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Case report

AA Renal amyloidosis associated with a gastrointestinal stromal tumor

Amiloidosis Renal AA asociada a tumor del estroma gastrointestinal

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ABSTRACT

Introduction: AA amyloidosis is an uncommon complication of solid malignancies and is usually associated with chronic inflammatory conditions. Its association with gastrointestinal stromal tumors (GISTs) is exceptionally rare, with only a few cases reported in the literature.
Case report: We describe a 64-year-old woman with metastatic duodenal GIST and peritoneal carcinomatosis. Four months after diagnosis, she developed severe nephrotic syndrome, acute kidney injury, and rapidly progressive renal failure requiring hemodialysis. Kidney biopsy revealed glomerular and vascular AA amyloid deposits confirmed by Congo red staining and immunohistochemistry for serum amyloid A protein, together with acute tubular necrosis. Extensive evaluation excluded other causes of secondary amyloidosis. Despite treatment with imatinib and evidence of limited radiological tumor response, renal function did not recover and the patient ultimately died from infectious and hemorrhagic complications.
Discussion: GIST-associated AA amyloidosis is an extremely rare entity. Reported cases share the presence of large tumors with necrotic areas and marked systemic inflammation, supporting a role for sustained serum amyloid A overproduction in amyloid deposition. Renal involvement is often severe and frequently progresses to kidney replacement therapy.
Conclusion: GIST should be considered a potential cause of AA amyloidosis in patients presenting with nephrotic syndrome or kidney dysfunction in the setting of a solid tumor with high tumor burden and persistent systemic inflammation. Early recognition of this association may facilitate diagnosis and management of a potentially devastating complication.

Palabras clave:
Amiloidosis AA
Tumor del estroma gastrointestinal (GIST)
Síndrome nefrótico

RESUMEN

Introducción: La amiloidosis AA es una complicación infrecuente de las neoplasias sólidas y se asocia habitualmente a procesos inflamatorios crónicos. La asociación con los tumores del estroma gastrointestinal (GIST) es excepcional, con escasos casos descritos en la literatura.
Caso clínico: Presentamos el caso de una mujer de 64 años diagnosticada de GIST duodenal metastásico con carcinomatosis peritoneal. Cuatro meses después del diagnóstico desarrolló síndrome nefrótico grave y fracaso renal agudo dependiente de hemodiálisis. La biopsia renal mostró depósitos glomerulares y vasculares de amiloide AA confirmados mediante tinción con rojo Congo e inmunohistoquímica para proteína amiloide A, asociados a necrosis tubular aguda. El estudio etiológico descartó otras causas de amiloidosis secundaria. A pesar del tratamiento con imatinib y de evidenciarse cierta respuesta radiológica tumoral, la paciente no recuperó la función renal y falleció por complicaciones infecciosas y hemorrágicas.
Discusión: La amiloidosis AA asociada a GIST es una entidad extremadamente rara. Los casos publicados comparten la presencia de tumores voluminosos, con áreas de necrosis y elevada actividad inflamatoria, lo que

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sugiere un papel relevante de la sobreproducción sostenida de proteína sérica amiloide A. La afectación renal suele ser grave y con frecuencia conduce a terapia renal sustitutiva.
Conclusión: El GIST debe considerarse una posible causa de amiloidosis AA en pacientes con síndrome nefrótico o deterioro renal asociado a una neoplasia sólida con importante carga tumoral e inflamación sistémica. El reconocimiento precoz de esta asociación puede facilitar el diagnóstico y el manejo de una complicación potencialmente devastadora.

Introduction

Systemic AA amyloidosis is a clinicopathological entity secondary to chronic inflammatory conditions, characterized by the deposition of insoluble serum amyloid A (SAA) protein fibrils in tissues.[1–3] The kidney is the most frequently affected organ, usually presenting as nephrotic syndrome and, in some cases, progressing to end-stage renal disease.[4]

Gastrointestinal stromal tumors (GISTs) are uncommon neoplasms of the digestive tract, most frequently located in the stomach, followed by the small intestine. Most harbor mutations in the c-KIT gene (70–85%) or PDGFRA (5–10%).[6] Although cases of coexisting GIST and AA amyloidosis have been reported,[7–9] the causal relationship between the two entities has not been clearly established.

Case report

We report the case of a 64-year-old woman with no relevant medical history, diagnosed with duodenal GIST and peritoneal carcinomatosis.

The initial presentation consisted of anemia and constitutional (toxic) syndrome, with preserved renal function (creatinine 80 μmol/L) and hypoalbuminemia (26 g/L), without an initial urinalysis. C-reactive protein (CRP) at diagnosis was 135 mg/L. SAA levels were not available. Abdominal computed tomography (CT) revealed a large duodenal mass (19 × 15 cm) with a heterogeneous appearance and areas of necrosis, in contact with the gallbladder, pancreatic head, and multiple loops of small bowel. Multiple peritoneal implants were observed in the pelvis, greater omentum, and left paracolic gutter.

Given the constitutional syndrome, treatment with dexamethasone 4 mg/day was started, with clinical improvement. Biopsy was consistent with GIST, with a proliferative index (Ki-67) of 2%, and next-generation sequencing detected a pathogenic variant in exon 11 of the c-KIT gene. With a diagnosis of duodenal GIST with extensive peritoneal dissemination and a c-KIT exon 11 mutation (imatinib-sensitive), treatment with imatinib 400 mg/day was started.

As a notable complication, she developed diabetes mellitus (DM) after starting corticosteroid therapy, requiring low-dose insulin and sitagliptin, with good metabolic control (HbA1c 5.6%).

Four months after diagnosis, the patient developed acute kidney injury with nephrotic syndrome and edema, creatinine 217 μmol/L, hypoalbuminemia 18 g/L, urinalysis with a protein/creatinine ratio of 53 g/g and an albumin/creatinine ratio of 24 g/g, and isomorphic microhematuria (14 RBC/HPF) in the setting of urinary catheterization. She also had normocytic normochromic anemia (hemoglobin 79 g/L) without thrombocytopenia or evidence of hemolysis, with TSH, folate, and vitamin B12 within normal range, ferritin 354 μg/L, and serum iron 2.4 μmol/L, suggesting an inflammatory profile. CRP at that time was 152 mg/L. Although a slight initial decrease was observed after starting imatinib, CRP values remained persistently elevated during follow-up. SAA levels were again not available at this point. Given the clinical situation, imatinib was temporarily discontinued and admission to the nephrology department was decided to clarify the cause of renal deterioration.

She was hemodynamically stable, with blood pressure 123/70 mmHg and glucose 93 mg/dL, eupneic, with preserved urine output (>0.8 mL/kg/h). Serologic and immunologic workup showed no abnormalities: protein electrophoresis without a monoclonal component, free light chains and immunoglobulins within range, normal C3 and C4, and anti-PLA2R antibodies <2 U/mL. An ultrasound-guided kidney biopsy was performed without complications.

During admission, she developed progressive worsening of renal function, oliguria refractory to diuretic treatment, and pleural effusion, requiring initiation of hemodialysis. Because of the high thrombotic risk, a CT angiography was performed, showing decreased lesion density and a slight reduction in the size of both the primary tumor and the peritoneal implants, with changes consistent with treatment effect, although the magnitude of tumor shrinkage was below that required to establish a partial response according to RECIST 1.1.[10] Deep vein thrombosis was detected in the left lower limb, along with inferior vena cava thrombosis extending to both renal veins, for which therapeutic-dose anticoagulation was started. Since the oncologic disease still showed signs of radiologic response and there was no evidence suggesting that the amyloidosis was secondary to treatment, imatinib was continued, as it was considered the most effective therapeutic option. Subsequent lines of treatment available for GIST generally have a lower probability of response and are mainly based on antiangiogenic agents, whose toxicity profile was not the most appropriate given the patient's clinical situation.

Kidney biopsy showed 10 glomeruli, all with deposits of eosinophilic material in the mesangium and in some interstitial vessels. This material was PAS-positive and silver-negative, with positive Congo red staining and positive anti-amyloid A antibody staining. Interstitial inflammation with acute tubular necrosis was also present. Immunofluorescence was negative. The diagnosis was AA amyloidosis with acute tubular necrosis[11] (Fig. 1).

Although histological review of the tumor mass did not yield sufficient tissue to conclusively assess the presence of amyloid, the amyloidosis was interpreted as secondary to the GIST, in the context of

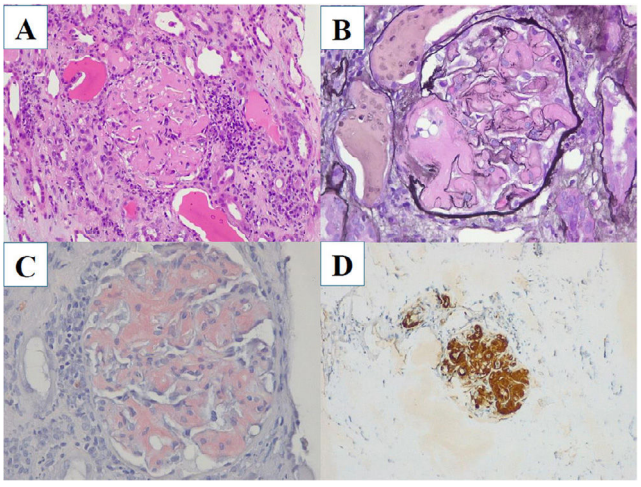

Figure 1. (A–D) Glomerulus with mesangial deposition of amorphous eosinophilic material on hematoxylin-eosin staining (A), non-argyrophilic on methenamine silver staining (B). Congo red staining shows positivity of these deposits at the mesangial level (C), confirming AA amyloid deposition by immunohistochemistry (D). Magnification ×400.

a large neoplasm associated with marked systemic inflammation, good metabolic control of recently diagnosed steroid-induced DM, and the absence of other identifiable inflammatory processes; therefore, treatment with imatinib was resumed.

The patient remained on hemodialysis without recovery of renal function or improvement of the nephrotic syndrome. During hospitalization, she developed severe complications, including *Staphylococcus aureus* bacteremia secondary to phlebitis and massive bleeding from the tumor mass, manifesting as hematemesis. The patient died 4 months after the diagnosis of GIST.

Discussion

AA amyloidosis and neoplasms

The most common glomerular involvement associated with solid tumors includes membranous nephropathy, IgA nephropathy, membranoproliferative glomerulonephritis, and podocytopathies.[12–14] Other glomerular entities, such as amyloidosis, may also be linked to malignant processes, particularly in its AL form in the setting of hematologic malignancies. Systemic AA amyloidosis, on the other hand, is rarely associated with solid tumors, accounting for less than 10% of its causes.[15] This association has been recognized for more than a century, with renal cell carcinoma being the most frequently identified tumor in these cases.[16–18] Proposed pathophysiological mechanisms include direct SAA production by malignant cells and hepatic stimulation secondary to inflammatory cytokines (IL-1β, IL-6, TNF-α) secreted by tumor cells or tumor-associated macrophages.[19] Other factors, such as genetic predisposition, appear to play a determining role in the development of significant amyloid deposits.[20]

Bharati et al. proposed a set of clinical observations to help establish a causal relationship between AA amyloidosis and tumor: (a) absence of other inflammatory, infectious, or neoplastic causes that could account for the amyloidosis; (b) amyloid deposition within or around the tumor; (c) decrease or normalization of C-reactive protein; and d) improvement in renal function or proteinuria after tumor resection.[20]

Renal involvement is common and may present as severe nephrotic syndrome, acute kidney injury, or rapidly progressive glomerulonephritis, often requiring kidney replacement therapy. In many cases, renal symptoms predominate over those of the tumor itself.[4,7,18,20]

The prognosis of cancer-associated AA amyloidosis is poor, with complications arising from renal damage being the leading cause of death.[21] Older age at diagnosis and severe renal presentation have been identified as poor prognostic factors.[1] Nevertheless, cases of clinical and pathological remission after complete tumor resection have been described, making surgical treatment the therapy of choice.[22,23]

GIST

GISTs are mesenchymal neoplasms that can arise anywhere along the gastrointestinal tract and present with a broad clinical spectrum. They typically behave as silent lesions until they reach a considerable size. Clinically, they may present with abdominal pain, dyspepsia, or constitutional symptoms. Tumor bleeding or rupture can lead to potentially life-threatening intraperitoneal hemorrhage.[5,6,24]

The main prognostic factors are tumor size, mitotic index, location, and tumor rupture.[25–27]

The liver and peritoneum are the most frequent sites of metastasis.[28] Most tumors express the KIT receptor (CD117),[6] with c-KIT mutations in 70–85% of cases and PDGFRA mutations in 5–10%.[29]

Complete surgical resection is the only potentially curative strategy.[30] In high-risk GISTs with imatinib-sensitive mutations, adjuvant treatment with imatinib for 3 years is also indicated, which has shown an overall survival benefit in this population.[31]

AA amyloidosis and GIST

The association between GIST and AA amyloidosis has been documented in the literature on three occasions:

In the first case, Jaakkola et al.[7] described a 59-year-old man with a 9-year history of type 2 DM who developed acute kidney injury and nephrotic syndrome with proteinuria of 34 g/24 h four days after resection of an 8.5 cm pelvic mass adherent to the rectum, bladder, and prostate. This proved to be a GIST with a high mitotic index and multiple necrotic lesions, with positive Congo red staining in vessels of the bladder wall and rectum. Kidney biopsy showed amyloid in the glomerulus, interstitium, and vessels, with positive anti-AA serum staining. Despite surgical resection, proteinuria remained massive at 3 months and worsening renal function led to initiation of hemodialysis. The patient remained free of metastases or recurrence over 18 months of follow-up. This case shares a clinical picture and a time to kidney replacement therapy similar to the case described here. However, in that case the patient had other potential causes of AA amyloidosis: morbid obesity (BMI: 48) and gout, which can concomitantly increase SAA.[32,33]

The second case, published by Overstreet et al.,[8] described amyloid deposition in the spleen and adrenal gland after resection of a gastric GIST in a 69-year-old man, with liver metastases 6 months after surgery. However, it does not detail the patient's medical history or clinical presentation.

In the most recent case, Muñiz-Pacios et al.[9] described a 64-year-old man with high-risk gastric GIST, with AA amyloid deposition in biopsies of the tumor and of the gastric and colonic mucosa. He subsequently developed nephrotic syndrome with microhematuria; kidney biopsy could not be performed because of the severity of the clinical picture. Given the results of the intestinal biopsies, a diagnosis of renal amyloidosis was assumed, and in addition to tumor resection, imatinib was started 15 months after diagnosis. However, at 19 months he started hemodialysis because of progression of chronic kidney disease.

These cases share the presence of large GISTs, a high mitotic index, and areas of necrosis, suggesting greater systemic inflammation and SAA production. However, the pathophysiology of the association between GIST and AA amyloidosis requires further study.

In our case, following the clinical criteria proposed by Bharati et al., it was not possible to confirm the presence of amyloid in the tumor tissue because of the limitations of the available sample, nor to assess a potential improvement after resection, given the unresectable nature of the tumor. Nevertheless, GIST is considered the most likely cause of AA amyloidosis in this context, given the close temporal relationship between tumor progression and renal deterioration, the marked biological aggressiveness of the tumor —with extensive necrotic areas and a high proliferative index— and the presence of an intense, persistent systemic inflammatory response, in the absence of other clinically identifiable causes of chronic inflammation after a thorough evaluation.

The recent diagnosis of corticosteroid-induced DM, together with adequate metabolic control during admission, makes a significant contribution to the development of amyloidosis or to the observed renal deterioration unlikely. On the other hand, inferior vena cava thrombosis extending to both renal veins, interpreted as a complication of the nephrotic syndrome and the prothrombotic state associated with the neoplasm, as well as the acute tubular necrosis seen on kidney biopsy —possibly in the context of a particularly aggressive nephrotic syndrome— likely acted as concomitant factors contributing to the rapid worsening of renal function and the need for hemodialysis, rather than as independent primary causes.

Conclusion

Although uncommon, GIST is a cause of AA amyloidosis with potentially severe renal consequences. This case underscores the importance of including AA amyloidosis in the differential diagnosis of glomerular involvement in patients with solid tumors, particularly those with a high tumor burden or biologically aggressive behavior.

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Declaration of competing interest

The authors declare no conflicts of interest.

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