also better associated with recurrence when the upper tertile was used as cut-off point (Table 1). In the multivariate Cox's regression analysis, SPF of the gated population contributed prognostic information in addition to SPF of the ungated population when both variables were included in the analysis.

The strengthened correlation with recurrence in the DNA aneuploid breast carcinomas, when using the cytokeratin method, is in concordance with earlier findings in DNA-euploid breast carcinomas [5]. This is probably due to the flow cytometric exclusion of contaminating cells, which may overlap in the DNA aneuploid region and falsely enhances the SPF. The exclusion is indicated by the decreased SPF found with the cytokeratin method in the present study ($P = 0.0002$) as well as by Kimmig and associates [9]. To facilitate comparison between methods, SPF was divided either by the upper tertile, or treated as a continuous variable in the logistic regression analysis and, furthermore, cells were taken from the same suspension for both methods. Our conclusion is that SPF calculated from cytokeratin-positive cells provides prognostic information in addition to ungated S-phase values in DNA aneuploid breast carcinomas.

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Reversible Neurotoxicity During Interleukin-2 Therapy for Metastatic Renal Cell Carcinoma

J.M. van Laar, M.A. van Buchem, N. Weyl and F.J. Cleton

IMMUNOTHERAPY WITH interleukin-2 (IL-2) is commonly employed to treat metastatic renal cell carcinoma (RCC). However, the occurrence of systemic side-effects may lead to discontinuation of therapy. These include fever, hypotension, oliguria and oedema due to a vascular leak syndrome [1]. It is thought that the adverse effects are mediated by the interplay of activated endothelial cells, lymphocytes and natural killer cells as well as cytokines, such as TNFα (tumour necrosis factor). Since the severity of side-effects depends on dosage and mode of administration, current practice favours low dose, subcutaneous (s.c.) administration of IL-2. The present case report demonstrates that even this may lead to (reversible) neurotoxicity.

A 45-year-old female was referred to our hospital in November 1991 because of metastatic RCC. In 1984, she had undergone unilateral nephrectomy and retroperitoneal lymph node dissection for RCC (T3N0M0). After a disease-free interval of 7 years, she presented elsewhere with abdominal discomfort and vaginal bleeding due to an ovarian tumour. Because of this, hysterectomy and ovariectomy were performed. Microscopical examination of the ovarian tumour revealed the presence of metastatic RCC. During follow-up, metastatic RCC was also detected in the left adrenal gland. Therefore, on 4 December 1991, cyclic treatment with OKT3 monoclonal antibody and low-dose s.c. IL-2 (twice daily 3.6×10^6 IU/m^2) was initiated. Although mild fever and anorexia were present initially, the patient did not develop neurological symptoms in this period. The treatment resulted in stable disease until November 1993, when a CT (computed tomography) scan demonstrated an increase of the adrenal metastatis. Consequently a rechallenge with low dose s.c. IL-2 (twice daily 3.6×10^6 IU/m^2 was initiated on 11 November 1993. On day 14 after initiation of therapy, however, the patient complained of headache, disturbed vision, slowness of thought, nausea and vomiting. On day 22, she developed paresis of her left arm, dysarthria and incontinence. On both occasions, physical examination did not reveal additional abnormalities such as hypotension or meningism. Cortisol deficiency was excluded. A CT scan of the brain before and after intravenous administration of contrast medium failed to show any

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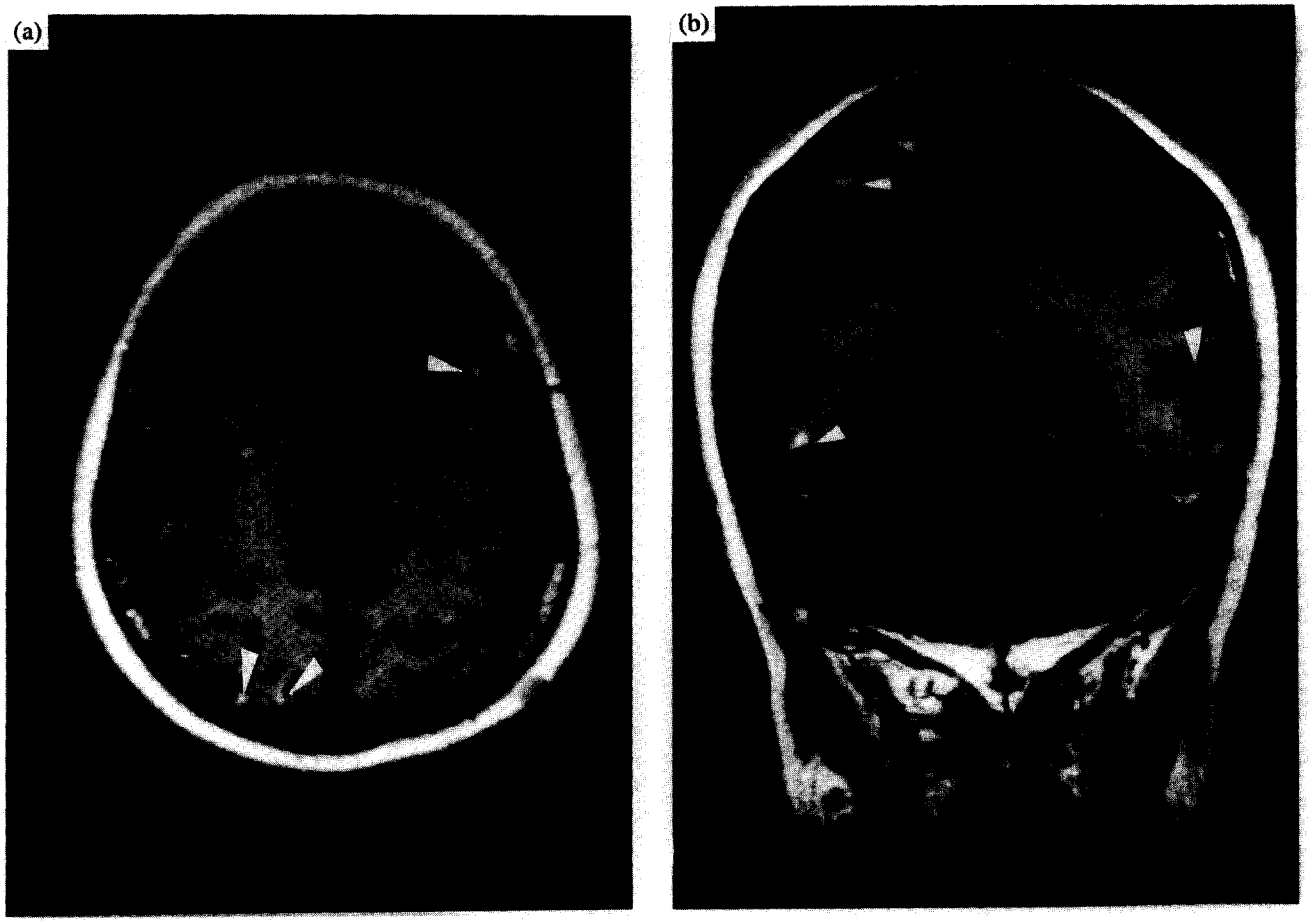

Figure 1. MRI performed on day 35 after initiation of IL-2 therapy: (a) axial and (b) coronal T1-weighted images showing areas of contrast-enhancement (indicated by arrows) in the grey and subcortical white matter.

intracranial pathology. IL-2 treatment was discontinued, and by day 25 all symptoms had disappeared. Again, a CT scan of the brain, as well as examination of cerebrospinal fluid, were normal. In contrast, magnetic resonance imaging (MRI) performed on day 35 showed multiple areas of increased signal intensity on T2-weighted images in both cerebral hemispheres. On T1-weighted images, some of these areas were slightly hypointense compared to the surrounding cerebral parenchyma. Most areas showed enhancement after intravenous administration of Gadolinium–DTPA, indicating a disturbance of the blood–brain barrier (Figure 1). The lesions were found in the grey matter and in the subcortical white matter. Follow-up MRI performed 3 weeks later showed a decrease in the size of the lesions on T2-weighted images and failed to show enhancement. Five months later, a further decrease in the size of the lesions on the T2-weighted images was observed with MRI. Interestingly, the waxing and waning of neurological deficits was preceded by a transient leucocytosis (peak level 39.9×10^9/l on day 14), predominantly accounted for by eosinophils (18.3×10^9/l).

The patient's case history demonstrates the neurotoxic potential of low dose IL-2 immunotherapy. Whereas IL-2 therapy, like other cytokine therapies, for example, interferon-alpha [2], is often accompanied by mild symptoms such as headache and lethargy, it may also have serious neurological sequelae, as illustrated by the present case history. This confirms previously reported observations of transient focal neurological deficits [3] and presumed neurological ischaemic attacks [4] and additionally stresses the diagnostic value of MRI. The data obtained by MRI in our patient suggest the presence of multiple lesions, possibly inflammatory, with a disturbed blood–brain barrier, accompanied by focal oedema in the acute phase, finally resulting in areas of scar tissue (gliosis). Based on similar clinical and radiological findings in a patient treated with IL-2 for metastatic melanoma, others have postulated that activated lymphocytes might be involved in the formation of such infiltrates [5]. Indeed, perivascular infiltration by activated T lymphocytes as well as perivascular haemorrhages were found at autopsy in the brain of another patient treated with IL-2 for metastatic melanoma [6]. The clinicopathological features in that case were thought to be triggered by an autoreactive process involving activated T lymphocytes directed against myelin because of its resemblance to acute encephalomyelitis. Whether the lesions in our patient were induced by a similar mechanism or even were causally related to the administration of IL-2 cannot be definitively concluded, because of differences in disease course and laboratory findings. With regard to the latter, the concomitance of clinical symptoms and eosinophilia in the present case may also indicate a pathogenetic role for activated eosinophils. Repeated cycles of IL-2 immunotherapy induce sustained high levels of IL-5 [7], leading to mobilisation and activation of eosinophils [8]. Furthermore, IL-2-related eosinophilic myocarditis [9] and cholecystitis [10] in combination with eosinophilia have been reported.

Whatever the precise pathogenetic mechanisms involved, it can be concluded that, in patients repeatedly treated with low dose s.c. IL-2 for RCC, severe neurological symptoms may

develop. In our patient, the symptoms were associated with multiple lesions as visualised with MRI, and appeared to be reversible after discontinuation of IL-2.

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