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Cancer Screening in Membranous Nephropathy: A Narrative Review

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ABSTRACT

Membranous nephropathy is the most common cause of nephrotic syndrome in Caucasian adults. Membranous nephropathy associated cancer has been reported in the literature and is an important secondary cause of membranous nephropathy. Early diagnosis is key as long-term immunosuppression has oncogenic effects and may lead to progression. Current evidence suggests a potential role of biomarkers and imaging for cancer screening in these patients.

Keywords: Nephropathy; Cancer; Biomarkers; Immunosuppression; Diagnoses

Abbreviations: MN: Membranous Nephropathy; PLA2R: Phospholipase A2 Receptor; THSD7A: Thrombospondin type 2 Domain containing 7A; NELL-1: Nerve Epidermal growth factor-Like 1; PET-CT: Positron Emission Tomography-Computed Tomography

INTRODUCTION

Membranous Nephropathy (MN) is the most common cause of nephrotic syndrome in Caucasian adults [1]. Primary MN, an autoimmune disease, is the most common form of MN. Secondary causes include drugs, malignancy, chronic infection, SLE, or sarcoidosis [2]. MN-related cancer has been reported in the literature for decades and is an important secondary cause of MN [3].

Prompt diagnosis and treatment are essential, as the treatment differs between primary MN and secondary MN. Long-term immunosuppressive therapy is known to have oncogenic effects and may increase neoplastic progression. Currently, there is no consensus amongst clinicians about the need to perform cancer screening in patients with glomerular diseases. Due to the lack of evidence-based data, no cancer-screening programme has been established by the nephrological societies. This has led to some questioning the cost-effectiveness of cancer screening in patients who have been newly diagnosed with glomerular disease.

However, repeated screening during follow-up may be justified in cases of treatment failure or relapse despite appropriate therapy. There is a greater risk of malignancy months or years after the diagnosis in MN, which highlights the importance of cancer screening in these patients. The current Kidney Disease Improving Global Outcomes (KIDIGO) guidelines recommend cancer screening in patients with MN, although they do not detail how and when it should be performed. In this narrative review, we have discussed the epidemiology of cancer in patients with MN and current evidence on the potential role of histology and serum antigens as biomarkers to help in selecting patients for screening.

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LITERATURE REVIEW

Epidemiology

The frequency of cancer in patients with MN has been reported to be between 5 to 20% [4]. Important risk factors include age and smoking history [5]. Similar findings have been observed in other studies investigating the prevalence of cancer in patients with MN. Lefaucher et al. noted a global cancer prevalence rate of 10% in a cohort of 240 patients diagnosed with MN. A meta-analysis by Leeaphorn also observed a 10% cancer prevalence rate. The median age of patients diagnosed with MN in this study was 66.75 ± 6.75 years.

The most common cancers linked with MN were lung cancer, prostate cancer, and haematological malignancies, as observed in the registry study by Bjørkneklett et al. [6]. In this Norwegian registry study, 161 patients with MN had a standardised international ratio of cancer of 2.25/100 years [7]. Comparable findings were noted by Lefaucheur et al. who reported that the annual incidence of cancer was 2.1/100 years within 0-5 years and 2.8/100 years within 5-15 years from the date of MN diagnosis [8].

Importantly, Bjorkneklett et al., found that the annual incidence of cancer continued to increase in patients with MN 5 years after the biopsy-proven diagnosis, when compared to the age-sex-adjusted general population [9]. In addition, the diagnosis of cancer preceded the diagnosis of MN in 20 ± 6.8% of cases and 33/161 patients developed malignancy over a mean follow-up duration of 6.2 years. The median time from the diagnosis of MN to the diagnosis of cancer was 60 months (0-157 months range) and prognosis was poor with a high mortality rate. The findings of these studies illustrate the need for a cancer screening protocol. An important limitation of the studies by Bjørkneklett et al. and Lefaucheur et al. was that the primary population group was mostly of Caucasian origin. But what about the patients with MN who were not of a Caucasian background?

Two Chinese studies by Qu et al., and Zhang et al., reported that malignancy-associated MN was the most prevalent in older individuals aged more than 65 years. Interestingly, in both studies, the cohort had worse renal functions compared to patients with primary MN. This may explain the high mortality rates associated with malignancy-related MN.

Histology and Serum Antigens as Biomarkers

Renal histological findings in patients with cancer-associated MN are inconsistent and variable. In the study by Lefaucheur et al., more than eight inflammatory cells were found within the glomeruli in MN-associated cancer, suggestive of a causal link. However, this finding has not been replicated in other studies. Renal deposition pattern of IgG subsets on renal biopsy immunofluorescence staining has been proposed as a potential biomarker of cancer-related MN. IgG4 pattern on immunofluorescence staining is a pathognomonic sign in patients with primary MN.

In patients with secondary MN, cancer-associated MN, Ig G1/G2 subsets have been detected on immunofluorescence staining in sampled renal biopsies. This observation has led some to propose more intensive cancer screening in patients who test positive for these subsets. However, there is no consensus, as some studies did not yield similar findings. More research is needed to validate the association of histological findings with cancer diagnosis.

Novel serological biomarkers have been reported to help distinguish primary and secondary forms of MN, including cancer-related MN. PLA2R antibody against transmembrane glycoprotein M-type Phospholipase A2 Receptor (PLA2R) is the primary biomarker for primary MN in up to 80% of cases. In secondary MN, its prevalence was variable from 0 to 64%, with up to 30% in malignancy-related MN. It is worth noting that not all patients with malignancy-related MN have the characteristic finding of Ig G1/Ig G2 subsets. Some patients test positive for PLA2R antibody and IgG4 deposits on renal biopsy, which is consistent with primary MN [10].

Plaiser and Ronco claimed this finding was due to coincidence rather than a causal link.

Thrombospondin Type 2 Domain containing 7 A (THSD7A), another transmembrane protein expressed in podocytes, is found in 1 to 3 % of cases of primary MN. In patients who test negative for PLA2R, its incidence rate is 10% [11].

The association between THSD7A and malignancy-related MN has been investigated.

In a series of 49 patients with THSD7A-associated MN, eight patients (16%) developed cancer [12]. However, the authors inferred causality in only three patients [13].

Likewise, Ren et al. reported a cancer incidence rate of 6 to 25% in their study population who were positive for THSD7A [14].

Further supporting evidence comes from the studies of Larsen et al. and Liu et al. who suggested that there is an increased risk of malignancy in the following groups:

- Negative serum anti-PLA2R antibody and negative glomerular PLA2R antigen.
- Positive serum anti-THSD7A antibody and positive glomerular THSD7A antigen.
- Predominant Ig G1/G2/G3 deposition [15].

Plaiser and Ronco reported that the incidence rate of THSD7A antibodies was low in patients with malignancy-related MN [16]. However, they recommended a targeted screening approach for occult malignancy in patients similar to the population group assessed by Larsen et al., and Liu et al., as some patients with positive THSD7A antigen/antibody have been found to have cancer-related MN [17]. Nevertheless, they have acknowledged that more epidemiological data is needed before a definitive association can be made [18].

DISCUSSION

Recently, Caza et al., and Sethi et al., found a strong association between NELL-1 antigen (Nerve Epidermal growth factor-like 1) and cancer [19]. NELL-1 is a protein kinase C-binding protein. Sethi et al. reported that it is found in up to 16% of cases of primary MN who are PLA2R negative [20]. Importantly, 33% of the population cohort in the study by Caza et al. had malignancy and were positive for NELL-1. This was higher than the rate of 11.7% reported by Sethi et al. who also found an association between NELL-1 and cancer. Histology in these patients showed incomplete global IgG staining, positive Ig G1 staining, and negative staining for IgA, IgM, and C1q. Although NELL-1 was detected in the serum, Caza et al., felt more data were needed to correlate its serum levels with malignancy.

Imaging

Role of Positron Emission Tomography-Computed Tomography (PET-CT): PET-CT has shown promising results in detecting cancer in patients newly diagnosed with MN. Feng et al., demonstrated high diagnostic accuracy and moderate to high sensitivity and specificity of 18 F-fluorodeoxyglucose PET-CT for detecting cancer in patients with MN suspected of having paraneoplastic manifestations. They screened 124 patients, who were not suspected to have cancer based on a physical examination, for occult malignancy at the time of diagnosis of MN. Among them, 49 patients underwent screening with 18 F-fluorodeoxyglucose PET-CT and 75 patients underwent conventional screening. In the 18 F-FDG-PET-CT cohort, 5/49 patients (10.2%) were confirmed to have malignancies. In the conventional screening group, 1/75 patients (1.33%) were found to have cancer.

Similarly, a preliminary retrospective analysis by Sheikhbahaei et al. showed that 18 F-FDG PET-CT was as efficient as targeted cancer screening in patients newly diagnosed with MN. They analysed 21 studies in which 1293 patients, suspected of having paraneoplastic syndrome, underwent FDG-PET or FDG-PET-CT to detect cancer. They concluded that PET scans had high diagnostic accuracy and moderate to high sensitivity in detecting underlying malignancy.

CONCLUSION

Targeted cancer screening should be performed in patients newly diagnosed with MN. This should be based on high-risk factors such as age and smoking history. More research is needed for identifying histological and serological biomarkers for diagnosing cancer-associated MN, although there are promising results with NELL-1. In patients who are newly diagnosed with MN, PET-CT may have a role in detecting early cancer.

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