Cancer screening in membranous nephropathy: How deep should we go? – A case report and literature review

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INTRODUCTION

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in white adults, accounting for approximately 40% of all cases. Although the discovery of an antibody targeting the podocyte phospholipase A2 type M receptor (anti-PLA2R) dramatically changed the diagnostic approach of this disease, a non-negligible number of cases (around 20%) are associated with systemic conditions, namely cancer. Here, we report a rare case of MN associated with a nasopharyngeal carcinoma and discuss the pitfalls underlying cancer screening in membranous nephropathy.

BRIEF CASE DESCRIPTION

A 70-year-old man was sent by the assistant physician to our Nephrology outpatient clinic for a one-month history of lower limb edema and deterioration of renal function. The patient referred weight gain (5kg), without any other complaint. He denied systemic symptoms such as fever, loss of appetite or fatigue.

His past medical history was remarkable for a long period of poorly controlled hypertension and he was an active heavy smoker (40 pack-years). He drank alcohol only on social occasions (around 30g per month). He denied history of thromboembolic events. No history of renal disease was present in his family. His medication included furosemide (80 mg), irbesartan (300 mg), indapamide (2.5 mg), amlodipine (5mg) and simvastatin (20 mg). On physical exam, he was hypertensive (170/100 mmHg) and with bilateral lower limb pitting edema below knee. His lab panel revealed decreased renal function (serum creatinine 1.5 mg/dL (1.2 mg/dL, 1 year earlier)) and slight hypoalbuminemia (32.4 g/L). The urine sediment did not present leucocytes and erythrocytes. The twenty-four-hour urine presented nephrotic range proteinuria (9.6 g). The kidney ultrasound revealed normal sized kidneys with slight reduced corticomedullar differentiation.

DISCUSSION

There is no consistent definition for malignancy related MN as well as no formal algorithm for screening. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) Guidelines for Glomerulonephritis recommend...
performing “appropriate investigations” to exclude secondary causes in all cases of biopsy-proven MN (not graded recommendation)\(^5\). On the same topic, the need for more studies investigating the most cost-effective cancer screening strategy is additionally recognized\(^3\).

The frequency of reported cancer in MN ranges from 5% to up more than 20%\(^4\). In one of the largest series reported, Lefaucheur et al documented a global rate of 10% in a cohort of 240 patients with MN, but reaching nearly 30% in men older than 65 years\(^5\). Carcinomas such as lung, breast, prostate and gastrointestinal system were the most frequent implicated lesions\(^5\). Age and type of tumor combined support the common practice of employing a screening workup close to that used in the general population, which includes an endoscopic study and mammography complemented by a chest X-ray/CT scan. This strategy can, however, miss the diagnosis as illustrated by our case. In the series reported by Lefaucheur et al, 21% of patients had a non-carcinoma neoplasia, including hematologic malignancies\(^5\). The clear correlation between cancer treatment, even in atypical locations, and MN remission underscores the importance of an appropriate stepwise screening when the suspicion is high\(^5\). Additionally, MN can be the first paraneoplastic manifestation of a cancer, allowing its early diagnosis and treatment, as observed in our case. In the series reported by Lefaucheur et al, metastasis were present in only 23% of the malignancies (excluding hematologic ones)\(^5\). The finding of a neoplasia also prevents the patient from being exposed to inappropriate and potential harmful immunosuppression.

Which factors increase the odds of MN associated with cancer? In which patients should a more thorough investigation be performed when the initial screening is negative? Some clinical, serologic and histopathologic findings that might help in this decision have been proposed. As referred above, age is an important indicator and the risk increases significantly in patients older than 65 years\(^5\). However, it should be emphasized that cancer incidence is increased in all age strata of MN patients, as compared to the general population\(^5\). The role of gender is less clear. While Birkeland and Storm found an excess of cancer in men with MN\(^7\), this association has not been confirmed in other series\(^5\). Regarding exposure, it has been clearly shown that the proportion of heavy smoking (≥ 20 pack-years) is higher in patients with MN associated with neoplasia\(^5\), as documented in our patient. Pollution has been increasingly discussed as a hypothetical cause of MN\(^5\); however it is unexplored if it could be a common link between MN and cancer or if a high level of suspicion should be considered in patients with MN and a high pollution exposure level. Thromboembolic disease occurs in 25% of patients with cancer-associated MN and only 7% of patients with primary MN and so the occurrence of this complication also raises the suspicion of neoplasia\(^9\).

Some findings in renal tissue have also been described; however the association with malignancy related MN in not consistent across all studies. In the Lefaucheur et al series, an increased number of inflammatory cells infiltrating the glomeruli in patients with MN associated with cancer was shown, particularly if a threshold of eight or more cells was considered\(^9\). In contrast, Alnasrallah et al. find no association in their series; the median time from MN to cancer diagnosis was 40 months which suggests that some cases of MN were probably not cancer related\(^9\). The renal pattern of IgG subclasses has also been proposed as a biomarker. Some authors observed that IgG1 and IgG2 deposition was more intense in malignancy-related MN than primary MN\(^10\), although this was not replicated by others\(^11\). The lower deposition of IgG4 in these patients as compared to primary MN has also been reported and seems more consistent\(^11,12\). However, no reliable pattern of IgG subclasses is validated for clinical use and more research is needed\(^13\).

Since its discovery in 2009, anti-PLA2R has shown to be an excellent biomarker of MN, mainly as compared to other glomerular diseases. The high specificity and predictive positive value of this biomarker significantly increases the pre-test probability of primary MN (even potentially excluding the need of a renal biopsy for diagnosis is some cases)\(^14\). However, it does not definitely rule out the presence of cancer and several cases have been reported in patients with anti-PLA2R positive MN with a proportion up to 30%\(^15,16\). However, some of these patients did not enter in remission after tumor excision, which does not exclude the presence of coincidental diseases\(^17\). So, in our opinion and in line with the literature, it is probably prudent to screen for cancer PLA2R positive patients until formal guidelines for the use of this biomarker are provided, although we are aware that the presence of this biomarker significantly increases the probability of primary MN. Since the discovery of a new autoantigen, Thrombospondin type-1 domain-containing 7A (THSD7A), some studies have found a higher incidence of cancer (approximately 20%) in patients with MN associated with this biomarker, suggesting that THSD7A could be a useful indicator of malignancy-related MN\(^18\). However, again, this finding is not consistent in all series and more recently, other authors have reported relatively low rates of neoplasia\(^17,19\). The very recently described neural epidermal growth factor-like 1 protein (NEHL-1) seems to be a biomarker of PLA2R negative primary MN, but its value in other clinical grounds, including patients with cancer, still awaits more studies\(^20\).

The hypothetical mechanism by which neoplasia may be associated with MN relies mainly on the formation of antibodies against tumor antigens formed in situ or in circulation and trapped in glomerular membrane\(^21\). Accordingly, the definite pathophysiologic link between MN and cancer is the detection of tumor antigens in renal tissue as postulated by Cambier and Ronco\(^22\). However, most reported case series did not perform this investigation and future studies should consider this point.

As mentioned above, the evidence supporting a neoplasia screening workup in glomerular diseases is weak and there are no studies on cost-effectiveness, so it is difficult to implement a formal screening algorithm or score. Plaisir and Ronco have recently suggested a global strategy for cancer screening in glomerular diseases encompassing two steps: a routine screening (considering age and gender), and a targeted screening according to clinical and laboratorial data including symptoms, smoking history and anti-PLA2R. As observed in our case, the workup proposed by the authors implicitly underscores the importance of a high pre-test clinical suspicion derived from clinical and laboratorial clues\(^9\). That high level of clinical suspicion prompted us to perform an extended CT scan, although the most appropriate exam to search for an occult malignancy is not established in this context. A recent retrospective study has shown that 18F-fluorodeoxyglucose positron emission tomography/CT could be an efficient way to detect an early neoplasia in patients with suspected
paraneoplastic syndromes and further studies would be important in patients with MN.²³

Every clinician should be alert for the possibility of cancer in all stages of management of a patient with membranous nephropathy, even in the long-term follow-up after clinical remission.⁵,⁶,¹⁷ We think that, again, the level of initial clinical suspicion, the development of unexpected suspicious new symptoms and the lack of response to immunosuppression should all be considered to define the need for re-screening.

In conclusion, there is no reliable and definite clinicopathologic indicator of malignancy-related MN. Anti-PLA²R is currently an essential tool in the diagnosis of primary MN, although it does not definitely rule out the presence of cancer. The proportion of cancer-associated MN increases with age, but the risk of neoplasia is increased in all patients with MN and for a long time after the diagnosis. The most cost-effective cancer screening workup in MN patients remains to be defined and a high level of clinical suspicion should be considered when the most frequent cancers are excluded, particularly in patients with anti-PLA²R negative. Malignancy treatment is essential for the control of the glomerular disease but, importantly, MN can also constitute an early paraneoplastic sign of a cancer still amenable for treatment as illustrated by our case.

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