



CASE REPORT

Beyond T cell toxicity – Intrathecal chemokine CXCL13 indicating B cell involvement in immune-related adverse events following checkpoint inhibition: A two-case series and literature review

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Abstract

Background and purpose: This study was undertaken to raise awareness of a role of B cells in immune checkpoint inhibitor (ICI)-associated neurological immune-related adverse events (nirAE).

Methods: A systematic literature review was made, with case observations of a melanoma and a non-small cell lung cancer (NSCLC) patient who developed ICI-associated nirAE with cerebrospinal fluid (CSF) findings indicating B cell involvement.

Results: Two patients receiving ipilimumab/nivolumab for melanoma and chemotherapy/pembrolizumab for NSCLC developed nirAE in the form of myocarditis/myositis/myasthenia gravis overlap syndrome (triple M) and cerebellitis plus longitudinal transverse myelitis (c-LETM), respectively. Intrathecal inflammation with chemokine C-X-C motif ligand (CXCL13) elevation was present in both patients; the triple M case had acetylcholine receptor antibodies, antititin reactivity, altered CD4/CD8 T cell ratio in blood, and depressed programmed death-1 (PD-1) expression on CSF T cells; the c-LETM case showed intrathecal antibody production and plasma cells. Both patients insufficiently responded to first-line treatment. The NSCLC case improved upon administration of B cell-depleting therapy with rituximab, whereas the melanoma patient died before escalation therapy was initiated. Literature research revealed one additional ICI-associated LETM case with intrathecal CXCL13 elevation, three cases with ICI-associated aquaporin-4 antibody neuromyelitis spectrum disorder, and evidence of B cell-mediated toxicity based on antibody-mediated immune pathologies in ICI-associated immune-related adverse events.

Conclusions: The case observations highlight the plethora of uncertainties in diagnosis and treatment of ICI-associated nirAE, exemplify the heterogeneity of immune mechanisms involved, and suggest a role of B cells, which may be underdiagnosed. Intrathecal CXCL13 may serve as a biomarker of B cell involvement in nirAE, supported by intrathecal

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immunoglobulin synthesis, presence of plasma cells, and/or recruitment of cognate immune cells.

KEYWORDS

cerebrospinal fluid, chemokine CXCL13, immune checkpoint inhibitor, immune-related neurological adverse events

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are monoclonal antibody therapeutics targeting coinhibitory immune receptors on cancer-specific cytotoxic T cells and significantly enhance patient survival [1]. ICI-treated patients with metastatic cancer usually receive combination regimes of two different classes of ICIs or ICI in combination with cytotoxic chemotherapy [1]. Ipilimumab (ipi; anti-CTLA-4-IgG1; Yervoy, Bristol Myers Squibb [BMS]) with nivolumab (nivo; anti-PD-1-IgG4, Opdivo, BMS) are widely used in the treatment of metastatic melanoma [1]; chemoimmunotherapy with carboplatin-based chemotherapy and pembrolizumab (pembro; anti-PD-1-IgG4; Keytruda, Merck/MSD) is first-line treatment for non-small cell lung cancer (NSCLC) [2].

Unleashing adaptive immune activity by interfering with negative control mechanisms, however, implies the risk of immune-related adverse events (irAE). IrAE occur in approximately 30%–60% of ICI-treated patients and most commonly affect the gastrointestinal tract, skin, liver, and endocrine glands [1], e-7. Along with a higher efficacy, anti-programmed death-1 (PD-1) and anti-CTLA-4 combination therapy involves severe grade 3–4 irAE in 32%–59% [3, 4], such as myocarditis, with mortality rates as high as 25%–50% [1].

Neurological irAE (nirAE) are comparatively rare and potentially devastating and can affect the central, peripheral, and autonomic nervous systems [1]. Incidence estimates based on small case series and/or literature reviews range from 0.9% to 14% [5, 6], and may increase to 31% if immune-related and non-immune-related ICI-associated neurotoxicities are considered [7]. Johnson et al. [8] probably provide the most reliable data on the clinical spectrum based on a disproportionality analysis of the World Health Organization pharmacovigilance database VigiBase (2008–2018), reporting ICI-associated fatality rates between 6% and 12% with a median onset of 61–80 days [8]. ICI-associated myasthenia gravis showed the highest fatality rates (~20%), with acute onset (median 29 days) and frequently concurring myocarditis and myositis.

The immune pathology of (n)irAE is poorly understood, and cytotoxic T cell responses against antigens present in both tumors and healthy tissues are considered a main cause [1]. Accumulating evidence, however, points at involvement also of cytokine-mediated mechanisms and preexisting antibodies and/or antibody-mediated toxicity implicating a role of B cells [4, 9], e-1.

We present two cancer patients with ICI-associated nirAE showing evidence of B cell involvement; one developed myocarditis/myositis/myasthenia gravis overlap syndrome (triple M case) with fatal outcome, the other cerebellitis and longitudinal transverse myelitis

(c-LETM case). We furthermore conducted a systematic MEDLINE search for all articles up to December 2023 involving B cells and chemokine C-X-C motif ligand (CXCL13) in ICI-associated irAE (Figure S1), and discuss the latest evidence regarding the underlying immune mechanisms, including a role of B cells and the challenge of diagnosing and treating severe nirAE.

CASE OBSERVATION I: TRIPLE M CASE

A 75-year-old female with a history of arterial hypertension and chronic immune thyroiditis (thyroidectomy in 2017, since then hormone substitution therapy) was diagnosed with primary metastatic melanoma grade IV according to the American Joint Commission of Cancer classification in October 2022 (timeline shown in Figure 1a) [10]. Computer tomography of the thorax revealed a mass in the left upper lobe of the lung. A bronchoscopy-guided biopsy of an 18F-fluorodeoxyglucose positron emission tomography (PET)-positive lymph node allowed cancer diagnosis; the nosology of a PD-1 ligand (PDL-1)-positive, ALK-D5F3- and pan-TRK-negative melanoma was confirmed by histopathology, and the patient was started on combination therapy with ipi/nivo (1 and 3 mg/kg bodyweight, respectively).

Twenty-one days later, she reported new onset of double vision, rapidly evolving fatigue, and ascending muscular and generalized weakness without myalgia. Neurological examination revealed incomplete bilateral horizontal gaze palsy. Laboratory findings showed cerebrospinal fluid (CSF) pleocytosis (27 cells/ μ L, normal range=0–4), with predominant activated mononuclear cells and highly elevated CXCL13 levels (316 pg/mL, normal range <20 pg/mL). The blood–CSF barrier was intact, and there was no evidence of intrathecal immunoglobulin synthesis. Serologic testing (CSF and serum) for common herpes viruses and polymerase chain reaction (PCR) for herpes simplex (HSV) and varicella zoster virus (VZV) in CSF showed no evidence of viral activity. In blood, troponin (589 ng/L, normal range=0–14 ng/L), creatine phosphokinase (CPK; 5826 UI/L; normal range=38–174 UI/L), and liver enzymes (glutamate pyruvate transaminase: 200 U/L, normal range=10–50 U/L; glutamate oxaloacetate transaminase: 291 U/L, normal range=10–50 U/L) were elevated. Markers of systemic inflammation (C-reactive protein, white blood cell count) were normal. Autoantibody screening furthermore revealed anti-skeletal muscle reactivity, which was positive for anti-acetylcholine receptor (anti-AChR; 4.88 nmol/L, normal range <0.5) and striatal antititin antibodies (strong positive), and anti-dense fine speckled 70 kDa molecular weight antibodies. All other autoantibodies of the Euroline paraneoplastic neurologic syndromes (~12 Ag)

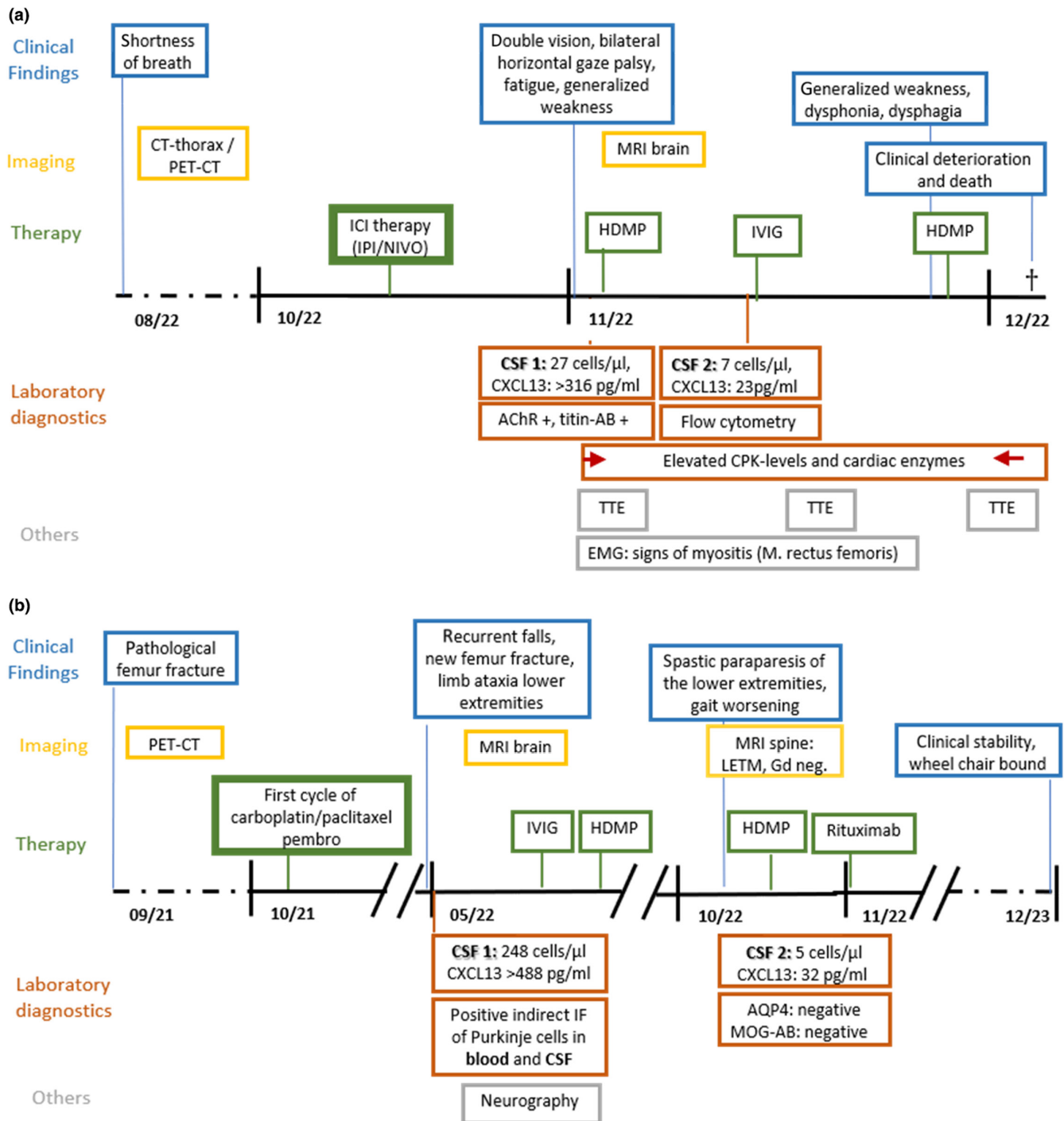


FIGURE 1 Timeline of the cases. (a) The triple M case. (b) The cerebellitis and longitudinal transverse myelitis case. AB, antibody; AChR, antibodies to acetylcholine receptor; AQP4, anti-aquaporin 4 antibody; CPK, creatine kinase; CSF, cerebrospinal fluid; CT, computed tomography; CXCL13, chemokine C-X-C motif ligand; EMG, electromyography; Gd, gadolinium; HDMP, high-dose methylprednisolone; ICI, immune checkpoint inhibitor; IF, immunofluorescence; IPI, ipilimumab; IVIG, intravenous immunoglobulin; LETM, longitudinal extensive myelitis; MOG-AB, myelin oligodendrocyte glycoprotein antibody; MRI, magnetic resonance imaging; neg., negative; NIVO, nivolumab; pembro, pembrolizumab; PET-CT, 18F-fluorodeoxyglucose positron emission tomography; TTE, transthoracic echocardiography.

immunoblot (EUROIMMUN, Lübeck, Germany) were negative, as were myositis-specific antibodies (Euroline myositis profile -16 Ag; EUROIMMUN). Cerebral magnetic resonance imaging (MRI), 12-lead electrocardiogram, and transthoracic echocardiogram (TTE) were

normal. Electromyography of the rectus femoris muscle showed pathological spontaneous activity indicative for myositic changes.

ICI-induced myositis/myocarditis/myasthenia gravis overlap syndrome was suspected, and the patient received a 5-day cycle

of intravenous (i.v.) methylprednisolone (5 g in total), tapered to a maintenance dose of 60 mg/day. During admission, troponin levels constantly increased to a maximum of 1736 ng/L but TTE remained normal. Follow-up CSF examination showed a decrease in cell count (7/μL) and CXCL13 levels (23 pg/mL). Flow cytometry revealed low PD-1 expression on CSF T cells, accumulation of CXCL13-responsive CXCR5⁺ T cells of a predominant inflammatory Th1 and Th17 phenotype in CSF compared to blood, and a highly altered CD4/CD8 T cell ratio (19, normal range = 1–5) in blood (Figure S2).

Because the clinical picture did not improve, the patient received a 5-day cycle with i.v. immunoglobulin (IVIG; 150 g in total) and was discharged but 2 weeks later readmitted with generalized proximal muscular weakness, dysphonia, dyspnea, and dropped head. The patient received a second cycle of high-dose methylprednisolone, because she refused treatment escalation with plasmapheresis. Further escalation with rituximab could not be realized, because the patient rapidly deteriorated and died only 46 days after initiation of ICI combination therapy. Over that time, CPK levels (196 UI/L) had significantly decreased, whereas troponin levels (1142 ng/L) remained elevated.

CASE OBSERVATION II: c-LETM CASE

A 75-year-old female smoker (>20 pack-years) with a history of diabetes mellitus type II and arterial hypertension was diagnosed with NSCLC in summer 2021 (timeline shown in Figure 1b). Intraoperative biopsy of a left-sided pathological femur fracture followed by a PET scan secured the diagnosis of a PDL-1-negative, primary enteric carcinoma, which had metastasized to lung, bone, mediastinum, and spleen. The pulmonary cancer was treated with six cycles of a combination of carboplatin, paclitaxel, and pembro, followed by pembro maintenance therapy (three weekly 200 mg flat fixed dosage). Computed tomography staging after 3 months showed regression of the pulmonary focus. Five months after treatment initiation, the patient underwent surgery of a left-sided per trochanteric femur fracture after a fall. She furthermore reported a new onset of ataxia of the lower extremities as a cause of the fall, first noticed approximately 4 months after chemotherapy.

MRI of the cerebrum showed no signs of pathology, but lumbar puncture revealed marked CSF pleocytosis, with 248 cells/μL, predominantly activated mononuclear cells and some plasma cells, highly elevated CXCL13 (>488 pg/mL), and a pronounced disruption of the blood–CSF barrier. Serologic testing for common herpes viruses in CSF and blood and CSF PCR for HSV and VZV showed no evidence of viral activity. Indirect immunofluorescence assay on primate cerebellar sections (neurology mosaic 1, EUROIMMUN) showed fluorescence of Purkinje cells in both serum and CSF. The Euroline paraneoplastic immunoblot panel (12-Ag) was negative (EUROIMMUN). Clinical markers of systemic inflammation (C-reactive protein, white blood cell count, procalcitonin) were normal. Neurography of the extremities showed a predominantly sensory axonal polyneuropathy.

ICI-mediated cerebellitis was suspected; maintenance therapy with pembro was stopped, and treatment with a 5-day course of IVIG (150 g in total) and an additional 5-day cycle of i.v. methylprednisolone (1 g/day) was started. Clinically stabilized, the patient was discharged with a tapering cortisone regimen. Five months later, she was readmitted due to reduced muscle strength of the lower extremities and difficulties in walking. Neurological examination showed spastic paraparesis of the lower extremities, most prominently bilaterally in the hip and knee joints. Deep tendon reflexes and Babinski sign were normal. A follow-up lumbar puncture showed mild pleocytosis (5 cells/μL), mild CXCL13 elevation (33 pg/mL), and an intact blood–brain barrier but intrathecal IgA synthesis. An MRI of the spine revealed LETM from thoracic vertebra 5 to 7 (Figure S3). ICI-induced LETM was suspected, and the patient received another 5-day cycle of methylprednisolone (1000 mg/day). Serological testing for autoantibodies related to LETM such as anti-aquaporin-4 (AQP4) and antimyelin (myelin oligodendrocyte glycoprotein [MOG]) antibodies were negative. Samples sent to a reference laboratory for a second opinion revealed borderline positive MOG IgG antibodies in a fixed cell-based assay. Because spinal MRI was performed at clinical deterioration only, an isolated cerebellitis as initial manifestation, spinal ataxia developing into LETM, or a combination of both are possible.

Due to further gradual deterioration, we decided for treatment escalation with rituximab (1000 mg). Follow-up MRI of the spine showed stable disease. Currently, 26 months after initiation of chemotherapy, the patient remains clinically stable.

SYSTEMATIC LITERATURE REVIEW

Literature review identified 22 ICI-associated records (16 irAE, five nirAE, and one preclinical study) related to involvement of B cells, autoantibodies, and/or CXCL13, the majority (83%) published from 2018 until December 2023 (Appendix S1: Reference List e1–e21). nirAE records comprised three neuromyelitis opticus spectrum disorder (NMOSD) cases, one LETM case, and one observational study reporting B cell subset alterations in autoantibody-positive nirAE.

DISCUSSION

To recapitulate, two female patients in their mid-70s presented with intrathecal inflammation and CXCL13 elevations indicating B cell involvement in ICI-associated nirAE. They differed regarding time of onset of nirAE, cancer type, combination therapy, organ involvement, and final outcome, highlighting the heterogeneity of nirAE; they were clinically challenging as they insufficiently responded to first-line treatment for nirAE. Our literature research based on “B cells” and “(n)irAE” produced only a few but recent hits, revealing that a role of B cells is only beginning to be considered.

Regarding the triple M case, detection of antititin and anti-AchR antibodies together with markedly elevated cardiac and muscle

enzymes suggested myositis/myocarditis/myasthenia-like overlap syndrome. The short time until symptom onset was in line with reported myasthenia gravis-like irAE [8] and indicated a surge of pre-existing antibodies. Antistriatal antibodies, although rare, indicate serious irAE with fatality rates of almost 50%; their presence proposedly even may cause the overlapping triad via common muscle antigens [e-24]. Mechanistically, the immune injury may be mediated by antibody binding to specific myocardial structures, and antistriatal antibodies should be screened in patients with MG-like syndrome [e-24].

The 5 months-delayed onset of nirAE in the c-LETM case suggests an immune pathology possibly related to the chemotherapy-induced massive release of tumor and self-antigens, with anti-PD-1 therapy promoting the development of paraneoplastic antibodies against Purkinje cells, resulting in cerebellitis and possibly also in LETM. Approximately 20 cases of ICI-associated LETM are described [11], e-7 including two pembrolizumab-treated patients developing autoreactive antibodies against unknown neural antigens, suggesting antibody-mediated toxicity [12], e-7. Further evidence regarding antibody-mediated B cell toxicity comes from three reports of anti-AQP4 antibody-positive NMOSD developing secondary to ICI treatment with anti-PD-1 [e25–e27].

Although a reporting bias cannot be excluded, causality is feasible. B cell differentiation, activation, antibody production, and antibody affinity maturation are highly dependent on professional B cell helper CD4 T follicular (Tfh) cells, which express high levels of PD-1 and therefore are potential off-target cells of anti-PD-1 therapy [13]. Also, a direct mechanism of B cell-mediated ICI toxicity appears possible via PD-1-expressing CD21^{lo} B cells responding with activation and proliferation in a subset of ipi/nivo-treated melanoma patients, their increase correlating with the frequency, timing, and severity of irAE [e-1].

Against the background that in our patients the ICI-associated antibody responses differed regarding peripheral (antititin/anti-AChR) versus central (anti-Purkinje cells) autoimmune target antigens, both showed evidence of intrathecal inflammation with CSF pleocytosis and CXCL13 elevation, indicating B cell involvement. CXCL13 is a key player involved in Tfh–B cell interactions required for B cell activation, maturation, and antibody production in lymph nodes [14] but also at sites of chronic inflammation including inflamed meninges [15]. CXCL13 exerts its potent chemoattractant activity via the cognate receptor CXCR5, which is expressed on B and Tfh cells [14]. Intrathecal CXCL13 elevations occur in infectious and immune-mediated central nervous system disorders and is strongly associated with CSF pleocytosis and B cell-related activity [14, 16]. Intrathecal B cell activation involving plasma cells and intrathecal antibody synthesis was evidenced in the c-LETM case. Infection being diagnostically ruled out, ICI-associated B cell-mediated toxicity appears likely. Charabi et al. [e-7] reached a similar conclusion in the only other report describing intrathecal CXCL13 elevation in an ICI-associated LETM case with novel patterns of neuronal tissue reactivity. In contrast, the triple M case is the first observation of intrathecal inflammation on top

of myocarditis/myositis/myasthenia-like overlap syndrome, revealing an even broader immune pathology across organ systems. Intrathecal B cell activation was not evident but may have been suppressed by corticosteroid treatment. Instead, immune phenotyping revealed intrathecal enrichment of circulating CXCR5⁺CD4⁺ T cells with depressed PD-1 expression, indicating the presence of possibly overactivated anti-PD-1 off-target Tfh-like cells. The severely altered CD4⁺/CD8⁺ T cell ratio in blood further points at an increased susceptibility for autoimmune processes including (n)irAE.

Besides diagnosis, treatment is another challenge in ICI-mediated toxicity. Consensus guidelines recommend discontinuation of ICIs and intravenous high-dose glucocorticoids in severe cases [17]. However, astonishingly little knowledge exists about exactly how glucocorticoids act and the phenomenon of resistance to glucocorticoids. In cases of corticosteroid-refractory (n) irAE, additional immune therapies such as IVIG and/or plasma exchange may be necessary [18, 19], with the possible ambivalent effect of diluting therapeutic antibodies, thereby weakening tumor control. In the case of myocarditis/myositis/myasthenia, LETM, or paraneoplastic antibodies, long-term active immune suppressants should be considered in addition to steroids, but there is no consensus. Options are broad-spectrum immunosuppressive agents with good blood–brain barrier penetration modulating proinflammatory T cell activity such as cyclophosphamide, or targeted agents such as B cell-depleting rituximab or the anti-tumor necrosis factor antibody infliximab [20].

To conclude, our observations highlight the importance considering the individual immune pathology of patients with nirAEs and emphasize the importance of comprehensive diagnostics and ongoing research on the role of B cells in intrathecal ICI-associated toxicities. Immune phenotyping and screening for pre-existing antititin/AChR antibodies may help in identifying and flagging patients susceptible for severe B cell-mediated toxicity for a rapid, targeted, and possibly life-saving intervention. Especially in cases with evidence of intrathecal CXCL13 elevation, B cell-depleting agents may improve patient outcome. B cell involvement might be less rare than underinvestigated.

AUTHOR CONTRIBUTIONS

Ferdinand Otto: Writing – original draft; writing – review and editing; conceptualization; methodology; validation; investigation.

Michael Seiberl: Writing – review and editing. **Lara Bieler:** Writing – review and editing. **Tobias Moser:** Writing – review and editing. **Waltraud Kleindienst:** Writing – review and editing. **Walter Wallner-Essl:** Visualization. **Peter Koelblinger:** Writing – review and editing. **Peter Wipfler:** Writing – review and editing. **Andrea Harrer:** Conceptualization; methodology; supervision; validation; writing – review and editing; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data available upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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