Pulmonary artery involvement due to Behçet's syndrome and Hughes Stovin syndrome: a comparative study

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Abstract

Objective

Hughes-Stovin syndrome (HSS) is a rare inflammatory condition defined as pulmonary artery aneurysms (PAA) associated with deep vein thrombosis. It is similar to vascular involvement of Behçet's syndrome (BS), but differs in the absence of typical skin-mucosal findings. Whether HSS is a distinct entity or a form fruste of BS is debated. We formally compared HSS cases retrieved from the literature to BS patients with PAI followed by a tertiary centre.

Methods

A systemic literature search using 'Hughes Stovin syndrome' as the key word covering the period between 2000 and 2023 revealed 58 (43 M/15 F) case reports (PROSPERO: CRD42023413537). We identified 74 (62M/12 F) BS patients with PAI followed up in a tertiary centre in Turkey from 2000 until 2020. We evaluated two cohorts head-to-head in terms of demographic and clinical features.

Results

BS and HSS patients were found to be comparable with regard to several demographic, clinical and histopathological features. However, PAA were significantly more frequent and isolated pulmonary artery thrombosis (PAT) less common in HSS than that found in BS. Moreover, patients with HSS were more likely to be treated with anti-coagulants and vascular or surgical interventions, whereas less likely to receive immunosuppressive treatment.

Conclusion

Our study indicates that HSS is indeed an 'incomplete form of BS'. It can be considered as evidence supporting the notion that the vascular phenotype develops independently from skin-mucosa lesions and uveitis in BS. However, HSS has been described mainly focusing on aneurysms, overlooking the aspect of in-situ thrombosis.

Key words

Hughes-Stovin syndrome, Behçet's syndrome, pulmonary artery aneurysms, pulmonary artery thrombosis

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Introduction

Behçet's syndrome (BS) is a chronic inflammatory disease of unknown aetiology, observed mostly among the populations of Middle-East, Far-East and Mediterranean basin (1). It tends to affect young individuals with almost equal incidence among men and women. There is typically a relapsing course associated with frequent and severe attacks especially in the early years, however, the severity decreases over the years and the attacks gradually become less frequent and milder during the follow-up (2).

BS was first described in 1937 by a Turkish dermatologist named Hulusi Behçet as a triple symptom complex that includes recurrent oral and genital ulcers along with hypopyon uveitis (3). It became later evident that BS can affect many other organ systems such as the joints, cardiovascular, neurological and gastrointestinal systems (1). Among these, lung involvement characterised by pulmonary artery aneurysms (PAA) and in-situ thrombosis (PAT) is particularly important, because of its significant morbidity and mortality among young males (4-11).

Hughes Stovin syndrome (HSS) first introduced in 1959 by two British doctors, John Patterson Hughes and Peter George Ingle Stovin, is a rare inflammatory condition characterised by the occurrence of aneurysm and thrombosis in the pulmonary arteries (12). In addition to PAA, patients may have thrombosis in the large veins and elevated acute phase responses in the laboratory (13-14). HSS is similar to vascular involvement of BS, but differs from BS in the absence of typical skin-mucosal findings (13-14). Still, there is debate on whether it could be a form fruste of BS or a distinct entity. Its incidence cannot be determined and aetiopathogenesis has not been fully explained. Patients are apparently treated as in BS (13-14). The knowledge related with HSS is limited as the bulk of the current evidence comes solely from sporadic case reports.

In this study, our objective was to conduct a comprehensive head-to-head comparison of BS and HSS, an approach not previously explored. To achieve this, we scrutinised HSS cases reported in the literature and assessed BS cases with pulmonary artery involvement (PAI) monitored at a tertiary medical centre. We evaluated various aspects, including demographics, clinical features, management, and outcomes.

Patients and methods

BS cases with pulmonary artery involvement

We identified 98 patients with PAI between January 2000 and January 2020 at the Behçet Disease Research Centre at U.I.-C, Cerrahpaşa Faculty of Medicine, Istanbul, Turkey. After excluding 13 patients who did not meet the International Study Group (ISG) criteria (15) and two patients with only bronchial artery involvement, an additional 9 patients were excluded due to missing clinical and radiological data. This left us with 74 patients (62M/12F) for our study. We retrospectively reviewed the file data of these patients and compared it with the data of HSS cases found in the literature.

HSS cases

We did a systemic literature review to evaluate HSS cases. We developed a study protocol consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (19622511) (16) and registered at International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023413537). The process included assessing study eligibility criteria, selecting studies, data collection, and summarising results in a Microsoft Excel checklist to ensure consistency across reviewers. Details are shown in the flowchart in Figure 1. PubMed, Scopus and Web of Science (WOS) databases were searched with the keyword 'Hughes Stovin syndrome' covering the period between January 2000 and July 2023. Reviews, non-English language articles, clinical images, vignettes with limited information and those in which definite or possible BS is defined were excluded. Only case reports were considered.

Two reviewers (BO and MSA) independently screened titles, abstracts and

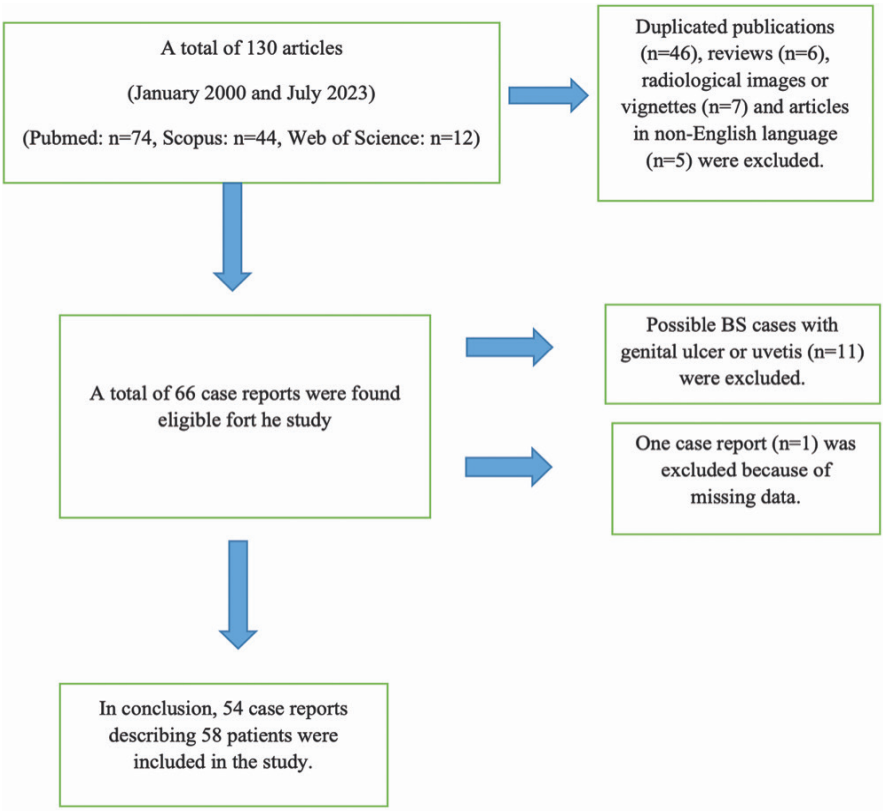

Fig. 1. Flow chart of preparation of Hughes-Stovin syndrome cases.

the full texts retrieved from the searches and assessed these for eligibility against the predetermined inclusion criteria (PICOS). Clinical vignettes or images were not included in the search. Only articles written in English language and case reports were examined. In case of disagreement, a third reviewer'(ES) decision was accepted. A total of 130 case reports and reviews (PubMed: n=74, Scopus: n=44, WOS: n=12) were identified. Forty-six duplicates, 6 reviews or radiological case series, 7 radiological images or vignettes and 5 articles in non-English language were excluded. 11 case reports describing definite or possible BS cases with genital ulcers and or uveitis and 1 case report with insufficient information were also excluded. As a result, 54 case reports describing 58 patients with HSS were included in the study (17-70) (Table I). Of these, 45 (77.6%) were published after 2010. Both HSS and BS patients were analysed with a standard evaluation form. The form includes features such as disease duration, laboratory data, vascular involvement sites, and treatment given. Patient's ethnicity was recorded if not available that of the first author's was noted.

Statistical analysis

Descriptive statistical analysis was performed. Continuous values with normal distribution were expressed as mean and standard deviation, categorical values were expressed as median [IQR] and frequencies as n (%). Student's t-test for continuous values and Fisher's exact or chi-square tests for categorical values were used for statistical comparison between two groups. A Kaplan-Meier plot was used for survival analysis and the log-rank test was used to determine differences in survival. Survival duration was cut at 5 years. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed with the SPSS software programme (v. 21) (Chicago, IL, USA).

Ethical statement

This study was approved by the Clinical Researches Ethics Committee, Istanbul Education and Research Hospital, University of Health Sciences, Istanbul, Turkey (14/01/2022-10).

Results

We studied 74 patients with BS and 58 with HSS. A total of 31 (41.9%) patients with BS were diagnosed after 2010, whereas 45 (77.6%) cases with HSS were published after the same year.

Demographic and clinical characteristics

All BS patients were of Turkish origin. HSS cases were originated mainly from Middle-East and Africa (32.8%) and central Asia (20.7%) (Table II).

BS (62M/12F) and HSS (43M/15F) cases were similar in terms of mean age at disease onset (29.51±8.28 *vs*. 30.82±10.82 years) and male predominance (83.8% *vs*. 74.1%) (Table III). To note, 9.5% and 8.6% were juvenile onset (≤16 years of age) in BS and HSS, respectively. Haemoptysis was the most common symptom in both diseases (77% *vs*. 86.2%). Other presenting symptoms were also similarly distributed between BS and HSS cohorts (Table III). A total of 92.6% in BS and 86.0% in HSS had elevated acute phase response at presentation. As expected, the median follow-up period was significantly longer among BS patients (5 years) compared to that observed in HSS patients (12 months). As we have explained in the Methods earlier, we had excluded 11 possible BS patients from the HSS cohort. Yet, there were 16 (27.6%) additional patients with BS stigmata in the HSS cohort such as recurrent oral ulceration (n=10), erythema nodosum (n=1), arthralgia (n=1), transverse myelitis (n=1), HLA B51 positivity (n=2), and pathergy positivity (n=1).

Radiologic features of pulmonary artery involvement

While PAAs were significantly more common in HSS, isolated PAT was significantly more frequent in BS (Table IV). PAA with or without PAT were detected in 49 (66.2%) BS patients and 56 (96.6%) HSS cases (p<0.001). Isolated PAT was observed in 25 (33.8%) BS patients and 2 (3.4%) HSS cases. PAT accompanying PAA was observed in 43 (58.1%) BS patients and 32 (55.2%) HSS cases.

We did a secondary analysis to see the

Table I. Hughes-Stovin syndrome cases obtained from the literature.

Ref. no.	Age of Onset/Gender	Behçet'specific skin and mucosa lesion	Cough	Haemoptysis	Shortness of Breath	Chest pain	Pulmonary involvement	Non-pulmonary vascular involvement	Immuno-suppressive treatment	Surgery	Embo-lisation
17	21/M	-	+	+	-	-	PAA	+	+	-	-
18	37/F	OA	+	+	-	-	PAA	-	+	-	-
18	33/M	OA	+	+	-	-	PAA	-	+	-	-
19	43/M	-	+	-	-	-	PAA	-	-	-	-
20	18/M	-	+	+	-	-	PAA and PAT	+	+	-	-
21	33/M	-	+	+	+	-	PAA and PAT	-	+	-	-
22	35/M	-	+	-	+	-	PAA	+	+	+	-
23	35/F	EN	+	+	-	-	PAA and PAT	-	+	-	-
24	25/M	-	-	-	+	-	PAA	-	+	-	-
25	48/F	-	-	-	-	-	PAA	+	-	-	-
26	19/M	-	+	+	-	-	PAA and PAT	+	+	-	-
27	41/M	-	+	+	+	-	PAA and PAT	-	+	-	-
28	53/M	-	+	+	+	-	PAA and PAT	+	-	-	-
29	28/F	-	+	+	-	+	PAA and PAT	+	+	-	-
30	12/M	Pathergy (+)	+	+	-	+	PAA	+	+	+	-
31	48/M	-	+	+	-	-	PAA and PAT	+	+	-	-
32	42/M	OA	+	+	+	-	PAA and PAT	-	+	-	-
33	42/M	-	+	+	-	-	PAA and PAT	+	+	-	+
34	23/F	OA	+	+	+	-	PAA and PAT	-	+	+	-
35	24/M	-	+	+	+	-	PAA and PAT	-	+	-	-
36	26/M	-	+	+	+	-	PAA	+	-	-	-
37	34/M	-	-	+	-	-	PAA and PAT	+	+	-	-
38	26/M	-	-	+	-	-	PAA	-	+	-	-
38	16/M	-	-	-	-	-	PAT	+	+	-	-
39	297F	-	+	+	-	+	PAA and PAT	-	+	+	+
40	27/M	OA	-	+	-	-	PAA and PAT	-	+	-	-
41	18/M	-	+	+	-	-	PAA and PAT	+	+	-	+
42	25/M	-	+	+	+	-	PAA and PAT	+	+	+	-
43	35/M	-	-	+	+	-	PAA ve PAT	+	-	-	+
44	50/F	-	+	+	+	-	PAA	+	+	+	-
45	11/M	-	+	+	-	-	PAA	+	+	-	-
46	48/M	-	+	-	+	-	PAA and PAT	+	+	+	+
47	28/F	-	-	-	-	-	PAA	+	+	-	-
48	41/M	-	+	-	-	-	PAA	-	+	-	-
49	47/M	-	+	+	+	+	PAT	+	-	+	+
50	45/M	-	-	+	+	-	PAA and PAT	+	+	+	+
51	42/M	-	-	+	-	-	PAA	+	+	-	-
52	41/F	-	-	+	-	-	PAA and PAT	-	+	-	+
53	19/F	OA	-	+	-	-	PAA	-	+	+	-
54	18/M	-	+	+	-	-	PAA	+	+	-	-
55	34/M	-	-	+	-	-	PAA and PAT	+	+	-	-
56	21/M	-	+	+	-	-	PAA and PAT	-	+	+	-
57	33/M	-	+	+	+	+	PAA	-	+	-	+
58	29/M	OA	-	+	-	-	PAA and PAT	+	-	-	-
59	38/M	OA	-	+	-	-	PAA	-	+	-	-
60	24/F	-	+	+	-	-	PAA and PAT	+	+	-	+
61	20/M	-	-	+	+	-	PAA	+	+	-	-
62	48/F	-	+	-	+	-	PAA and PAT	-	+	+	-
63	26/M	-	-	+	-	-	PAA	-	+	+	-
64	24/M	-	+	+	+	-	PAA and PAT	-	+	-	-
65	24/M	-	+	+	+	+	PAA and PAT	+	+	+	+
65	24/M	OA	+	+	+	-	PAA and PAT	+	+	-	-
65	32/M	-	+	+	-	-	PAA and PAT	-	+	-	-
66	30/M	OA	+	+	+	-	PAA and PAT	-	+	-	-
67	28/M	-	-	+	+	-	PAA and PAT	+	+	+	-
68	27/M	-	+	-	-	-	PAA and PAT	+	+	-	-
69	15/M	-	+	+	+	+	PAA and PAT	-	+	+	-
70	11/F	-	+	+	+	-	PAA and PAT	-	+	-	-

M: male; F: female; OA: oral aphthae; EN: erythema nodosum; PAA: pulmonary artery aneurysms; PAT: pulmonary artery thrombosis.

differences between those who were diagnosed or published before (<2010) and after 2010 (≥2010). Before 2010, those with isolated PAA were similarly distributed between the BS and HSS cohorts, respectively (9/43 *vs*. 2/13, p=1.0). After 2010, however, those with isolated PAT were significantly more common among BS patients

Table II. Ethnicity of HSS cases based on country and continent (n=58).

Continent	n (%)	Country	n
Middle-East and Mediterranean basin	18 (31.1)	Egypt	6
		Tunisia	2
		Turkey	4
		Iranian	2
		Jordan	1
		Oman	1
		Saudi Arabia	1
		Morocco	1
Central Asia	12 (20.7)	India	11
		Afghanistan	1
North America	9 (15.5)	Undefined	6
		African-American	3
Europe	7 (12.1)	Germany	1
		France	1
		Greece	2
		Spain	1
		Holland	1
		Albania	1
Far East Asian	6 (10.3)	Korea	5
		Taiwan	1
South America	5 (8.6)	Brazil	1
		Mexican	1
		Chile	1
		Argentina	1
		Colombia	1
Africa	1 (1.7)	Kenya	1

Table III. Demographic characteristics and presenting symptoms.

	BS-Pulmonary involvement n=74	HSS n=58	*p*
Male, n (%)	62 (83.8)	43 (74.1)	0.197
Age, mean ± SD, years	29.51 ± 8.28	30.82 ± 10.82	0.436
Juvenile onset*, n (%)	7 (9.5)	5 (8.6)	1.000
Follow-up time, median [IQR]	5 (3-8 years)	12 [4.5-17.75] months]	<0.001
Presenting signs/symptoms, n (%)			
Fever	24 (32.4)	23 (39.7)	0.465
Weight loss	22 (29.7)	12 (20.7)	0.316
Haemoptysis	57 (77.0)	50 (86.2)	0.263
Cough	42 (56.8)	40 (69.0)	0.206
Chest pain	17 (23.0)	7 (12.1)	0.118
Shortness of breath	39 (52.7)	25 (43.1)	0.297
High acute phase response†, n (%)	63/68 (92.6)	37/43 (86.0)	0.332

BS: Behçet's syndrome; HSS: Hughes-Stovin syndrome.
*≤16 years of age.
†Acute phase values were reported in 68 patients in the BS and 36 in the HSS group.

when compared to that among HSS patients (16/31 *vs*. 0/45, $p<0.001$).

A total of 35 (47.3%) and 25 (43.1) patients with BS and HSS, respectively had multiple arterial involvement (≥3). Information regarding anatomical location and size of PAA was available in all among BS patients whereas in 39 patients (67.2%) among the HSS cases. The lower lobe was most frequently involved among both BS (59.7%) and HSS patients (59.4%), respectively. When the largest PAA was considered, the median pulmonary aneurysm diameter was measured as 2.4 and 2cm in BS and HSS, respectively.

Non-pulmonary vascular involvement

There was no difference between the groups regarding the types and frequency of non-pulmonary vascular involvement. Lower extremity DVT (59.5% *vs*. 48.3%) was the most common form of involvement followed by inferior vena cava (20.3% *vs*. 24.1%) and intracardiac thrombosis (32.4% *vs*. 27.6%) in both BS and HSS. It was noted that right chambers of the heart were primarily involved in both syndromes. Dural sinus, superior vena cava, and hepatic veins were identified as less frequently involved veins (Table V). Additionally, non-pulmonary arterial involvement was observed in both BS (5.4%) and HSS (12.1%) cohorts.

Histopathological examination

Histopathological examination was available in 14 (18.9%) of BS and 13 (22.4%) of HSS cases. These were obtained through lobectomy or segmentectomy in 3 patients with BS and 8 with HSS. Wedge resection of a lung nodule was done using video assisted thoracoscopic surgery (VATS) in 7 patients with BS and 2 with HSS. Surgical excision of intracardiac thrombus and endarterectomy were performed in one patient in each group. Additionally, lung tissues were obtained while doing cavity repair in 2 patients with BS. Biopsy from lymphoid tissues was taken with mediastinoscopy in one patient with HSS.

As shown in Table VI, histopathological features consisted mostly of vasculitis which seems non-specific, arterial elastic layer disruption leading to aneurysms, organised thrombus, infarction, organising pneumonia in both groups. Similarly, intracardiac thrombotic material or endarterectomy specimens exhibited organising thrombus with non-specific inflammatory exudate in both BS and HSS.

Medical and surgical treatment

As shown in Table VII, there were significant differences in the treatment between the groups. HSS cases were treated with less immunosuppressive and/or glucocorticoids than BS cases (87.9% *vs*. 100%), ($p=0.003$). On the other hand, they received anticoagulant treatment at a much higher rate (48.3% *vs*. 14.9%, $p<0.001$). VCI filter, vascular intervention or embolisation and

Table IV. Pulmonary artery involvement type and descriptive features.

	BS-Pulmonary involvement n=74	HSS n=58	*p*
Pulmonary artery involvement type			
PAA with or without PAT	49 (66.2)	56 (96.6)	<0.001
Isolated PAT	25 (33.8)	2 (3.4)	
PAT with PAA	43 (58.1)	32 (55.2)	0.860
Number of pulmonary arteries involved, n (%)			
1 artery	23 (31.1)	23 (39.7)	0.166
2 arteries	16 (21.6)	10 (17.2)	
≥3 arteries	35 (47.3)	25 (43.1)	
Pulmonary artery anatomical localisation	74 patients	39 patients	
Main	28 (15.9)	5 (9.1)	0.663
Upper	31 (17.6)	10 (18.2)	
Middle	12 (6.8)	1 (1.8)	
Lower	105 (59.7)	39 (70.9)	
Total lesion	176	55	
Aneurysm size			0.515
median (IQR)	2.4 (2.0-3.0) cm	2 (1.75-3.25) cm	
minimum-maximum	0.5-7 cm	1-9 cm	

PAA: pulmonary artery aneurysms; PAT: pulmonary artery thrombosis; IQR: inter-quartile range.

Table V. Non-pulmonary vascular involvement.

	BS-Pulmonary involvement n=74	HSS n=58	*p*
Lower extremity deep vein thrombosis, n (%)	44 (59.5)	28 (48.3)	0.221
Inferior vena cava thrombosis, n (%)	15 (20.3)	14 (24.1)	0.674
Hepatic vein, n (%)	6 (8.1)	1 (1.9)	0.134
Superior vena cava thrombosis, n (%)	6 (8.1)	2 (3.4)	0.465
Dural sinus thrombosis, n (%)	9§ (12.2)	5* (8.6)	1.000
Non-pulmonary arterial involvement, n (%)	4 (5.4)	7 (12.1)	0.211
Cardiac thrombosis, n (%)	24 (32.4)	16 (27.6)	0.573
Right atrium	7 (9.5)	5 (9.3)	
Right ventricle	16 (21.6)	10 (17.2)	
Right atrium and ventricle	1 (1.4)	1 (1.9)	

*Chronic thrombosis in one or more dural sinuses (superior and sagittal sinus: n=1, left sigmoid and transverse sinus: n=1, sagittal sinus: n=1, unspecified: n=2) was found in 5 patients in the HSS group. §In the BS group, chronic thrombus (sagittal sinus: n=8, transverse: n=4, cavernous: n=1, sigmoid: n=1) was observed in one or more dural sinuses in 9 patients.
Multiple thrombotic arterial occlusions (superficial femoral artery, popliteal artery, distal abdominal aorta and left common iliac artery and left tibial arteries) were detected in one patient in the HSS group. Various involvements in other HSS cases (abdominal aortic thrombosis: n=1, aneurysm in the right femoral artery: n=1, left internal iliac arterio-venous aneurysm: n=1, left renal artery and left superior mesenteric artery thrombosis: n=1, left hepatic artery aneurysm: n=1, splenic and mesenteric artery aneurysm: n=1) were observed. In BS patients, 4 patients had arterial involvement (thrombosis of the left superficial femoral artery: n=1, popliteal artery aneurysm n=1, occlusion in the brachiocephalic artery: n=1, superior cerebellar artery aneurysm: n=1).

surgical intervention were used more commonly in HSS cases (Table VII). More than one surgical operation was described in a total of 17 HSS cases such as lobectomy or segmentectomy (n=13), endarterectomy (n=1), right atrial embolectomy (n=1), excision of atrial vegetation by sternotomy (n=1) and valve replacement (n=1). Surgical intervention was performed in 7 patients in BS patients; these were defined as lobectomy or segmentectomy (n=3), bullectomy and pleural repair (n=1), empyema surgery after a complicated embolisation (n=1) right atrial thrombus excision (n=1) and endarterectomy (n=1). Apart from lung surgery, peripheral arterial surgical interventions were documented in 1 patient with BS and 2 with HSS.

Mortality

As seen in the Kaplan-Meier plot, the 5-year mortality rate was similar between BS and HSS patients (12/74 *vs.* 3/58) (log Rank *p*=0.178) (Fig. 2). All but one patient who died were male in BSS while all 3 were male in HSS. All fatalities in both BS and HSS occurred before 2010. It has to be noted that, the prognosis of two additional patients with HSS was deemed to be poor as indicated 'transferring for lung transplantation' and 'requiring endarterectomy', respectively (67, 70).

Discussion

Our comparative study revealed that HSS and BS are almost identical. Not only the demographic and clinical characteristics, but also the presentation with fever and high acute phase response, anatomical location of involved pulmonary artery, mean size of pulmonary artery aneurysm, lung parenchymal pathology findings, accompanying systemic venous thrombosis or arterial disease outside the lungs and mortality rate were also quite similar.

The similarities between HSS and BS have been observed by others, as well (13, 14, 18, 36, 38, 53). As emphasised by Erkan *et al*., young male predilection, strong association with systemic thrombosis, multiple and bilateral involvement in the lungs with a tendency towards lower lobes and fatal outcome due to the rupture of the aneurysms are indeed valid for both syndromes (36). Diverse inflammatory features associated with BS such as recurrent oral ulcers, erythema nodosum, arthralgia, HLAB 51 and pathergy positivity and transverse myelitis were documented in patients with HSS despite strict exclusion of probable BS cases (18, 23, 32-34, 40, 47, 53, 54, 58, 59, 65, 66, 70). Furthermore, ethnic origin of the patients with HSS also overlaps with that of BS as shown in our study (Table II). One review of the literature showed that 159 of 207 cases (77%) with PAA due to BS were from the Middle East and the Mediterranean basin, regions where BS is most prevalent (71). As found in the current study HSS cases were predominantly originated from the same geographical areas as well.

Table VI. Histopathological examination.

Behçet's syndrome-pulmonary involvement, n=14 (18.9%)		
Anatomical location	Procedure	Histopathological description
Lung tissue (n=4)	Nodule - lung wedge resection (VATS)	Haemorrhagic infarct and fibrosis alveolitis in surrounding tissue
Lung tissue (n=2)	Nodule - lung wedge resection (VATS)	Organised pneumonia
Lung tissue (n=1)	Nodule - lung wedge resection (VATS)	Necrotising granulomatous inflammation, necrosis, haemorrhagic infarct
Lung tissue (n=2)	Lobectomy	Ruptured giant saccular aneurysm formation with total disruption in the arterial wall. A fistulous penetration of arterial aneurysm into the bronchial tissue. Destruction of the elastic fibres in the media of the pulmonary artery, adventitial fibrosis and thrombus occupying almost the entire lumen. Signs of vasculitis and occlusive vasculopathy in small sized arteries of the surrounding pulmonary parenchyma. Lymphoplasmocytic infiltration within the arterial walls of small and medium sized arteries and the vasa vasorum of the arteries. Neighbouring parenchyma includes areas of haemorrhagic infarction and organised pneumonia.
Lung tissue (n=1)	Segmentectomy	Pulmonary artery with occlusive thrombus. Vascular wall thickening with inflammatory infiltrate and fibrosis in the pulmonary artery.
Lung tissue (n=2)	Cavity repair	Infarction, necrotic changes
Cardiac tissue (n=1)	Thrombus excision	Organising acute thrombus with inflammatory exudate
Lung tissue (n=1)	Endarterectomy	Chronic thrombus with fibrotic changes
Hughes-Stovin syndrome n=13, (22.4%)		
Anatomical location	Procedure	Histopathological description
Lung tissue (n=1)	Nodule - lung wedge resection (VATS)	Lymphocytic vasculitis
Lung tissue (n=1)	Nodule - lung wedge resection (VATS)	Pulmonary infarction and lymphocytic infiltration of the vessels suggesting vasculitis
Lung tissue (n=1)	Lobectomy	Vascular wall thickening with dense inflammatory infiltrate and aneurysm with thrombus and haemorrhage in pulmonary arteries.
Lung tissue (n=1)	Segmentectomy	Enlarged vascular structures in the bronchial submucosa with rupture
Lung tissue (n=1)	Lobectomy	Multifocal arterial thrombosis with marked luminal narrowing, partial destruction of arterial wall, and marked intimal fibrosis
Lung tissue (n=1)	Lobectomy	Pulmonary artery wall showing a lymphocytic inflammatory infiltrate in the arterial wall, marked dilatation of the lumen, intraluminal thrombosis, multifocal intimal fibrinoid necrosis, and elastic layer fragmentation.
Lung tissue (n=2)	Lobectomy	Capillaritis, haemorrhage and multiple clots / Vasculitis
Lung tissue (n=1)	Lobectomy	Active vasculitis and fibrosis with destruction of elastic tissue
Lung tissue (n=1)	Segmentectomy	Necrotising lymphocytic vasculitis with pulmonary infarction
Thrombus material (n=1)	Endarterectomy	Inflammatory findings
Cardiac tissue (n=1)	1) Endomyocardial biopsy, 2) Thrombus excision	1) Detached fibrin with acute and chronic inflammation 2) Organising acute thrombus with inflammatory exudate
Lymphoid tissue (n=1)	Mediastinoscopy	Reactive changes

VATS: video assisted thoracoscopic surgery.

Histopathological examination in both HSS and BS cases reveals findings consistent with infarct, organising pneumonia, organised thrombus, and vasculitis. Vascular wall destruction and aneurysm formation as a result of perivascular lympho-monocytic cell infiltration and obliterating endarteritis of the vasa vasorum are seen in both diseases (Table VI). Moreover, there is a good response to immunosuppressive treatment rather than anti-coagulants in HSS, similar to that seen in BS. These shared features suggest a common underlying inflammatory process in these syndromes, reinforcing the idea that HSS and BS are indeed the same disease.

There were however some significant differences that, we believe, have stemmed mainly from methodological approaches used to gather BS and HSS cohorts. While most of the HSS cases had presented with PAA, patients with isolated PAT were significantly more common in the BS cohort. Compared to BS, HSS cases were treated more frequently with anti-coagulation and less commonly with immunosuppressive treatment. Additionally, vascular interventions and surgical operations were used more frequently in the follow-up of HSS cases than that seen in the BS cohort. It has to be noted that, HSS cohort was basically an artificial cohort composed of case reports coming from mainly surgery departments whereas that of BS was a real-time patient cohort followed in a rheumatology centre with distinctly longer follow-up. These discrepancies between two cohorts could explain inequalities in radiological features and lack of standardisation in management.

There may be other reasons why HSS patients have more PAA, but fewer

isolated in-situ thrombosis compared to BS. One possible explanation is that HSS has historically been defined solely in the context of aneurysms, with in-situ thrombosis being an unknown aspect. Even for those dealing with BS, isolated in situ thrombosis without aneurysm in PAI was not recognised until more recently (4, 5, 7, 9). In early BS case series before 2000, PAA were almost always the sole lesion associated with pulmonary arteries (4, 5). PAT may have been overlooked because of the limited imaging techniques or subtler clinical presentations compared to patients with aneurysms. Indeed, in the current study, among 74 BS patients, there were only 20.9% (9/43) with isolated PAT before 2010, whereas after 2010, this has raised to 51.6% (16/31) (p=0.012). Similarly, increased rates of PAT have been reported in recent clinical series of BS with PAI (72-74). We have showed that isolated PAT and PAA have similar clinical findings and respond to the same immunosuppressive therapy, suggesting that they represent the same clinical spectrum (7, 9). Importantly, cases with PAA who were previously documented to have solo PAT suggest that PAT could be indeed the precursor in this spectrum (7, 29, 49, 75). On the HSS side, however, the concept of isolated PAT apparently has not been recognised yet. The second reason could be selection and reporting bias, as well. PAA, with its demonstrative imaging features and severe clinical course, may be more prominently acknowledged and reported compared to isolated PAT, which might have indistinct radiological features and could be challenging to differentiate from pulmonary emboli associated with non-BS causes. This potential bias may lead to an underestimation of isolated PAT cases in the literature.

In our study, we noted that patients with HSS were less commonly given immunosuppressive therapy but underwent intravascular or surgical interventions more frequently compared to BS patients. These concerning trends might be attributed to the fact that patients are primarily monitored by surgery clinics. While one might expect increased mortality due to the lesser use of immunosuppressive therapy, we found no significant difference in mortality rates between BS and HSS. However, this observation should be interpreted cautiously due to the unequal follow-up durations, with HSS having a median follow-up of 12 months compared to 5 years in BS. Additionally, reporting bias could have resulted in less frequent documentation of case reports leading to deaths in the HSS group.

In recent years, a prevailing perspective has emerged, suggesting that BS incorporates several distinct clinical phenotypes (76). Among these phenotypes, the vascular subtype has gained recognition as a unique group as indicated by factor analysis studies (77). Vascular phenotype is characterised by male predilection, venous/arterial or cardiac lesions accumulating with each attack, whereas lower frequencies of genital, ocular and joint involvement (1, 78). Notably, approximately 30% of BS patients with vascular involvement do not exhibit skin-mucosa lesions at the time of diagnosis (79). The presence of HSS can be regarded as evidence that the vascular phenotype develops independently in BS. This concept of vascular

Table VII. Medical and interventional treatment.

	BS-Pulmonary involvement n=74	HSS n=58	p-value
Any glucocorticoids or immunosuppressives, n (%)	74 (100)	51 (87.9)	0.003
Glucocorticoid, n (%)	74 (100)	50 (86.2)	0.001
Azathioprine, n (%)	57 (77.0)	17 (29.3)	<0.001
Cyclophosphamide, n (%)	65 (87.8)	30 (51.7)	<0.001
Anti-TNF agents, n (%)	21 (28.4)	6 (10.3)	0.016
Colchicine, n (%)	26 (35.1)	3 (5.2)	<0001
Anti-coagulant therapy, n (%)	11 (14.9)	28 (48.3)	<0.001
Anti-aggregants, n (%)	9 (12.2)	3 (5.2)	0.227
VCI filter, n (%)	0	4 (6.9)	0.035
Vascular intervention or embolisation n (%)	7 (9.5)	15 (25.9)	0.018
Surgical intervention, n (%)	7 (9.5)	17 (29.3)	0.006

BS: Behçet's syndrome; HSS: Hughes-Stovin syndrome; VCI: vena cava inferior; TNF: tumour necrosis factor.

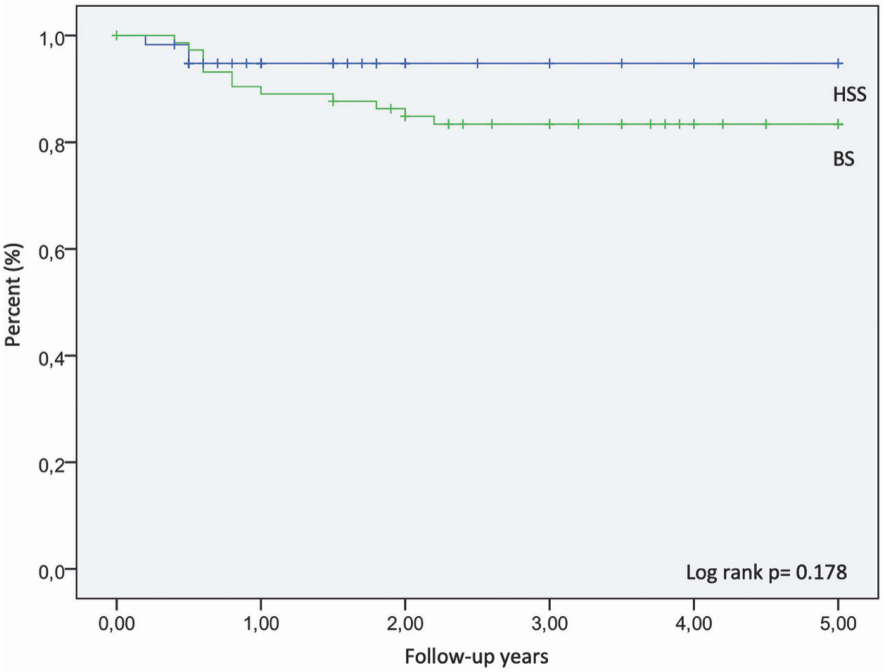

Fig. 2. Kaplan-Meier plot comparing 5-year survival rates in patients Behçet's syndrome (BS) and Hughes-Stovin syndrome (HSS).

involvement in BS, separate from skin and mucosal findings, extends to other major organ systems as well. In BS, eye and parenchymal neurologic system involvements can similarly manifest without the characteristic skin-mucosa lesions. Interestingly, these major organ manifestations are rather rare whereas quite pathognomonic, given their distinctive features in contrast to much more common skin-mucosa lesions (1, 80, 81).

With these data at hand, we propose categorising HSS as an "incomplete Behçet syndrome", aligning with previous suggestions (36). We believe that employing a separate terminology, such as HSS, unnecessarily complicates our understanding of the pathogenesis of BS and delays the diagnosis, hence the initiation of appropriate immunosuppressive treatments. Moreover, unwarranted surgical and intravascular interventions may increase the risk of complications and mortality in these cases. It is also important to note that, there is inevitably a delay in diagnosis when patients present with particularly large PAA. Isolated PAT in combination with systemic thrombosis should be regarded as the initial phase in PAA and promptly treated with immunosuppressive agents to prevent a grim outcome.

Our study has limitations. The different methodology that we have used cause obviously the main limitation. HSS case reports in the literature may be subject to potential selection and reporting biases. BS and HSS cohorts obviously differ in terms of follow-up time and lack of standardisation in clinical examination and management approaches. For the sake of a fairer comparison, we had to exclude probable BS and HSS cases, from the HSS and BS cohorts, respectively. Finally, it is essential to note that we did not compare our findings with published BS-PAI cases, as it was not the primary objective of our study. This remains a potential subject for future research.

Conclusions

The occurrence of PAA and the simultaneous presence of systemic thrombosis represent a nearly unique manifestation of BS. On the other hand, the same combination of features was also coined earlier as HSS. As revealed in the current study, several evidences including histopathological findings indicate that HSS is indeed an 'incomplete form of BS'. Furthermore, the term 'HSS' do not cover isolated PAT which could be a precursor of PAA and additionally, creates an ambiguity in our understanding the pathogenesis.

BS incorporates several distinct clinical phenotypes. Among them, the vascular phenotype has recently gained recognition as a distinct clinical phenotype with a predisposition for vascular events and a less frequent occurrence of eye and genital lesions. Indeed, HSS can be considered as evidence supporting the notion that the vascular phenotype develops independently from skin-mucosa lesions and uveitis in BS. Whether vascular phenotype in BS merits its own set of diagnostic criteria warrants exploration in the future.

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References

1. YAZICI H, SEYAHI E, HATEMI G, YAZICI Y: Behçet syndrome: a contemporary view. *Nat Rev Rheumatol* 2018; 14: 107-19. https://doi.org/10.1038/nrrheum.2017.208
2. KURAL-SEYAHI E, FRESKO I, SEYAHI N *et al*.: 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(1): 60-76. https://doi.org/10.1097/00005792-200301000-00006
3. BEHÇET H, MATTESON EL: On relapsing, aphthous ulcers of the mouth, eye and genitalia caused by a virus. 1937. *Clin Exp Rheumatol* 2010; 28 (Suppl. 60): S2-5.
4. HAMURYUDAN V, ER T, SEYAHI E *et al*.: Pulmonary artery aneurysms in Behçet syndrome. *Am J Med* 2004; 117(11): 867-70. https://doi.org/10.1016/j.amjmed.2004.05.027
5. HAMURYUDAN V, YURDAKUL S, MORAL F *et al*.: Pulmonary arterial aneurysms in Behçet's syndrome: a report of 24 cases. *Br J Rheumatol* 1994; 33(1): 48-51. https://doi.org/10.1093/rheumatology/33.1.48
6. HAMURYUDAN V, OZ B, TUZUN H, YAZICI H: The menacing pulmonary artery aneurysms of Behçet's syndrome. *Clin Exp Rheumatol* 2004; 22 (Suppl. 34): S1-3.
7. SEYAHI E, MELIKOGLU M, AKMAN C *et al*. Pulmonary artery involvement and associated lung disease in Behçet disease: a series of 47 patients. *Medicine* (Baltimore) 2012; 91(1): 35-48. https://doi.org/10.1097/md.0b013e318242ff37
8. SEYAHI E, BASKURT M, MELIKOGLU M *et al*. The estimated pulmonary artery pressure can be elevated in Behçet's syndrome. *Respir Med* 2011; 105(11): 1739-47. https://doi.org/10.1016/j.rmed.2011.07.022
9. SEYAHI E, YAZICI H: Behçet's syndrome: pulmonary vascular disease. *Curr Opin Rheumatol* 2015; 27(1): 18-23. https://doi.org/10.1097/bor.0000000000000131
10. ESATOGLU SN, SEYAHI E, UGURLU S *et al*. Bronchial artery enlargement may be the cause of recurrent haemoptysis in Behçet's syndrome patients with pulmonary artery involvement during follow-up. *Clin Exp Rheumatol* 2016; 34(6): 92-96.
11. TUZUN H, SEYAHI E, GUZELANT G *et al*.: Surgical treatment of pulmonary complications in Behçet's syndrome. *Semin Thorac Cardiovasc Surg* 2018; 30(3): 369-78. https://doi.org/10.1053/j.semtcvs.2018.07.008
12. HUGHES JP, STOVIN PG: Segmental pulmonary artery aneurysms with peripheral venous thrombosis. *Br J Dis Chest* 1959; 53(1): 19-27. https://doi.org/10.1016/s0007-0971(59)80106-6
13. KHALID U, SALEEM T: Hughes-Stovin syndrome. *Orphanet J Rare Dis* 2011; 13(6): 15. https://doi.org/10.1186/1750-1172-6-15
14. EMAD Y, RAGAB Y, KECHIDA M *et al*.: A critical analysis of 57 cases of Hughes-Stovin syndrome (HSS). A report by the HSS International Study Group (HSSISG). *Int J Cardiol* 2021; 331: 221-29. https://doi.org/10.1016/j.ijcard.2021.01.056
15. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's disease. *Lancet* 1990; 335(8697): 1078-80. https://doi.org/10.1016/0140-6736(90)92643-v
16. MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG; PRISMA GROUP: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151(4): 264-69. https://doi.org/10.7326/0003-4819-151-4-200908180-00135
17. BAWASKAR P, CHAURASIA A, NAWALE J, NALAWADE D: Multimodality imaging of Hughes-Stovin syndrome. *Eur Heart J* 2019; 40(43): 3570. https://doi.org/10.1093/eurheartj/ehz292
18. DEMIRKAN S, GULTEKIN Y: Hughes-Stovin syndrome as an outcome of Behçet disease or as a different entity. *Korean J Thorac Cardiovasc Surg* 2018; 51: 64-68. https://doi.org/10.5090/kjtcs.2018.51.1.64
19. RIBEIRO BN, RIBEIRO RN, ZANETTI G, MARCHIORI E: Hughes-Stovin syndrome: an unusual cause of pulmonary artery aneurysms. *Radiol Bras* 2016; 49(3): 202-3. https://doi.org/10.1590/0100-3984.2015.0048
20. CHALAZONITIS AN, LACHANIS SB, MITSEAS P *et al*. Hughes-Stovin syndrome: a case report and review of the literature. *Cases J* 2009; 2: 98. https://doi.org/10.1186/1757-1626-2-98.
21. ILYAS M, BHAT TA, DEV G: Hughes-Stovin syndrome-a rare entity with combination of venous thrombosis and multiple pulmonary arterial aneurysms. *Indian J Thorac Cardiovasc Surg* 2018; 34(3): 429-31. https://doi.org/10.1007/s12055-017-0591-1
22. EMAD Y, RAGAB Y, EL-SANTAWI H, EL-MARAKBI A, RASKER JJ: A case of Hughes-Stovin syndrome (incomplete Behçet's disease) with

extensive arterial involvement. *Z Rheumatol* 2019; 78: 365-71. https://doi.org/10.1007/s00393-019-0640-9
23. ABDELBARY M, EL-MASRY A, RABIE MS: Life threatening hemoptysis from Hughes-Stovin syndrome: Is it that rare? *Respir Med Case Rep* 2016; 19: 98-102. https://doi.org/10.1016/j.rmcr.2016.08.003
24. SILVA R, ESCOBAR A, VEGA R, TAPIA R: Síndrome Hughes-Stovin. Caso clínico Hughes-Stovin syndrome. Report of one case. *Rev Med Chil* 2013; 141: 922-26. https://doi.org/10.4067/S0034-98872013000700013
25. JAMBEIH R, SALEM G, HUARD D, JONES K, AWAB A: Hughes-Stovin syndrome Presenting with Hematuria. *Am J Med Sci* 2015; 350(5): 425-26. https://doi.org/10.1097/maj.0000000000000571
26. VALDES-CORONA LF, KIMURA-HAYAMA E, MENDEZ-CANO VH, HERNANDEZ-VILLEGAS CA, HERNANDEZ-MOLINA G: Hughes-Stovin syndrome: an uncommon cause of pulmonary aneurysms. *Rheumatology* (Oxford) 2020; 59(8): 2183-84. https://doi.org/10.1093/rheumatology/kez663
27. PANKL S, MERALDI A, PEGORARO P *et al*.: Síndrome de Hughes-Stovin. *Medicina* (B Aires) 2015; 75: 95-98.
28. AL-ZEEDY K, JAYAKRISHNAN B, RIZAVI D, ALKAABI J: Hughes-Stovin syndrome and massive hemoptysis: a management challenge. *Oman Med J* 2015; 30: 59-62. https://doi.org/10.5001/omj.2015.11
29. KESKIN M, POLAT G, AYRANCI A *et al*.: Insidious Hughes-Stovin syndrome: journey from pulmonary embolism to pulmonary arterial aneurysm. *Turk Thorac J* 2020; 21(5): 350-53. https://doi.org/10.5152/turkthoracj.2018.19088
30. FABI M, LAMI F, ZOMPATORI M: Persistent fever with chills and an endocardial mass in a child: an unusual presentation of Hughes-Stovin syndrome. *Cardiol Young* 2017; 27(3): 605-8. https://doi.org/10.1017/S1047951116001608
31. FISCHER A, KORMAN DS, WEST SG: Radiologic vignette: Hughes-Stovin syndrome. *Arthritis Rheum* 2005; 53(1): 114-16. https://doi.org/10.1002/art.20907
32. AOUD SE, FRIKHA F, SNOUSSI M, BAHLOUL Z: Moderate hemoptysis caused by Hughes-Stovin syndrome. *Clin Pract* 2014; 4(3): 647. https://doi.org/10.4081/cp.2014.647.
33. MARGOLESKYN J, TORNES L, VOSOUGHI A: Transverse myelitis presenting in a patient with Hughes-Stovin syndrome. *Mult Scler Relat Disord* 2015; 4(3): 281-83. https://doi.org/10.1016/j.msard.2015.04.004
34. AL-JAHDALI H: Massive hemoptysis and deep venous thrombosis presenting in a woman with Hughes-Stovin syndrome: a case report. *J Med Case Rep* 2010; 4: 109. https://doi.org/10.1186/1752-1947-4-109
35. KIM H-O, KIM HC, PARK Y *et al*.: A case of Hughes-Stovin syndrome associated with hyperhomocysteinemia. *Clin Rheumatol* 2010; 29: 807-9. https://doi.org/10.1007/s10067-010-1393-7
36. ERKAN D, YAZICI Y, SANDERS A, TROST D, YAZICI H: Is Hughes-Stovin syndrome Behçet's disease? *Clin Exp Rheumatol* 2004; 22 (Suppl. 34): S64-68.
37. TSAI C-L, LU T-C, TSAI K-C, CHEN W-J: Hemoptysis caused by Hughes-Stovin syndrome. *Am J Emerg Med* 2005; 23: 209-11. https://doi.org/10.1016/j.ajem.2004.05.009
38. EMAD Y, RAGAB Y, SHAWKI AEL-H, GHEITA T, EL-MARAKBI A, SALAMA MH: Hughes-Stovin syndrome: is it incomplete Behçet's? Report of two cases and review of the literature. *Clin Rheumatol* 2007; 26(11): 1993-96. https://doi.org/10.1007/s10067-007-0609-y
39. CURCI NE, BILFINGER TV: Successful multimodality treatment of a young woman with Hughes-Stovin syndrome. *Am Surg* 2012; 78(5): 304-5.
40. MAHFOUDHI M, TURKI S: A pulmonary aneurysm: don't forget Hughes-Stovin syndrome. *Pan Afr Med* 2015; 20: 445. https://doi.org/10.11604/pamj.2015.20.445.5938
41. TZILALIS VD, VOURLIOTAKIS G, TSIRONIS IA, TSILIGIRIS VD, BROUNTZOS EN: Use of an Amplatzer Vascular Plug-in embolization of a pulmonary artery aneurysm in a case of Hughes-Stovin syndrome: a case report. *J Med Case Rep* 2011; 5: 425. https://doi.org/10.1186/1752-1947-5-425
42. BK A, TYMKO C, SUBEDI R, VIRK J, CHAUDHURI D: Hughes-Stovin syndrome, a rare form of Behçet's disease presenting as recurrent intracardiac thrombus. *Cureus* 2020; 12(5): 7907. https://doi.org/10.7759/cureus.7907
43. JARAMILLO N, GOMEZ-BUENO M, SUAREZ AG *et al*. Combined pulmonary vasodilator therapy and endovascular intervention for Hughe-Stovin syndrome. *Int J Cardiol* 2015; 15: 178. https://doi.org/10.1016/j.ijcard.2014.08.091
44. KINDERMANN M, WILKENS H, HARTMANN W, SCHAFERS H-J, BOHM M: Hughes-Stovin syndrome. *Circulation* 2003; 108(23): 156. https://doi.org/10.1161/01.cir.0000106680.35316.16
45. VRIES WD, KOPPELMAN GH, ROOFTHOOFT MT, BOOTSMA H, LEIJSMA MK, ARMBRUST W: Pulmonary medium vessel vasculitis in an 11-year-old boy: Hughes-Stovin syndrome as a variant of polyarteritis nodosa? *Pediatr Rheumatol Online J* 2011; 9: 19. https://doi.org/10.1186/1546-0096-9-19
46. LEE J, NOH J-W, HWANG JW *et al*.: Successful cyclophosphamide therapy with complete resolution of pulmonary artery aneurysm in Hughes-Stovin syndrome patient. *Clin Rheumatol* 2008; 27: 1455-58. https://doi.org/10.1007/s10067-008-0951-8
47. AMEZYANE T, BASSOU D, ABOUZAHIR A *et al*.: Unusual right ventricular thrombus in a woman with Hughes-Stovin syndrome. *Intern Med* 2010; 49: 207-8. https://doi.org/10.2169/internalmedicine.49.2941
48. ALI-MUNIVE A, VARON H, MALDONADO D, TORRES-DUQUE C: Giant aneurysms of the pulmonary artery and peripheral venous thrombosis (Hughes-Stovin syndrome): regression with immunosuppressant therapy. *Arch Bronconeumol* 2001; 37(11): 508-10. https://doi.org/10.1016/s0300-2896(01)75131-9
49. KETCHUM ES, ZAMANIAN RT, FLEISCHMANN D: CT angiography of pulmonary artery aneurysms in Hughes-Stovin syndrome. *Am J Roentgenol* 2005; 185: 330-32. https://doi.org/10.2214/ajr.185.2.01850330
50. KIM JT, OH TY, CHANG WH: Rare case of multiple pulmonary artery aneurysms with caval thrombosis - Hughes-Stovin syndrome. *Eur J Cardiothorac Surg* 2007; 31(3): 561-62. https://doi.org/10.1016/j.ejcts.2006.12.005
51. KHALIL A, PARROT A, FARTOUKH M, MARSAULT C, CARETTE M: Large pulmonary artery aneurysm rupture in Hughes-Stovin syndrome: multidetector computed tomography pattern and endovascular treatment. *Circulation* 2006; 114: 380-81. https://doi.org/10.1161/circulationaha.106.614636
52. KABLYA IM, REVERON C: Multimodal endovascular management of a Jehovah's Witness patient with Hugues-Stovin syndrome presenting with ruptured pulmonary artery aneurysm and cardiopulmonary thromboembolism. *Eur J Cardiothorac Surg* 2015; 47: 158-61. https://doi.org/10.1093/ejcts/ezu529
53. LEE W-Y, HOON CS, KIM HR: Massive hemoptysis caused by atypical Behçet's disease. *Korean J Thorac Cardiovasc Surg* 2014; 47: 178-80. https://doi.org/10.5090/kjtcs.2014.47.2.178
54. NICHANAMETLA S, KRISHNAN N, VEER SN: Multiple pulmonary artery aneurysms in Hughes-Stovin syndrome. *Arthritis Rheumatol* 2021; 73(9): 1737. https://doi.org/10.1002/art.41759
55. HAMDY F, THARWAT S, ABDELWAHAB HW, OKASHA H, ELTORABY EE: Hughes-Stovin syndrome without venous involvement - Unusual presentation of a rare disease: case report and review of the literature. *The Egyptian Rheumatologist* 2020; 42(2): 159-63. https://doi.org/10.1016/j.ejr.2019.09.001
56. ROBINSON C, MILLER D, WILL M, DHAUN N, WALKER W: Hughes-Stovin syndrome: the diagnostic and therapeutic challenges of peripheral pulmonary artery aneurysms. *QJM* 2018; 111(10): 729-30. https://doi.org/10.1093/qjmed/hcy110
57. HAJSADEGHI S, NAGHSHIN R, NIKFAM M, POURMOJARAB A, ABDI S: Successful closure of pulmonary artery aneurysm in a patient with Hughes-Stovin syndrome. *Acta Angiologica* 2017; 23(1): 20-24. https://doi.org/10.5603/aa.2017.0007
58. MAHMOUD MI, SAADANY A, HASSAN M, ESSAM H: A rare cause of haemoptysis in a male with unprovoked deep venous thrombosis. *Breathe* (Sheff) 2016; 12: 12-19. https://doi.org/10.1183/20734735.010715
59. CHOH NA, JEHANGIR M, MIR KM: Hughes-Stovin syndrome: A rare cause of hemoptysis. *Lung India* 2011; 28(4): 285-86. https://doi.org/10.4103/0970-2113.85691
60. AGARWALA MK, CHIDAMBARAM S, VENKATESHWARLU J, DRONAMRAJU A, DAL A: Hughes-Stovin syndrome: an unusual cause for recurrent hemomptysis. *Indian J Vasc Endovasc Surg* 2017; 4: 129-31. https://doi.org/10.4103/ijves.ijves_55_16.
61. BARMAN B, BHATTACHARYA P, HANDIQUE A, ISSAR NK: Hughes-Stovin syndrome: a case report. *Int J Med Sci Public Health* 2015; 4(4): 580-82 https://doi.org/10.5455/ijmsph.2015.07122014104
62. FARBER HW, MCDERMOTT S, WITKIN AS, KELLY NP, MILOSLAVSKY EM, STONE JR: Case 11-2018: A 48-year-old woman with

recurrent venous thromboembolism and pulmonary artery aneurysm. *N Engl J Med* 2018; 378: 1430-38. https://doi.org/10.1056/nejmcpc1800323
63. DEAN R, AMZUTA I: Management considerations in a complicated case of Hughes-Stovin syndrome. *Lung Pathology* 2020; 158(4): 1579. https://doi.org/10.1016/j.chest.2020.08.1420
64. KHAN IA, SULLERE V: Hughes-Stovin syndrome. *Int J Appl Basic Med Res* 2023; 13(2): 117-20. https://doi.org/10.4103/ijabmr.ijabmr_501_22
65. SACHDEV G, YADAV S, BALAKRISHNAN C, NANAVATI R: Hughes-Stovin syndrome: an experience of management of 3 cases from a tertiary health care centre. *Clin Med Insights Arthritis Musculoskelet Disord* 2023; 16: 11795441231168648. https://doi.org/10.1177/11795441231168648
66. YALÇIN S, ENSARIOGLU K, KURT B, OZISLER C: Hughes-Stovin syndrome: a rare cause of thrombosis and pulmonary artery aneurysm. *Cureus* 2023; 15(4): e37121. https://doi.org/10.7759/cureus.37121
67. COLE A, MANDAVA A: Hughes-Stovin syndrome and the acute management of recurrent pulmonary aneurysms. *Cureus* 2022; 14(9): e28672. https://doi.org/10.7759/cureus.28672
68. VYAS V, BRYANT SM, SHAH A, SAVICI D: Disseminated *Mycobacterium chelonae* infection with Hughes-Stovin syndrome. *Proc* (Bayl Univ Med Cent) 2021; 34(5): 595-96. https://doi.org/10.1080/08998280.2021.1918817
69. VILLACIS-NUNEZ DS, WEST Z, KHAN AY *et al*.: Successful medical-surgical management of intracardiac thrombosis and pulmonary pseudoaneurysms in an adolescent with Hughes-Stovin syndrome. *J Investig Med High Impact Case Rep* 2023; 11: 23247096231166672. https://doi.org/10.1177/23247096231166672
70. BHATTACHARYA D, SASIKUMAR D, ANOOP A, VALAKADA J, NAIK N, DHARAN BS: Pulmonary artery aneurysm: harbinger of an ominous disease. *Ann Pediatr Cardiol* 2022; 15(1): 77-79. https://doi.org/10.4103/apc.apc_49_21
71. CELIK S, YAZICI Y, SUT N, YAZICI H: Pulmonary artery aneurysms in Behçet's syndrome: a review of the literature with emphasis on geographical differences. *Clin Exp Rheumatol* 2015; 33(6): 54-59.
72. UZUN O, ERKAN L, AKPOLAT I, FINDIK S, ATICI AG, AKPOLAT T: Pulmonary involvement in Behçet's disease. *Respiration* 2008; 75(3): 310-21. https://doi.org/10.1159/000101954
73. EROGLU DS, TORGUTALP M, BAYSAL S *et al*.: Clinical characteristics of pulmonary artery involvement in patients with Behçet's syndrome: single-centre experience of 61 patients. *Clin Rheumatol* 2021; 40(10): 4127-34. https://doi.org/10.1007/s10067-021-05748-x
74. YILDIRIM R, OGUZMAN S, DINLER M, BILGE NSY, KASIFOGLU T: Scoping beyond pulmonary artery involvement; pulmonary involvement in Behçet's disease; a retrospective analysis of 28 patients. *Clin Rheumatol* 2023; 42(3): 849-53. https://doi.org/10.1007/s10067-022-06423-5
75. MANOLE S, RANCEA R, VULTURAR R, SIMON SP, MOLNAR A, DAMIAN L: Frail Silk: Is the Hughes-Stovin syndrome a Behçet syndrome subtype with aneurysm-involved gene variants? *Int J Mol Sci* 2023; 24(4): 3160. https://doi.org/10.3390/ijms24043160
76. SEYAHI E: Phenotypes in Behçet's syndrome. *Intern Emerg Med* 2019; 14(5): 677-89. https://doi.org/10.1007/s11739-019-02046-y
77. 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(11): 2393-96.
78. FEI Y, LI X, LIN S *et al*. Major vascular involvement in Behçet's disease: a retrospective study of 796 patients. *Clin Rheumatol* 2013; 32(6): 845-52. https://doi.org/10.1007/s10067-013-2205-7
79. 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: 2018-22. https://doi.org/10.1093/rheumatology/keu233
80. TUGAL-TUTKUN I, ONAL S, OZYAZGAN Y, SOYLU M, AKMAN M: Validity and agreement of uveitis experts in interpretation of ocular photographs for diagnosis of Behçet uveitis. *Ocul Immunol Inflamm* 2014; 22(6): 461-8. https://doi.org/10.3109/09273948.2013.854393
81. UYGUNOGLU U, SIVA A: An uncommon disease included commonly in the differential diagnosis of neurological diseases: Neuro-Behçet's syndrome. *J Neurol Sci* 2021; 426: 117436. https://doi.org/10.1016/j.jns.2021.117436