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. 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 2b (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 and 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 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 afebrile 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 right lower 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 spread. Gd enhancement, or increase in multiple sclerosis lesion burden. Serial MRI was performed and quantified according to a standardised protocol to reposition any treatment error. 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 antigravity strength in the left leg. She remained unable to stand, transfer independently, or walk. After another three days off treatment, IL-2/IFN-α 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 knee arthroplasty. 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 a neuroinflammatory process, 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. Administration of cytokines 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 immunological activity in plaques from patient and myelin breakdown products and demyelination respectively.

Despite our patient’s neurological deterioration, she experienced a gratifying anti-tumour response to IL-2/IFN-α. 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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vals, which in most cases will be determined by the patient’s age.

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