

# Nephrotic syndrome in an adult patient with minimal change disease

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## ABSTRACT

Minimal change disease (MCD) is a glomerulopathy that may manifest as nephrotic syndrome. It is most common in children; while, it only accounts for 20–25% of cases of adult nephrotic syndrome. This article presents a case of an adult with MCD presented with generalized edema. Initially, Focal segmental glomerulosclerosis (FSGS) was suspected. However, the patient's dramatic response to steroids, his acute presentation and the histopathology features of his renal biopsy favored MCD. The initial management comprised of steroids to which the patient responded. A year later, the patient relapsed and mycophenolate mofetil was added. There is lack of guidelines to manage adult MCD, in contrast to child MCD. The clinical picture of the patient is the key to guide decisions about management in absence of evidence-based guidelines.

**Keywords:** Glomerulopathy nephrotic syndrome, Minimal change disease, Steroids, Mycophenolate mofetil

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## INTRODUCTION

Kidneys are the organs responsible for controlling electrolytes levels, acid–base balance and blood pressure. The basic unit of the kidney is the nephron which consists of the glomerulus that filtrates the blood and tubules which in turn process the filtrate. Glomerulus is a group of capillaries surrounded by the Bowman's capsule forming a structure known as the renal corpuscle. There are three types of cells that form the glomerulus namely endothelial cells, epithelial cells (Podocytes) and mesangial cells. Changes in these cells lead to pathological processes which may manifest as asymptomatic hematuria, proteinuria, glomerulonephritis, nephritic syndrome or nephrotic syndrome [1].

Nephrotic syndrome is a collection of signs and symptoms resulting from glomerular lesions in the kidney; glomerulopathy. It is characterized by proteinuria, hypoalbuminemia, edema and hyperlipidemia. There are primary and secondary causes of nephrotic syndrome, and by far the most common cause of it is focal segmental glomerulosclerosis (FSGS) in adults and minimal change disease (MCD) in children [2]. In Bahrain, MCD (also known as Nil disease, lipoid nephrosis) was the most common histological lesions seen in the renal biopsies done in the period between 1990 and 2002 [3].

Light microscopy shows glomeruli with normal appearance in patients with MCD. However, electron microscopy shows effacement of podocytes' foot processes [4]. The underlying pathogenesis of MCD is still unclear, but there is a hypothesis suggesting that the damage to the podocytes is attributed to a T cell derived factor. Patients with MCD show response to steroids, but in the cases of steroid resistance or dependence, immunosuppressive

agents are indicated. Evaluation of the success or the failure of the treatment is based on the clinical picture of the patient [5].

In this paper, we will present a case of MCD, aiming to discuss the diagnosis, treatment and follow-up of such cases. We choose this case because there is no clear guidelines that favor one treatment over another in management of adult MCD.

## CASE REPORT

A 30-year-old morbidly obese male presented on the 21<sup>st</sup> of February 2012 with one week history of generalized edema. The edema was predominantly involving his limbs and the periorbital areas. Patient also complained of reduction in urine quantity. Otherwise, patient had no fever, cough, headache, or shortness of breath. This patient has hypertension for 14 years, diabetes mellitus type II for three years and hypothyroidism. There is no family history of similar presentation. He never smoked nor consumed alcohol. He works as a cashier.

## Physical Examination

On inspection, the patient was conscious, alert, not in respiratory distress, and not jaundiced. Grade +++ edema involving the upper and lower limbs was seen along with redness and brown spots on the right leg. Abdomen was soft and there was no organomegaly. Chest was clear and there were no added sounds. Cardiovascular examination revealed normal S1 and S2 and no pericardial rub.

## Investigations

Mid-stream urine was collected and analyzed revealing proteinuria +++, glycosuria ++, hemoglobin+, 5–10 RBCs, and hyaline and granular casts. Liver function tests revealed hypoalbuminemia (12 g/L) and low total protein (41 g/L). Thrombin time was prolonged

(22 sec) and fibrinogen level was high (627 mg/dl). The patient's cardiac enzymes were not elevated. His urea, electrolytes and creatinine were normal. Patient had hyperlipidemia. Renal Ultrasound was normal. A renal biopsy was performed on 5th March 2012 which is 12 days from admission. Microscopic examination of the specimen showed one of the eight glomeruli was globally sclerosed, mild interstitial fibrosis and tubular atrophy. Immunofluorescence showed no staining for IgG, IgM, IgA, C1q, albumin, or fibrinogen. A specimen was sent to Germany for electron microscope. In the electron microscopy, there was diffuse effacement of the podocytes' foot processes. No segmental sclerosis, no immune-complex deposits and no changes consistent with diabetic kidney disease were detected. The patient was diagnosed with MCD.

## Management

In his initial management intravenous diuretics (furosemide 100 mg BD) along with IV 100 ml of 20% albumin were administered. Perindopril and a beta-blocker were administered to manage the patient's hypertension. Additionally, low molecular weight heparin (LMWH) 50 mg enoxaparin was administered. On 27th February 2012, the patient was given 1 g methylprednisolone intravenously for three days. The patients urine output was monitored by input/output chart. Weight, Urea + electrolytes, cholesterol, LFT, glucose were monitored daily. And 24 hr urine was collected to monitor proteinuria levels.

Patient was discharged after correlation of his clinical picture and biochemical profile. The patient lost 18 kg weight, proteinuria on urine dipstick disappeared and serum albumin increased steadily close to normal range. The patient was discharged to be followed-up in clinic yet the patient failed to attend his appointments.

On 26th February 2013, one year later, the patient attended his clinic appointment, proteinuria and generalized edema developed once again. He was admitted to manage his relapse. He was given intravenous diuretics,

Table 1: Differential Diagnosis

Renal Diseases	Heart Diseases	Liver Diseases	Others
<b>Nephrotic Syndrome</b>	<b>Heart Failure</b>	<b>Liver Failure</b>	<b>Hypothyroidism Congenital Milroy's syndrome</b>
<b>Primary</b>			
– MCD			
– FSGS			
– FSGS			
– Membranous glomerulonephritis			
– Membranoproliferative glomerulonephritis			
<b>Secondary</b>			
– Amyloidosis			
– Diabetic kidney disease			
<b>Acute kidney Injury</b>			

Table 2: To identify the patients un-responsive to steroid, we will define the remission and relapses

Complete remission	24-h proteinuria of $\leq 0.3$ g Serum albumin of $\geq 3.5$ g/dL “for at least 1 month”
Partial remission	24-h proteinuria of $> 0.3$ g and $< 3$ g + a rise of serum albumin of $\geq 3$ g/dL+
Relapse	Stable renal function. 24-h proteinuria of $\geq 3$ g/day “more than 3 days” +hypoalbuminemia

Table 3: Three doses of albumin should be administered with specific indications [12]

Dose and description	Indications
1 g/kg 20% albumin (5 ml/kg) over four – six hours + two mg/kg of intravenous frusemide mid-infusion	Hypovolaemia
10 ml/kg 4.5/kg 4.5% albumin	

Table 4: Complications of MCD nephrotic syndrome

Disease-associated	Drug-related
<ul style="list-style-type: none"> <li>• Infections: peritonitis, sepsis, pneumonia</li> <li>• Thrombotic tendency: Venous thrombosis, pulmonary embolism</li> <li>• Anemia</li> <li>• Hypovolemic crisis: tachycardia, hypotension, abdominal pain</li> <li>• Acute renal failure</li> </ul>	<ul style="list-style-type: none"> <li>• Corticosteroids: Cushing syndrome “obesity, hypertension, cataract and glaucoma”</li> <li>• Cyclosporin: Nephrotoxicity, hirsutism</li> <li>• MMF: Nausea, vomiting, bone marrow suppression</li> <li>• Hormonal and mineral alterations: hypothyroidism, bone disease, hypocalcaemia</li> </ul>

albumin plus steroid injections. Then, the patient was discharged on 80 mg prednisolone OD plus 500 mg of mycophenolate mofetil (MMF) BD to be further modified on next clinic appointment. The patient was seen the next week in clinic, his condition was stable. Prednisolone was reduced to 60 mg OD and MMF was increased to 1 g BD.

## DISCUSSION

### Literature review

Minimal change disease is considered as a disease of unknown etiology in most cases. However, in some cases etiology can be identified; these include viral infections, allergies, malignancy and some medications. The specific pathogenesis is still unknown, but there is a hypothesis stating that it is due to T cell activation and resultant cytokine or permeability factors mediate injury to the glomerular foot processes. There are slit diaphragms that

connect the podocytes together allowing only the small molecules and water to pass. Disruption of these slits is seen in the MCD leading to proteinuria [1].

In addition, new studies suggest that increased expression of CD80 (B7-1) on podocytes was identified as the mechanism which lead to nephrotic syndrome. CD80 is inhibited by binding to regulatory T cell receptor (CTLA-4). CTLA-4 receptor appears to be altered in MCD; as a result CD80 is over-expressed and seen in the urine. Normal CD80 expression is seen in patients with other glomerular diseases and normal people and not in urine [6].

### Case description

The patient presented with generalized edema. History was taken and physical examination was done. The clinician ordered mid-urine stream analysis which showed +++ proteinuria, then the nephrologist was consulted. The nephrologist ordered a biopsy to diagnose the renal pathology.

### Diagnosis

Common cause of nephrotic syndrome in adults is FSGS which was initially suspected in this patient. The patient is morbidly obese and FSGS does occur in association with obesity. Yet the patient’s presentation was acute suggestive of an acute cause of nephrotic syndrome rather than proteinuria associated with patients risk factors. The histopathology and the electron microscopy did not rule out FSGS. The histopathology report showed that one of eight glomeruli was globally sclerosed, mild (app 10%) interstitial fibrosis and tubular atrophy. All of these pathological findings are consistent with FSGS. The electron microscopy result revealed effacement of podocytes’ foot processes. This finding, being a ‘podocytopathy’, is not specific for MCD and it does occur in FSGS. However, histopathology showed no expansion in mesangial matrix or cellularity, which is usually found in FSGS. Furthermore, patients with FSGS usually have poor response to steroids; whereas, this patient had a good response. Therefore, this patient was diagnosed with MCD; keeping in mind that relapsing steroid resistant MCD cases could also be FSGS variants which can be identified in repeat biopsies.

In patients with MCD, sclerosis of glomeruli is not seen. Thus, the question is; what is the cause for glomerular sclerosis and interstitial fibrosis in this patient? As we already mentioned this patient has a long history of diabetes and hypertension; both of which can cause glomerular sclerosis and interstitial fibrosis.

Membranous glomerulonephritis (MG) is also a frequent cause of adult nephrotic syndrome. Membranous glomerulonephritis is characterized by deposition of immune complexes, mainly consisting of IgG and

complement, in the renal corpuscle. Membranous glomerulonephritis was excluded because there was no staining for IgG under immunofluorescence.

This patient has been diagnosed with diabetes and MCD. Renal biopsy showed no changes that correlate with diabetic nephropathy. This is an important finding that is essential to rule out in any patient with nephrotic syndrome and known to have diabetes. Distinguishing the cause of the proteinuria in such patients is important as the treatment differs. If the patient subsequently develops proteinuria, the cause of it should be investigated by renal biopsy and the type of proteinuria to avoid mismanagement [7]. Diabetes leads to a selective proteinuria while MCD lead to a non-selective proteinuria. Diabetic nephropathy is managed by controlling hyperglycemia and hypertension; while, MCD is managed by steroids and immunosuppressants [8]. Tight control of sugars during steroid therapy is also essential to avoid renal disease secondary to prolonged steroid induced hyperglycemia.

## Treatment

There is a lack of clear guidelines for the treatment of adults with MCD and nephrotic syndrome. For example, although some studies state that adult MCD is steroid-responsive in approximately 80% of cases, a systemic review published by Cochrane collaboration concludes that there is no evidence to support the efficacy of any agent for inducing and prolonging of remission for adults MCD nephrotic syndrome [8–10]. However, in the clinical setting the following drugs show good outcome:-

**Corticosteroids:** Corticosteroids remain the mainstay treatment of MCD in adults. The drug of choice is prednisolone with a recommended dose of 1 mg/kg/day, not exceeding 80 mg. In adults, there are no randomized controlled trials (RCTs) that provide evidence on the dose of corticosteroids that should be given or the frequency or duration.

## Treatment options of patient unresponsive to steroids

**Alkylating agents:** Alkylating agents such as cyclophosphamide or chlorambucil can be used in children with multiple relapses. Despite the lack of studies in adult MCD, it is likely that alkylating agents result in prolonged remissions, as shown in RCTs in children. Cyclophosphamide, at two-three mg/kg/day, is more commonly used than chlorambucil, without clear evidence of the superiority of one over the other. However, other studies showed that there is low-quality evidence to suggest the value of alkylating agents in adult relapsing MCD [9].

**Cyclosporin A:** Cyclosporin A (CsA) has been used in adults with MCD because it is an inhibitor of calcineurin. Calcineurin activates T-cell, and when it is inhibited T-cell activation does not occur. The recommended dose of CsA is below five mg/kg/day.

**Mycophenolate mofetil:** There are few studies about mycophenolate mofetil (MMF) efficacy in the treatment of adult MCD. The evidence that either support or refuse MMF usage is absent but considering the encouraging results obtained in childhood MCD, MMF may be used in the treatment adult MCD.

## Treatment of other complications

**Infection:** This is a common complication in patients with nephrotic syndrome. This needs a serious intervention to prevent further complications. Intravenous immunoglobulin (IVIG), thymosin, oral transfer factor and BCG vaccine injection have positive effects on the prevention of nosocomial infections.

**Albumin:** This is used to help avoid diuretic induced hypotension. The clinical indications for albumin infusion are

- Clinical hypovolemia
- Symptomatic edema

Consider: low serum albumin alone is not an indication for intravenous albumin.

**Blood pressure and hyperlipidemia:** For the initial episode of nephrotic syndrome associated with MCD, statins not to be used to treat hyperlipidemia, and ACE-I or ARBs not be used in normotensive patients to lower proteinuria.

**Anticoagulants:** Used when

- Low serum albumin values below 25 g/l.
- Immobility resulting from edema or obesity
- Malignancy

Prophylactic anticoagulant (e.g., LMW heparin 5000 units S.C. B.D.) is common practice in high risk patients [10].

**This Patient Treatment:** The patient was given intravenously diuretics and albumin to reduce his edema. Low molecular weight heparin (LMWH) 50 mg was administered to prevent thrombosis. One gram methylprednisolone was given to the patient six days after admission to induce remission. The patient was discharged with steroid prescription.

The patient relapsed a year later; non-adherence to his medication is the most likely explanation for his relapse. He was admitted and was given steroid injection to induce remission. In the second discharge, the patient was given MMF because he was not compliant with previous medication. The MMF was chosen because alkylating agents or CsA in a non-compliant patient will

lead to more side-effects than benefit. Prednisolone OD plus 500 mg mycophenolate mofetil (MMF) BD were prescribed on discharge. For unknown reason, our patient did not take any vaccines which are essential to prevent infections.

## Prognosis and complications

Minimal change disease has an excellent prognosis even in adults. More than 90% of the patients will respond to oral steroids. However, there is a high rate of relapses. Minimal change disease rarely lead to end stage renal disease, some patients with MCD may end up with FSGS. The FSGS is a more aggressive disease, with less treatment options and more of a tendency towards eventual renal failure compared to MCD [11].

The complications of MCD nephrotic syndrome can be divided into two categories: Disease-associated and drug-related complications (Table 4).

## Follow-up

During the follow up for patients with long-term steroids there is a need to monitor the blood pressure, weight, glucose levels, LFTs, renal profile, and proteinuria (Glucosuria, HbA1c). It is also recommended to vaccinate the patients with pneumococcal vaccine and varicella zoster vaccine. Ophthalmology review and bone studies are also recommended.

## Future research

We discussed the clinical presentation, diagnosis and treatment of a MCD case. And we discussed the possible medication for such cases based on recent research. There is a lack of studies which compare the efficacy of the drugs to each other. Therefore, we recommend the development of new researches to compare the efficacy of the different drugs used in the treatment of adult MCD. And based on these researches, clear evidence-based guidelines should be produced. Research regarding the use of immunosuppressants in contrast to steroids at the early stage in MCD could be investigated. Research should also focus on the possible beneficial effect of rituximab in the treatment of MCD. The patient wants to go for weight reduction surgery. It will be interesting to follow-up the patient's condition post-surgery to establish the influence of the procedure on future relapses thus providing more areas of interest for research.

## CONCLUSION

The lessons we learned from this case study are; first, the essence of the compliance and regular follow-up to

achieve the aims of the treatment. Second, teamwork is necessary for the success of management. Third, the clinical picture is an important determinant of management strategy in absence of clear guidelines. And in such cases, relevant treatments should be considered carefully and the option which best suits the patient should be taken. Thus, emphasizing the fact that absence of evidence is not evidence of absence; or in another words, lack of clear evidence about a specific treatment or drug does not necessary mean that it is not effective.

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## Author Contributions

Yusuf Alalwan – Substantial contributions conception and design, Acquisition and analysis of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to published

Mahmood Alawainati – Substantial contributions conception and design, Acquisition and analysis of data, drafting the article, Revising it critically for important intellectual content, Final approval of the version to published

## Guarantor

The corresponding author is the guarantor of submission.

## Conflict of Interest

Authors declare no conflict of interest.

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