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Behçet syndrome: the vascular cluster

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Abstract: Although skin-mucosa lesions are common in almost all patients with Behçet syndrome (BS), clinical properties may differ from one patient to another. Within BS, there are subsets with different organ involvement and hence probably different pathological pathways. These subsets can be described as a) solo skin-mucosa disease with no major organ involvement, b) eye disease, c) seronegative spondyloarthropathy-like disease (arthritis, enthesopathy, and folliculitis), d) Crohn-like disease, and finally the topic of this chapter: e) vascular disease. In the vascular disease subset, not surprisingly, several types of vascular involvement may be observed in the same individual. These subsets may make up the total clinical picture all at the same time or step by step with each relapse. Significant correlations exist between cerebral vascular thrombosis and pulmonary artery involvement, intracardiac thrombi and pulmonary artery involvement, Budd–Chiari syndrome, and inferior vena cava syndrome. Lower extremity vein thrombosis is often present in these associations and even precedes them. The recognition of these clusters is not only important in diagnosis and management but also in basic science, including genetic studies.

Key words: Behçet syndrome, clusters, vein thrombosis

1. Introduction

Behçet syndrome (BS) is most frequently classified, rather deservedly, as a systemic vasculitis. On the other hand, there are features of BS in which vasculitis is not the main pathology. Notably, joint disease, oral and genital ulcerations, acne lesions, and a substantial portion of erythema nodosum lesions fall into this category. No clear-cut histologic vasculitis has been shown in gut disease associated with BS, while the situation is somewhat more complicated in central nervous system (CNS) disease. While bona fide vascular inflammation is not present in the more common form of CNS involvement in BS, vascular involvement can surely be considered the main pathology in dural sinus thrombi, the less common (20%) form of CNS disease. On the other hand, we must admit that there are no data that clearly show that the initial pathology in dural sinus thrombosis (DST) in BS is in the vessel wall rather than a systemic hypercoagulability or a combination of the two.

In 2002, based on a factor analysis among 272 consecutive patients, it turned out that 5 factors (clusters) could explain about 80% of the variation in a 14-item matrix (1). The Table shows these clusters. In the vascular disease cluster, several types of vascular involvement may accumulate in the same individual. These may occur at once or step by step with each relapse. Lower extremity vein thrombosis (LEVT) is often present in these vascular clusters and may even precede other types of vascular involvement.

The main purposes of this review is to discuss a) how the vascular cluster in this scheme expanded and b) what more we learned about the various pathologies in this cluster in the ensuing years.

2. Expansion of the vascular cluster

In our factor analysis CNS disease was not among the items (1) that made up the matrix simply because there were relatively few patients with this pathology to yield meaningful statistics. On the other hand, our Israeli colleagues had already reported that CNS involvement in BS was associated with peripheral vascular disease (2). After we saw in our factor analysis that there were clusters in BS, we hypothesized that it should be the dural sinus, rather than the parenchymal type of CNS disease more likely to be associated with peripheral vascular involvement. In our subsequent study among 88 patients with CNS disease, 15/77 (19%) of the patients with parenchymal disease and 7/11 (64%) of the patients with dural sinus thrombi had peripheral vascular disease (P = 0.01) (3).

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Table. Clusters (factors) in Behçet syndrome based on factor analysis study (Ref. 1).

Factors	Type of clinical involvement
Factor I	Oral ulcers + genital ulcers+ erythema nodosum
Factor II	Superficial vein thrombosis + deep vein thrombosis
Factor III	Uveitis
Factor IV	Acne + arthritis

It has been recognized for some time that pulmonary arterial aneurysms (PAAs) (the most deadly lesion of BS) are also associated with peripheral vascular disease (4,5). This contention held true in an in-depth study of lung involvement (6) with 81% (36/41) of the patients with pulmonary vascular disease also having peripheral vascular involvement. The same clustering was also evident in a more recent survey of vascular involvement among 882 patients with vascular disease attending our dedicated BS clinic (7). In this group of patients and in a correspondence analysis it was convincingly demonstrated that vena cava inferior and superior syndrome, pulmonary artery disease, dural sinus thrombi, Budd–Chiari syndrome, and deep vein thrombosis of the extremities clustered together. It was only the peripheral arterial involvement (8) that stood apart (7). It is worth noting that while the mean onset of pulmonary and peripheral vascular disease was quite close to a year in this analysis, the onset of peripheral arterial disease was about 8 years later, at a mean age of 39, suggesting different pathogenic mechanisms (9).

3. Recent issues related to the vasculitis cluster

3.1. Isolated pulmonary artery thrombosis (PAT) as an important component of lung involvement in BS

Our previously referred to study (6) about pulmonary vascular involvement, in addition to its conformation of the association of vascular disease in the lungs and in the periphery, also highlighted that PAT is also not an infrequent clinical finding in BS. In Seyahi et al.'s study (6), of the 47 patients with pulmonary artery involvement 34 had PAA while 13 had isolated PAT. There were also patients who had both and in 3 patients the PATs progressed into PAAs.

It is important to note while the main presenting symptom in either condition is hemoptysis, this tends to be much more copious in PAA. Another diagnostically important issue is that while an ordinary chest radiograph is sensitive enough to pick up almost all cases of PAA the same modality misses about half of the PATs. On the other hand, PAA and PAT of BS are managed similarly and both carry a similar prognosis.

3.2. Intrathoracic lesions other than PAA or PAT

These can be of many forms. Up to 80%–90% of patients with pulmonary vascular disease have nodular lesions. These can be due to infarction, nonspecific granuloma, or bronchilitis obliterans organizing pneumonia (6). Such lesions are seen most commonly in patients accompanying PAA or PAT and are particularly important in management since they can also be interpreted as due to infection in a patient receiving immunosuppressives for his or her pulmonary vascular disease. Other intrathoracic lesions include cavities (47%), ground grass lesions (45%), mediastinal lymphadenopathy (21%), pleural effusion/thickening (45%), pericardial effusion (21%), and intracardiac filling defects (28%).

3.3. Pulmonary artery hypertension

In a controlled study among BS patients with and without pulmonary vascular disease, healthy controls, and patients with scleroderma included as diseased controls, we found out that close to 1/5 of BS patients had mildly (35–45 mmHg) elevated systolic pulmonary artery pressure (10). In addition, as in systemic sclerosis, some patients had impaired lung diffusion capacity and mild disturbances of cardiac function suggesting small vessel disease in these patients as well.

3.4. A more benign form of Budd–Chiari (BC) syndrome

BC syndrome (obstruction of the hepatic outflow) is one of the most, if not the most, severe complications of BS (11). However, we recently realized that there are more benign forms.

In a chart review in our dedicated BS outpatient clinic, out of around 9000 registered patients, there were 43 patients who had been labeled as having BC syndrome. These patients were analyzed in detail and if they were still alive they were called back for reassessment. Moreover, the clinical features of the same group of patients were compared to those of 300 randomly selected BS patients from the same clinic. Twenty had died and 23 were available for reassessment. The outstanding differences between BC syndrome as a whole group and the 300-patient control group of BS were: a) there were significantly more males and patients with vascular disease elsewhere including dural sinus thrombi and b) there was less neurologic, eye,

and CNS disease in the BC group. The patients with BC syndrome could be divided into two main groups: those patients who had ascites when they presented (n = 33) and those who did not (n = 10). The prognosis was strikingly better in the latter group. It remains to be seen whether very early recognition of BC syndrome, before the onset of hepatic disease, will improve the prognosis.

3.5. A formal comparison of the lower extremity vein thrombosis (LEVT) of BS with LEVT due to other causes

Recently we had the opportunity to formally, for the first time, compare the clinical and Doppler ultrasonographic features of LEVT associated with BS and idiopathic or due to other causes (12). The findings in 78 consecutive BS patients with BS (71 males, 7 females; mean age 38.6 ± 10.3 years) with LEVT were compared to those in 50 control patients (29 men, 21 women; mean age 42.0 ± 12.5 years) with LEVT not having BS. Apart from more males in the BS group, BS patients had more bilateral involvement, and their Doppler findings indicated a more organized and symmetric pattern of venous disease as compared to the control group. Finally, one half of the BS group developed a severe postthrombotic syndrome and a third had venous claudication, while these postthrombotic complications were present in only around 10% of the patients in the other group. In brief, the clinical severity of LEVT among the BS patients is distinctly more severe.

3.6. The debate whether anticoagulation is useful in thrombosis associated with BS

The decades old debate continues whether patients with BS and thrombosis in the lungs or at extrapulmonary sites should be anticoagulated (13). Our group has for many years been of the opinion that since the main reason for thrombi in BS was endotheliitis and the frequency of pulmonary emboli did not seem to be increased in BS (13), a syndrome with a LEVT frequency of at least 25%–30%, this was unnecessary. In addition, the frequent association of PAA with LEVT necessitated great caution (4–6). Recently several new pieces of information have supported our contention. Importantly, we had the opportunity to observe that those lesions interpreted by our radiology colleagues as pulmonary emboli in ventilation perfusion scans tended to persist for months or years in BS patients, whereas they certainly disappear in a few months in patients with true to form emboli (6). Moreover, two recent cohort studies from other groups indicated that immunosuppression was more important in managing/preventing thrombi in BS (14,15). Having said all this, however, we recently observed in our observational cohort study of LEVT we already referred to (12) the postthrombophlebitic syndrome was more common among those patients in whom we had stopped a previously started anticoagulation, when they first presented at our dedicated outpatient care. While this observation may certainly be the result of confounding by indication bias, it again surely brings up the necessity for a proper, randomized controlled trial of anticoagulation in thrombotic complications of BS.

3.7. Atherosclerosis and BS

This is another debated issue. Our group again over the years held the view that atherosclerosis was not appreciably increased in BS (16). This rather counterintuitive contention about a chronic inflammatory disease had no uniform back up and, in fact a recent metaanalysis of 9 studies reported that subclinical atherosclerosis was increased in BS as evidenced by impaired flow mediated inflammation and in increased intima media thickness (IMT) (17). There was notable heterogeneity, which the authors also emphasized, in this analysis. Furthermore, it obviously remains to be seen whether this increased 'subclinical' atherosclerosis would ever translate into a clinical atherosclerosis in a syndrome that predominantly affects veins rather than arteries and tends to go away in the majority of patients with the passage of time (18). We have to specifically point out here that a) contrary to what is observed in other chronic inflammatory diseases like RA and SLE, the increased mortality in the early disease decreases with time (18); b) coronary calcification scores are not appreciably increased among patients with severe vascular disease (19); c) in a controlled study among BS, rheumatoid arthritis (RA), and ankylosing spondylitis patients and healthy controls, it was only among the RA patients that coronary atherosclerotic plaques and IMT were increased (20) and finally, probably most significantly, d) in a controlled study, the frequencies of angora pectoris and myocardial infarction were not increased among BS patients (21).

4. Conclusions

There is strong, both old and new, clinical evidence that vascular involvement is an important disease cluster in BS. Apart from its obvious management and prognosis implication, this contention should alert our colleagues in basic science, including genetics, to tailor their pathogenesis search in the light of this awareness.

References

1. Tunc R, Keyman E, Melikoglu M, Fresko I, Yazici H. Target organ associations in Turkish patients with Behçet's disease: a cross sectional study by exploratory factor analysis. J Rheumatol 2002; 29: 2393-296.

2. Krause I, Leibovici L, Guedj D, Molad Y, Uziel Y, Weinberger A. Disease patterns of patients with Behçet's disease demonstrated by factor analysis. Clin Exp Rheumatol 1999; 17: 347-350.

3. Tunc R, Saip S, Siva A, Yazici H. Cerebral venous thrombosis is associated with major vessel disease in Behçet's syndrome. Ann Rheum Dis 2004; 63: 1693-1694.

4. Hamuryudan V, Yurdakul S, Moral F, Numan F, Tüzün H, Tüzüner N, Mat C, Tüzün Y, Ozyazgan Y, Yazici H. Pulmonary arterial aneurysms in Behçet's syndrome: a report of 24 cases. Br J Rheumatol 1994; 33: 48-51.

5. Hamuryudan V, Er T, Seyahi E, Akman C, Tüzün H, Fresko I, Yurdakul S, Numan F, Yazici H. Pulmonary artery aneurysms in Behçet syndrome. Am J Med. 2004; 117: 867-870.

6. Seyahi E, Melikoglu M, Akman C, Hamuryudan V, Ozer H, Hatemi G, Yurdakul S, Tuzun H, Oz B, Yazici H. Pulmonary artery involvement and associated lung disease in Behçet disease: a series of 47 patients. Medicine (Baltimore) 2012; 91: 35-48.

7. Tascilar K, Melikoglu M, Ugurlu S, Sut N, Caglar E, Yazici H. Vascular involvement in Behçet's syndrome: a retrospective analysis of associations and the time course. Rheumatology (Oxford) 2014; 53: 2018-2022.

8. Tuzun H, Seyahi E, Arslan C, Hamuryudan V, Besirli K, Yazici H. Management and prognosis of nonpulmonary large arterial disease in patients with Behçet disease. J Vasc Surg 2012; 55: 157-163.

9. Yazici H, Ugurlu S, Seyahi E. Behçet syndrome: is it one condition? Clin Rev Allergy Immunol 2012; 43: 275-280.

10. Seyahi E, Baskurt M, Melikoglu M, Akman C, Olgun DC, Simsek E, Hamuryudan V, Kucukoglu S, Yazici H. The estimated pulmonary artery pressure can be elevated in Behçet's syndrome. Respir Med 2011; 105: 1739-1747.

11. Seyahi E, Caglar E, Ugurlu S, Kantarci F, Hamuryudan V, Sonsuz A, Melikoglu M, Yurdakul S, Yazici H. An outcome survey of 43 patients with Budd-Chiari syndrome due to Behçet's syndrome followed up at a single, dedicated center. Semin Arthritis Rheum 2015; 44: 602-609.

12. Seyahi E, Cakmak OS, Tutar B, Arslan C, Dikici AS, Sut N, Kantarci F, Tuzun H, Melikoglu M, Yazici H. Clinical and ultrasonographic evaluation of lower-extremity vein thrombosis in Behcet syndrome: an observational study. Medicine (Baltimore) 2015; 94: e1899.

13. Seyahi E, Yazici H. To anticoagulate or not to anticoagulate vascular thrombosis in Behçet's syndrome: an enduring question. Clin Exp Rheumatol 2016; 34(1 Suppl 95): S3-4.

14. Desbois AC, Wechsler B, Resche-Rigon M, Piette JC, Huong Dle T, Amoura Z, Koskas F, Desseaux K, Cacoub P, Saadoun D. Immunosuppressants reduce venous thrombosis relapse in Behçet's disease. Arthritis Rheum 2012; 64: 2753-2760.

15. Alibaz-Oner F, Karadeniz A, Yılmaz S, Balkarlı A, Kimyon G, Yazıcı A, Çınar M, Yılmaz S, Yıldız F, Yaşar Bilge Ş et al. Behçet disease with vascular involvement: effects of different therapeutic regimens on the incidence of new relapses. Medicine (Baltimore) 2015; 94: e494.74.

16. Seyahi E, Yazici H. Atherosclerosis in Behçet's syndrome. Clin Exp Rheumatol 2007; 25(4 Suppl 45): S1-5.

17. Merashli M, Ster IC, Ames PR. Subclinical atherosclerosis in Behcet's disease: a systematic review and meta-analysis. Semin Arthritis Rheum 2016; 45: 502-510.

18. Kural-Seyahi E, Fresko I, Seyahi N, Ozyazgan Y, Mat C, Hamuryudan V, Yurdakul S, Yazici H. The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore) 2003; 82: 60-76.

19. Seyahi E, Memisoglu E, Hamuryudan V, Tepe S, Aker UT, Balci H, Ongen Z, Yurdakul S, Yazici H. Coronary atherosclerosis in Behçet's syndrome: a pilot study using electron-beam computed tomography. Rheumatology (Oxford) 2004; 43: 1448-1450.

20. Seyahi E, Ugurlu S, Cumali R, Balci H, Ozdemir O, Melikoglu M, Hatemi G, Fresko I, Hamuryudan V, Yurdakul S et al. Atherosclerosis in Behçet's syndrome. Semin Arthritis Rheum 2008; 38: 1-12.

21. Ugurlu S, Seyahi E, Yazici H. Prevalence of angina, myocardial infarction and intermittent claudication assessed by Rose Questionnaire among patients with Behcet's syndrome. Rheumatology (Oxford) 2008; 47: 472-475.