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Table 1. HDMTX induced neurotoxicity in osteosarcoma patients

No	Study/ Author	Year	Age – Gender	Diagnosis	Route of administration	Signs and symptoms of neurotoxicity	Imaging findings	Onset – timing	Management	Outcome
1	Ayalon I et al.[14]	2019	14-M	Osteosarcoma of the Rt tibia	IV -HDMTX	-status epilepticus/ tonic-clonic seizure -altered mental status -fever	MRI: subtle diffusion restriction in the posterior subcortical white matter, more prominent on the Lt periventricular white matter, extending to the parietotemporal and centrum semiovale area - apparent diffusion coefficient map	5 days after 2nd dose	-aminophylline (2.5 mg/kg/dose per day for 4 days) -high-dose steroids (dexamethasone).	Minimal residual neurological deficits (anisocoria, facial asymmetry, and instability on tandemk gait)
2	Cruz-Carreras MT et al.[20]	2017	2nd patient 17-F	osteosarcoma of the Rt femur	IV -HDMTX & calcium leucovorin rescue	-slurred speech -weakness -numbness on the Rt side of the face and Rt arm -flattening of the Rt nasolabial fold -absent gag reflex -Rt facial paralysis	MRI brain: area of restricted diffusion in the Lt corona radiate and centrum semiovale without any associated FLAIR signal abnormality or enhancement	5 days after a course of IV MTX	-aminophylline -DM (30 mg po) -leucovorin after the episode	-Symptoms resolved in 4 h but recurred after an MRI was performed, with Rt facial paralysis -Symptoms resolved completely 2 days after treatment
3	Afshar M et al.[29]	2014	14-F	Osteogenic sarcoma	IV HDMTX	-Waxing and waning sensorium and mild dysmetria	N/R	2 days after the last dose of MTX	-DM 2.5 mg/kg q.d. for 2 days	-Symptoms resolved in 24 h
4	Dropcho EJ.[12]	2011	12-M	osteosarcoma of the Rt femur	IV HDMTX	-confused and agitated -Lt arm and leg weakness -Rt arm weakness -mild lethargy -slurred speech	- CT scan: unremarkable - Brain MRI scan: 1. T2-weighted and FLAIR images: several areas of hyperintense signal in the centrum semiovale bilaterally, worse on the Rt side. The lesions did not enhance with gadolinium. 2. Diffusion-weighted and ADC images: consistent with acute cytotoxic edema	4th day after the 3rd cycle	- leucovorin -aminophylline IV	-Symptoms resolved completely in 7 days of onset

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5	Müller J et al.[30]	2008	10-M	Osteosarcoma of the Lt fibula	HDMTX infusion	-somnolent -urinary incontinency -decreased reflexes -mild nystagmus -narrow pupils, but reactive to light	N/R	20 minutes after the end of the 1st HDMTX infusion	-Parenteral dexamethasone - Forced diuresis with 4000ml/ m^2 infusion with furosemide every 6 hours -Calcium folinate	-Neurological symptoms resolved in 24h
6	Inaba H et al.[31]	2007	Patient 1: 14-M	Patient 1: Osteosarcoma	Patient 1: IV HDMTX	Patient 1: -hemiparesis -bilateral weakness -dysphasia -confusion / emotionality	Patient 1: MRI (2 days after the onset): 1. Restricted diffusion on DWI 2. Increased T2 and/or FLAIR signal Anatomic locations: 1. Unilateral cerebral white matter (focal) 2. Bilateral corticospinal tracts in the Internal capsule and midbrain (focal)	Patient 1: 8 days after the 5th course of HDMTX	Patient 1: -aminophylline -lorazepam	Patient 1: -Symptoms resolved in 3 days
7	Mittal R et al.[4]	2005	10-M	Osteosarcoma of the Lt proximal tibia	HDMTX & calcium leucovorine	-diplopia -one episode of seizures -disorientation -semiconscious -ophthalmological examinations: mild abnormality in the conjugate movements of the eyes, with essentially normal fundi	-CT brain: normal -MRI brain (14 days after the 5th dose of HDMTX): normal	3 days after the 5th dose of HDMTX	-oropharyngeal suction -oxygen was givenby face mask -moved to the ICU for supportive care	-Symptoms resolved completely in 48h
8	Drachtman RA et al.[15]	2002	Patient 1: 16-M Patient 2: 13-M	Osteogenic sarcoma both patients	IV HDMTX	Patient 1: -Dysarthria -CN VII palsy Patient 2: -Rt CN VII palsy -Lt hemiparesis -dysarthria -impaired gag	Patient 1: -MRI: normal -CT: normal Patient 2: -MRI: normal -CT: normal -MRA: normal	Patient 1: 7 days after last MTX Patient 2: 7 days after last MTX	Patient 1: DM 1 mg/kg x 1 Patient 2: DM 1 mg/kg TID	Patient 1: -Symptoms resolved in 30 minutes Patient 2: -Symptoms resolved in 3 days
9	Kiu MC et al.[21]	1994	16-M	Osteogenic sarcoma of the Lt femur	HDMTX infusion & leucovorin rescue	-alternative hemiparesis -dysarthria -intermittently stuporous, agitated, confused	CT brain: normal	5 days after the 2nd course of HDMTX	-IV leucovorin 100mg (every 6h for 3 days)	-Symptoms resolved completely in 72h

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10	Walker RW et al.[17]	1986	19 patients Age range: 13-42 14M/5F	osteogenic sarcoma (8 patients with lung metastases)	IV HDMTX & leucovorin rescue -8 patients: IV vincristine 1 day following the HDMTX -6 patients: were treated with bleomycin, cyclophosphamide, and dactinomycin	-behavioral abnormalities (inappropriate laughter, lethargy, unresponsiveness) -focal sensorimotor or reflex signs (mono- or hemiparesis with aphasia +/- paresthesia or numbness) -generalized seizures -signs alternated from one side to the other	CT brain: normal	-1-13 days after treatment -after 1 dose: 1 patient -after 2 doses: 9 patients -after 3 doses: 3 patients -after 4 doses: 4 patients -after 5 doses: 1 patient -after 6 doses: 1 patient	No specific treatment	-Usually lasted from 15 minutes to 72 hours -Resolved abruptly
11	Jaffe N et al.[19]	1985	9 patients average age 12 years (3F/6M)	Osteosarcoma	HDMTX-CFR *Patient 2: concurrently with cisplatin	Patient 1: **a)** -Lt Facial weakness -Lt upper limb paresis -sleepy -uncooperative -no response to painful stimuli **b)** -Rt Facial weakness -speech impediment-Broca-type aphasia -Rt hemiparesis Patient 2: **a)** -Speech impediment -Lt upper extremity weakness **b)** -Rt Facial weakness -Rt upper limb paralysis -dystonic movements -speech impediment -emotional disturbances Patient 3: **a)** Focal facial seizure, loss of consciousness	Patient 1: CT scan: normal Patient 2: CT scan: normal Patient 3: CT scan: normal Patient 4: CT scan: Slight enlargement of ventricles	Patient 1: a) day 5 (2) * b) day 4-5 (7) Patient 2: a) day 16 (4) b) day 9 (5) Patient 3: a) day 6 (39) b) day 1 (40) Patient 4: a) day 2 (2) b) day 26 (6)	N/R	-Symptoms resolved in all patients -HDMTX-CF treatment was reinstituted in all patients -Recurrent neurologic dysfunction in 5 of the 9 patients. -Complete resolution in all patients again. -No permanent neurologic deficit

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						b) Generalized seizure Patient 4: **a)** -twitching of hand and eyebrow -nystagmus -convulsion and loss of consciousness -status epilepticus with Lt frontal cerebral predominance **b)** Convulsion Patient 5: **a)** Generalized seizure lasting approximately 1h **b)** Status epilepticus lasting 1-2 days Patient 6: Rapidly progressive ascending neuromuscular paralysis extending to bulbar area Patient 7: Generalized seizure, loss of consciousness Patient 8: Grand mal seizure, intermittent loss of consciousness for 24 hr Patient 9: -bitemporal headache -weakness Lt arm -slurring of speech		Patient 5: a) day 6 (9) b) day 4 (11) Patient 6: day 7 (N/R) Patient 7: day 50 (20) Patient 8: day 4 (15) Patient 9: day 8 (6)		

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12	Fritsch G et al.[32]	1984	12-F	Osteogenic sarcoma of the Rt humerus metastatic to the Rt lung	HDMTX infusion	-slurred speech -unable to swallow -bilateral paresis of the external rectus eye muscles -ataxia -Rt hemiparesis	CT scan: -16 days after the HDMTX infusion: periventricular hypodensity, particularly around the frontal horns -14 months after the HDMTX infusion: areas of decreased attenuation around the frontal horns, and a hypodense lesion in the left temporal lobe	9h after the completion of the 11th HDMTX infusion	-calcium leucovorin l00 mg every 3 hours -forced diuresis	-Symptoms resolved completely after 30 hours -Five years after the episode: absent deep tendon reflexes, no other sign of neurologic dysfunction
13	Packer RJ et al.[22]	1983	Patient 1: 6-F Patient 2: 18-F	Patient 1: osteogenic sarcoma of the Lt femur Patient 2: osteogenic sarcoma of the Lt distal femur metastatic in the lung	Patient 1: HDMTX-CFR Patient 2: HDMTX-CFR	Patient 1: -brief trance-like episodes without loss of postural tone or associated motor movements and intermittent episodes of visual loss - unconsciousness followed by Lt body tonic-clonic seizure -Examination: Lt hemiparesis involving face and arm greater than leg without sensory loss. Patient 2: -Lt sided weakness of the face, arm, and leg and decreased sensation of the Lt arm. -Examination: slurred speech without aphasic difficulties and Lt hemiparesis involving face, arm, and leg equally	Patient 1: -CT brain: a large noncontrast enhancing hypodense lesion in the Rt posterior frontal lobe - Contrast-enhanced CT and a brain scan (10 days later): normal Patient 2: -Contrast-enhanced CT: normal -Brain scan (4 days later): normal - Contrast-enhanced CT (10 days later): normal	Patient 1: 5 days after the 3rd course of HDMTX-CF Patient 2: 6 days after the 2nd dose of HDMTX-CF	Patient 1: -Valium -phenobarbital -phenytoin Patient 2: N/R	Patient 1: -Symptoms resolved completely -Within one hour: fully alert, oriented and seizure free. -Cleared her hemiparesis over 72 hours. Patient 2: -Symptoms resolved in 5 days

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14	Allen JC et al.[18]	1978	Patient 1: 22-M Patient 2: 21-M Patient 3: 13-F Patient 4:18-M	Patient 1: osteogenic sarcoma of the Rt femur Patient 2: osteogenic sarcoma of the Rt pelvis Patient 3: osteogenic sarcoma of the Lt humerus Patient 4: osteogenic sarcoma of the Rt femur	Patient 1: VCR HDMTX CFR Patient 2: VCR HDMTX CFR Patient 3: BCD 4 bi-weekly HDMTX CFR VCR Patient 4: BCD VCR HDMTX CFR	Patient 1: -Rt hemiparesis and aphasia -Lt hemiparesis with Lt sided focal seizures Patient 2: -Lt gaze palsy -Lt hemiparesis -dysarthria -bilateral Babinski signs -intermittently stuporous, agitated, and confused Patient 3: -headache, dizziness, photophobia, and fever -Lt hemiparesis -Rt hemiparesis -dysarthria -extreme emotional agitation Patient 4: -dysarthria -dysphasia -palsies of the Lt 9th, 10th,11th, and 12th cranial nerves -Lt hemiplegia, and Lt hemianesthesia	Patient 1: -Contrast-enhanced CT head: normal. -Bilateral carotid angiogram: normal Patient 2: -Contrast-enhanced CT head: normal. -CAT scan (10 months later): area of decreased density in the Rt frontal lobe, consistent with old ischemic infarction. Patient 3: Contrast-enhanced CT head: normal CT scan (3 months later): normal Patient 4: -Contrast-enhanced CT head: normal -CT scan (6 months later): normal -Bilateral carotid angiography: normal	Patient 1: 13 days after the 2nd course of CMT Patient 2: 32 days after the 1st course of BCD/ 10 days after the 3rd course of HDMTX Patient 3: 2 months after the last BCD/8 days after the 4th course of HDMTX Patient 4: 14 days after the 1st BCD / 9 days after the 1st course of VCR/HD MTX	Patient 1: N/R Patient 2: heparinization for 72 hours Patient 3: N/R Patient 4: N/R	Patient 1: -Gradually improved -Residual mild Rt hemiparesis Patient 2: -Symptoms resolved completely in 3 days -Died of metastatic disease 18 months later -Autopsy: no gross or microscopic abnormalities of the brain Patient 3: 3 months later: mild Rt hemiparesis Patient 4: Symptoms resolved completely

Notes: * No. of courses prior to neurologic events in parenthesis;

Abbreviations: M, male; F, female; Lt, left; Rt, right; DM, dextromethorphan; CFR, citrovorum factor rescue; VCR, Vincristine; CMT, chemotherapy; MRI, Magnetic resonance inaging;CT, Computer tomography; BCD,Bleomycin, Cyclophosphamide, Actinomycin D; N/R, not reported.

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MTX, as part of the MAP regimen, is administered at a dose of 12 g/m² intravenously, where a dose greater than 500 mg/m² is defined as high [1,9,23]. In order to decrease the risk of MTX induced toxicity, supportive measures should be taken. Some of these measures include hydration, urine alkalization, avoid the coadministration of drugs that interact with MTX, dose reduction in case of renal impairment, and folinic acid administration. The administration of larger doses of folinic acid has been related to better outcomes regarding the prevention of neurotoxicity following treatment with HDMTX [24]. Nevertheless, the time and dose of administration as part of the rescue protocol has been repeatedly debated. Conclusively if folinic acid rescue is given in sufficiently high enough dose 24-36 hr after the initiation of treatment with MTX most neurotoxic events should be prevented [25]. Serum MTX, creatinine levels and urine output should be measured repeatedly as well. However, in some cases, including ours, these actions do not prevent the development of toxicities [1,23]. It should be mentioned that most cases who develop MTX induced neurotoxicity appear to have normal MTX plasma levels, something that was observed in our case as well [9].

All patients who develop neurological symptoms and signs after the treatment of HDMTX should undergo further investigation [9]. The investigation in our case included an appropriate history, clinical examination, brain CT scan and MRI, and lumbar puncture. Brain CT scan and lumbar puncture usually do not reveal any abnormal findings in acute MTX induced neurotoxicity, as in our case [8,9]. MRI findings may include (diffuse or focal) restricted diffusion in subcortical white matter involving the periventricular and/or centrum semiovale areas in the apparent diffusion coefficient map but also T2 signal alterations which are usually seen when symptoms are resolved [9,12,14,20,26–28]. Nevertheless, there are some cases that have no pathological findings on MRI suggestive of MTX induced neurotoxicity [2,8].

Management of HDMTX related neurotoxicity with normal MTX serum levels can be challenging. The pathogenesis remains unclear, and there is no established treatment for this condition. It has been suggested that aminophylline, an adenosine receptor antagonist can be used. Also, dextromethorphan, a noncompetitive NMDA antagonist may improve symptoms. Although a few therapeutic approaches have been suggested, there is no consensus on which one is the best, and further investigation is needed to define optimal treatment [1,3,12,14]. Also, recurrence of neurological manifestation with the administration of HDMTX is uncommon. Some authors omit the treatment with MTX when a neurotoxic event is developed, while others do not [4,9]. In our case, MTX was discontinued after the second episode of facial nerve palsy.

Conclusion

Facial nerve palsy could be an unusual manifestation of neurotoxicity induced by IV HDMTX and should always be in a clinician's differential diagnosis when a patient is presenting with its associated symptoms and signs. As shown in our case, imaging findings can be non- diagnostic therefore, if the condition is highly suspected the initiation of folinic acid rescue protocol and further measures should not be delayed.

Ethics approval

Ethical approval is not required for this study in accordance with local or national guidelines.

Patient consent for publication

Consent for publication of the case details and associated images was obtained from the patient.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Authors' contributions

Data was acquired and analyzed by Irene Tsappa and Pampina Pilavaki. Both Irene Tsappa and Pampina Pilavaki made substantial contributions to conception and design of the review and were both involved in creating the manuscript and collecting the relevant literature. Irene Tsappa and Eleni Fotiou made substantial contribution to creating the case report and were involved in drafting the manuscript. Anastasia Constantinidou made substantial contributions to the selection of the data and was involved in drafting and revising the manuscript for important intellectual content. All authors contributed to data analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Data availability statement

The data that support the findings of this case report are not publicly available due to the fact that they contain information that could compromise the privacy of the patient but are available from AC upon reasonable request.

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