibodies were measured with a commercial cell-based assay mosaic (Euroimmun) including NMDAR, Caspr2, LGi1, AMPAR 1–2, and GABA-B R. Onconeural antibodies were measured using indirect immunofluorescence on rat brain tissue, followed, if any staining was detected, by a line blot including Hu, Ri, Yo, Amphyphisin, CV2, Ma2, SOX1, GAD65, tititn, Recoverin, Zi4, and Tr. In addition, Pavia laboratory performed second-level diagnostic including homemade tissue-based assays optimized for surface neuronal antigens and in-house cell-based assays. All laboratories were part of the AINI network for standardization in neuroimmunology [15].

Disease definitions and levels of diagnostic certainty

Diagnoses were classified using the most recent consensus disease definitions and the level of diagnostic certainty was graded, from "definite" to "possible", using the provided criteria [12].

The study was conducted in accordance with the Declaration of Helsinki. The retrospective study was approved by institutional ethic committee (No. 20190026431).

The data of this study are available from the corresponding author upon reasonable request.

Results

Demographic, neurological, and oncological background

Twenty-seven patients who developed neurological symptoms attributable to ICI treatment were identified. Twenty were males (74%), with a median age of 69 years (range 44–79 years). Demographic and oncological data are summarized in Table 1 and reported in detail in Supplementary Table 1. Two patients (#6 and #13) have already been reported elsewhere [16, 17], and one (#21) was presented in conference abstract [18].

One patient, who subsequentially developed a myositis/MG syndrome (#16), had a 10-year history of idiopathic mixed axonal and demyelinating polyneuropathy; another

patient (#26) had a preexisting moderate diabetic neuropathy. One patient (#25) had a 16-year history of multiple sclerosis [MS] previously under treatment with dimethyl fumarate, interrupted concurrently with the initiation of the ICI treatment. Another patient (#27) had not further characterized multifocal areas of demyelination in bilateral hemispheric white matter discovered during cancer staging. No other known previous neurological or autoimmune pathologies were reported in the remaining patients.

Most common indications for ICI treatment were melanoma, non-small cell lung cancer, renal cell carcinoma, and urothelial carcinoma, reflecting the prevailing indications to immunotherapy in the evaluated timeframe. The majority of the patients were exposed to anti-PD1/PDL1 compounds (Table 1).

NirAE onset and main neurological syndromes

Median time from ICI start to toxicity onset was 43.5 days (interquartile range, IQR = 22.25–106.5 days), and patients underwent a median of 3 ICI cycles (IQR = 1.75–6) (Fig. 1a, Table 2). Neurological irAES affected the PNS in 20 patients (74%), the CNS in 4 (15%), and both in one (4%). Median time to symptoms onset was shorter for peripheral toxicities compared to CNS toxicities (36 versus 144.5 days, $p = 0.045$, Wilcoxon signed-rank test; Fig. 1b). Of note, one patient (#24) received 47 cycles of pembrolizumab without neurological side effects but developed a subacute polyradiculoneuropathy shortly after the first cycle at a different schedule (from 200 mg every 2 weeks to 400 mg every 4 weeks).

Median nirAE severity, assessed according to CTCAE grading v5.0, was three (range 1–5); all but three (89%) experienced severe toxicities (i.e. CTCAE grading ≥ 3).

Most common neurological manifestations (Table 2) were represented by inflammatory polyradiculoneuropathies (iPRN, $n = 6$), isolated myositis ($n = 5$), and overlap syndromes (myositis + iPRN, $n = 5$; myositis/MG overlap syndrome, $n = 2$). Further PNS manifestations encompassed seronegative Miller-Fisher-like syndrome ($n = 2$), polyneuropathy ($n = 2$), seronegative MG ($n = 1$), and cranial mononeuropathy ($n = 1$).

Central nervous system involvement was protean and included encephalitis (isolated, $n = 1$ or in combination with cerebellitis, $n = 1$), myelitis ($n = 1$), bilateral optic neuritis ($n = 1$), MS ($n = 1$), encephalopathy ($n = 1$), focal seizures ($n = 1$), and delusions ($n = 1$).

Level of diagnostic certainty was definite for 19/34 diagnoses (56%), probable for 3/34 (9%), and possible for 12/34 (35%).

Table 1 Demographic and oncological characteristics of the 27 reported patients with neurological irAEs from ICI treatment

Sex ratio (males/females)	2.86 (20/7)
Age at nirAE onset, years (range)	69 (44–79)
Malignancy, *n* (%)	Melanoma, 8 (30%) NSCLC, 7 (26%) RCC, 4 (15%) Urothelial carcinoma, 4 (15%) SCLC, 2 (7%) Colorectal carcinoma, 1 (4%) Undifferentiated carcinoma of unknown origin, 1 (4%)
ICI treatment, *n* (%)	Anti-PD1, 18 (67%) - Nivolumab, 10 (37%) - Pembrolizumab, 8 (30%) Combination therapy, 4 (15%) - Ipilimumab + nivolumab, 4 (15%) Anti-PDL1, 3 (11%) - Atezolizumab, 3 (11%) Anti-CTLA4, 1 (4%) - Ipilimumab, 1 (4%) Sequential therapies, 1 (4%) - Ipilimumab then pembrolizumab, 1 (4%)

Abbreviations: *nirAE* neurological immune-related adverse event, *ICI* immune checkpoint inhibitors, *NSCLC* non-small cells lung cancer, *RCC* renal cell carcinoma, *SCLC* small cells lung cancer

Clinical presentation

Detailed clinical and paraclinical available data are available in Supplementary Table 2.

Myositis and MG/myositis overlap syndromes ($n = 9$) Myositis patients showed a consistent clinical presentation, composed of limb-girdle weakness ($n = 7$, 78%), myalgias ($n = 6$, 67%), ptosis ($n = 5$, 56%), dysphagia ($n = 4$, 44%), head drop ($n = 4$, 44%), and diplopia ($n = 2$, 22%). Myopathic changes at EMG were reported in five cases (56%). In three cases (33%), there were also clinical (areflexia, ascending numbness) and neurophysiological evidence of concomitant acute polyradiculoneuropathy. Signs of impaired neuromuscular junction at EMNG were seen in four patients (44%; decremental response to RNS in two, 22%, increased jitter at sfEMG in two additional patients, 22%). Two of them showed the presence of autoantibodies against acetylcholine receptor. Interestingly, in one case (#10), a first testing was normal; nevertheless, repeated RNS performed in concomitance with symptoms progression (appearance of overt fatigability) documented the pathological response. CPK levels were elevated in all seven analyzed cases (100%, range 400–22,000 U/L, median 3145 U/L). Three patients underwent muscle MRI: imaging finding was consistent with bilateral, multifocal muscular inflammation and edema, manifest as T2 STIR hyperintensities (Fig. 2a–h). No cases of thymic alterations were identified.

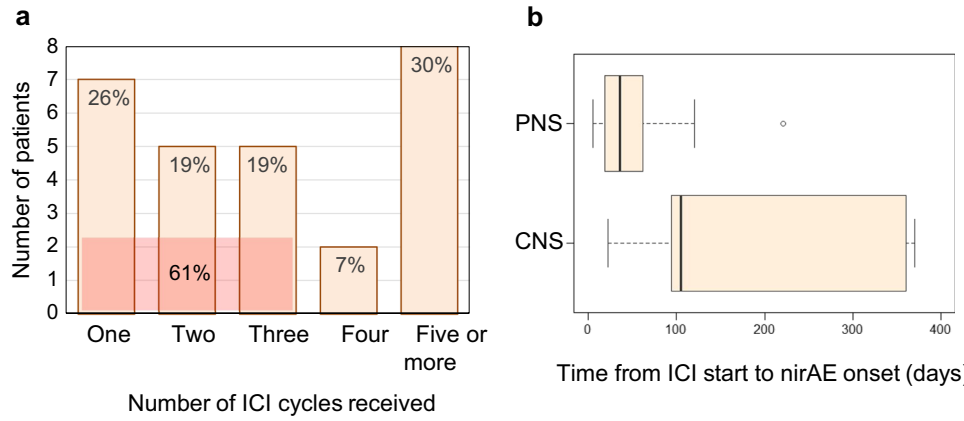

Fig. 1 (**a**) Number of ICI cycles received. Almost two-thirds of patients (17/27, 61%) developed the toxicity after the first one to three administrations. (**b**) Time from ICI initiation to nirAE onset. Median time to onset was shorter for peripheral versus CNS toxicities (36 versus 144.5 days, $p = 0.045$, Wilcoxon signed-rank test)

Inflammatory polyradiculoneuropathies ($n = 6$) Isolated iPRN manifested with limb weakness ($n = 5$, 63%), hypoesthesia ($n = 4$, 67%), and proprioceptive ataxia ($n = 2$, 40%). NCS showed mixed, axonal, and demyelinating injury in four cases (67%), mainly axonal in one (17%), and with prevalent demyelination in one (17%). CSF study was performed in five patients and showed increased proteins in four (80%) and slightly increased cell count in one (20%). Antiganglioside and onconeural antibodies were absent in tested patients (0/2 and 0/4, respectively). In two patients, lumbosacral MRI displayed contrast enhancement of cauda equina roots, with associated diffuse thickening in one case (Fig. 2i–k).

Miller-Fisher-like syndrome ($n = 2$) Two patients developed a Miller-Fisher-like syndrome with ptosis, ophthalmoplegia, dysphagia, and dysphonia. Nerve conduction studies displayed a demyelinating polyneuropathy in both. Antiganglioside and onconeural antibodies were negative (0/2). CSF analysis showed lymphocytic pleocytosis in one. Both had unremarkable brain and spine MRI.

Peripheral neuropathy ($n = 2$) Two cases of length-dependent peripheral neuropathy were reported. Both patients had a history of neurotoxic drugs exposure; however, temporal relationship with ICI exposure pointed to an immune-related aetiology. Both manifested with sensory impairment and paraesthesia, with progressively evolving severe legs weakness in one. At NCS, both had severe sensorimotor polyneuropathy, with prevalent axonal features in one and mixed axonal and demyelinating in the other.

Myasthenia gravis, seronegative ($n = 1$) A woman developed fluctuating ptosis, diplopia, and mild dysphonia after two administrations of nivolumab. Electrophysiological studies disclosed increased jitter at sfEMG. AChR antibodies testing was negative.

Cranial mononeuropathy ($n = 1$) One patient had isolated third cranial nerve palsy manifested with subacute diplopia after four administrations of nivolumab. Brain MRI was negative.

Encephalitis ($n = 2$) Two patients were diagnosed with encephalitis. One developed a complex clinical picture with anxiety, insomnia, intention tremor, right-sided myoclonic jerks and hypertonus, dystonic tongue movement, and dysphagia. Brain MRI showed minimal, patchy contrast enhancement in deep left temporal lobe (Supplementary Fig. 1). CSF analysis was within normal limits. The other one came to medical attention for diplopia and gait ataxia. Brain MRI displayed a swollen left temporal lobe with T2/FLAIR hyperintensity and patchy contrast enhancement of the uncal portion with mass effect on left oculomotor nerve (*not shown*). Clinical evaluation showed associated cerebellar signs. CSF examination displayed increased proteins and oligoclonal banding (mirror bands in CSF and serum with additional bands in CSF only). A clinical diagnosis of encephalitis and cerebellitis was made. Both patients had negative onconeural antibodies screen.

Vasculitis ($n = 1$) A woman with a 16-year history of well-controlled MS started pembrolizumab for metastatic NSCLC, and concurrently discontinued treatment with dimethyl fumarate. A few days after the sixth cycle, she presented with fever, followed a few days later by somnolence, apathy, disinhibition, gait ataxia, and a worsening of a preexistent appendicular ataxia. CSF analysis disclosed increased proteins and a lymphocytic pleocytosis (26 cells/mm^3). EEG displayed a diffuse slowing. Multiple infra- and supratentorial punctiform and faint contrast-enhancing lesions with a perivascular distribution were seen at brain MRI, without corresponding abnormalities in T2- or diffusion-weighted sequences (Fig. 3a–h). Known preexisting demyelinating lesions were unchanged. Screening for

Table 2 Clinical characteristics, treatment, and outcome of the 27 patients with neurological toxicities from ICI treatment

Median time from ICI start to nirAE onset, days	43.5 (IQR 22.5–106, range 5–885[†])
Median number of ICI cycles received, n	3 (IQR 1.75–6, range 1–48[†])
Affected nervous system, *n* (%)	Peripheral nervous system, 20 (74%) Central nervous system, 6 (22%) Both, 1 (4%)
Neurological syndrome, *n* (%)	<u>Peripheral nervous system</u> - Myositis, 9 (33%)[‡] - Inflammatory polyradiculoneuropathy, 9 (33%)[‡] - Myasthenia gravis, 5 (19%)[‡] - Miller-Fisher-like syndrome, 2 (7%) - Polyneuropathy, 2 (7%)[‡] - Cranial mononeuropathy, 1 (4%) <u>Central nervous system</u> - Encephalitis, 2 (7%)[‡] - Vasculitis, 1 (4%) - Cerebellitis, 1 (4%)[‡] - Myelitis, 1 (4%) - Bilateral optic neuritis, 1 (4%) - Multiple sclerosis, 1 (4%) - Delusions, 1 (4%)[‡]
Median CTCAE severity at nirAE peak	3 (IQR 3–4, range 1–5)
First-line treatment, *n* (%)	High-dose glucocorticoids, 22 (81%) IVIg, 3 (11%) High-dose glucocorticoids + IVIg, 1 (4%) No treatments, 1 (4%)
Second-line treatments, *n* (%)	Yes, 7 (26%) - IVIg, 5 (19%) - Plasma exchanges, 4 (15%) - Mycophenolate mofetil, 1 (4%) No, 20 (74%)
Neurological outcome at last available follow-up, *n* (%)	Complete remission, 7 (26%) Partial improvement, 8 (30%) Stable deficit, 4 (15%) Progressing symptoms, 2 (7%) Death, 4 (15%)Not available, 2 (7%)
Median CTCAE severity at last follow-up	2 (IQR 1–3.5, range 0–5)
ICI treatment management, *n* (%)	Permanently discontinued, 21 (78%) Continued as planned, 2 (7%) Temporarily suspended, 1 (4%) Temporary suspended and resumed with a different schedule, 1 (4%) Not available, 2 (7%)

[†]One patient received 47 cycles of pembrolizumab 200 mg every 3 weeks without nirAEs but developed subacute inflammatory PRN a few weeks after the first cycle at 400 mg every 6 weeks [‡]Overlap syndromes in 7 (inflammatory polyradiculoneuropathy + myositis + myasthenia gravis, $n=2$; myositis + myasthenia gravis, $n=2$; inflammatory polyradiculoneuropathy + myositis, $n=1$; encephalitis + cerebellitis, $n=1$; polyneuropathy + delusions, $n=1$). Abbreviations: *ICI* immune checkpoint inhibitors, *nirAE* neurological immune-related adverse event, *IVIg* intravenous immunoglobulins, *IQR* interquartile range

onconeural and anti-glial fibrillary acidic protein antibodies and was negative. Cerebral angiitis was the final diagnosis.

Optic neuritis ($n=1$) One patient manifested reduced visual acuity in the right eye after the seventh cycle of ipilimumab plus nivolumab therapy. Approximately 2 weeks later, symptoms involved contralateral eye. Visual acuity was reduced to 20/40 in the right eye and only hand movement could be perceived in the left. CSF analysis and brain MRI were normal. Onconeural, anti-aquaporin-4 (AQP4), and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies were not detected. A diagnosis of ICI-induced bilateral optic neuritis was posed.

Myelitis ($n=1$) The patient developed subacute paraparesis, a T9 sensory level, and urinary incontinence shortly after the second administration of nivolumab for renal cell carcinoma. Spine MRI revealed a nodular intra-axial enhancing abnormality at T8–T9 level, accompanied by whole spine T2/STIR hyperintensity extending from T3 to the conus

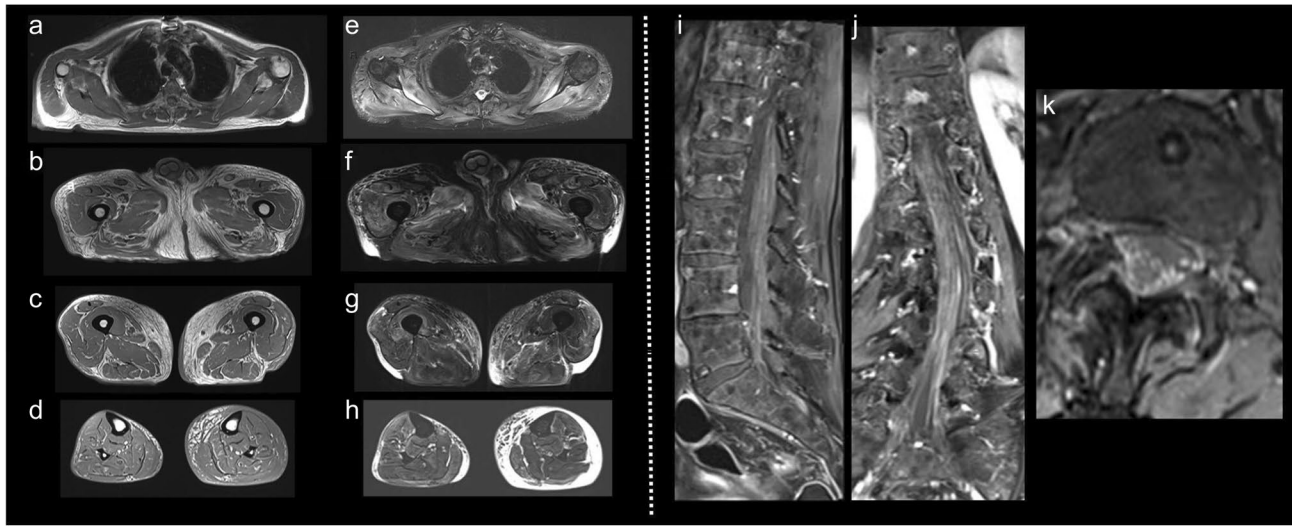

Fig. 2 Radiological features in patients with peripheral neurotoxicities. (**a–h**) Muscle MRI of patient #26 with myositis: axial T1-weighted (**a–d**) and T2-STIR weighted (**e–h**) images of the scapular (**a,e**) and pelvic (**b,f**) girdles and inferior limbs (**c,d,g,h**). T1-weighted images show diffuse muscle hypotrophism with moderate fat substitution at the level of the glutei (**b**), of the thigh (**c**), and leg (**d**) muscles, while T2-STIR images show diffuse hyperintensity of the scapular girdle and paravertebral muscles (**e**), together with muscle edema recognizable also at the level of the adductors (**f**) and multifocally at the level of the inferior limbs (**g,h**). Relevant diffuse subcutaneous edema is also evident, mainly on the left side in the inferior limbs. (**i–j**) Lumbosacral MRI of patient #2 with inflammatory polyradiculoneuropathy: sagittal (**i**), coronal (**j**), and axial (**k**) T1-fat suppressed post-gadolinium images show diffuse thickening and marked enhancement of the caudal roots

(Fig. 3i–j). CSF analysis showed increased proteins and oligoclonal banding with mirror pattern. Search for onconeural, anti-AQP4, and anti-MOG antibodies was negative. Subsequent evolution (symptoms reduction and remission of T2 FLAIR alteration with persisting nodular enhancement after glucocorticoids administration) led to the diagnosis of ICI-induced myelitis and spinal metastasis of the known tumour.

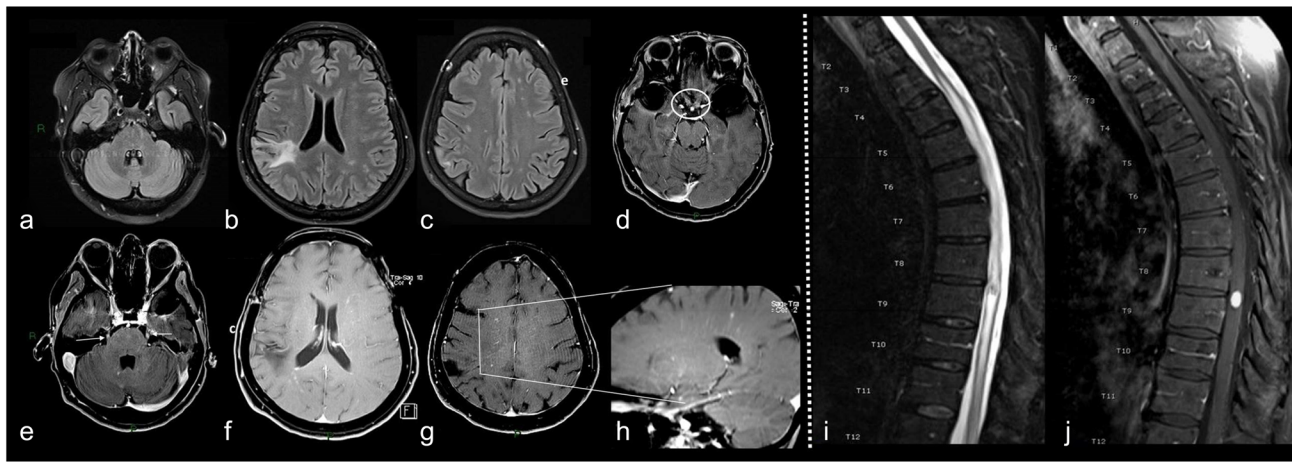

Fig. 3 Radiological features in patients with CNS toxicities. (**a–h**) Brain MRI of patient #25 with cerebral angiitis: axial FLAIR (**a–c**) and post contrast T1-weighted images, axial (**d–g**) and sagittal (**h**). Multiple punctate foci of T2 hyperintensity are evident in the pons (**a**) and in the subcortical white matter bilaterally (**b,c**), with a previous known encephalomacic area in the right temporo-parietal junction (**b**). Numerous punctate areas of enhancement are documented post-gadolinium injection, both infra (**e**) and supratentorially (**f,g**) with a linear perivascular shape (**h**). Enhancement of the optic chiasm (**d**, ovoid) and of the proximal cisternal tract of the trigeminal nerves (**e**, arrows) is also evident. (**i–j**) Spine MRI of patient #21 with myelitis: sagittal T2 (**i**) and post contrast T1-weighted (**j**) images, showing wide intramedullary T2-hyperintensity, extended from T3 to conus (**i**) surrounding a markedly enhancing intramedullary metastasis at T8–T9 level (**j**)

Multiple sclerosis ($n=1$) A woman in her 60 s presented a progressive worsening of right leg weakness and spasticity with associated right foot hypoesthesia while under treatment with pembrolizumab for NSCLC. Remarkably, the patient had multiple infra- and supratentorial, T2 hyperintense white matter lesions, discovered in a brain MRI performed 1 year before symptoms onset during the staging of the NSCLC, not further investigated. She was hospitalized for worsening of symptoms, and brain MRI showed stability of previously identified lesions, while spine MRI disclosed two focal enhancing lesions at C7 and D6 levels. CSF analysis was positive for CSF-specific OCB. Somatosensory- and visual-evoked potentials showed centrally prolonged latencies. A diagnosis of multiple sclerosis was posed.

Other relevant systemic irAEs were reported in six patients (22%). Two patients with myositis developed myocarditis (2/9, 22%).

Treatment and outcome

NirAE management and patient outcome are summarized in Table 2 and reported in detail in Supplementary Table 3. Twenty-three patients (85%) received high-dose glucocorticoids as first-line treatment, in one case (4%) in association with intravenous immunoglobulin (IVIg). Three patients (11%) received first-line IVIg. One patient (4%) with grade 1 myositis/MG complex (self-limiting monolateral ptosis) did not receive any treatment.

Outcome was available for 26 of 27 patients. Four patients treated with high-dose glucocorticoids (4/22 with available follow-up, 18%) had a complete remission of symptoms, while 12 (55%) had a partial improvement, one (5%) a clinical stabilization, and five (23%) showed no response. All three patients treated with first-line IVIg showed a partial response (100%).

Seven patients (26%) received further lines of treatment, including IVIg ($n=5$), plasma exchange ($n=4$, 3–6 sessions), and mycophenolate mofetil ($n=1$). Three patients improved; all three underwent plasma exchange (in association to IVIg in one). Three patients deteriorated to death despite treatments (IVIg, $n=3$; plasma exchanges, $n=1$; mycophenolate mofetil, $n=1$); in one case, a severe neurological deficit persisted.

Four (15%) nirAEs resulted in death (encephalitis, $n=1$; myositis/MG complex with concomitant myocarditis, $n=2$; iPRN, $n=1$). Seven (26%) patients experienced a complete remission of symptoms, while eight (30%) had only a partial improvement. Four (15%) patients showed a stabilization of their deficit, while two (7%) had progressive symptoms at last available timepoint. Median CTCAE grading at last follow-up was 2 (range 0–5). When considering separately PNS and CNS toxicities, the rate of improved patients was higher for peripheral adverse events, but in a non-significant manner (72% versus 40% respectively, $p=0.30$, Fisher's exact test). Rate of fatal events was similar in the two groups (17%, 3/18 in the PNS group versus 20%, 1/6 in the CNS group).

Management of ICI treatment was available for 25 patients. The vast majority of them (21/25, 84%) definitively discontinued ICIs. One patient (4%) with grade 2 polyneuropathy and delusions underwent temporary suspension; two patients (7%) with grade 3 iPRN and grade 1 myositis respectively continued the immunotherapy, after resolution of the symptoms. One patient (4%) who presented grade 3 PRN after the switch from pembrolizumab 200 mg every 3 weeks to 400 mg every 6 weeks was successfully rechallenged with the previous schedule a few weeks from symptoms resolution. None of them experienced a relapse of the neurological symptoms nor new nirAEs.

Discussion

In the present study, we describe a cohort of twenty-seven ICI-treated patients diagnosed with nirAEs at specialized neurological centers included in the Neuro-oncology Study Group of the Italian Neurological Society (SIN). Data were collected in a real-life setting with the aim to bolster the knowledge about the clinical and paraclinical spectrum of nirAEs.

Neurological irAEs developed mostly after one to three ICI administrations (61%), similarly to what reported in most case series [9, 19–21] and a recent literature review [22]. Nevertheless, we saw nirAEs occurring after more than 1 year of immunotherapy, requiring continuous monitoring. Time to onset was longer for CNS toxicities, as also suggested by the recent literature [23]. Noteworthy, one patient (#25) developed grade 3 PRN concomitantly with the first pembrolizumab dose at 400 mg after tolerating well 47 administrations of the drug at the posology of 200 mg every 3 weeks. This suggests the need of further vigilance when patients are exposed to a change in drug schedules as this may cause the disruption of self-tolerance even in patients already exposed to ICIs.

All but three patients experienced severe toxicities (CTCAE grading ≥ 3). Nevertheless, CTCAE grading should be interpreted with caution, as we saw mild neurological symptoms not warranting drug interruption being later identified as the onset of serious toxicities (e.g. mild paresthesia for inflammatory polyradiculoneuritis; mild legs weakness for myositis), that can rapidly progress. Neurologists should be always included in the diagnostic framework of patients developing new neurological symptoms during ICI treatments, regardless of severity as defined by currently available grading criteria.

Three patients had previously clinically defined or silent neuroinflammatory disorders. In one case (#28), pembrolizumab led to the first clinical manifestation and subsequent diagnosis of multiple sclerosis in a woman with a previously radiologically isolated demyelinating disorder. In another notable case (#26), immunotherapy resulted in diffuse encephalopathy in a woman with a previous history of well-controlled MS. MRI displayed multifocal perivascular enhancement clearly distinct from a classic MS relapse, suggesting a different, ICI-induced mechanism. A similar case has been recently reported by Garcia and colleagues [24]. Fortunately, both our patients improved after high-dose glucocorticoids. The exact role and incidence of ICI treatment in decompensating preexistent neuroinflammatory disorders remains poorly defined. A retrospective series suggested a more severe course for nirAEs occurring in patients with preexistent detectable paraneoplastic CNS autoimmunity [21]. The risk/benefit ratio of immunotherapy in those patients should be carefully evaluated. In patients needing an active immunomodulation, a shift toward more selective immunomodulating compounds has been recently advocated [25], to reduce the potential deleterious effect on the oncological efficacy. Screening for subclinical positive neural autoantibodies before starting ICI treatment can also be discussed, particularly for tumors associated with paraneoplastic syndromes (e.g. SCLC, thymoma) [21], to further guide the clinician.

Neuromuscular structures were the most commonly involved targets of nirAEs, with proportions similar to those reported in other works (58–80%) [19–23]. A multiple PNS involvement was seen in a relevant number of patients, with major clinical overlap between the muscle and the neuromuscular junction damage. It is noteworthy that most cases with a clinical diagnosis of ICI-related MG, if not all, show signs of myositis when extensively studied [20, 26–28]. Clinical presentation may be misleading, as ICI-related myositis often present in a "MG-like" pattern of diplopia, ptosis, and dropping head [9, 20, 29]. Positive anti-AChR titers should also be interpreted with caution as they have been recently demonstrated to predispose to ICI-related myositis [30]. Nonetheless, four of our myositis patients demonstrated impaired NMJ at RNS or sfEMG, supporting the hypothesis of multiple targets in at least a subset of cases. The exact impact of the myositis versus the myasthenic component for these patients remains to be determined; we were not able to demonstrate a clear benefit from cholinesterase inhibitors in our series. Although the association between myositis and MG appeared to be the most common in the context of ICI-associated neurological syndromes, it was not the unique one. We described here three cases in which neuromuscular impairment was associated with polyradiculoneuropathy. Some associations have been probably underestimated in previous reports as in oncological patients with complex neurological syndromes some signs may remain unnoticed. As an example, one of our patients (#10) with myositis/MG complex had also moderately reduced deep tendon reflexes, which could be explained by the already known neurological status. However, NCS showed the co-occurrence of a severe axonal polyneuropathy (of note, the patient had no previous exposure to neurotoxic chemotherapies) as possibly aggravating the symptoms. Similarly, in one of the most detailed series of ICI-related myositis to date, Shelly et al. reported a concomitant presence of peripheral nerve involvement in up to 50% of patients [20]. We thus recommend an extensive workup for all patient who experience nirAEs, especially neuromuscular, to fully estimate the extension of neurological damage. A particular attention should be given to identify myositis, as it is associated with the higher fatality rates, particularly when involving the myocardium. The myopathic process may involve the cardiac muscle in a relevant proportion of cases (20% in our cohort, 20–40% in published series [9, 11, 20, 31]). Myocarditis results in high fatality rates [32] and should be actively searched in all patients with neuromuscular irAEs to allow a timely intervention and the necessary multidisciplinary management.

Regarding treatments, our series confirms the efficacy of high-dose glucocorticoids in most patients [19–23]. However, in cases not improving after a few days of corticotherapy, or upfront in life-threatening events, additional interventions were required. Intravenous immunoglobulins and plasma exchange were usually considered second-line treatments; the latter, particularly, appeared promising in our series, although data must be interpreted with caution due to their retrospective nature and the possible presence of selection bias. Plasma exchange may be helpful in both reducing circulating proinflammatory factors and ICI levels [33].

Differing from non-ICI-related forms, inflammatory neurological syndromes of our patients did not present chronic or relapsing/remitting evolution; hence, no patient in our cohort required maintenance immunosuppressive treatments. Nevertheless, relapsing or chronic forms have been reported in the literature [34–36].

Most patients discontinued ICI treatment; only four (14%), with mostly mild forms, resumed ICIs. Serious nirAEs are considered a major contraindication to ICI resumption [37]. However, some recent reports highlighted the feasibility of ICI rechallenge after serious nirAEs [38, 39], and pharmacovigilance data suggest a low rate of recurrence after ICI reintroduction for neurological toxicities compared to other irAEs [40]. Nevertheless, evidence is still limited, and relapse risk should not be underestimated. The choice of resuming ICIs after severe nirAEs should be reserved to patients necessitating active antineoplastic treatments, and carefully discussed with the patient, the treating oncologist, and a reference neurologist.

Study limitations

Study concept (multicentric spontaneous reporting) did not allow us to analyze nirAE incidence or associations between ICI classes and specific syndromes. As data were entered by

neurologists, a referring bias toward more severe or complex cases is likely. The retrospective nature of the data itself limits the strength of our conclusions. Data collection is ongoing and prospectively included patient will allow us to increase the quality of evidence.

Conclusions

Neurological immune-related adverse events from ICI treatments are rare but increasingly recognized toxicities in complex oncological patients. They affect primarily the neuromuscular structures but encompass a broad range of CNS and PNS presentations. The clinical picture may be misleading, and a thorough examination is needed to fully estimate the extent of the damage. A prompt recognition is mandatory to timely withheld immunotherapy and administrate glucocorticoids. In corticoresistant or severely affected patients, second-line treatments as plasmapheresis or IVIg may result in additional benefit. Myocarditis is a severe complication frequently associated to ICI-related myositis and MG that should be actively searched to allow the proper multidisciplinary management. An increased surveillance should be maintained in patients with preexisting neuroinflammatory disorders.

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Author contribution Al.P., L.D., and E.M. designed and conceptualized the study; Al.P. and L.D. analyzed the data and drafted the manuscript for intellectual content; P.B., M.G., E.A., E.R., R.R., F.B., V.V., E.G., A.V., M.V., M.Z., V.P., B.G., C.C., and M.DV. had major role in the acquisition of data, interpreted the data, and revised the manuscript for intellectual content; An.P. interpreted the radiologic analyses and revised the manuscript for intellectual content.

Availability of data and material Further anonymized clinical will be made available from the authors upon reasonable request.

Code availability Not applicable.

Declarations

Ethical approval The retrospective study was approved by institutional ethic committee (No. 20190026431).

Informed consent Informed consent was waived for de-identified, retrospective data.

Conflict of interest The authors declare no competing interests.

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