Case report

Mechanisms of Kidney Disease in Sneddon's Syndrome: Case Report and Literature Review

Louise Ghislain[1]*, Selda Aydin[2,3], Liliane Marot[2,4], Nathalie Demoulin[1,3], and Johann Morelle[1,3]

[1]Division of Nephrology, Cliniques universitaires Saint-Luc; [2]Department of Pathology, Cliniques universitaires Saint-Luc; [3]Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain; [4]Division of Dermatology; Cliniques universitaires Saint-Luc; Brussels, Belgium.

*LG is a trainee in Nephrology

Correspondence to: Prof. Johann Morelle, Division of Nephrology, Cliniques universitaires Saint-Luc, Avenue Hippocrate 10, B-1200 Brussels, Belgium; T +32 2 7641855, F +32 2 7642836, E johann.morelle@uclouvain.be

Wordcount: 1731 + 128 (abstract)

ABSTRACT

Sneddon's syndrome is a rare, non-inflammatory thrombotic vasculopathy characterized by the combination of *livedo racemosa,* recurrent stroke, and histopathological skin lesions of *endarteritis obliterans*. Although multiorgan involvement suggests its systemic nature, detailed pathological description of affected organs - including the kidney - is exceptional.

We report a case of Sneddon's syndrome with chronic kidney disease, associated with skin and kidney features of *endarteritis obliterans.* The clinical presentation of our patient is compared to previously reported cases of Sneddon's syndrome with biopsy-proven kidney disease. We also discuss the differential diagnosis, pathophysiological mechanisms, relationship with antiphospholipid syndrome, and management of patients with Sneddon's syndrome and kidney disease.

This clinical observation supports the systemic nature of Sneddon's syndrome, and provides insights into the mechanisms by which this rare but probably underdiagnosed disease alters kidney function.

Keywords: chronic kidney disease - cutaneous rash - stroke - vasculopathy

BACKGROUND

Sneddon's syndrome is a rare clinical entity first reported in 1965 as the combination of *livedo racemosa* and multiple cerebral infarcts [1]. It generally affects young and middle-aged women, with a yearly incidence of 4 cases *per* million. Approximately 50% of cases are associated with antiphospholipid antibodies or systemic lupus erythematosus, while remaining cases are idiopathic. The disorder is usually sporadic, but familial cases with an autosomal dominant pattern of inheritance have been reported; however, the etiology of the disease remains unknown. The main diagnostic criteria include *livedo racemosa*, focal neurological deficits, and typical histopathological findings on skin biopsy. The most pathognomonic histological feature is *endarteritis obliterans,* defined as a severe intimal endothelial and medial smooth muscle cell proliferation that leads to vascular occlusion and thrombosis, in small and medium-sized cutaneous arteries at the dermo-hypodermic border is *endarteritis obliterans*.

In addition to cutaneous and neurological manifestations, Sneddon’s syndrome may affect other organs, including the heart, eyes and kidneys [1]. Chronic kidney disease (CKD) is highly prevalent in this population, affecting up to two thirds of the patients [2]. Detailed description of pathological changes on kidney biopsy are however scarce, and the mechanisms of kidney disease in Sneddon’s syndrome remain unclear.

Here we report a case of typical Sneddon’s syndrome with CKD, in whom kidney biopsy showed signs of vasculopathy and *endarteritis obliterans* similar to those found in the skin, supporting the systemic nature of the disease. We detail the long-term evolution of the patient, review all reported cases of patients with Sneddon’s syndrome and biopsy-proven kidney disease, and discuss potential

mechanisms of this severe systemic vasculopathy.

CASE DESCRIPTION AND LITERATURE REVIEW

A 47-year-old Caucasian woman was referred to the outpatient clinic of nephrology for the evaluation of CKD. The patient's medical history was remarkable for recurrent strokes during the last 2 years (Fig. 1A). Workup for stroke ruled out atrial fibrillation or other sources of atheroembolism, and showed serum creatinine level of 2.1 mg/dl, corresponding to an estimated glomerular filtration rate (eGFR, derived for the Modification of Diet in Renal Disease equation) of 27 ml/min/1.73m^2. No previous creatinine values were available for comparison. Blood pressure had repeatedly been normal (110-120/70-80 mmHg) during hospitalizations for stroke, and the patient never experienced hypertensive emergencies nor malignant hypertension. There was no family history of renal disease, hypertension or stroke.

On physical examination, blood pressure was 165/85 mmHg; body mass index, 29 kg/m^2; and a generalized rash was observed on the trunk and legs (Fig. 1B). There were no features suggestive of systemic sclerosis, such as Raynaud's phenomenon, skin thickening, sclerodactyly, telangiectasia, digital ulcers, or abnormal nailfold capillaries. Systematic workup showed a serum creatinine level of 2.5 mg/dl (eGFR 21 ml/min/1.73m^2); a bland urinary sediment; a urinary protein to creatinine ratio of 0.6 g/g; and bilateral small kidneys (<90 mm) on ultrasound, in the absence of renal cyst, urinary tract obstruction, or renal artery stenosis. Plasma level of C-reactive protein, complete blood count and complement levels were normal. There was no evidence of monoclonal gammopathy, hepatitis B and C, or human immunodeficiency virus infection. Screening for antinuclear, anti-Jo1, anti-Scl 70, anti-Ro/SSA, anti-La/SSB, anti-RNP, anti-neutrophil cytoplasmic, lupus

anticoagulant, anticardiolipin, and anti-ß$_2$ glycoprotein I antibodies was negative. Repeat cardiac ultrasounds consistently showed the absence of left ventricular hypertrophy (septum thickness 6-8 mm). Fundoscopic examination revealed no abnormalities.

Skin biopsy (Fig.2 A-B) showed subendothelial proliferation of small-sized arteries of the deep *dermis*, without injury of the internal elastic lamina nor inflammatory cell infiltration. The *epidermidis* and *dermis* were unremarkable, and there were no immune deposits.

Kidney biopsy contained 14 glomeruli, 5 of which were globally sclerotic. Interstitial fibrosis and tubular atrophy occupied 25-50% of the renal cortex. Small and medium-sized interlobular arteries exhibited a strong intimal proliferation, a dense and circumferential subintimal fibrosis, and oedema of the adventitia (Fig.2 C-D). Immunofluorescence studies showed no immunoglobulin or complement deposits. The presence of typical lesions of *endarteritis obliterans* both in the skin and in the kidney supported the diagnosis of Sneddon's syndrome with renal involvement.

The initiation of angiotensin converting enzyme inhibitor perindopril (10 mg o.d.) and calcium channel blocker barnidipine (20 mg o.d.) enabled optimal blood pressure control (120-135/75-80 mmHg). Acetylsalicylic acid and clopidogrel were introduced after multidisciplinary evaluation by nephrologists, hematologists and neurologists. The patient experienced no recurrence of stroke during the 5-year follow-up. However, significant disabilities remained, including dysarthria and mild cognitive impairment. Mild proteinuria (0.5-1.0 g/day) persisted, and CKD slowly progressed to end-stage kidney disease, with a mean annual loss in eGFR of -2.2 ml/min/1.73 m^2. The patient was started on chronic in-center hemodialysis at the age of 52.

Table 1 summarizes the main characteristics of all cases of Sneddon's syndrome with kidney biopsy reported to date [3-6], including the present case. All patients were females and aged between 20 and 59 years. They had hypertension, various stages of CKD, and non-nephrotic range proteinuria. The search for antiphospholipid antibodies was negative in all of them. Pathological lesions of *endarteritis obliterans* were systematically identified in kidney biopsies. Low-dose aspirin was used in all patients and some were also treated with either immunosuppressive agents and/or oral anticoagulants.

DISCUSSION

We report an exceptional case of Sneddon's syndrome with CKD, in whom kidney biopsy showed typical lesions of *endarteritis obliterans* such as those found in the skin, highlighting the systemic nature of the disease.

Sneddon's syndrome should be considered a potential cause of CKD and histopathological kidney features suggest direct damage of the renal vasculature by the disease. In a patient with CKD, skin lesions and recurrent strokes, the differential diagnosis also includes cholesterol crystal embolism and polyarteritis *nodosa*, and relies on detailed histopathological examination. The pathognomonic lesion of cholesterol crystal embolism is the presence of clear spaces within arterioles - where cholesterol crystals have been dissolved by routine processing, while polyarteritis *nodosa* is characterized by prominent vascular wall inflammation in medium-sized arteries, commonly associated with aneurysms and irregular constrictions of larger vessels. On the contrary, Sneddon's syndrome leads to typical lesions of *endarteritis obliterans*, as in our patient and in previously reported cases (Table 1) [3-6]. Of note,

lesions of *endarteritis obliterans* may be missing in the latest stages of the disease, when the vascular plug - initially composed of activated mononuclear cells and fibrin - has become acellular and fibrotic [2]. At this stage, vascular lesions can hardly be distinguished from thrombotic microangiopathies, especially those predominantly affecting arterioles [7], such as malignant hypertension, scleroderma renal crisis, and antiphospholipid syndrome. Integrating data from the clinical history (strokes, hypertension, Raynaud's phenomenon, pregnancy complications, thrombotic events), physical examination (livedo *racemosa*, skin changes, blood pressure), and lab tests (biological evidence of thrombotic microangiopathy, presence of antinuclear and/or antiphospholipid antibodies) is essential to the diagnosis. In our patient, recurrent stroke, *livedo racemosa*, absence of skin changes, pathognomonic histological lesions on skin and kidney biopsy, and absence of autoantibodies established the diagnosis of Sneddon's syndrome with kidney involvement. As hypertension is also highly prevalent in patients with Sneddon's syndrome (up to 65%), it is important to remember that lesions of intimal proliferation are not observed in hypertensive nephrosclerosis, typically characterized by myointimal hyperplasia of interlobular and afferent arteriolar vessels, hyaline arteriolosclerosis, and global glomerulosclerosis [8].

The relationship between Sneddon's syndrome and the antiphospholipid syndrome is complex, and both diseases may be parts of a continuous spectrum. The antiphospholipid syndrome is currently defined by thrombosis, pregnancy complications, or both in patients with persistent antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin antibodies, or anti-β2 glycoprotein I antibodies [9]. However, non-criteria manifestations (including thrombocytopenia, heart valve disease, and cutaneous, neurologic, and renal manifestations) are common,

and a high proportion of patients previously defined as ‘seronegative’ display novel non-criteria markers (such as antiphosphatidylserine/prothrombin antibodies) [10]. As a result, a more comprehensive classification for antiphospholipid syndrome is urgently needed [11]. The high prevalence of classical antiphospholipid antibodies (50%) among patients with Sneddon’s syndrome, and striking similarities in the clinical and histopathological presentation between both diseases suggest they may represent different expressions of the same disease [12-13]. Of note, antiphospholipid syndrome also leads to a vascular kidney disease characterized by an intense cellular proliferation in the intima and media of small vessels – exactly as in Sneddon’s syndrome [14-16]. Mechanisms involved in the pathogenesis of the antiphospholipid syndrome have been reviewed elsewhere and include increased expression of adhesion molecules on endothelial cells; impairment of coagulation pathways; increased expression of tissue factor; platelet activation and aggregation; complement activation; and activation of the mammalian target of rapamycin pathway in endothelial cells [11, 15-17]. Investigating a potential link between those diseases is important, as recent insights into the pathophysiology of the antiphospholipid syndrome [11, 17] have led to the development of novel targeted therapies, which may potentially also be used in Sneddon’s syndrome.

Recent insights also unveiled the first genetic predisposition factors to Sneddon’s syndrome. Loss-of-function mutations in the *CECR1* gene (cat eye syndrome chromosome region, candidate 1), encoding adenosine deaminase 2, were first associated with a spectrum of vascular and inflammatory phenotypes, ranging from early-onset recurrent stroke to systemic vasculopathy or vasculitis [18]. Initially reported in children, mutations in *CECR1* were later found in familial cases of Sneddon’s syndrome, and shown to segregate with the disease [19]. Mechanistic

studies demonstrated adenosine deaminase 2 acts as a growth factor for endothelial and leukocyte development and differentiation, and adenosine deaminase 2 deficiency is associated with compromised endothelial integrity, endothelial cell activation, and inflammation [18]. Whether *CECR1* gene mutations or polymorphisms and/or altered expression/function of adenosine deaminase 2 also predispose to sporadic Sneddon's syndrome remains unknown.

Currently, the optimal management of patients with Sneddon's syndrome is not established. Immunosuppressive agents showed no benefit, and long-term anticoagulation is warranted in patients with an established diagnosis of antiphospholipid syndrome. In patients without antiphospholipid antibodies, observations suggest that antiplatelet therapy (using acetylsalicylic acid and/or clopidogrel) reduces cerebral events, and preserves cognitive status [7, 20]. Similarly, in our patient, treatment with low-dose aspirin and clopidogrel and a strict control of blood pressure using angiotensin converting enzyme inhibitors were associated with the absence of stroke recurrence, and with a slow decline of kidney function (-2.2 ml/min/1.73 m^2/year).

In conclusion, Sneddon's syndrome is a systemic vasculopathy involving the skin, brain, and potentially the kidney. Nephrologists should be aware of the renal complications of this rare yet life-threatening and disabling disease. Future studies will need to clarify the mechanisms and optimal management of patients with Sneddon's syndrome.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Wu S, Xu Z, Liang H. Sneddon's syndrome: a comprehensive review of the literature. *Orphanet J Rare Dis* 2014;9:215.
2. Zelger B, Sepp N, Stockhammer G, Dosch E, Hilty E, Ofner D, Aichner F, Fritsch PO. Sneddon's syndrome. A long-term follow-up of 21 patients. *Arch Dermatol* 1993;129:437-447.
3. Al Meshari K, Al Eisa A, Akhtar M. Sneddon's Syndrome: A Systemic Arterio-occlusive Disorder. *Am J Kidney Dis* 1995;26:368-372.
4. Ohtani H, Imai H, Yasuda T, Wakui H, Komatsuda A, Hamai K, Miura A. A Combination of Livedo Racemosa, Occlusion of Cerebral Blood Vessels, and Nephropathy: Kidney Involvement in Sneddon's Syndrome. *Am J Kidney Dis* 1995;26:511-515.
5. Macário F, Macário MC, Ferro A, Gonçalves F, Campos M, Marques A. Sneddon's syndrome: a vascular systemic disease with kidney involvement? *Nephron* 1997;75:94-7.
6. Duval A, Darnige L, Glowacki F, Copin MC, Martin De Lassalle E, Delaporte E, Auxenfants E. Livedo, dementia, thrombocytopenia, and endotheliitis without antiphospholipid antibodies: seronegative antiphospholipid-like syndrome. *J Am Acad Dermatol* 2009;61:1076-8.
7. Francès C, Papo T, Wechsler B, et al. Sneddon syndrome with or without antiphospholipid antibodies. A comparative study in 46 patients. *Medicine (Baltimore)*. 1999;78:209-19.
8. Luke RG. Hypertensive nephrosclerosis: pathogenesis and prevalence. Essential hypertension is an important cause of end-stage renal disease.

Nephrol Dial Transplant 1999;14:2271-8.

9. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4:295-306.

10. Zohoury N, Bertolaccini ML, Rodriguez-Garcia JL, et al. Closing the Serological Gap in the Antiphospholipid Syndrome: The Value of "Non-criteria" Antiphospholipid Antibodies. *J Rheumatol*. 2017;44:1597-1602.

11. Garcia D, Erkan D. Diagnosis and Management of the Antiphospholipid Syndrome. *N Engl J Med*. 2018;378:2010-2021.

12. Francès C, Piette JC. The mystery of Sneddon syndrome: relationship with antiphospholipid syndrome and systemic lupus erythematosus. *J Autoimmun*. 2000;15:139-43.

13. Hughes GR, Khamashta MA. Seronegative antiphospholipid syndrome. *Ann Rheum Dis* 2003;62:1127.

14. Nochy D, Daugas E, Droz D, et al. The intrarenal vascular lesions associated with primary antiphospholipid syndrome. *J Am Soc Nephrol*. 1999;10:507-18.

15. Giannakopoulos B, Krilis SA. The pathogenesis of the antiphospholipid syndrome. *N Engl J Med*. 2013;368:1033-44.

16. Bienaimé F, Legendre C, Terzi F, Canaud G. Antiphospholipid syndrome and kidney disease. *Kidney Int* 2017;91:34-44.

17. Canaud G, Bienaimé F, Tabarin F, Bataillon G, Seilhean D, Noël LH, Dragon-Durey MA, Snanoudj R, Friedlander G, Halbwachs-Mecarelli L, Legendre C, Terzi F Inhibition of the mTORC pathway in the antiphospholipid syndrome.

257 *N Engl J Med* 2014;371:303-12.

258 18. Zhou Q, Yang D, Ombrello AK, et al. Early-onset stroke and vasculopathy
259 associated with mutations in ADA2. *N Engl J Med*. 2014;370:911-20.

260 19. Bras J, Guerreiro R, Santo GC. Mutant ADA2 in vasculopathies. *N Engl J*
261 *Med*. 2014;371:478-80.

262 20. Flöel A, Imai T, Lohmann H, et al. Therapy of Sneddon syndrome. *Eur*
263 *Neurol*. 2002;48:126-32.

FIGURE LEGEND

Figure 1. Clinical presentation of Sneddon's syndrome.

A. Brain magnetic resonance imaging showing multiple and bilateral ischemic lesions in the cortical and subcortical tissues.

B. Widespread cutaneous rash predominating on the legs and the trunk, and characterized by an irregular and non-infiltrated violaceous net-like pattern of the skin. Progressive skin discoloration started around the age of 42.

Figure 2. Pathological findings on skin and kidney biopsy.

A-B. On skin biopsy, small-sized arteries of the deeper *dermis* show typical lesions of *endarteris obliterans* (arrowheads), with intimal and medial proliferation; the absence of inflammatory cell infiltrate in the vascular wall or in the surrounding connective tissue. The *epidermidis* and the *dermis* were unremarkable. Immunofluorescence typically shows no immunoglobulin or complement deposition.

C-D. The kidney biopsy shows similar lesions, with hyperplasia and thickening of the intima of medium-sized arteries, leading to the occlusion of the vascular lumen (*endarteritis obliterans,* arrowheads). Non-sclerotic glomeruli showed no remarkable lesion, including no endocapillary or mesangial proliferation; mesangial enlargement; swollen endothelial cells; fibrinoid necrosis nor thrombi in blood vessels. Masson's trichrome and Periodic acid-Schiff stainings, original magnification 29x.

TABLE

Table 1. Cases of Sneddon's syndrome with kidney biopsy reported in the current literature, and comparison with the present case.

Author, year	Sex	Age - years	High BP	CKD stage	Urinalysis	AntiPL Ab	*Endarteritis obliterans* on kidney biopsy	Treatment	Renal outcome
Al Meshari, 1995	F	20	+++	IIIa	Mild proteinuria (0.4 g/d)	Neg.	Yes	Low-dose AAS	NA
Ohtani, 1995	F	59	+	I	Mild proteinuria (1.7 g/d), hematuria	Neg.	NA	Low-dose AAS, corticosteroids, cyclophosphamide and VKA	NA
Macario, 1997	F	35	-	II	Mild proteinuria (2.0 g/d)	Neg.	Yes	NA	NA
Duval, 2009	F	51	+	IIIa	Mild proteinuria (0.6-1.6 g/d)	Neg.	Yes	Low-dose AAS	NA
Present case	F	47	+	IV	Mild proteinuria (0.5-1.0 g/d)	Neg.	Yes	Low-dose AAS and clopidogrel	Slow eGFR decline (-2.2 ml/min/year) ESKD at the age of 52

BP, blood pressure; CKD, chronic kidney disease; antiPL Ab, antiphospholipid antibody; F, female; d, day; Neg., negative; AAS, acetylsalicylic acid; VKA, vitamin K antagonist; NA, not available; ESKD, end-stage kidney disease.