Clinical Kidney Journal

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Leading European Nephrology

Clinical Kidney Journal, 2017, vol. 10, no. 2, 229–232

doi: 10.1093/ckj/sfw110
Advance Access Publication Date: 26 December 2016
Exceptional Case Report

EXCEPTIONAL CASE REPORT

Nephrotic syndrome due to minimal change disease secondary to spider bite: clinico-pathological case of a non-described complication of latrodectism

Gonzalo P. Méndez[1], Daniel Enos[2], José Luis Moreira[2], Fátima Alvaredo[3], David Oddó[1]

[1]Department of Pathology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, RM, Chile, [2]Nephrology Unit, Clínica Los Andes, Los Angeles, Provincia de Bío Bío, VIII[a] Región, Chile and [3]Nephrology Unit, Hospital Universitario Río Hortega, Valladolid, Spain

Correspondence and offprint requests to: Gonzalo P. Méndez; E-mail: gmendez@med.puc.cl

Abstract

The patient was an 18-year-old man who developed nephrotic syndrome after a 'wheat spider' bite (*Latrodectus mactans*). Due to this atypical manifestation of latrodectism, a renal biopsy was performed showing minimal change disease. The nephrotic syndrome subsided after 1 week without specific treatment. This self-limited evolution suggests that the mechanism of podocyte damage was temporary and potentially mediated by a secondary mechanism of hypersensitivity or direct effect of the α-latrotoxin. The patient did not show signs of relapse in subsequent checkup. This is the first reported case of nephrotic syndrome due to a minimal change lesion secondary to latrodectism.

Key words: latrodectism, minimal change disease, nephrotic syndrome, proteinuria, spider bite

Background

Latrodectism is the envenomation secondary to spider bite from the females of the genus *Latrodectus* spp. ('black widows') [1]. These arachnids are distributed in the temperate zones of all continents, especially in Australia, the Americas and Europe [1–5]. The species *Latrodectus mactans* is the most common and most important for medical epidemiology in North and South America, with cases in the USA, Chile, Argentina and Uruguay [2–4]. Latrodectism presents predominantly as neurovegetative symptoms with low mortality [2, 4, 5]. The injected venom (α-latrotoxin) produces severe sympathetic and parasympathetic central nervous system effects, which include pain, diaphoresis, agitation, muscle spasms and high blood pressure [1, 2, 5]. Kidney involvement is very uncommon but when it occurs it is characterized by a decrease of glomerular filtration rate that results in oliguria and eventually anuria [2, 6]. Edema is usually localized [5] and in some cases in the palpebral zone [7]. Proteinuria has been described only in isolated cases [8].

Up to this communication, there are no described cases of latrodectism where the renal involvement corresponded to a nephrotic syndrome (NS).

Case report

The patient was a previously healthy 18-year-old male with no history of allergies and was employed as an agricultural laborer

Received: March 7, 2016. **Accepted:** September 29, 2016

in the area surrounding the city of Los Angeles, in South-Central Chile. While he was working threshing wheat, he suddenly felt an acute pain in his right forearm, and he could identify a bite from a 'wheat spider' (*L. mactans*). He was taken to the emergency room and admitted to hospital due to severe signs of latrodectism. He presented intense neurovegetative symptoms and signs during first hours of evolution and up to 24 h after, including psychomotor restlessness, inability to sleep, diaphoresis, alternating facial flushing with pallor, chills, severe frontal headache, upper and lower limbs pain, jaw and lower extremities tremor, mild hypothermia (35.7–36.2°C) and tachycardia (108 BPM). Symptoms persisted despite patient being given treatment with parenteral hydration, continuous IV infusion of dipyrone with morphine, 10 mg chlorphenamine IV and 100 mg ketoprofen IV (S.O.S.). The patient also presented during this time progressive and intense facial edema with high blood pressure (>150/90 mmHg), requiring an assessment by nephrologist. Five milligrams of amlodipine p.o. daily were added. Urine sediment revealed hematuria (35–40 RBC) and proteinuria >300 mg/dL.

Hemogram was normal and it showed Hct 41.6%, Hb 9 mmol/L (14.5 g/dL), MCV 80.6 μm^3 (80.6 fL), MCH 28.1 pG/cell and MCHC 34.9 g/dL. The three blood series had normal morphology and platelet count was 230 $\times 10^9$/L (230 $\times 10^3/\mu L$). LDH was normal (239 IU/L).

On the second day, 100 mg of hydrocortisone IV was added every 8 h for local allergic reaction, pain control and neurological manifestations, and chlorzoxazone (10 mg every 12 h p.o.) and carvedilol (25 mg every 12 h p.o.), with better control of hypertension.

On the third day, he presented 3.7 g/24 h of proteinuria and plasma albumin 4.78 μmol/L (3.3 g/dL; NV: 3.5–4.5), with normal serum creatinine (70.7 μmol/L) (0.8 mg/dL). Positive ANA (1:40) was found. The antibodies against ENA, DNA, c-ANCA, p-ANCA, HIV, HBV and HCV were all negative. Serum levels of C3, C4, IgM, IgG and IgA, as well as muscle enzymes, remained normal. A renal biopsy was requested that same day.

On the fourth day, hydrocortisone, analgesics, muscle relaxants and anti-allergic medications were suspended, continuing only with carvedilol and amlodipine. Serum creatinine was normal (60.99 μmol/L) (0.69 mg/dL).

Hemogram from Days 2, 3 and 5 post-bite was normal, but on Day 5 there was a spike in the eosinophil count that reached 5%.

On the seventh day the renal biopsy was performed.

On the eighth day the patient was discharged, without pain, with normal blood pressure (receiving 12.5 mg of carvedilol every 12 h and 10 mg of amlodipine per day), and with minor facial edema, but still with microscopic hematuria and proteinuria in isolated sample (300 mg/dL). Serum creatinine remained normal (58.34 μmol/L) (0.66 mg/dL).

Four weeks after his discharge, hematuria and proteinuria were negative in the urine sediment; serum albumin was normal (5.65 μmol/L) (3.9 g/dL), and he did not have edema. Amlodipine was removed and carvedilol was tapered to 12.5 mg a day.

A new checkup was scheduled 1 month later, but the patient never followed up with this nor any other subsequent appointments.

The renal biopsy findings were as follows: by light microscopy there were seven glomeruli, none of them sclerosed and with normal architecture. There was no evidence of proliferative changes affecting mesangium, capillaries or Bowman's space. The glomerular tufts did not show scarring, sclerosing or tip lesions. Tubules did not reveal signs of acute injury such as loss of brush border of proximal segments, flattening of epithelium, luminal distension, intraluminal cellular debris, vacuolization, necrosis or mitosis. The interstitium did not show inflammatory cells or edema. Tubular atrophy and fibrosis were not recognized (Figure 1). The immunofluorescence was negative for immune complexes. Electron microscopy examination showed an intense podocyte lesion with severe foot processes effacement (80%) and cytoplasmic degenerative changes (Figure 2) that were consistent with a secondary minimal change-type lesion (Figure 2). The basement membranes were normal and endothelial cells did not reveal tubuloreticular inclusions. Electron-dense deposits were absent.

Discussion

We discuss the first case of latrodectism which, in addition to the classic neurovegetative symptoms, presented a self-limiting NS of 1 week, secondary to a minimal change-type glomerular lesion. As mentioned previously, renal involvement in latrodectism is not frequent and mainly corresponds to an acute renal failure [2, 6], a situation that did not occur in our case. Our case of NS was characterized by facial edema, hypoalbuminemia, 3.7 g/day of proteinuria, hypertension and hematuria.

NS due to a spider bite seems to be an extremely unusual event and has not been described, presenting more typically in relation to ant bites or other insects, and bee or wasp stings, and mostly showing a secondary minimal change lesion (not always documented by ultrastructure) [9–13]. Anecdotally, a case of NS by focal segmental glomerulosclerosis secondary to an ant bite has been described [14]. In most of these cases the potential pathogenesis of podocyte injury is not clearly presented, being attributed in some cases to an allergic-type mechanism [10, 11], demonstrating increased levels of IgE against bee and wasp venom [11]. The evolution of those cases, as in ours, was favorable in terms of the resolution of the NS, although most required pharmacological management with oral prednisone or boluses of methyl-prednisolone [9–14].

Regarding the pathogenesis of our case, even though the patient had no history of allergies, we can hypothesize that because of the temporal relationship between the bite and the

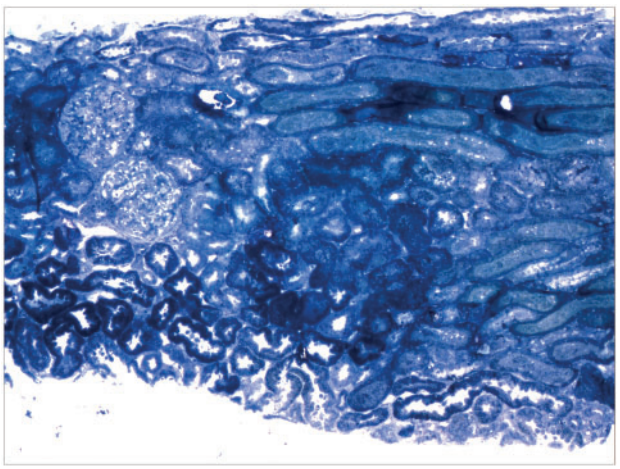

Fig. 1. Light microscopy. Cortical zone showing two glomeruli (on left) with normal architecture and no evidence of proliferative, inflammatory or sclerosing lesions. There is no interstitial inflammation and tubules do not reveal signs of injury or necrosis (Toluidine Blue stain, original magnification ×100).

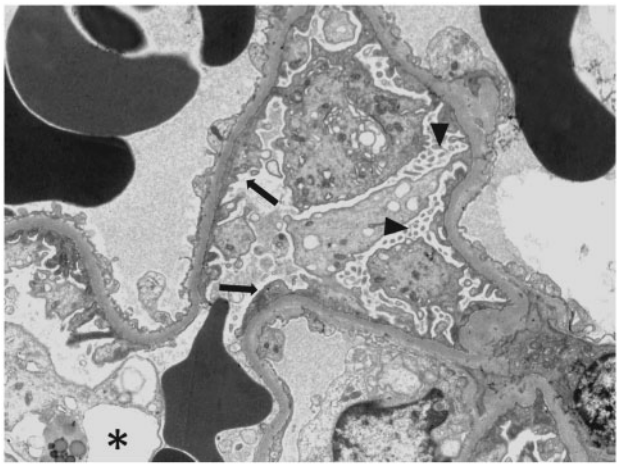

Fig. 2. Electron microscopy. Segment of a glomerulus with three capillary loops showing podocytes with intense foot processes effacement (arrows), cytoplasmic vacuolization (asterisk) and microvillous transformation (arrow heads). Electron-dense deposits are not observed (uranyl acetate-lead citrate, original magnification ×8000).

appearance of the nephrosis, as well as the self-limiting symptoms, temporary eosinophilia and the minimum steroidal treatment received, the NS was the result of a podocyte lesion that could be generated by secondary hypersensitivity to some of the α-latrotoxin components, with temporary cytokine production, potentially responsible for the podocyte damage and disruption in the permeability of the glomerular basement membrane. Cases of minimal change disease due to allergy mechanisms are often related to nonsteroidal anti-inflammatory drugs (NSAIDs) and they show variable extension of interstitial inflammation [15]. Even though we propose an allergy-related mechanism for the podocyte injury, we did not see interstitial inflammation in the biopsy. This could be explained considering the patchy distribution often seen in interstitial infiltrates at microscopic analysis; therefore, a sampling error factor could possibly be the reason for not seeing that finding. We can also speculate that due to the very short period of time for the toxin at blood circulation, the immunologic response did not have enough magnitude to trigger a tubulointerstitial allergic reaction, but only affected a more sensitive structure, the podocytes in the glomerular compartment [16].

It is also possible to consider that the spider venom could have a direct toxicity effect on the podocytes, either by its proteolytic properties or more likely by its effect on membranes that create channels permeable to the extracellular calcium (Ca^{2+}), an event that apparently would happen not only in neurons but also in other cells [17].

Ca^{2+} has a predominant role in homeostasis, signal transduction and remodeling of the podocyte actin cytoskeleton, fundamental in maintaining the ultrafiltration barrier undamaged [18]. Therefore, in theory, if in our case the α-latrotoxin could generate this marked increase of intracellular Ca^{2+} levels in the podocytes, its normal internal homeostasis could be temporarily affected, generating alterations in its cytoskeleton that resulted in extensive damage to the foot processes and the resulting nephrosis. We agree that it would have been very interesting to have had the antidote to α-latrotoxin as, in theory, this could have decreased the nephrosis in parallel with the neuromuscular symptoms, if we consider the increase of intracellular Ca^{2+} as the probable mechanism of podocyte damage.

The major differential diagnosis related to the pathogenesis of the minimal change lesion found in our case is the possible effect on the podocyte cells that may have produced the initial administration of an NSAID such as ketoprofen. However, we believe that due to the low dose, coupled with the emergence of the NS early post-bite and its particular evolution within the week of hospitalization, it is unlikely that it played an important role in this disease. In addition, the literature does not describe cases of NS with minimal change disease from consumption of ketoprofen, and we identified only one case where it was identified as membranous nephropathy during a long-term intake [19].

Nevertheless, considering these interesting etiopathogenic possibilities, we wonder why nephrosis is not a common complication in latrodectism, which leads us to firmly conclude that these hypothetical scenarios of allergic reaction and structural podocyte damage required a potentially genetic and immunological susceptibility of the host that received the toxin.

In conclusion, latrodectism can be included as a new cause, though a very rare one, of secondary minimal change disease, which must be taken into consideration as a particular complication in patients with an early and intense edema after the spider bite.

NS is a very unusual complication of bites from spiders of the genus *Latrodectus* and, therefore, this case corresponds to the first communication of a minimal change disease secondary to latrodectism, and demonstrated by ultrastructural analysis.

Conflict of interest statement

None declared.

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