Treatment of a nephrotic syndrome by endoscopic removal of a villous adenoma of the duodenum

Traitement d’un syndrome néphrotique par l’exérèse endoscopique d’un adénome villeux duodénal

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Summary We report the case of a patient diagnosed with a villous adenoma of the duodenum showing high degree dysplasia who developed a nephrotic syndrome (NS) due to a membranous nephropathy (MN), demonstrated by renal biopsy. Only the endoscopic resection of the duodenal adenoma could control the NS. The first manifestation of a MN is often the development of a NS. Up to 20% of patients older than 65 years who develop a MN have cancer. Tumours most often identified are those of lung, prostate and digestive tract. A renal biopsy is required to identify this type of nephropathy. If a diagnosis of MN is made, an associated tumour should be looked for.

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Résumé Nous rapportons le cas d’une patiente, porteuse d’un adénome tubulovilleux du duodénum avec une dysplasie de haut grade, qui a développé un syndrome néphrotique sur une glomérulonéphrite extra-membraneuse (GNEM), démontrée par biopsie rénale. Celui-ci n’a pu être contrôlé que par la résection endoscopique de l’adénome duodénal. La première manifestation d’une GNEM est souvent l’apparition d’un syndrome néphrotique. Jusqu’à 20% des patients âgés de plus de 65 ans qui développent GNEM sont atteints d’un cancer. Les tumeurs les plus fréquemment retrouvées sont celles du poumon, de la prostate et du tractus digestif. Il est donc indispensable de réaliser une biopsie rénale en cas de syndrome néphrotique pour identifier le type d’atteinte glomérulaire. Si le diagnostic de GNEM est posé par la biopsie rénale, une recherche de néoplasie associée doit être entreprise.

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Clinical case

An 84-year old woman was admitted on the acute care elderly unit because of bilateral edema of eyelids and of the lower limbs that appeared a few weeks before admission.

In 1996, she had undergone total colectomy for an adenocarcinoma of the colon, followed by chemotherapy. She was considered in remission. In 2006, gastroscopy showed a villous adenoma with low grade dysplasia of the second segment of the duodenum.

On examination, the weight was 73.4 kg, the blood pressure 130/80 mm Hg. There was bilateral edema of the eyelids and the lower limbs. The remainder of the examination was normal.

Total protein was 59 g/L and albumin 31 g/L, blood urea was 62 mg/dl and creatinine 1 mg/dl. Creatinine clearance calculated according to the simplified MDRD formula was 47 ml/min. Serum sodium was 134 mmol/L and total cholesterol 321 mg/dl. Testing was negative for hepatitis B and C as well as for anti-nuclear antibodies, anti-dsDNA and anti-ENA antibodies. A 24-hour urine collection showed a proteinuria of 3404 mg/L, i.e. 8 g/24 h. The protein/creatinine ratio was 7953 mg/g.

These findings are consistent with a nephrotic syndrome (NS). A renal biopsy showed thickening of the glomerular basal membrane. Spikes were visible on immersion microscopy. Holes were seen in the basal membranes on tangential sections. They corresponded to sub-epithelial immune complex deposits. Immune peroxidase staining showed sub-epithelial deposition of Ig G, C3d and C4d.

Electron microscopy confirmed the presence of a moderate amount of sub-epithelial deposits.

The histological diagnosis was one of a membranous nephropathy (MN) grade I.

In view of the past medical history of the patient, the digestive tract was again assessed. CT of the abdomen showed no recurrence of colic cancer. Gastroscopy again identified a villous lesion in the second part of the duodenum. The biopsies revealed a tubulovillous adenoma with high grade dysplasia. Colonoscopy showed a normal anastomosis.

Initially, the NS was treated with captopril only, with no effect. Next, a treatment associating methylprednisolone 32 mg/day and cyclophosphamide 100 mg/d was started. After 1 month, the edema of the eye lids had vanished and that of the lower limbs had considerably diminished. Glomerular filtration rate according to the MDRD formula was now superior to 60 ml/min. Total protein and albumin levels were normal. The urinary protein/creatinine ratio had lowered to 4747 mg/g. As proteinuria persisted with cyclophosphamide was stopped after the resection in view of the risk for infection.

Two months later, all edema had disappeared. There was a slight deterioration of the renal function, the glomerular filtration estimated with the simplified MDRD formula was 52 ml/min. The protein/creatinine ratio had halved and was 1368 mg/g. The patient had a second mucosectomy in February 2009, complicated by gastro-intestinal bleeding. The resection of the polypoid lesion was now complete. Steroid therapy was slowly reduced and stopped 3 months after the second resection.

A year later, the patient is doing well and the NS has completely disappeared.

Discussion

MN is the main cause of NS in people older than 60; it is rare in children.

The primitive form is considered to be due to immune complex deposition in the sub-epithelial region of the glomerular capillary membrane. Secondary forms, which represent one third of cases, are associated with autoimmune disorders (systemic lupus erythematosus and other systemic diseases due to impaired immunity), with diabetes type 1, with infections (hepatitis B and C, parasitosis . . .), with drugs (NSAIDs, penicillamin, ACE inhibitors . . .) or with cancer.

In patients older than 65 with MN, the incidence of tumors is in the range of 5 to 20% depending on the studies [1-5].
Nephrotic syndrome and duodenal villous edema

This incidence of malignancy is 10 times higher than in the general population. It increases with age, and there is no sex difference.

MN is mainly associated with cancer of the lung, prostate or gastro-intestinal tract (gastric or colic) and, less frequently, with hematomal malignancies.

To our knowledge, this is the first case description of a NS associated with a tubulovillous adenoma of the duodenum with high-grade dysplasia.

The arguments in favor of a link between the duodenal polyp and the NS are the fact the NS appears concomitantly with the evolution of the polyp to high grade dysplasia and that it disappears after its complete endoscopic resection, whilst the NS only partially responds to steroid therapy and cyclophosphamide. After 1 year follow-up there is no evidence of recurrence of either the proteinuria or the duodenal lesion.

In the literature, there have been a few case reports of reappearance of the NS at the time of recurrence of the malignancy. It may be the first symptom indicating recurrence [6–8].

In many cases of malignancy-associated nephropathies, especially in older patients, renal disease may precede the clinical expression of a tumor by 12 to 18 months; when they identify MN, clinicians should look for an underlying malignancy [9,10,16].

Considering the types of cancer most frequently associated with MN, screening could consist of a search for fecal occult blood, a colonoscopy in patients over 50, a mammography in women over 40, PSA testing in men over 50 and a chest X-ray or chest CT [3,8,11].

A renal biopsy is required to determine the cause of a NS occurring in the elderly and to decide on the appropriate treatment [17].

Several hypotheses have tried to explain the pathophatology of the association of MN with malignancy.

Immune complexes containing tumor-associated antigens could form in the bloodstream and be deposited in the glomerular basal membrane or tumor antigens could be directly deposited in the glomerular membrane and immune complexes could then be formed in situ [1,3,4,6,11–15].

Some authors have highlighted several tumor antigens in renal biopsies of patients but without evidence of their pathologic nature. These antigens are the following: CEA, PSA, melanoma Ag, renal RTE antigen [4,12].

Indeed, the increased glomerular permeability to proteins that is found in MNs can result from massive deposits of tumor antigens and their corresponding antibodies without their being responsible of the pathogenesis of the nephropathy.

A viral etiology is also mentioned and implies that certain viruses such as those of the herpes group or of hepatitis could first cause the MN and then the tumor through their oncogenic viral activity, an impairment of the renal clearance of biologic mediators associated with oncogenesis or through both mechanisms [12,15].

The third hypothesis concerns immunosuppressive therapies used in the treatment of nephropathies. These treatments could facilitate the proliferation of tumor cells [12,15].

In patients with malignant tumors, proteinuria seems to be a negative prognostic factor. Certain authors give a mortality rate up to 75% 1 year after the diagnosis of MN and 3 months after the diagnosis of cancer [12].

Our patient benefited from a complete resection of a dysplastic polyp and there is no recurrence of the NS or the adenoma 1 year later. The treatment of MN associated with malignancy is that of the underlying tumor through different therapies such as surgery, chemotherapy or radiotherapy [2,4,6–8].

Symptoms and complications linked to the NS have to be treated in the same way as in idiopathic MN.

Some authors claim the immunosuppressive therapy should be avoided for fear of increasing viral replication or progression of malignancy.

Our patient received cytotoxic treatment associating cyclophosphamide and steroids, which reduced proteinuria and edema. This therapy could be stopped after endoscopic resection of the duodenal lesion. It is through this resection that full remission of the NS was obtained.

In conclusion, considering the high prevalence of malignancy associated MN, a renal biopsy should be performed in patients presenting with NS, especially in those beyond 65. Those in whom MN is confirmed by biopsy should be screened for cancer. The most frequent tumors affect the digestive tract, lungs and prostate. The treatment of the NS is that of the underlying tumor.

Conflict of interest

None.

References


