

Case Report

Suspected Severe Immune Effector Cell-Associated Neurotoxicity Syndrome in a Patient with Multiple Myeloma Treated with Elranatamab

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Abstract: Elranatamab, a bispecific antibody (BsAb) targeting CD3 and B-cell maturation antigen (BCMA), has shown promising efficacy in refractory multiple myeloma. There are conflicting data on the prevalence of serious neurological adverse effects, specifically on the prevalence of immune effector cell-associated neurotoxicity syndrome (ICANS). We report a rare case of suspected grade 3 ICANS in a patient affected by stage IIA multiple myeloma on treatment with elranatamab due to lymph node progression. A 79-year-old man was admitted to hospital due to weakness of the trunk and lower limbs, slow speech and ideomotor slowing that had developed two days after his last administration of elranatamab. The neurological symptoms rapidly progressed to confusion, focal seizures and disorientation. He was febrile, blood tests showed leukopenia, thrombocytopenia and high C-reactive protein (CRP) and procalcitonin (PCT). Brain computed tomography (CT) scan was negative, and electroencephalogram (EEG) showed generalized slowing with no epileptiform abnormalities. Brain magnetic resonance imaging (MRI) showed severe global parenchymal atrophy and severe chronic microangiopathy. Cerebrospinal fluid (CSF) analysis was not performed because of thrombocytopenia. Grade 3 ICANS was suspected although the coexistence of a septic event could not be excluded. Dexamethasone and levetiracetam were prescribed. After a rapid clinical worsening due to severe sepsis and recurrent Salmonella infection, the patient died. Only a few cases of $\geq$ grade 3 ICANS have been described in the literature. Clinicians should be aware of the potential severe neurotoxicity of BCMA-targeted therapies so that they can promptly recognize it during the diagnostic process.

Keywords: Elranatamab; Immune Effector Cell-Associated Neurotoxicity Syndrome; Multiple Myeloma

1. Introduction

Elranatamab is an effective drug for triple-class-exposed relapsed/refractory multiple myeloma (TCE-RRMM) [1]. Common adverse events include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) even if their incidence appears to be lower than in other B-cell maturation antigen (BCMA)-

targeted therapies [2]. We present a case of a patient with multiple myeloma and neurological symptoms with unclear aetiology. The differential diagnosis included sepsis-associated encephalopathy and grade 3 ICANS following elranatamab administration.

2. Case Report

A 79-year-old man was diagnosed with stage IIA multiple myeloma in February 2010. He initially received bortezomib, dexamethasone and thalidomide, followed by autologous stem cell transplantation (ASCT) in June 2010. He had diabetes and he was treated with insulin. The patient had a history of thyroidectomy for hyperplastic nodule, colon diverticulosis, gallbladder microlithiasis, previous perianal abscess and previous sepsis due to *Streptococcus pneumoniae*. He had no history of headache, seizures or neurological abnormalities. In November 2014 second-line therapy with bortezomib and dexamethasone was administered due to evidence of disease progression. In March 2015 hematopoietic stem cell mobilization therapy with plerixafor and subsequent ASCT were performed. Consolidation therapy with bortezomib and dexamethasone was subsequently administered for a total of two cycles. In April 2018, due to evidence of bone progression of the disease on positron emission tomography (PET) and magnetic resonance imaging (MRI), third-line therapy with carfilzomib, lenalidomide and dexamethasone was performed and then discontinued due to an infectious complication (pleural empyema) and a deterioration in performance status. In January 2020, fourth-line therapy with daratumumab, lenalidomide and dexamethasone was administered. Subsequently, radiotherapy was performed on the cervical spine with a total dose of 14 Gray.

In November 2024, cervical lymphadenomegaly compatible with extramedullary localization of multiple myeloma was identified and a fifth-line therapy with subcutaneous elranatamab was prescribed according to the recommended dose-escalation schedule. The patient received 12 mg on day 1 followed by 32 mg on Day 4 and 76 mg on Day 8. Treatment was continued at 76 mg once weekly (**Figure 1**). During the ramp-up phase the patient experienced an accidental fall without loss of consciousness followed by progressive bed rest. Approximately 36 h after administration of the first incremental dose he developed fever, mild desaturation and worsening asthenia raising suspicion of grade 1 CRS. Blood cultures were negative and the episode rapidly resolved after administration of antibiotic prophylaxis with amoxicillin/clavulanate and paracetamol.

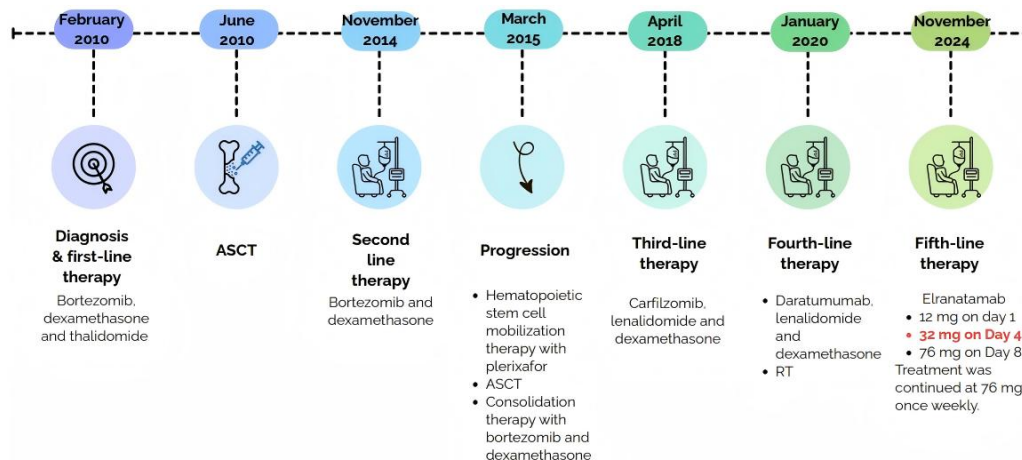


Figure 1. Chronological timeline of the clinical history.

Note: Autologous stem cell transplantation (ASCT), radiotherapy (RT).

During the sixth week of elranatamab treatment, two days after the last administration, the patient developed acute neurological symptoms, including weakness of the trunk and lower limbs with complete inability to maintain an upright posture or walk, slow speech and ideomotor slowing. The neurological examination revealed impaired attention and disorientation, as well as difficulty following commands and expressing needs, which resulted in significantly impaired written and verbal communication. No focal motor or sensory deficits were identified. There was no clinical evidence of seizures. The patient was evaluated by a neurologist who raised the clinical suspicion of grade 3 ICANS according to American Society for Transplantation and Cellular Therapy (ASTCT)

consensus criteria. The Immune Effector Cell-Associated Encephalopathy (ICE) score was 2/10. The patient initially refused hospital admission and was discharged with corticosteroid therapy. Shortly thereafter, in January 2025 he was admitted to the emergency room with fever, hypotension, confusion, focal seizures and disorientation. Blood test revealed leukopenia (white blood cell count: 2,800 cells/uL; reference range: 4,000–10,000 cells/uL), thrombocytopenia (platelet count: 28,000/uL; reference range: 150,000–450,000/uL), elevated C-reactive protein (CRP) levels (23 mg/dl; reference range 0–0.5 mg/dl) and elevated procalcitonin (PCT) levels (18 ng/ml; reference range 0–0.5 ng/ml). Blood gas analysis showed lactic metabolic acidosis. Brain computerized tomography (CT) scan was negative. Sepsis-related clinical deterioration was suspected and empirical antibiotic therapy with piperacillin/tazobactam was initiated; following positive blood cultures for *Escherichia coli*, therapy was subsequently switched to ceftriaxone. Additionally, azithromycin was prescribed following the onset of diarrhoea. Stool cultures were positive for *Salmonella* and negative for *Clostridium difficile*.

Given the medical history, clinical examination and laboratory data, a clinical suspicion of an underlying grade 3 ICANS was raised. According to the international ICANS management recommendations, dexamethasone 10 mg intravenous (IV) every 6 hours and levetiracetam 1,000 mg IV every 12 h were prescribed [3]. Dexamethasone was administered for 48 hours, and then the dose was progressively tapered to 10 mg IV every 12 h for 24 h followed by 5 mg IV every 12 h for 24 h and then discontinued. Electroencephalogram (EEG) performed one day after initiation of antiseizure therapy showed generalized slowing without epileptiform abnormalities. Levetiracetam was continued for 3 weeks and subsequently discontinued. No additional immunomodulatory therapy was administered. Brain MRI showed severe global parenchymal atrophy and severe chronic microangiopathy but no cerebral oedema. Cerebrospinal fluid (CSF) evaluation was deferred due to an unfavorable risk-benefit ratio stemming from concurrent thrombocytopenia and sepsis (platelet count threshold: 30,000/uL for oncology patients), particularly because MRI did not reveal findings suggestive of central nervous system (CNS) infection. Platelet transfusion was not considered. A gradual improvement in the patient's clinical condition and a reduction in inflammatory markers were observed, probably due to a positive response to antibiotic therapy which acted as an important confounding factor in the diagnostic process. Atrial fibrillation was also detected after clinical improvement. He began a physical therapy rehabilitation program with partial benefit because of the recurrence of orthostatic intolerance, presyncope and exercise intolerance. He was transferred to a long-term care facility. Here the patient worsened, showing a recurrence of diarrhoea, fever and hypotension indicating severe sepsis. Blood and stool cultures were still positive for *Salmonella*. After a rapid clinical deterioration, the patient died of septic shock. In our opinion, it was a probable complication of a late cycle of elranatamab which developed in a clinical condition already compromised by suspected ICANS.

3. Discussion

TCE-RRMM describes patients who have relapsed after or are refractory to the three main therapeutic classes: immunomodulatory drugs, proteasome inhibitors and anti-CD38 monoclonal antibodies. BCMA is a cell surface protein widely overexpressed on malignant plasma cells thus making it an ideal treatment target for patients with TCE-RRMM. BCMA-directed therapies include antibody-drug conjugates, chimeric antigen receptor (CAR) T-cells and bispecific antibodies (BsAbs) [4]. CAR T-cell therapy is a form of immunotherapy in which a patient's own T cells are genetically engineered to express CARs on their surface. These receptors enable T cells to recognize and bind to specific antigens expressed on cancer cells, thereby enhancing their ability to target and kill malignant cells [5]. Elranatamab, a BsAb targeting CD3 and BCMA, has shown promising efficacy in TCE-RRMM [2]. Common serious adverse events include neutropenia, infections (69.9%), anaemia, lymphopenia and thrombocytopenia (which usually occur during later cycles), as well as CRS and neurologic problems collectively called ICANS (which are actually observed during early cycles) [2].

CRS is caused by the massive activation and proliferation of T cells responsible for the release of large amounts of proinflammatory cytokines. This process causes a systemic response characterized by fever, hypotension, hypoxia and, in the most severe cases, multiorgan dysfunction. ICANS is considered the most severe complication of CAR-T cell therapy which occurs in 20% to 60% of patients (severe ICANS accounts for 12% to 30% of cases) [6].

The MagnetisMM-3 trial, a multicenter open-label phase 2 study, reported an elranatamab-associated CRS and ICANS incidence of 56.3% and 3.3% respectively. All CRS and ICANS events were grade 1 or 2 and the median time to onset was 2 days for CRS, mostly after the first three doses and with the step-up doses [1]. The onset of

ICANS occurs approximately 5 days following CAR-T cell infusion but it can occur more than 3 weeks after CAR-T cell infusion [7]. Higher B cell tumour burden, older age, CAR-T dose and use of fludarabine increase ICANS risk. Elevated serum CRP, cytokines and CRS symptoms predict neurotoxicity. Pre-existing neurological conditions and CAR constructs influence ICANS likelihood [8]. The earliest manifestations of ICANS are tremor, dysgraphia, impaired attention and apraxia. Expressive aphasia, especially naming objects, is a very specific symptom of ICANS and may progress to global aphasia. Other clinical manifestations include myoclonus or tremor, increased tone, mild lethargy progressing to obtundation, stupor or even coma. Mild symptoms may appear with fever but the progression to severe neurotoxicity may rapidly develop [8]. ICANS is a clinical diagnosis; CSF analysis, EEG and MRI are mainly useful in ruling out alternative diagnoses. Specifically, they allow the detection of any subclinical electrographic seizures and diffuse cerebral oedema respectively. The latter is a rare, fulminant complication the pathophysiology of which remains unclear. The available data show some clinical variability in the presentation of neurotoxicity associated with different CAR products [9]. Although the toxicities associated with BCMA-targeted T-cell-redirecting therapies are similar due to their mechanisms of action, the frequency and severity may vary between agents appearing to be very low in elranatamab-associated therapy (no Parkinson-like or fatal neuropathy events) [1]. Supportive treatments for ICANS include corticosteroids, tocilizumab and levetiracetam for seizure prophylaxis.

Neurological symptoms are a common clinical manifestation associated with different conditions: hepatic failure, severe hypertension, eclampsia, infections, electrolyte imbalances and treatments involving immunosuppressive or cytotoxic drugs. It may be challenging to clearly identify the underlying condition. ICANS may also present with overlapping features of other encephalopathies. Its remarkable clinical presentation is an awake, mute patient who is unresponsive verbally and physically to examination [9]. ICANS is classified in grade 1 to 4. Its grading is based on the ICE score integrated into an overall neurologic assessment (**Table 1**). A patient with an ICE score of 0 is not automatically grade 4 unless the other criteria defining grade 4 are met (**Table 2**).

Table 1. Immune Effector Cell-Associated Encephalopathy (ICE) assessment according to American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria [9].

ICE Assessment	Score
Orientation: oriented to year, month, city, hospital	4
Naming: able to name 3 objects (e.g., clock, pen, button)	3
Following commands: able to follow a simple command	1
Writing: ability to write a standard sentence	1
Attention: able to count backwards from 100 by tens	1
Maximum ICE score	10

Table 2. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) grading according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria [9].

ICANS Grade	ICE Score	Level of Consciousness	Seizures	Motor Findings	Raised Intracranial Pressure/Cerebral Oedema
Grade 1	7–9	Awakens spontaneously	N/A	N/A	N/A
Grade 2	3–6	Awakens to voice	N/A	N/A	N/A
Grade 3	0–2	Awakens only to tactile stimulus	N/A	N/A	N/A
Grade 4	0	Patient is unarousable or requires vigorous or repetitive tactile stimulation to achieve or maintain arousal	Prolonged seizure ≥ 5 min or repetitive clinical/electrical seizures without return to baseline between seizures	Deep focal motor weakness such as hemiparesis	Diffuse cerebral oedema, decerebrate or decorticate posturing, or cranial nerve VI palsy

Note: ICANS grading is determined by the most severe event among the individual neurological domains. The ICE score is one component of the overall assessment and should be interpreted together with level of consciousness, seizures, motor findings and signs of intracranial hypertension/cerebral oedema.

Factors associated with a higher risk of ≥ grade 3 ICANS include higher disease burden, low platelet count and the early development of severe CRS. Data from pivotal studies report a very low incidence of grade 3–4 ICANS [1–3]. This is in contrast with data collected in real-world reports and multicenter studies. ICANS usually overlaps and correlates with CRS thus causing an augmentation in cardiovascular risk [5].

ICANS is associated with an increase in inflammatory cytokines in the CSF resulting in an alteration of the blood-brain barrier (BBB) which allows inflammatory mediators and immune cells to enter the CNS causing neurotoxicity.

Excessive cytokine release can damage endothelial cells potentially resulting in brain oedema or microhemorrhages. The interaction between these elements leads to a cascade of immuno-inflammatory events involving endothelial cells, astrocytes, microglia and plasma mediators. In addition, CAR-T cell therapy probably induces a higher release of cytokines in the bloodstream compared to BsAbs. However, further investigations are needed [3].

Compared with CAR-T cell therapy, ICANS appears to be relatively uncommon with elranatamab; however, the available evidence is largely derived from clinical trials and may underestimate the incidence in routine clinical practice. In the pivotal phase 2 MagnetisMM-3 study, ICANS occurred in 3.3% of patients receiving elranatamab at the recommended dosing schedule [1]. Most cases occurred after the first step-up dose (2.7%) while one patient (0.5%) developed ICANS after the second step-up dose and another (0.5%) after subsequent doses. Recurrent ICANS occurred in 1.1% of patients. The median time to onset was 3 days after the most recent dose (range 1–4 days) and the median duration was 2 days (range 1–18 days). Importantly, ICANS can occur concurrently with CRS, following resolution of CRS or in the absence of CRS [1].

Real-world experience suggests that the incidence may be more variable than reported in pivotal trials. In a recent multicenter U.S. retrospective cohort of 130 patients receiving commercial elranatamab, ICANS occurred in 17% of patients, with grade ≥ 2 events in 7.7%. The median time to onset was 2 days (range 0–21 days), and the median duration was 2 days (range 1–10 days) [10]. Conversely, a French real-world cohort reported ICANS in 3% of patients, with all events being grade 1–2 [11]. These differences may reflect the broader and more heterogeneous population treated in routine practice, including older and frailer patients, greater comorbidity burden, prior BCMA-directed therapy, differences in disease characteristics and variations in monitoring and supportive-care strategies.

The pathophysiology of ICANS is not completely understood. Most data were obtained from CAR-T-cell therapy and caution is required when generalising the pathophysiological mechanisms to T-cell-engaging BsAbs. Current evidence supports a multifactorial model in which systemic immune activation, endothelial dysfunction, disruption of the BBB and subsequent CNS inflammation contribute to neurotoxicity [12–14].

Systemic activation of immune effector cells and host myeloid cells may result in the release of pro-inflammatory cytokines, including interleukin-1 (IL-1) and interleukin-6 (IL-6). Preclinical studies have demonstrated a differential role of monocyte-derived IL-1 and IL-6 in CAR-T-cell-associated CRS and neurotoxicity, supporting the contribution of myeloid-cell-mediated inflammation to these toxicities [13]. In addition, translational studies in patients treated with CD19-directed CAR-T cell therapy have demonstrated endothelial activation, increased BBB permeability and vascular dysfunction in patients with severe neurotoxicity, providing evidence for the role of endothelial injury and BBB disruption in ICANS [14].

Further studies have suggested that inflammatory mediators and interactions between peripheral immune cells, endothelial cells and central nervous system-resident cells may contribute to CNS inflammation and neurological dysfunction. However, the relative contribution of astrocytes, microglia, specific cytokine pathways, and other cellular mechanisms remains incompletely defined, and these mechanisms should therefore be regarded as proposed rather than established [12].

In the setting of elranatamab, these mechanisms are biologically plausible because BsAbs promote T-cell activation and cytokine release; however, direct mechanistic evidence linking these pathways to ICANS induced by elranatamab remains limited.

In the present case, the interpretation is further complicated by concomitant systemic bacterial infection and sepsis which may themselves induce systemic inflammation, endothelial dysfunction, BBB alterations and encephalopathy. Thus, although the clinical presentation and temporal relationship with elranatamab were consistent with ICANS, the diagnosis cannot be established with certainty.

4. Conclusions

The management of ICANS represents one of the most complex and delicate challenges in BCMA-directed therapies. It is a potentially serious and life-threatening toxicity that requires continuous monitoring, a multidisciplinary approach and timely interventions. The prognosis is generally favourable if early recognized. Most cases resolve spontaneously while severe forms may result in long-term neurocognitive complications. The pharmacological treatment of ICANS is primarily based on corticosteroids and supportive care.

An important diagnostic consideration relates to the multifactorial aetiology of the neurological clinical findings probably associated with the overlap between sepsis-associated encephalopathy and elranatamab-related neu-

rotoxicity. At the time of neurological deterioration, the patient had fever, hypotension, leukopenia, thrombocytopenia, markedly elevated inflammatory markers, *Escherichia coli* bacteremia and concomitant *Salmonella* infection that make sepsis-associated encephalopathy an important element to consider in the diagnostic process. Sepsis-associated encephalopathy is a frequent neurological complication of severe systemic infection. It is characterised by altered mental status ranging from confusion and disorientation to more severe disturbances of consciousness. Its pathophysiology is complex and may involve systemic inflammation, endothelial and BBB dysfunction, microcirculatory disturbances and neuroinflammation. Several features may support a suspicion of ICANS in our patient, particularly the temporal relationship with elranatamab administration, the acute neurological manifestations and the documented ICE score of 2/10. However, these findings are not specific for ICANS. The concomitant systemic infection represents a significant confounding factor and an alternative or concomitant potential cause of the neurological manifestations. Further limitations may include the absence of CSF analysis and the non-specific findings of MRI and EEG.

Taken together, these findings support the clinical suspicion of ICANS but do not allow a definitive diagnosis. We consider grade 3 ICANS a likely contributor to the clinical presentation, although a definitive diagnosis cannot be established given concurrent sepsis and lack of CSF analysis. The patient probably developed complications of both early and late cycles of elranatamab respectively.

Author Contributions

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Institutional Review Board Statement

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Informed Consent Statement

Written informed consent for publication of this case report and any accompanying images was obtained from the patient.

Data Availability Statement

The data supporting this case report are available from the corresponding author upon reasonable request, subject to applicable patient privacy and confidentiality requirements.

Conflicts of Interest

The authors declare no conflict of interest.

AI Use Statement

The authors declare that no artificial intelligence (AI) tools were used in the preparation of this manuscript.

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