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MR Findings in Methotrexate-Induced CNS Abnormalities

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MR of the brain was performed in eight patients (mean age, 14.9 years) with osteogenic sarcoma during or after IV treatment with high-dose methotrexate. MR detected brain abnormalities in four patients, three of whom had concomitant neurologic dysfunction. Pathologic findings demonstrated on MR were (1) chronic brain edema, demonstrable over a period of 3–14 months (proved by autopsy in one patient); (2) multifocal white matter necrosis; and (3) deep brain atrophy.

MR appears to be valuable in the detection of abnormalities induced by treatment with high-dose methotrexate.

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The chemotherapeutic agent methotrexate (MTX) inhibits the enzyme dihydrofolate reductase, thus preventing folic acid from converting to tetrahydrofolic acid. MTX is a lipid-insoluble substance, which, under normal conditions, does not cross the blood brain barrier. Toxic effects of MTX have been reported in the bone marrow, gastrointestinal tract, and liver. The neurotoxic effects of MTX include chemical arachnoiditis, motor dysfunction, or disseminated necrotizing leucoencephalopathy [1–4]. The aim of this study was to use MR imaging to assess previously unreported treatment-induced abnormalities of the CNS.

Subjects and Methods

All patients who had undergone systemic high-dose methotrexate (HD-MTX) therapy exceeding a dosage of 5 mg/m^2 at one cycle underwent MR of the brain. Those patients who had additional brain irradiation or intrathecal administration of MTX or other antineoplastic drugs were excluded from the study. At our institution, only patients with primary osteogenic sarcoma met the criteria. The present series consists of eight patients, four females and four males 12–23 years old (average age 14.9 years).

Patients were considered to have high-risk osteogenic sarcoma if one of the three following criteria was present [5]: (1) a large primary tumor involved more than one-third of bone; (2) the chondroid ground substance formation in the biopsy material was more than 20% of the tumor area; and (3) the reduction of bone scan activity after 4 weeks of treatment was less then 20%. Osteogenic sarcoma was classified as low risk if all of the three following criteria were fulfilled: (1) less than one-third of bone was involved; (2) less than 20% chondroid ground substance was in the tumor material; and (3) more than 20% bone scan response was present at week 4. In the present series, six of eight patients were classified as high risk and two of eight as low risk. The therapy protocol and dosage are given in Table 1 [6–8]. A total of 13 MR examinations were performed. The time interval between the last MTX treatment and MR varied from 1 month to 10 years.

MR was performed on a superconductive magnet system* operating at a field strength of 1.5 T. T1-weighted images were obtained with an inversion recovery, 1400/50/450/2 (TR/TE/TI/excitations), or a partial saturation spin-echo technique, 600/20/4 (TR/TE/excitations); T2-weighted images were obtained with spin-echo pulse sequences of 2500/30,60/2. Imaging was performed in transverse, sagittal, and coronal planes with a data matrix of 256 × 128

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TABLE 1: Treatment Protocol and HD-MTX[a] Dosage in Osteosarcoma Patients

Case No.	Age (years)	Gender	Protocol	MTX (12 g/m²/cycle)	Number of Cycles	Total Dose of MTX	Total Dose of MTX/m²	Time Interval Between Last Treatment and MR
1	12	F	T7[b]	8–12 g/m²/cy, stepwise increase	16	237 g	170 g/m²	10 years
2	14	M	T7	12 g/m²/cy	18	385 g	240 g/m²	7 years
3	12	M	COSS-82[c]	12 g/m²/cy	8	104 g	96 g/m²	4 years
4	15	M	COSS-85	12 g/m²/cy	5	100 g	60 g/m²	2 years
5	15	F	COSS-86	12 g/m²/cy	7	126 g	84 g/m²	3, 7 weeks 6, 14 months
6	15	F	COSS-86	12 g/m²/cy	14	280 g	168 g/m²	During therapy
7	23	M	COSS-86	12 g/m²/cy	2	40 g	24 g/m²	1 month
8	13	F	COSS-86	12 g/m²/cy	2	40 g	24 g/m²	1 month

[a] High-dose methotrexate.

[b] T7 protocol [6] = Adriamycin 45 mg/m², bleomycin 12 mg/m², cyclophosphamide 600 mg/m², dactinomycin 450 mcg/m², vincristine 1.5 mg/m², HD-MTX 8–12 g/m², Citrovorum-rescue factor 5–15 mg, postoperatively every 6 hr.

[c] COSS 82-86 protocol [7, 8] = cooperative osteosarcoma study. HD-methotrexate with calcium leucovorin rescue 18 g/m², Adriamycin 90 mg/m², vincristine 1.5 mg/m², bleomycin 15 mg/m²/day × 2 days, cyclophosphamide 600 mg/m²/day × 2 days, dactinomycin 600 mcg/m²/day × 2 days, Ifosfamide 2 g/m²/day × 5 days, high-dose cis-platinum 90 mg/m².

pixels. Slice thickness varied from 5.3 to 8 mm. In all patients ventricular size was established by measuring the ventricular index as described by Pedersen et al. [9] and by Nagata et al. [10].

Histologic Technique

After fixation with 10% formalin solution, the brain was cut in sections corresponding to the plane of MR. For histologic investigations, brain specimens of several cortical and white matter areas were taken, embedded in paraffin, and cut in 5-μm-thick sections. These were stained with hematoxylin and eosin and Masson's trichrome.

Case Reports

Case 1

Twelve-year-old girl with osteogenic sarcoma of the right humerus. Initial therapy was started with bleomycin, cyclophosphamide, dactinomycin, and HD-MTX. Surgical resection of the bone tumor was performed after the sixth HD-MTX treatment, and resection of lung metastases after the 10th treatment. During infusion of the 11th course of MTX therapy the patient experienced severe vomiting and diarrhea. Prolonged toxic serum levels of MTX were noted. Nine hours after MTX infusion, clinical signs of an acute encephalopathy occurred: slurred speech, difficulty swallowing, bilateral paresis of external rectus eye muscles, ataxia, and right hemiparesis. The symptoms disappeared within 3 hr, with full recovery.

CT and MR Findings. CT, performed 16 days after HD-MTX infusion, showed periventricular hypodensities, especially around the frontal horns. Follow-up studies with CT demonstrated areas of decreased attenuation values over a period of 14 months. Ten years after the onset of the transient encephalopathy MR revealed normal signal intensity patterns of the cerebral white matter on T1- and T2-weighted images.

Case 5

Fifteen-year-old girl with osteogenic sarcoma of the left distal tibia. Treatment was started according to the cooperative osteosarcoma study (COSS 86). Ten days after the seventh HD-MTX treatment the patient experienced severe Candida septicemia, which was treated by amphotericin B (1 mg/kg/day) and flucytosine (100 mg/kg/day). During the following days the patient developed clinical symptoms and neurologic disturbances: convulsions, intermittent loss of consciousness, generalized seizures, and status epilepticus. CSF protein electrophoresis showed a picture consistent with an altered blood brain barrier characteristic of encephalopathy. There were no detectable antibodies in the CSF to suggest a viral encephalopathy.

CT was performed during the acute episode and did not demonstrate any abnormality. A study 2 weeks later revealed small focal areas of contrast enhancement in the region of the basal ganglia. The attenuation values of the cerebral white and gray matter appeared normal.

Three weeks later, T1-weighted MR images revealed multiple foci (diameter, 1–3 mm) of decreased signal intensity within the deep white matter, the centrum semiovale, and in the region of the basal ganglia (Fig. 1). The lesions were surrounded by a hyperintense rim. On T2-weighted images the foci remained of low signal intensity and were surrounded by a thick rim of marked hyperintensity. Radiologic signs of diffuse brain atrophy with marked widening of the subarachnoid space and increased ventricular index were present. Repeat MR performed 4 weeks later demonstrated bright hyperintensity of the whole white matter in both cerebral hemispheres and in two-thirds of the corpus callosum. Foci of low signal intensity and brain atrophy were found to be unchanged.

Six months after the onset of neurologic symptoms a significant improvement was recognized clinically and radiologically. The diffuse bright hyperintensity of the white matter had disappeared. Only patchy areas of hyperintensity in the periventricular white matter were recognizable, and the foci of low signal had completely resolved.

Fourteen months after the acute episode the patient suffered from a slight spastic paresis of the right leg but otherwise had fully recovered. MR showed pronounced brain atrophy with an increased ventricular index and persistent areas of low signal intensity in the periventricular white matter in both hemispheres, which were hyperintense on T2-weighted spin-echo images.

Case 6

Fifteen-year-old girl with osteogenic sarcoma of the left distal femur. Treatment was instituted according to the high-risk protocol of the cooperative osteosarcoma study (COSS 86). MR, performed during the 10th treatment with HD-MTX, demonstrated severe brain abnormalities. Since there were no clinical symptoms of HD-MTX neurotoxicity, treatment was continued. The patient died of intercurrent hepatic failure 3 months later.

MR demonstrated diffuse hyperintensity of the whole cerebral white matter on T2-weighted SE images (Fig. 2). The white matter of the brainstem and the cerebellum showed no abnormality.

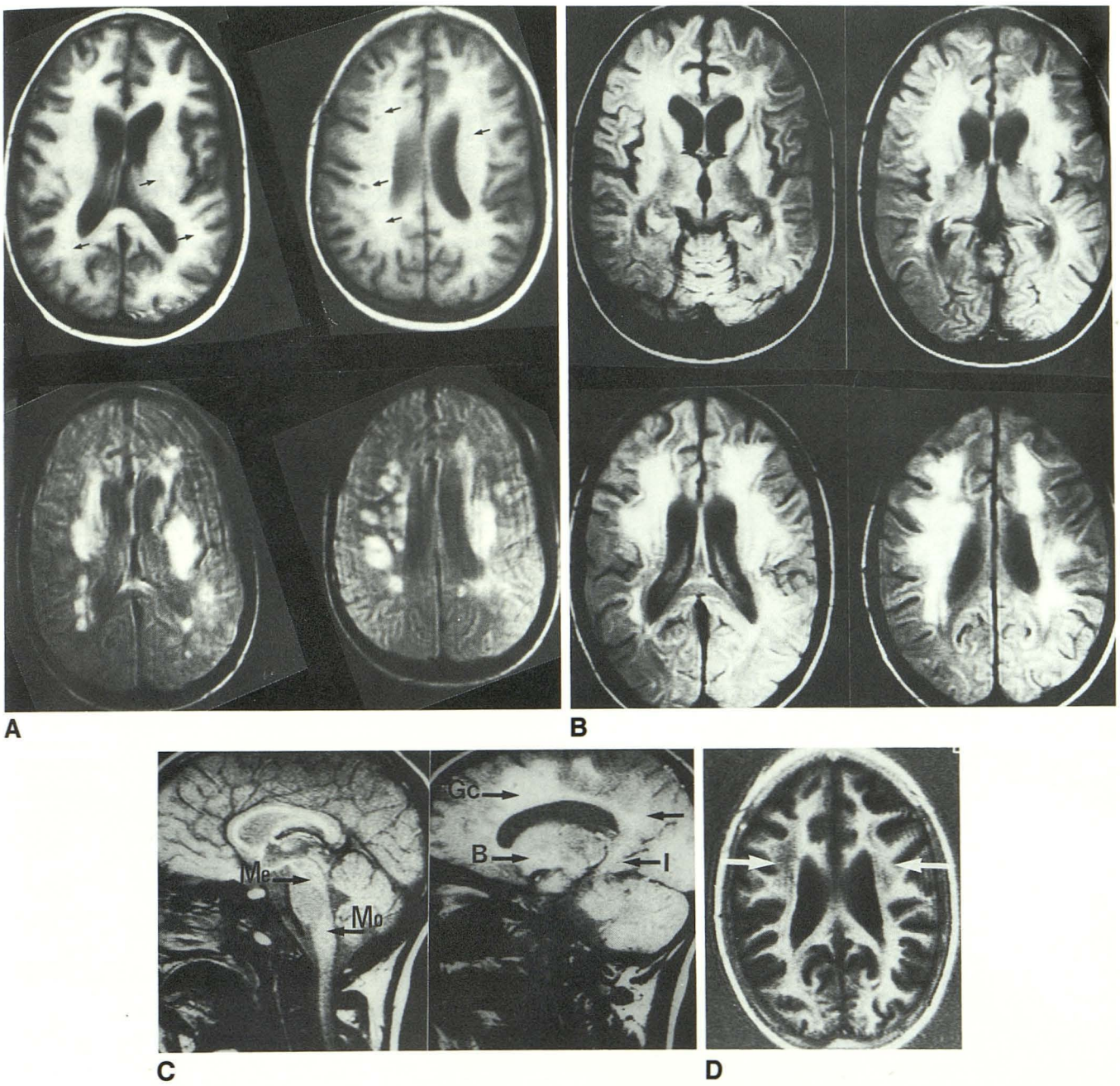


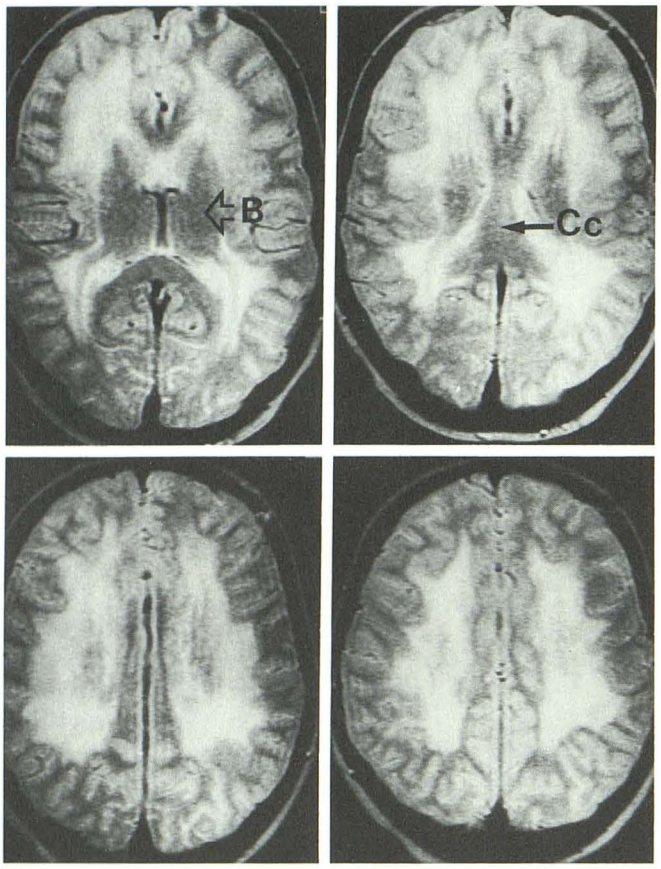
Fig. 1.—Case 5: low-risk osteogenic sarcoma of distal tibia.

A, MR 3 weeks after onset of cerebral dysfunction. T1-weighted SE images (350/30) (*upper row*) demonstrate multiple foci of decreased signal intensity with hyperintense rims (*arrows*). Mixed-sequence SE images (1500/100) (*lower row*) reveal multiple lesions of increased signal intensity in periventricular and subcortical white matter.

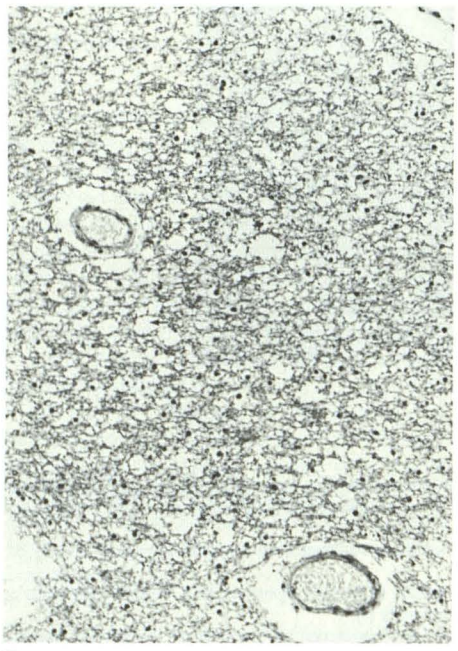
B, MR 4 weeks later. Focal lesions have extended by confluence. Proton-density-weighted SE images (1800/30) demonstrate diffuse hyperintensity of cerebral white matter and corpus callosum.

C, Same study as Fig. 1B. Mixed-sequence SE images (1600/60) demonstrate areas of high signal intensity in mesencephalon (Me), medulla oblongata (Mo), cingulate gyrus (Gc) and corpus callosum (*arrow*), basal ganglia (B), and isthmus gyri parahippocampalis (I).

D, Follow-up study 14 months after onset of neurologic symptoms. T1-weighted IR image (1400/35/450) demonstrates areas of decreased signal intensity within the periventricular white matter (*arrows*). Higher sections (not shown) revealed similar changes in centrum semiovale on both sides. Note ventriculomegaly.



A



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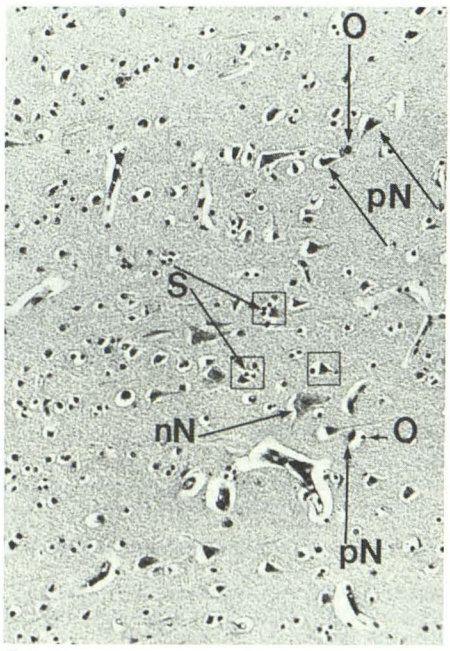

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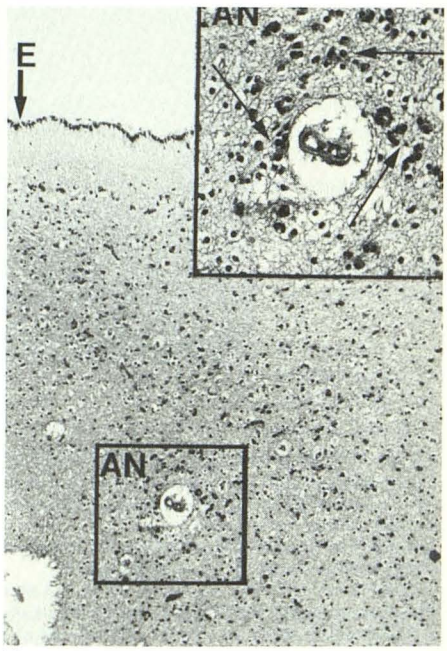

D

Fig. 2.—Case 6: high-risk osteogenic sarcoma of left distal femur. No clinical symptoms or neurologic dysfunction.

***A*, MR after 10th course of treatment with high-dose methotrexate demonstrates diffuse hyperintensity of cerebral white matter on T2-weighted SE images (2500/60). Note normal signal intensity pattern within basal ganglia (B), corpus callosum (Cc), and cortical regions.**

***B*, Histopathology of occipital white matter shows distinct spongiosis of white matter secondary to chronic brain edema. (Masson's trichrome stain, ×202)**

***C*, Histopathology of occipital cortex demonstrates dark, shrunken, and pyknotic neurons (pN) surrounded by high-density oligodendrocytes. S = satellitosis, nN = normal neuron, O = normal oligodendrocyte. (Masson's trichrome stain, ×202)**

***D*, Histopathology of paraventricular white matter shows distinct proliferation of astrocytes, especially in subependymal layer. Ventricular ependyma (E). Insert: astroglial nodule (AN). (Masson's trichrome stain, ×202)**

Case 2

Fourteen-year-old boy with osteosarcoma of the left tibia, diagnosed and treated according to the T7 protocol (see Table 1). The patient experienced no clinical symptoms or neurologic deficits suggestive of encephalopathy. MR, performed 7 years after the first treatment course, revealed an increased ventricular index, consistent with deep brain atrophy; a normal signal intensity pattern of the cerebral gray and white matter; and no widening of the subarachnoid spaces.

Cases 3, 4, 7, and 8

In these patients neither clinical symptoms nor MR examinations identified any brain abnormality. The time interval between first treatment with MTX and MR was 4 years in case 3, 2 years in case 4, and 1 month in cases 7 and 8.

None of the patients had evidence of intracerebral metastases at any stage of the malignant process.

Gross Pathology and Histopathologic Findings (Case 6)

Histopathology showed evidence of increased intracranial pressure at the base of the brain, widespread areas of edema within the white matter of the frontal and occipital lobe, and hemorrhagic diathesis. In several cortical areas disseminated pyknosis of ganglion cells and reactive satellitosis were encountered. In the subcortical areas and the white matter perivascular spongiosis and hemosiderophages were present. The white matter showed distinct spongiosis associated with chronic brain edema, and paraventricular areas with astrocytic proliferation (astroglial nodules). In the basal ganglia, there were dark shrunken ganglion cells and reactive gliosis. Necrosis of the neuropil could not be found. No areas of demyelination were present and signs of inflammation were absent. The findings were suggestive of chronic brain edema and toxic metabolic damage of the ganglion cells in the cortex and in the basal ganglia. In addition, astrocytic proliferation in the paraventricular areas and basal ganglia, and oligodendroglial proliferation (satellitosis) of the brain cortex were found.

Discussion

IV administration of HD-MTX can cause different types of neurologic dysfunction [2, 3]. With regard to etiology, various factors have to be considered, since, in the early stage, there are emboli of necrotic tumor tissue from micrometastases [11] and toxic serum and CSF-MTX levels [12]. A more severe, delayed, and chronic form of neurotoxicity resembling focal encephalopathy has been observed by Allen et al. [13] in patients receiving very large doses of MTX at short intervals. Temporary neurologic abnormalities induced by HD-MTX were also detected by Jaffe and Traggis [2], who attributed them to an increased dosage and more frequent administration of HD-MTX.

Histopathologic findings of disseminated necrotizing leucoencephalopathy in leukemia and lymphoma patients receiving MTX have been reported by Rubinstein et al. [14]. Microscopic findings included confluent foci of demyelination, coagulative necrosis, loss of oligodendroglia, astrocytic hypertrophy, axonal swellings, and severe status spongiosus. In one case, these authors described generalized acute edema. The multifocal areas of coagulative-type necrosis apparently extended by confluence and disseminated in the cerebral white matter in a random manner. Usually, the surrounding white matter showed marked status spongiosus and moderate astrocytic response. While three patients in their series developed neurologic illness, two patients never showed a clinical picture of progressive encephalopathy. These patients were treated by systemic and intrathecal use of methotrexate, Cytosinarabinoside, cyclophosphamide, hydrocortisone, and whole brain irradiation. Patient 5 in our series, we believe, had this type of focal leucoencephalopathy. Both CT and MR demonstrated multiple foci in the white matter, consistent with focal necrosis. Similar gross pathology and histologic findings were reported by Glass et al. [15] in three patients.

In the present series, long-standing white matter hyperintensity was found in three patients. In patient 1, decreased attenuation values of the frontal and parietal white matter were demonstrated by CT during a period of 14 months and then completely resolved. In patient 5, diffuse hyperintensity of the white matter was shown by MR during a period of 6 months. In patient 6, diffuse hyperintensity of the whole cerebral white matter persisted over a period of 3 months. Autopsy and microscopy in this case revealed chronic brain edema and severe status spongiosus. Multiple lesions were present in case 5, each of them demonstrating a hyperintense rim on T1-weighted images. This finding possibly could represent a hemorrhagic diathesis or the presence of hemosiderophages, as was shown by histopathology in case 6, which was similar.

The causal relationship between systemic HD-MTX administration and the presence of CNS abnormalities as described is not proved, as other factors could have been acting alone or in concert with MTX to cause the abnormalities: for example, concomitant drugs (vincristine, cytosine arabinoside, Adriamycin, antibiotics, prednisone) or other paraneoplastic abnormalities, micrometastases, or superimposed cerebral infections. Histopathology in case 6 could not demonstrate metastatic emboli or evidence of inflammatory cells. Other, previously reported histopathologic studies showed findings similar to ours, without evidence of superimposing infection or the presence of micrometastases.

Brain atrophy, present in three patients in this series, is a frequent sequel in patients with malignant diseases. Its different etiologies include malnutrition, administration of hydrocortisone, IV or intrathecal administration of chemotherapeutic agents, or irradiation [16–20]. The child's age at the onset of malignancy affects the severity of brain atrophy.

While intracerebral calcifications are a well-known consequence of combined treatment of radiotherapy and IV and/or intrathecal MTX therapy, we did not encounter calcific deposits in the present series.

Disruption of the blood brain barrier during or following IV HD-MTX treatment may not be accompanied by clinical signs or neurologic deficits. MR appears to be a more sensitive means of detection of early changes of MTX-induced enceph-

alopathy and therefore should be used to monitor patients undergoing this form of chemotherapy. The question arises to what extent the assessment of MR brain abnormalities would alter the treatment protocol. In case of abnormal MR findings in patients undergoing high-dose MTX therapy, we perform further extensive clinical work-up, including CSF examination and myelin basic protein analysis. If the results suggest or are consistent with encephalopathy, alternative treatment protocols are chosen, omitting antineoplastic drugs with a neurotoxic effect.

REFERENCES

1. Powers JM. Metabolic diseases of the nervous system. In: Rosenberg RN, ed. *The clinical Neurosciences. Neuropathology.* New York: Churchill Livingstone, **1983**:528–529
2. Jaffe N, Traggis D. Toxicity of high-dose methotrexate (NSC-740), and citrovorum factor (NSC-3590), in osteogenic sarcoma. *Cancer Chemother Rep* **1975**;6:31–36
3. Bleyer WA. Neurologic sequelae of methotrexate and ionizing radiation: a new classification. *Cancer Treat Rep* **1981**;65:89–98
4. Packer RJ, Grossman RI, Belasco J. High-dose systemic methotrexate: associated acute neurologic dysfunction. *Med Pediatr Oncol* **1983**;11:159–161
5. Winkler K, Bielack S. Chemotherapy of osteosarcoma. *Semin Orthop* **1988**;48–58
6. Rosen G, Marcove RC, Caparros B, Nirenberg A, Kosloff C, Huvos AG. Primary osteogenic sarcoma. *Am Cancer Soc* **1979**;43:2163–2177
7. Winkler K, Beron G, Delling G, et al. Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor response. *J Clin Oncol* **1988**;329–337
8. Rosen G, Marcove RC, Huvos AG, et al. Primary osteogenic sarcoma: eight-year experience with adjuvant chemotherapy. *J Cancer Res Clin Oncol* **1983**;106:55–67
9. Pedersen H, Gyldensted M, Gyldensted C. Measurement of the normal ventricular system and supratentorial subarachnoid space in children with computed tomography. *Neuroradiology* **1979**;17:231–237
10. Nagata K, Basugi N, Fukushima T, et al. A quantitative study of physiological cerebral atrophy with aging. A statistical analysis of the normal range. *Neuroradiology* **1987**;29:327–332
11. Allen JC, Rosen G. Transient cerebral dysfunction following chemotherapy for osteogenic sarcoma. *Ann Neurol* **1978**;3:441–444
12. Fritsch G, Urban Ch. Transient encephalopathy during the late course of treatment with high-dose methotrexate. *Cancer* **1984**;9:1849–1851
13. Allen JC, Rosen G, Mehta M, Harlen B. Leukoencephalopathy following high-dose IV methotrexate chemotherapy with leukovorin rescue. *Cancer Treat Rep* **1980**;64:1261–1273
14. Rubinstein LJ, Herman MM, Long TF, Wilbur JR. Disseminated necrotizing leukoencephalopathy: a complication of treated central nervous system leukemia and lymphoma. *Cancer* **1975**;35:291–305
15. Glass JP, Lee YY, Bruner J, Fields WS. Treatment-related leukoencephalopathy. *Medicine (Baltimore)* **1986**;3:154–162
16. Bentson J, Reza M, Winter J, Wilson G. Steroids and apparent cerebral atrophy on computed tomography scans. *J Comput Assist Tomogr* **1978**;2:16–23
17. Peylan-Ramu N, Poplack DG, Blei CL, Herdt JR, Vermess M, di Chiro G. Computer assisted tomography in methotrexate encephalopathy. *J Comput Assist Tomogr* **1977**;2:216–221
18. Peylan-Ramu N, Poplack DG, Pizzo PA, Adornato BT, di Chiro G. Abnormal CT scans of the brain in asymptomatic children with acute lymphocytic leukemia after prophylactic treatment of the central nervous system with radiation and intrathecal chemotherapy. *N Engl J Med* **1978**;15:815–818
19. Ochs JJ, Parvery LS, Whitaker JN, et al. Serial cranial computed-tomography scans in children with leukemia given two different forms of central nervous system therapy. *J Clin Oncol* **1983**;12:793–798
20. Brecher ML, Berger P, Freeman AI, et al. Computerized tomography scan findings in children with acute lymphocytic leukemia treated with three different methods of central nervous system prophylaxis *Cancer* **1985**;56:2430–2433