The Turkish Journal of Pediatrics 2023; 65: 523-530
https://doi.org/10.24953/turkjped.2022.598

Case Report

Rhombencephalitis and longitudinal extensive myelitis associated with dinutuximab use in high-risk neuroblastoma

Fırat Atak[1], Güzide Burça Aydın[2], İbrahim Öncel[3], Sibel Öz[3], Kader Karlı Oğuz[1]

[1]Department of Radiology, Hacettepe University School of Medicine Ankara; [2]Department of Pediatric Oncology, Hacettepe University School of Medicine Ankara; [3]Department of Pediatric Neurology, Hacettepe University School of Medicine Ankara, Türkiye.

ABSTRACT

Background. Dinutuximab is a monoclonal antibody that targets the GD2 antigen used in the treatment of high-risk neuroblastoma. Dinutuximab-associated rhombencephalitis and myelitis is a rare, steroid-responsive, serious, but reversible pathology. To date, three transverse myelitis cases and one rhombencephalitis case due to dinutuximab have already been reported. Moreover, a recently published article identified five inflammatory CNS demyelination cases (four myelitis and one rhombencephalitis). We present a 5-year-old patient with rhombencephalitis and myelitis following dinutuximab-beta treatment.

Case. A 5-year-old patient with a left-sided retroperitoneal mass infiltrating the left kidney and multiple lytic bone lesions was diagnosed with neuroblastoma with a percutaneous biopsy from the abdominal mass. Surgery was performed after a prominent treatment response was detected on the abdominal CT. Radiotherapy was applied to the abdomen. While she was still undergoing maintenance treatment with 13-cis retinoic acid, a metaiodobenzylguanidine (MIBG) scan detected new bone lesions, and brain MRG identified pachymeningeal involvement. A new chemotherapy regimen was started and decreased MIBG uptake was seen in all previous bone lesions. However, newly developed eighth rib metastasis was seen in the following MIBG scan. Autologous stem cell transplantation was done. Soon after, dinutuximab-beta, together with temozolomide and irinotecan, was initiated. Following the third cycle hypotension, somnolence, paraparesis, and unilateral fixed dilated pupil were developed. Afterward, hemiballismus-like irregular limb movements were observed. Work-up studies were unremarkable, except for hypodensity in the brain stem on the brain CT. MRI revealed T2 hyperintensity of the brainstem and spinal cord extending from the cervicomedullary junction to the T7 level. Moreover, incomplete contrast enhancement and facilitated diffusion were observed. Imaging findings suggested demyelination. Steroids and intravenous immune globulin (IVIG) treatment were initiated. Both imaging abnormalities and clinical symptoms resolved partially at one month and disappeared at six months.

Conclusions. Awareness of the radiological findings of dinutuximab toxicity will lead to prompt diagnosis and treatment.

Key words: dinutuximab, rhombencephalitis, myelitis, neuroblastoma.

Monoclonal antibody treatment is an emerging and effective modality for cancer treatment. It has become possible with the demonstration of relatively specific surface proteins in cancer cells and the development of monoclonal antibodies in mice with the developing hybridoma technology.[1,2] Cell destruction can be brought about by several mechanisms: direct action (inhibition of cell survival signaling through receptor binding, induction of apoptosis, delivery of a drug or cytotoxic agent by conjugated antibodies), immune-mediated cell killing mechanisms (antibody-dependent cellular toxicity, complement-dependent cytotoxicity, regulation of T cell function) and disruption of tumor vasculature or stroma.[1,2]

✉ Fırat Atak
firatmd@gmail.com

Received 9th June 2022, revised 25th September 2022, 8th March 2023, accepted 26th March 2023.

Gangliosides are glycosylated lipid molecules. Monoclonal antibodies targeting them have been used in the treatment of various tumors. GD2 antigen is an example of a ganglioside, which is found in small amounts on the surface of neurons, skin melanocytes, and peripheral sensory nerves.[3,4] Anti-GD2 monoclonal antibodies are currently used to treat neuroblastoma based on their high expression on the surface of neuroblastoma cells.

Dinutuximab, a monoclonal antibody that targets the GD2 antigen, has been routinely used in the maintenance treatment of pediatric patients with high-risk neuroblastoma who have partially responded to first-line therapy or with relapsed or refractory disease.[3,5] Pain, tachycardia, hypertension, hypotension, fever, and urticaria are the most common side effects of dinutuximab.[3,4]

So far, three cases of transverse myelitis and one rhombencephalitis case associated with dinutuximab have been published in the literature.[3,4] In addition, a recent study reported a case with brain stem lesions and four cases of transverse myelitis due to dinutuximab.[5] However, to the best of our knowledge, there are still no cases involving the spinal cord and brain stem simultaneously, as in our case. Herein, we present a case with some distinct clinical features, concurrent brainstem and spinal cord involvement, and one-year follow-up information.

Case Report

A 5-year-old patient was admitted to our hospital with a large intraabdominal tumor in the left retroperitoneal compartment three days after the ultrasound was conducted due to recurrent abdominal pain. Abdominal computed tomography (CT) revealed a left-sided retroperitoneal mass extending between the suprarenal space and iliac bifurcation (TR 8.7 cm, AP 6.5 cm), infiltrating the left kidney, encircling the renal artery and vein, and crossing to the contralateral side through the retroaortic area. Furthermore, metaiodobenzylguanidine (MIBG) scan identified multiple bone lesions at the time of diagnosis. Neuroblastoma with MYCN amplification was diagnosed from a percutaneous biopsy of the abdominal mass. The bone marrow aspiration biopsy was positive for infiltration. According to the Turkish Pediatric Oncology Group, the patient received a high-risk neuroblastoma chemotherapy regimen, including ifosfamide, doxorubicin, dacarbazine, vincristine, cisplatin, cyclophosphamide, and etoposide. After six months of chemotherapy, CT showed an excellent response to induction chemotherapy with a tumor volume decrease (TR 3.8 cm, AP 1.8 cm). But, the tumor still infiltrated the left kidney and involved the renal hilum. The patient underwent surgery, and the tumor, along with the left adrenal gland, kidney, and perirenal fat (four lymph nodes were metastatic on the pathology specimen), were grossly resected. Following radiotherapy for the abdomen, the MIBG scan was normal. Maintenance treatment with 13-cis retinoic acid was started.[6]

While she was still on maintenance treatment for 18 months, multiple MIBG-positive new medullary bone lesions involving the vertebral column, pelvis, sacrum, bilateral proximal lower extremities, and bilateral orbital walls were detected. Brain MRI revealed some calvarial lesions, some of which were accompanied with soft tissue lesions and pachymeningeal focal thickening, which was suspicious for neuroblastoma involvement. The patient was received six cycles of ifosfamide, carboplatin, and etoposide. Decreased uptake was seen in all previous bone lesions on the first MIBG scan, but two months after a new focal lesion on the left eighth rib was revealed. Afterward, she underwent autologous stem cell transplantation after six courses of busulfan and melphalan. Dinutuximab-beta (DB) with irinotecan and temozolomide (TEMIRI) chemotherapy was initiated due to a lack of regression in bone lesions.

Following the third cycle of DB and TEMIRI, he experienced hypotension, tachycardia,

somnolence, and paraparesis. Also, the patient had a unilaterally fixed dilated pupil. Soon after, left-sided hemiballismus-like high-amplitude irregular movements were detected. In addition, she became unresponsive to verbal stimuli within hours. The chronological flow of chemotherapy protocols, imaging studies, and essential dates from the diagnosis to the incident are shown in Figure 1. Work-up studies were unremarkable, except for an expansile diffuse hypodensity in the brain stem on the CT. A brain MRI revealed swelling and T2 hyperintensity in the brain stem. An incomplete ring enhancement was seen on T1-weighted images following intravenous Gadolinium-based contrast material injection, and the lesions showed facilitated diffusion as shown by increased ADC values. Linear and punctate susceptibility foci in the pons were seen on SWI (Fig. 2). Cervical spinal MRI showed longitudinal extensive T2 hyperintense lesion extending from the cervicomedullary junction to the T7 level, involving most of the spinal cord's cross-sectional area and showing eccentric, patchy contrast enhancement similar to that in the brain stem (Fig. 3). Due to the swelling of the brain stem, a lumbar puncture was not performed. After DB treatment was discontinued, the patient received 30 mg/kg/day pulse methylprednisolone for seven days and 0.4 g/kg/day intravenous immune globulin (IVIG) for five days. Left-sided hemiballismus-like symptoms quickly disappeared, her consciousness began to recover, and she gradually regained lower extremity motor strength. Then, she continued to take prednisolone at a dose of 1 mg/kg/day for 4 weeks. Following the regression of the brainstem and spinal cord lesions on follow-up MRI at one month, steroids were tapered and discontinued in four weeks (Fig. 4).

After her discharge from the hospital, she continued receiving TEMIRI chemotherapy, and her last dose (8th cycle) was in September 2021. At the 9th-month follow-up examination, her neurological examination was normal. The patient still has several sequela bone lesions on the pelvis and bilateral orbital walls. Her last brain MRI was normal except for the stable lesion in the orbital portion of the right frontal bone. She is still in remission. Informed consent was received from the family.

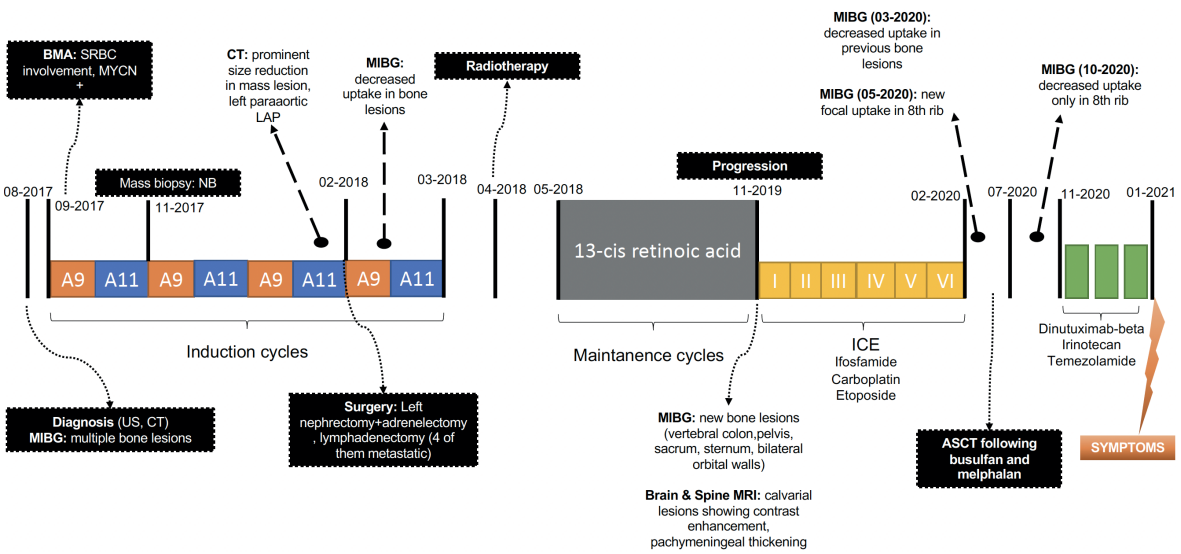

Fig. 1. Flow chart of treatment and important date marks (A9, A11: chemotherapy cycles; BMA: bone marrow aspiration; SRBC: small round blue cell; NB: neuroblastoma; MIBG: Metaiodobenzylguanidine; ASCT: autologous stem cell transplant).

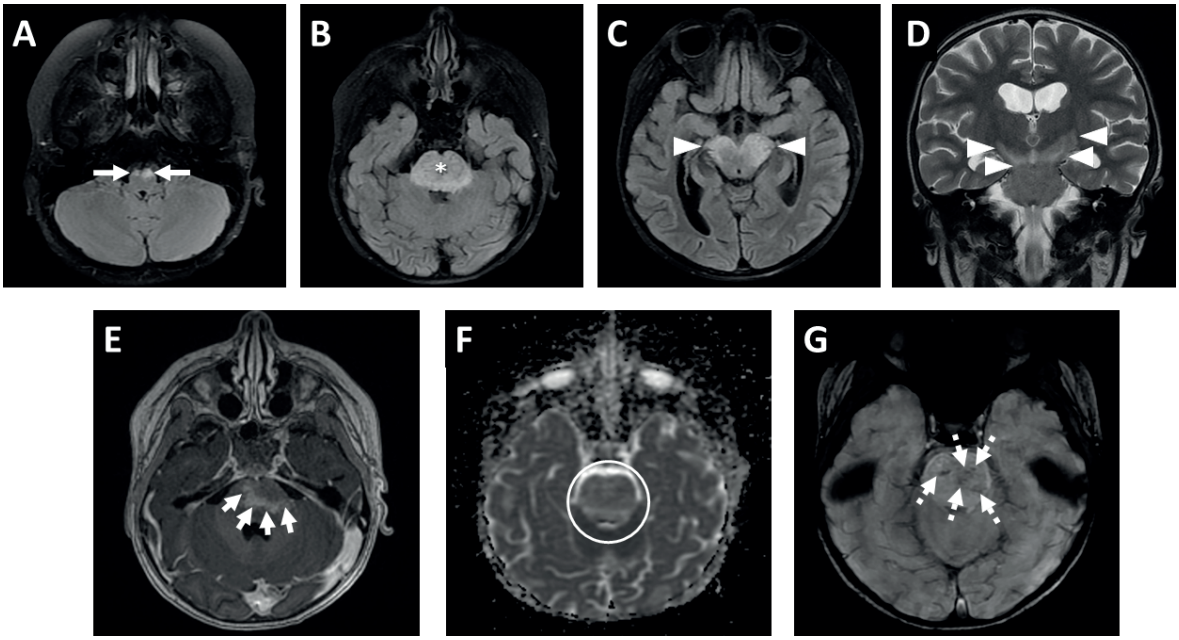

Fig. 2. Brain MRI at the time of diagnosis of a 5-year-old girl with recurrent high-risk neuroblastoma who was unresponsive to verbal stimuli had paraparesis and left unilateral fixed dilated pupil after the third dose of dinutuximab. Axial FLAIR (*A-C*) and coronal T2-weighted (*D*) images demonstrate hyperintense signal on medullary pyramids (*long arrows*), pons (*asterisk*), and cerebral peduncles extending to the left internal capsule posterior limb (*arrowheads*). The lesion also demonstrated incomplete ring enhancement (*short arrows*) on the T1-weighted postcontrast thin-section image (*E*) and increased diffusion (*circle*) on the ADC map (*F*). In addition, linear and dot-like susceptibility foci (*dashed arrow, G*) in the pons on SWI images should be noted.

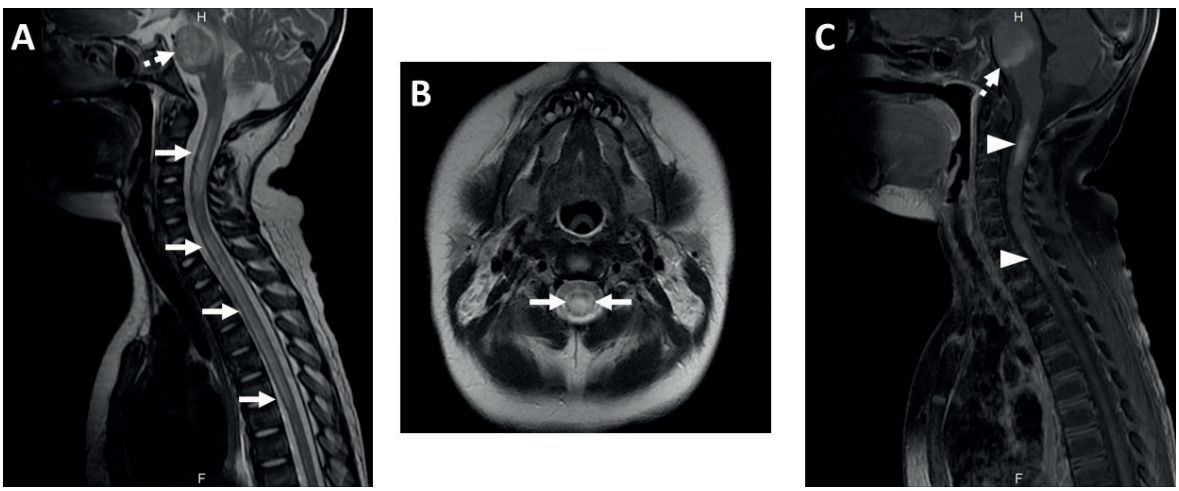

Fig. 3. Sagittal and axial T2-weighted images of spinal MRI performed at the time of diagnosis (*A-B*) demonstrate longitudinally and transversally extensive (*arrows, A*) increased T2 signal extending from cervicomedullary junction to T7, with patchy contrast enhancement (*arrowheads, C*) on sagittal fat-suppressed T1-weighted images. In addition, note large T2 hyperintensity and contrast enhancement (*dashed arrow, A-C*) within the pons.

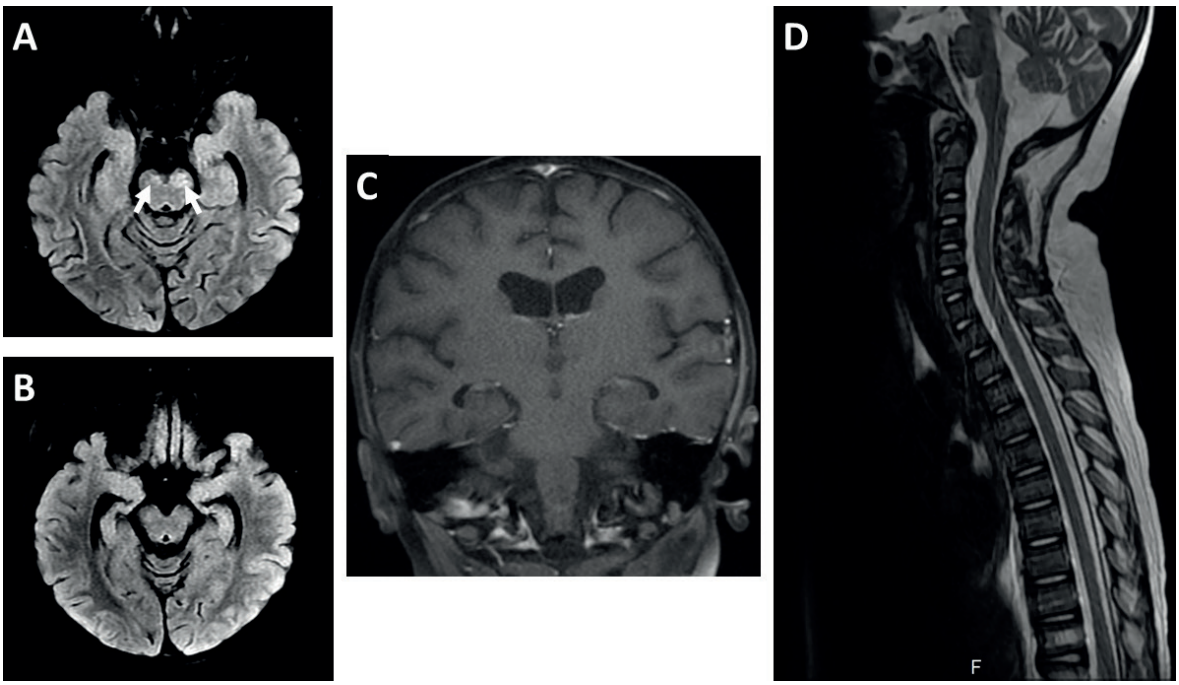

Fig. 4. The residual hyperintensity on bilateral cerebral peduncles on axial FLAIR images (*arrows, A*) after one-month, is completely resolved on six-month follow-up (*B*). Neither contrast enhancement on brain stem on coronal T1-weighted spin-echo image (*C*) nor residual spinal cord lesions on sagittal T2-weighted image (*D*) is seen on one-month follow-up brain and cervicothoracic spinal MRI.

Discussion

Two cases of rhombencephalitis and seven cases of transverse myelitis that developed following dinutuximab therapy have already been described in the literature.[3-5] Herein, we present the first case of concurrent rhombencephalitis and transverse myelitis with a detailed description of peculiar radiological features.

Some monoclonal antibodies might impair the balance of the immune system and promote an abnormal inflammatory reaction and demyelination. Until 2017, of 64 monoclonal antibodies identified, 54 reported with neurological adverse effects including peripheral neuropathy, neuromuscular diseases, polyradiculopathies, myelitis, central nervous system (CNS) demyelinating diseases (multiple sclerosis [MS], MS-like demyelinating multifocal lesions, pre-existing MS exacerbation, neuromyelitis optica spectrum disorder, optic neuritis), CNS non-demyelinating diseases (leptomeningitis, meningoencephalitis, vasculitis, cranial nerve involvement, autoimmune encephalitis).[7,8] Commonly described agents causing neurotoxicities in the literature were TNF-alfa blockers, immune checkpoint inhibitors, and kinase inhibitors.[8,9]

Various central and peripheral neurotoxicities have also been reported in association with anti-GD2 immunotherapy ranging from neuropathic pain, confusion, and sensorimotor neuropathy to coma, seizure, and psychosis.[5] In the Children's Oncology Group trial, in children who received dinutuximab combined with interleukin 2 (IL-2) and granulocyte monocyte - colony stimulating factor (GM-CSF), CNS toxicity manifested as encephalopathy, confusion, psychosis, and coma was reported in 4.4% of patients.[5,10] Furthermore, in the recently published study investigating DB-related central neurotoxicities in a total of 1102 patients at least grade 3 neurotoxicity was found in 4% of the patients and severe neurotoxicity in 2.2%.[5] Also, they concluded that the events

predominantly occurred in the patients receiving combined treatment with DB and IL-2. Reported CNS findings in ten available MRI studies were as follows: four transverse myelitis (one thoracolumbar involvement, two thoracic involvement, and one not reported), one cytotoxic brain stem lesions, two posterior reversible encephalopathy syndrome (PRES), one encephalomyelitis, two encephalitis, one sensory axonal neuropathy, one demyelinating neuropathy of the dorsal roots, one involvement of the vestibulocochlear nerve.[5] One study reported that another chimeric anti-GD2 antibody, m3F8, was associated with PRES in five patients presenting with visual symptoms, headache, and seizure.[11] In our patient, the clinical and radiological hallmarks of PRES were excluded.

Some debates continue regarding the utility of IL-2 and its role in neurotoxicity. It has been previously described that neurotoxicity is more common in those receiving combination therapy with IL-2.[5] Wieczorek et al.[5] reported that the majority of grade 3/4 neurotoxicities (79.5%) occurred in patients treated with DB plus IL-2. Five CNS demyelination cases manifested as myelitis and cytotoxic brain stem lesions due to dinutuximab and IL-2 combination therapy. Our patient was receiving dinutuximab combined with chemotherapy. A case of transverse myelitis developed due to the same treatment regimen was already published by Ding et al.[3]

Our patient had a rapid recovery after treatment with steroids and IVIG. At the 6-month follow-up, no residual clinical symptoms were observed, while some subtle changes were identified within the brain stem. Wieczorek et al.[5] stated that most patients (33/38, 86.8%) with neurotoxicity recovered from symptoms with steroid and IVIG treatment. However, complete resolution was achieved with plasmapheresis in two patients who did not respond to first-line therapy.[5]

Symptoms appeared following the third cycle in our patient. As all patients develop neurotoxicity after consecutive courses with dinutuximab, as reported by Ding et al.[3] and Zama et al.[4], the authors proposed that prior exposure to the drug might cause alloreactivity against neural tissues. However, in another study, the fact that severe neurotoxicity was observed during the first cycle in most patients raises doubt on this interpretation.[5]

Altered consciousness, paraparesis, and unilateral fixed dilated pupil were observed in our patient. In addition, left-sided irregular proximal limb movements were seen, and due to the similarity of hemiballismus, it was evaluated primarily in favor of an extrapyramidal symptom. The neurological symptoms observed in our patient are among the most common symptoms mentioned by Wieczorek et al.[5] Authors reported that the most common side effects were paraparesis or hypotonia, urinary retention, seizures, ataxia or gait disturbances, and cranial nerve palsies.[5] Altered consciousness (somnolence and coma) was reported in three patients, two of which were manifested as encephalitis in MRI.[5] Hyperkinesis, which may be similar to hemiballismus-like limb movements in our patient, was detected in one patient, but the authors gave no other characteristic details. MRI findings of that patient were reported to be compatible with encephalitis. Also, case #1 with fixed pupil and brain stem lesions in the predefined study was similar to our case.[5] In addition, sixth cranial nerve palsy was found to cause strabismus in a patient who manifested as brain stem lesions.[4] In light of these, it should be kept in mind that cases with brain stem involvement may present with cranial nerve palsy.

Brainstem lesions showed T2 hyperintensity, facilitated diffusion, and open-ring contrast enhancement without an accompanying extra-axial mass. These features suggested a tumefactive demyelinating lesion in the brain, which led to the radiological differential diagnosis of inflammatory and demyelinating diseases in this case. These include NMOSD, neuro-Behçet disease (NBD), and neurosarcoidosis (NS), all of

which occur very rarely in childhood. Of these, no area postrema, optic nerve, periaqueductal white matter lesions, or T2 bright spotty lesions in the spinal cord were observed in favor of NMO. Neither of our patients had any systemic findings to suggest other inflammatory diseases like systemic lupus erythematosus (SLE) and Sjögren syndrome (SS), which may present with extensive myelitis rarely in children.[12] Although the MRI pattern of brainstem involvement could suggest NBD, especially in a Turkish patient, diagnosis is challenging in the absence of other clinical components of the disease, mainly oral and genital aphthous ulcers. For NS, which is extremely rare in the pediatric age group, our patient had no systemic manifestations, as seen in approximately 90% of the patients.[13] Our case was on follow-up of high-risk neuroblastoma with no such confounding findings on his already available imaging studies of thoracoabdominal CT and MIBG scan. Although a possible diagnosis in a patient with malignancy and receiving chemotherapy, infectious involvement mainly due to listeria, enterovirus 71, and herpes viruses was precluded due to the absence of fever or systemic findings and lack of relatively specific imaging findings. Neuroblastoma involvement could be considered obvious; however, in the present case, the brainstem and spinal cord were affected intrinsically rather than through external compression or infiltration of an extra-axial mass.[14] Therefore, CNS involvement in neuroblastoma was ruled out.

To summarize, myelitis and rhombencephalitis following DB treatment is a steroid-responsive, serious but transient pathology that can develop mostly after the second dose regimen. Clinical and radiological findings seen in dinutuximab toxicity are, however, nonspecific. Therefore, differentiation can only be made by combining clinical, laboratory, and radiological findings. Considering the efficacy of the steroid treatment, radiologists should be familiar with imaging findings of dinutuximab-related neurotoxicities for prompt diagnosis and treatment.

Ethical approval

Informed consent was received from the family.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: KKO and GBA; data collection: FA; analysis and interpretation of results: FA, IO, SO, KKO; draft manuscript preparation: FA, KKO. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Scott AM, Wolchok JD, Old LJ. Antibody therapy of cancer. Nat Rev Cancer 2012; 12: 278-287. https://doi.org/10.1038/nrc3236
2. Coulson A, Levy A, Gossell-Williams M. Monoclonal antibodies in cancer therapy: mechanisms, successes and limitations. West Indian Med J 2014; 63: 650-654. https://doi.org/10.7727/wimj.2013.241
3. Ding YY, Panzer J, Maris JM, Castañeda A, Gomez-Chiari M, Mora J. Transverse myelitis as an unexpected complication following treatment with dinutuximab in pediatric patients with high-risk neuroblastoma: a case series. Pediatr Blood Cancer 2018; 65: e26732. https://doi.org/10.1002/pbc.26732
4. Zama D, Morello W, Masetti R, et al. Inflammatory disease of the central nervous system induced by anti-GD2 monoclonal antibody in a patient with high risk neuroblastoma. Pediatr Blood Cancer 2014; 61: 1521-1522. https://doi.org/10.1002/pbc.24982
5. Wieczorek A, Manzitti C, Garaventa A, et al. Clinical phenotype and management of severe neurotoxicity observed in patients with neuroblastoma treated with dinutuximab beta in clinical trials. Cancers (Basel) 2022; 14: 1919. https://doi.org/10.3390/cancers14081919

6. Aksoylar S, Varan A, Vergin C, et al. Treatment of high-risk neuroblastoma: National protocol results of the Turkish Pediatric Oncology Group. J Cancer Res Ther 2017; 13: 284-290. https://doi.org/10.4103/0973-1482.183205

7. Gill C, Rouse S, Jacobson RD. Neurological complications of therapeutic monoclonal antibodies: trends from oncology to rheumatology. Curr Neurol Neurosci Rep 2017; 17: 75. https://doi.org/10.1007/s11910-017-0785-3

8. Pérez-De-Lis M, Retamozo S, Flores-Chávez A, et al. Autoimmune diseases induced by biological agents. A review of 12,731 cases (BIOGEAS Registry). Expert Opin Drug Saf 2017; 16: 1255-1271. https://doi.org/10.1080/14740338.2017.1372421

9. Rimkus CM, Schoeps VA, Boaventura M, et al. Drug-related demyelinating syndromes: understanding risk factors, pathophysiological mechanisms and magnetic resonance imaging findings. Mult Scler Relat Disord 2021; 55: 103146. https://doi.org/10.1016/j.msard.2021.103146

10. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med 2010; 363: 1324-1334. https://doi.org/10.1056/NEJMoa0911123

11. Kushner BH, Modak S, Basu EM, Roberts SS, Kramer K, Cheung N-KV. Posterior reversible encephalopathy syndrome in neuroblastoma patients receiving anti-GD2 3F8 monoclonal antibody. Cancer 2013; 119: 2789-2795. https://doi.org/10.1002/cncr.28137

12. Law LY, Riminton DS, Nguyen M, Barnett MH, Reddel SW, Hardy TA. The spectrum of immune-mediated and inflammatory lesions of the brainstem: Clues to diagnosis. Neurology 2019; 93: 390-405. https://doi.org/10.1212/WNL.0000000000008015

13. Ungprasert P, Ryu JH, Matteson EL. Clinical manifestations, diagnosis, and treatment of sarcoidosis. Mayo Clin Proc Innov Qual Outcomes 2019; 3: 358-375. https://doi.org/10.1016/j.mayocpiqo.2019.04.006

14. D'Ambrosio N, Lyo JK, Young RJ, Haque SS, Karimi S. Imaging of metastatic CNS neuroblastoma. AJR Am J Roentgenol 2010; 194: 1223-1229. https://doi.org/10.2214/AJR.09.3203