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Methotrexate Induced Neurotoxicity in Osteosarcoma: Case Report and Narrative Review of the Literature

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Abstract

Methotrexate (MTX) is a cytotoxic antimetabolite, which interferes with folic acid metabolism. The term high dose Methotrexate (HDMTX) refers to doses over 500 mg /m2 which are currently used to treat not only hematological malignancies but also solid neoplasms. Patients receiving intravenous (IV) HDMTX as part of their regime often experience a variety of side effects such as oral and gastrointestinal mucositis, nephrotoxicity and bone marrow suppression. Approximately 11% of these patients develop neurological symptoms and signs suggestive of MTX induced neurotoxicity, a condition, which is further, classified as acute, subacute and chronic depending on the time of onset. In this report we present a 22-year-old female with a high grade chondroblastic osteosarcoma of the pelvis who developed an isolated central facial nerve palsy acutely after the administration of IV HDMTX. Furthermore, we conducted a narrative review using Pubmed and included all patients with osteosarcoma who developed a transient or a permanent neurologic deficit during their treatment with IV HDMTX. Most patients presented with symptoms involving higher cognitive function, seizures and stroke like symptoms. To our knowledge this is the first case with isolated central facial nerve palsy acutely after the administration of IV HDMTX.

Keywords: IV HDMTX; Facial nerve palsy; Cranial nerve VII; Osteosarcoma

Abbreviations

MTX, Methotrexate; HDMTX, high-dose Methotrexate; IV, intravenous; GCS, Glasgow coma scale; CSF, cerebrospinal fluid; RFC, reduced Folate carrier; NMDA, N-methyl-D-aspartate; CT, Computer tomography; MRI, Magnetic resonance imaging; PCR, Polymerase chain reaction; M, male; F, female; Lt, left; Rt, right; DM, dextromethorphan; CFR, citrovorum factor rescue; VCR, vincristine; CMT, chemotherapy

Introduction

Methotrexate (MTX) is a commonly used cytotoxic drug classified as an antimetabolite. It inhibits purine and thymidine synthesis by intervening in the folic acid metabolism, leading ultimately to cell death [1–3]. High-dose methotrexate (HDMTX) is used in both solid neoplasms and hematological malignancies including osteosarcomas, lymphomas, and acute lymphoblastic leukaemia [1,4]. Patients under this treatment may experience a variety of side effects. Oral mucositis, gastrointestinal toxicity, nephrotoxicity, and myelosuppression are the commonest ones [5,6]. Only up to 11% of patients may develop a form of neurotoxicity [1]. MTX induced

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neurotoxicity is further classified as acute, subacute, and chronic. The spectrum of neurological presentation varies with patients being completely asymptomatic to experiencing rigorous symptomatic demyelination [1,2,7–9]. Although neurotoxicity induced by MTX is mostly seen after intrathecal administration, the aforementioned diagnosis should always be included in a physician's differential when a patient exhibits symptoms and signs suggestive of a temporary or a permanent neurologic deficit, when presented within hours, weeks or months after intravenous HDMTX administration. Osteosarcoma accounts for > 10% of solid neoplasms and it is the most common primary bone malignancy. It usually appears on the metaphysis of long bones although other sites of disease such as the axial skeleton and maxillofacial bones have been identified as being the primary site of the disease as well, especially in adults. Curative treatment of high-grade osteosarcoma in patients with localized disease is achieved by a combination of chemotherapy followed by surgery. In a neoadjuvant setting, MAP regimen comprising of Doxorubicin, Cisplatin and High-dose methotrexate is used as a 1st line treatment for operable high-grade osteosarcoma.

Herein, we report the case of a young female patient with a diagnosis of high grade chondroblastic osteosarcoma who developed central facial nerve palsy within hours of the administration of intravenous (IV) HDMTX as part of MAP regimen, on two separate occasions. To our knowledge this is the first case of acute neurotoxicity induced by IV HDMTX involving only the facial nerve.

Case presentation

A 22-year-old female with a diagnosis of high grade chondroblastic osteosarcoma of the pelvis was admitted to hospital to receive HDMTX as part of the 2nd cycle of the MAP regimen comprising doxorubicin, cisplatin and HDMTX at 37,5 mg/m2, 60 mg/m2, 12 gr/m2 respectively [10]. Her past medical history was only significant for hypothyroidism for which she was treated with oral thyroxin at 75 mcg daily over 6 years. To this point she had already received the 1st cycle of the regimen without exhibiting any symptoms suggestive of MTX induced neurotoxicity. However, 6 hours after the administration of the third infusion of HDMTX, the patient reported left lower face musculature weakness. Through clinical examination left sided mouth drooping was noticed with the ability to frown remaining unaffected, suggestive of right facial nerve palsy involving the contralateral (right) upper motor neuron component of the nerve (Shown in Fig. 1). During the episode, she was afebrile with normal vital signs and her Glasgow coma scale (GCS) was 15/15. The rest of the neurological examination was unremarkable with no other signs of neurological deficit or meningism.

Laboratory studies showed normal renal and liver function without any electrolyte imbalances as well as normal white cell, red cell and platelet count. Since her thyroid function was well controlled and these symptoms have never been reported before by the concomitant use of MTX and levothyroxine, MTX induced neurotoxicity was suspected, and the patient proceeded to have a computed tomography (CT) scan of the brain with and without contrast which was normal. Increased intracranial pressure was excluded therefore, lumbar puncture was performed in order to exclude arachnoiditis, and all cause meningitis. The cerebrospinal fluid (CSF) came back normal with a negative PCR panel for the most common bacteria, viruses and yeast. Furthermore, gram stain was negative, thus both bacterial and viral meningitis were excluded, arachnoiditis as well. CSF MTX levels were never sent due to the fact that this test is not available at out laboratory. Moreover, there was no pleocytosis, nor an elevated protein content ruling out aseptic meningitis a condition that is rarely seen acutely after intravenous administration of this cytotoxic agent.

MTX was promptly discontinued after the clinical diagnosis was made and therapeutic doses of folinic acid (at a dose of 15 mg, 4 (10/BSA) times daily) were immediately introduced in order to reduce the possibility of a permanent deficit. Furthermore, urinary alkalization was continued as per protocol and the patient was sent for a magnetic resonance imaging (MRI) of the brain 12 hours later, at which timepoint her symptoms had completely resolved. MRI revealed no

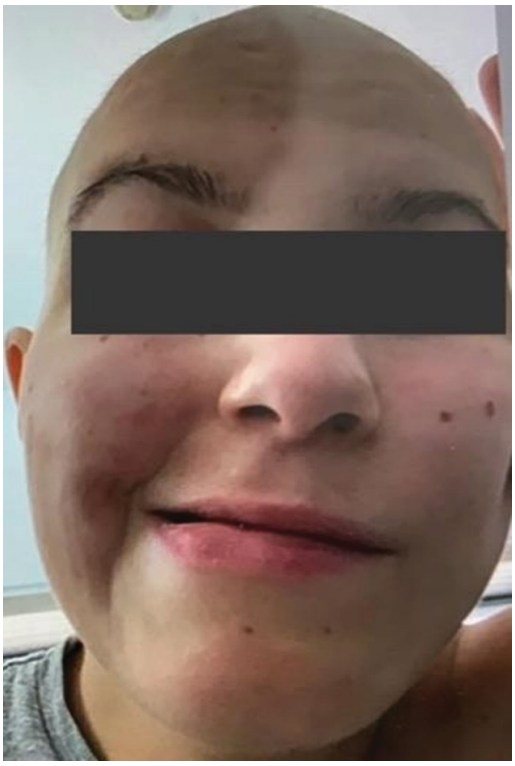

Figure 1: Right facial nerve palsy involving the contralateral (right) upper motor neuron component of the nerve.

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pathological findings and consecutive MTX serum levels, taken before and after the initiation of folinic acid, where within normal limits.

Despite the fact there were no radiological findings indicative for a focal neurologic deficit the patient developed rapid neurological improvement after the administration of folinic acid. Given the quick recovery, a decision was made to rechallenge with MTX at a 20% dose reduction as the fourth cycle of MTX in total, a dose which she had already received on her last cycle due to previously seen myelosuppression. Twelve hours into this infusion, the patient experienced exactly the same symptoms. Same measures where again taken and the patient fully recovered within 12 hours of onset without residual deficits, continuing her treatment without MTX thereafter.

Discussion

MTX interferes with DNA synthesis by inhibiting dihydrofolate reductase, a key enzyme in the production of purines and thymidine. MTX is transported into the cells through reduced folate carrier (RFC), so that polyglutamation can occur. Subsequently, it binds and inhibits dihydrofolate reductase, which converts dihydrofolate into tetrahydrofolate. Thus, the reduction of tetrahydrofolate, which is necessary for the purines and thymidine synthesis, interrupts DNA synthesis and eventually reduces cell proliferation [1,2,11].

MTX induced neurotoxicity usually occurs after intrathecal or high dose intravenous administration [1,3]. The pathophysiological mechanism is not well understood yet, although a few hypotheses have been proposed. It has been suggested that increasing levels of adenosine and/or homocysteine, and changes in tetrahydrobiopterin synthesis and metabolism may be associated with MTX induced neurotoxicity. Dihydrofolate reductase is needed for the metabolism of homocysteine. The inhibition of this enzyme leads to the accumulation of homocysteine in the blood and cerebrospinal fluid. Subsequently, homocysteine can be toxic and directly injure the vascular endothelium or can lead to N-methyl-D-aspartate (NMDA) receptor activation and eventually cause neurotoxicity. Furthermore, direct neuronal injury by MTX is also considered a possible cause of neurotoxicity [1,8,12–14]. Neurological findings can vary amongst patients. Neurotoxicity is categorized as acute if patients develop symptoms within hours of the administration, which was the case on this occasion. It is further classified as subacute and chronic if symptoms occur within days-weeks or months-years, respectively [7,13]. Acute and subacute neurotoxic manifestations include headache, confusion, disorientation, drowsiness, stroke-like symptoms (e.g. acute hemiparesis, ataxia), and seizures. Chronic toxicity may comprise cognitive and behavioral alterations, and chronic leukoencephalopathy [1,3,8,13]. Symptoms commonly resolve spontaneously within 15 minutes to 72 hours of their appearance, without any long-term complications. The onset of acute neurotoxicity findings usually occurs after the second or third course of HDMTX [9]. Few cases of MTX induced neurotoxicity have been reported in patients with osteosarcoma. We therefore conducted a narrative review using as key words the terms “Methotrexate” AND “neurotoxicity” AND “case reports” in Pubmed (English Language). In this review we only included patients with osteosarcoma who received HDMTX as part of their protocol and developed a permanent or a transient neurologic deficit. All cases are presented in detail in Table 1. In total 45 cases have been reported to date. Most of them involved disturbances of higher cognitive function, stroke like symptoms and seizures. Of those only 1 case presented with isolated facial nerve palsy of subacute onset [15].

Allen JC et al. presented cases of MTX induced neurotoxicity in bone sarcoma patients. However, this article was not included in our review since only its abstract was available [16]. Russell W et al. reported 19 patients diagnosed with osteogenic sarcoma and HDMTX associated neurotoxicity [17]. Of note, 4 of these patients were initially presented by Allen JC et al. in 1978. This was the first report that described osteogenic sarcoma patients with neurotoxicity related to HDMTX [17,18].

The clinical manifestations of MTX induced neurotoxicity vary amongst individuals. The imaging findings as well. Ayalon et al. presented a patient who developed status epilepticus, altered mental status and fever following the second course of high-dose MTX [14]. Similar findings were observed in some patients as part of a case series reported by Jaffe N et al [19]. Moreover, some other patients were noted to exhibit stroke like symptoms with or without altered mental status [12,20,21]. Atypical clinical findings were also described according to the area involved in CNS neurotoxicity. Few authors describe facial paralysis as part of their clinical presentation [15,19,20,22]. Nevertheless, isolated facial nerve paralysis following IV HDMTX in a patient with osteosarcoma has never been described before. Drachtman et al. reports 2 patients with osteogenic sarcoma who developed an episode of subacute facial nerve palsy 7 days after the administration of HDMTX. These patients were only treated with dextromethorphan 1mg/kg and their symptoms had completely resolved at 30 min and 3 days after the onset [15]. In contrast, our case report shows that facial nerve paresis, an unusual side effect, may develop not only subacutely but also acutely after the administration of intravenous HDMTX in osteosarcoma patients. To our knowledge, this is the first case report that demonstrates such a condition, and this diagnosis should always be in a physician’s differential when a patient presents with a neurological deficit rapidly after the commencement of this cytotoxic agent.

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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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