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. These reports noted rapid progression 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 2b (IFN-α). Although IL-2/INF-α therapy temporally 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 metastases to the distal right femur and right lower lobe of the lung. Neurological examination six weeks after total knee arthroplasty and immediately before starting IL-2/INF-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 paraesthesia, 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/m2/24 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 encephalopathy and mild myalgias. Three days after beginning IL-2/INF-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 left lower limb, 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/INF-α therapy was discontinued. Brain and spinal cord MRI showed no evidence of metastatic spread, Gd enhancement, or increase in multiple sclerosis lesion burden. Serial MRI was performed and quantified according to a standardised protocol to minimise interobserver error. Analysis of CSF showed increased intrathecal IgG synthesis without any pleocytosis or evidence of breakdown of the blood-brain barrier. Three days after discontinuation of rIL-2/INF-α (21 February), visual acuity had improved to 20/20 in both eyes and she had antigravity strength in the left leg. She remained unable to stand, transfer independently, or walk. After another three days off treatment her gait was again restarted at a 50% dose reduction. Repeat neurological examination on the last day of IL-2/INF-α and 10 days later showed no change from the examination on 21 February 1992.

She received a second 25 day course of IL-2/INF-α therapy (23 March to 18 April), at a 50% dose reduction, followed by a right frontal craniotomy. 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 increase in plaque load. The patient remains in remission from renal cell carcinoma four years after IL-2/INF-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 probably implicated in a case of fatal encephalomyelitis beginning four days after the initiation of IL-2 therapy, in a neurologically normal patient with metastatic melanoma. 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 acute inflammation, 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.13 Administration of exogenous IL-2 could theoretically accelerate this process, through in vivo stimulation of activated T cells and macrophages, without producing a significant change in the appearance of standard T2 weighted or gadolinium enhanced MRI. This hypothesis may be tested in the future by employing magnetic resonance spectroscopy and magnetic transfer imaging to directly assess the appearance of plaques.

Despite our patient's neurological deterioration, she experienced a gratifying antitumour response to IL-2/INF-α therapy. Until clinicians gain further experience with IL-2 therapy in patients with multiple sclerosis, decisions to initiate treatment must be made empirically based on the patient's overall functional status.

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References


A rostrocaudal gradient of nitrate plus nitrite concentrations in CSF

Lumbar CSF concentrations of nitrate plus nitrite are increasingly being used to investigate neurological disease.10-12 These compounds 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 neuraxis.13 There is some experimental evidence to support this.14 We have recently reported an age related decrement in the concentration of CSF nitrate plus nitrite in a paediatric reference population aged between 0-65 years.15 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 taken to 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) of the child when the height was taken into account in a partial correlation analysis, there was no longer any relation between log concentrations (nitrate plus nitrite) and age (r = 0.07, P = 0.677).

Because a 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 metabolic nitrite is generated higher in the neuraxis than the lumbar sac, which provides indirect evidence that lumbar CSF nitrate plus nitrite is generated in the neuraxis, presumably from the breakdown of nitric oxide.

These findings do not, however, detract from the use of appropriate reference inter-

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