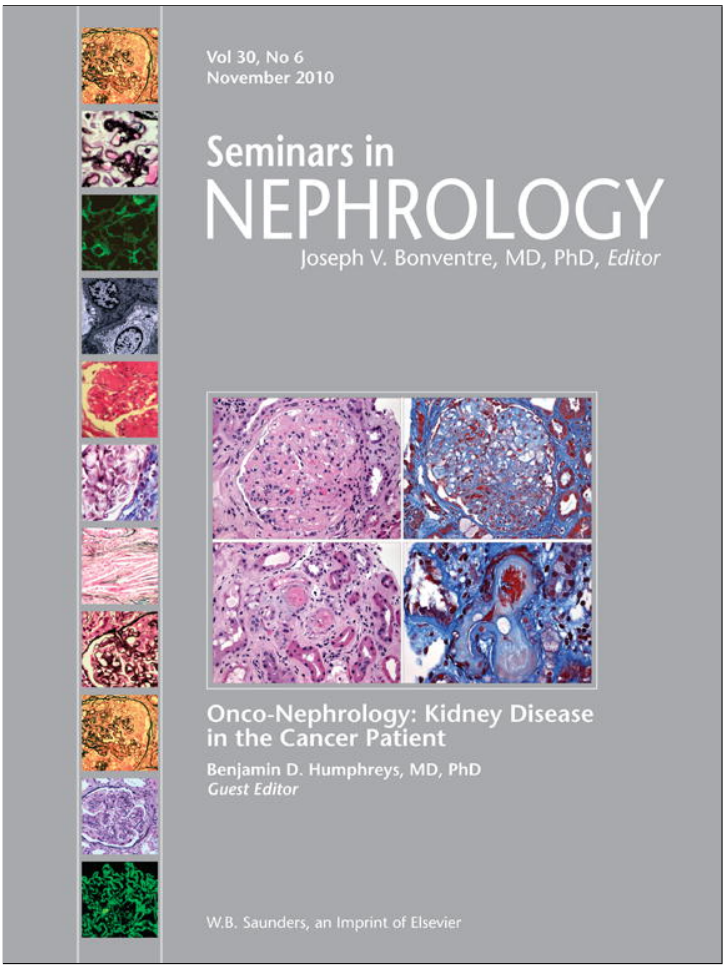

Membranous Nephropathy and Malignancy

Laurence H. Beck Jr, MD, PhD

Summary: An association between the glomerular disease membranous nephropathy (MN) and malignancy has long been appreciated, but evidence supporting this relationship remains limited, speculative, and, at times, controversial. Reports that the two disease processes often evolve in parallel, as well as the occasional findings of tumor antigens or tumor-reactive antibodies within glomerular immune deposits, are all supportive of an association. However, the diagnosis of both MN and malignancy in the same individual also may be coincidental, especially in an older demographic group in which both diseases tend to occur. This article briefly reviews the proposed pathogenetic mechanisms of idiopathic and secondary forms of MN, as well as the arguments for and against the contention that malignancy-associated MN is itself a distinct clinical entity. In addition, the recent identification of the M-type phospholipase A_2 receptor as a major glomerular antigen in idiopathic MN has the potential to offer fresh tools that might help resolve some of the controversy, and ultimately aid in the decision of how aggressively to screen for malignancy in an individual diagnosed with MN.
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Membranous nephropathy (MN), a common cause of the nephrotic syndrome, is a glomerulopathy defined at the histopathologic level by the presence of immune complexes on the extracapillary side of the glomerular basement membrane (GBM). Approximately 75% of the cases of MN in developed countries are idiopathic, or primary, membranous nephropathy (IMN). The remainder are associated with a variety of conditions thought to secondarily cause MN; these include systemic lupus erythematosus, hepatitis B antigenemia or other chronic infections, and, historically, a number of drugs and toxins such as therapeutic gold salts, D-penicillamine, and agents containing mercury. An association with malignancy, especially solid tumors, has been noted for decades, and serves as the subject of this review article.

The first substantial report of a possible link between malignancy and MN came in 1966 when Lee et al[1] reported that 11% of patients with the nephrotic syndrome also had carcinoma; the histologic diagnosis in 8 of these 11 cases was MN. This association has been the subject of several excellent case series and review articles in the intervening decades,[2-9] but remains a topic still regarded on occasion with some skepticism. Some investigators argue strongly that the putative connection should lead to aggressive screening for malignancy in patients diagnosed with MN in the absence of other clear secondary causes,[6,8] whereas others believe that the existing literature has overstated the relationship.[5] This article does not attempt to repeat a comprehensive analysis of data from the primary literature (the reader is directed to the articles referenced earlier), but instead highlights recent findings in the immunopathology of MN, especially as they might relate to malignancy-associated MN, and pro-

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Address reprint requests to Laurence H. Beck Jr, MD, PhD, Boston University School of Medicine, Department of Medicine, Renal Section, Evans Biomedical Research Center, 5th Floor, Room 547, 650 Albany St, Boston, MA 02118. E-mail: lhbeckjr@bu.edu
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poses ways in which this field may once again move forward.

Most case series report that malignancy can temporally be related to MN in 6% to 22% of those patients with this renal diagnosis[7] in whom other secondary causes have been excluded. Cancer tends to be discovered within 12 months of the diagnosis of MN; approximately 80% are found before or at the time of the renal diagnosis, with the remainder being detected afterward.[4,6] The prevalence of solid tumors in those with MN is particularly striking; in a study detailing the association of the broader categories of nephrotic syndrome and neoplasia, MN was the renal diagnosis in 69% of those patients with carcinoma.[4] The most common carcinomas historically associated with MN have been lung and gastrointestinal.[7-9] More recent reports also have detected an association between MN and prostate cancer[8,10]; the investigators speculated that the recent availability of prostate-specific antigen testing and modern imaging have increased detection of this slow-growing malignancy that may remain clinically inapparent for years.[8] It is notable that certain other common cancers such as breast and bladder carcinoma, as well as skin and neurologic malignancies, are underrepresented in these case series. Not surprisingly, individuals with MN and cancer tend to be older,[10,11] and may have a history of heavy smoking.[8]

PROPOSED PATHOGENESIS OF IDIOPATHIC AND SECONDARY FORMS OF MN

MN is not a single entity, but rather a common histopathologic pattern of injury caused by several disparate underlying disorders. Common to all are the immune deposits that form in a predominantly subepithelial location, beneath the foot processes of the visceral glomerular epithelial cell, or podocyte. The precise origin of these deposits has been the topic of much research in the past 50 years. Early work suggested that these deposits were the result of circulating immune complexes (CICs) of particular size, charge, and affinity. Studies in Heymann nephritis, an experimental rat model of human MN, convincingly established an alternate mechanism, in which the target antigen was located on the podocyte foot process, and the subepithelial immune deposits were the result of circulating antibodies binding in situ to this native glomerular antigen.[12,13]

Milestones in Our Understanding of MN

A cursory introduction to several key historical findings in the field of MN is necessary for a better understanding of the events that may play a role in malignancy-associated MN. In the Heymann nephritis model of MN, rats are immunized against an antigenic fraction derived from rat proximal tubular brush border and develop subepithelial deposits virtually identical to those observed in human disease. Researchers ultimately discovered that the target antigen was a large transmembrane endocytic receptor known as megalin.[14-16] In the rat, but not in human beings, megalin is additionally present on the foot processes of podocytes, allowing circulating antimegalin antibodies to cross the GBM, bind megalin at the podocyte cell surface, and ultimately form subepithelial immune deposits in situ. Complement, activated by the immune deposits, leads to insertion of the terminal complement components C5b-9 (the membrane attack complex) into the podocyte cell membrane, causing cell injury, effacement of the foot processes, and proteinuria (reviewed by Nangaku et al[17]). Despite the finding that megalin is not present in human glomeruli,[18] many investigators continued to pursue the idea that an epithelial antigen was targeted in human disease, which helped to fuel investigations attempting to link MN with solid, largely epithelium-derived, tumors.

Strong support for a podocyte-expressed antigen playing a role in human disease initially came from case reports describing a rare situation known as *alloimmune antenatal MN*, in which infants with the clinical and pathologic features of MN were born to mothers genetically deficient in the protein neutral endopeptidase (NEP).[19,20] These mothers had been alloimmunized against fetally expressed NEP, and the circulating anti-NEP antibodies, after crossing the placenta and fetal GBM, targeted NEP on the fetal podocyte to cause disease. Thus, in both the rat model of Heymann nephritis and alloimmune antenatal MN in human beings, an-

tibodies generated against a target protein expressed on the podocyte lead to the in situ formation of subepithelial deposits, podocyte injury, and consequent proteinuria.

Our laboratory recently has identified, in the majority of cases of adult IMN, circulating autoantibodies reactive with the transmembrane glycoprotein M-type phospholipase A_2 receptor (PLA_2R).[21] This protein is expressed by the human podocyte, again suggesting a mechanism of disease that fits the paradigm established in Heymann nephritis. These anti-PLA_2R autoantibodies were highly specific for IMN, and were not found in normal individuals, in patients with other causes of the nephrotic syndrome, or, important for this discussion, in cases of secondary MN. We also showed that the PLA_2R antigen co-localizes with IgG4 in the subepithelial deposits of IMN biopsy specimens, and that IgG reactive with PLA_2R could be eluted from the tissue sections. The level of circulating anti-PLA_2R antibodies parallels the course of the clinical disease, declining or disappearing before a partial or complete remission of proteinuria, and reappearing with recurrence of the nephrotic syndrome.[22,23] Because additional circulating autoantibodies recently have been identified in IMN,[24,25] it will be important to establish the relative pathogenicity of each, as well as the possibility of synergistic effects, in future animal transfer experiments.

Immune Deposits in Secondary MN

The mechanisms underlying the formation of subepithelial immune deposits in secondary forms of MN are less well understood, but may involve the glomerular deposition of CICs. This putative mechanism is best typified by a secondary form of MN that can occur in lupus, an autoimmune disease featuring CICs that contain DNA and other nuclear material. Although many proliferative forms of lupus nephritis show immune complexes that deposit in a subendothelial position, membranous lupus nephritis is unusual in that most of the deposits are subepithelial. Components of DNA have been detected by immunogold electron microscopy within these subepithelial deposits,[26] although it has not been proved that such complexes are directly pathogenic. Physicochemical properties of the antigen-antibody complex, such as charge and antigen-antibody affinity, have been postulated to be important in determining the ultimate location of the deposits. Low-affinity antigen-antibody interactions may allow immune complexes, initially trapped in a subendothelial position, to dissociate and reform on the abluminal side of the GBM. Small preformed circulating complexes additionally have been shown to have a longer half-life in a subepithelial location, perhaps owing to lack of immune clearance in this location.[27] It also has been suggested that cationic antigens such as the hepatitis B e antigen initially may become planted in the GBM beneath the podocyte foot process, with free circulating antibodies later targeting in situ these non-native antigens. The mechanisms underlying drug- or toxin-induced secondary MN are not clear.

In malignancy, both T cell– and B cell–mediated immune responses are mounted against tumor-expressed antigens, and there is clear evidence that cancer patients have increased levels of CICs.[28] The antigenic targets of the humoral response may include tumor-restricted proteins such as re-expressed fetal proteins (eg, carcinoembryonic antigen) or products of viral oncogenes,[2,4] either of which potentially could be shed into the circulation as free antigens or CICs. Alternatively, the tumor may present an otherwise immunologically privileged antigen, or by molecular mimicry provoke a humoral response against a normal host protein. These potential mechanisms by which tumor antigens and CICs could give rise to MN are depicted in Figure 1. It also is conceivable that an extrinsic process is responsible for both malignancy and MN. For example, viral infection (circulating viral antigens in association with tumor-promoting oncogenes) or an underlying abnormal immune response (combining a predisposition to autoimmunity with impaired immune surveillance) independently could cause MN and malignancy. Also worth mentioning, and relevant to studies with long-term follow-up data, is the risk of malignancy resulting from immunosuppressive agents (especially alkylating agents) used in the treatment of MN.

With such a variety of CICs possible in malignancy, one might expect the situation to re-

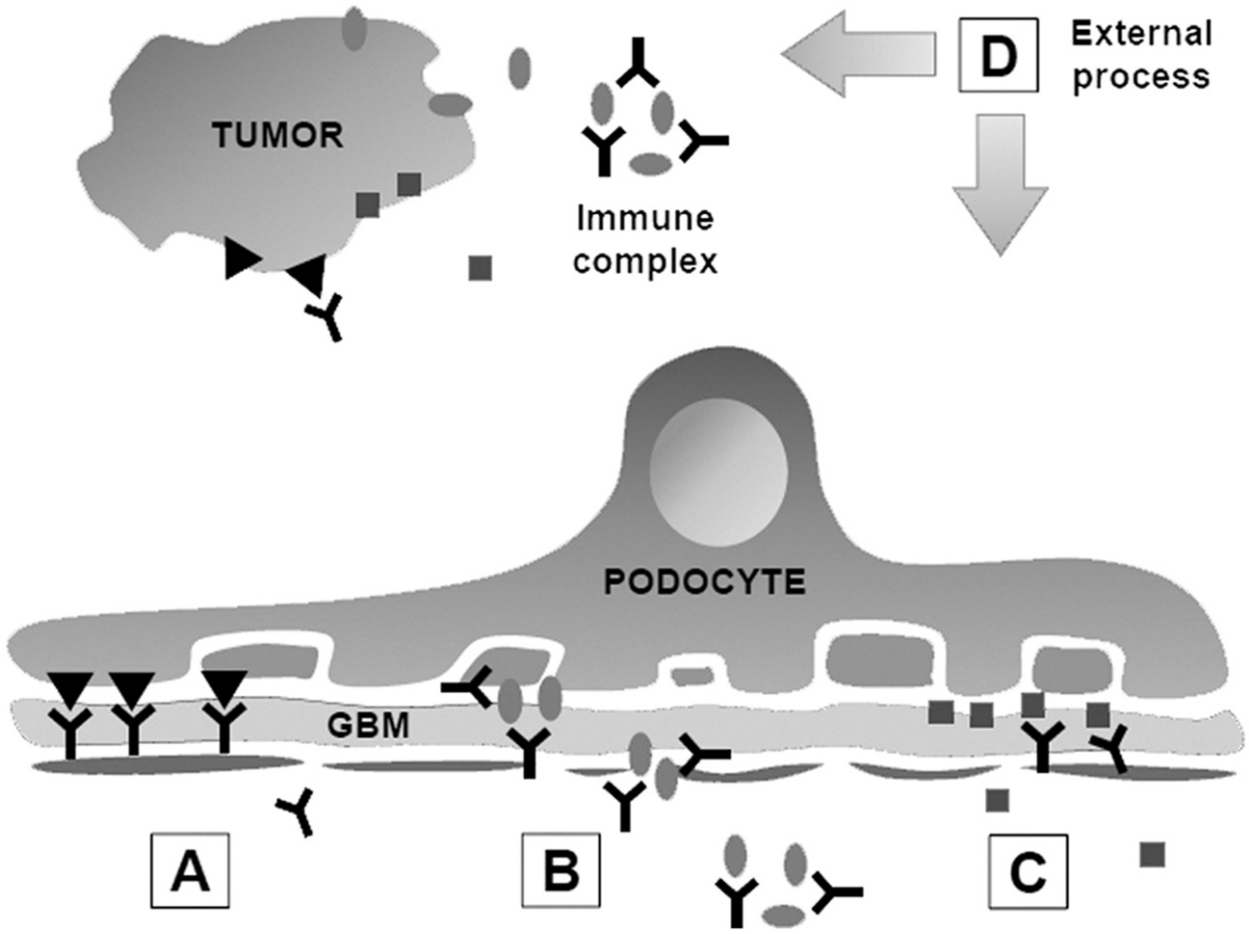

Figure 1. Mechanisms by which solid tumors and MN may be linked. MN is defined by subepithelial deposits that form in the GBM beneath the foot processes of the glomerular visceral epithelial cell, or podocyte. Antibodies may be generated against a tumor antigen identical to, or bearing an epitope similar to, an endogenous podocyte antigen, thereby leading to in situ immune complex formation (A). Alternatively, shed tumor antigens may form circulating immune complexes that become trapped in the capillary wall (B). Complexes may initially form in a subendothelial location, dissociate, and reform in a subepithelial position. Tumor antigens also may, based on size and charge, become planted in a subepithelial location where they react with circulating antibodies at a later stage (C). Finally, extrinsic processes, such as infection with an oncogenic virus or altered immune function (D), potentially could cause both malignancy and MN.

semble lupus nephritis, in which the majority of cases involve subendothelial immune complexes that would be more apt to induce a proliferative glomerulonephritis. Indeed, autopsy case series in malignancy largely have shown small subendothelial or mesangial glomerular deposits,[29] especially in gastrointestinal malignancies,[30] but have not confirmed a higher prevalence of subepithelial deposits as would have been predicted by an association of solid tumors with the nephrotic syndrome and MN in particular. Other studies have reported an absence or similarly low prevalence of glomerular deposits in individuals with solid tumors (reviewed by Bacchetta et al[9]). In short, the precise pathogenetic mechanisms by which cancer might lead to MN have yet to be elucidated.

MALIGNANCY-ASSOCIATED MN: A DISTINCT ENTITY?

With this background in hand, let us review the reasons why a causal relationship between malignancy and MN has not been universally accepted. Evidence for such an association was presented as early as 1966, when Lee et al[1] observed that solid tumors had been found in 11% of cases of otherwise idiopathic nephrotic

syndrome. Similar reports have followed on a regular basis,[2-9] each attempting to bring further clarity to the topic. One major argument against a causal association between malignancy and MN stems from the fact that they are both, for the most part, diseases of older (male) individuals, and might merely represent two disease processes that occur coincidentally in an individual of this demographic group.

Many of the studies referenced earlier have shown that malignancy is, in fact, observed in patients diagnosed with MN at rates higher than those predicted by actuarial or national registry data. Complicating this fundamental argument, however, is the potential detection bias likely to be present in all reports published after the initial recognition of a link between MN and malignancy. Individuals presenting to clinical attention with the nephrotic syndrome and MN, in the absence of secondary features such as antinuclear antibodies (ANA) or hepatitis B antigenemia, may have undergone more screening for cancer than their age-matched counterparts in the general population. A role for such bias in perhaps overstating the association between malignancy and MN is supported by a population-based analysis from Denmark that found higher than expected rates of malignancy within 1 year of the diagnosis of glomerular disease, but also found that the observed-to-expected ratios diminished over time and became insignificant at 5 years.[31] In contrast, a French collaborative group, after performing a subanalysis of their data in which they restricted malignancy cases to only those that were clinically evident before or at the time of renal diagnosis, still found a higher than expected incidence of cancer compared with age- and sex-adjusted national cancer rates,[8] minimizing a role for detection bias.

There are certain pathologic features supporting the contention that malignancy-associated MN is indeed an entity distinct from IMN. Analysis of the IgG subclasses comprising the subepithelial deposits in malignancy-associated MN shows a predominance of IgG1 and IgG2,[32] rather than IgG4, as is typical in IMN.[33,34] One group also reported an increased number of immune cells within the glomerulus in biopsy tissue from individuals with MN and cancer, perhaps related to these differences in IgG subclass.[8] Although it was initially thought that those with malignancy-associated MN tended to have heavier proteinuria and virtually always showed the nephrotic syndrome, this has not been substantiated in later reports.[8,10]

Confirmation of a truly causal relationship between malignancy and MN relies on several criteria.[7,9] There should be no obvious alternate cause (ie, established secondary causes first need to be excluded by serology and history) and there should be a temporal relationship between malignancy and glomerular disease. Complete removal of the tumor via surgery, chemotherapy, or other ablative methods should ultimately (but not necessarily immediately) lead to clinical remission of MN with resolution of proteinuria. Similarly, a recurrence of the malignancy should be accompanied by a return of proteinuria. This temporal association of remission and recurrence is schematically depicted in Figure 2. It should be kept in mind that MN may remit spontaneously in approximately one third of idiopathic cases, and thus the return of proteinuria with recurrence of the tumor much more strongly supports a causal association than does the remission of proteinuria at some point after tumor removal.

Case reports abound detailing remission of proteinuria once the tumor has been eradicated (reviewed by Burstein et al[6] and Bacchetta et al[9]), but few if any convincingly report recurrence of both disease processes. Proteinuria may persist despite removal of the tumor, which could be owing to residual structural changes in the kidney, as observed by Couser et al,[35] or the possibility that a smoldering yet undetected tumor continues to incite a low-level immune response, sustaining the glomerular injury. It is more difficult to explain the recurrence of tumor in the absence of proteinuria if the two processes are causally related. In a case of MN associated with bronchogenic carcinoma,[36] the investigators reported resolution of proteinuria after resection of the carcinoma, but a failure of the proteinuria to return after the patient was found to have recurrent lung cancer. Without serologic and pathologic studies, it is impossible to extract any hard data from these observations; for example, the re-

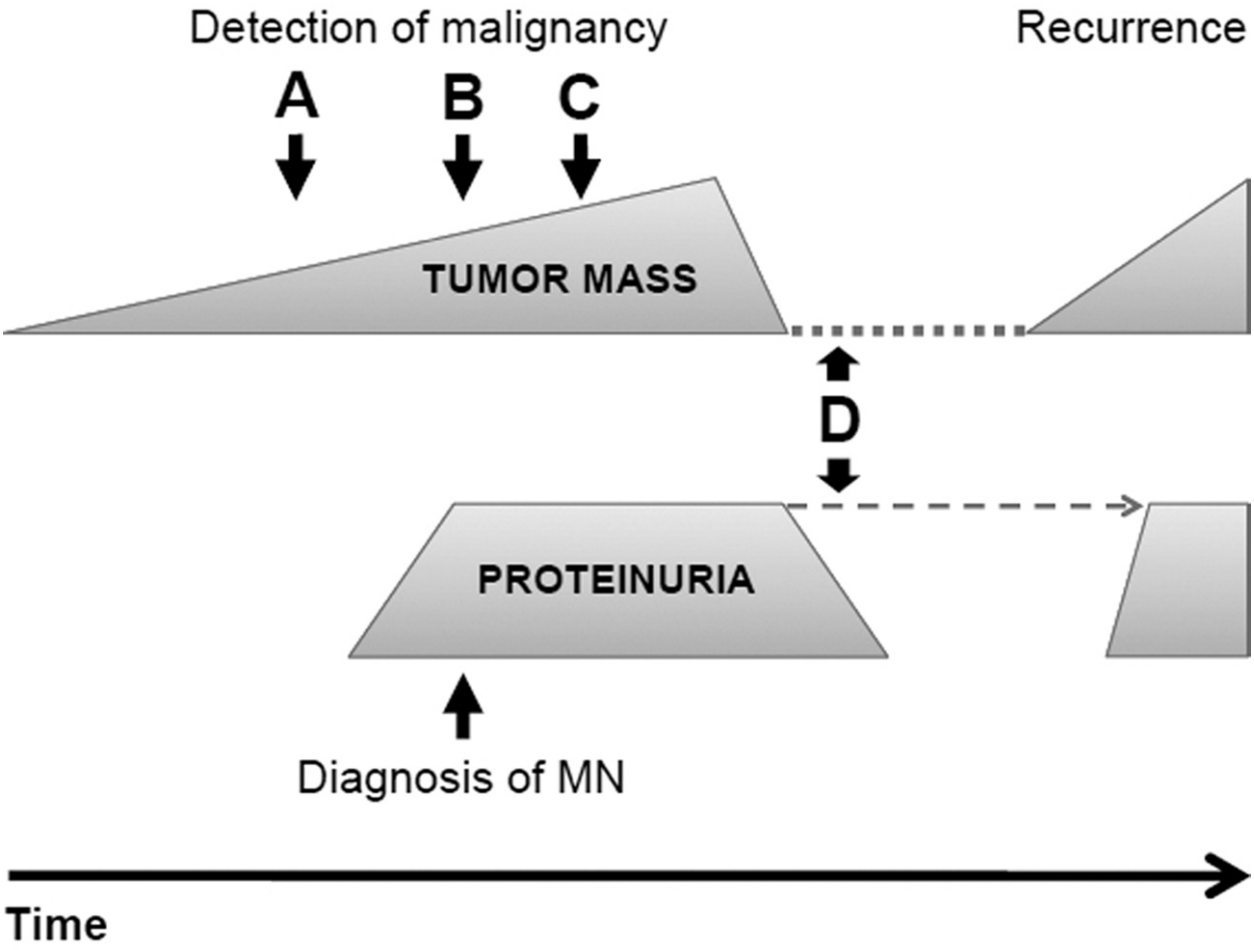

Figure 2. Temporal relationships between malignancy and MN. This figure assumes a causal relationship between malignancy and MN. MN typically is diagnosed after proteinuria and/or nephrotic syndrome has prompted the performance of a kidney biopsy. Malignancy usually is detected before (A) or simultaneously with (B) the diagnosis of MN, but may be found afterward (C) in approximately 20% of reported cases. Recurrence of malignancy may give rise to proteinuria in a shorter time frame owing to prior sensitization of the immune system against tumor antigens. The subclinical presence of malignant cells and shed antigen (dotted line) potentially could continue to perpetuate the glomerular disease and proteinuria (D) despite an apparent clinical remission of the cancer.

current tumor may have been a new primary malignancy, or could have lost expression of the particular antigen putatively responsible for the MN.

The most demanding piece of evidence involves the establishment of a pathophysiologic basis for the association of MN and malignancy, using serologic and immunohistologic approaches. Kaplan et al[3] suggested that "the most incontrovertible evidence" for an association of MN and malignancy is the demonstration of tumor antigen in the GBM, which indeed has been shown for particular (eg, carcinoembryonic antigen) as well as nonspecific antigens in a number of early studies.[35,37-40] The presence of tumor antigen in the glomerulus in conjunction with a corresponding antibody from the circulation does not necessarily mean that they are causative of disease because the antigen and/or antibody could be deposited passively as a result of increased flux through the GBM caused by the breakdown of the filtration barrier.[7] Although a handful of articles dating back to the 1970s show a tumor antigen in the glomerulus, or circulating antibodies that recognize malignant or glomerular tissue, there is still no smoking gun that overwhelmingly implicates a specific tumor antigen in a causative role for malignancy-associated MN (reviewed by Alpers and Cotran[5] and Ronco[7]).

Therefore, it is unlikely that any further analysis of the existing literature will resolve this issue. Although there is persuasive evidence that MN may be associated with certain types of solid tumors, the possibility still lingers that the findings may merely be coincidental. However, the hypothesis that cases of malignancy in patients with MN may merely represent chance occurrences with IMN is finally testable, in that the majority of these patients (upward of 70%) should have circulating autoantibodies to PLA_2R, similar to a population with IMN alone.[21] Given the only recent identification of these autoantibodies and the historically low incidence of patients identified with MN and malignancy, this issue has not yet been addressed to any substantial extent and it may take some time to achieve conclusive results.

Nevertheless, we have encountered one such patient at our institution with nephrotic syndrome from biopsy-proven MN who had been diagnosed with prostate cancer 2 years earlier and had no other features suggestive of secondary MN. Serum from this individual, collected at a time when he was heavily nephrotic, showed no reactivity with recombinant PLA_2R, but did display reactivity with another similarly sized, native glomerular antigen (Fig. 3). This as-yet-unidentified protein is clearly not PLA_2R because it shows a much smaller shift in electrophoretic mobility than PLA_2R after deglycosylation (data not shown), and immunoprecipitation with serum from this patient does not yield PLA_2R (Fig. 3). In addition, there is no co-localization by immunofluorescence of PLA_2R and IgG4 within the immune deposits of his renal biopsy specimen (data not shown); instead, PLA_2R staining is found to persist within the podocyte, a finding more consistent with a secondary process such as lupus-associated MN.[21] Future studies such as this may be able to distinguish IMN from secondary MN in malignancy-associated cases and ultimately define malignancy-associated MN as a distinct secondary form of MN.

RECOMMENDATIONS

Despite the limitations noted earlier, the epidemiologic and serologic evidence for a true association of malignancy with MN is not to be ignored, especially because it has appeared time and time again, and has never convincingly been refuted. Given this suggestive relationship, and because of the risks associated with missing the diagnosis of a malignant tumor, many have recommended screening for common cancers in older patients with newly diagnosed MN without any other obvious cause. Because immunoassays for circulating autoantibodies to podocyte antigens (eg, PLA_2R) that might otherwise be able to distinguish idiopathic from secondary MN are not currently available outside of the research setting, it is reasonable to perform age- and sex-appropriate screening for cancer once known secondary causes of MN have been excluded. This might include colonoscopy, mammography, prostate-specific antigen testing, and imaging of the chest in those with a history of smoking. It is important to emphasize that the risk is not limited to a 12-month period surrounding the time of renal biopsy, and that this prolonged risk period (whether owing to a slow-growing malignancy, immunosuppressive therapy, or increased surveillance) appears to persist for at least 5 years.[10] Therefore, close follow-up evaluation is necessary even if malignancy is not detected on initial screening at the time of the renal diagnosis.[7]

We are hopeful that, as assays for anti-PLA_2R become more widely available, suspected cases of malignancy-associated MN routinely will be tested for this autoantibody. Although other circulating autoantibodies have been shown to exist in IMN,[24,25] for the moment, anti-PLA_2R appears to have the best reported specificity for distinguishing IMN from secondary causes.[21] If the ultimate prevalence of anti-PLA_2R in malignancy-associated MN turns out to be in the 70% to 80% range, then the occurrence of the two disease processes is likely to be coincidental. If instead a much lower prevalence is found (which may not be zero because there certainly will be some cases in which the finding of malignancy and IMN is in fact coincidental), then malignancy-associated MN is likely to represent a distinct entity. In addition, immunolocalization of podocyte PLA_2R on renal biopsy may be an additional means to separate idiopathic from secondary variants of MN. If these

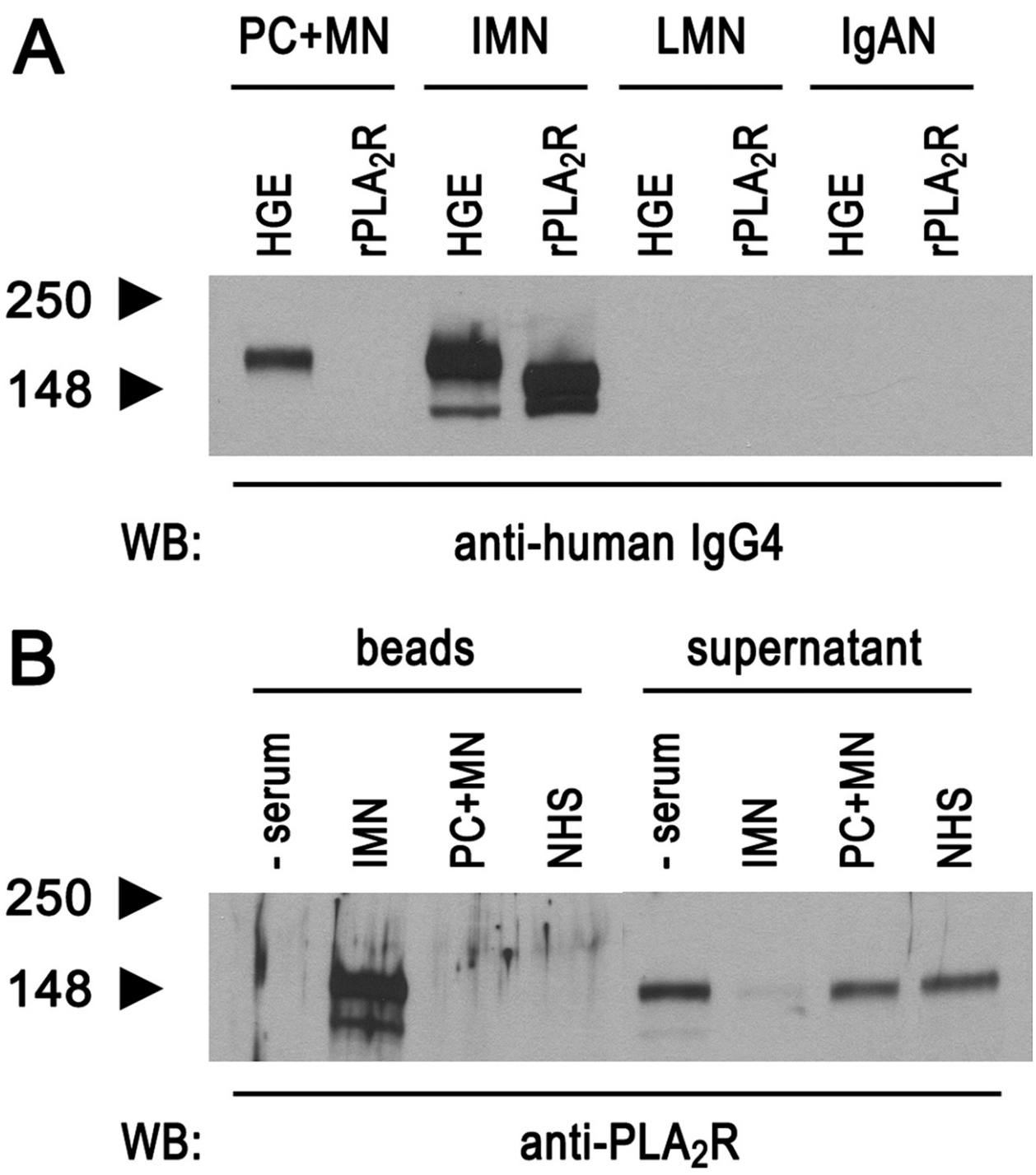

Figure 3. Lack of circulating anti-PLA_2R antibodies in an individual with MN associated with prostate cancer. (A) Sera from individuals with prostate cancer-associated MN (PC+MN), IMN, lupus-associated MN (LMN), and IgA nephropathy (IgAN) were tested for reactivity with human glomerular extract (HGE) or recombinant (r)PLA_2R, as described in the study by Beck et al.[21] Only the IMN serum detects both native and $rPLA_2R$, whereas the PC+MN serum is reactive with a similarly sized glomerular antigen, but not $rPLA_2R$. (B) To ensure that this glomerular antigen was not in fact PLA_2R, immunoprecipitation was performed from HGE with sera from individuals with IMN and PC+MN, and with normal human serum (NHS), as described by Beck et al.[21] A reaction omitting serum also was included as a negative control. PLA_2R was detected in the immunoprecipitate (beads) only with the IMN serum, and PLA_2R correspondingly was depleted from the starting fraction (supernatant) only with the IMN serum.

data can be accumulated and validated in future series, a patient who is diagnosed with MN but has no telling serologic features (anti-PLA_2R, ANA, hepatitis B e antigen, and so forth) to suggest another cause should be screened aggressively for malignancy. Perhaps the debate over the existence of malignancy-associated MN may one day come to an end.

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