AA amyloidosis is an emerging cause of nephropathy in obese patients

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Letter to the Editor

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Dear Sir,

AA amyloidosis (AAA) is a rare disease secondary to chronic inflammatory states. The purpose of our study was to suggest that obesity was a potential cause for AAA since low-grade inflammation has been found in morbid-obesity [1]. Thus we conducted a retrospective study between 2006 and 2015. Inclusion criteria for this study were: i) patients sent in the Center since 2006; ii) histologic demonstration of amyloid showing apple-green bi-refringence in polarized light after Congo red and immunohistochemically-classified as AA; iii) with extensive explorations showing no common etiology for AAA including infectious diseases, autoantibodies especially anti-CCP, chest and abdominal scan and/or positron emission tomography (PET) scan, and genetic testing for monogenic auto-inflammatory diseases; iiii) with obesity defined by body mass index (BMI) ≥ 30 Kg/m^2, classified as moderate (BMI = 30–34.9 Kg/m^2), severe (BMI = 35–39.9 Kg/m^2), and morbid (≥40 Kg/m^2). The study complies with the French regulations regarding clinical research and respects the Declaration of Helsinki.

Our study included 13 patients which represented 4% with all type amyloidosis and 12% of AAA amyloidosis referred in the French national center for AAA. The clinical and biological characteristics of the patients at time of AAA diagnosis are reported in Table 1. Most patients had mild to moderate proteinuria, 4 patients had nephrotic syndrome. Seven patients had moderate chronic kidney disease (CKD), 5 had severe CKD, and one had end-stage renal failure. Four patients had proteinuria under 0.5 g/day associated with moderate (3 patients) to severe (1 patient) CKD. All patients had a chronically elevation of acute phase reactants proteins (C reactive protein (CRP) and serum amyloid A (SAA)). AAA was diagnosed on renal biopsy for all patients, and was also documented by minor salivary glands biopsy for 4 patients, intestinal tract biopsy for 2 patients and thyroid biopsy in one patient who had a goiter. Renal biopsy revealed predominant AA amyloid deposits in glomerular capillaries in the 9 patients with higher proteinuria, and predominant vascular amyloid deposits in the 4 other patients with CKD and mild proteinuria (≤1 g/day). Obesity was moderate in 6 patients, severe in 4 patients, and morbid in 3 patients. Only one patient had a family history of end-stage chronic renal failure. Five patients had diabetes. No case was referred to our center before 2010. All patients underwent large explorations in a reference center for inflammatory diseases which allowed excluding another cause of chronic inflammation including immunologic disorders, infectious diseases, malignancy, and autoinflammatory diseases. We concluded than no other cause but their obesity explained chronic inflammation, and enhanced AAA.

The putative role of obesity-associated chronic inflammation and the occurrence of AAA in humans were first described in 2005 in two sisters with extreme obesity due to a genetic leptin receptor deficiency [2]. Another case was described in Spain in 2009 [3]. In our series, inflammatory markers were mildly but chronically increased as it was previously described [3; 4]. Unlike cases published so far which included extremely obese (BMI 50 to 63 Kg/m^2) patients [2; 3], the obesity in our series was milder (median BMI = 35 Kg/m^2). The severity of renal disease at the time of AAA diagnosis in our series and in the literature is striking. In fact, renal biopsy in obese patients is not systematically done in case of mild renal impairment or proteinuria because it is often considered as a renal dysfunction linked to obesity itself [5] or due to diabetic nephropathy in case of associated diabetes. In our series, biopsies were performed in case of progressive deterioration of chronic renal function and/or nephrotic-range proteinuria. Contrasting with the classical description in the literature of 90% glomerular form and 10% of vascular form of amyloid pattern [6], our series showed a larger proportion of vascular form. This underlines that the diagnosis of AAA should be raised not only in case of proteinuria but also in case of renal failure with mild or no proteinuria, and biopsy should thus be performed. Since renal biopsy cannot easily be done in obese patients, a less invasive procedure such as minor salivary gland biopsy should be considered at first line.

The occurrence of amyloidosis in obese mice had already been observed in 1977. Amyloid deposits were found in the adrenal glands, the liver, the spleen and the kidneys which suggested a similarity with secondary amyloidosis, known nowadays as AAA [6]. Recent experimental studies confirmed that a high fat diet in mice was associated with the occurrence of renal AAA; these high fat diet challenged mice had significant elevated systemic SAA compared to low fat diet mice; other pro-inflammatory cytokines were increased especially tumor necrosis factor (TNF)-α and interleukine-6 [4]. Part of the systemic inflammation associated with obesity originates from adipose tissue in which many inflammatory cells accumulate, especially macrophages [7]. The production of SAA by adipocytes in obese patients has thus been shown and may contribute to the increased circulating SAA levels along with SAA liver product [2].

It has been shown that caloric restriction with significant weight-loss was associated with reduced SAA plasma levels [2; 8]. Since low SAA is associated with better prognosis in patients with AAA [9], we suggest that intensive weight-loss program, inducing significant reduction of SAA levels, should slow down the progression of AAA.

In conclusion, AAA should be considered as a potential cause of nephropathy in obese patients, even in moderate obesity. Proteinuria can be mild in case of predominant vascular AA amyloid deposition. Thus, histological exploration should be performed in case of severe or rapidly progressive renal failure and/or proteinuria. In case of chronic elevation of circulating acute phase reactants, minor salivary gland biopsy with Congo-red staining may be considered the first-line

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Table 1
Patient features (N = 13) at the time of AA amyloidosis diagnosis.

Age	56 years [43–74]
Sex	12 women (92%)/1 man (8%)
Origin	France (7)/Italy (2)/North Africa (3)/Pakistan (1)
Protéinuria	1 g/24 h [0.06–7]
Serum creatinine	176 μmol/L [120–1524]
CRP	21 mg/L [12–67]
SAA[a]	19 mg/L [8–41]
Sites of biopsies confirming AAA	Kidney (N = 13) Minor salivary glands (N = 4, one negative) Intestinal tract (N = 2) Thyroid (N = 1)
BMI	35 Kg/m^2 [30–50]
Type 2 diabetes (number of patients)	5

CRP: C reactive protein; SAA: Serum amyloid A; AAA: AA amyloidosis; BMI: body mass index.
Results are given in medians; range was indicated into brackets.
[a] SAA was available for 7 patients.

diagnostic test since renal biopsy cannot easily be performed in these patients. Considering the link between obesity, inflammation, and AAA, we recommend to improve the low-grade inflammation by intensive weight-loss program that should lower the progression of amyloid deposits.

Conflict of interest

All authors received no financial support for this work and declare no conflicts of interest.

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