Patterns of renal involvement in a cohort of patients with inflammatory bowel disease in Egypt

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Abstract

***Background and study aim* : Renal complications are frequent extraintestinal manifestations in inflammatory bowel disease (IBD). We aimed in our study to describe the spectrum of renal affection in our IBD patients.**
***Patients and methods :* This study is a retrospective analysis of renal biopsies done for IBD patients who developed renal diseases, at Cairo University Hospital, from June 2005 to Jan. 2016.**
***Results :* Among 896 IBD patients, 218 patients (24.3%) developed renal affection. The onset of renal disease mandated renal biopsy at 5.6 ± 7.4 years after IBD diagnosis. Nephrotic range proteinuria was the most common indication for a renal biopsy [81 (37.15%) patients]. Amyloidosis was the most common renal pathological diagnosis [56 patients (25.7%)] followed by immunoglobulin A (IgA) nephropathy [35 patients (16.1%)], focal segmental glomerulosclerosis (FSGS) [32patients (14.7%)], crescentic glomerulonephritis (CGN) [32 patients (14.7%)], membranous nephropathy (MN) [18 patients (8.25%)], minimal change disease [17 patients (7.7%)], chronic interstitial nephritis (CIN) [10 patients (4.6%)], acute tubular necrosis (ATN) [8 patients (3.7%)], thrombotic microangiopathy (TMA) [6 patients (2.75%)], and acute interstitial nephritis (AIN)[4 patients (1.8%)]. Variable renal histopathology diagnoses did not correlate with age, duration of IBD diagnosis, or drugs used for IBD treatment. Crescentic GN was significantly correlating with ASCA, ANCA-p, and ANCA-c in serum.**
***Conclusion :* Amyloidosis is a common renal pathological diagnosis in our patients, and is followed by IgA nephropathy, and FSGS.**
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Keywords : IBD; Renal complications; Amyloidosis, IgA nephropathy.

Introduction

Extraintestinal manifestations are common complications of inflammatory bowel disease (IBD) occurring with a variable incidence ranging from 6% to 47% of IBD patients (1). Various forms of renal and urological complications were found to develop in 4 to 23% of IBD patients (2). Of these complications; kidney stones and enterovesical fistulas are the most common manifestations. On the other hand; forms of renal parenchymal involvement are not uncommon and their spectrum have been described before (2, 3). We have tried to describe the patterns of renal affection in a cohort of IBD patients with renal dysfunction in our community and to analyze them in the context of previous reports.

Patients and methods

Cairo University Hospital is a major hospital and a tertiary referral center serving patients from Cairo and also patients referred from all other governorates of Egypt. We obtained the hospital records of 896 IBD patients for whom a diagnosis of Ulcerative colitis (UC), or Crohn's disease (CD) was confirmed between June 2005 and January 2016. Of these IBD patients; 218 developed renal affection throughout the follow-up duration. These patients with renal complications underwent renal biopsy, and we analyzed the results of these renal biopsies.

The Medical data were obtained from patient files, dating to the time of presentation of renal disease and biopsy. These data included epidemiological data, and laboratory parameters and immunology screening. The severity of IBD was recorded based upon the Montreal Classification of IBD severity (4).

The histopathological findings of IBD were recorded according to the guidelines of the British Society of Gastroenterology; and described as the presence or absence of each of the following pathological features: cellular infiltrate, focal inflammation, micro-fistulization, non caseating granulomas, vascular congestion, crypt abscesses, mucin depletion, and malignant change (5).

Kidney Biopsy

All of the renal biopsies were performed according to established indications for renal biopsy: the patient suffering from nephritic or nephrotic syndromes, unexplained renal failure, sub-nephrotic range proteinuria, or glomerular hematuria (6-8). The renal biopsy specimens were evaluated by light and immune fluorescence microscopes by a specialized nephro-pathology team in the pathology department according to standardized methods (9).

Light Microscopy

Briefly, the kidney biopsy specimens were fixed in buffered formalin, dehydrated in graded alcohols,

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and embedded in paraffin using standard techniques. Serial 3-mm-thick sections were cut and treated with hematoxylin and eosin, Jones methenamine silver, Masson trichrome, or periodic acid-Schiff reagent. Pathological diagnosis of granulomatous interstitial nephritis depended upon the detection of interstitial nephritis in which the inflammatory infiltrate contained at least one aggregate of epithelioid histiocytes admixed with lymphocytes with or without multinucleated giant cells. To differentiate amyloid from other hyaline deposits, Red Congo stain was used. Amyloid material has a high affinity for Congo Red stain; amyloid deposits exhibit a characteristic green birefringence when examined with polarized light.

Immunofluorescence Microscopy

The samples were transported in Michel media, washed in buffer, and frozen in a cryostat. The samples cut in 5 mm sections, were rinsed in buffer and reacted with fluorescein-tagged polyclonal rabbit antihuman antibodies to IgG, IgA, IgM, C3, C4, C1q, fibrinogen, k or l light chains (Dako, Carpenteria, CA; USA; Kent Laboratories, Bellingham, WA, USA) for 1 hour and rinsed; a cover slip was applied using aqueous mounting media.

Statistical Analyses

We performed all of the statistical calculations using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. The data were statistically described in terms of means and standard deviations, frequencies and percentages when appropriate. We performed a two-sample test of proportions (Z-test). A P value less than 0.05 was considered to be statistically significant.

Results

Clinical and laboratory data

The study involved 218 patients with IBD and renal affection [143 (65.6%) males, and 75 females (34.4%)]. The mean age of the cohort was 37.3±8.9 years. Of these patients, 161 (73.85%) had UC, and 57 (26.15%) had CD. Their mean serum creatinine of the patients at the time of renal biopsy was 1.159±1.027 mg/dl (Table 1). The onset of renal disease occurred a mean of 5.6 ± 7.4 years after the IBD diagnosis. Forty six patients were affected by extra-intestinal disease (24 patients had episcleritis and iridocyclitis, 19 patients had ankylosing spondilitis, and 3 patients had erythema nodosum).

Kidney biopsy indications

Nephrotic range proteinuria was the most common indication for renal biopsy in our cohort [81 (37.15%) patients], followed by subnephrotic range proteinuria [38 patients (17.4%)]. Persistent isolated hematuria was the least common indication for renal biopsy [13 patients (5.9%)] after urological causes were excluded (Table 2).

Table 1. — **Laboratory criteria of involved patients at time of renal biopsy**

Parameter	Mean	SD	Minimum	Maximum
Serum Creatinine (mg/dl)	1.159	1.0271	0.400	7.000
Urea (mg/dl)	42.870	30.0356	10.000	190.000
Serum albumin (g/dl)	3.174	0.4929	2.100	4.300
Proteinuria (gm/day)	2.868	1.0313	1.000	6.000
Uric acid (mg/dl)	4.887	1.1059	2.500	8.200
ESR (mm/ 1sthour)	74.913	12.5579	55.000	100.000
Calcium (mg/dl)	8.174	0.6306	6.800	9.000
Phosphorous (mg/dl)	3.874	0.8181	2.500	5.800
ALT Iu/ml	43.339	25.1384	15.000	96.000
C4	21.264	8.2287	5.600	38.000
C3	121.278	24.4093	78.000	187.000
Hemoglobin (gm/dl)	10.294	2.7666	3.700	16.200
Platelet (x1000/ml)	249.390	100.1178	11.000	515.000
WBCs (x1000/ml)	7.463	2.6323	2.700	24.800

ESR erythrocyte sedimentation rate, C3 complement factor 3, C4 complement factor 4, ALT alanine transaminase.

Table 2. — **Indications for renal biopsy in involved patients**

Indication for renal biopsy	N (%)	
Nephrotic range proteinuria	81	(37.15%)
Subnephrotic range proteinuria	38	(17.4%)
Acute nephritis	35	(16.1%)
Recurrent hematuria and persistent proteinuria	33	(15.15%)
Impaired kidney function (serum creatinine > 1.5mg/dl)	18	(8.2%)
Isolated hematuria after exclusion of urological causes	13	(6%)

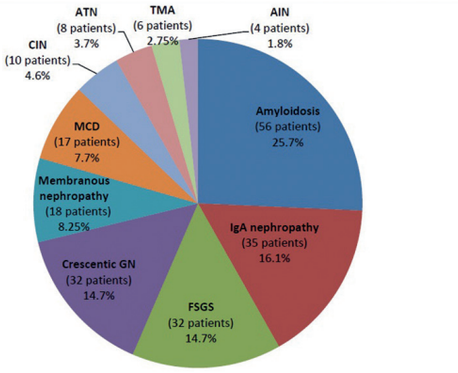
Kidney biopsy findings

The most common renal pathological diagnosis in our patients was renal amyloidosis [56 patients (25.7%)].The second most common renal pathological diagnosis was mesangial proliferation with IgA deposits [35 patients (16.1%)], followed by FSGS [32 patients (14.7%)], crescentic glomerulonephritis (GN) [32 patients (14.7%)], membranous nephropathy [18 patients (8.25%)], minimal change disease (MCD) [17 patients (7.7%)], chronic interstitial nephritis (CIN) [10 patients (4.6%)], acute tubular necrosis (ATN) [8 patients (3.7%)], thrombotic microangiopathy (TMA) [6 patients (2.75%)], and acute interstitial nephritis (AIN) [4 patients (1.8%)] (Figure 1, Table 3).

Analysis of our data revealed that amyloidosis developed secondarily to CD rather than UC (P= 0.0015),

Table 3. — **Spectrum of renal pathological diagnosis of involved patients**

Pathological diagnosis	(N) % of kidney affected patients	% of all IBD patients	UC, [CD]	P value
Amyloidosis	(56 patients) 25.70%	6.25%	24, [32]	**0.0015**
IgA nephropathy	(35 patients) 16.10%	3.9%	22, [13]	0.49
Crescentic glomerulonephritis	(32 patients) 14.70%	3.6%	21, [11]	0.647
Focal segmental glomerulosclerosis	(32 patients) 14.70%	3.6%	18, [14]	0.325
Membranous glomerulopathy	(18 patients) 8.25%	2.0%	17, [1]	0.78
Minimal change disease	(17 patients) 7.70%	1.9%	11, [6]	0.794
Chronic interstitial nephritis	(10 patients) 4.60%	1.1%	9, [1]	0.877
Acute tubular necrosis	(8 patients) 3.70%	0.9%	7, [1]	0.911
Thrombotic microangiopathy	(6 patients) 2.75%	0.7%	3, [3]	0.838
Acute interstitial nephritis	(4 patients) 1.80%	0.04%	3, [1]	0.995



Iga : Immunoglobulin A. FSGS : Focal segmental glomerulosclerosis. MCD : Minimal change disease. ATN : Acute tubular necrosis. AIN : Acute interstitial nephritis. CIN : Chronic interstitial nephritis. TMA : Thrombotic micr-angiopathy.

Fig. 1. — Distribution of renal pathological diagnosis in involved IBD patients.

but with no specific relation to gender (P=0.107), nor with IBD location as assessed by the Montreal Classification [P=0.063] (Table 3).

The other variable renal histopathology diagnoses also did not correlate with the age of patients, or the duration of the IBD diagnosis. Furthermore, no correlation was found between the renal histopathology diagnosis and the severity of IBD as assessed by the Montreal Classification or with any specific pathologic features of IBD.

In terms of interstitial nephritis, we did not find a relation between interstitial nephritis and ASA in our IBD patients.

Immunology parameters

All of our patients were negative in terms of the presence of Anti-Nuclear Antibodies (ANA), and Anti-Double stranded Antibodies (ADNA). Anti-Saccharomyces Cerevisiae Antibodies (ASCA) were positive in only 31 patients [including 26 out of 57 (45.6%) CD patients, and 5 out of 161 (3%) UC patients]. Anti-Cytoplasmic Antibodies-p (p-ANCA) were detected in 7 patients [including 2 of 57 (3.5%) CD patients, and 5 of 161 (3%) UC patients]. Anti-Cytoplasmic Antibodies-c (c-ANCA) were also detected in 7 patients [including 3 out of 57 (5.2%) CD patients, and 4 out of 161 (2.5%) UC patients]. The presence of ASCA, ANCA-p, and ANCA-c in serum was significantly correlated with the detection of crescentic GN in renal biopsies (P= 0.001, 0.013, and 0.018, respectively).

IBD treatment

5-aminosalicylic acid (5-ASA) was the most common IBD drug and used by 215 patients, 3 of whom had hypersensitivity to this drug. Oral steroid therapy was used by 57 patients (CD16, UC 41) and metronidazole by 69 patients (CD12, UC 57). Azathioprine was used by 79 patients, Cyclosporine was used by 53 patients, Etanrecept was by only 29 patients (9 CD, 20 UC), and infliximab was prescribed for 28 patients (7 CD, 21 UC). Drugs used for IBD had no correlations with any of the renal histopathological diagnoses detected.

Complications of renal biopsy

Of our IBD patients subjected to renal biopsy, 6 patients (2.8%) developed transient hematuria after biopsy, and 1 patient (0.45%) of them had peri-nephric hematoma confirmed by computerized tomography (CT) imaging with blood hemoglobin drop necessitating blood transfusion and percutaneous arterial catheterization to stop the bleeding. None of the patients required a nephrectomy.

Discussion

Monitoring of kidney functions and urinary protein excretion at least once per year is advised for IBD patients (10). Development of nephritic or nephrotic syndromes,

unexplained renal failure, sub-nephrotic range proteinuria, or glomerular hematuria mandate a renal biopsy according to established general recommendations (6-8) to precisely define the histopathological pattern of renal affection.

Regardless of its cause, amyloidosis is a disease in which insoluble fibrillar protein aggregates precipitate in the extracellular tissues of various organs, eventually affecting their functions (11)

In secondary amyloidosis (AA), the amyloid fibrils are derived from serum amyloid A protein, which is an acute-phase reactant protein developing in chronic inflammatory or infectious diseases.

After chronic inflammatory arthropathy, chronic infections, and periodic fever syndromes, CD ranks as the fourth most common cause of secondary amyloidosis (12).

Several previous reports have described IBD-associated amyloidosis (13-18), with a variable incidence ranging between 0.5 and 0.9% in the United States (19, 20), 2% in England (21), and 6 and 8% of patients with CD in Northern Europe (22-24).

Among the various renal diseases that were detected in the study cohort, amyloidosis was the most common renal pathological diagnosis [56out of 218 patients (25.7%)].

The risk of IBD-associated amyloidosis was reported to be 10 - 15 fold higher in CD cases than in UC cases (25). It is also more common in male IBD patients (2).

In this study, amyloidosis developed more frequently in CD individuals than UC individuals [P=0.0015]. However, no specific preponderance to gender [P=0.107], or IBD location as assessed by the Montreal Classification was observed [P=0.063].

A diagnosis of amyloidosis in our patients relied upon the detection of characteristic green birefringence of the amyloid deposits with the Congo Red stain. Unfortunately, immunohistochemical examination with anti-amyloid AA-specific monoclonal antibodies was unavailable in our laboratory for definite confirmation of the type of the amyloid fibrils.

Concerning IBD associated IgA nephropathy, the first two cases were reported in 1984 by Hubert (26). This investigator described the development of IgA nephropathy during relapse of IBD. He also demonstrated the remission of IgA nephropathy after successful treatment of IBD. This remission was proven by repeat kidney biopsy. Several subsequent case reports have also described IBD-associated IgA nephropathy (27-33).

Similarly, we found IgA nephropathy in this study to be a common IBD-associated renal disease along with renal amyloidosis.

I gA is well known to play an important defensive role in the gastrointestinal mucosa. The pathogenesis of this secondary form of IgA nephropathy may be attributed to concomitant factors including mucosal inflammation with subsequent chronic immune stimulation together with loss of tolerance, and dysregulated IgA production and transport (34).

Furthermore, both IBD and IgA nephropathy have been found to be associated with HLA-DR1 refering to another link in the genetic susceptibility form (33).

Crescentic GN which is a severe form of proliferative inflammation affecting the renal glomeruli has been previously reported to be a variant of renal involvement in IBD patients (35).

In this study; crescentic GN was the next most common form of renal involvement after renal amyloidosis, and IgA nephropathy. It affected 32 out of 218 patients (17.4%). More importantly, the presence of crescentic GN was significantly correlated with positive serum ASCA that has been found to be associated with highly aggressive phenotypes of IBD (36).

Additionally, crescentic GN was found to be correlated with serum ANCA-p, and ANCA-c. Such a relation has been suggested but not confirmed previously in IBD patients (37). This finding should again raise the issue of whether the ANCA found in IBD patients have the same antigenic targets of ANCA found in renal vasculitis (38). Inflammatory bowel disease-associated interstitial nephritis has been frequently described to accompany the usage of ASA (2, 39, 40). However, in this study we did not find a similar relation between interstitial nephritis and ASA in our IBD patients.

The ultrasound guided-renal biopsy procedure was performed according to standard guidelines. Such a technique is associated with a low incidence of complications comparable to the incidence reported by Camilla et al. (41). It appears to be quite safe as an essential diagnostic tool to establish the nature of renal involvement and to determine the correct management plan.

As a non invasive alternative, urinary markers such as alpha-1-microglobulin [alpha-1-M] and N-acetyl-beta-D-glucosaminidase [NAG] were evaluated to assess renal function in IBD patients (42, 43). These tubular enzymes were found to be a sensitive and specific screening marker of renal damage in IBD patients, but they are not yet available as a screening tool, and could not clearly define the exact pattern of renal involvement.

Conclusions

Among the renal diseases that affected our IBD patients, amyloidosis was the most common renal pathological diagnosis. IgA nephropathy was next, and FSGS and crescentic GN followed. Crescentic GN was significantly correlated with the detection of ASCA, ANCA-p, and ANCA-c in the serum of our patients. No relations were found between the various forms of GN diagnosed and the IBD drugs used in the treatment of our patients.

Ethical Committee Approval

The local ethical committee of the Internal Medicine department, School of Medicine, Cairo University, approved this work.

Human and Animal Rights

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

"Informed consent was obtained from all individual participants included in the study".

Conflict of interest: The authors have declared that no conflict of interest exists.

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