ISSN 1669-9106 MEDICINA (Buenos Aires) 2024: 84: 774-779

Case report

SYSTEMIC AUTOINFLAMMATORY DISEASE, IgA GLOMERULONEPHRITIS AND RENAL CORTICAL NECROSIS: COINCIDENCE OR CAUSATION?

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Received: 22-XI-2023
Accepted: 14-V-2024

Abstract

We present a patient with a rare systemic autoinflammatory disease (mevalonate kinase deficiency -MKD-) with the identification of two heterozygous variants (c.1129G>A and c.32C>T) in the Mevalonate Kinase gene, detected by next generation sequencing and a highly prevalent glomerulonephritis (IgA nephropathy). The patient presents clinically with a monthly recurrent periodic fever from 12 days of age, accompanied by mucocutaneous lesions (maculopapular rash in extremities, aphthous stomatitis), joint (arthralgias in ankles, wrists and knees), lymphoid (cervical lymphadenopathy, splenomegaly), gastrointestinal (diarrhea, abdominal pain) and kidney (hematuria and proteinuria) with repeated biopsies showing IgA nephropathy alternating activity with chronicity. During follow-up. The patients presented a poor therapeutic response to multiple immunosuppressive regimens used for 7 years (corticosteroids, azathioprine, mycophenolate, cyclophosphamide, rituximab and tocilizumab), and finally a good response to canakinumab. Four years after starting canakinumab, during the course of an infection due to a muscle abscess, the clinical presentation is complicated by a severe renal microvascular event (renal cortical necrosis -RCN-) with acute kidney injury and dialysis requirement. Therecurrent episodes of inflammation due to MKD could act as triggers for the reactivation of glomerulonephritis (which would explain the poor response to immunosuppressants and the rapid progression to histological chronicity) and to generate a microenvironment that predisposes the development of RCN in the face of a non-serious infection. A defect in IgA molecules has been described in MKD, a phenomenon also observed in IgA nephropathy. This raises the challenging hypothesis of a common pathogenetic link between all the patient's clinical manifestations.

Key words: IgA glomerulonephritis, kidney cortex necrosis, hereditary autoinflammatory diseases, mevalonate kinase deficiency, canakinumab, acute kidney injury

Resumen

Enfermedad autoinflamatoria sistémica, glomerulonefritis por IgA y necrosis cortical renal: ¿causalidad o casualidad?

Presentamos un paciente con una rara enfermedad autoinflamatoria sistémica (deficiencia de mevalonato quinasa -DMQ-) con la identificación de dos variantes heterocigotas (c.1129G>A y c.32C>T) en el gen Mevalonato Quinasa, detectadas por secuenciación masiva en paralelo y una glomerulonefritis de alta prevalencia (nefropatía por IgA). El paciente presentó un cuadro de fiebre periódica recurrente mensual desde los 12 días de vida, acompañada de lesiones mucocutáneas (*rash* maculopapular en extremidades, estomatitis aftosa),

compromiso articular (artralgias en tobillos, muñecas y rodillas), linfoideo (linfoadenopatía cervical, esplenomegalia), gastrointestinal (diarrea, dolor abdominal) y renal (hematuria y proteinuria) con repetidas biospias mostrando nefropatía por IgA alternando actividad y cronicidad. Durante el seguimiento, tuvo una pobre respuesta terapéutica a múltiples esquemas inmunosupresores utilizados durante 7 años (corticoides, azatrioprina, micofenolato, ciclofosfamida, rituximab y tocilizumab), y buena respuesta finalmente a canakinumab. Cuatro años posteriores al inicio de canakinumab, durante el curso de una infección por un absceso muscular, el cuadro clínico se complica con un evento microvascular renal grave (necrosis cortical renal -NCR-) con fallo renal agudo y necesidad de diálisis. Los episodios recurrentes de inflamación por la DMQ podrían actuar como gatillos para la reactivación de su glomerulonefritis (lo que explicaría la escasa respuesta a inmunosupresores y la progresión rápida a cronicidad histológica) y para generar un microambiente que predisponga el desarrollo de una NCR ante una infección no grave. En la DMQ se ha descripto un defecto en las moléculas de IgA, fenómeno también observado en la nefropatía por IgA. Esto plantea la desafiante hipótesis de un vínculo patogénico común entre todas las manifestaciones clínicas del paciente.

Palabras clave: glomerulonefritis por IgA, necrosis de la corteza renal, enfermedades autoinflamatorias hereditarias, deficiencia de mevalonato quinasa, canikinumab, lesión renal aguda

The systemic autoinflammatory diseases (SAIDs) are genetically based entities characterized by a wide range of disorders with systemic and organ-specific inflammation. The diagnosis is complex and late, while the availability of new therapeutic agents has resulted in an improvement in the quality of life of patients[1].

Hyperimmunoglobulin D syndrome (HIDS) is a type of SAID associated with Mevalonate Kinase deficiency (MKD), an autosomal recessive genetic disorder due to mutations in the gene that encodes this enzyme[1]. There are very few published reports of subjects with this syndrome and kidney involvement[2-4], and it is not possible to establish a clear causal relationship or a mere concurrence of comorbidities.

Repeated autoinflammatory episodes, with associated infections could generate glomerular compromise, either generating or favoring the appearance of forms such as crescentic vasculitis or glomerulonephritis[2,3]. An immune mechanism such as T cell activation or cytokine release that relates both conditions is also possible[1]. The phenotypic expression of the various SAIDs could also be related to the appearance of renal manifestations, although its relationship with specific mutations has not been established to date[5]. Another complication of SAIDs is related to an increased risk of thrombosis. Hypercoagulable states have been reported in SAIDs cases, supporting the hypothesis of an interrelationship between inflammatory and thrombotic states[6].

We report a patient with a rare SAIDs and a highly prevalent glomerulonephritis characterized by a poor therapeutic response to multiple immunosuppressive schemes used. In the long-term the clinical picture is complicated by a renal microvascular event, raising the challenging hypothesis of a common pathogenic link between all the clinical manifestations of the patient.

Clinical case

A 38-year-old male patient with a history of recurrent febrile episodes since 12 days of life, without a relevant family history, and grandparents of Italian descent. These episodes, which occurred mostly in the evenings, persisted from 3 to 7 days, together with asthenia, chills, maculopapular rash mainly on extremities. Other manifestations, such as aphthous stomatitis, cervical lymphadenopathy, splenomegaly, episodic diarrhea and an appendectomy at 3 years of age (in the context of abdominal pain) were recorded from medical records examination. Arthralgia in ankles, knees and wrists they also appeared frequently. Episodes recurred periodically, every month, requiring symptomatic treatment with NSAIDs. In addition, he presented frequent episodes of pharyngotonsillitis requiring antibiotics.

He consulted the nephrology service in 2011 at the age of 26, due to intermittent macroscopic hematuria during episodes of fever and mild proteinuria. In biochemical analyses, serum creatinine was 0.6 mg/dl, presence of hemoglobin ++ in urine and a urinary protein/creatinine (P/C) ratio of 0.5 g/g. The serological (HCV, HBV, HIV), immunological (FR, ANA, ANCA), immunochemistry (C3, C4) and immunofixation profiles in serum and urine were normal, with the exception of the immunoglobulin (Ig) A dosage, which was slightly elevated (397 mg/dl for a normal reference value of less than 350 mg/dl). A kidney biopsy that revealed IgA glomerulonephritis, without inflammatory activity and no histological chronicity; thus, he was treated with a low-sodium diet (< 2 g of sodium/day) and ramipril 5 mg/day.

Due to suspicion of adult Still's disease, the rheumatology team begins treatment with prednisone 5 mg/day and azathioprine 100 mg/day for 6 months, and then tocilizumab 480 mg monthly during 2 years. Despite the treatment, systemic clinical manifestations accompanied by recurrent periodic febrile syndrome persisted. In 2014, at 29 years of age, he presented a reduction in proteinuria (P/C <0.3 g/g), but with persistence of gross and microscopic hematuria, with a serum creatinine of 0.8 mg/dl. A second renal biopsy confirmed IgA glomerulonephritis, with inflammatory activity and a striking increase in features of chronicity compared to the previous biopsy. Tocilizumab was stopped and IV methylprednisolone pulses plus IV cyclophosphamide (500 mg every 15 days for 3 months) were given, followed by prednisone (starting with a single dose of 60 mg, with a progressive decrease of 10 mg/day, until continuing with 10 mg/day) and nephroprotection with ramipril 5 mg/day. Due to this observed clinical/histological discrepancy (lack of proteinuria or kidney failure, in presence of histological increase in inflammation and chronicity), a third renal biopsy was performed to assess response to treatment 6 months later, with improvement in inflammatory parameters. Mycophenolate mofetil was added as maintenance immunosuppression. In 2015, at 30 years of age, a surveillance fourth renal biopsy performed to monitor the disease showed an increase in inflammatory activity; therefore, rituximab (1 g on 3 occasions) was administered.

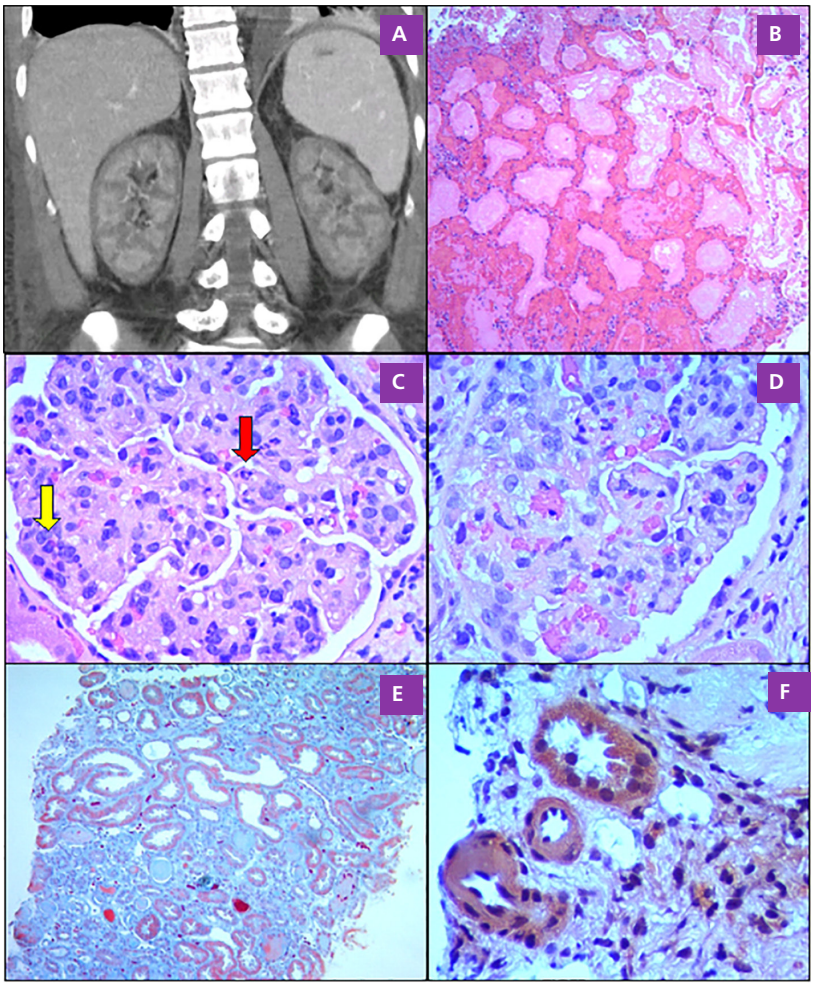
In 2018, mycophenolate mofetil was suspended, steroids were minimized and canakinumab 150 mg monthly treatment was begun, with an excellent clinical response and complete disappearance of systemic symptoms.

At mid-2022, at 37 years of age, the patient was admitted due to high-grade fever secondary to soft tissue abscessed cellulitis and abscesses in the left paraspinal muscle secondary to infection by methicillin-resistant *Staphylococcus aureus*. He was temporarily withheld from canakinumab and initially received vancomycin (1 gr every 12 hours IV for 11 days). Subsequently clindamycin was administered, according to antibiogram sensitivity (600 mg every 8 hours IV until the time of discharge). Concomitantly, the patient developed an increase in proteinuria and acute kidney injury, without sepsis or hypotension. Serum creatinine increased to 7.9 mg/dl and renal replacement therapy with conventional intermittent hemodialysis was started. This feature was characterized for acute normochromic normocytic anemia, LDH increased to 1092 U/L, without schistocytes, iron deficiency, or thrombocytopenia. Immunological profiles were normal (complement, rheumatoid factor, ANA, Anti-DNA, ANCA, cryoglobulins), serological (VDRL, HBV, HBV, HIV) and prothrombotic (lupus anticoagulant, anticardiolipin, anti B2-glycoprotein 1), except for a slight increase in serum fibrinogen (618 mg/dl for a normal value < 400 mg/dl). Renal doppler was normal, and after evaluating the risks and benefits (high suspicion of ischemic vascular damage with normal operator-dependent Doppler ultrasound vs. risk of iodinated contrast), it was decided to perform a triphasic iodinated abdominal CT, which showed marked bilateral diffuse renal cortical hypoperfusion (Fig. 1A).

A fifth renal biopsy showed evidence of an infarction with ischemic necrosis and interstitial hemorrhage in 30% of the sample, and IgA glomerulonephritis with fibrocellular crescents, associated with fibrosis and moderate chronic interstitial inflammation in the parenchyma (Figure 1B-F). Pulses of IV methylprednisolone were administered, followed by steroid maintenance with oral prednisone (starting at a single dose of 60 mg, with a progressive decrease of 10 mg/day, until continuing with 5 mg/day) and colchicine 0.5 mg/day. A slow and favorable response to infection was observed and at the time of hospital discharge, after 17 days of hospitalization, the diuretic rate improved. In outpatient control, antibiotic treatment was continued with clindamycin PO 300 every 8 hours for 28 days until the abscesses in the left paraspinal muscle disappeared.

In 2023, a genetic study was carried out that revealed two heterozygous variants in the *Mevalonate Kinase* gene associated with Hyper Ig-D syndrome: c.1129G>A (p. Val-377Ile), recorded as pathogenic (rs28934897) and c.32C>T (p.Pro11Leu) of uncertain significance (rs876661001). The genetic study was carried out by obtaining genomic DNA from a blood sample; the Library was prepared following the protocol based on capture enrichment (Library construction, SureSelect XT V6 kit - Agilent). Sequencing was performed by paired-end synthesis using the NovaSeq Sequencing System platform (Illumina). The mapping, alignment and variant calling procedure was carried out using the human reference genome GRCh38, using a protocol developed in Bitgenia, based on good practices established by the Broad Institute (Eli and Edythe L. Broad Institute of Harvard and MIT). Variant file analysis was performed using B-platform software. The variants were identified following the nomenclature recommendations of the HGVS. The interpretation of their impact was carried out in the context of the clinically relevant transcript (MANE SELECT). The analysis focused on the coding sequence of these transcripts, 20bp flanking the ends of the exons (above the introns) and other specific genomic regions that have been shown to cause disease at the time

Figura 1 | A: Triphasic iodinated abdominal CT (portal phase) showed marked bilateral diffuse renal cortical hypoperfusion. B: The fifth renal biopsy showed an infarction with ischemic necrosis and interstitial hemorrhage in 30% of the sample (HE). C: Glomeruli with mesangial (red arrow) and endocapillary hypercellularity (yellow arrow) (HE). D: Glomerulus with fibrocellular crescent (HE). E: Interstitial fibrosis with moderate chronic interstitial inflammation and moderate tubular atrophy (Masson). F: Arteriolar hyalinosis (Congo red negative)



of trial design. Subsequently, untranslated regions and other non-coding regions were not analyzed.

Due to the reappearance of his systemic symptoms, patient restarted canakinumab, with an excellent clinical response. The first intra-treatment immunoglobulin D measurement was not increased.

Currently, the patient is asymptomatic; his last creatinine value was 1.42 mg/dl, with persistence of microhematuria and proteinuria around 300 mg/day.

This report was evaluated and approved by the Institutional Ethics Committee. The patient signed an informed consent allowing the publication of the study.

Discussion

Mevalonate kinase deficiency (MKD) has been associated in the early 1980s with a SAID called HIDS. The clinical relevance of the IgD for the diagnosis of MKD appears poor and elevated serum IgD is not a mandatory requirement for the diagnosis of HIDS due to MKD[7]. This disease is inherited with an autosomal recessive trait[1]. Most patients are compound heterozygotes for two different mutations in the MVK gene[5,8]. Among these mutations, the most frequently found is V377I, as in the case of our patient[5,9].

The case reported here is typical of the SAIDs associated with MKD. Much less reported is the glomerular involvement among the manifestations of MKD. As in familial Mediterranean fever (one of the most frequent SAIDs), the presence of amyloidosis is one of the most cited nephrological disorders[10]; however, in the present case and despite several decades of disease, the presence of AA amyloidosis was not demonstrated in the repeated renal biopsies. The finding present in the renal biopsies corresponds to mesangial glomerulonephritis with IgA deposits, one of the glomerulopathies with the highest global incidence, which could mean a mere association between a rare SAIDs and very frequent glomerulonephritis.

However, a plausible pathogenic relationship could also be established between both entities. Based on the mechanism of multiple hits described in IgA nephropathy, the initial event in the pathogenic sequence is related to the production in the digestive and respiratory mucosa of IgA1 deficient in galactose and with low addition of sialic acid that it would act as an autoantigen, favoring the production of galactose-deficient anti-IgA1 antibodies[11]. This first event described in the primary forms of IgA glomerulonephritis would also be present and exacerbated in MKD. In this form of SAIDs, a defect has been described in the incorporation of sialic acid into the IgA molecule, added to high levels of IgA and IgD[12]. The evolution of the glomerulonephritis observed in this patient, showing a marked progression of histological damage in a short time with no response to the different immunosuppressive schemes, could be related to this mechanism of hyperproduction of abnormal IgA.

Infectious events usually serve as triggers for the reactivation or worsening of IgA glomerulonephritis. In this sense, patients with HIDS have an alteration in the immune mechanisms related to the function of T cells, since IgD could function as a surface receptor of these cells in addition to participating in certain mechanisms of innate immunity[1]. The coexistence of repeated infectious and inflammatory episodes, added to an increase in the quantity and a defect in the quality of IgA, could explain the pathogenic relationship between both entities present in the patient.

Canakinumab was associated with a significant improvement in the patient's clinical manifestations, as reported in the literature. However, a higher rate of infectious events, including visceral abscesses, have been described as observed in this patient[13].

The final renal episode corresponds to bilateral renal cortical necrosis. This event is unusual and generally reported in relation to severe systemic infectious, sustained hypotension, hemolytic uremic syndrome, or intravascular coagulation[14]. The patient had a deep infection with slow resolution of the symptoms, but without accompanying septic involvement or hypotension. Neither typical manifestation of thrombotic microangiopathies were found. Patients with SAIDs had a high incidence of thrombotic manifestations such as stroke, myocardial infarction and venous thrombosis perhaps in relation to elevated levels of PAI-1 or protein C deficiency in cases of nephrotic syndrome associated with amyloidosis as well as injury with endothelial and platelet activation not related to amyloidosis[6]. In this case, the development of renal cortical necrosis did not occur in the context of severe sepsis with hypotension, but rather was facilitated by the inflammatory condition sustained by the underlying disease and a superimposed infection.

Renal vasculitis, macrovascular thrombosis and even IgA nephropathy have been reported in SAIDs[15], while a renal microvascular compromise such as that observed in this patient under canakinumab´s treatment and with a pre-existing glomerular involvement has not been still reported in MKD.

The pathogenic mechanisms described allow us to assume that MKD and the SAIDs related have been instrumental -causative- in the development of the renal manifestations.

Acknowledgment: To Fundación Nefrológica de Córdoba, Córdoba, Argentina, for the contribution to cover the cost of publication.

Conflict of interest: None to declare

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