AMYLOIDOsis and CROHN’S disease

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ABSTRACT

Secondary amyloidosis is a rare but serious complication of inflammatory bowel disease that may influence the prognosis even more than the underlying disease. Due to a better knowledge of the association of secondary amyloidosis to inflammatory bowel disease, early diagnosis of this complication is becoming more frequent, but its treatment continues to pose a challenge.

We report 4 cases of patients with Crohn’s disease and amyloidosis diagnosed in the inflammatory bowel disease Units of Toledo and Ciudad Real, which represent 0.68% of the patients with Crohn’s disease of our health areas. There have been not cases of amyloidosis in patients with ulcerative colitis. In our 4 patients the secondary amyloidosis was clearly related to Crohn’s disease, which was often of fistulising type. The predominant clinical picture of amyloidosis was nephrotic syndrome. The patients responded to medical and surgical treatment of Crohn’s disease and colchicine, which improved renal function in all cases except in one who required kidney transplantation.


INTRODUCTION

Amyloidosis is a clinical condition that is caused by the deposition of an extracellular protein material composed by a low molecular weight, insoluble, rigid, amorphous, fibrillar structure (amyloid) with beta-folded arrangement. It causes disruption of the structure of organs and tissues, with the subsequent impairment in their function (1).

Secondary amyloidosis or amyloidosis A (AA) is formed by N-terminal fragments of serum amyloid protein or serum amyloid (SAA). This is an acute phase reactant which appears during sustained inflammation, as it occurs in tumors, infectious diseases (tuberculosis, familial Mediterranean fever, bronchiectasis, osteomyelitis, etc.) and chronic inflammatory diseases (rheumatic mainly, but also inflammatory bowel disease (IBD) (2,3).

AA is a rare but severe association of the inflammatory bowel disease (IBD), being more frequent in Crohn’s disease (CD) than ulcerative colitis (UC) (2,4). AA might influence prognosis even more than IBD itself (4,5).

MATERIAL AND METHODS

We review the existing clinical records in the IBD Unit of the Hospital Virgen de la Salud of Toledo and the General Hospital of Ciudad Real until December 2009. In total, 1,140 records of patients with IBD were reviewed, 920 records from Toledo (457 with CD and 463 UC) and 220 records from Ciudad Real (130 with CD and 90 with UC). We selected patients who had developed amyloidosis during the course of IBD, analyzing their personal and family backgrounds, as well as their clinical presentation, prescribed treatment and clinical outcome.

We found four cases with IBD who were diagnosed with AA (3 from Toledo and 1 from Ciudad Real). All of them had CD. There wasn’t a single patient with UC and AA.
The diagnosis of IBD was made with clinical, laboratory, radiological, endoscopic and pathologic criteria. In all cases the diagnosis of amyloidosis was confirmed histologically.

**CLINICAL CASES (Table I)**

**Clinical case 1**

A 28 year old man, with primary hypothyroidism was diagnosed of colonic CD, affecting the ascending colon with inflammatory pattern. The patient developed simultaneously clinical and laboratory findings compatible with nephrotic syndrome. Renal biopsy confirmed the suspicion of AA (Figs. 1, 2 and 3). Steroid treatment was prescribed for CD and colchicine for AA, with good outcome. After 12 years of follow up the patient has only been treated with 5-ASA without colchicine or corticosteroids. The patient was at clinical and endoscopical remission, with normal renal function and mild proteinuria well under the nephrotic range.

**Clinical case 2**

A 41 year old man, smoker, was diagnosed of ileocolonic CD at the age of 26. During follow-up the patient presented a perianal fistula and an episode of intestinal subocclusion secondary to CD exacerbation. An enterovesical fistula, which required surgical intervention (ileocolonic resection) was also diagnosed. Coinciding with the exacerbation, he began with lower limb edema, impaired renal function and proteinuria in nephrotic range. Renal biopsy was performed and confirmed the suspicion of renal AA. He was treated with colchicine with improvement of clinical and renal function. CD recurred afterwards at the anastomosis, the disease being controlled with azathioprine. The patient suffers nowadays from mildly symptomatic perianal fistula and is currently in treatment with...
azathioprine plus mesalazine. The renal function is normal and proteinuria is under the nephrotic range.

**Clinical case 3**

A 58 years old male non-smoker, diagnosed of a retroperitoneal germ cell tumor requiring surgery and chemotherapy at the age of 32, began four months earlier with diffuse abdominal pain, nausea and vomiting, and diarrhea without pathological products. Blood analysis showed chronic anemia, impaired renal function and proteinuria in the nephrotic range. The small bowel barium X-ray showed a pattern of edema-stenosis in the distal ileum (Figs. 4 and 5). The patient underwent upper endoscopy, which was normal. Descendent duodenal biopsies were taken. Colonoscopy was suggestive of ileal CD, the diagnosis being confirmed in biopsies. Intestinal AA was diagnosed too, both in duodenal and colonic biopsies (Figs. 6 and 7). He was treated with corticosteroids and colchicine in the acute exacerbation of the IBD. CD is currently in clinical and endoscopic remission and treated with 5-aminosalicylates. The patient has proteinuria under nephrotic range but a slight impairment of renal function persists.

**Clinical case 4**

A 48 year old woman was diagnosed of terminal ileum CD at the age of 40 years, with inflammatory-stenosing pattern by abdominal CT and colonoscopy. The patient was allergic to penicillin, had hypothyroidism on replacement therapy, eradicated *H. pylori* infection, and microcytic anemia refractory to iron therapy. Treatment was prescribed with 5-ASA. At 43 years old progressive renal failure was objectived. 5-ASA was removed without improvement of renal function. Azathioprine treatment was started and had to be suspended due to an allergic reaction. She required multiple treatments with budesonide and prednisone. She was followed by the nephrology department because of deterioration of renal function. They decide to obtain a renal biopsy, and she was diagnosed of renal AA. The patient did not improve with medical therapy.
apy but treatment with colchicina was not attempted. She needed dialysis because of progression of the disease and renal transplant at the age of 47. Currently she is being treated with enteral nutrition supplements, tacrolimus and mycophenolic acid, which helps both CD and renal transplantation.

**DISCUSSION**

Association between AA and CD is rare, being first described in 1936 by Moschkowitz (6), and later by Olsan and Sussman in the late forties (7). In the largest series of patients published the incidence was less than 1% (2,4), being similar in our series (0.68%). We have not diagnosed any single patient with AA and ulcerative colitis, which seems somewhat reasonable, since the published prevalence of this association is even lower, with an incidence of around 0.07% (8).

The interval time from the diagnosis of CD to the development of AA is very variable ranging between 1 and
42 years (4). Sometimes the diagnosis of AA is made simultaneously with CD. In our series the median time until the diagnosis of AA was two years. This is so because among the 4 cases there are two in which the diagnosis of both diseases was made simultaneously. This form of presentation is being not so infrequent, as described in the literature (3,9,10).

It has been observed that there is a greater frequency of this association in males (1-4,10), as it happens in our series (75% of our patients are male). We are unable to explain this fact yet.

The clinical pattern more often associated with this partnership is the fistulizing-stenotic form of CD, usually accompanied by suppurative complications (2,4). In our series 3 of the 4 patients described had stricturing pattern, showing 1 of them fistula complication (case 2). The AA is often associated with ileal location, as it happens also in our series (75%).

It hasn’t been observed that patients with IBD who develop AA show more extraintestinal manifestations than patients who do not develop AA (2,4,5). None of our 4 patients had extraintestinal manifestations.

The most common clinical presentation is renal AA, reaching in some series up to 90% (4,11-15). Renal AA manifests as renal failure and proteinuria, and may progress to nephrotic syndrome as it happened in all our patients. Some patients may even reach severe renal failure requiring dialysis and renal transplantation as described in case 4 of our series. Data that help in the differential diagnosis with acute renal failure are that renal AA is usually accompanied by hypotension instead of hypertension, and that the size and morphology of kidneys is normal (13).

Amyloid may also be deposited in the gastrointestinal tract causing malabsorption, as was the case in 3 patients of our series. It should be suspected if malabsorption is greater than what would be expected if only CD persists after surgical resection of the affected area.

The diagnosis requires histological confirmation in the target organ, as it happened in our cases with renal biopsy (cases 1, 2, and 4), showing a high diagnostic efficacy. In the case of not being able to obtain biopsies of the theoretically affected organ, samples can be obtained from locations more accessible and with less risk, such as abdominal fat, or rectum, but with a lower diagnostic sensitivity (11). In case 3 of our series samples were obtained from duodenum and colon, and showed amyloidosis in these locations. No renal biopsy was taken because of the risk of it, and the diagnosis of renal amyloidosis was deemed very likely because of the clinical picture and the presence of AA in the locations described. In the histological study Congo red staining, was performed showing typical green birefringence with polarized light microscopy. In addition, specifically immunohistochemistry for AA is done, which differentiates between different types of amyloid.

Early diagnosis of the association between IBD and AA improves the prognosis of these patients. It allows them to benefit sooner of the most suitable treatment in each case, thereby avoiding further loss of organ function.

The goal of treatment in these patients is twofold. First, treat the underlying disease, the CD, to avoid the formation of amyloid precursor protein (serum amyloid, SAA), which is then deposited in the tissues. Second, treat the AA already established in the affected organ.

Although the series described is small it has been observed in many publications the efficacy of colchicine in AA with good results (5,15-17). This was the result in cases 1, 2 and 3 of our series, with stabilization, improvement or even normalization of renal function.

Dimethylsulfoxide has also been used as a treatment of AA secondary to IBD, with improvement of proteinuria and creatinine clearance, maintaining the improvement one year after completing the treatment (18).

In recent years, there have been some cases published that describe good response of AA to treatment with tumor necrosis factor antagonist (anti-TNF-alpha), particularly with infliximab (IFX) (19-22). This is based on the good response that anti-TNF-alpha have had in AA to inflammatory arthritis in different studies (23-25). In those studies infliximab is able to decrease or even normalize the serum levels of SAA, and to reduce proteinuria levels, but the improvement in renal function is poorer. Although not clearly demonstrated, some authors suggest that anti-TNF-alpha not only can reduce the synthesis of SAA, but also reduce the established deposit of amyloid (26). None of the patients described in our series received biological treatment.

In some cases the improvement induced by anti-TNF-alpha is not sufficient and the patient may end up needing dialysis and/or renal transplantation. But this treatment can serve as a bridge for patients with moderate or severe renal failure to get better to dialysis and/or renal transplantation (22).

Dialysis and renal transplantation are the only alternative left to patients whose disease is not controlled with medical treatment, and has progressed to terminal renal failure (1,14). This occurred in case 4 of our series, but this patient did well after the transplant because the immunosuppressive drugs required for maintenance of transplantation also help to keep CD inactive.

One issue still under discussion is if whether the resection of the affected bowel by IBD has a beneficial role in preventing the progression of AA. There are reports of regression of amyloidosis after surgical excision (27-29), as might have occurred in case 2 of our series. However in our case we can not attribute this benefit only to the surgical resection because the patient also received drug treatment for CD and AA. In other studies, the benefit is doubtful, and it can not be forgotten that the operative mortality may be greater in patients with amyloidosis and IBD (4,14,30), even though it wasn’t the case in our patient.

It is true that at present the association between IBD and AA is better known. Therefore, it is diagnosed earlier,
going from a postmortem diagnosis (31), to a diagnosis diagnosed in life. We also have treatments and alternative therapies that have improved the prognosis of such patients. But we must not forget that AA remains a potentially lethal disease as described in various publications (14,15,32,33), with serum creatinine level that has been most strongly associated with survival (4,34). Therefore, in a patient with CD that begins with impaired renal function association with AA must be considered in the differential diagnosis.

In summary we can conclude that in patients with CD amyloidosis is a rare complication, being much rarer in patients with UC. It predominates in males with ileal or ileocolic CD and severe clinical forms. Amyloidosis usually manifests as impaired renal function and nephrotic syndrome. Sometimes it is diagnosed simultaneously with CD. The treatment is based on colchicine and medical-surgical control of the EC, which in most cases prevent progression and improve outcome of both diseases.

REFERENCES