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Exceptional Case

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Membranous nephropathy, leiomyoma and autoimmune myasthenia: more than a coincidence?

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Abstract
Membranous nephropathy (MN) has been associated with several infectious, immunological and malignant conditions, but had only rarely been reported with malignant and other immune disorders in the same patient. We describe the case of a 56-year-old male with MN who was also diagnosed with a gastrointestinal stromal tumour (GIST), myasthenia gravis (MG) and thymic hyperplasia. Thus, we report here for the first time the coincidence of these conditions in the same patient. There was a recurrence of nephrotic syndrome without impairment of renal function 5 years after removal of the GIST (3 years after thymectomy). The possible basis for the relationship between these diseases is discussed, and some common genetic and immune physiopathological pathways are hypothesized.

Keywords: gastrointestinal stromal tumour; membranous nephropathy; myasthenia; thymus

Introduction

Membranous nephropathy (MN) is the most frequent cause of biopsy-proven nephrotic syndrome in adults. In most cases, MN is idiopathic. An abnormal activation of T-lymphocyte-regulated mechanisms is known to play a key pathogenic role, leading to on-site formation or entrapment of immune complexes at the glomerular membrane [1]. However, up to one-third of the MN cases have been related to certain drugs or toxic exposure, as well as to systemic diseases that would trigger immune-mediated glomerular damage. Among these, the association of MN with infections, connective tissue diseases and cancer has been widely described [2]. Because the risk of cancer increases with age, some authors have questioned the strength of the association between malignancy and MN, especially when renal disease precedes the diagnosis of cancer [1, 2]. In contrast, the relationship of MN with autoimmune diseases is generally well accepted, since the formation of immune complexes in these disorders can easily explain either their deposition in the glomerular membrane or their on-site development. The majority of these cases have been linked to connective tissue disorders, such as lupus erythematosus or rheumatoid arthritis, while reports of MN in association with other autoimmune diseases are more exceptional [1].

We describe a patient with MN in whom a gastric leiomyoma was detected upon follow-up. Surgical removal of the cancer was followed by remission of the nephropathy. Myasthenia gravis (MG) was also diagnosed later on. We discuss the coincidence of these diseases (renal, malignant and autoimmune) in the same patient and the possible common underlying physiopathological mechanisms.

Case report

A 56-year-old male was referred to the nephrology clinic because of hypertension and oedema. Previous medical history was unremarkable, except for cholecystectomy (lithiasis) and a possible hiatal hernia (endoscopy had not been carried out). Upon admission he had clinical and biochemical data of a nephrotic syndrome with normal renal function [serum creatinine 70 µmol/L (0.8 mg/dL)]. Immune biochemistry (including antinuclear antibodies and antineutrophil cytoplasmic antibodies), complement, rheumatoid factor and hepatitis B, hepatitis C and human immunodeficiency virus (HIV) serology were negative or within the normal range. An ultrasound scan showed that both kidneys had normal size and shape. A kidney biopsy revealed 34 glomeruli with normal features, except for a slight epithelial hyperplasia. Immunofluorescent staining confirmed a diffuse granular pattern of IgG and C3 along the glomerular basement membrane. Since no sample was included for electron microscopy, the possibility of subendothelial immune deposits could not be completely ruled out.

Symptomatic and anti-proteinuric treatments, including furosemide, enalapril, statin and aspirin, were initially

prescribed, leading to symptomatic improvement but renal function parameters worsened [serum creatinine 123 µmol/L (1.4 mg/dL), proteinuria 10 g/24 h]. Enalapril was increased to the maximum tolerated dose (up to 40 mg/day), without benefit. Then Ponticelli's [1] therapy regimen, including steroids and chlorambucil, was started. One month later (at the end of the first course of steroids and before starting chlorambucil), the patient was admitted for gastrointestinal bleeding and worsening of renal function [serum creatinine 158 µmol/L (1.8 mg/dL)]. An endoscopy showed a large leiomyomatous mass with central ulceration in the posterior gastric wall. A partial gastrectomy with complete tumour removal was carried out after clinical stabilization. The histological study revealed features of a gastric stromal tumour. The patient did not receive complementary chemotherapy. After surgery, proteinuria decreased (down to 2.3 g/24 h) and the renal function normalized [serum creatinine 88 µmol/L (1.0 mg/dL)]. Three months after discharge (Figure 1), the nephropathy was in complete remission and the patient was only on a low dose of enalapril (5 mg/day).

In subsequent reviews, the patient remained asymptomatic, except for asthenia and weakness that were attributed to chronic anaemia after gastrectomy. Despite iron therapy, asthenia and muscle weakness gradually worsened, even for minimal physical activity (especially with the upper limbs). A subsequent addition of palpebral ptosis prompted a referral for neurologic and neurophysiologic examination. Electromyography (30% decrease upon repetitive stimulation) and the presence of anti-acetylcholine receptor (anti-AchR) antibodies confirmed the diagnosis of MG. Determination of anti-MUSK antibodies was not available. Treatment with pyridogstigmine was initiated with good clinical recovery. Thymectomy was then also recommended, since an enlarged thymus was observed in a magnetic resonance imaging of the cervico-thoracic region. The histological examination confirmed the presence of thymus hyperplasia, but not thymoma. At that time (2 years after the initial diagnosis), the MN remained inactive. Five years later, recurrence of proteinuria (up to the nephrotic range) was detected. Doubling the dose of enalapril (to 10 mg/day) was then enough for minimizing proteinuria (Figure 1). Currently, 11 years after diagnosis, MN is in complete remission, there is no evidence of gastric cancer recurrence and there is a good control of myasthenia with a low dose of pyridogstigmine.

Discussion

In this report, we draw attention to the unusual presentation of MN, gastrointestinal stromal tumour (GIST) and autoimmune myasthenia—in that chronological order—in the same patient. We speculate that there might be a plausible biological basis for a physiopathological link between the three disorders.

The work-up of patients with MN in order to rule out secondary causes is a challenge in clinical practice. This is important when nephropathy precedes the clinical onset of the underlying cause which, if corrected in time, could lead not only to a better prognosis of the primary disease, but also to an improvement of the renal disease. This is especially crucial in the case of an underlying malignancy in order to improve cancer prognosis as well as to avoid complications from an otherwise unnecessary immunosuppressive therapy for MN [1, 2]. The case described here emphasizes the importance of ruling out malignancy in clinical practice before starting immunosuppressive treatment. Histological and immunological features may allow for discrimination between idiopathic and secondary forms of MN. While idiopathic cases show immune complex deposits usually limited to the

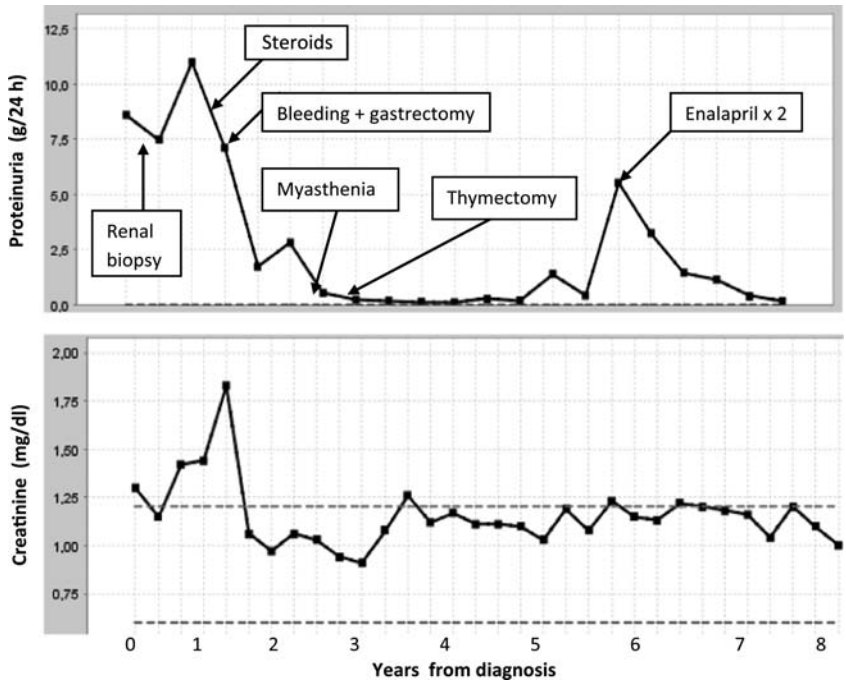

Fig. 1 Patient's renal function outcome.

membrane and sub-epithelial region, these deposits can also be found at mesangial and sub-endothelial levels, especially when associated with autoimmune disorders [1–3]. The patient reported here had basal membrane deposits. Unfortunately, since an electron microscopy examination was not available we could not define further details of immune deposits. In idiopathic cases, immunohistological studies of the deposits conclude that these are mainly of the IgG4 subclass, while other immunoglobulins predominate in secondary forms [2]. IgG1 and IgG2 are those more frequently associated with malignancy [2, 3]. The presence of antibodies against the phospholipase A2 receptor (IgG4 subclass) has been identified in idiopathic, but not in secondary forms [2]. However, since the techniques for the detection of these immunological variants are not available in most centres, careful work-up and clinical follow-up are still the cornerstone for differential diagnosis between idiopathic and secondary forms, as was the case in the patient reported here.

Between 5 and 20% of MN cases have been associated with tumours, particularly in patients over 65 years. This risk may persist even several years after diagnosis and include lung, breast, prostate, digestive tract tumours and haematological malignancies [1, 2]. Among the digestive tumours, MN has been mainly described in association with adenocarcinomas [2]. Mesenchymal GISTs are attributed to a smooth muscle origin and have been classically labeled as leiomyomas. However, immunohistochemical studies have shown their variable correlation with cell lines derived from the interstitial cell of Cajal which may resemble muscular, neural and even an undifferentiated origin [4]. In contrast to what could be expected due to these different cellular origins, paraneoplastic syndromes are rare in GISTs except for hypoglycaemia or hypercalcaemia. MN has only exceptionally been described in association with jejunal GIST [5]. These tumours are generally asymptomatic until they reach a large size and ulceration occurs. In 60% of cases, gastrointestinal bleeding is their first manifestation, as was the case in our patient [4].

Recently, mutations in the proto-oncogene KIT (c-Kit) that encodes a transmembrane protein of the tyrosine kinase receptor have been identified in the origin of up to 80% of GISTs [4]. In 5–15% of KIT-negative GISTs, other genetic alterations also affecting tyrosine kinase receptors—like the platelet-derived growth factor (PDGF) receptor—have been recognized [6]. Selective inhibitors of tyrosine kinase such as imatinib, which can block both c-kit and PDGF receptors, have improved the prognosis of these patients, [4, 6]. In our case, 11 years ago, surgery was the only available therapy; a complete resection provided control of the tumour and prevented recurrences. Interestingly, experimental studies suggest that imatinib may improve animal models of nephritis like lupus and cryoglobulinaemia associated to membranoproliferative glomerulonephritis [7, 8]. Indeed, in a case previously described, imatinib given before GIST surgery was enough for MN improvement [5]. These results might be more likely related to the inhibition of the PDGF receptor. The increase of pro-fibrotic factors such as PDGF frequently described in MN and other glomerulopathies might reflect a pathological pathway of renal damage [9], which could be activated in the patient reported here as well as in the case described by Cimic *et al* [5]. Although the previous steroid treatment received by the patient could also have contributed to MN remission, the dramatic improvement of the nephropathy observed in the months after gastric surgery without any other concomitant immunosuppressive treatment strongly suggests a causal relationship between both diseases. The relapse of nephrotic proteinuria 5 years later might be explained by residual structural changes in the kidney or by a sustained low-level immune response [2]. In fact, doubling the enalapril dose was enough to induce remission at that time.

In this report, we also describe that both MN and GIST preceded the diagnosis of other immune-mediated syndrome, MG, an autoimmune disorder of the neuromuscular junction often caused by the presence of anti-AchR, anti-muscle specific tyrosine kinase (MUSK) and other antibodies [10, 11]. While some patients can show several antibody types, others are seronegative and autoantibody status may be useful in defining clinical subsets of MG [11, 12]. Our patient had elevated serum anti-AchR antibodies, while no determination of other antibodies was available at that time. The presence of anti-AchR has been linked with thymic hyperplasia and thymoma, and could be considered as a paraneoplastic disorder [10]. The thymus is a lymphoid organ involved in the development and differentiation of T lymphocytes and plays a key role in the lymphocytic selection suppressing the immune response to autoantigens. Under normal conditions, the thymus contains 'myocyte-like cells' that express Ach receptors. The current model of MG pathogenesis is that in an altered thymus tissue, the development of autoreactive T clones or removal of regulatory T cells that suppress the immune response facilitate Ach receptor binding of the T cell, subsequent B-cell stimulation, formation of autoantibodies and development of the disease [13]. *In vitro* studies have underlined the crucial role of c-kit receptor and its ligand in the proliferation and differentiation of T-cell progenitors [14]. Furthermore, c-kit overexpression is related to thymic carcinoma and thymoma, and there is anecdotal experience suggesting activity of imatinib in thymic tumours [15].

The relationship between MG and other autoimmune disorders has been consistently reported [16]. The association between MG and MN has also been described [17, 18]. In our patient, MG was related to anti-AchR antibodies, which are mainly IgG1 and trigger a complement-mediated damage at the neuromuscular junction, whereas anti-MUSK antibodies are of the IgG4 subtype, do not activate the complement and their relationship with thymic growth is rare [10, 11]. IgG1 antibodies are also of the same isotype most commonly identified in MN related with malignancy. We hypothesize that the thymic alteration may have contributed to the generation of antibodies that unexpectedly targeted autoantigens of the glomerular membrane. The concurrent presence of a GIST and later recognition of a thymus hyperplasia would support this hypothesis. The relationship between MN and thymoma or thymic hyperplasia has been previously suggested, in fact being the second cause of nephrotic syndrome associated with thymus pathology after minimal-change nephropathy [18]. Our patient had a recurrence of nephrotic syndrome 3 years after thymectomy in spite of a good clinical control of the myasthenia and no evidence of new thymus growth. The onset or worsening of nephrotic syndrome long after thymectomy has been observed by others and may be attributed to the persistence of impaired cellular immunity [17, 19]. Interestingly, this is reminiscent of reports of other immune disorders which may present or exacerbate even many years after thymectomy without evidence of thymus

regrowth, suggesting the possibility of age-dependent, thymectomy-induced autoimmune diseases [20, 21]. The possible link between MG and extra-thymic tumours (lung, lymphoma) through a common immune background is controversial [22]. This is the first case reported with concurrence of MG and GIST and the relationship between both the disorders is unclear. In this patient, the diagnosis and removal of a GIST preceded by 2 years the onset of MG. Although purely speculative, the coexistence of MN in the same patient suggests that a common physiopathological background might link all of these disorders. The previously reported overexpression of both c-kit and PDGF receptors in GISTs [4, 6] and thymoma [15] further supports this hypothesis.

In summary, we present a case of MN that preceded the diagnosis of a GIST as well as the onset of another autoimmune disease, MG, associated with thymus hyperplasia. This rare combination has not been previously described and may point to commonalities in disorders of immunopathologic regulation leading to abnormal tissue damage. The case also illustrates T-cell different IgG subclasses triggered mechanisms as well as the possible role of PDGF in MN glomerular injury. The report of a rare clinical association of diseases with possible overlapping pathogenetic mechanisms may help us identify common dysfunctional pathways and potential therapeutic targets.

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