Attending Rounds: An Older Patient with Nephrotic Syndrome

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Summary
Nephrotic syndrome in older adult patients is a common clinical conundrum. Membranous nephropathy (MN) is a lesion frequently found to underlie the nephrotic state in such patients. Determining with reasonable certainty whether the nephrotic syndrome and MN is primary (idiopathic) or due to an underlying disease such as neoplasia can be a daunting clinical challenge. By way of a presentation of an illustrative case and a focused review of the relevant literature, the approach to evaluation of such patients, with an emphasis on the putative causative role of neoplasia in MN, is analyzed and a potential contemporary pathway for acquiring the correct diagnosis is offered.


Introduction
A 71-year-old retired bank executive has been referred to you for evaluation of fatigue, edema, and proteinuria discovered by his family physician several weeks ago. He was well until approximately 1 month ago when he began to notice ankle swelling and weight gain accompanied by easy fatigability. He was examined by his family physician, who noted a BP of 160/88 mmHg and a pulse of 82 beats per minute (regular). The patient weighed 76 kg. The optic fundi were unremarkable. Lymphadenopathy was absent. Other than 1+ pedal edema, occasional wheezes in both lung fields, and reduced pedal pulses bilaterally, the remainder of the physical examination was normal. Laboratory data obtained before the referral showed that hemoglobin was 11.7 g/dl, hematocrit was 37%, white blood cell count was 8200/mm³, platelet count was 235,000/mm³, and mean corpuscular volume was 88 fl. The serum creatinine was 1.1 mg/dl. (Using the Chronic Kidney Disease Epidemiology Collaboration equation, the estimated GFR [eGFR] was 67 ml/min per 1.73 m².) Serum electrolytes were within normal limits. Serum albumin was 3.1 g/dl, serum total cholesterol was 290 mg/dl, serum calcium was 9.2 mg/dl, and serum uric acid was 7.3 mg/dl. Serum bilirubin, alkaline phosphatase, fasting blood glucose, phosphate, and globulins were all within normal limits. Urinalysis with a dipstick test revealed 3+ proteinuria without blood. A prostate-specific antigen was 4.6 ng/ml. An electrocardiogram showed evidence of an old anterior myocardial infarction. The report of a chest radiograph was unremarkable.

When the patient was first seen for further evaluation, his past medical history was noted to be positive for a myocardial infarction at age 68 years, after which he underwent a successful coronary revascularization and stent placement. He did not have diabetes mellitus. He had smoked two packages of cigarettes daily for 20 years until his heart attack. Medications included a baby aspirin daily, 75 mg/d of clopidogrel, a β blocker, 20 mg/d of atorvastatin, and a nonsteroidal anti-inflammatory drug (NSAID) occasionally for osteoarthritis. There was no family history of renal disease, diabetes, or cancer. He had no drug allergies. Physical examination findings reported by the family physician were confirmed, but the edema was now 2+ and extended to the mid-calf. The prostate examination showed mild enlargement but no nodules. A stool sample was negative for occult blood. A urinalysis in the office revealed 4+ protein and a trace of blood. The urine sediment revealed 4–5 red blood cells per high-powered field. A few granular and hyaline casts were present. Serum creatinine remained at 1.1 mg/dl and a repeat serum albumin was now 2.6 gm/dl. A spot morning urine protein/creatinine ratio was 9.8. The patient was prescribed 20 mg of furosemide twice daily for the edema.

Differential Diagnosis
The presence of nephrotic syndrome (NS) has been confirmed and no cause is immediately evident, although the occasional use of an NSAID is of some concern. Among older adult patients aged >65 years presenting with NS, the most common causes identified by kidney biopsy are membranous nephropathy (MN), minimal change disease (MCD), and amyloidosis, with approximately 60% of all cases accounted for by these three lesions (1). Less common lesions among older patients undergoing a biopsy for diagnosis of NS are FSGS, proliferative GN, and diabetic nephropathy (1,2). A membranoproliferative pattern of injury can be seen in association with a monoclonal deposition disease, such as light chain deposition disease (3), which is more common in older adults than younger patients. Diabetic nephropathy is less

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commonly encountered, largely because patients with diabetes and NS seldom undergo renal biopsy unless “atypical” features are present such as onset of NS <5 years from discovery of diabetes, rapid progression of renal impairment, or absence of proliferative retinopathy and other microvascular complications of diabetes. Thus, the infrequency of diagnosis of diabetic nephropathy in the older adult patient is more a manifestation of ascertainment bias than a true lack of susceptibility. Autoimmune diseases such as lupus nephritis are distinctly uncommon in the older adult, particularly in men. Although crescentic GN (e.g., that due to antineutrophil cytoplasmic or antiglomerular basement membrane autoantibodies) is relatively common in the older adult, it seldom presents with isolated NS (3).

MCD is encountered in approximately 12%–15% and MN is encountered in approximately 30%–40% of renal biopsies in older adult participants with isolated NS (1,2). Both MN and MCD can be a primary idiopathic glomerular disease or secondary to any number of conditions such as neoplasia, drugs, or infection (4,5). Approximately 10%–12% of renal biopsies in older participants believed to have primary idiopathic NS on clinical grounds will reveal amyloidosis (1,2). Amyloidosis in the older adult is most often of the primary variety, although secondary and hereditary amyloidosis have also been described in such participants. Performance of a kidney biopsy is essential to delineate the various causes of NS in this age group, and will greatly aid in focusing the diagnostic evaluation in a cost-effective manner and in planning appropriate treatment. Many experienced clinicians recommend deferring additional laboratory or imaging procedures until the histopathologic diagnosis of NS has been made by renal biopsy.

Diagnostic Evaluation

One week after discontinuance of aspirin and clopidogrel, the patient was admitted to the hospital for an overnight stay and a percutaneous kidney biopsy was performed without complications. He was discharged the following morning with instructions to limit vigorous activities and to resume taking aspirin and clopidogrel 1 week later. The biopsy was undertaken in the hospital because of concerns regarding risk of bleeding. Although prior aspirin use is associated with only a slight increase in risk of mild bleeding and no increase in risk of major bleeding episodes (6), few data are available regarding the risk of bleeding from kidney biopsies when combinations of antplatelet drugs are being administered to patients for protection from recurrent coronary thrombosis. Most authorities recommend discontinuance of antplatelet drug therapy at least a week before an elective procedure that may involve a bleeding risk, such as a percutaneous kidney biopsy. Kidney biopsies can be safely undertaken on an outpatient basis with less than overnight observation in highly selected cases at low risk of complications, but are probably not advisable in cases such as this.

Three days after discharge, the report from the pathologist identified the renal lesion as stage 2–3 MN (Figure 1). Four of 18 glomeruli were globally sclerotic. The tubulointerstitial areas showed focal mild to moderate interstitial fibrosis and tubular atrophy, but no interstitial edema was evident. There was mild to moderate arteriolar nephrosclerosis. Immunofluorescence showed 3+ diffuse, peripheral capillary granular deposits of IgG and weaker but positive deposits of C3 and IgM. No IgA or C1q was present. Both \( \kappa \) and \( \lambda \) light chains were present in equal intensity. Electron microscopy showed extensive subepithelium-like dense deposits and some increase in basement membrane thickening. There were no mesangial electron-dense deposits. A Congo red stain was negative. An occasional capillary loop contained a rare PMN. A diagnosis of primary idiopathic MN was suspected; however, concerns remained regarding an underlying secondary cause, such as a malignancy, because of the patient’s age and medical history.

After receipt of the biopsy report, additional tests were performed. Hepatitis B and C serologies were negative, serum C3 was 118 mg/dl and serum C4 was 19 mg/dl (both normal), antinuclear antibody titer was 1:80 (speckled), and an anti-double-stranded-DNA antibody was negative. A spiral computed tomography (CT) scan of the chest was ordered to look for lung lesions that may have been overlooked in the routine chest radiograph in light of the history of long-term cigarette smoking.

Discussion

In summary, this older adult male patient has new onset of NS due to underlying MN, having morphologic features by light, immunofluorescence, and electron microscopy compatible with, but not necessarily diagnostic of, the primary idiopathic form of the disease. These included exclusively subepithelium-like deposits containing IgG and C3 but no C1q or mesangial electron-dense deposits. Amyloidosis, MCD, FSGS, MPGN, and monoclonal Ig deposition diseases were satisfactorily excluded, and further investigation of these possibilities was no longer needed or appropriate. Renal function was relatively well preserved, but the true GFR may be much less than demonstrated by the eGFR values due to the effect of marked proteinuria and hypoalbuminemia to increase the tubular secretion of creatinine (through unknown mechanisms); this lowers the serum creatinine level and thereby spuriously elevates the calculated eGFR values (7). The patient has a background of atherosclerotic coronary artery disease, hypercholesterolemia, and heavy smoking, as well as physical signs of peripheral arterial disease.
He takes an occasional NSAID for osteoarthritis but this has been of many years duration and is mostly likely a non-contributory coincidental finding, although occasional case reports have implicated NSAID use in cases of MN (8).

The focus in such patients would now shift to a determination of whether primary idiopathic MN is the correct diagnosis, or whether the lesion is secondary to a systemic disease process, such as neoplasia. Laboratory testing has rendered chronic hepatitis B and C viral infection a very unlikely cause and the normal complement levels with low titer antinuclear autoantibodies and absence of C1q in the glomerular deposits make lupus MN very unlikely as well. On the basis of this analysis, it would be appropriate to review and discuss the connection between MN and neoplasia.

It has been recognized for over 4 decades that MN has a propensity to be associated with underlying neoplastic disease, both of malignant and benign forms (5,9–14). The overall prevalence of cancer in participants with MN has been reported to be 5%–25%, depending heavily on the age of the participants. Nearly every known neoplastic process has at some time been associated with MN, most often by case reports or limited series of observations. Not surprisingly, the most common associations are with the more prevalent neoplastic diseases such as lung, colon, breast, prostate, and stomach cancer. However, other less common malignancies such as renal cell carcinoma, lymphoma, chronic leukemia, and even multiple myeloma have also been reported in patients with MN. Neoplastic disease is often clinically evident at the time of diagnosis of MN or appears months or even years after the diagnosis of MN has been established (15). Most commonly, however, the diagnosis of MN by renal biopsy triggers an investigation for an underlying but unknown neoplasia that subsequently proves to be positive. The extraordinary diversity of the neoplasia-MN connection poses difficulties concerning the extent of the investigative process that should be undertaken in the absence of any history or clinical findings suggesting a possible specific source or site. Under most circumstances, the search for an underlying neoplasia is limited to screening for the most common causes when no clues directing the clinician to a particular organ or system are present.

The association of MN and neoplasia is most evident in older participants, usually aged ≥60 years (5,9–14). This age dependency for the association also gives rise to a series of conundrums and questions. Is the association merely a coincidence, because many neoplastic processes and MN both increase in prevalence with age, or is the association a causal one? Does the tumor evoke an immunologic series of events that leads to deposition of immune complexes in the glomerular capillaries thus evoking MN? Or is there something involved in the pathogenesis of MN that also promotes the emergence of clones of neoplastic cells? Do one or more of the drugs used to treat MN enhance the development of tumors?

A description of an association of MN with neoplasia, especially through case reports and small series of observations, cannot definitely answer these legitimate and clinically relevant questions. However, as with the association of cigarette smoking and lung cancer, application of the Bradford Hill criteria designed to evaluate epidemiologic data in a manner to approximately define causality can bring us closer to resolution of these conundrums (16). The Bradford Hill criteria include an analysis of the following: (1) the strength of the association, its consistency, and its specificity; (2) the temporality of the association; (3) the biologic gradient (dose response); (4) biologic plausibility; (5) coherence; (6) reversibility; (7) and analogy and alternate explanations.

The first two of these criteria have been examined on multiple occasions in the literature and have generally supported a causal influence of malignancies on the development of MN (5,9–14). In a pivotal study, Leflaucher et al. examined a cohort of 240 patients with biopsy-proven MN (17). Among them, 24 patients (10%) were discovered to have a malignancy at the time of renal biopsy or developed one within a year after the diagnosis. Eighteen of the 24 patients (75%) were aged ≥65 years and 72% were men. Marked proteinuria (>10 g/d) was found in 25% of patients and an eGFR of <60 ml/min per 1.73 m² was found in 54%. All stages of MN were noted on renal biopsy. The occurrence of cancer of varying types increased with age and was much higher in the patients with MN than predicted from general population-based incidence reports, with a standardized incidence ratio of 9.8 (95% confidence interval [95% CI], 5.5–16.2) for men and 12.3 (95% CI, 4.5–26.9) for women with MN compared with the general population. Carcinomas accounted for 83% of cases and the most frequent sites were lung and prostate. The strongest predictors for a cancer-associated MN were advanced age, smoking, and leukocytic infiltration of the glomeruli (all features present in the current case). Indeed, the diagnostic value of leukocyte infiltration in glomeruli was very good. More than eight leukocytes per glomerulus had a sensitivity of 75% and a specificity of 92% for the identification of cancer-associated MN.

Interestingly, 25% of the patients with cancer-associated MN experienced a thrombotic event and a pulmonary embolus occurred in one case. The prevalence of venous thromboembolism in patients with MN that was not associated with cancer was not given. However, these findings might indicate a special risk for thromboembolic disease when cancer is associated with MN, although MN in the absence of cancer is also associated with a higher risk of venous thromboembolic events, especially when the serum albumin concentration is greatly depressed (<2.8 g/dl) (16,19). Thus, an association between cancer and MN with a propensity for the development of venous thromboembolic disease is plausible but unproven (19). One of the main weaknesses of this study is its observational nature and confounding by investigational intent; namely, the higher incidence of cancer in MN may have been due to a more vigorous search for neoplasia when the diagnosis of MN was made by renal biopsy.

Björneklett et al. extended these observations by examining the long-term course of 161 patients with MN followed for a median of 6.2 years after diagnosis (15). Of the 161 patients, 33 (21%) developed cancer, 72% after the diagnosis of MN. The median time for diagnosis of MN to diagnosis of cancer was 5 years (range, 0–13 years). During the 15 years after biopsy diagnosis, the standardized incidence ratio for cancer was 2.25 (95% CI, 1.44–3.35). This study suggested that the predilection for cancer in
participants with MN persists for many years. A weakness of this observational study is that postdiagnosis treatments were not monitored; thus, the use of cytotoxic-oncogenic agents in the management of MN could have had an influence on the results. Nevertheless, it does point out the necessity for long-term surveillance of patients with MN for the subsequent emergence of a malignancy. It also raises the notion that some common, but presently unknown, factors may predispose some patients to both MN and malignancies, perhaps of a genetic nature (e.g., a defect in a tumor-suppressor gene).

Cancer seems to have a strong, consistent, and temporal association with MN, particularly among older participants. A biologic gradient for the cancer-MN connection may not be relevant, because the extent of the tumor mass does not seem to relate to the occurrence of glomerular disease. Small or large tumors seem equally able to evoke MN (19,20). It may well be that the host response to the tumor is more important than the tumor burden itself in causing MN. It is also worth noting here that many other glomerular lesions have also been reported to occur in association with malignancy (9–14).

Biologic plausibility is an important aspect of relating cancer to MN, but we have only scant evidence for such a causal linkage. Rarely, tumor neoantigens or antitumor antibodies have been localized to the immune deposits seen in MN with cancer (20,21). Patients with malignancy have an increased prevalence of glomerular IgG deposits compared with noncancer patients; however, these deposits are mostly in the subendothelial or mesangial locales, rather than in subepithelial-like sites so typical of idiopathic MN (22). Experimentally, rats bearing transplanted colon cancer–derived tumors develop immune deposits and electron-dense deposits in glomeruli, but a picture of MN is not seen (23). To my knowledge, there are no animal models of MN due to transplanted, induced, or spontaneous malignancy, which creates a real deficit in our understanding of the relationship between MN and cancer.

The possibility also exists that cancer augments the same immune processes responsible for primary idiopathic MN. We now recognize that 75%–85% of primary idiopathic MN is due to the in situ reaction of circulating M-type antiphospholipase A2-receptor (anti-PLA2R) autoantibodies and their relevant epitopes on the podocyte, resulting in the formation of subepithelial-like immune complexes, activation of the alternative complement pathway and proteinuria (24,25). Such susceptibility to primary idiopathic MN and autoantibody formation is under the control of genes at the major histocompatibility locus on chromosome 6 and by polymorphisms in the PLA2R gene on chromosome 2 (26). Although initial reports indicated that anti-PLA2R autoantibodies were seldom observed in cancer-associated MN, more recent studies using an enhanced Western blot assay have indicated that as many as 30% of patients with cancer-associated MN have such autoantibodies (25). This assay is sensitive enough to detect antibodies is almost 90% of patients with presumed primary idiopathic MN.

Patients with cancer-associated MN with and without anti-PLA2R autoantibodies have different Ig subclass distributions for IgG4 and behave differently on clinical follow-up, suggesting that cancer-associated MN may consist of two varieties: one anti-PLA2R autoantibody-induced behaving similarly to primary idiopathic MN in a minority of patients and the other that is not induced by anti-PLA2R autoantibodies occurring in the majority of patients (25). These two varieties cannot be reliably distinguished morphologically by light or electron microscopy, except perhaps for leukocyte infiltration of glomeruli, as noted above. However, immunofluorescence is of greater value in separating cancer-associated MN from primary idiopathic MN. It is well established that the immune deposits are composed chiefly of the IgG4 subclass of the IgG isotype in primary (idiopathic) MN induced by anti-PLA2R autoantibodies (24). On the other hand, glomerular immune deposits in cancer-associated MN are more often IgG1, IgG2, or IgG3 subclass dominant, and IgG4 is variably present in smaller amounts (27). In a recently published series from China, only 1 of 8 cases (13%) of cancer-associated MN was positive for IgG4 in glomeruli, whereas 36 of 42 cases (86%) of apparently primary idiopathic MN had glomerular IgG4 deposits (28). IgG1 or IgG2 (or IgG3) deposition of 2–3+ intensity was observed in 7 of 8 (88%) cases of cancer-associated MN but in only 8 of 42 (20%) cases of primary idiopathic MN. Thus, in addition to anti-PLA2R autoantibody testing (if available), immunofluorescence using IgG class–specific reagents may useful in sorting out the possibility that cancer underlies MN. However, due to the small number of cases examined thus far, further studies of the utility of this approach are needed.

Coherence and reversibility issues have been addressed by the observation that the NS in MN associated with malignancies can regress after eradication of the malignancy or a reduction of the tumor burden by surgery or chemotherapy and that it may relapse when the malignancy returns (5,9–14). Other than a direct causal effect of neoplasia (most likely by immunologic means), alternate explanations for the association of MN and neoplasia are tenable. The association could be due to some process common to the pathogenesis of both MN and cancer but operating through different pathways. The persistence of an elevated cancer risk for decades after diagnosis of MN would be compatible with this supposition, but other explanations are possible.

In summary, the suspicion that this patient with NS might have a cancer-associated form of MN is very reasonable. His age, smoking history, and findings on kidney biopsy (leukocyte infiltration of glomeruli) place him at an elevated risk for this association. Carcinoma of the lung seems to be mostly likely, but any neoplastic process is theoretically possible. It is not practical to screen for all possible malignancies and some may be so small as to evade a cursory physical or radiologic examination. The best approach, in my opinion, would be to ask the pathologist to assess the IgG subclass distribution in the glomerular IgG deposits. If the deposits are not IgG4 dominant, then I would pursue an evaluation for a malignancy consisting of a chest CT scan, a repeat examination of the prostate for nodules, and a colonoscopy, if one had not been performed in the prior 6 months. In a woman with the same presentation, I would recommend a careful breast examination, a mammogram, and a perhaps a cervical Papanicolaou cytology, although the yield of the latter would likely be quite low. Additional imaging for subdiaphragmatic neoplasia, such as an abdominal lymphoma, might be
the biopsy is IgG4 dominant by immuno-

If available, measurement of anti-PLA2R autoantibodies might be of help. If the biopsy is IgG4 dominant by immunofluorescence, anti-

The patient most likely has primary idiopathic MN and an exhaustive search for a malignancy could be curtailed. On

In men, perform a rectal examination and prostate-specific antigen if not already done as part of routine preventative care

Check stool for occult blood and arrange for colonoscopy if not already done as part of routine preventative care

Consider abdominal computerized tomography (CT) scan to evaluate for subdiaphragmatic neoplastic processes

Step 4. Evaluate for suspected underlying malignancy if appropriate based on step 4 findings or a suspicious history or physical examination

In women, perform a breast examination and mammography if not already done as part of routine preventative care

In men, perform a rectal examination and prostate-specific antigen if not already done as part of routine preventative care

Consider abdominal computerized tomography (CT) scan to evaluate for subdiaphragmatic neoplastic processes

(i.e., renal cell carcinoma, lymphoma, etc.)

Table 1. Suggested step-wise approach to the evaluation of NS in an older adult (>65 years of age)

<table>
<thead>
<tr>
<th>Step 1. Initial studies</th>
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<tbody>
<tr>
<td>Perform a complete history and physical examination, emphasizing family history, medication use, infection history, and assessment of systemic manifestations</td>
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<tr>
<td>Perform a urinalysis and microscopically examine a freshly obtained urine sediment</td>
</tr>
<tr>
<td>Confirm NS with 24-hour urine protein (&gt;3.5 g/dl) or spot urine protein/creatinine ratio (&gt;3.0) and serum albumin &lt;3.4 g/dl</td>
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<tr>
<td>Measure serum creatinine concentration and calculate estimated GFR</td>
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<tr>
<td>Measure a serum biochemical profile, fasting lipids, and a complete blood count</td>
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<tr>
<td>Measure hemoglobin A1c and examine the retina with dilated pupils (if patient has diabetes)</td>
</tr>
<tr>
<td>Measure serum-free light chains and perform a serum and urine immunofixation test for monoclonal proteins</td>
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<tr>
<td>Consider an abdominal fat pad biopsy/aspiration if amyloidosis is suspected</td>
</tr>
<tr>
<td>Assess renal size and configuration by abdominal ultrasound</td>
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</table>

| Step 2. Perform a kidney biopsy, if no contraindications exist, with complete histopathological assessment with light, immunofluorescence, and electron microscopic studies (including a Congo red stain if appropriate) |

| Step 3. Targeted evaluation based on glomerular and extraglomerular lesions if a lesion of MN is found by renal biopsy |
| Measure hepatitis B surface antigen and hepatitis C antibody |
| Measure antinuclear antibody and anti-DNA antibody (particularly if features of SLE are noted on biopsy) |
| Measure serum C3 and C4 complement |
| Measure anti-PLA2R autoantibody (Western blot or alternative if available) |
| Request immunofluorescence for IgG subclass deposition |
| Request immunofluorescence for PLA2R deposits (if available) |
| If IgG4+ and anti-PLA2R+ (serum and or glomerular deposits), consider the most likely diagnosis is primary idiopathic MN and manage accordingly |
| If IgG1–3 dominant and IgG4 weak or absent, regardless of the results with anti-PLA2R, consider the possibility of an underlying neoplasia |

| Step 4. Evaluate for suspected underlying malignancy if appropriate based on step 4 findings or a suspicious history or physical examination |
| Conduct a computed tomography scan of the chest, especially in patients with a smoking history |
| Check stool for occult blood and arrange for colonoscopy if not already done as part of routine preventative care |
| In women, perform a breast examination and mammography if not already done as part of routine preventative care |
| In men, perform a rectal examination and prostate-specific antigen if not already done as part of routine preventative care |
| Consider abdominal computerized tomography (CT) scan to evaluate for subdiaphragmatic neoplastic processes |

NS, nephrotic syndrome; MN, membranous nephropathy; anti-PLA2R, antiphospholipase A2-receptor.
left-sided mass consistent with a carcinoma of the lung. The renal biopsy was stained with IgG subclass-specific reagents. IgG4 staining was weak or absent, whereas IgG2 and IgG3 staining were both dominant (Figure 2). Anti-PLA2R autoantibodies were not measured. The patient is awaiting consultation for treatment of his lung cancer. He has responded well to diuretics. Atorvastatin therapy has been intensified and he is now taking an angiotensin receptor blocker. His BP is now 148/80 mmHg. His serum cholesterol remains elevated at 225 mg/dl. His current urine protein is 4.4 g/d, his serum creatinine is now 1.2 mg/dl, and his serum albumin level has risen to 3.0 g/dl. Consideration of prophylactic warfarin therapy is in abeyance until the treatment of his lung cancer is decided upon; the rise in his serum albumin concentration has lowered concern regarding a VTE event somewhat.

**Final Diagnosis.** MN and NS secondary to cancer of the lung.

**Disclosures.**

None.

**References.**


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