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Methotrexate Encephalopathy

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PROPHYLACTIC CRANIAL radiation, combined with intrathecal instillation of cytotoxic drugs, has improved disease-free survival in acute lymphoblastic leukaemia (ALL) [1]. However, associated neurological complications range from minor disturbances in cognitive function to profound brain damage, culminating in disseminated and necrotising leucoencephalopathy [2]. Since such cases of methotrexate encephalopathy are rare and the exact roles of irradiation to the neuraxis, intrathecal drugs alone, instillation into the ventricular system [3], different cytotoxic agents or combinations of drugs and irradiation [4] remain controversial, we report a further detailed neuropathological study.

A 17-year-old man presented with anaemia due to a pre-B-cell ALL with meningeal involvement. Hyperleucocytosis (400×10^9/l) was corrected with cytapheresis and standard chemotherapy [5], which led to complete haematological remission at 6 weeks. The persistence of lymphoblasts in his spinal fluid necessitated the placement of an Ommaya reservoir in the anterior horn of the right ventricle, and intrathecal therapy was continued with alternating instillation of 12.5 mg/m^2 methotrexate and 30 mg/m^2 cytarabine twice weekly; each injection was accompanied by 1 mg dexanethasone. 1 week after the start of the intraventricular cytotherapy the patient commenced cranial irradiation with orthovoltage HVL 3.5 mm copper, and over a 36-day period received 16 fractions, each of 2 Gy, given on 3 days per week, to a total of 32 Gy, with successful eradication of central nervous system (CNS) disease. He was maintained on daily 6-mercaptopurine, weekly methotrexate and monthly drug intensification [5]; 3 months' surveillance showed haematological and CNS remission.

Shortly thereafter the patient was noticed to be less alert. Computed tomography (CT) of the skull showed very mild cerebral atrophy and confirmed correct placement of the Ommaya reservoir.

Within 1 month he developed emotional lability, dementia with akinetic mutism and drug-related peripheral neuropathy. The spinal fluid was free of leukaemia and without evidence of bacterial or viral infections. Repeated CT showed bilateral

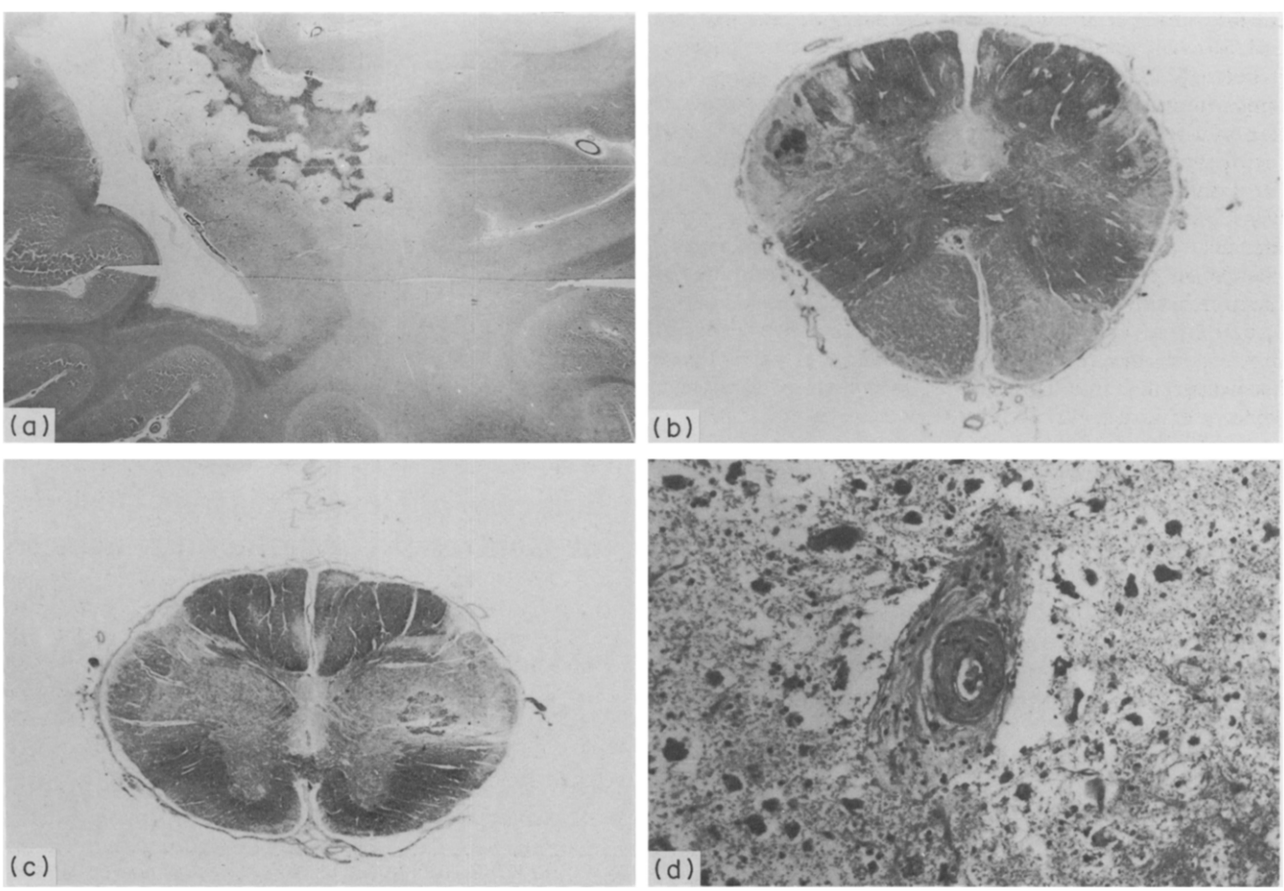

Fig. 1. Histopathology of the neuraxis. Sections show areas of coagulative necrosis within the periventricular white matter of right hemisphere (a), dorsolateral quadrant of medulla (b), and left lateral funiculus of upper cervical cord (c). (Luxol blue/cresyl violet, × 3.5). One of the many thickened vessels showing prominent perivascular fibrosis is shown (d). (Haemotoxylin–eosin, × 170).

symmetrical periventricular hypodense areas, which did not enhance with contrast. The encephalopathy was considered to be treatment-related and therapy was withdrawn. There was continued deterioration and the patient died without disease recurrence 6 months later.

Immediate postmortem examination of the neuraxis confirmed appropriate placement of the catheter tip and showed a swollen brain, with diencephalic compression and bilateral tentorial herniation. Coronal sections of the cerebral hemispheres revealed extensive symmetrical areas of yellow and chalky-white discolouration, occupying the periventricular regions and most of the centrum semi-ovale. Similar foci of necrosis were evident in the corpus callosum, the white matter of the temporal lobes, cerebellum and spinal cord funiculi. The cortical ribbon was essentially unremarkable, but the basal ganglia were pale and poorly defined. Atrophy of the head of the right caudate nucleus was noted.

Histopathology (Fig. 1) showed widespread coagulative necrosis and a variety of changes in the microvasculature of the brain, including thickening of vessel walls, with hyalinisation and/or perivascular fibrosis and cuffing by lymphocytic cells.

The course and pathology exemplify methotrexate neurotoxicity, with the pathogenesis remaining uncertain [6, 7]. It is postulated that radiation damages vessels, leading to oligaemia, with potentiation in the toxic effects of the methotrexate or, by disrupting the blood–brain barrier, allowing large amounts of drugs to reach the white matter [6]. However, the present case is unusual in that the intrathecal instillations preceded cranial irradiation. A second remarkable feature is the extent and severity of the necrosis, occurring maximally in tissues bathed in CSF, which include the spinal cord, in contrast to previous reports [6]. This neuro-anatomical distribution suggests that methotrexate concentration in the spinal fluid is an important factor in determining the severity of the necrosis.

In seeking to identify factors which may have caused extraordinarily high concentrations of the drug in CSF pathways, we considered the role of direct intraventricular instillation, but remain unaware of kinetic studies that would incriminate such a mechanism as opposed to the more conventional translumbar intrathecal administration; catheter misplacement could not be invoked in this instance. It is also possible that active meningeal disease, which may have impaired clearance of methotrexate from the spinal fluid, may have led to an extraordinarily high concentration of the drug along these pathways.

Finally, the contributing role of radiation also remains controversial. However, it has previously been noted that encephalopathy can develop at the time of irradiation in patients with active meningeal disease treated with a sequence of intrathecal methotrexate followed by cranial irradiation [8]. It is noteworthy that prior cranial irradiation is not an absolute prerequisite for the development of methotrexate-induced encephalopathy [9], although such cases are rare. These studies lead us to conclude that CSF concentrations of methotrexate play a role in the development of this form of encephalopathy in certain instances and that intraventricular administration of methotrexate may be particularly hazardous if given in the presence of active meningeal leukaemia.

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Influence of Dexamethasone Dose on the Control of Chemotherapy-induced Nausea and Vomiting

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DURING THE PAST 10 years there have been significant advances in the management of chemotherapy-induced emesis. Combination antiemetic therapy is now well established, even though the contribution of individual drugs is often poorly defined. Dexamethasone has antiemetic properties [1], and enhances the efficacy of metoclopramide [2], ondansetron [3] and other agents [4]. However, the optimum dose of corticosteroid which needs