Rapid neurological deterioration in a patient with multiple sclerosis treated with systemic interleukin-2 and interferon-α2b for metastatic renal cell carcinoma

Previous case reports documented recrudescence 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-α2b (IFN-α2b). 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.


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 showed immediately before starting IL-2/IFN-α therapy showed 2/20 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 treatment 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 ciprofloxacin. 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 enerythematous rash and mild myalgias. Three days after beginning IL-2/IFN-α therapy, her neurological condition began a rapid and progressive deterioration without associated fever. Neurological examination one week after beginning treatment disclosed paraplegia with moderate weakness of the upper limbs, visual acuity of 20/100 OD and 20/50 OS, and a complete right internuclear ophthalmoplegia. She was admitted to the hospital and IL-2/IFN-α therapy was discontinued. Brain and spinal cord MRI showed no evidence of metastatic Gd enhancement, or increase in multiple sclerosis lesion burden. Serial MRI was performed and quantified according to a standardized protocol and the results were reviewed with the neuroradiologist. Analysis of CSF showed increased intrathecal IgG synthesis without any pleocytosis or evidence of breakdown of the blood-brain barrier. Three days after discontinuing IL-2/IFN-α (21 February), visual acuity had improved to 20/20 in both eyes and she had antiglaucoma in the left leg. She remained unable to stand, transfer independently, or walk. After another three days of treatment she was restarted at a 50% dose reduction. Repeat neurological examination on the last day of IL-2/IFN-α and 10 days later showed no change from the examination on 21 February.

She received a second 25 day course of IL-2/IFN-α therapy (23 March to 18 April), at a 50% dose reduction, followed by a right radial neurectomy. Neurological examination one week after operation showed significant progression of left leg weakness and atrophy of intrinsic hand muscles. Brain MRI six weeks after operation showed no Gd enhancement or increased plaque load. The patient remains in remission from renal cell carcinoma four years after IL-2/IFN-α therapy.

Whereas the precise mechanism for neurological deterioration in this case remains uncertain, we propose that treatment with IL-2 focally accelerated immune mediated demyelination without formation of new multiple sclerosis plaques. Systemic immune activation was precipitously implicated in a case of fatal encephalomyelitis beginning four days after the initiation of IL-2 therapy, in a neurologically normal patient with metastatic renal cell carcinoma. Histopathological changes of acute perivascular inflammation and a CSF formula consistent with breakdown of the blood-brain barrier were demonstrated in this case. These features would be expected in inflammatory demyelination, which requires breakdown of the blood-brain barrier and recruitment of systemic mononuclear cells into the brain. By contrast, chronic active plaques in patients with progressive multiple sclerosis already contain the necessary T cells, antigen, antigen presenting cells, and costimulatory signals for further demyelination.1 The mechanism by which naitrate plus nitrite concentrations in CSF

Lumbar CSF concentrations of nitrate plus nitrite are increasingly being used to investigate neurological diseases.1,2 These 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.3 There is some experimental evidence to support this.4

We have recently reported an age related decrement in the concentration of CSF nitrate plus nitrite in a paediatric reference population aged 0-63 years.5 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 nitrate plus nitrite 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 = 0.65, P < 0.001) than between log concentrations (nitrate plus nitrite) and age (r = 0.64, P = 0.677).

Because lumbar CSF is thought to act as a sump in humans, this finding implies a rostrocaudal gradient in CSF nitrate plus nitrite concentrations. In turn, a rostrocaudal gradient implies that nitrate is generated higher in the neuraxis than the lumbar sac, which provides indirect evidence that lumbar CSF nitrate plus nitrite is generated in the brain presumably from the breakdown of nitric oxide. These findings do not, however, detract from the use of appropriate reference inter-