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Serological markers for primary membranous nephropathy

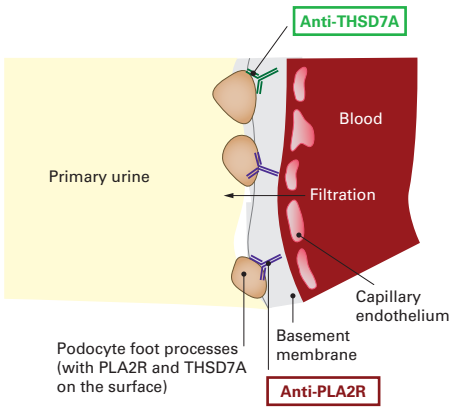
- **Anti-PLA2R autoantibodies: marker with the highest specificity and sensitivity**
- **Anti-THSD7A autoantibodies: supplementary marker especially in anti-PLA2R-negative patients**
- **Worldwide exclusive qualitative and quantitative test systems (ELISA, ChLIA and IIFT) for determination of the two markers**

Biomarkers for primary membranous nephropathy (pMN)

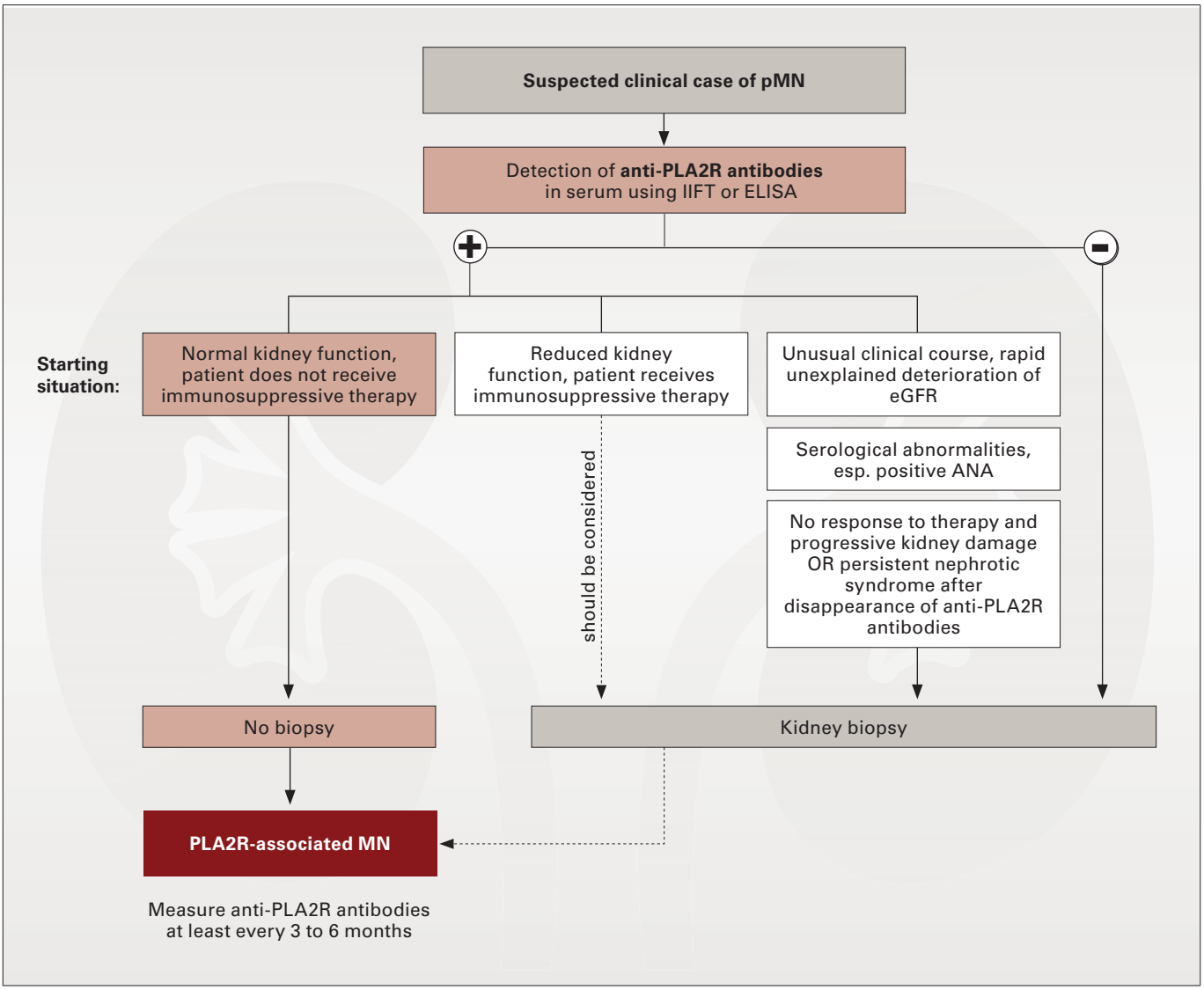
Membranous nephropathy (MN) is a chronic inflammatory disease of the renal corpuscles (glomeruli), which can take very different courses. A third of patients have no major kidney function impairment and experience spontaneous remission without medication, a third show no symptomatic changes and have persistent proteinuria, and another third have severe worsening of symptoms, developing nephrotic syndrome and requiring a kidney transplant. The gold standard for the diagnosis of MN is usually kidney biopsy. However, the invasive method is very stressful for patients and does not allow differential diagnosis between primary (pMN) and secondary (sMN) membranous nephropathy (MN resulting from an underlying disease).

In 2009, Beck et al. identified the **phospholipase A2 receptor (PLA2R)**, which is expressed in the cell membrane of podocytes of healthy glomeruli, as a specific target antigen for autoantibodies in pMN.[1] By detecting anti-PLA2R antibodies, the diagnosis of pMN can be made with high accuracy – in some cases even without a biopsy (see figure below).[2] In 2014, Tomas et al. described another target antigen of autoantibodies in patients with pMN: **THSD7A (thrombospondin type-1 domain-containing 7A)**.[3]

Filtration barrier of the kidney



Diagnostic guideline for suspected primary membranous nephropathy[2]



Modified from KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int 100(4S):S1-S276 (2021).

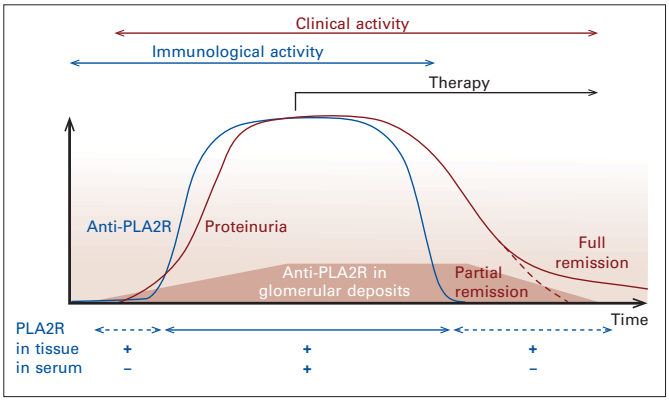
Anti-PLA2R autoantibodies

- **Most important serological marker for pMN**
- **Specificity over 99 %, prevalence approx. 80 %**
- **The serological determination of anti-PLA2R enables differential diagnosis, monitoring of the disease course and therapy, prognosis and risk assessment after transplantation**

Since the discovery of anti-PLA2R antibodies as highly specific marker of pMN and the development of serological test systems, the antibodies have become the subject of numerous research projects. Publications show that the serum antibodies have a specificity of almost 100 % and a prevalence of 70 % to 80 % in pMN.[4] Sensitivities differ depending on the detection method and are slightly higher for the indirect immunofluorescence test (IIFT; 83.2 %) and chemiluminescence immunoassay (ChLIA; 83.9 %) than for ELISA (73.5 %). ELISA and ChLIA enable quantitative determination of the antibody concentration, as is required for monitoring of the disease course and therapy.[5, 6]

Monitoring of the disease course and therapy

Today, it is known that the anti-PLA2R antibody titer correlates with the clinical activity of the disease. With successful immunosuppressive therapy, the titer decreases within a short time, accompanied by a delayed reduction of clinical symptoms (proteinuria). The determination of the antibody titer is therefore a suitable tool for monitoring the disease status and the patient's response to therapy.[7, 8]



Modified from Francis JM, et al. Am J Kidney Dis 68(1):138-47 (2016).

Making a prognosis

High anti-PLA2R antibody levels are also a risk factor for an unfavourable outcome of the disease (no remission) or the need for a longer treatment duration until clinical remission. Presumably due to the associated pronounced proteinuria, high antibody levels are also associated with a rapid loss of kidney function. In addition, the probability of spontaneous remission seems to be smaller for patients with high antibody titers than for those with relatively low titers. Thanks to its predictive value, the marker can significantly support the doctor's therapy decision.[9–11]

Risk assessment after transplantation

Furthermore, regular determination of the anti-PLA2R antibody titer in pMN patients with kidney transplants can help to predict possible relapses. There is evidence that high titers are associated with an increased risk of disease recurrence both before and after transplantation.[12, 13]

Anti-THSD7A autoantibodies

- **Supplementary serological marker**
- **Up to 10 % of anti-PLA2R-seronegative pMN patients are anti-THSD7A positive**
- **Anti-THSD7A autoantibodies can be associated with malignant tumours**

The prevalence of anti-THSD7A antibodies is given with values of up to 10 %. Although antibodies against PLA2R and THSD7A can occur in parallel in rare cases, anti-THSD7A antibodies have been found predominantly in anti-PLA2R-seronegative pMN patients. A study by Hoxha et al. (2016) suggests that the clinical picture of anti-PLA2R- and anti-THSD7A-positive pMN patients differs in that malignant tumours were found more frequently in anti-THSD7A-positive patients. As a supplement to anti-PLA2R antibodies, anti-THSD7A antibodies are therefore another marker in serological pMN diagnostics. Due to their high specificity, they are equally suited for differentiation from secondary MN as anti-PLA2R antibodies. Moreover, simultaneous determination of anti-PLA2R and THSD7A antibodies increases the serological detection rate. [3, 14–16]

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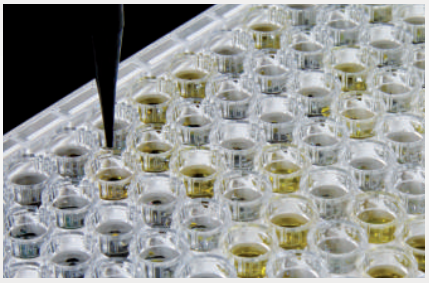
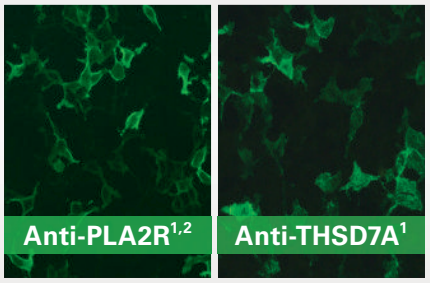
Worldwide exclusive test systems from EUROIMMUN for the detection of anti-PLA2R and anti-THSD7A autoantibodies

Anti-PLA2R ChLIA (IgG) for IDS-i10

Anti-PLA2R ELISA (IgG)



Anti-PLA2R IIFT
Anti-THSD7A IIFT



[1] Transfected cells [2] Computer-aided evaluation with EUROPattern possible

Test system	Test name	Information	Order number
ChLIA	Anti-PLA2R ChLIA (IgG)	Recombinant antigen	LA 1254 G
ELISA	Anti-PLA2R ELISA (IgG)	Recombinant antigen	EA 1254 G
IIFT	Anti-Phospholipase A2 Receptor (PLA2R) IIFT	Transfected cells	FA 1254-50
	Anti-Phospholipase A2 Receptor (PLA2R) IIFT EUROPattern	Transfected cells; automatable immunofluorescence microscopy (EUROPattern)	FC 1254-50
	Anti-THSD7A IIFT	Transfected cells	FA 1254-51
	IIFT: Membranous Nephropathy Mosaic 1	Transfected cells	FA 1254-1

References

[1] Beck LH Jr, et al. **M-type phospholipase A_2 receptor as target antigen in idiopathic membranous nephropathy.** N Engl J Med 361:11-21 (2009). / [2] KDIGO. **KDIGO 2021 clinical practice guideline for the management of glomerular diseases.** Kidney Int 100(4S):S1-S276 (2021). / [3] Tomas NM, et al. **Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy.** N Engl J Med 371: 2277-2287 (2014). / [4] Rodas LM, et al. **Antiphospholipase 2 receptor antibody levels to predict complete spontaneous remission in primary membranous nephropathy.** Clin Kidney J 12(1): 36–41 (2019). / [5] Dähnrich C, et al. **Development of a standardized chemiluminescence immunoassay for the detection of autoantibodies against human M-type phospholipase A2 receptor in primary membranous nephropathy.** Kidney Int Rep 5(2):182-188 (2019). / [6] Hoxha E, et al. **A new chemiluminescence immunoassay for phospholipase A2 receptor 1 autoantibodies allows early identification of autoantibody recurrence in patients with membranous nephropathy.** Kidney Int Rep 6(4):928-935 (2021). / [7] Beck LH Jr, et al. **Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy.** J Am Soc Nephrol 22(8):1543-50 (2011). / [8] Hofstra JM, et al. **Anti-phospholipase A2 receptor antibodies correlate with clinical status in idiopathic membranous nephropathy.** Clin J Am Nephrol 6(6):1286-91 (2011). / [9] Hofstra JM, et al. **Antiphospholipase A2 receptor antibody titer and subclass in idiopathic membranous nephropathy.** J Am Soc Nephrol 23(10):1735-43 (2012). / [10] Hoxha E, et al. **Phospholipase A2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy.** Clin J Am Soc Nephrol 25(6):1357-66 (2014). / [11] Timmermans SA, et al. **Evaluation of anti-PLA2R1 as measured by a novel ELISA in patients with idiopathic membranous nephropathy: a cohort study.** Am J Clin Pathol 142(1):29-34 (2014). / [12] Gupta G, et al. **Pre-transplant phospholipase A2 receptor autoantibody concentration is associated with clinically significant recurrence of membranous nephropathy post-kidney transplantation.** Clin Transplant 30(4):461-9 (2016). / [13] Seitz-Polski B, et al. **Prediction of membranous nephropathy recurrence after transplantation by monitoring of anti-PLA2R1 (M-type phospholipase A2 receptor) autoantibodies: a case series of 15 patients.** Nephrol Dial Transplant 29(12):2334-42 (2014). / [14] Hoxha E, et al. **An indirect immunofluorescence method facilitates detection of thrombospondin type 1 domain-containing 7A-specific antibodies in membranous nephropathy.** J Am Soc Nephrol 28(2):520–531 (2017). [15] Iwakura T, et al. **Prevalence of enhanced granular expression of thrombospondin type-1 domain-containing 7A in the glomeruli of japanese patients with idiopathic membranous nephropathy.** PLoS One 10(9):e0138841 (2015). [16] Larsen CP, et al. **THSD7A staining of membranous glomerulopathy in clinical practice reveals cases with dual autoantibody positivity.** Mod Pathol 29(4):421-6 (2016).

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