Case Study

Membranous Nephropathy

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HISTORY

A forty-three year old female applied for a $200,000 ten year decreasing term policy. She admitted a history of "kidney disorder" on the application. She was not being treated or having any symptoms but stated that she was under observation. A routine paramed exam showed height 5'4", weight 140 lbs, and blood pressure 110/70. The BCP was normal. The HOS showed 210 mg/dl proteinuria. A reflex determination for microalbuminuria was not done. The WBC's, RBC's, and granular casts were within normal range. An APR was obtained.

ADDITIONAL INFORMATION

The APR disclosed that the PI had presented approximately 3 1/2 years prior to the application with a complaint of edema. A workup showed heavy proteinuria of 3.2 grams per 24 hours with a serum creatinine of 1.0 mg/dl and a creatinine clearance equal to 93 ml/minute/1.73 m² (normal: 88-128 ml/minute/1.73 m²).

A renal biopsy was performed and showed diffuse thickening of the glomerular basement membrane and capillary wall with no increase in cellularity. This was consistent with membranous nephropathy. Serologies for hepatitis B and C were negative. There was no indication for lupus erythematosus. Treatment with prednisone was offered to her, but she declined.

She has been followed periodically since then. Her blood pressure has remained normal. She was treated with Lasix for the edema. Six months prior to the APR, a 24-hour urine showed the proteinuria had decreased to 2.4 grams per day but a creatinine clearance had decreased to 77 ml. The nephrologist commented that perhaps it was not a full 24-hour urine collection, as the total creatinine was only 790 mg per day (the collection three years prior had a total creatinine 1,120 mg/dl). The serum creatinine was normal at 0.9 mg/dl. Clinically she was doing well.

Is she insurable?

DISCUSSION

Membranous Nephropathy (MN) is the most common cause of idiopathic adult nephrotic syndrome (NS). Histologically, there is a characteristic diffuse thickening of the glomerular basement membrane and capillary wall with little or no increase in cellularity. In mild cases, the capillary wall thickness is relatively normal and not discernible by light microscopy. Therefore, immunofluorescence or electron microscopy may be required. Immune complexes are visible as subepithelial deposits between the basement membrane and the epithelial cells. Immunofluorescence shows capillary wall deposition of IgG and C3 in granular or lumpy-bumpy pattern. The process by which these complexes seem to pass through the basement membrane and lodge in the subepithelial space is not understood. Some experimental studies have suggested that these complexes do not pass through the basement membrane, but the complexes grow by an in situ mechanism in which free antigen and antibody are deposited separately.¹

The diagnosis of MN may be suspected by the typical presentation of an adult with nephrotic syndrome, but only a renal biopsy can establish the exact diagnosis. The mean age at diagnosis is 40-50 years old. An acute presentation as glomerulonephritis can occur but is felt to be rather rare. An asymptomatic presentation, in which proteinuria is found on a routine urinalysis, can occur in up to 20% of the cases. The majority of the cases present as an adult nephrotic syndrome with edema and
heavy proteinuria. Hypertension may be present at initial presentation, and occasionally mild hematuria.

The majority of cases of MN are idiopathic in nature. There are a variety of disease processes that have been associated with this disorder. The list includes cancer, systemic lupus erythematosus, medications, infections with hepatitis viruses, severe untreated rheumatoid arthritis, sarcoidosis, and even syphilis. If it is found in association with a malignant disease, it is usually a solid cancerous tumor. This may be present in up to 10% of cases of MN in adults. In the vast majority of these cases, the tumor has already been diagnosed and only in a very small percentage of cases is one dealing with occult malignant disease. If chronic hepatitis is the underlying cause, it is most likely chronic hepatitis B accompanied by Be antigenemia. On rare occasions MN has been found with hepatitis C. Medications that have been implicated in MN include penicillamine and gold.3

The natural history of MN is quite variable. If caused by drugs, the entity disappears if the drug is discontinued. In hepatitis B, remission occurs when the antigenemia clears. The improvement is often quite slow, and may reflect the slow rate at which the complexes are removed from the subepithelial space. In the idiopathic variety, patients can be placed into certain classifications at 5-10 years after diagnosis. There are four distinct groups, with each group comprising approximately 1/4 of the total. The first group is spontaneous remission. The second group is persistent non-nephrotic proteinuria. The third group is persistent nephrotic syndrome. The last category is slow but gradual progression to renal failure. In trying to determine who will fall into each of these four groups, the prognosis is best for women and children with non-nephrotic proteinuria. Fewer than 10% of these patients will have progression at ten years.5 The worst prognosis is in men who present with nephrotic syndrome and have elevated plasma creatinine at initial diagnosis. If progression occurs, it will do so within three years.4 Therefore, maintaining a normal plasma creatinine or creatinine clearance is a good prognostic sign.

Renal transplantation can be done in those who develop renal failure, and recurrence of the MN in transplants is rare. A not uncommon complication of MN is development of renal vein thrombosis. This may occur in up to 10-15% of patients, although this is usually not accompanied by pulmonary emboli and renal function is usually not affected. Consideration for chronic anticoagulation with Coumadin should be given to patients with this complication.

The ideal treatment for MN is uncertain. Steroids have been used over a short course, but many studies have not shown any significant benefit other than a slight decrease in the proteinuria. Other protocols using cytoxan, chlorambucil, or cyclosporine have been tried.6 The long term benefits of any of these treatment programs has not been established. Often the more aggressive programs are used for those with the most advanced disease and declining renal function.

There are certainly several observations in this case that could lead to debate regarding insurability. First, despite a stable serum creatinine, there was a mild decrease in her 24-hour creatinine clearance. Was this decline secondary to an actual worsening of the renal function or simply secondary to an incomplete 24-hour collection? A repeat 24-hour urine for creatinine clearance could help to clarify this situation, although this is an unusual study for insurance companies to require for establishing insurability. It would appear that repeating the serum creatinine would not be helpful, as this is a less sensitive indicator of overall renal functioning.

Secondly, the PI may fit well into one of the more favorable prognostic categories because of her female sex, the not extremely high initial 24-hour protein level, and the improvement in the proteinuria from 3.2 to 2.4 grams per day. Also, she is now 3 1/2 years since the initial diagnosis and time frame wise is not showing an obvious clinical worsening of her condition.

Lastly, this is a ten-year decreasing term policy. With no significant decline in her clinical picture and renal function over 3 1/2 years of the disease process, it would seem likely that, even if she were to undergo a decline in her renal function, it may take many more than ten years to develop. Although the long term prognosis may be less certain, the prognosis over the next ten years would appear to be much more favorable. The expected death rate at this age is 3.09 deaths per 1000 (based upon the 1980 CSO mortality table). If you conclude that she has less than a 25% chance of progressing to chronic renal failure, is it possible to correlate this with some type of calculated excess death rate?

In conclusion, membranous nephropathy has a variable prognosis, with certain subtypes showing about normal life expectancy and other types a rather poor long term outlook. The histological appearance of the renal biopsy and observation of the clinical course and renal function over a period of several years are the most important determinants by which to judge mortality. The author acknowledges the assistance of James A. Bilyeu, M.D., Keith T. Clark, M.D., and James C. Harris, M.D. in the preparation of this manuscript.
References


