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Uncharted Territory: Frequent Relapsing, Steroid Sensitive Secondary Minimal Change Nephrotic Syndrome Cause by Solid Tumor of the Gastro-Esophageal Junction

—(Case Presentation and Review of the Literature)

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Abstract

We reported a biopsy proved case of minimal change nephrotic syndrome in a 72-year-old patient. The minimal change nephrotic syndrome has been steroid sensitive, but the patient had 7 relapses over a span of 5 years. Each time the dose of steroid is tapered, a relapse of the nephrotic syndrome occurred. Eventually, the patient was complaining of dysphagia and difficulty swallowing. Hospital work-up with barium swallow, endoscopy, and CT of the chest, abdomen and pelvis, revealed a focal stenotic lesion with mild to moderate esophageal dysmotility 7/15/2022. A diagnosis of an ulcerating lesion with biopsy confirmed a neuro-endocrine carcinoma of the gastro-esophageal junction was entertained. The CT of the chest/abdomen/pelvis, 7/19/2022, has shown, an esophageal mass of 5.1 × 5.6 × 7 cm of the gastro-esophageal junction with ulceration. No evidence of spread beyond the esophagus and stomach. The histology revealed a poorly differentiated neuroendocrine tumor of the gastro-esophageal junction. The patient underwent several rounds of chemotherapy, radiation, and surgery culminating in tumor control. His nephrotic syndrome was resolved after the tumor has been controlled by surgery and chemotherapy.

Keywords

Frequent Relapsing Nephrotic Syndrome, Steroid Sensitive Nephrotic Syndrome, Secondary Nephrotic Syndrome, Solid Gastro-Intestinal Tumor, Minimal Change Nephrotic Syndrome, Neuro-Endocrine Tumor of the Gastro-Esophageal Junction, Paraneoplastic Glomerulopathy

1. Introduction

In adults, minimal change disease (MCD) represents approximately 10% - 15% of patients with idiopathic nephrotic syndrome [1]. Nephrotic syndrome has been associated with malignant tumors in 11% of cases [2] [3]. Membranous nephropathy is the most frequent form of paraneoplastic glomerulopathy associated with solid tumors [3]. Minimal-change disease (MCD) is mainly associated with Hodgkin's lymphoma or hematological malignancies. However, it has also been linked with different solid tumors, like thymoma, colorectal carcinoma, ovarian, pancreatic and renal cell carcinoma [4].

We presented a case of frequent relapsing, steroid sensitive minimal change nephrotic syndrome in a 72-year-old man associated with solid tumor of the gastro-esophageal junction (GEJ). To our knowledge this is a rare association of MCD occurred with neuro-endocrine solid tumor of the gastro-esophagus. Steroids and immunosuppressive therapy were given with frequent relapses of the MCD as soon as the dose of steroids was tapered. A complete resolution of the nephrotic range proteinuria was soon accomplished with improvement of his clinical condition when the solid tumor is brought under control with surgery and neoadjuvant chemotherapy.

The aim of presenting this case is to draw attention to the possibility that rare paraneoplastic MCD associated with solid tumor must be considered and ruled out before embarking on symptomatic treatment with steroids and immunosuppression which can negatively affect the tumor course.

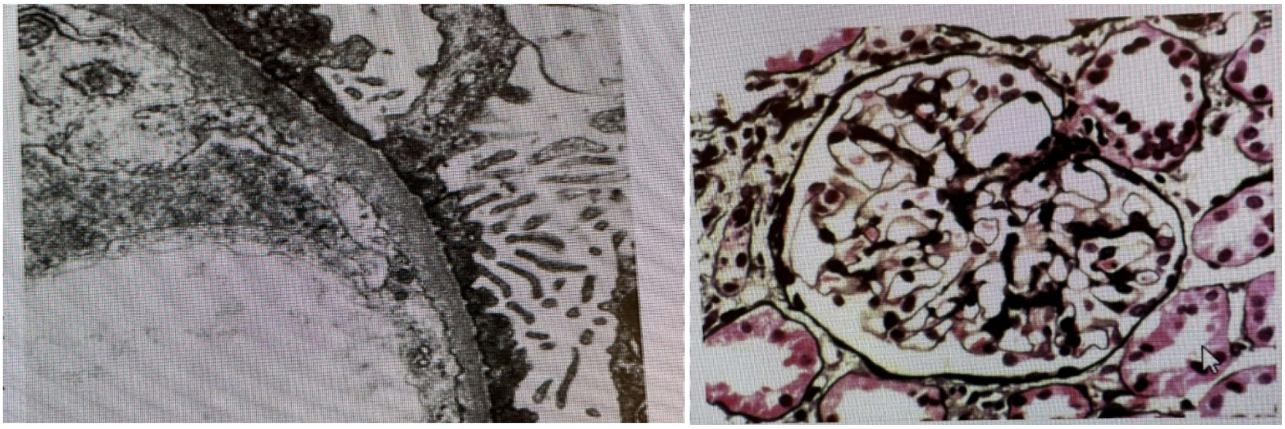
2. Case Report

A 72-year-old Caucasian male, with past medical history significant for hypertension, nephrotic syndrome (minimal change disease) by kidney biopsy, hyperlipidemia, osteoporosis, hypothyroidism, and anemia related to chemotherapy.

His physical examination revealed an obese Caucasian man with no significant shortness of breath, alert and oriented × 3. His heart, chest and abdominal examination were unremarkable. He has mild lower extremities edema at the time of encounter.

His kidney biopsy in 2017 revealed minimal change nephrotic syndrome responsive to steroids (**Figure 1**). However, he had multiple relapses of his NS whenever the dose of steroids is reduced. He was started on rituximab along with steroids to abate the frequent relapses of his disease. All his laboratory works up before starting the rituximab was negative or normal including, complement levels, hepatitis screen, serum protein electrophoresis, coagulation function and thyroid function. Antinuclear antibodies (ANA), anti-double strand DNA antibody, anti-neutrophil antibody (ANCA), and anti-phospholipase A2 receptor (PLA2R) antibody were negative. The MCD clinical course data are shown in **Table 1**.

He was admitted to the hospital with a complaint of dysphagia and weakness for more than 2 weeks. The hospital work-up including imaging studies and upper



(a) (b)

Figure 1. Showed the light microscopy (normal looking glomerulus) and the electron microscopic pictures of kidney biopsy of minimal change nephropathy with fusion of the foot processes of the epithelial cells (Magnification 800×).

Table 1. Patient's data characteristics.

Data characteristics	date	Data characteristics	date
Pr/Cr 0.437 g/mg Albumin 3.3 g/dl B/C 11/0.9 mg/dl eGFR > 90 ml/min	10/7/2022	Pr/Cr 0.535 g/mg Albumin 1.8 g/dl B/C 8/0.8 mg/dl	12/05/2019
Pr/Cr < 0.086 Albumin 2.1 g/dl B/C 10/0.7 mg/dl eGFR > 90 ml/min	7/15/2022	Pr/Cr 7.947 g/mg Albumin 0.9 g/dl B/C 45/0.9 mg/dl eGFR > 90 ml/min	10/29/2019
Pr/Cr < 0.086 g/mg Albumin 2.1 g/dl B/C 10/0.7 mg/dl eGFR > 90 ml/min	5/12/2022	Pr/Cr 0.080 g/mg Albumin 2.9 g/dl B/C 9/0.8 mg/dl eGFR > 90 ml/min	08/13/2019
Pr/Cr 0.098 g/mg Albumin 2.9 g/dl B/C 10/0.8 mg/dl eGFR > 90 ml/min	08/26/2021	Pr/Cr < 0.165 g/mg Albumin 3.0 g/dl B/C 7/0.8 mg/dl eGFR > 90 ml/min	03/15/2019
Pr/Cr 0.081 g/mg Albumin 2.9 g/dl B/C 8/1.0 mg/dl eGFR 74 ml/min	12/03/2020 Patient started on rituximab for recurrent relapses	MCD resolved on steroids.	2/2018 (first relapse on 7/2018.
Pr/Cr 2.660 g/mg Albumin 1.5 g/dl B/C 13/1.0 mg/dl eGFR 74 ml/min	11/09/2020	Pr/Cr 0.437 g/mg Albumin 3.3 g/dl B/C 9/0.8 mg/dl eGFR > 90 ml/min	10/24/2018

Continued

Pr/Cr 9.149 g/mg Albumin 1.4 g/dl B/C 12/1.0 mg/dl eGFR 74 ml/min	10/20/2020	Pr/Cr 0.093 g/mg Albumin 3.0 g/dl B/C 11/1.0 mg/dl eGFR 75 ml/min	08/12/2018
Pr/Cr 0.040 g/mg Albumin 3.6 g/dl B/C 7/0.8 mg/dl	3/02/2020	Pr/Cr 0.068 g/mg Albumin 3.0 g/dl B/C 12/0.9 mg/dl eGFR 84 ml/min	02/27/2018

Pr/Cr—protein creatinine ratio; B/C—BUN and creatinine; eGFR—estimated glomerular filtration rate.

gastro-intestinal endoscopy with biopsy of the mass lesion revealed neuro-endocrine tumor (**Figure 2**). He was started on neoadjuvant chemotherapy with cisplatin and etoposide and radiotherapy before surgery. Surgical removal of the gastro-esophageal mass was completed with clear margins of the surgical incision. The surgical removal of the mass was carried out on 8/2022.

A total of 7 relapses of his MCD in a span of 5 years have been recorded. His relevant data are shown in **Table 1**. After the chemotherapy and radiation with removal of the tumor by surgery, his MCD subsided with no further relapses. His last albumin was 3.3 g/dl, and protein creatinine ratio 0.437 with normal BUN and creatinine and eGFR of > 90 ml/min.

3. Discussion

Paraneoplastic syndrome refers to constellation of clinical manifestation not directly related to tumor burden, invasion or metastasis but caused by the secretion of tumor cell products, such as hormones, cytokines, growth factors and tumor antigens [5].

The association of solid tumors has been reported in the literature with paraneoplastic glomerular disease. Adenocarcinoma of the lung and the gastrointestinal tract are among the most associated with glomerular disease [3] [4]. MCD is strongly associated with Hodgkin's Lymphoma and hematological malignancies [5]. The occurrence of MCD with solid tumors have rarely been described in the literature. MCD has been associated with ovarian carcinoma, and other solid tumors with 10 cases have been reported in the literature [2] [5]-[12]. Approximately 64 cases of solid tumors have been reported in the literature to be associated with MCD and from those at least 26 (40%) cases were associated with thymoma [4].

It is not determined if the nephrotic syndrome is really a paraneoplastic manifestation, however, one criterion is particularly fulfilled in all these cases: the clinical remission of the NS observed after complete removal of the tumor or full remission of the underlying malignancy has occurred.

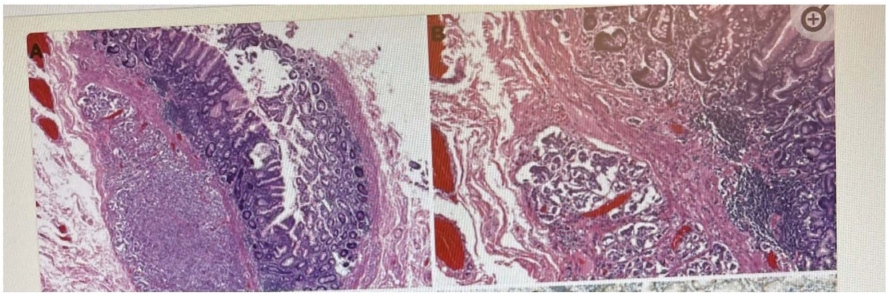


Figure 2. H & E staining by light microscopy showed the neuro-endocrine tumor of the gastro-esophageal junction (low magnification). The section on the right with (400 × magnification) showed the tumor confined to the serosa with no evidence of spread.

Remission of NS achieved by surgical removal and or chemotherapy of the underlying tumor speaks volume to the association. These criteria were fulfilled in our patient. The link between the decreased level of proteinuria and the clinical remission of the cancer as reflected by decreasing urinary protein excretion rate indicated that the tumor may secret cytokines or tumor markers responsible for inciting the disruption in the filtration barrier of the kidney and the development of nephrotic syndrome. If this assumption is correct, then the connection of the tumor and the MCD has also been satisfied [13].

The hypothetical theories put forward to explain the association of glomerulopathies as paraneoplastic phenomenon, came from the presence of unrecognized filtration factor for some forms of focal segmental glomerulosclerosis (FSGS). This observation is based on the recurrence of proteinuria in FSGS patients within hours of transplantation and remission following plasmapheresis or immunoadsorption. A permeability factor has been recently implicated in cases of FSGS not related to malignancies [14].

By the same token we strongly believe that a possible, yet undiscovered tumor-secreted product could at least partially explain this phenomenon. This theory warrants further thorough investigation, particularly, regarding MCD. The overproduction of vascular endothelial growth factor by the cancer cells has been suggested to contribute to the pathogenesis of this form of paraneoplastic glomerulopathy [15].

To our knowledge this is the first case of MCD associated with solid tumor of the GEJ. In this case, there has been circumstantial evidence of association between the clinical course of the cancer, the treatment of the cancer by surgery and chemotherapy, and the reduction of the level of proteinuria induced by such treatment.

It is critical to recognize that MCD is an entity caused by a paraneoplastic effect. The MCD in the past has been overlooked as paraneoplastic phenomenon associated with solid tumors. Immunosuppressive therapy used for MCD may conceivably induce a flare of the tumor or negatively impacted the tumor course. One must be cognizant of this possibility, therefore the decisions to initiate GE cancer therapy is essential to assure the remission of both the GE cancer and the MCD at the same time [7] [8] [9] [10] [11].

4. Conclusion

This case illustrated the close correlation of MCD with solid tumor of the GEJ. The remission of the NS after successful treatment of the neuroendocrine tumor of the GEJ with surgery and chemotherapy is clear indication that the MCD is a paraneoplastic phenomenon. We strongly believe that a possible, yet undiscovered tumor-secreted product could at least partially explain this fascinating phenomenon. This theory warrants further comprehensive investigation, specifically, regarding MCD. The overproduction of vascular endothelial growth factor by the cancer cells has been proposed to contribute to the pathogenesis of this form of paraneoplastic glomerulopathy, time only will tell if this assumption holds any truth.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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