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Scleroderma-like syndrome triggered by Gadolinium

Sir,

We read with interest the report by Grobner [1] of five end-stage renal disease patients who developed nephrogenic fibrosing dermopathy (NFD) following gadolinium exposure. We also observed a 48-year-old male dialysis patient with a similar complication after MR-angiography. The patient had been dialysis-dependent for 6 years as a consequence of membranous nephropathy. He suffered from widespread atherosclerotic disease (coronary heart disease and peripheral arterial disease), and had needed repeated angioplastic interventions.

For investigation of a new claudication, MR-angiography of the lower limbs, using gadodiamide, was performed. The procedure was chosen instead of a direct angiography, because the patient wanted to circumvent possible complications of arterial puncture.

When he was dialysed the day after the examination, he complained of burning sensations and reddening of the lower and upper extremities. In the subsequent weeks, the skin became indurated and shiny, and the joints of the affected limbs became stiff.

Systemic sclerosis was considered, but the clinical appearance was also interpreted as a myxoedema by one colleague. Further evaluation could confirm neither systemic sclerosis (no auto-antibodies, oesophageal motility undisturbed) nor a thyroid dysfunction. On presentation to an academic dermatology department, the clinical diagnosis of systemic sclerosis was nevertheless made, based on the skin appearance alone. A deep-skin biopsy from an affected area, taken 6 weeks after the MR-angio, showed broadening and sclerosis of the dermis extending to the subcutis. Adjacent muscular tissue and vessels were free from inflammation—a dense immunostaining for CD34 as a marker of fibrocytes was absent, and the diagnosis of NFD was discarded.

Mobility of affected joints responded to daily physical therapy. However, painful indurations remained, most pronounced after the long interdialytic interval.

Pulse injections of 250 mg methylprednisolone brought a short-term relief. Daily treatment with 50 mg imurek was well-tolerated and improved the symptoms, constantly. The skin became smoother and less painful and the mobility of joints increased. The improvement was satisfactory not earlier than 9 months after the MR-angio and 3 months of imurek-treatment. The patient has now received a renal transplant and his condition has further improved.

We are convinced that our patient suffered this complication as a consequence of the gadolinium exposure. Since the skin appearance was indeed reminiscent of a myxoedema, we regard ‘scleromyxedema-like illness of renal disease’, coined by others for NFD [2], an appropriate descriptive term.

In contrast to Grobner’s report, the onset of symptoms was immediate in our patient and the histology of the affected skin was not as suggestive for NFD as in his cases. Finally, our patient seems to have responded to systemic immunosuppression, which had failed in Grobner’s patients.

Therefore, presentation of this gadolinium-related syndrome may be more heterogenous than suggested in Grobner’s article [1], and needs further characterization.

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Mathematical modelling of the course of chronic renal failure

Sir,

Nephron loss, in the course of chronic renal failure (CRF), causes an increase in the single nephron glomerular filtration rate (SNGFR) in the remaining nephrons, with a magnitude roughly correlating with the extent of nephron loss [1]. This compensatory hyperfiltration, although minimizing GFR loss in the short-term, has proven detrimental in the long-term due to its damaging effects on remnant glomeruli [2]. Considering the importance of serial monitoring of GFR in assessing disease activity in CRF, we developed a mathematical model to predict GFR based on the number of surviving nephrons. A general scheme is presented below.

Consider each nephron as a differential element $d_i$ (after sorting all nephrons at time $t=0$ in an ascending order of SNGFR) in the remaining nephrons, with its corresponding SNGFR as $R_i$. The nephron $d_i$ dies when $R_i$ reaches a critical value of $f_{\text{max}}$, which causes a uniform increase in SNGFR throughout the whole kidney [3,4]. Let $N(t)$ be the number of surviving nephrons at time $t$. We will then have $\text{GFR}[N(t)] = \int_0^{N(t)} R_i \, dt$. Having considered the simplest physiologically plausible case of
\( df_i(0) \) as a linear function of \( d_i \), and assuming \( N(0) = 2 \times 10^6 \) and \( \text{GFR}[N(0)] = 120 \text{ cc/min} \), the following formula was obtained after solving a second-order ordinary differential equation:

\[
\text{GFR}[N(t)] = 3 \times 10^{-11}N(t)^2 - 1.2 \times 10^{-4}N(t) \ln \frac{N(t)}{2 \times 10^6}
\]

GFR decline is minimized in early CRF due to the compensatory hyperfiltration in the remaining nephrons. However, compensation fails after a while and an accelerated progression towards end-stage renal disease (ESRD) ensues (Figure 1). This pattern is in close agreement with the time-dependent pattern of GFR fall observed in practice [6]. This is the first mathematical model of CRF which considers the common downhill pathway of diseases leading to ESRD. Also, we made an indirect estimate of the fatal SNGFR threshold (twice the mean SNGFR) using our model. The model can be improved by considering the time delay between the deaths of nephrons reaching the fatal threshold. Incorporating the continuous adverse effects of the underlying disease after the initial damage, such as those posed by advanced glycation end products [7], might also be beneficial. Although physiologically plausible, our model is highly theoretical, necessitating validation by clinical experiments.

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