Nephrotic syndrome associated with isotretinoin

Sir,
Isotretinoin, a synthetic retinoid, is now used commonly in the treatment of moderate to severe acne, poorly responsive to antibiotics and local therapy [1]. Known adverse effects are: cheilitis, dry lips, dry mouth, conjunctivitis, xerosis,

pruritis, hair thinning, nausea and vomiting, pain and tenderness of the bones, and headache [2]. Changes in liver function tests and lipid profile are also noted [2]. Renal involvement is very rare [3,4]. We report a case of nephrotic syndrome following the use of isotretinoin.

A previously healthy 19-year-old male was admitted to the outpatient department of nephrology with complaints of facial, pretibial and ankle oedema. He had a weight gain of 12 kg over the 2 months prior to admission. There was a history of severe acne, for which he was treated with isotretinoin (40 mg/day) for 4 months. There was no history of familial renal disease, hypertension, diabetes mellitus or the use of (other) drugs. There were no complaints of arthralgia, myalgia, exanthema or hair loss. Physical examination revealed a blood pressure of 130/80 mmHg and pulse rate 84 beats/min. There was significant peri-orbital, ankle and pretibial oedema. Relevant laboratory data included: ESR 83 mm/h (normal <15), Hb 8.3 mmol/l (normal 8.5–11.0) and leucocytes of 7.6×10^{-9}/l (normal $4–10 \times 10^{-9}$/l) with normal differential count. Serum creatinine was 89 μmol/l (normal 75–110); urea 4.0 mmol/l (normal 2.5–7.0); Na 142 mmol/l (normal 135–145); K 4.7 mmol/l (normal 3.5–5.0); total protein 46 g/l (normal 60–80); albumin 21 g/l (normal 35–50); cholesterol 8.0 mmol/l (normal 3.5–6.5). Urinalysis revealed no erythrocytes, leucocytes or casts; proteinuria amounted to 10.3 g/24 h. Serological studies, i.e. direct Coombs test, RA test, ANA and anti-dsDNA were all negative. Complement factor C3 level was 1.25 mg/l (normal 0.8–1.6) and C4 level 0.16 mg/l (normal 0.15–0.40) respectively. Virological screening (i.e. HBsAg, anti-HCV, anti-HIV) was negative. Renal ultrasound showed normal-sized kidneys. Histologic examination of a percutaneous renal biopsy revealed 18 glomeruli without light-microscopic aberrations. Immunofluoresence revealed only sporadic mesangial depositions of IgM and C3. Findings were compatible with a diagnosis of minimal change disease. Isotretinoin was stopped and prednisone (60 mg/day) was started. The nephrotic syndrome responded within 4 weeks of treatment and prednisone was tapered off until being stopped after 3 months. At the time of his latest follow-up, there are no symptoms or signs of recurrence of the nephrotic syndrome.

Thus, our patient developed a full-blown nephrotic syndrome concurrent with the use of isotretinoin. The first clinical manifestations (i.e. weight gain and oedema) were noted after using this drug for 2 months. Histologic examination revealed minimal change disease. Minimal change disease can be drug-induced, as has been observed with drugs such as ACE-inhibitors, 5-aminosalicylic acid, sulphasalazine and NSAID [5]. To date, no other cases of possible isotretinoin-induced nephrotic syndrome have been reported in the literature. However, Horber *et al.* [3] described renal impairment with hypercalcaemia and mild proteinuria in a 56-year-old patient treated for 36 months with etretinate (another synthetic retinoid) for superficial bladder tumour. After etretinate had been withdrawn hypercalcaemia disappeared and renal function remained stable. One year later, renal biopsy showed lymphoma infiltration. Pavesese *et al.* [4] described renal impairment (serum creatinine level 259 μmol/l) and proteinuria (0.8 g/l) in a 34-year-old male treated for 2 months with isotretinoin for severe acne conglobata. After discontinuation of isotretinoin, serum creatinine level returned to normal and proteinuria disappeared. Manufacturers information revealed that over the last 7 years, mild proteinuria has been reported 60 times, in most cases with a temporal relationship to isotretinoin in the absence of other risk factors (Department of Regulatory Affairs and Drug Safety, Roche Pharmaceuticals, Mijdrecht, The Netherlands). This has recently led to the inclusion of proteinuria as a potential complication in the international product information. In our patient, there was a close temporal relation between treatment with isotretinoin and the development of a full-blown nephrotic syndrome, and rapid improvement was noted after withdrawal of the drug and short-term treatment with corticosteroids. Although we can not exclude that the nephropathy was coincidental, combined data suggest that the nephrotic syndrome may have been caused by isotretinoin.

[1]Department of Medicine Jos A. H. van Oers[1]
[2]Department of Dermatology Jaap de Leeuw[2]
Albert Schweitzer Hospital Eric F. H. van Bommel[1]
Location Amstelwijck Dordrecht
The Netherlands

1. Ortonne JP. Oral isotretinoin treatment policy. Do we all agree? *Dermatology* 1997; 195 [Suppl 1]: 34–37
2. Windhorst DB, Nigra TH. Clinical toxity of oral retinoids. *J Am Acad Dermatol* 1982; 6: 675–682
3. Horber FF, Zimmerman A, Frey FJ. Impaired renal function and hypercalcaemie associated with etretinate. *Lancet* 1984: 1093
4. Pavese P, Kuentz F, Belleville C, Rougé PE, Elsener M. Renal impairment induced by isotretinoin. *Nephrol Dial Transplant* 1997; 12: 1299
5. Fillastre JP, Godin M. Drug-induced nephropathies. In: Cameron S, Davison AM, Grunfeld J-P, Kerr D, Ritz E, eds. *Oxford Textbook of Clinical Nephrology*. Oxford University Press, Oxford: 1992: 159–175