in Table 1. In addition, focal nuclear positivity for MDM2 here may have potential therapeutic implications, which was not mentioned in the previous studies. Mutational analysis for c-kit and PDGFRA was wild type in our case, which is similar to the previously reported cases. On the other hand, our case showed a positive missense mutation in exon 14 of the MET gene. The MET activation was found in around 15% of GIST, in a situation such as untreated GIST, during the response to imatinib and upon imatinib resistance. Neither a diagnosis of GIST nor any therapy in this line was offered.

The unusual morphology and aggressive clinical behaviour with fatal outcome observed in our case needs molecular and genetic analysis in a larger group of cases to characterise it further. Moreover, none of the literature has mentioned the recurrence of PAMT. This is the first case to our knowledge showing recurrence and distant metastasis with fatal outcome. Although most of the cases described in the literature were benign c-kit negative mesenchymal tumours, recurrence of the tumour after resection with distant metastasis in the present case certainly raises the question of its classification under the benign category.

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Thrombospondin type-1 domain-containing 7A-related membranous nephropathy associated with glomerular AL amyloidosis

To the Editor,

Immunoglobulin light chain amyloidosis (AL amyloidosis) is a systemic severe disease that predominantly affects the kidneys and the heart, with cardiac amyloidosis as a major determinant of outcome. Renal involvement typically manifests with nephrotic syndrome and/or deterioration of kidney function, with amyloid deposits mainly observed within the glomeruli and vessel walls. It usually occurs in patients with plasma cell clones but may also result, in rare cases, from Waldenström macroglobulinaemia (WM) and other B-cell lymphoproliferative disorders. Autologous stem cell transplantation (SCT) associated with high dose chemotherapy has improved haematological response and survival in selected patients with AL amyloidosis. Organ response is often delayed after a favourable haematological response, with organ recovery strongly associated with the depth of the haematological response achieved.^{1,2} Even in cases of successful haematological response, patients with AL amyloidosis can experience a progressive decline of renal function and a worsening of proteinuria.^{1,3} Iterative kidney biopsies may show the persistence of or increases in renal amyloid deposits^{3–5} without identifying recent amyloid deposits, and thus may not be helpful in the therapeutic management. We report a patient who presented with nephrotic syndrome 5 years after autologous SCT for systemic AL amyloidosis related to WM. Strikingly, renal biopsy demonstrated Thrombospondin type-1 domain-containing 7A (THSD7A)-related membranous nephropathy (MN) associated with glomerular AL amyloidosis.

In 2011, a 56-year-old man was diagnosed with biclonal WM, with monoclonal IgM lambda (32 g/L) and IgG lambda (12 g/L) spikes associated with a decrease in free light chain ratio [kappa/lambda (κ/λ) ratio = 0.18; normal range 0.26–1.65] on immunonephelometric assays.

At the time of WM diagnosis, whole-body magnetic resonance imaging revealed diffuse infiltration of the retroperitoneal and mesenteric adipose tissue due to biopsy-proven AL-lambda amyloidosis. Amyloid deposits were also observed on bone marrow and bladder biopsies.

Fig. 1 Long-term follow-up of proteinuria and albumin levels.

Magnetic resonance imagery showed left ventricular wall thickening (septum 19 mm) with heterogeneous late gadolinium enhancement, suggestive of cardiac amyloidosis. No renal biopsy was performed at the time of WM diagnosis, because renal function was not altered [serum creatinine concentration 0.83 mg/dL; estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation 114 mL/min/1.73 m²] with no significant proteinuria [urine protein/creatinine ratio (UPCR) 46 mg/mmol]. In 2012, after several lines of chemotherapy with no satisfactory haematological response, the patient received an autologous SCT leading to a normalisation of free light chain ratio (κ/λ ratio = 0.44) and a

decrease in the monoclonal IgM and IgG lambda spikes to below the threshold for quantification. UPCR and albumin levels at lymphoma diagnosis and during follow-up are summarised in Fig. 1.

The patient was referred to our Nephrology Department in November 2017. At admission, he presented with nephrotic syndrome (UPCR 522 mg/mmol and albumin concentration 2.3 g/dL) and microscopic haematuria (10⁴/mL) on urine sediment analysis. Physical examination revealed neither organomegaly nor palpably enlarged lymph nodes. Laboratory investigations revealed a decrease in eGFR to 74 mL/min/1.73 m², and detectable but non-quantifiable monoclonal IgG and IgM lambda spikes (<1 g/L) on

Fig. 2 (A) Abundant glomerular and arteriolar Congo red-positive amyloid deposits with characteristic birefringence under polarised light (B). Immunofluorescence studies revealed bright granular capillary wall staining for IgG (C, anti-IgG fluorescein isothiocyanate-conjugate), kappa (D, fluorescein isothiocyanate-conjugated antiserum against κ light chain) and lambda (E, fluorescein isothiocyanate-conjugated antiserum against λ light chain), whereas amyloid deposits displayed predominantly λ light chain staining. (F) Immunoperoxidase staining for THSD7A demonstrated strong capillary wall staining. Scale bars = 50 μ m.

Fig. 3 Electron microscopy findings. Ultrastructural analysis revealed randomly unbranched amyloid fibrils within the mesangium (A, arrow and B) and subepithelial non-organised deposits (A, arrowheads and C, arrowheads). A, $\times 15,000$, scale bar = 1 μm . B, $\times 50,000$, scale bar = 500 nm. C, $\times 40,000$, scale bar = 500 nm.

immunoelectrophoresis. Immunonephelometric assays showed the presence of free lambda light chains at a concentration of 35.7 mg/L (normal range 5.71–26.30 mg/L) with a normal κ/λ ratio of 0.79. Proteinuria was composed mostly of albumin (urine albumin/creatinine ratio 410 mg/mmol). Urine immunoelectrophoresis revealed the presence of small amounts of IgG lambda and free lambda light chains. Serum complement levels were within the normal range. Renal ultrasonography findings were unremarkable, and positron emission tomography-computed tomography (PET-CT) did not identify any hypermetabolic lesions.

A kidney biopsy was performed to explore this nephrotic syndrome in a patient previously diagnosed with extrarenal AL amyloidosis but with non-quantifiable monoclonal spikes 5 years after autologous SCT. The renal biopsy specimen consisted of renal cortex tissue, with 16 glomeruli. All the glomeruli displayed large mesangial Congo red-positive amyloid deposits, with apple-green birefringence (Fig. 2A,B). Immunofluorescence showed that anti- λ light chain antibody stained predominantly the amyloid deposits and revealed bright granular capillary wall IgG deposits with polytypic (kappa- and lambda-positive) subepithelial deposits (Fig. 2C–E). An analysis of the subepithelial IgG subclass distribution revealed positive staining for IgG1 and IgG4 (data not shown), suggesting primary MN. Consistent with light microscopy and immunofluorescence analysis findings, electron microscopy demonstrated amyloid fibrils within the mesangium and subepithelial non-organised deposits (Fig. 3). Immunohistochemistry with anti-phospholipase A2 receptor 1 (PLA2R) antibody was negative (not shown), whereas subepithelial deposits were stained with anti-THSD7A antibody (Fig. 2F). Circulating THSD7A antibodies were detected in the serum (1/50). The definitive pathological diagnosis was a co-occurrence of AL amyloidosis and THSD7A-related MN.

Our patient was treated with two doses of intravenous rituximab (375 mg/m²), 2 weeks apart. Two weeks after the second infusion of rituximab, circulating anti-THSD7A antibodies were no longer detectable, and we observed a significant decrease in UPCR associated with an increase in albumin concentration (Fig. 1). Two years later, with no additional treatment, our patient was in complete remission from the nephrotic syndrome with sustained haematological disease remission (normal κ/λ ratio of 1.12) (Fig. 1).

MN, one of the major causes of nephrotic syndrome in adults, is histologically characterised by granular IgG deposits in the subepithelial region of the glomerular basement membrane. Since the recent discovery of autoantibodies directed against a podocyte surface antigen, primary MN has been reclassified as an autoimmunity-mediated glomerular disease. Circulating antibodies against PLA2R and THSD7A

were the first to be identified, and account for about 70–80% and 2–5% of primary MN cases, respectively. A broad spectrum of medical conditions may be associated with the occurrence of MN and the recent identification by laser microdissection and mass spectrometry of new target antigens in MN has highlighted an antigen-based classification.⁶ Circulating anti-THSD7A antibodies have been previously identified in the setting of solid tumour-associated MN, with expression of THSD7A in tumoural cells.⁷ In our case, extensive screening (colonoscopy, oesophagogastroscopy and PET-CT) for potential underlying cancer was negative.

Secondary MN is one of the most frequent glomerular diseases occurring after allogeneic haematopoietic SCT⁸ and may be included in the spectrum of clinical manifestation related to chronic graft-versus-host-disease (GVHD). Chronic GVHD is associated with a loss of B-cell tolerance, with the production of antibodies to both allo- and auto-antigens, notably targeting surface membrane antigens. By contrast, secondary MN after autologous SCT remains poorly described.^{8–10} In these four previously reported cases, analysis of the glomerular IgG subclasses distribution was not performed and no circulating anti-PLA2R antibodies were detected in two patients.^{9,10}

The association of biopsy-proven renal amyloidosis and concomitant polytypic MN remains an exceptional finding. We report here the first case, to our knowledge, of simultaneous renal AL amyloidosis associated with THSD7A-related MN after a favourable haematological response. As no kidney biopsy was performed at initial presentation, we cannot accurately determine when fibril deposition in renal tissue began, or its kinetics. The presence of diffuse extra-renal amyloid deposits (retroperitoneum, bone marrow, and bladder) at the time of WM diagnosis and the successful treatment of the haematological disease suggest that amyloid deposits may have also involved the kidney at the time of initial presentation, although our patient had no significant proteinuria and normal eGFR. Amyloidosis burden in kidney biopsy may not correlate to proteinuria level at diagnosis in AL amyloidosis patients.¹¹

In AL amyloidosis patients achieving a favourable haematological response, iterative kidney biopsies may also reveal a regression of the immunoglobulin component¹² suggesting that, beyond the amyloid bulk, the amyloidogenic monoclonal light chain may display direct tissue toxicity. In our patient, despite the persistence of lambda light chain within amyloid deposits on immunofluorescence study, the voluminous glomerular amyloid deposits remain asymptomatic with a normal range of proteinuria 2 years after rituximab infusion, one of the cornerstones of the therapeutic management of primary MN. The rapid improvement of proteinuria and

albumin levels after two infusions of rituximab, without the need for additional haematological chemotherapy, and the sustained complete remission of nephrotic syndrome after 2 years of follow-up, strongly suggest that the nephrotic-range proteinuria was mostly due to glomerular damage related to MN rather than to AL amyloid deposits.

In conclusion, optimal management of renal progression in patients with AL amyloidosis remains challenging after haematological treatment. Careful nephrological investigations, in addition to the standard haematological tests, are required in patients with successful treatment of AL amyloidosis and worsening of laboratory renal parameters. In such patients, kidney biopsy should be systematically discussed to investigate potential alternative glomerular diseases.

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Spindle cell lipoma with lipofibromatosis-like change: expanding the spectrum of morphological heterogeneity

To the Editor,

Spindle cell lipoma (SCL) is a benign adipocytic neoplasm, first reported by Enzinger in 1975.¹ It most frequently occurs in the neck, shoulders and back region of middle-aged males. Histologically it is characterised by variable amounts of bland spindle cells, mature adipocytes, and ropy collagen bundles, described as thick, refractile and eosinophilic.² Despite this characteristic triad of histological features, it is well recognised that SCL can display diverse morphological heterogeneity, and multiple pathological subtypes have been described. Indeed, the morphological features can show some overlap with other benign and malignant soft tissue tumours, presenting a potential diagnostic dilemma. In this report, we describe a case of SCL showing lipofibromatosis-like change, morphological changes that to our knowledge have not been reported in the literature to date.

A 48-year-old man presented with a mass localised to the left occiput. An ultrasound scan was performed revealing a lesion measuring 32×29×17 mm with features suggestive of a lipoma. A subsequent excision was performed by the patient's GP. Pathological examination of the specimen received showed pieces of yellow to tan tissue with a uniform appearance and cut surface and no evidence of haemorrhage or necrosis. Microscopically, the sections showed mature adipose tissue with lobularity and intervening incomplete fibrous septa composed of long sweeping fascicles of spindle cells. These cells contained bland, elongate and frequently