cardiovascular manifestations is similar to that of systemic necrotizing vasculitis [7]. Early diagnosis and treatment can significantly reduce morbidity and mortality. Therefore we feel that nephrologists should consider this rare condition in the differential diagnosis of patients presenting with ocular–auditory and renal symptoms.

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When the kidney catches a cold: an unusual cause of acute renal failure

Sir,

We report the case of a 51-year-old man with no medical history and no treatment who developed acute renal failure (ARF) after cold water immersion. He was admitted to hospital in August after nearly drowning in a lake while trying to save his dog which was drowning. When he got back to the shore, he was exhausted and fainted briefly. He was transported to the hospital in a warm ambulance. Arriving at the hospital 1 h later, he was conscious but sleepy; his rectal temperature was 35.8°C, his blood pressure 130/70 mmHg and there was no haemodynamic failure during the observation period. Physical examination showed no abnormality. Laboratory studies showed: serum creatinine, 141 µmol/l; urea, 6.8 mmol/l; C-reactive protein <5 mg/l; leukocytosis count, 18 000/mm³, aspartate aminotransferase, 31 U/l; alanine aminotransferase, 27 U/l; creatine phosphokinase (CPK), 135 U/l; ionogram and coagulation functions were normal. An arterial blood gas sample showed moderate metabolic acidosis and hypoxaemia (pH 7.33, HCO₃⁻ 16.6 mmol/l, PCO₂ 32.6 mmHg and PO₂ 60 mmHg). Electrocardiogram and chest radiography were normal. The patient was discharged after a 24 h observation period.

He was re-admitted 5 days later, complaining of being tired and anuric. Biological analysis revealed ARF (creatininaemia 1600 µmol/l, urea 38 mmol/l) with hyperkalaemia (6.1 mmol/l), hyperphosphataemia (3.12 mmol/l), normocalcaemia (2.27 mmol/l) and metabolic acidosis (pH 7.34, bicarbonates 18.4 mmol/l). There was no elevation of muscle and hepatic enzymes, no red or white blood count disorder; blood protides and albumin were respectively 61 and 33.7 g/l, and proteinuria was 0.33 g/24 h. There was no infectious or immunological biological abnormality. Urinary analysis showed <1000 red blood cells/ml, 20 000 leucocytes/ml and atericule culture was sterile. Urinary ultrasonography was normal, and Doppler ultrasonography showed no stenosis of the renal arteries. The patient needed three sessions of dialysis over the succeeding 3 days and then renal function recovered spontaneously. Creatininaemia was 652 µmol/l 3 days after the last haemodialysis session, 125 µmol/l 10 days later and 90 µmol/l 7 weeks later. Given the clinical course of this ARF, no renal biopsy was performed and the diagnosis of acute tubular necrosis was retained.

ARF associated with severe hypothermia has been reported widely, but is usually the direct consequence of associated overt haemodynamic failure and/or rhabdomyolysis [1]. ARF related to cold water immersion has to our knowledge only been reported once, by Yoshitomi et al. [2], who described the case of a 27-year-old patient who developed histological acute tubular necrosis after nearly drowning in a lake, and then lying on the lake shore for 2 h while the external temperature was –5°C. Interestingly, in our case, the accident occurred in summer when the water temperature was not very cold, and our patient probably experienced only moderate hypothermia as assessed by his central temperature (35.8°C) upon arrival at the emergency room. Thus our observation illustrates that the association of prolonged water immersion with even moderate hypothermia can trigger acute tubular necrosis in a patient not particularly at risk of ARF. The mechanism responsible for the renal hypoperfusion is unclear. Water immersion increases venous return and thereby raises cardiac output, and natriuresis [3]. Conversely, removal from water acutely decreases cardiac output. Hypothermia may blunt or delay the normal haemodynamic response that allows maintenance of an adequate renal blood flow in this setting. In an animal experimental model, hypothermia, in contrast, has been shown to prevent ischaemia–reperfusion-induced renal injury [4]. Thus, rather than hypothermia per se, rewarming coincident with renal hypoperfusion after removal from water could be involved in the pathogenesis. Hypoxaemia associated with near drowning could have also played a role in the renal insufficient oxygen delivery. Whatever the mechanism involved, nephrologists should be aware of this rare cause of ARF.

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Erythropoietic proteins and antibody-mediated pure red cell aplasia: a potential role for micelles

Sir,

In a recent edition of NDT, Locatelli et al. [1] provided a useful review of the chronology and potential causes of anti-erythropoietin antibody-mediated pure red cell aplasia (PRCA) with erythropoiesis-stimulating agents, together with current actions and recommendations. The authors note the potential causal link between a change in the formulation of Eprex® (epoetin alfa), where the stabilizer human serum albumin was replaced with polysorbate 80 and glycine, and the recent upsurge in PRCA cases associated with its use [2]. However, a mechanism for how this formulation change breaks the immune tolerance to erythropoietin was not given.

In principle, two main mechanisms exist by which B cell tolerance to self antigens can be broken. One way of breaking tolerance is to present the self antigens in combination with a danger signal, such as denatured protein or endotoxins. The most potent way to induce antibodies to self antigens is to present the self antigens in highly structured arrays that resemble viral capsid-like structures. Several potential causes of antibody induction with Eprex have been put forward, including the presence of leached contaminants from the rubber stoppers of pre-filled syringes or the silicon oil used as a lubricant, which may act as ‘danger signals’.

We have shown recently the presence of surfactant molecule aggregations (otherwise known as micelles) in the Eprex formulation, which are caused by the high concentration of polysorbate 80. We have also shown that epoetin alfa is associated with these micelles, which may lead to the formation of structures with repeated epitope antigens. These, in turn, may be present at the surface of the micelles and break B cell tolerance. We employed gel permeation chromatography (GPC) and enzyme-linked immunosorbent assay (ELISA) to determine whether samples of Eprex (epoetin alfa) and NeoRecormon® (epoetin beta) formulations contained micelles and how much epoetin was micelle-associated [3]. The critical micelle concentration (CMC) is the concentration of a surfactant at which an appreciable number of micelles are formed, and CMCs for polysorbates 20 and 80 have been calculated previously [4]. Notably, Eprex contains 0.03% (w/v) Tween (polysorbate) 80, around 20 times its CMC; in contrast, NeoRecormon contains 0.01% (w/v) Tween 20, only approximately 1.5 times its CMC.

GPC analysis confirmed that the Eprex formulation contained micelles of polysorbate 80, while no micelles were detected with NeoRecormon. Subsequent analysis of the GPC fractions by ELISA demonstrated that with the Eprex samples, small amounts of epoetin were co-eluted with the polysorbate 80 micelles. No such co-elution was seen with NeoRecormon. The findings suggest that not only does the Eprex formulation contain polysorbate 80 micelles, but also that epoetin alfa molecules are solubilized in or attached to these micelles.

Micelle-associated epoetin is, therefore, a potential risk factor for immunogenicity in anaemic patients, and further investigation utilizing animal models may provide additional relevant data.

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Managing refractory uraemic pericarditis with colchicine

Sir,

Pericarditis is a complication of end-stage renal disease (ESRD), still occurring in 20% of uraemic patients before and at the initiation of haemodialysis [1]. Multiple factors contribute to the appearance of uraemic pericarditis, which responds readily to treatment and has a good prognosis in the majority of cases. We present a patient with ‘refractory uraemic pericarditis’ who ultimately responded to colchicine. The use of colchicine in uraemic patients with pericarditis has not been reported previously.

A 48-year-old woman, suffering from ESRD due to autosomal dominant polycystic kidney disease, attended our clinic in August 2000. She manifested tachycardia and deep heart tones without fever, dyspnoea, thoracic pain or cough. Laboratory tests were compatible with ESRD. There was no leukocytosis. Chest X-ray, electrocardiogram and heart ultrasound revealed a large amount of pericardial effusion (anterior wall, 9 mm; posterior wall, 17 mm), diastolic dysfunction and hypertrophy of the left ventricle; the ejection fraction remained within a satisfactory range (65%). The patient was enrolled in daily 3 h haemodialysis sessions without anticoagulation. A week later, a new ultrasound revealed a large amount of pericardial effusion (anterior wall, 7 mm; posterior wall, 15 mm). Moreover, after 3 weeks of intensive dialysis, a progression of the effusion was noticed (anterior wall, 12.4 mm; posterior wall, 21.1 mm), while the ejection fraction remained stable. The patient’s condition was also