Case Report

Minimal change disease with acute renal failure: a case against the nephrosarca hypothesis

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Abstract

An unusual but well-documented presentation of minimal change disease is nephrotic proteinuria and acute renal failure. One pathophysiological mechanism proposed to explain this syndrome is nephrosarca, or severe oedema of the kidney. We describe a patient with minimal change disease who presented with heavy proteinuria and acute renal failure but had no evidence of renal interstitial oedema on biopsy. Aggressive fluid removal did not reverse the acute renal failure. Renal function slowly returned concomitant with resolution of the nephrotic syndrome following corticosteroid therapy. The time profile of the clinical events is not compatible with the nephrosarca hypothesis and suggests an alternative pathophysiological model for the diminished glomerular filtration rate seen in some cases of minimal change disease.

Keywords: acute renal failure; glomerular filtration rate; minimal change disease; nephrosarca; proteinuria

Introduction

Minimal change disease with acute renal failure has been described since 1966, with >85 cases reported in the literature [1,2]. It has been associated with older age, systolic hypertension, vascular disease and more severe nephrotic syndrome [3,4]. However, the underlying pathophysiology that distinguishes this entity from the majority of minimal change disease with preserved glomerular filtration rate (GFR) has thus far remained elusive. Lowenstein and colleagues proposed a theory of nephrosarca, or interstitial oedema of the kidney, which physically causes vascular and/or tubular occlusion and consequent filtration failure [5]. Data in support of this hypothesis include the finding of severe interstitial oedema on biopsy in some [3,5] but not all reports [2,4].

A central tenet of this hypothesis is that the acute renal failure should and would improve simply with removal of excess extracellular fluid. Therefore, one would expect resolution of acute renal failure without, or prior to corticosteroid-induced disease remission as long as the excess oedematous fluid is removed. Functional data of this type have never been documented unequivocally in the literature [2]. We present a case of minimal change disease with acute renal failure which failed to undergo remission despite 16 l of ultrafiltration. The acute renal failure subsequently resolved along with remission of proteinuria following corticosteroid therapy without further reduction in extracellular fluid volume. We propose that reduction in glomerular ultrafiltration is part of the underlying defect in minimal change disease and is due to factors other than nephrosarca.

Case

A 61-year-old Caucasian male without any significant past history presented to his physician with swelling of his hands and feet, progressive dyspnoea and weight gain in excess of 10 kg in the week prior to admission. He also noted decreased frequency and quantity of urine during this period. He denied any chest pain or symptoms of cerebral or peripheral vascular disease. He reported no ingestion of nephrotoxic agents, no preceding history of sore throat, arthralgias, myalgias, skin rashes, nasal symptoms, haemoptysis, haematuria or dysuria. The patient denied a history of tobacco use. The physical examination indicated a blood pressure of 166/80 mmHg, heart rate of 90 and respiratory rate...
of 16/min. There were no skin lesions or lymphadenopathy, and all pulses were palpable. There was 3+ pitting pedal oedema to the upper thighs and periorbital oedema. Other than decreased breath sounds at lung bases, the remainder of the physical examination was unremarkable.

On admission, his plasma creatinine (P Cr) was 645 μmol/l (7.3 mg/dl) with a BUN of 39 mmol/l (110 mg/dl). His serum electrolytes, calcium, phosphorus and magnesium were within normal limits. His urinalysis at presentation had a specific gravity of 1.020, pH of 5.5, 20–25 white blood cells (WBCs), 15–20 red blood cells, and distinct red blood cell and haemoglobin casts. The haematology panel included WBCs, 11,000/mm 3 (20% lymphocytes, 7.4% monocytes, 68% granulocytes and 4% eosinophils), haematocrit of 37% and normal red cell morphology. Arterial blood gases revealed pH 7.46, pCO 2 33.5 mmHg and pO 2 75.9 mmHg. A renal sonogram on admission showed normal echogenicity and no hydronephrosis. The linear dimensions of the kidneys were as follows: (i) longitudinal renal length of 12.2 cm (right) and 12.5 cm (left); (ii) anterio-posterior thickness at mid-section of 5 cm (right) and 5.5 cm (left); and (iii) transverse length of 3 cm bilaterally. The plasma albumin concentration was 18 g/l and low-density lipoprotein (LDL) was 6.47 mmol/l (250 mg/dl). A 24 h urine collection with a Foley catheter showed 9.8 g of protein and a TOCrit of 37% and normal red cell morphology. Arterial blood gases revealed pH 7.46, pCO 2 33.5 mmHg and pO 2 75.9 mmHg. A renal sonogram on admission showed normal echogenicity and no hydronephrosis. The linear dimensions of the kidneys were as follows: (i) longitudinal renal length of 12.2 cm (right) and 12.5 cm (left); (ii) anterio-posterior thickness at mid-section of 5 cm (right) and 5.5 cm (left); and (iii) transverse length of 3 cm bilaterally. The plasma albumin concentration was 18 g/l and low-density lipoprotein (LDL) was 6.47 mmol/l (250 mg/dl). A 24 h urine collection with a Foley catheter showed 9.8 g of protein and a creatinine clearance (ClCr) of ~9 ml/min. Serum protein electrophoresis indicated hypoalbuminaemia, and urine protein electrophoresis showed primarily albuminuria. A complete serological work-up (rheumatoid factor, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, hepatitis B and C panel, anti-glomerular basement membrane antibody, human immunodeficiency virus, RPR, cryoglobulins, and complements C3 and C4) was negative.

A percutaneous renal biopsy was performed the morning after admission and it included a total of 17 glomeruli, two of which were globally sclerosed. The remaining glomeruli were normal in appearance on light microscopy without focal or segmental sclerosis and with normal vasculature. No evidence of interstitial oedema, interstitial infiltrate or tubular necrosis was observed. Immunofluorescence was negative (not shown). Ultrastructural examination showed large areas of visceral epithelial foot process effacement without evidence of immune deposits.

A diagnosis of minimal change disease with acute renal failure was made and treatment with 2 mg/kg of prednisone per day was initiated. Over the week following admission, P Cr progressed to 981 μmol/l (11.1 mg/dl), and the volume overload progressed despite salt restriction. High-dose intravenous diuretic therapy was basically ineffective. Haemodialysis was initiated on day 7 of hospitalization. The patient required a net negative 161 of ultrafiltration before he was clinically deemed to have achieved dry weight. A repeat sonogram obtained after the patient achieved his dry weight showed that the kidneys were exactly the same size as before ultrafiltration with normal echogenicity. Haemodialysis was continued for a total of 6 weeks. The proteinuria and renal function both improved after 5–6 weeks of prednisone therapy. At the time of discontinuation of haemodialysis, the endogenous ClCr was 31 ml/min (Figure 1). The prednisone was gradually tapered over a period of 1 year. At the time steroids were discontinued, the patient had a P Cr of 115 μmol/l (1.3 mg/dl), a 24 h urine protein excretion of 600 mg, and ClCr of 105 ml/min. A summary of the pertinent clinical data over the entire period is given in Figure 1.

**Discussion**

Although minimal change disease with acute renal failure is well documented in the literature, it is relatively uncommon when compared with the classic presentation of nephrotic syndrome with preserved GFR. There is little known about the aetiology of minimal change disease other than the occasional secondary varieties in which resolution of proteinuria is synchronous with elimination of the underlying condition. Equally scanty is information on the pathophysiology that underlies minimal change disease. What is the functional glomerular lesion in minimal change? Does minimal change disease with acute renal failure represent a distinct disease entity? We propose that minimal change disease with acute renal failure is not a separate entity but merely one end of a spectrum of disease.

Lowenstein and co-workers studied patients with minimal change disease presenting with acute renal failure and proposed that the intense extravasation of fluid into the renal interstitium actually caused acute renal failure [5]. Indeed, numerous pathological reports have commented on interstitial oedema [3,5]. The most convincing data for this hypothesis would be the resolution of acute failure only with relief of excessive volume, but evidence for this phenomenon is largely lacking [2]. Low albumin per se is unlikely to cause renal interstitial oedema as minimal or no extravasation is seen in patients with congenital analbuminemia. However, one can envisage and propose an associated primary problem in renal lymphatics impairing drainage in minimal change disease. The accumulation of high protein fluid in the interstitium can occur as a result of ultrafiltration of proteinaceous fluid from the mesangial side of the glomerular capillary and can induce severe interstitial oedema, or so-called nephrosarca. It is important to note that not all patients with this syndrome have evidence of interstitial oedema on biopsy [2,4]. Our patient, for example, had absolutely no interstitial oedema histologically, and his renal dimensions did not change with 161 of fluid removal and total resolution of severe peripheral oedema. As shown in Figure 1, the improvement of his GFR (ClCr as a surrogate) was clearly not concomitant with loss of fluid but rather with resolution of proteinuria. In concert, these findings speak strongly...
against the nephrosarca hypothesis as being the sole cause of acute renal failure in minimal change disease.

The majority of biopsies in patients with minimal change disease and acute renal failure reflect changes typical of ischaemic tubular damage [4]. Findings frequently described include dilatation of the tubules with flattening of the tubular epithelium and loss of the brush border [1,4]. Significant epithelial cell necrosis has been seen with variable frequency, and some biopsies have revealed proteinaceous casts occluding the tubules, thus implicating a role for obstruction in the pathophysiology [1,4]. Such tubular damage previously has been attributed to renal hypoperfusion resulting from decreased plasma oncotic pressure and subsequent volume contraction. The use of diuretics has been speculated to exacerbate the impaired perfusion and thus precipitate ATN [2,6]. However, there are no data to date to support these hypotheses. Instead, studies have indicated mild volume expansion with preserved renal plasma flow in nephrotic patients with minimal glomerular changes on biopsy [7]. Other reports ascribe the renal failure to alternative mechanisms such as overproduction of angiotensin II or redistribution of renal blood flow from cortical to juxtamedullary nephrons, but evidence to substantiate such proposals is largely lacking [6].

When dealing with the typical minimal change glomerulopathy, one is sometimes deluded into a false sense of security for three reasons: (i) the lack of microscopic histological changes; (ii) the normality of glomerular filtration function in the majority of cases; and (iii) the overall favourable response to corticosteroids. If one considers the physiology of glomerular filtration, it is evident that there is severe disturbance in the ultrafiltration function in minimal change disease. The glomerular ultrafiltration rate in a single nephron (SNGFR) is determined by the ultrafiltration coefficient \( U_f \) which is a product of the intrinsic hydraulic permeability, the surface area of filtration and the Starling driving forces which are set by the oncotic \( (\Pi_5 - \Pi_1) \) and hydraulic \( (P - \Pi) \) pressure gradients along the glomerular capillary.

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\text{SNGFR} = U_f \times (\Delta P - \Delta \Pi)
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The driving force for ultrafiltration at the glomerular capillary is the difference between the hydraulic pressure gradient \( (\Delta P) \) between the capillary lumen and Bowman’s space which drives ultrafiltration, and the oncotic pressure gradient \( (\Delta \Pi) \) between the capillary lumen and Bowman’s space which retards ultrafiltration. This driving force \( (\Delta P - \Delta \Pi) \) is graphically depicted in Figure 2A as the shaded area. In minimal change disease, the glomerular barrier fails to retain albumin in the capillary, and albumin enters Bowman’s space. This greatly diminishes \( \Delta \Pi \) or may even reduce it to zero, as shown in Figure 2B. The driving force for glomerular filtration is significantly

![Fig. 1. Summary of clinical course. BW = body weight; \( U_{pro} V \) = 24 h protein excretion; \( \text{Cl}_{\text{Cr}} \) = creatinine clearance; \( \text{Palb} \) = plasma albumin.](https://academic.oup.com/ndt/article-abstract/19/10/2642/1925558)
elevated, as hydraulic pressure will literally run unopposed, as shown in the shaded area in Figure 2B. In reality, one never encounters hyperfiltration in minimal change disease. In order for the GFR to remain normal, $\Delta P$, $U_f$ or both have to be drastically reduced. The current literature suggests that the lesion probably lies in $U_f$ rather than $\Delta P$. Dorhout Mees and co-workers studied patients with minimal change disease with a low GFR and found well preserved renal plasma flow (RPF) [7]. This observation is compatible with reduced $U_f$. The only way a drastic reduction in $\Delta P$ is compatible with preserved RPF is a simultaneous intense afferent arteriolar vasoconstriction and efferent arteriolar vasodilatation, which would seem rather unlikely. Moreover, the defect in charge selective filtration barrier [8] is also more in keeping with abnormalities in ultrafiltration. Anderson and Brenner measured glomerular haemodynamics in the puromycin rodent model of minimal change disease [9]. During the acute phase, the animals exhibit selective proteinuria and reduced GFR compared with control rats. Histological changes indicative of glomerular damage have been described, such as visceral epithelial vacuolization and bleb formation, mild mesangial expansion and mesangial foam cell accumulation. In addition, tubular collapse, tubular dilatation, cast formation and interstitial oedema were noted in plastic-embedded sections. Effacement of visceral epithelial foot processes was noted with transmission electron microscopy.

Glomerular filtration consists of passage across the fenestrated endothelium, the glomerular basement membrane and the slit diaphragm of the podocyte. Damage to the podocyte disrupts filtration at every level as this cell provides structural stability for the capillaries, maintains the integrity of the basement membrane and produces many proteins that comprise the slit diaphragm, glomerular basement membrane and cellular signalling processes [10]. To facilitate these functions, the podocyte has a complex structure with a cell body high in synthetic activity, an intricate cytoskeleton consisting of cytoplasmic processes that extend to capillaries, and foot processes that adhere to the glomerular basement membrane. The podocyte may play a regulatory role in determining capillary hydraulic pressure, filtration wall distension as well as glomerular basement membrane expansion, and thus $U_f$ [10]. Minimal change glomerulopathy may be a quintessential podocyte and $U_f$ disease.

In summary, we present a patient with minimal change disease complicated by acute renal failure who had no evidence of interstitial oedema on biopsy and whose acute renal failure did not improve with removal of 16 l of extracellular fluid. The eventual resolution of acute renal failure was temporally concomitant with remission of proteinuria in response to corticosteroids. The GFR in patients with minimal change disease is determined by changes in two counteracting physiological parameters, $U_f$ and $(\Delta P - \Delta \Pi)$. When the magnitudes of the changes are opposite but comparable, the GFR is relatively normal. When the fall in $U_f$ is greater than the increase in $(\Delta P - \Delta \Pi)$, a reduction in the GFR ensues. We propose that (i) not all patients with minimal change disease and acute renal failure are

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**Fig. 2.** Driving force for glomerular filtration. $\Delta P$ is the difference in hydrostatic pressure between the glomerular capillary and Bowman’s space which promotes ultrafiltration. $\Delta \Pi$ is the difference in oncotic pressure between plasma and glomerular ultrafiltrate which retards ultrafiltration. The net driving force for ultrafiltration $\Delta P - \Delta \Pi$ as a function of the length of the glomerular capillary (l) is represented by the shaded area.
accountable for by the nephrosarcoma hypothesis; (ii) the underlying mechanisms responsible for loss of the charge-selective barrier are also lowering $U_f$, and therefore minimal change disease with acute renal failure is simply a more severe presentation of the same underlying pathophysiology; and (iii) corticosteroid therapy induces remission of both proteinuria and acute renal failure.

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