Rapid neurological deterioration in a patient with multiple sclerosis treated with systemic interleukin-2 and interferon-α 2b for metastatic renal cell carcinoma

Previous case reports documented reactivation of psoriasis and rheumatoid arthritis in patients treated with systemic interleukin-2 for malignant conditions.1 We now report rapid worsening of another immune mediated disease multiple sclerosis in a patient with secondary progressive multiple sclerosis and metastatic renal cell carcinoma treated with systemic interleukin-2 (IL-2) and interferon-α (IFN-α). Although IL-2/IFN-α therapy temporarily accelerated the rate of progression of multiple sclerosis, the antitumour response was complete. This case highlights the potential role of IL-2 in the progression of neurological deficits in patients with multiple sclerosis. Clinicians and patients should be prepared for this potential complication, and studies employed to help clarify the mechanism(s) involved.

A 57 year old woman had developed relapsing-remitting symptoms of multiple sclerosis in 1983. Between December 1988 and 1991 she experienced a progressive decline in function without exacerbations. Yearly brain MRI documented new lesions in all studies and gadolinium (Gd) enhancing lesions in two of the three studies.

In October 1991 renal cell carcinoma of the right kidney was diagnosed with metastasis to the distal right femur and right lower lobe of the lung. Neurological examination six weeks after total knee arthroplasty was normal immediately before starting IL-2/IFN-α therapy showed 20/20 visual acuity, optic disk pallor, a partial right internuclear ophthalmoplegia, mild upper limb dysfunction (by nine hole peg testing) with normal strength, a moderate paraparesis, and an ability to walk comfortably with a walker.

On 10 February 1992, she began a 25 day course of therapy with rIL-2 at a dose of 0.5 mg/kg/24 hours by continuous intravenous infusion and rIFN-α at a dose of 15 million units subcutaneously every Monday, Wednesday, and Friday. Three hours after the initiation of therapy she developed a temperature of 38°C, nausea, vomiting, lethargy and muscle spasms. Urinalysis and culture disclosed a urinary tract infection, and treatment was initiated with ciprofloxacine. The next day her temperature was normal, and her symptoms resolved while the rIL-2 infusion was continued. She remained afibrile and signs of toxicity subsided, except for a subtle encephalitic rash and mild myalgias. Three days after beginning IL-2/IFN-α therapy, her neurological condition began to improve and she was discharged from hospital.

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A rostrocaudal gradient of nitrate plus nitrite concentrations in CSF

Lumbar CSF concentrations of nitrite plus nitrate are increasingly being used to investigate neurological disease.2 There are stable breakdown products of nitric oxide and the peroxynitrite anion and alterations in their concentrations in CSF are assumed to reflect nitric oxide synthase activity in the brain. There is some experimental evidence to support this.

We have recently reported an age related decrement in the concentration of CSF nitrite plus nitrate in a paediatric reference population aged between 0-1 and 17-4 years.3 Our method of collection of CSF is standardised and collects a fixed volume of fluid (the third 1 ml is used for nitrate plus nitrite concentrations) regardless of the size of the child. This means that the shorter the child, the more rostral the sampling site. To determine whether there is a rostrocaudal gradient for CSF nitrite plus nitrate we have reanalysed the data taking into account the length or height of the child.

There was a better inverse correlation between log concentrations (nitrate plus nitrite) and height (r = 0.001) than between log concentrations and age (r = 0.677). Because lumbar CSF is thought to act as a sump in humans, this finding implies a rostrocaudal gradient in CSF nitrite plus nitrite concentrations. In turn, a rostrocaudal gradient implies that nitric oxide generated in the brain is transported to the lower brainstem and the subarachnoid space, which would explain the relationship between nitrate and nitrite levels in CSF and the high nitrite levels in CSF above the lumbar sac, which provides indirect evidence that lumbar CSF nitrite plus nitrate is generated in the brain and transported to the lower brainstem and the subarachnoid space.