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Case Report

A CF patient with progressive proteinuric renal disease: a CF-specific nodular glomerulosclerosis?

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Abstract

Cystic fibrosis (CF) is a multisystemic disease but without a classical disease-specific renal phenotype. A 32-year-old male patient with CF (ΔF508/ΔF508) presented with a nephrotic syndrome. Renal biopsy revealed nodular glomerulosclerosis (NGS) occurring in the absence of diabetes mellitus, amyloidosis and any other known common cause of NGS. He had a progressive decline in estimated glomerular filtration rate (eGFR) to chronic kidney disease stage V (eGFR <15 mL/min/1.73 m^2) over a 3-year period despite optimal medical management. This is the fourth reported case of NGS in a patient with CF without diabetes and is the first to originate from a European country. This case supports the concept of a CF-related NGS.

Keywords: CF renal disease; cystic fibrosis; nebulized tobramycin toxicity; nodular glomerulosclerosis

Background

The prevalence of chronic kidney disease in the adult cystic fibrosis (CF) population is estimated to be between 27 and 42% [1]. There are a number of CF-associated factors contributing to renal impairment in this population, including aminoglycoside toxicity, diabetic nephropathy, non-steroidal anti-inflammatory drug toxicity, renal amyloidosis, nephrocalcinosis and IgA nephropathy [2]. Despite the multitude of factors impairing renal function in the CF population, there is no classical disease-specific renal phenotype.

We present a case of a potential novel CF renal phenotype in this cohort of patients.

Case report

In September 2005, a 32-year-old male patient with CF (ΔF508/ΔF508) presented to the Cork Adult Cystic Fibrosis Centre with a 6-month history of peripheral oedema. Past medical history was otherwise unremarkable with infrequent previous infective pulmonary exacerbations and no courses of intravenous antibiotics over the previous 10 years. There was no past history of hypertension, smoking, hearing impairment or diabetes mellitus. Examination showed a blood pressure of 134/82 mmHg and mild pitting oedema. Forced expiratory volume in 1 second (FEV1) % predicted was stable at 57% predicted (2.36 L/min) and serum (creatinine) was 169 μmol/L. Dipstick urinalysis demonstrated 4+ protein without haematuria. A spot urine protein-to-creatinine ratio revealed severe proteinuria at 691 mg/mmol (estimated at 6.1 g protein/24 h) with an associated hypoalbuminaemia (24 g/L). The patient repeatedly had normal oral glucose tolerance tests (OGTT) and normal haemoglobin A1c (all <6.2%). Autoimmune screen was negative. Findings were consistent with a nephrotic syndrome, and treatment with an angiotensin-converting enzyme inhibitor and natriuretic agent was instigated and a renal biopsy performed.

Renal biopsy findings revealed nodular glomerulosclerosis (NGS) (Figure 1A), identical to the classic Kimmelstiel–Wilson lesion of diabetes mellitus. Congo red staining for amyloid was negative, immunofluorescence was negative for immunoglobulin deposition (polyclonal, IgG, IgA, IgM, C3c) and electron microscopy excluded fibrillary glomerulonephritis, amyloidosis and monoclonal immunoglobulin deposition disease.

Despite standard conservative management, he remained proteinuric, with a progressive deterioration in estimated glomerular filtration rate. An intercurrent growth of a mucoid strain of *Pseudomonas aeruginosa* led to the initiation of alternate monthly nebulized tobramycin 300 mg bis in die (BID) in July 2007 at his annual assessment, in keeping with best international standards of care for patients with CF. This led to a sharp decline in his renal function, reverting back to a steady baseline rate of renal function decline on discontinuation of same after September 2007 (Figure 2). No other changes to his therapies were made around this period and he was not on any other nephrotoxic medications. Subsequent

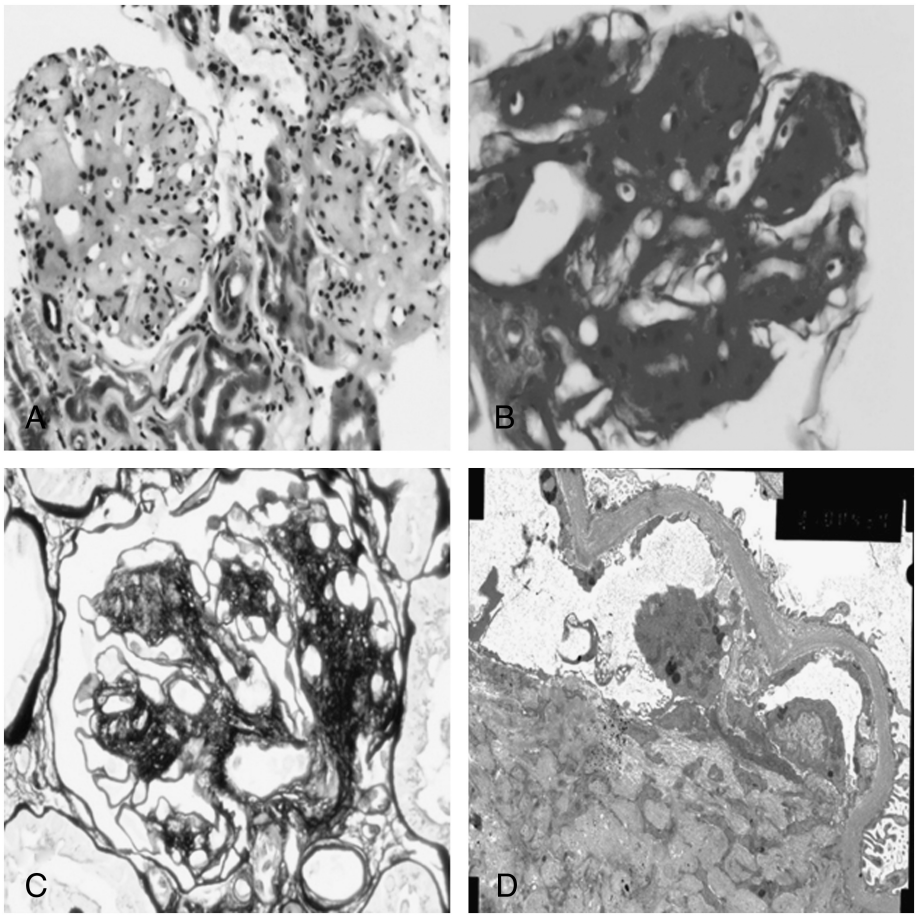

Fig. 1. (**A**) Haematoxylin and eosin-stained section demonstrating increased mesangial matrix with Kimmelstiel–Wilson-like mesangial nodules. (**B**) Periodic acid-Schiff positive staining of the nodular glomerulosclerotic lesion. (**C**) Periodic acid methenamine silver-stained section again highlighting the nodular lesion. (**D**) Electron microscopy of glomerulus demonstrating absence of amyloid fibrils and absence of evidence for monoclonal immunoglobulin deposition disease and fibrillary glomerulonephritis.

OGTTs have all remained normal. It is anticipated that he will require renal replacement therapy over the next 6 months and has been prepared for pre-emptive renal transplantation.

Discussion

This is the first reported case of NGS in a CF patient without diabetes mellitus in a European population and highlights the importance of multidisciplinary consultation in this cohort of patients.

The differential diagnosis for proteinuria in CF has, until recently, been predominantly limited to the identification of diabetic nephropathy, renal amyloidosis, IgA nephropathy, fibrillary glomerulonephritis and immunoglobulin deposition disease. Historically, the presence of

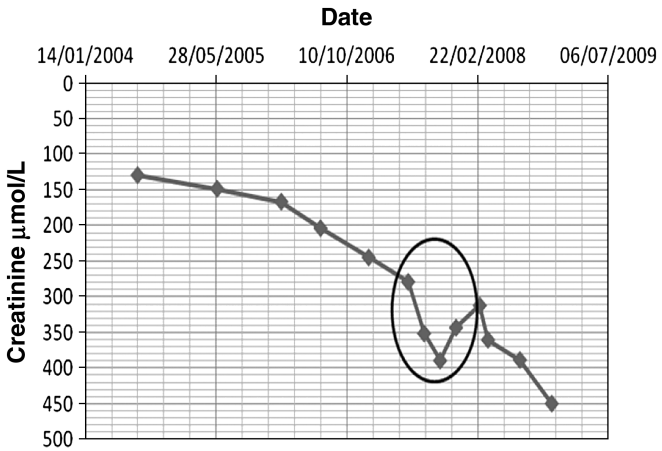

Fig. 2. Creatinine over time plot demonstrating the progressive decline in renal function and intercurrent reversible dip following the temporary initiation of nebulized tobramycin 300 mg BID in July and September 2007 (circled area).

NGS on renal biopsy was considered pathognomonic of diabetic nephropathy, designated the Kimmelstiel–Wilson lesion. NGS-like lesions have subsequently been described in a wide variety of conditions, most prominently amyloidosis and fibrillary glomerulonephritis [3].

Our findings are consistent with a previous Australian report describing NGS in CF patients in the absence of diabetes mellitus and other recognized causes of NGS [4], supporting the existence of a CF-related NGS. All patients described to date are male CF patients, >30 years of age, presenting clinically with nephrotic syndrome in the setting of repeatedly normal OGTTs. Interestingly, all patients progressed towards end-stage renal disease over the subsequent 4 years (personal communication with authors). Progressive renal failure is of increasing importance for patients with CF given that a creatinine clearance <50 mL/min/1.73 m^2 is frequently viewed as a contraindication to lung transplantation [5].

It is postulated that the pathogenesis of CF-related NGS in normoglycaemic, non-diabetic CF patients is similar to that of classic diabetic NGS, and may be mediated by specific binding to the receptor for advanced glycosylation end products (RAGE) [6]. In CF, chronic pulmonary infection/inflammation, in combination with reduced glutathione levels, contributes to an oxidative state; this oxidative state could result in the formation of advanced glycosylation end products (AGE) in conditions of normoglycaemia [4]. Patients with CF have a number of other potential mechanisms for RAGE activation in the absence of hyperglycaemia, including an increase in serum levels of the S100/calgranulin pro-inflammatory cytokines [4]. There is also emerging evidence that high-mobility group box 1 (HMBG-1), a potent inflammatory mediator known to be elevated in the serum of patients with CF [7], can cause an epithelial to mesenchymal transition; this has previously been shown to contribute to the renal accumulation of matrix protein by its action on RAGE [8]. We speculate that the pathogenesis of CF-related NGS is consequent to ligand binding of RAGE by S100/calgranulin, HMBG-1 and AGE.

Additionally, this is the first reported case of nebulized tobramycin-induced toxicity in a patient with CF with pre-existing chronic kidney disease. It is important to highlight the rapid decline in renal function on administration of nebulized tobramycin to our patient (Figure 2). This renal dysfunction was reversible following discontinuation of the nebulized antibiotic. Previous studies in non-CF patients with renal impairment describe nephrotoxic serum trough tobramycin levels up to 2.5 μg/mL following the administration of nebulized tobramycin 300 mg BD [9]. Another study reports acute renal failure secondary to nebulized tobramycin in a patient with CF without pre-existing renal disease [10]. The bioavailability of nebulized tobramycin is known to vary widely between patients, which is related to a number of factors including incomplete delivery of the aerosolized drug to the lung, possible systemic absorption from the oropharynx, the method of nebulization used [9] and the pre-existing renal function [9]. Serum aminoglycoside concentrations are not routinely monitored in CF patients on aerosolized therapy. We suggest that trough serum level monitoring should be considered for patients with pre-existent renal disease.

In summary, this report highlights the importance of renal biopsy in proteinuric renal disease in adult CF patients. As the management of patients with CF continues to improve, the increasing life spans may lead to an increased identification of proteinuric renal disease, the aetiology of which can include CF-related NGS. In addition, the potential for nephrotoxicity secondary to nebulized tobramycin in patients with pre-existing renal dysfunction is highlighted. It may be that, in these patients, monitoring of serum levels of tobramycin post-nebulization is required.

Conflict of interest statement. None declared.

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