Spinal cord infarction associated to retinal vein occlusion in a patient with chronic kidney disease

Amina Ghezzaz,[1] Cristina Cristea,[2] Amel Ferradji,[2] El Habib Aboubekr,[3] Lynda Bouhanna-Hamitouche,[4] Sadri Chahed,[1] Amir Mahdjoubi[1]

[1]Ophthalmology Department; [2]Neurology Department; [3]Nephrology Department; [4]Physical Medicine and Rehabilitation Department, Centre hospitalier Argenteuil, Paris, France

Abstract

A 70-year-old man presented to the emergency department with blood hypotension associated to a sudden paraplegia and thermalgesic analgesia. He had an history of colic and prostatic adenocarcinoma, hypertension and non-dialyzed Chronic Kidney Disease (CKD) related to an idiopathic membranous glomerulonephritis type 1 discovered 9 years ago. Magnetic resonance imaging confirmed a diagnosis of Spinal Cord Infarction (SCI). Few months later, he presented a blurred vision due to central Retinal Vein Occlusion (RVO), which was improved by Anti-VEGF therapy. This is the first reported case of a concomitance of retinal vascular event and SCI highlights the links between the central nervous system and retinal vascularization despite separate involvement of the two events in the arterial and venous systems. Additionally, CKD worsened the risk of cardiovascular incidents by induced oxidative stress, thrombophilia, chronic inflammation, and endothelial dysfunction. SCI occurrence indicates severe vascular dysfunction and elevates the risk of additional vascular disorders.

Introduction

Spinal Cord Infarction (SCI), a rare disease that constricts the extensive anastomotic vascularization of the spinal cord, is difficult to diagnose.[1] The occlusion of the anterior spinal artery, which vascularizes the anterior two-thirds of the spinal cord, is more frequent and manifests clinically as paraplegia and deficits in spinothalamic sensation, sparing the proprioceptive and vibrational senses, and autonomous dysfunction.[1]

Retinal Vein Occlusion (RVO) is a vascular disease caused by circulatory depression of the central or branch retinal vein.[2] However, its pathological origin remains unclear despite the identification of multiple risk factors such as: hypertension, diabetes, sleep apnea syndrome, thrombophilia, hyperhomocysteinemia, and glaucoma.[3] Interestingly, several studies have reported the association between RVO and cerebral stroke; both conditions shared a same vascular origins, have common anatomical/physiological characteristics, and risk factors.[4,5] Furthermore, the mortality rate after stroke is high among patients with a history of RVO.[6]

Chronic Kidney Disease (CKD) has been identified as a risk factor for both RVO and cerebral stroke.[7] Furthermore, although the presence of a retinopathy and relatively large venous diameters have been associated with an increased risk of cardiovascular disease and stroke in patients with CKD,[8] the association between retinopathy/RVO and SCI has not been reported.

This case study reports for the first time an uncommon presentation of the sequential occurrence of an SCI and central RVO in a patient with decompensated CKD secondary to idiopathic membranous nephropathy. Such an association underlines the importance of correction of risk factors after SCI and highlights the necessity of an ophthalmological exam after all the forms of stroke.

Case Report

A 69-year-old man presented to the emergency department with lumbar pain and acute bilateral motor weakness of the legs started 12-hour ago associated to blood hypotension. No history of a recent surgery or traumatism was reported while the patient had a 9-year history of chronic kidney disease associated with idiopathic membranous glomerulonephritis type 1 (predialysis) that was complicated by hypertension. The patient also had also a history of cancer; he underwent surgery (15 years ago) and local radiotherapy (14 years ago) for colic adenocarcinoma and prostate cancer, respectively. The former was in complete remission and the latter was maintained in remission with hormonotherapy (leuprorelin acetate).

Neurological exam, realized according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI),[9] revealed an important proximal motor deficit in the patient's lower limbs, which was graded at 1/5 for muscle strength of the quadriceps, iliopsoas, gluteus medius, and gluteus maximus; it was less severe in the distal muscles (grade 4/5). Deep tendon reflex was absent and plantar reflex was preserved in the right limb, and the left limb showed extensor plantar response. The sensory loss of limb was selective along with a bilateral loss of thermalgesic sensation till the L5 level in the right and L3 level in the left, with sparing of proprioception. The motricity and sensitivity of the superior members were well-preserved. The patient had a diminished rectal tonicity without anal dilation; however, no abnormality of the bladder or bowel function were noted. The patient was not able to walk.

The first Magnetic Resonance Imaging (MRI), performed 18 hours after the onset of symptoms, did not show any abnormalities. However, T2-weighted sagittal and axial images obtained 4 days later showed a

Correspondence: Amir Mahdjoubi; Ophthalmology Department, Centre hospitalier Argenteuil, 69 Rue du Lieutenant-Colonel Prudhon, 95100 Argenteuil, France.
Tel.: 0033.134232749 - 0033.134232696.
E-mail: amir.mahdjoubi@gmail.com

Key words: Spinal cord infarction; retinal vein occlusion; chronic kidney failure; stroke; Magnetic resonance imaging.

Acknowledgements: We acknowledge the contribution of the centre de recherche Clinique (CRC) department of *Centre hospitalier d'Argenteuil* for supporting and providing facilities for the revision and edition of this work.

Contributions: AG, AM, AF, CC, EB, LB data collecting and analysing; AG, AM Manuscript writing; SC manuscript reviewing.

Conflict of interest: The authors report no conflicts of interest.

Funding: This work was not supported by any specific grant.

Ethics approval and consent to participate:

Informed consent: Informed consent was obtained from all individual participants included in the study.

Received for publication: 28 March 2020.
Accepted for publication: 12 August 2020.

Neurology International 2020; 12:8558
doi:10.4081/ni.2020.8558

hyperintensity in the form of an anteromedial spot at the T12-L1 level. No other lesions, tumors, abscesses, or herniated vertebral discs were observed (Figure 1). Cerebrospinal fluid (CSF) examination showed no abnormalities. Blood tests yielded the following results: perturbation of renal parameters (creatinine, 605 µmol/L; urea, 34 mmol/L), mixed metabolic acidosis (pH, 7.21), rhabdomyolysis parameters (CPK, 22,000 IU/L), severe anemia, (hemoglobin, 6.8 g/dl), protein S deficiency (36%), prothrombin level >120%, and negative C-reactive protein.

The diagnosis of non-traumatic spontaneous SCI was retained and an anti-platelet treatment targeting platelet aggregation was initiated. The anemia was corrected by two rounds of red blood cell transfusion, followed by darbepoetin alfa administration. The hemodialysis was started at two sessions per week. Hypertension was treated with calcium channel blockers and diuretics. The patient was provided a wheelchair for rehabilitation before leaving the neurology department after being hospitalized for a month. At the Physical Medicine and Rehabilitation department, motor kinesitherapy was started to strengthen the iliopsoas, gluteus medius, gluteus maximus, and hamstrings muscles. The twice-daily sessions involved progressive efforts aimed to facilitate the patient's transition from bed to wheelchair. Subsequently, efforts were aimed to achieve a vertical posture, first, with walker-assisted gait recovery, and thereafter, with the use of parallel bars. Finally, the muscles were reinforced by staircase step-based workout. At the end of rehabilitation (5 months later), muscle strength of the right leg was graded at 4/5 for the iliopsoas, gluteus medius, and gluteus maximus muscles, and 3/5 for the quadriceps; for the left leg, it was graded 4/5 for the gluteus medius and gluteus maximus muscles, and at 3/5 for the iliopsoas and quadriceps. The patient was equipped with a knee-ankle-foot orthosis to prevent laxity of the legs during transition to vertical gait. The patient could perform daily activities autonomously using a walker. He was able to climb and descend stairs with the support of 2 grab bars and assistance from another person. However, the use of a wheelchair was maintained for external activities and for long-distance locomotion. For self-improvement and at-home improvement, the ergotherapist recommended the installation of technical aids, such as an electric stairlift, to preserve autonomy.

Unfortunately, during the rehabilitation, the patient experienced blurred vision in the right eye, 5 months after the SCI. His visual acuity at presentation was 20/200. Slit lamp examination findings were normal, but fundus examination revealed multiple retinal hemorrhages associated with venous tortuosity, cotton-wool spots, and optic nerve edema. The presence of macular edema was confirmed with Optical Coherence Tomography (OCT) (Heidelberg Engineering, Heidelberg, Germany). These findings informed a diagnosis of central RVO complicated by macular edema (Figure 2). The patient was administered intravitreal anti-vascular endothelial growth factor (aflibercept 25 mg/mL) injections.

The last follow-up, six months after the onset of RVO and 11 months after SCI, revealed no new neurological sign or systemic symptoms. Muscle strength remained at 4/5 for the iliopsoas, gluteus medius, and gluteus maximus muscles, and at 3/5 for the quadriceps of both legs; however, hypoesthesia and associated paresthesia persisted. The patient could move autonomously with a walker. MRI examination did not reveal any new abnormalities in the spinal cord or brain. Although fundus examination showed partial regression of the central RVO signs, OCT showed complete resorption of the macular edema. Moreover, the patient's renal function improved after hemodialysis.

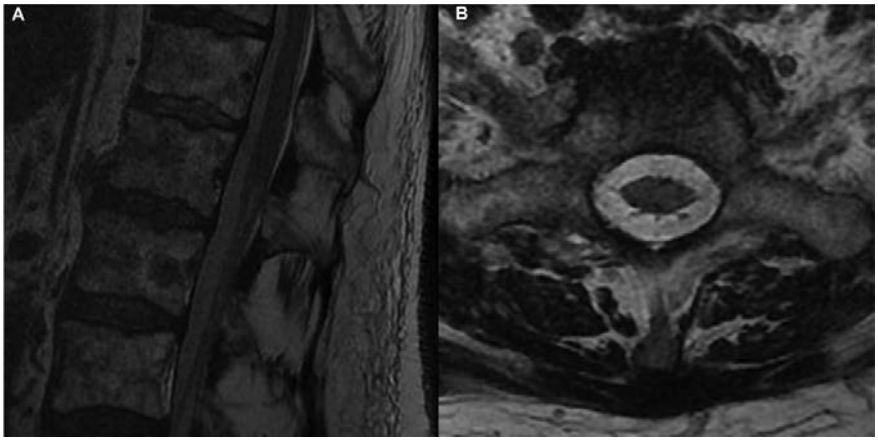

Figure 1. Magnetic resonance images acquired 4 days after the onset of paraplegia. T2-weighted sagittal (A) and axial (B) images show hyperintensity at the T12-L1 level in the form an anteromedial spot. No other spinal cord lesions were detected.

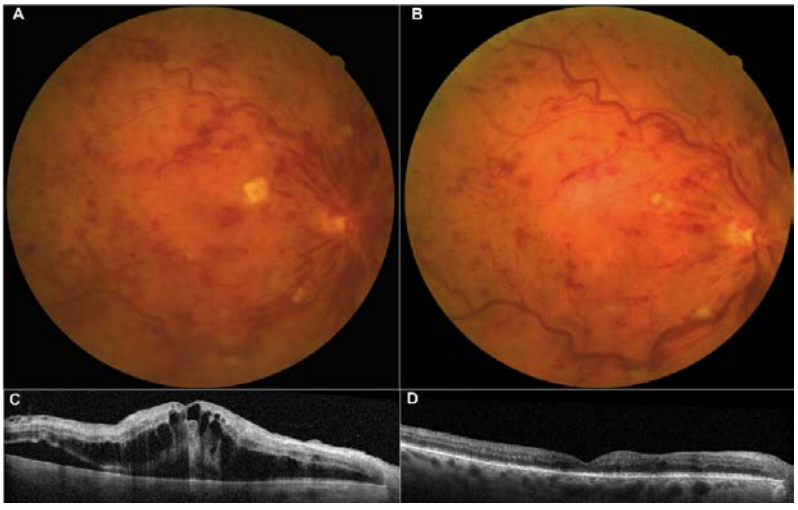

Figure 2. Fundus photography acquired at the onset of blurred vision (A) show signs of central retinal venous occlusion, such as retinal hemorrhage, venous tortuosity, cotton-wool spots, and optic nerve edema. Optical coherence tomography image shows a cystoid macular edema associated with serous retinal detachment (B). Six months later, the signs of central retinal venous occlusion show partial regression (C), with subtotal resorption of the macular edema after four intravitreal injections of anti-vascular endothelial growth factor drug (Aflibercept; D).

Discussion and Conclusions

SCI, with an estimated prevalence of 1.2% among patients who have experienced stroke, remains an elimination diagnosis.[10] Indeed, even in patients with signs suggestive of SCI—*e.g.*, abrupt onset of bilateral motor deficiency, dissociative anesthesia with selective loss of thermalgesic sensitivity and involvement of the anterior artery—the MRI results can appear normal in the first few hours after the ischemic event, and even across all follow-up visits in up to 45% of SCI cases.[11] In our case, the clinical presentation was typical of SCI, and T2-weighted MR images obtained 4 days after symptom onset confirmed the presumptive diagnosis of SCI. However, the ischemic site was situated in the lower level of the spinal cord, which accounts for the limited presentation of autonomic disorders. The fulfillment of three major criteria of SCI as proposed by Zalewski *et al.* (clinical presentation, MRI findings, and non-inflammatory CSF profile) supported the diagnosis of probable spontaneous SCI.[12]

Multiple etiologies can result in SCI such as: atherosclerosis, systemic hypotension, infection, emboli, vasculitis, aortic dissection, decompression sickness, and iatrogenic causes during vascular or neurological surgery.[13] Furthermore, previous case studies have reported that patients with thrombophilia, such as those with protein S deficiency or prothrombin mutation, experience episodes of SCI.[14,15] In our case, beside a prolonged history of cancer treatment, the patient presented systemic hypotension at SCI onset, along with severe anemia and a thrombophilic profile (protein S, 36%; total protein, >120%), which by extension may be indicative of severe CKD. Indeed, CKD induces hypertension, endothelial dysfunction, chronic inflammation, oxidative stress, anemia, nitric oxide (NO) reduction, hyperhomocysteinemia, and other systemic dysfunctions that promote atherogenesis and arteriosclerosis.[7] The coagulation abnormalities might also be due to CKD, which is generally accompanied by a thrombophilic state and protein S deficiency.[16] Hence, these multiple factors, in conjunction with cancer treatment-induced atherosclerosis, which observed at presentation and throughout his clinical history, yielded a favorable environment for thrombosis.[17]

An additional vascular accident in the retina that occurred only a few months after the first SCI event exacerbated the patient's condition. The rates of stroke and all-cause mortality increases with RVO, even if the latter involves the venous retinal system.[6] Moreover, venular widening observed in RVO has been identified as a risk factor for lacunar strokes, which are a consequence of small vessel occlusion.[18] Interestingly, a large case series identified shared risk factors between RVO and stroke.[3] RVO can thus be considered as an indirect sign of deteriorating vascular state, despite selective involvement of the veins. This may be explained by the narrow physical connections between arteries and veins in the optic nerve head and retina, wherein they share a common adventitial sheath; hence, a thick-walled, atherosclerotic central retinal artery can compresses the thin-walled ventral vein.[3]

On other hand, CKD exacerbates the frequency and severity of risk factors for cardiovascular diseases and increases the incidence of RVO and strokes.[19,20] However, after adjustment of the aforementioned systemic disorder-induced confounding factors, several studies have reported that CKD in itself is a risk factor for cardiovascular diseases.[6] Admittedly, in our case, the patient developed CKD after idiopathic membranous glomerulonephritis type 1, and previous case studies have reported the occurrence of RVO after development of membranous glomerulonephritis without uremia.[18] This association was attributed to coagulation disorders and hypovolemia, consequent of nephrotic syndrome. Although our patient manifested hypotension with acute kidney dysfunction at the onset of SCI, CKD was observed 9 years ago, and moreover, he had severe uremia. Thus, the underlying mechanism for RVO development can be explained by a vascular disorder induced by pre-existing uremia in addition to hypovolemia and thrombophilia.

The most probable explanation for the association of SCI and RVO, in this case, is the presentation of several well-documented risk factors for cardiovascular diseases, such as blood hypertension, anemia, and cardiotoxicity induced by cancer treatment. The CKD facilitated a prothrombotic environment, which was exacerbated by oxidative stress, thrombophilia, chronic inflammation, hyperhomocysteinemia, endothelial dysfunction, and decreased synthesis of vitamin D and NO. We surmise that all these factors contributed to the development of severe atherosclerosis, which resulted in SCI due to thrombosis and occlusion of the anterior spinal artery. This SCI, despite anti-platelet treatment, resulted in central RVO a few months later; the latter incident was likely caused by the compression of the central retinal vein by a rigid retinal artery.

In conclusion, the present case illustrates that beyond being a rare, disabling disease, SCI can also predict a high risk of future cardiovascular events, such as ocular vascular disease, especially in patients with chronic kidney disease (CKD). This report thus highlights that mitigation of associated risk factors, including early management of CKD, is required to prevent vascular complications associated with stroke. Finally, further studies are required to evaluate the state of retinal vascularization in patients with SCI, especially since retinal vascularization abnormalities were noted in patients suffering from stroke. Such assessment would indicate a bad vascular state in patients with spontaneous SCI.

References

1. Vuong SM, Jeong WJ, Morales H, Abruzzo TA. Vascular Diseases of the Spinal Cord: Infarction, Hemorrhage, and Venous Congestive Myelopathy. Seminars in Ultrasound, CT and MRI 2016;37:466–81.
2. Ip M, Hendrick A. Retinal Vein Occlusion Review. Asia Pac J Ophthalmol (Phila) 2018;7:40–5.
3. Risk factors for central retinal vein occlusion. The Eye Disease Case-Control Study Group. Arch Ophthalmol 1996;114:545–54.
4. Park SJ, Choi NK, Yang BR, et al. Risk of stroke in retinal vein occlusion. Neurology 2015;85:1578–84.
5. Zhong C, You S, Zhong X, et al. Retinal vein occlusion and risk of cerebrovascular disease and myocardial infarction: A meta-analysis of cohort studies. Atherosclerosis 2016;247:170–6.
6. Wu CY, Riangwiwat T, Limpruttidham N, et al. Association of retinal vein occlusion with cardiovascular events and mortality: a systematic review and meta-analysis. Retina (Philadelphia, Pa) 2019;39:1635-45.
7. Cherng YG, Lin CS, Shih CC, et al. Stroke risk and outcomes in patients with chronic kidney disease or end-stage renal disease: Two nationwide studies. PLoS ONE 2018;13:e0191155.
8. Grunwald JE, Ying G-S, Maguire M, et al. Chronic Renal Insufficiency Cohort (CRIC) Study Group. Association between retinopathy and cardiovascular disease in patients with chronic kidney disease (from the Chronic Renal Insufficiency Cohort [CRIC] Study). Am J Cardiol 2012;110:246–53.
9. Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med 2011;34:535–46.

10 Sandson TA, Friedman JH. Spinal cord infarction. Report of 8 cases and review of the literature. Med (Baltimore) 1989;68:282–92.
11. Yadav N, Pendharkar H, Kulkarni GB. Spinal Cord Infarction: Clinical and Radiological Features. J Stroke Cerebrovasc Dis 2018;27:2810-21.
12. Zalewski NL, Rabinstein AA, Krecke KN, et al. Characteristics of Spontaneous Spinal Cord Infarction and Proposed Diagnostic Criteria. JAMA Neurol 2018;76:56-73.
13. Nasr DM, Rabinstein A. Spinal Cord Infarcts: Risk Factors, Management, and Prognosis. Curr Treat Options Neurol 2017;19:28.
14. Hakimi KN, Massagli TL. Anterior spinal artery syndrome in two children with genetic thrombotic disorders. J Spinal Cord Med 2005;28:69–73.
15. Ramelli GP, Wyttenbach R, von der Weid N, Ozdoba C. Anterior spinal artery syndrome in an adolescent with protein S deficiency. J Child Neurol 2001;16:134–5.
16. Bauer A, Limperger V, Nowak-Göttl U. End-stage renal disease and thrombophilia. Hamostaseologie 2016;36:103–7.
17. Mukai M, Komori K, Oka T. Mechanism and Management of Cancer Chemotherapy-Induced Atherosclerosis. J Atheroscler Thromb 2018;25:994–1002.
18. Masoodi I, Wani IA, Hussain S, Najar MS, Reshi AR, Qurashi FA, Khan S. Sudden retinal vein thrombosis in a patient with nephrotic syndrome. BMJ Case Rep 2011;2011.
19. Lindley RI, Wang JJ, Wong M-C, et al. Multi-Centre Retina and Stroke Study (MCRS) Collaborative Group. Retinal microvasculature in acute lacunar stroke: a cross-sectional study. Lancet Neurol 2009;8:628–34.
20. Masson P, Webster AC, Hong M, et al. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. Nephrol Dial Transplant 2015;30:1162–9.