Clinical Immunology 263 (2024) 110207

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Porto-sinusoidal vascular disorder and nephrotic-range proteinuria due to venous vasculitis in Behçet's disease

T.B. van der Houwen [a], M.E. Annink [a], J.J.T.H. Roelofs [b], R.B. Takkenberg [c], J.A.M. van Laar [d], N.C. van der Weerd [e], A.E. Hak [a,f], A.J. Kwakernaak [a,e,*]

[a] Department of Medicine, Division of Clinical Immunology and Allergy, Vasculitis Center of Expertise, Amsterdam Institute for Immunology and Infectious Diseases, Amsterdam University Medical Center, location Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands
[b] Department of Pathology, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Center, location Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands
[c] Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, location Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands
[d] Department of Medicine, Division of Clinical Immunology and Allergy and Department of Immunology, Erasmus University Medical Center, Erasmus University Rotterdam, Rotterdam, the Netherlands
[e] Department of Nephrology, Amsterdam University Medical Center, location Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands
[f] Department of Rheumatology, Amsterdam University Medical Center, location Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Behçet's disease
Venous vasculitis
Porto-sinusoidal vascular disorder
Nephrotic-range proteinuria

ABSTRACT

Behçet's disease (BD) is an autoinflammatory disease with multifactorial and polygenic etiology, potentially involving arteries and veins of any size resulting in variable vessel vasculitis. We report a case of an Iranian male who presented with porto-sinusoidal vascular disorder due to venous vasculitis as initial manifestation of BD. Despite immunosuppression, anticoagulation and venous recanalization, he subsequently developed severe nephrotic-range proteinuria mimicking a primary renal disease which was completely and immediately ameliorated by stenting of the vena cava. This demonstrates that the proteinuria was caused by increased intraglomerular pressure due to venous outflow obstruction as a consequence of venous vasculitis. To our knowledge, this is the first report of massive proteinuria caused by venous obstruction of the caval vein in the context of BD. Altogether, this case demonstrates the extensive spectrum of vascular disease in BD.

1. Introduction

Behçet's disease (BD) is a rare autoinflammatory disease with multifactorial and polygenic etiology. Vasculitis, which can affect blood vessels of any size, is a serious manifestation of BD and results in elevated risk of both venous and arterial thrombosis that can manifest at any location. We describe a patient with extensive vascular stenosis and thrombosis due to venous vasculitis as the presenting manifestation of BD. In addition, he developed massive proteinuria that mimicked a primary renal disease, but turned out to be a complication of the venous vasculitis as well.

2. Case

A 32-year-old Iranian male presented to the emergency room with hemodynamic instability caused by massive hematemesis and melena. His medical history was unremarkable. Gastroduodenoscopy demonstrated esophageal variceal bleeding for which a self-expandable metallic stent was placed in the esophagus to achieve hemodynamic stability. Contrast-enhanced computed tomography (CT) scan and subsequent phlebography showed extensive stenosis and thrombosis of the superior and inferior caval vein (SVC and IVC, resp.) extending cranially into the brachiocephalic and subclavian veins and caudally into the hepatic veins (i.e. Budd-Chiari Syndrome; BCS; Fig. 1). In addition, a substantial collateral network along esophagus, liver and peritoneum was found, consistent with a chronic course of the disease. Liver enzymes and synthesis function were normal, and ultrasound and elastography showed no intraparenchymal abnormalities or liver fibrosis, compatible with porto-sinusoidal vascular disorder (formally known as non-cirrhotic portal hypertension). Placement of a transjugular

* Corresponding author.
E-mail address: a.j.kwakernaak@amsterdamumc.nl (A.J. Kwakernaak).

https://doi.org/10.1016/j.clim.2024.110207
Received 15 November 2023; Accepted 4 April 2024
Available online 11 April 2024

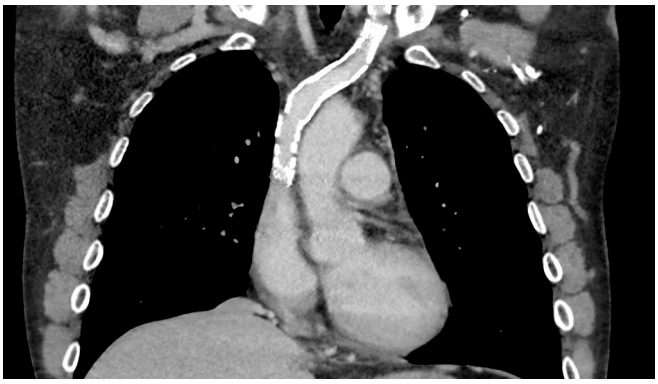

Fig. 1. CT-scan of the thorax at initial presentation showing extensive venous stenosis and thrombosis of the caval vein.

portosystemic intrahepatic shunt (TIPS) was considered but due to the extensive thrombosis not possible. Therefore, surgical recanalization and stenting of the left jugular vein, azygos vein and SVC was performed and the patient received multiple rounds of endoscopic rubber band ligation. Nonselective beta-blockade and anticoagulation was subsequently started. Analysis of the severe venous thrombosis and stenosis was initiated (Table 1). There was mild systemic inflammation (CRP of 29 mg/L) and upon inquiry he reported longstanding recurrent episodes of canker sores and we noted pseudofolliculitis on his chest and back and scaring of his scrotum. He also reported testicular and lumbar pain upon exercise, most likely due to the altered venous blood flow. The pathergy test was positive and we diagnosed him with Behçet's disease (BD). He was HLA-B51 positive. Ophthalmologic evaluation showed no uveitis or retinal vasculitis. We started remission-induction treatment with high dose glucocorticosteroids and TNF-α blockade, in addition to colchicine. Although immunosuppressive treatment is the corner stone of vascular disease in BD, we continued anticoagulant treatment to reduce the risk of in-stent thrombosis (target range of international normalized ratio (INR): 2.0–3.0). Moreover, there were limited safety concerns for anticoagulation as all varices were successfully treated and no pulmonary or abdominal aneurysms were detected upon extensive imaging studies. He had a good biochemical and clinical response to treatment with normalization of systemic inflammation and improvement of the canker sores and pseudofolliculitis and glucocorticosteroids were tapered and discontinued over a period of 12 weeks.

His disease course was subsequently complicated by progressive proteinuria from initially 1.7 g/L up to 7.2 g/L, and mild renal insufficiency (creatinine increase from 107 to 142 umol/L), without edema, hypoalbuminemia and/or dyslipidemia, and no urinary sediment abnormalities. At this time, no systemic inflammation was present and his INR was on target. Renal vein thrombosis was ruled out by duplex ultrasound and a renogram showed no abnormalities either. Specific renal auto-immune and infection serology was negative and serum electrophoresis and free light chain ratio were normal (see Table 1). We subsequently performed a renal biopsy with normal light microscopy (Supplementary Figure 1A) and negative immunofluorescence. Amyloidosis was excluded by Congo red staining. Electron microscopy showed mild podocyte foot process effacement (Supplementary Figure 1B) consistent with a secondary podocytopathy. Although the degree of podocyte effacement was not extensive enough for a diagnosis of minimal change glomerulopathy, and nephrotic syndrome was lacking, we initiated a trial treatment with glucocorticosteroids that resulted initially in proteinuria reduction. However, proteinuria became unresponsive and progressed to 10 g/L, still without nephrotic syndrome characteristics. In the meantime his exercise-induced testicular and lumbar pain progressed to the point that it became continuously present. We repeated CT-scan and phlebography that showed progression of the stenotic tract in the IVC with new thrombus formation and severe pre-

Table 1
Laboratory investigation.

Test	Result				Reference values
	A		B		
Blood count					
Hemoglobin (mmol/L)	6,7	↓	7,2	↓	8,5–10,5
MCV (fL.)	83		88		80–100
Leukocytes (x10^9/L)	7,0		8,0		4,0–10,5
Platelet count (x10^9/L)	240		229		150–400
C-reactive Protein (mg/L)	29	↑	0,6		< 5
Hepatic panel					
ASAT (IU/L)	19		24		14–43
ALAT (IU/L)	19		21		< 45
AF (IU/L)	136	↑	112		< 128
GGT (IU/L)	46		40		< 102
Bilirubin (umol/L)	8	↑	6	↑	4–24
Renal function					
Potassium (mmol/L)	4,3		4,5		3,4-4,9
Creatinine (umol/L)	107		142	↑	61–113
eGFR (ml/min/1.73m^2)	80		56	↓	> 60
Urea (mmol/L)	6,0		6,3		2,9-8,6
Albumin (g/L)	36		50		35–50
Urinalysis					
Protein (g/L)	1,7	↑	7,2	↑	< 0,15
Erytrocytes	Neg.		Neg.		Neg.
Leukocytes	Neg.		Neg.		Neg.
Infectious serology					
Hepatitis B (anti-HBc IgG)	Neg.		–		Neg.
Hepatitis C (IgG)	Neg.		–		Neg.
HIV (antigen and IgG)	Neg.		–		Neg.
Immunology					
Lupus anticoagulant	Neg.		–		Neg.
Anti-B2GP1 (IgM and IgG)	Neg.		–		Neg.
Anti-cardiolipin (IgM and IgG)	Neg.		–		Neg.
JAK2 mutation	Neg.		–		Neg.
PNH clone	Neg.		–		Neg.
HLA-B51	Pos.		–		Neg.
IgA (g/L)	3,4		1,8		0,70-4,0
IgG (g/L)	14		6		0,6-16
IgM (g/L)	1,3		1,4		0,4-2,3
Anti-PLA2R	–		Neg.		Neg.
ANA	–		Neg.		Neg.
M-protein	–		Neg.		Neg.
Free light chain ratio	–		1,66		0,25-1,66

Laboratory investigation carried out at initial presentation (column A) and during progression of proteinuria (column B). ANA: anti-nuclear antibody; anti-B2GP1: anti-beta-2-glycoprotein 1; anti-PLA2R: anti-phospholipase A2 receptor; ALAT: alanine aminotransferase; ASAT: aspartyl aminotransferase; AF: alkaline phosphatase; eGFR: estimated glomerular filtration rate (CKD-EPI); GGT: gamma-glutamyltransferase; HIV: human immunodeficiency virus; JAK2: Janus Kinase 2; MCV: mean corpuscular volume; M-protein: monoclonal M-protein; PNH: paroxysmal nocturnal hemoglobinuria.

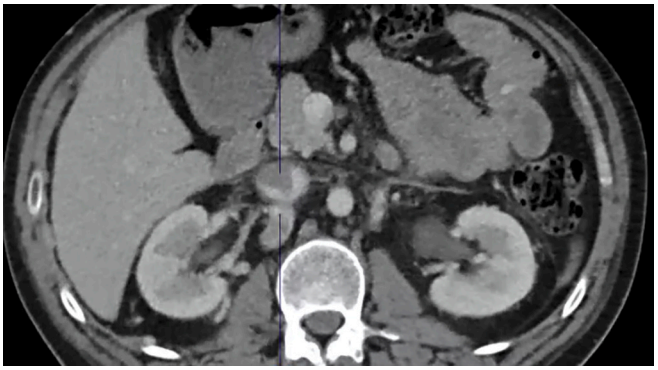

Fig. 2. CT-scan of the abdomen showing progression of the stenotic tract in the IVC and new thrombus formation with severe pre-thrombotic dilatation of the IVC extending to the renal veins.

thrombotic dilatation of the IVC extending all the way to the renal veins, resulting in severely obstructed venous flow (Fig. 2). We performed endovascular recanalization and placed additional stents in the IVC that diminished his testicular and lumbar pain and resulted in immediate and complete normalization of proteinuria and kidney function, all within the time span of one day. Although his INR was in the therapeutic range at presentation, we noted that his time in therapeutic range (TTR) during the previous months was below the target of 70% despite strict regulation by the Dutch national thrombosis service. We switched acenocoumerol to fenprocoumon and increased his INR target from 2.0 to 3.0 to 2.5–3.5. Ongoing vasculitis due to BD activity was unlikely in absence of symptoms and systemic inflammation, and neutralizing TNF-α blockade antibodies were ruled out. Inadherence to immunosuppressive treatment was denied by the patient and substantiated by pharmacy refill records. The remarkable clinical improvement upon recanalization, without alteration of his immunosuppressive regiment, confirmed that ongoing vascular inflammation was not the causative factor of the ongoing vascular thrombosis. Furthermore, he continued doing well on stable immunosuppression with no recurrence of pain, thrombosis, vasculitis or proteinuria over >2 years of follow-up.

3. Discussion

We report a case with extensive vascular stenosis and thrombosis of the caval vein and its main branches, as a consequence of venous vasculitis, resulting in porto-sinusoidal vascular disorder, as initial presentation of BD. Symptoms stabilized after initiation of glucocorticosteroids, TNF-α blockade, colchicine, anticoagulation and venous recanalization. In absence of systemic inflammation, ongoing venous obstruction of the IVC ensued and resulted in massive proteinuria that mimicked a primary renal disease. Additional revascularization of the IVC, and not intensification of immunosuppression, ameliorated the proteinuria immediately, completely and permanently.

BD is classified as an autoinflammatory disease with its etiology laying in the innate immune system. [1] The disease is systemic in nature with orogenital ulcerations, pseudofolliculitis and uveitis as cardinal symptoms. Less commonly, BD presents with arthritis, gastrointestinal, neurologic or vascular disease. [2] A positive pathergy test is highly suggestive of BD. [3] Although HLA-B51 is associated with increased susceptibility to BD, it's role as a diagnostic tool is limited as it cannot discriminate between BD patients and healthy subjects. [4] International classification criteria such as the International Study Group (ISG) and International Criteria for Behçet's Disease (ICBD) should be used with caution in the clinical setting as they are primary developed to ensure homogeneous patient recruiting for research. [5,6]

The vascular complications of BD consist predominantly of 'variable-vessel' vasculitis, affecting vessels of any type and size, at any location, and is strongly associated with thrombosis. [3,7] The neutrophilic inflammation of the endothelium weakens the vessel wall and induces thrombus formation by generating platelet/neutrophil complexes, excessive production of thrombin and impairment of fibrinolysis. [8] Aside from superficial and deep vein thrombosis, which together affect up to 40% of BD patients, venous vasculitis and thrombosis in BD tends to localize to atypical sites, such as the SVC, IVC, portal vein, and also cerebral sinuses [9]. In a cohort of 1200 BD patients, 1.4% and 0.4% developed an occlusion of the SVC and the IVC, respectively [10]. Thrombotic obstruction of the hepatic outflow tract, anywhere from the hepatic veins to the right ventricle, can lead to porto-sinusoidal vascular disorder. As highlighted by this case, BD-related BCS is associated with thrombosis of the IVC rather than the hepatic veins [11].

To our knowledge, this is the first case of BD with severe nephrotic-range proteinuria due to stenosis and thrombosis of the IVC. The exact frequency of renal involvement in BD remains unknown because well-defined cohorts are limited, but varies in literature between <1% and 29% depending on the used definition of renal disease [12]. BD can affect the kidneys in several ways. Renal vein thrombosis and renal arterial aneurysm formation are considered the typical hallmarks of renal vascular involvement in BD. [13] A feared cause of proteinuria in BD is AA-amyloidosis but this incidence decreases as treatment becomes more effective and accessible. Other causes of proteinuria in BD are focal segmental glomerulosclerosis and mesangial proliferative glomerulopathy, with minimal change glomerulopathy being described only once buth with incomplete histological proof as electron microscopy was not performed [14–16]. Causes of nephritic syndrome in BD are proliferative glomerulonephritis, mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis and crescentic glomerulonephritis [12]. Lastly, microinfarctions and treatment-related kidney function decline have been reported as well. [13]

In our case, the podocyte effacement as demonstrated by renal biopsy, guided us towards the diagnosis of a podocytopathy. While the level of podocyte effacement was mild, and nephrotic syndrome was absent, we began a trial of glucocorticosteroid treatment which initially led to a reduction in proteinuria. In the course of the disease it became clear that the proteinuria and podocytopathy resulted from a high intraglomerular pressure due to ongoing stenosis and thrombosis of the IVC. The association between IVC thrombosis and proteinuria has been reported before, all in non-BD patients. [17,18] We have no data on renal venous pressures in our patient, however, the ultimate proof of causality between proteinuria and the venous congestion was the complete and immediate resolution of proteinuria after stenting of the IVC.

The current available literature, summarized by the European Alliance of Associations for Rheumatology (EULAR), recommends tailoring of appropriate management of vascular manifestations in BD to the specific vessel involved [19]. In severe vascular disease, such as porto-sinusoidal vascular disorder, BCS and vena cava syndrome, the treatment of preference is glucocorticosteroids with either TNF-α blockade or cyclophosphamide. Head-to-head comparison between these two treatment modalities has not been performed. In this case we choose TNF-α blockade because of age and preference of the patient. One could postulate that remission-induction treatment with TNF-α blockade may have been inadequate and re-remission-induction treatment with cyclophosphamide would have been indicated, however, as we stated before, BD activity was unlikely as systemic inflammation was absent. The fact that the patient remained clinically stable without intensification of immunosuppression also argues against inflammation as being the driver of the complications that subsequently arose. Nevertheless, we did not perform a PET-CT to substantiate this further.

Anticoagulant therapy is considered inferior to immunosuppressive therapy for treatment of vascular manifestations in BD, consistent with the inflammatory origin of thrombosis in BD. A recent review paper states the role of anticoagulants in BCS or VCI thrombosis in BD as controversial [20]. Anticoagulants can however be added in cases of refractory venous thrombosis after establishing the patient has a low bleeding risk, with specific attention for detection of aneurysms [19]. Interestingly, vascular disease progressed in our patient most likely due to organization and fibrosis of this residual thrombotic material that impairs blood flow and ultimately led to progressive occlusion.

Given the complexity and the extent of vascular involvement, this case illustrates the need for a multidisciplinary approach for treatment of vascular manifestations of BD, with collaboration among specialties such as clinical immunology/rheumatology, (intervention)radiology, hepatology, pathology and nephrology.

Learning points

1. Behçet's disease is an autoinflammatory disease with a broad spectrum of clinical features, including inflammation of blood vessels of any type and size, at any location. Porto-sinusoidal vascular disorder, due to venous vasculitis, can be a primary manifestation of Behçet's disease.
2. This report is the first to describe nephrotic-range proteinuria resulting from venous vasculitis of the inferior caval vein in Behçet's

disease. Nephrotic-range proteinuria, in absence of renal vein thrombosis and negative proteinuria work-up, should raise suspicion of a vascular problem located distal from the renal vasculature.
3. Immunosuppressive therapy is considered the mainstay of treatment of vascular disease in Behçet's disease. Anticoagulants can be added in cases of refractory venous thrombosis after establishing the patient has a low bleeding risk. Recanalization may be necessary in severe (irreversible) vascular disease.

Author contributions

TBvdH, MEA and AJK wrote the manuscript. AEH and JAMvL provided intellectual input from a clinical immunology perspective, NCvdW provided intellectual input from a nephrology perspective and RBT from a hepatology perspective. JJTHR evaluated the renal biopsy. The manuscript was revised and approved by all authors.

Funding

This case report received no external funding.

Institutional review board statement

Ethical review and approval were waived for this case report due to the observational nature.

Informed consent statement

Written informed consent has been obtained from the patient to publish this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2024.110207.

References

[1] A. Gul, Pathogenesis of Behcet's disease: autoinflammatory features and beyond, Semin. Immunopathol. 37 (4) (2015) 413–418.
[2] A. Bettiol, F. Alibaz-Oner, H. Direskeneli, G. Hatemi, D. Saadoun, E. Seyahi, et al., Vascular Behcet syndrome: from pathogenesis to treatment, Nat. Rev. Rheumatol. 19 (2) (2023) 111–126.
[3] F. Davatchi, C. Chams-Davatchi, H. Shams, F. Shahram, A. Nadji, M. Akhlaghi, et al., Behcet's disease: epidemiology, clinical manifestations, and diagnosis, Expert Rev. Clin. Immunol. 13 (1) (2017) 57–65.
[4] F. Lotscher, F. Kerstens, M. Krusche, N. Ruffer, I. Kotter, F. Turkstra, MHC-I-opathy Esgo., When it looks like Behcet's syndrome but is something else: differential diagnosis of Behcet's syndrome: a two-centre retrospective analysis, Rheumatology (Oxford) 62 (11) (2023) 3654–3661.
[5] Criteria for diagnosis of Behcet's disease. International study Group for Behcet's disease, Lancet 335 (8697) (1990) 1078–1080.
[6] F. Davatchi, Diagnosis/classification criteria for Behcet's disease, Pathol. Res. Int. 2012 (2012) 607921.
[7] E. Seyahi, Phenotypes in Behcet's syndrome, Intern. Emerg. Med. 14 (5) (2019) 677–689.
[8] R.M. de Vargas, M.L.N. da Cruz, M.P.H. Giarllarielli, B.M. Sano, G.I. da Silva, K. F. Zoccal, C. Tefe-Silva, Vascular involvement in Behcet's disease: the immunopathological process, J. Vasc Bras. 20 (2021) e20200170.
[9] G. Emmi, A. Bettiol, E. Silvestri, G. Di Scala, M. Becatti, C. Fiorillo, D. Prisco, Vascular Behçet's syndrome: an update, Intern. Emerg. Med. 14 (5) (2019) 645–652.
[10] M.A. Kuzu, C. Ozaslan, C. Koksoy, A. Gurler, A. Tuzuner, Vascular involvement in Behcet's disease: 8-year audit, World J. Surg. 18 (6) (1994) 948–953, discussion 53–4.
[11] J. Zhou, D. Zhang, Z. Wang, Y. Hou, J. Liu, X. Zeng, et al., The clinical features, image findings and risk factors of vena cava syndrome in Behcet's syndrome, Clin. Exp. Rheumatol. 40 (8) (2022) 1526–1534.
[12] T. Akpolat, M. Dilek, K. Aksu, G. Keser, Ö. Toprak, M. Cirit, et al., Renal Behçet's disease: an update, Semin. Arthritis Rheum. 38 (3) (2008) 241–248.
[13] T. Akpolat, M. Dilek, K. Aksu, G. Keser, O. Toprak, M. Cirit, et al., Renal Behcet's disease: an update, Semin. Arthritis Rheum. 38 (3) (2008) 241–248.
[14] G.H. Malik, I.A. Sirwal, K.A. Pandit, Behcet's syndrome associated with minimal change glomerulonephritis and renal vein thrombosis, Nephron 52 (1) (1989) 87–89.
[15] Y. Akiyama, T. Suzuki, M. Tanaka, S. Ohno, F. Imai, K. Kobayashi, et al., A case of Behcet's disease associated with aortic regurgitation and nephrotic syndrome, Ryumachi 35 (6) (1995) 910–914.
[16] D. Leonard, C. Cortese, H.M. Wadei, I.E. Porter Ii, N. Aslam, Behcet's syndrome and focal segmental glomerulosclerosis with nephrotic syndrome - successful treatment with etanercept, Clin. Nephrol. 89 (5) (2018) 371–375.
[17] Y. Apostolova, P. Mehier, S.D. Qanadli, M. Pruijm, Inferior vena cava thrombosis as a possible cause of nephrotic-range proteinuria: two case reports, J. Med. Case Rep. 15 (1) (2021) 569.
[18] W.L. Baird Jr., D.P. Buchanan, The nephrotic syndrome following thrombosis of the inferior vena cava, Am. J. Med. 32 (1962) 128–130.
[19] G. Hatemi, R. Christensen, D. Bang, B. Bodaghi, A.F. Celik, F. Fortune, et al., 2018 update of the EULAR recommendations for the management of Behçet's syndrome, Ann. Rheum. Dis. 77 (6) (2018) 808–818.
[20] A. Bettiol, F. Alibaz-Oner, H. Direskeneli, G. Hatemi, D. Saadoun, E. Seyahi, et al., Vascular Behçet syndrome: from pathogenesis to treatment, Nat. Rev. Rheumatol. 19 (2) (2023) 111–126.