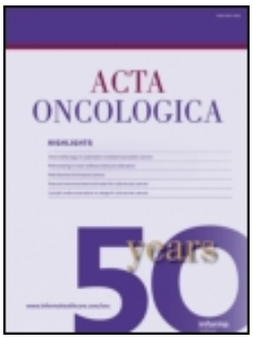

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Severe hyponatremia caused by hyperglycaemia due to interferon alpha therapy in advanced renal cell carcinoma

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in the field of oncoplastic breast surgery. Cross-speciality training in this field is not being offered and in order to become an oncoplastic breast surgeon in Scandinavia, most trainees need to be dually trained in general and plastic surgery. This method of unfocused training may take far too many years to complete, many of which may be irrelevant to the trainee's needs. It is time to move forwards. Scandinavian breast units already offering oncoplastic techniques to their patients should strive to set up ambitious oncoplastic training programs. Furthermore, as the hype surrounding oncoplastic breast surgery may have been driven more by enthusiasm than evidence, the long academic tradition of the Scandinavian training system should put them in the forefront of future research in this area.

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Severe hyponatremia caused by hyperglycaemia due to interferon alpha therapy in advanced renal cell carcinoma

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To the Editor

Renal cell carcinoma (RCC) accounts for approximately 3% of all adult malignancies and 2% of all cancer-related deaths [1]. Palliative treatment options for advanced RCC consist nowadays of Interferon-alfa (IFN-alfa) in combination with bevacizumab and preceded by cytoreductive nephrectomy in good prognosis patients and of targeted therapy against growth factor receptors and vascular endothelial receptors in intermediate and poor prognosis patients [2,3]. The mean response rate of IFN-alfa monotherapy is 17%. Most frequently reported side effects of this treatment are fever, malaise, myalgia, headache, anorexia and nausea. We report the history of a middle-aged man with a rare complication of IFN-alfa therapy.

A 59-year-old man was admitted because of fatigue, weight loss and anorexia. His medical history revealed hypertension, gout and a renal cell carcinoma of the left kidney 6 years ago, for which he underwent a tumour nephrectomy. Four years later a partial colectomy was performed because of local recurrence with extension in the flexura lienalis. Six months later a pulmonary metastasis was seen on a routine chest CT-scan. He was treated within the framework of a randomized phase

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II-study, consisting of IFN-alfa 2b three times weekly 9 million units in combination with a placebo or targeted therapy with the recombinant, humanized monoclonal antibody against vascular endothelial growth factor (bevacizumab) every 2 weeks. This patient was randomized to the bevacizumab group. Other co-medication consisted of enalapril, hydorchlorthiazide, doxazosine and allopurinol. During this treatment stable disease was achieved. However, after 6 cycles of treatment, his clinical condition suddenly deteriorated with general weakness, malaise and loss of weight. Physical examination showed a blood pressure of 160/80 mmHg with a heart rate of 95 beats/min, weight loss of 11 kg in 2 weeks, and a slightly lower turgor.

The initial laboratory investigations showed a sodium level of 122 mmol/l (normal 137 to 144 mmol/l), a potassium level of 5.8 mmol/l (normal 3.4 to 4.6 mmol/l), urea of 17.9 mmol/l (normal 3.0 to 7.0 mmol/l), and creatinine of 192 μmol/l (normal level for this patient 90 μmol/l). Our first differential diagnosis was (prerenal) kidney failure due to malaise with low oral fluid intake and ongoing use of diuretics. However, additional laboratory investigations soon revealed the true cause of the extreme hyponatremia, i.e., a severe hyperglycaemia with a glucose level of 62 mmol/l in the absence of acidosis / ketosis. Serum osmolality was 357 msmol/kg and urine osmolality 525 msmol/kg, indicating the presence of a pseudohyponatremia caused by hyperglycaemia. Glycated haemoglobin was 11.3% and C-peptide 1.17 nmol/L.

So, our patient suffered from hyperglycaemic hyperosmolar syndrome as a major acute complication of new arousing or decompensated previous existent type 2 diabetes mellitus (DM). Prompt treatment was started, consisting of fluid replacement, insulin therapy, restoration of electrolyte disturbances and temporary discontinuation of IFN-alpha 2b and placebo/bevacizumab. After 10 days he was discharged of the hospital with a required daily dose of insulin of 220 IU. The patient restarted immunotherapy at the outpatient ward. In the following period, improvement of glycaemic control and a decrease of daily dose of insulin to 58 IU was obtained. After another five cycles of treatment, progressive disease was seen. As the performance status was still good, targeted therapy with another angiogenic inhibitor was started.

The development of DM in our patient was most likely due to IFN-alfa 2b. We are unaware of bevacizumab being associated with DM or insulin resistance. The normal C-peptide and the elevated HBA1c percentage are consistent with type 2 DM (caused by insulin resistance), which could have been developed or aggravated by IFN-alfa. Type 1 DM is an autoimmune disease mediated by the destruction of pancreatic β-cells leading to absolute insulin deficiency. Auto antibodies to pancreatic β-cells are markers of the ongoing autoimmune destruction.

IFN-alfa treatment appears to be an independent risk factor to develop glucose intolerance [4] or diabetes mellitus temporarily requiring insulin [5,6]. IFN can induce glucose intolerance by impairment of the early phase of insulin response to glucose and by reduction of the sensitivity of peripheral tissues and liver to insulin [7]. On the other hand, IFN-alfa is a cytokine involved in the immuno pathology that leads to β-cell destruction [8–10] and its administration is related to other autoimmune processes [11].

In RCC, one case report was published of hyperglycaemia due to insulin resistance caused by IFN-*gamma* [12]. In a phase II-study in advanced RCC patients treated with IFN-alpha 2b, one of 22 patients experienced a grade 4 hyperglycaemia [13]. Distinction between insulin resistance or β-cell injury (autoimmune DM) was not made.

In a patient with chronic active hepatitis B, exacerbation of a previous controlled diabetic has been reported during IFN-alfa treatment [14]. In chronic hepatitis C (HCV), treatment with IFN-alfa resulted in *de novo* DM in 0.08–0.7% of cases according to two retrospective studies [15,16]. The distinction between autoimmune and non-autoimmune DM could not be made in these studies because pancreatic auto antibodies were not investigated. However, there is probably also a direct relationship between hepatitis C virus infection and DM (mainly type 2) [4]. Thirty-three reported cases of type 1 DM during or soon after IFN therapy for chronic hepatitis C were described from 1992 till 2003 [17–19]. Fabris et al. reviewed 31 of these cases in which various types of IFN, doses IFN and durations of therapy were given [17]. The latency of DM type 1 after IFN therapy commencement ranged from 10 days to 4 years. Most of the cases (74%) required permanent insulin treatment. According to this review the development of DM type 1 during IFN treatment resulted from the amplification of previously existing autoimmunity against pancreatic β-cells. Some suggest that a clinician should investigate pancreatic auto antibodies before and during the treatment to determine the risk of future DM development [17–20].

In conclusion, DM is a rare but serious complication of IFN-alfa therapy. The cause of DM during IFN-alpha can be insulin resistance as well as β-cell injury. Furthermore, exacerbation of a previously existing DM can also occur. The onset of the disease may be particularly abrupt. It is important for clinicians to be aware of this possible serious side effect of IFN-alfa.

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Oxaliplatin-induced long QT syndrome in a patient with appendiceal adenocarcinoma

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To the Editor,

A 44-year-old woman with appendiceal adenocarcinoma presented for her eleventh cycle of oxaliplatin, folinic acid (FA) and infusional 5-fluorouracil (5-FU) (e.g., FOLFOX-4). Before the chemotherapy session began, blood pressure was 120/78 mmHg, respiratory rate was 18 per minute, heart rate was

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