The kidneys in inflammatory bowel disease

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SUMMARY
Extraintestinal manifestations and complications are common in patients with inflammatory bowel disease (IBD) and may involve almost any organ or system. Renal or urinary complications occur in 4-23% of patients often in those with severe long-standing disease. The most common manifestations are kidney stones, enterovesical fistulas and ureteral obstruction. Genital involvement is uncommon in IBD. Patients with IBD have a risk of nephrolithiasis 10-100 times greater than that for the general hospital population. Glomerulonephritis (GN) in IBD has been reported in at least 27 patients; of these 7 had CD, 17 had UC and 3 were indeterminate. Histology changes range from minimal change nephropathy to rapidly progressive crescentic GN which may be accompanied by active tubulointerstitial nephritis. Tubulointerstitial abnormalities are not uncommon in autopsy studies of IBD patients. Granulomatous interstitial nephritis, interstitial nephritis with hyperoxaluria and renal tubular acidosis have also been reported. Inflammatory bowel disease is an uncommon cause of secondary amyloidosis. Complications from medical therapy are relatively rare in the majority of drugs used to treat IBD. There is little or no nephrotoxicity with many drugs used including corticosteroids, azathioprine and 6-mercaptopurine, metronidazole and low dose methotrexate. The drugs with significant potential renal toxicity are the aminosalicylates (sulfasalazine, mesalamine, 5-ASA, olsalazine) and cyclosporine. Surgical complications following bowel surgery include ureteral injury, urinary retention and sexual dysfunction.

Key words: renal, urinary, genital, drugs, therapy, inflammatory bowel disease, Crohn’s, ulcerative colitis, glomerular, tubular, interstitial, kidneys.

1. EPIDEMIOLOGY
Extraintestinal manifestations and complications are common in patients with inflammatory bowel disease (IBD) and can involve almost any organ or system. Renal or urinary complications occur in 4-23% of patients, often in those with severe long-standing disease (Tables 1, 2). The most common manifestations are kidney stones, enterovesical fistulas and ureteral obstruction¹. Fistulas between the gastrointestinal tract and the urinary system are uncommon, occurring in 1-8%, being more common in patients with ileal or ileocecal disease than in those with colonic disease. Ureteral obstruction is not caused by stones in 50-73% of cases of CD and in 50% of cases of UC². This non-calculus obstruction (NCO) is on the right in the great majority of patients. Genital in-

Table 1. Renal complications in IBD
1. Glomerulonephritis (from minimal change nephropathy to rapidly progressive crescentic GN)
2. Tubulointerstitial abnormalities (interstitial nephritis, granulomatous interstitial nephritis, nephrocalcinosis, renal tubular acidosis)
3. Amyloidosis
4. Renal hypertension
5. Iatrogenic complications: medications, aminosalicylates, cyclosporine, xylitol at high dose, sodium phosphate (colon cleansing)
6. Miscellaneous complications
7. Pyonephrosis/Pyelonephritis
Table 2. Urologic complications in IBD

1. Fistulas
   - enterovesical
   - rectovesical
   - rectourethral
   - anourethral
   - urethrococutaneous
   - vesicocutaneous
   - ileourethral
   - enterourachovesical
   - ileal pouch-vesical
2. Acute/chronic pyelonephritis
3. Nephrolithiasis (uric acid, calcium oxalate, calcium phosphate)
4. Non calculous obstructive uropathy
5. Genital involvement (penis, scrotum, vulva, prostate gland)
6. Iatrogenic complications (Surgical complications)
7. Miscellaneous complications

Table 3. Stone types and pathophysiology in IBD (Adopted from reference 2)

<table>
<thead>
<tr>
<th>Stone type</th>
<th>Risk factors</th>
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<tr>
<td>1. Uric acid</td>
<td>Diarrhea, ileostomy, hyperuricemia</td>
</tr>
<tr>
<td>2. Calcium oxalate</td>
<td>Ileal resection or disease, enteric hyperoxaluria</td>
</tr>
<tr>
<td>3. Calcium phosphate</td>
<td>Bed rest, steroids, increased urine Ca (mobilization from bone and decreased tubular reabsorption of Ca)</td>
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Inflammatory bowel disease is an uncommon cause of secondary amyloidosis. Only a few dozen with CD have been reported with amyloidosis, the association with UC being even less common. The reported prevalence of secondary amyloidosis in IBD patients varies from 0.5-29% in CD and from 0-0.4% in UC with a lower prevalence clinically and a higher prevalence at autopsy. Complications from medical therapy are relatively rare in the majority of drugs used to treat IBD. There is little or no nephrotoxicity with many drugs used including corticosteroids, azathioprine or 6-mercaptopurine, metronidazole and low dose methotrexate. The drugs with significant potential renal toxicity are the aminosalicylates (sulfasalazine, mesalamine, 5-ASA, olsalazine) and cyclosporine. Surgical complications following bowel surgery include ureteral injury, urinary retention and sexual dysfunction. These are uncommon according to some studies whereas higher rates are reported in others, particularly with proctocolectomy. There are reports of various genitourinary malignancies in IBD patients, including renal cell, bladder, prostate and vulvar carcinoma. However, two large studies found no increased risk of renal or urinary malignancies in IBD patients.

2. IMMUNOLOGY

A study of 13 patients diagnosed with ulcerative colitis was conducted to determine whether the presence of ANCA in those patients is associated with renal pathology. Renal damage was not observed in ANCA-positive patients with colitis even after 1 year of follow up, suggesting that the ANCA found in these patients did not share the antigenic targets with the ANCA commonly found in renal vasculitis. Therefore the potential of ANCA of inducing renal lesions (if any) is dependent on their own antigenic specificity. As far as anti-brush border antibodies (ABBA) are concerned, seventy-four serum samples from patients with Crohn’s disease were analysed for the presence of antibodies against various tissue antigens. With indirect immunofluorescence microscopy, 61% of the patient sera were shown to possess antibodies (in a titre of 1:25 or more) reacting with rat brush border membrane antigens in the proximal tubules of the kidneys, in the gastric parietal cells, and in the bile canaliculi of the liver. Serum samples submitted for routine immunofluorescence antibody screening served as controls; 10% of these sera contained anti-brush border anti-bodies. There is also an antigenic relationship between human kidney, colon and the common antigen of enterobacteriaceal.
3. ANIMAL MODELS OF IBD NEPHROTOXICITY

In cats the diagnosis of cholangiohepatitis should be further evaluated for IBD and pancreatitis but there is no indication to search for nephritis. Rabbits which were immunized with intestinal antigens derived from rabbits, guinea pigs, and germ-free rats revealed interstitial nephritis. These changes did not occur when non-intestinal antigens were used for immunization. In rats the use of hyperosmolar enemas can induce nephritis throughout massive acidosis and electrolyte disturbances with hypocalemia and hypernatremia. Consequently, sodium phosphate solutions should probably not be used in patients with inflammatory bowel disease with a high risk of laceration of the mucosa or perforation of the bowel or direct toxic effect on kidneys. E 3040, a new class of anti-inflammatory drug used to treat IBD is suggested to have a uricosuric action, probably in the proximal tubules, using the hyperuricemia model rat. Inflammatory changes also occur in kidneys of the mutant mice with interleukin-2 (IL-2) receptor gamma chain-deficiency. The suspected nephrotoxic potential of 5-ASA was examined in Wistar rats at doses of 200mg 5ASA/kg. In those doses applied, 5-ASA did not of altering renal excretion in rats.

4. TESTS AND MARKERS OF RENAL FUNCTION IN IBD PATIENTS

Proximal and distal tubular damage markers as well as markers of glomerular toxicity are presented in Table 4. Kidney biopsy evaluation in IBD patients may be performed as usual by all the following methods: light microscopy, immunohistochemistry and electron microscopy. Radiology evaluation in IBD patients with any kind of suspicion or evidence of renal or urologic damage may be performed by the usual methods. Routine radiology may reveal findings compatible with renal tubular acidosis (nephrocalcinosis, nephrolithiasis and osteomalakia). More sophisticated methods include spiral CT or MRI.

Urodynamics and partial function of the kidneys can be assessed on the basis of the findings of two-nuclide dynamic renal scintigraphy with 131I- hippuran and 99mTc-pentatech. Also the use of the radiolabelled neuropeptide (111 In-DTPA-Arg1) - Substance P for visualisation of inflammation in IBD as well as the 99mTc or {99mTc} HMBAO-leukocytes or 99mTc-DTPA with human immunoglobulin (HIG) demonstrate activity in the kidneys and bladder up to 24 hours after the initial infusion. A renographic monitoring of the renal function with Hippuran in patients with Crohn’s disease treated with low dose was cyclosporin was proposed in a controlled study where a correlation has been found between the residual activity 20 minutes after the injection and the degree of interstitial fibrosis seen in renal biopsies.

5. OTHER ASSOCIATIONS WITH IBD RENAL INVOLVEMENT

Inflammatory bowel disease and IBD-related renal involvement can coexist with other organ or system deteriorations or disease. The rare triad sclerosing cholangitis, IBD and gromerulonephritis has twice been reported. Also nonspecific ulcerative rectocolitis and lupus erythrematosus with renal involvement has been

Table 4. Laboratory methods of assessing renal deterioration in IBD

<table>
<thead>
<tr>
<th>1. Glomerular toxicity:</th>
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<tr>
<td>- albumin</td>
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<tr>
<td>- transferrin</td>
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<tr>
<td>2. Proximal tubular damage</td>
</tr>
<tr>
<td>- membrane-bound enzymes</td>
</tr>
<tr>
<td>a. Alaninoaminopeptidase (AAP)</td>
</tr>
<tr>
<td>b. Dipeptidylpeptidasse 4 (DDP4)</td>
</tr>
<tr>
<td>c. Aminopeptidase M</td>
</tr>
<tr>
<td>d. Intestinal type alkaline phosphatase</td>
</tr>
<tr>
<td>e. γ-Glutamyl transferase (γ-GT)</td>
</tr>
<tr>
<td>- lysosomal enzymes</td>
</tr>
<tr>
<td>a.N-acetyl-beta-D-glucosaminidase (b-NAG)</td>
</tr>
<tr>
<td>- a1-microglobulin</td>
</tr>
<tr>
<td>- b2-microglobulin</td>
</tr>
<tr>
<td>3. Clearance of creatinine</td>
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<tr>
<td>4. Urine microscopy.</td>
</tr>
<tr>
<td>5. Clinical chemistry (urea, creatinine, K,Na etc)</td>
</tr>
<tr>
<td>6. Distal tubular damage</td>
</tr>
<tr>
<td>- Tamm-Horsfall protein</td>
</tr>
<tr>
<td>- Glutathione transferase π</td>
</tr>
<tr>
<td>7. renal biopsy evaluation</td>
</tr>
<tr>
<td>- light microscopy</td>
</tr>
<tr>
<td>- immunohistochemistry</td>
</tr>
<tr>
<td>- electron microscopy</td>
</tr>
<tr>
<td>8. Radiology</td>
</tr>
<tr>
<td>- routine radiology (excretory urography,pyelography).</td>
</tr>
<tr>
<td>- C.T, MRI</td>
</tr>
<tr>
<td>9. Nuclear medicine/scintigraphy</td>
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reported. IBD, ankylosing spondylitis, associated cutaneous vasculitis, glomerulonephritis and circulating IgA complexes have been reported in two patients.

6. RENAL HYPERTENSION IN IBD

Renal hypertension usually develops as a complication of renal failure in IBD as result of amyloidosis and is clinically expressed as nephrotic syndrome with peripheral edema. Renal hypertension can also be the presenting symptom of an asymptomatic non-calculus obstructive uropathy or as a result of chronic cyclosporine toxicity (arteriolopathy, interstitial fibrosis and tubular atrophy).

7. HEMODIALYSIS-KIDNEY TRANSPLANTATION AND IBD

In a large prospective 16 years study in 580 renal transplant recipients an unusual syndrome resembling IBD occurred in 7 patients. In some cases the progression of amyloidosis may be delayed or even brought to a halt after surgical treatment of CD. One case with malabsorption of oral cyclosporin in a renal transplant recipient with Crohn’s disease which improved after i.v administration of the drug emphasizes the role of bowel inflammation in a renal transplant recipient. An original surgical intervention is the bilateral autotransplantation of the kidneys with direct drainage into the urinary bladder, which may be a viable therapeutic option in complicated patients with short-gut syndrome and severe refractory calcium oxalate nephroureterolithiasis.

The successful management with pyridoxine in severe hyperoxalemia-related renal failure treated with hemodialysis in a CD patient with ileal resection emphasizes the role of impaired vitamin B6 status (pyridoxine) in inducing hyperoxalemia in CD patients. A case of AA amyloidosis complicating Crohn’s disease leading to renal dysfunction with rapid deterioration and consequent hemodialysis failing to avoid the fatal complications of heart amyloidosis has been reported. Acute renal failure, although rare, is a complication of enteric hyperoxaluria in Crohn’s disease. This type of renal failure may be reversible if recognized and treated early with hemodialysis.

8. RENAL AND UROLOGIC COMPLICATIONS IN CHILDREN WITH IBD

Several pediatric cases of renal parenchymal pathology in association with CD have been reported. IgA nephropathy and thin basement membrane disease in association with CD has been reported in 2 children presenting with recurrent bouts of gross hematuria in the first child, and persistent isolated microscopic hematuria in the second, with renal biopsy in this latter case compatible with thin basement membrane disease. Also glomerular nephropathy with IgA mesangium deposits and CD has been reported in a 12-year-old girl presenting with hematuria and acute renal failure. The microscopic hematuria persisted but the nephropathy did not relapse even during a further digestive exacerbation. In a study with 26 patients aged 8-18 years with CD ileocolitis it has been suggested that, although there is a theoretical risk of renal tubular damage from the prolonged use of sulfasalazine, these patients are at no greater risk of renal injury than their counterparts not receiving the medication. Despite reports to the contrary, one publication reports the teratogenicity of sulfasalazine in kidneys in two infants born to a mother with IBD who received treatment with sulfasalazine throughout pregnancy. In this twin pregnancy the first twin, a female, had a left Potter-type IIa polycystic kidney and a rudimentary left uterine cornu. The second twin, a male, had some features of Potter’s facies, hypoplastic lungs, absent kidneys and ureters and talipes equinovarus. Urinary tract calculi predominantly calcium phosphate stones in children, although very uncommon, must always be taken into account as urologic complications of IBD in young patients. Secondary amyloidosis in CD of childhood and hypocomplementemic membranoproliferative glomerulonephritis in a child with UC is also reported. Although CRP is superior to ESR for inflammatory processes in children one must have in mind that this parameter is affected in nephrotic syndrome and renal failure.

9. COLON SURGERY IN IBD: RENAL AND UROLOGIC DISORDERS

Hydronephrosis is a rare unrecognized complication following restorative proctocolectomy with ileal pouch-anal anastomosis. Loin pain was the presenting symptom in two cases with the one developing impaired renal function. Obstructive uropathy could be, as described in one case, the initial manifestation of CD and left-sided hydronephrosis or right pyelic dilatation can be the first sign of CD. Also occult obstructive uropathy can complicate CD. Genitourinary complications following bowel surgery include ureteral injury, urinary retention and sexual dysfunction. Higher rates of these complications are reported in patients undergoing proctectomy.
Urinary retention can be caused by pelvic autonomic nerve damage and is seen in less than 16% of proctocolectomies but may be more common in long term anticholinergic users. The diagnosis is established with IVP or retrograde pyelography. Treatment involves catheter drainage, perhaps followed by cholinergic rehabilitation. Male sexual dysfunction (permanent or temporary impotence or ejaculatory failure) occurs in up to 27% and is due to damaged pelvic autonomic nerves. The risk of sexual dysfunction is higher in CD (12%) than in UC (6%) patients and especially in older patients with rectal dissection. Permanent impotence is uncommon but semen should be preserved as a precaution. Female sexual dysfunction is less common in women and is due to perineal fistulas and vaginal stenosis. It is reported that colectomies can improve female sexual function by improving general health status. Dysfunction of an ileal urinary conduit is rare and associated with hematuria and abdominal pain. Therapy includes steroids or creation of a new ileal or jejunal conduit. The effect of colon surgery in enteric hyperoxaluria is extensively discussed in the following paragraphs.

10. RENAL AND GENITOURINARY MALIGNANCIES IN IBD

There are reports of various genitourinary malignancies in patients with IBD including renal cell, bladder, prostate and vulvar carcinoma. Three of the reported cases of renal carcinoma occurred in patients with other risk factors for this malignancy. An increased risk of malignancy might be expected given the presence of chronic inflammation, especially in the peri-fistulae regions, increased exposure to diagnostic radiation and the role of immunosuppressive therapy. However large studies have found no increased risk of renal or urinary malignancies in IBD patients, although an increased risk of vulvar squamous cell carcinoma is reported. This potential increased risk of malignancy may be particularly important for virally-mediated tumors during immunosuppression therapy, and thus, all women on immunosuppression should have screening for cervical cancer on a regular basis.

11. URINARY TRACT INVOLVEMENT IN IBD

11.1 FISTULAS AND OBSTRUCTIVE UROPATHY

As far as entero-urinary fistulas are concerned CD is the third most common cause of enterovesical fistulas (EVF) after diverticulitis and cancer and is the most common cause of ileovesical fistulas. The majority of EVFs involve the sigmoid colon or terminal ileum and the bladder. Less common are rectovesical, rectourethral, urethrocutaneous, vesicocutaneous, ilcoureteral, enterourachovesical and ileal pouch-vesical fistulas. Most patients are between 40-50 years of age and there is a male predominance (1.4 to 7-fold) due to the interposition of the uterus and adnexae between the bowel and bladder in women. Clinical symptoms of the above described fistulas are bladder irritability, dysuria, urinary urgency, suprapubic discomfort, pneumaturia, fecaluria, chronic or recurrent urinary tract infections, urorrhea (rectal passage of urine). Diagnosis can be established with CT scan although MRI, cystoscopy, cystography, barium enema, endoscopy and endoscopic ultrasound may be of great help in selected cases. Bourne test is useful after barium enema, in which centrifuged urine is x-rayed to look for barium. Therapy of these fistulas is a very delicate topic of IBD treating strategy. Spontaneous closure of these fistulas occurs but is a rare phenomenon and surgical resection of the fistula, bladder wall and involved bowel is the definitive treatment. Operative morbidity and mortality rates are low, as is fistula recurrence. If resection is not possible a diverting colostomy may be the alternative choice of the surgeon. Conservative management for poor surgical candidates with antibiotics, antiflammatory or immunosuppressive agents may offer a satisfactory solution. Conservative management should always precede surgical intervention in order to reduce inflammation and ameliorate patients' general status.

11.2 NONCALCULUS OBSTRUCTIVE UROPATHY

In IBD noncalculus obstruction (NCO) is unrelated to age, gender or disease duration or activity. This type of obstruction occurs in 50-73% of CD and in 50% of UC patients and is usually caused by retroperitoneal or by a surgical complication (sutures) or by colon cancer. NCO is on the right in the majority of patients (71-100%) whereas bilateral or left-sided obstruction is reported in 0-29% of patients. Symptoms are bladder irritability, pyelonephritis, pyonephrosis or even hypertension. The treatment of NCO includes several options. Ureterolysis, whereby the ureter is freed from the surrounding fibroinflammatory tissue, is the final step. Conservative management with drugs for IBD, nephrostomy, ureteral stent, or drainage of associated abscesses must always precede more invasive procedures, such as ureterolysis or even nephrectomy.
11.3 NEPHROLITHIASIS

Patients with IBD, especially operated adults with ileocolic CD, have a risk of nephrolithiasis 10-100 times greater than that for the general population. Stones occur preferently on the right and are composed primarily of calcium oxalate or uric acid. Urate stones form as a result of intestinal fluid and bicarbonate losses which lead to concentrated acidic urine. This favors the precipitation of urate which may not correspond with the relatively low levels of uric acid in the blood stream. In addition inhibitors of crystallization (electrolytes and glucosaminoglycans) are lost with diarrhea and low urinary potassium, magnesium and pH decrease the excretion of citrate, another crystallization inhibitor. Therapy of uric acid nephrolithiasis includes treatment of diarrhea, alkalinizing the urine and increasing fluid intake. If stones recur allopurinol is of great help but it interacts with azathioprine/6-MP. Calcium oxalate stones are related to increased urinary oxalate excretion caused by increased intestinal absorption, termed enteric hyperoxaluria (EHO). Enteric hyperoxaluria (greater than 48mg/24h) is firstly related to bile salt malabsorption in the diseased or resected distal ileum which causes bile salt deficiency and fat malabsorption (secondary hyperoxaluria). Malabsorbed fats bind intraluminal calcium, decreasing the amount of calcium bound to oxalate (this last complex is poorly absorbed) resulting in increased oxalate absorption. Secondary EHO is related to increased colonic permeability to oxalate caused by the malabsorbed bile salts and fatty acids, perhaps enhanced by changes in colonic epithelial tight junctions due to decreased intraluminal calcium. This EHO is uncommon with ileal resections of less than 30cm and renal oxalate excretion is related to the amount of ileum resected. Because most oxalate is absorbed in the colon, EHO is rare in patients with colectomy, ileostomy or jejunostomy. Finally hyperoxaluria can be seen in long term parenteral nutrition, minimal oral intake, even in patients with colectomies, perhaps due to increased endogenous oxalate synthesis, (primary hyperoxaluria). Hyperoxaluria, decreased urine volume, decreased levels of crystallization inhibitors, ureteral obstruction, high urine levels of uric acid, acid urine, corticosteroid use and prolonged bed rest are factors that can promote stone formation. Oxalate also can cause interstitial nephritis and nephrocalcinosis resulting in acute or chronic renal insufficiency. Calcium oxalate stones can be avoided by treating enteric hyperoxaluria, increasing fluid intake, a low fat and oxalate diet, calcium supplementation cholestyramine and pyridoxine (B6) which decreases oxalate synthesis. In case of recurrence, alkalinization of urine, citrate and Mg supplementation are indicated. Sulfa crystals in the kidneys and the urine resulting from sulfasalazine or sulfapyridine therapy can easily be avoided as a cause of drug induced urolithiasis. A rare fatal case of reno-cebral oxalosis (calcium oxalate crystals) by xylitol administered in an unusually high concentration as postoperative parenteral feeding following ileocecal resection has been reported. Although it has been suggested, it is a matter of doubt enteric hyperoxaluria per se is the cause of stone diathesis in IBD. Bilateral autotransplantation of the kidneys with direct drainage into the urinary bladder may be an attractive and viable therapeutic option in complicated patients with short-gut syndrome and severe refractory calcium oxalate nephroureterolithiasis. Acute renal failure, although rare, as a complication of enteric hyperoxaluria, if recognized and treated early with haemodialysis may be reversible.

12. AMYLOIDOSIS IN UC AND CD

The reported cases of UC and secondary amyloidosis are much fewer than those reported on CD. The reported prevalence varies from 0-0.4% and is reported to be 0.07% in the largest more recent study. Renal involvement is evident in most of cases with various degrees of expression which range from asymptomatic proteinuria to nephrotic syndrome.

Only a few dozen cases with CD and secondary amyloidosis have been reported. The reported prevalence of secondary amyloidosis in CD varies from 0.5% to 29% with a lower prevalence clinically and a higher prevalence at autopsy. Amyloidosis is more common in ileocolitis (1.3-1.6%) than in ileitis (0.3-0.5%) or colitis (0.6-1.3%) and has a male predominance. The majority of patients have renal involvement with asymptomatic proteinuria or manifestations of nephrotic syndrome. In CD, more than UC, levels of serum amyloid which is an acute phase protein, in general, are elevated in proportion to disease activity. Systemic AA amyloidosis complicating CD has been found in 0.5-6% in America and Europe and is relatively rare in Japan. A case with systemic AA amyloidosis complicating CD and leading to renal dysfunction, end stage renal failure then hemodialysis and death has been reported. Differential diagnosis of primary systemic amyloidosis presenting as regional enteritis should always be considered.

The response of IBD related secondary amyloidosis to treatment has varied. It is reported that medical or surgical treatment has stabilized or improved renal disease but there exist reports suggesting no benefit with
any of these manipulations, moreover significant morbidity and mortality after surgery has been reported. This surgery should be addressed only to selected cases with refractory bowel disease with the presence of amyloidosis as secondary criterion. Colchicine at doses of 0.6-1.5mg/day may be of help, decreasing the amount of total SAA (serum associated amyloid). As treatment of renal amyloidosis in CD, plasmapheresis and azathioprine are suggested and for patients with end stage renal disease, kidney transplantation offers long term survival and quality of life.

13. NEPHROTOXIC DRUGS IN IBD

13.1 Aminosalicylates

The 5-aminosalicylic (5-ASA) is currently the treatment of choice for IBD patients. It can be administered as sulfasalazine (5-ASA+ sulfapyridine) mesalazine (5-ASA+ resins of gels) and olsalazine (two molecules of 5-ASA). Two men with longstanding UC who were treated with sulfalazine (2g/day) for several years and developed chronic renal failure are reported. Renal biopsy showed histological changes consistent with drug induced chronic interstitial nephritis. One of these patients underwent renal transplantation and the other lives with impaired but stable renal function. However systemic absorption and plasma concentrations of 5-ASA delivered from sulfasalazine were found to be lower than from equivalent doses of delayed or slow-release mesalazine formulations. The detectable excretion of tubular proteins - confirmed by increased alkaline phosphatase activity most likely to originate from proximal tubular epithelial cell is pathological and often precedes the clinical manifestation of chronic drug induced damage to the kidney. Recent studies have confirmed the presence of alterations of sensitive markers of renal dysfunction in patients with IBD, although no relation between aminosalicylate dose or extent or duration of disease was seen. An interesting study in patients with inactive ulcerative colitis treated with olsalazine or mesalazine showed that olsalazine use resulted in less overall circulating 5-ASA load which could well imply reduced potential for long term nephrotoxicity. However 11% of non-5-ASA treated patients with IBD were also excreting tubular proteins. The cases of acute renal failure associated with aminosalicylate therapy may describe a dose independent allergic condition, which may represent a clinical entity different from the findings reported. At present no clinical data have been presented suggesting that chronic treatment with aminosalicylates is unsafe unless a hypersensitive reaction occurs. In the largest cohort of 5-ASA users in which renal events have been evaluated there was an occurrence rate of 0.2 per 100 person-year (based on one case) in high-dose 5-ASA users. The rates were zero for all low-dose groups.

13.2 Cyclosporine

Cyclosporine A (CsA), a cyclic 11-amino acid peptide of fungal origin, has a hitherto unknown selective and reversible effect, mainly on T helper/inducer cells to which CsA is a potentially toxic drug. An early survey of more than 2000 renal transplant patients, of whom more than 25% had received high CsA doses (> 15mg/kg/day) showed that renal dysfunction occurred in 52%, hypertension in 39%, dysfunction in 18%, gingival hyperplasia in 15% and nausea in 9%. A correlation between the initial CsA dose and the degree of chronic nephrotoxicity in renal biopsy specimens from non-transplant patients warranted concern for further studies; however the risk of irreversible renal damage seems limited if CsA is given in a relatively low starting dose (5-7.5 mg/kg/day). Chronic CsA nephropathy is characterized by arteriolopathy, striped interstitial fibrosis and tubular atrophy. A multivariate analysis confirmed the importance of avoiding high initial doses of CSA. It has been suggested that the direct renal effect of CsA is a vasoconstriction of glomerular arterioles with a secondary decrease in glomerular filtration rate (EFR) and an increased proximal tubular fractional reabsorption rate. One result of these changes is an increased tubular transit time; another may be the tubular atrophy and interstitial fibrosis seen after long term CsA treatment. A preliminary report of an uncontrolled study in 21 CD patients suggests that both GFR and renal blood flow decrease after 6 months on low-dose CsA treatment. Plasma cyclosporin levels and serum creatinine did not help predict the extent of changes in renal function. At low doses cyclosporin causes changes in renal hemodynamics that may not be reversed by dose reduction. Further studies are needed to show whether renography can be used to distinguish between patients at high and low risk of chronic nephrotoxicity. Nephrotoxicity is related to the dose of cyclosporine but not to the duration of treatment. Controlled studies of IBD patients treated with 5mg/kg/day orally have shown nephrotoxicity in 0-19% and one controlled trial of intravenous CsA in UC had no nephrotoxicity in 11 patients. A review of 27 reports involving 343 patients with IBD treated with oral or i.v. CsA 6% had a >30% increase in serum creatinine and all but one normalized with drug withdrawal. Concomitant use of other nephrotoxic agents should be avoided and patients with preexisting renal dysfunction prob-
ably should not be treated with cyclosporine. Hippuran renography (o-iodohippurate sodium) is a sensitive method of measuring effective renal plasma flow and renal tubular function. Following an injection of $^{131}$I hippuran two values are measured; firstly the time taken to achieve maximal activity and, secondly, the residual activity 20 minutes after the injection ($T_{20}$). A correlation has been found between the $T_{20}$ and the degree of interstitial fibrosis seen in renal biopsies obtained from five patients with diabetes treated with CsA (unpublished data). 38 Danish patients with chronically active CD treated with doses of CsA 5.0-7.5 mg/kg/day took part in a study with renographic monitoring. The median final $T_{20}$ was significantly greater in both kidneys in patients who had received CsA than in those who had received a placebo. This suggests that the tubular cells might be sensitive to small changes, and, therefore, the methods used sometimes cannot detect changes in the renal blood flow. This is in keeping with a slight but significant increase in the median plasma creatinine which is cleared by glomerular filtration and tubular secretion. Recent studies have suggested that CsA is not directly toxic to the tubular cells but that the tubulopathy is secondary to primary changes in renal hemodynamics. We must finally emphasize the possibility of malabsorption of CsA in renal transplant recipients with CD.

13.3 COLONIC LAVAGE AND RENAL FAILURE IN IBD

The colonic lavage or cleansing in IBD patients before endoscopic procedure still remains always under consideration and question when renal failure exists or could easily appear. Oral sodium phosphate colonic lavage solution is very safe and only three patients from the general population developed acute renal failure in Canada. On the other hand 45% of the surveyed members of the Canadian Association of Gastroenterology (CAG) reported excluding its use in all patients with renal failure. All other kind of colonic lavage solutions are not contra-indicated during colon preparation in IBD patients unless renal failure is evident. In IBD patients with renal failure the author’s opinion is that their preparation should be adjusted and done only in the hospital area with careful renal monitoring during and after preparation. The type of diet, the use of enemas and the mild colon preparation may exceed the usual time of the routine preparation.

13.4 OTHER MEDICATIONS

Several drugs through various mechanisms have been reported to be nephrotoxic in IBD (Table 5). There are case reports about the nephrotoxic action of xylitol and E3040, an antiinflammatory drug which has uricosuric action, using the hyperuricemia model rat. Sodium phosphate enemas can extremely rarely, induce acute renal failure. Also non-steroid antiinflammatory drugs used for IBD musculoskeletal disorders may lead to acute renal failure. Antibiotics, non-disease special, such as cefuroxime axetil can extremely rarely induce bilateral renal cortical necrosis. The main 2 categories of nephrotoxic drugs in IBD are aminosalicylates and cyclosporine.

14. RENAL DETERIORATION IN IBD

14.1 RENAL DETERIORATION IN CD

IgA nephropathy is reported in one child with CD who presented with recurrent bouts of gross hematuria, in another child with CD who presented with hematuria and acute renal failure, and in several other cases. Membranous glomerulonephritis in CD of the small bowel has also been reported. Thin basement membrane disease biopsy-proven is reported in a child with CD and haematuria. Renal failure can be acute due to IgA nephropathy or amyloidosis or due to ASA therapy, which may induce tubulointerstitial nephritis or as complication of enteric hyperoxaluria with oxalosis of the renal tissue. Tubulointerstitial nephritis has been associated with ASA therapy but there are cases of patients who where not on ASA and are regarded as extraintestinal

Table 5. Reported nephrotoxicity of drugs used in IBD

1. Aminosalicylates (5-ASA, mesalamine, sulfasalazine, olsalazine)
   - glomerulonephritis
   - interstitial nephritis
   - minimal change nephropathy with nephrotic syndrome
   - in utero exposure (mesalamine)-Kidney absence and ureter abnormalities in neonate
   - tubulo-interstitial nephritis
2. Cyclosporine
   - arteriolopathy- striped interstitial fibrosis-tubular atrophy
3. Xylitol
   - oxalate stone formation in parenchyma (renal, brain)
   - death
4. Sodium phosphate enemas
   - acute renal failure due to dehydration during colonic cleansing.
5. Non steroid antiinflammatory drugs (naproxen)
   - interstitial nephritis
manifestation of IBD. There are studies suggesting that although there is a theoretical risk of renal tubular damage from the prolonged use of ASA, patients with IBD are no at greater risk of renal injury that their counterparts not receiving this medication. Kidney granuloma has also been reported in a patient with CD.

14.2.1 Glomerulonephritis (GN)

Focal glomerular sclerosis presenting as nephrotic syndrome in two patients with longstanding UC, improving rapidly after colectomy and steroid treatment has been reported. IgA nephropathy in two UC patients has also been reported, one in Japan and one in France. This kind of glomerulonephritis due to IgA mesangial deposits presenting with hematuria suggests, according to those papers, that the IgA secretion by the intestinal mucosa with the formation of immune complexes is trapped in the glomerular mesangium. In total 17 patients with UC have been reported with GN.

14.2.2 Interstitial nephritis and tubular damage

It has been attributed to ASA therapy but has also been reported in patients who were not on ASA. The urinary enzymes beta-N-acetylglucosaminidase (b-NAG), dipeptidylpeptidase 4 (DPP4) and alanine aminopeptidase (AAP) were measured as markers of renal tubular damage in 43 consecutive patients with UC. B-NAG levels were elevated in 28% of UC patients. The highest values of this pathological enzymuria were measured in patients with active UC before start of therapy. After successful treatment the enzymuria are turned to almost normal values despite the use of 5-ASA or sulphasalazine. This indicates that this could be an extraintestinal manifestation of IBD.

14.2.3 Potential pyelonephritis

It is reported that the asymptomatic significant bacteriuria in ulcerative colitis and cholepathias does not mean pyelonephritis but is a sign of the fact that the kidneys are in a condition endangered by pyelonephritis (potential pyelonephritis). That is why an aimed antibacterial treatment and subsequently bacteriological controls of the urine may prove necessary.

14.3 GLOMERULONEPHRITIS IN IBD

It has been reported in at least 27 patients: 7 with CD, 17 with UC and 3 with indeterminate colitis. There is no association with duration of disease and IBD can present with or after the GN. There is a male preponderance and association with the active inflammation in the bowel or biliary system. Histology ranges from minimal change nephropathy and IgA nephropathy to rapidly progressive crescentic GN with or without tubulointerstitial nephritis. The glomerular injury is suggested to happen in relation to immune complex deposition; immune complex activation, increased immunoglobulin turnover and glomerular immunoglobulin and or complement deposits have been demonstrated in IBD patients with GN. Patients often present with hematuria or nephrotic syndrome oliguria, proteinuria, elevated serum creatinine and oedema. Therapy is offered by steroids and with bowel resection.

15. RENAL AND UROLOGIC MONITORING IN IBD

Renal and urologic complications are not so uncommon in IBD patients and particularly in men and in CD. Thus, a real need for establishing rules that offer the possibility of monitoring, early detection and prevention of further deterioration is needed. The time of diagnosing a deterioration may be too late for critical and reversible therapeutic intervention. Periodic urinalysis, measurement of serum creatinine, detection of microalbuminuria and further, invasive or otherwise, methods needed, (scintigraphy, IVP, cystoscopy) are of great importance in order to early detect and treat a renal or urologic deterioration in IBD (Table 4). Especially in patients with previous renal or urologic problems or in patients who are receiving potentially nephrotoxic drugs, this monitoring strategy should be more intensive. Reversible renal and urologic damage is a real fact in IBD but we should believe that these deteriorations are either part of the extraintestinal manifestations of the disease or represent therapy complications. Every doctor who is responsible for IBD patients should, as a first step control bowel disease and as a second step look after further extraintestinal complications.

REFERENCES

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