Case Report

C1q Nephropathy Developing in a Case of Gastric Carcinoma

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ABSTRACT. C1q is a key intermediary in the classical complement pathway. It is known to be activated by several factors including immunoglobulins and charged molecules and is an initiator of the complement cascade. C1q nephropathy (C1qN) is a rare idiopathic glomerulonephritis characterized by predominant presence of glomerular deposits of C1q fraction of complement. Although few uncommon associations of C1qN have been seen with various disorders, we present the first case of C1qN diagnosed in an elderly male with gastric adenocarcinoma. Few months after the onset of symptoms related to gastric-outlet obstruction, the patient presented with oliguria and anasarca. A gastric biopsy revealed a well-differentiated gastric adenocarcinoma, while a renal biopsy showed mesangial hypercellularity with C1q dominant immunofluorescence deposits. The development of C1qN in this case may be a result of the activation of C1q by necrotic or apoptotic cancer cell debris. C1q has been shown to induce apoptosis experimentally in other cancers. The findings suggest a complex role for C1q in initiating tumor apoptosis and subsequent linkage with apoptotic cell products and immunoglobulins to initiate renal damage.

Introduction

C1q nephropathy (C1qN) refers to a rare glomerular disorder in which C1q deposits are seen in the mesangium on immunofluorescence (IF) microscopy and mesangial electron dense deposits are seen on electron microscopy. The defining feature is intense dominant or codominant staining for C1q in patients without evidence of systemic lupus erythematosus or type 1 membranoproliferative glomerulonephritis. The prevalence of C1qN varies from 0.2% to 16% and seems to be higher in children. C1qN may present with proteinuria, full-blown nephrotic syndrome, or nephritic illness. Single case reports of the association of C1qN with systemic illnesses are on record. Here, we present the first case of C1qN occurring concomitantly with gastric adenocarcinoma. The probable pathogenesis of this association is discussed.

Case Report

Informed consent was obtained from the...
A 68-year-old male presented with a history of acidity, loss of appetite, weakness, vomiting, and dysphagia along with fullness in the upper central abdomen for a period of five months. He also complained of oliguria and intermittent leg swelling for two months. He underwent an upper gastrointestinal tract endoscopy which demonstrated a large fungating growth in the antrum near the pylorus.

Computed tomogram of the whole abdomen demonstrated irregular wall thickening involving the antropyloric region of stomach with a mass showing luminal compromise, leading to proximal dilatation of the stomach and hold up of gastric residue (Figure 1). Multiple enlarged perigastric, retroperitoneal, and peripancreatic lymph nodes were seen; the largest measuring 18 mm x 17 mm. An endoscope-guided gastric mass biopsy was performed. The gastric biopsy revealed a well-differentiated adenocarcinoma, which showed diffuse positivity for CK-7 on immunohistochemistry. The tumor was negative for CK-20, Her2neu, and PDL-1 (Figure 2).

Blood investigations revealed serum urea of 98 mg/dL and serum creatinine of 3.88 mg/dL. Mild proteinuria (100 mg/dL) and microscopic hematuria (5–10 rbc/hpf) were also present (Table 1). Serum complements were normal. Antinuclear antibody was negative. A renal core biopsy was performed. The renal biopsy showed 15 glomeruli, of which three showed global sclerosis. Of the viable glomeruli, three showed the presence of segmental mesangial hypercellularity. The rest of the glomeruli were unremarkable. There was no evidence of endocapillary hypercellularity, segmental sclerosis, necrosis, or crescents. The tubules showed focal tubular atrophy. There was presence of mild interstitial fibrosis with mild lymphocytic infiltrate. Blood vessels in the biopsy were unremarkable. IF revealed predominantly the presence of segmental mesangial

Table 1. Blood investigations.

| Parameter       | Results  | Normal range                  |
|-----------------|----------|-------------------------------|
| Blood urea      | 98 mg/dL | 7–20 mg/dL                    |
| Serum creatinine| 3.88 mg/dL| 0.6–1.2 mg/dL in adult males  |
| Proteinuria     | 100 mg/dL| 0–20 mg/dL in random urine sample |
| Hematuria       | 5–10 RBC/HPF| <4 RBC/HPF                     |

RBC: Red blood cell, HPF, High power field.
granular deposits of C1q (3+) along with IgG (2+), IgA, IgM, C3c were negative (Figure 3).

A diagnosis of well-differentiated gastric adenocarcinoma along with C1qN was rendered. The patient was provided palliative therapy for the gastric malignancy and immunosuppression for the C1qN. However, his renal parameters did not improve, and he succumbed to an episode of massive intra-abdominal bleed, a month after diagnosis.

**Discussion**

C1qN refers to a pattern of glomerular injury with varying histopathologic findings, including no glomerular lesions demonstrable on light microscopy to lesions resembling focal segmental glomerulosclerosis (FSGS) and proliferative glomerulonephritis. Rare case reports of association of C1qN have been found with deforming arthritis, Gitelman syndrome, chromosome 13 deletion, and severe atopic dermatitis. A case of C1qN along with BK virus nephropathy has been reported in a renal-transplant recipient. C1qN has been reported in association with malignancy in one previous case which showed the presence of disseminated lung and liver lesions on radiology though no histopathologic confirmation of the malignancy was available.

The association between renal disease and malignancy has been reported infrequently in various glomerulopathies. Association of membranous nephropathy has been noted, especially in elderly patients with solid-organ malignancies including those of lung, prostate, and gastrointestinal tract. Glomerular lesions have also been seen in association with Hodgkin’s disease, chronic lymphocytic leukemia, and plasma cell dyscrasias. Here, we report a case of C1qN with concomitant revelation of gastric malignancy. To the best of our knowledge, this is the second case of malignancy reported in association with C1qN and the first case report of C1qN accompanied with adenocarcinoma of gastric origin. Resolution of the nephropathy on treatment of the gastric malignancy could have established a cause-and-effect relationship; this was not possible in the current case due to advanced malignancy and death of the patient. However, the possibility of an association between the C1qN and gastric malignancy cannot be refuted, especially since the nephropathy followed the development of the malignancy.

C1q is a protein belonging to the collectin family and is a key intermediary of innate immunity. It is activated by binding to immunoglobulins, charged molecules, DNA, RNA, and viral and bacterial products, and this binding initiates the classical complement cascade. It has also been suggested that the binding of necrotic or apoptotic cells can similarly activate C1q. It can be surmised that the binding of some antigenic epitopes from necrotic or apoptotic cell debris from the gastric carcinoma led to the activation of C1q in the present case. The subsequent binding of immunoglobulins to form immune complexes and their deposition in the renal mesangium could have resulted in the mesangial lesions and C1q deposits.

There is experimental evidence that C1q induces apoptotic death of prostate, breast, and neuroblastoma cancer cells through the induction of tumor suppressor WOX1. This may suggest that C1q acts in a complex manner in

**Figure 3.** Photomicrograph of renal biopsy showing a glomerulus with mesangial hypercellularity (arrow) (H and E, ×200). Inset showing mesangial deposits of C1q (Fluorescein isothiocyanate, ×200).
malignancies, first by initiating apoptosis and tumor suppression and then by binding with apoptotic cell products and immunoglobulins and localizing in the mesangium and initiating renal damage. Increased C1q production may be the body’s protective mechanism against tumors, excess of which in turn deposits in the mesangium causing C1qN.

The optimal treatment of C1qN is not clearly defined. Unfavorable outcomes are associated with nephrotic range proteinuria and FSGS variant. The possibility of an association with malignancy also needs to be borne in mind since it may have a bearing on the treatment and prognosis of these patients.

**Conflict of interest:** None declared.

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