Anti-TNF therapy in renal amyloidosis in refractory rheumatoid arthritis: a new therapeutic perspective

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ABSTRACT

Amyloidosis is a heterogeneous group of diseases characterized by extracellular deposits of a material composed of aggregates of amyloid – a poorly coupled protein – far from the site of synthesis, causing target organ dysfunction and clinical disease. Systemic amyloidosis A (AA), secondary to infections and chronic inflammation, especially rheumatoid arthritis (RA), is the most common form of amyloid deposition. Treatment of AA consists in the control or resolution of the baseline condition. The objective of the present study was to report a case of secondary renal amyloidosis in a patient with long-term refractory RA who presented sustained clinical improvement after the use of anti-TNFα (etanercept).

Keywords: renal amyloidosis, rheumatoid arthritis, anti-TNFα, etanercept.

INTRODUCTION

Amyloidosis is a rare heterogenous group of diseases characterized by extracellular deposits of amyloid, causing target-organ dysfunction and clinical disease.[1] It has a wide range of signs and symptoms, depending on the organs involved, including nephrotic-range proteinuria, hepatosplenomegaly, congestive heart failure, carpal tunnel syndrome, and macroglossia.[2] The abbreviations used for different types of systemic amyloidosis include: AL (immunoglobulin light chains – primary), AA (reactive – secondary), and Aβ2M (β2 microglobulin, associated with dialysis). Amyloidosis AL and AA represent approximately 95% of the cases.[3] Amyloidosis AA, secondary to chronic inflammation, is the most common type of systemic amyloidosis.[1] It represents an important and rare complication of rheumatoid arthritis (RA) caused by deposits of amyloid originated from acute-phase proteins. This process results in target-organ dysfunction and failure, implying a worse prognosis.[4] The diagnosis is confirmed by histopathology showing positive Congo red staining of amyloid deposits.[5] Current therapeutic approaches have shown poor results, except for the treatment of primary amyloidosis with alkylating agents, which is limited by the high toxicity of those agents. Due to the possibility of controlling the inflammatory activity, anti-TNF agents represent and alternative treatment of secondary types.[6,7] The Brazilian Journal of Rheumatology has published three cases of amyloidosis, two on primary amyloidosis[3,8] and one secondary to hemodialysis,[9] over the last ten years. The objective of this report was to illustrate secondary renal amyloidosis as a rare complication of RA, and to discuss the use of anti-TNFα (etanercept) agents as a new therapeutic perspective.

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CASE REPORT

A 66 years old female with RF positive RA for 24 years, according to the criteria of the American College of Rheumatology, presented with aggressive disease refractory to treatments used in the past for the baseline disease. Despite treatment with non-steroidal anti-inflammatories, corticosteroids, diphosphate of chloroquine, methotrexate, azathioprine, and leflunomide, severe synovitis in wrists in metacarpophalangeal and proximal interphalangeal joints developed and persisted with atrophy of interossei muscles, frozen wrists, ulnar deviation, and rheumatoid nodules in the upper limbs, persisted. Three months before hospitalization, the patient developed gravitational edema of the lower limbs ascending to the genital region, and mild face edema. Blood pressure levels were normal. Complementary exams showed preserved kidney function, dyslipidemia, hypoalbuminemia, 24-hour proteinuria of 5,833 mg/dL, and normal ultrasound of the urinary tract. Renal biopsy was positive for amyloidosis on Congo red staining (Figure 1). One year after the diagnosis of renal amyloidosis and treatment with azathioprine, 100 mg/day, leflunomide, 20 mg/day, and prednisone, 10 mg/day, she had a creatinine clearance of 112.72 mL/min with an increase in 24-h proteinuria to 16,567 mg/dL, and persistence of the articular involvement; treatment was maintained for another five months, until the patient returned with the required laboratorial exams to institute anti-TNF therapy. During that time, articular inflammatory activity persisted, inflammatory function tests remained altered (elevated CRP and ESR), and proteinuria showed a reduction from 16.6 to 7.04 g/dL. Since nephrotic-range proteinuria persisted after 17 months of the same treatment (Figure 2), another treatment option, with a biological agent, was instituted. Six months after the onset of etanercept, marked improvement of the arthritis, with a reduction in DAS 28 from 8.06 to 4.53, was observed, along with preserved renal function with reduction of proteinuria to 2.08 g/dL, indicating that progression of the renal disease was under control with weekly subcutaneous administration of 50 mg of etanercept.

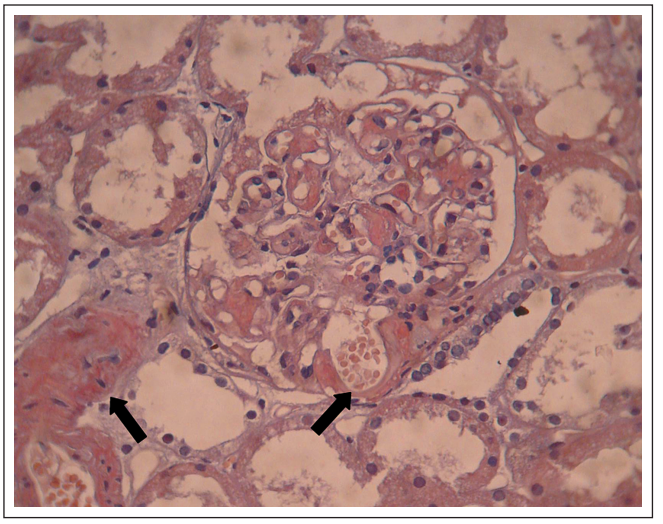

Figure 1
Histological view of a glomerulus with the presence of amyloid deposits (arrows). Congo red staining. Augmentation 400x.

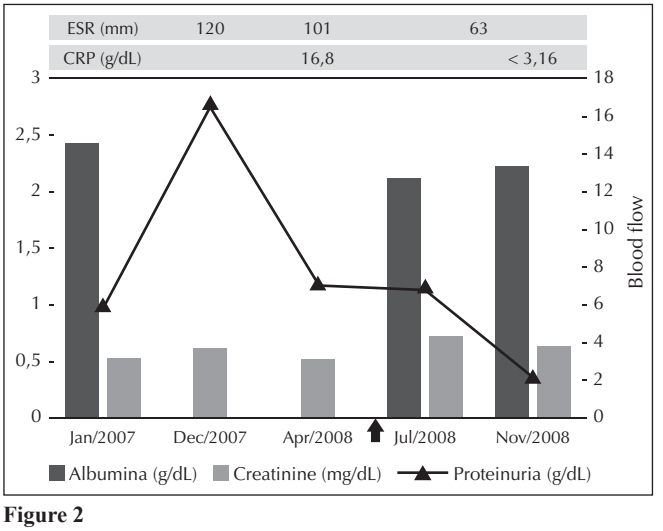

Figure 2
Evolution of laboratorial exams from January 2007 to November 2008.
⬆: 1st dose of etanercept (06.02.08); ESR: erythrocyte sedimentation rate; mm: millimeter; CRP: C-reactive protein; g: gram; dL:deciliter; mg: milligram.

DISCUSSION

Histochemically, amyloid A (AA) amyloidosis is a rare complication of chronic inflammatory diseases, including malignancies, infectious diseases, and rheumatic disorders, which are responsible for approximately two thirds of the cases, especially RA (75%). The incidence of AA amyloidosis after 15 years of RA is approximately 10%. Its development is related to inadequate treatment associated with aggressive, long-standing disease, often evolving to renal failure, nephrotic-range proteinuria, or both.[1] In a study with 25 patients with RA and AA amyloidosis, Aresté *et al*.[10] observed a 42 ± 8 months survival and 38% mortality rate (eleven patients), confirming that this complication is severe and it is associated with a poor prognosis. In case of clinical suspicion of amyloidosis AA, the diagnosis should be confirmed by rectal or fat pad biopsy or, whenever possible, histopathological exam of the involved organ. Evaluation of subcutaneous abdominal fat represents a good diagnostic alternative because it is minimally invasive, but it looses in sensitivity (60-70%) when compared to his-

topathological exam of the involved organ with Congo red staining (90%), which is more sensitive in highly suspicious cases.[1] This technique was introduced by Bernhold in 1922. Amyloid is characterized by red-orange coloration, under normal light, but the diagnosis is confirmed by apple-green birefringence under polarized light.[11] In the case presented here, kidney biopsy confirmed the diagnosis of amyloidosis, on Congo red staining, but immunohistochemistry, to define the subtype, was not performed; however, due to the history and evolution of the diseases, we hypothesized this was a case of AA amyloidosis. Small, non-controlled studies have shown that the use of cytotoxic agents and immunosuppressants in secondary amyloidosis improve survival and preserve kidney function.[12] Some studies have indicated that eprodisate, which belongs to a class of compounds that inhibit polymerization of amyloid fibrils and their deposition in tissues, as an alternative treatment in renal AA amyloidosis, delaying the reduction in renal function, although it did not have a significant effect on disease progression.[13] In the present case, the patient did not show clinical improvement with the drugs used, with persistent elevated levels of proteinuria, when an anti-TNFα agent was introduced to control progression of RA and renal amyloidosis. Due to the concomitant improvement of the joint disease, inflammatory function tests, and levels of proteinuria after the introduction of etanercept, improvement of the renal and articular diseases was attributed to treatment with this drug. Series of cases have described the efficacy of anti-TNFα therapy in patients with AA amyloidosis secondary to rheumatic diseases, probably due to the prompt and sustained clinical remission of RA.[1,6] Improvement seems to be related to inhibition of TNF-induced hepatic production of AA amyloid and deposition.[1] Thus, biological agents represent and alternative for the control of amyloidosis secondary to RA[6,7]. Gottenberg *et al*.[14] and Elkayam *et al*.[15] demonstrated a reduction in proteinuria and stabilization of the kidney function in patients with RA and spondyloarthritis in patients on anti-TNFα therapy. Clinical assays are necessary to determine the impact of this treatment on secondary amyloidosis, evaluating its safety and efficacy.[6] Summarizing, the presence of amyloidosis as a secondary complication of RA implies on marked morbidity and mortality, and the use of anti-TNFα agents represent a promising therapeutic alternative for the control of the rheumatic and renal diseases.

REFERÊNCIAS

REFERENCES

1. Mueller OS. Amyloidosis. Current rheumatology diagnosis & treatment, 2nd ed., USA: Mc Graw Hill; 2007.
2. Kyle RA. Amyloidosis: a convoluted story. Br J Haematol.2001; 114(3):529-38.
3. Alambert CO, Sarpi MO, Dedivitis RA, Alambert PA, Sementilli A, Arantes LP. Macroglossia como primeira manifestação clínica da amiloidose primária. Rev Bras Reumatol. 2007; 47(1):76-9.
4. Nakamura T, Higash S, Tomoda K, Tsukano M, Baba S, Shono M. Significance of SAA1.3 allele genotipe in Japonese patients with amyloidosis secondary to rheumatoid arthritis. Rhematology. 2006; 45:43-9.
5. Merline G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med .2003; 346:583-96.
6. Fernández-Nebro A, Tomero E, Ortiz-Santamaría V, Castro MC, Olivé A, de Haro M. Treatment of rheumatic inflammatory disease in 25 patients with secondary amyloidosis using tumor necrosis factor alpha antagonists. Am J Med. 2005; 118:552-6.
7. Ortiz-Santamaria V, Valls-Roc M, Sanmartã M, Olive A. Anti-TNF treatment in secondary amyloidosis. Rheumatology (Oxford). 2003; 42(11):1425-6.
8. Bortoli R,Lima IVS,Queiroz AC, Santiago MB. Amiloidose manifestando-se com pseudo-hipertrofia muscular. Rev Bras Reumatol.2007; 47(6):455-7.
9. Rocha FAC, Siqueira Neto JI, Aragäo Júnior AGM, Menezes DB. Quadriparesia espástica por amiloidose: relato de caso. Rev Bras Reumatol. 1998; 38(1):41-4.
10. Aresté JF, Solé JMN, Vaquero CG, García JV, Escofet DR. Secondary amyloidosis in rheumatoid arthritis. A clinical study of 29 patients. An Med Interna. 1999; 16:615-9.
11. Stoopler ET, Sollecito TP, Chen SY. Amyloid deposition in the oral cavity: a retrospective study and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;95:674-80.
12. Gillmore JD, Hawkins PN, Pepy MB. Amyloidosis a review of recent diagnostic and therapeutic developments. Br J Haematol.1997; 99:245-56.
13. Dember LM, Hawkins PN, Hazenberg BP, Gorevic PD, Merlini G, Butrimiene I *et al*. Eprodisate for the treatment of renal disease in AA amyloidosis. N Engl J Med. 2007; 356(23):2349-60.
14. Gottenberg JE, Merle-Vincent F, Bentaberry F, Allanore Y, Berenbaum F, Fautrel B *et al*. Anti-tumor necrosis factor alpha therapy in fifteen patients with AA amyloidosis secundary to inflammatory arthritides: a follow-up report of tolerability and efficacy. Arthritis Rheum.2003; 48:2019-24.
15. Elkayam O, Hawkins PN, Lachmann H, Yaron M, Caspi D. Rapid and complete resolution of proteinuria due to renal amyloidosis in a patient with rheumatoid arthritis treated with infliximab. Arthritis Rheum.2002; 46:2571-3.