

Pulmonary artery aneurysms in Behçet disease

Aneurismas de artérias pulmonares na doença de Behçet

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Abstract

Pulmonary artery aneurysms (PAAs) are the most common type of pulmonary involvement in Behçet's disease. However, the relationships between clinical features and prognosis have not been sufficiently evaluated. This article describes the results of a comprehensive review, revealing that PAAs have a predilection for hemoptysis manifestations, increased dimensions, right lower lobar location, multiplicity and concurrent intramural thrombus formation. Surgical intervention was needed in one third of patients. Patients with massive hemoptysis and PAA rupture warranted emergency operations. Conservatively treated patients were prone to PAA progression; interventional embolization was associated with higher risks of recurrence and reintervention for PAAs; and surgically treated patients exhibited the highest mortality rates. In conclusion, PAAs in Behçet's disease are characterized by a predilection for hemoptysis manifestations, right lower lobar location, multiplicity, and concurrent intramural thrombus formation. Both the condition itself and the surgical operations it warrants are linked with high mortality due to PAA hemorrhage.

Keywords: hemoptysis; therapeutic embolization; vasculitis.

Resumo

Os aneurismas das artérias pulmonares (PAA) são as manifestações mais comuns dos pulmões na doença de Behçet. No entanto, as relações entre as características clínicas e o prognóstico ainda não foram devidamente explicadas. O objetivo do presente artigo foi fazer uma ampla revisão da literatura sobre esta questão. As fontes de dados contaram com uma ampla revisão bibliográfica dos anos de 1990 a 2013, sobre os seguintes temas: doença de Behçet, síndrome de Hughes-Stovin, aneurisma de artéria pulmonar e pseudoaneurisma da artéria pulmonar. Os PAA evoluíram com predileção por hemoptise, aumento de dimensões, localização no lobo inferior direito, multiplicidade e formação de trombo intramural. A intervenção cirúrgica foi necessária em um terço dos pacientes. O tratamento cirúrgico emergencial foi indicado na vigência de ruptura do PAA e de hemoptise maciça. Os pacientes tratados conservadoramente evoluíram com propensão para a progressão do PAA. A embolização dos PAA foi associada a uma taxa maior de recidiva e de reintervenção. Houve diferença significativa entre os grupos quanto às taxas de mortalidade, tendo o grupo do tratamento cirúrgico apresentado a maior taxa. Dentre as variáveis citadas, a hemoptise, o envolvimento da artéria lobar e a ruptura do PAA foram fatores preditivos de maior risco de mortalidade. Houve diferenças significativas nas taxas de mortalidade entre os pacientes cirúrgicos e intervencionistas, e entre os três grupos de pacientes: cirúrgico, intervencionista e conservador. Os pacientes tiveram uma sobrevida global de 61,7% em um seguimento médio de 22,5 meses. Os PAA, na doença de Behçet, apresentaram as seguintes predileções: tendência a hemoptise, multiplicidade, localização no lobo inferior direito e presença de trombos intramurais. As rupturas e hemorragias dos PAA, aliadas ao necessário tratamento cirúrgico emergencial, resultaram no aumento de mortalidade destes pacientes.

Palavras-chave: hemoptise; embolização terapêutica; vasculite.

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■ INTRODUCTION

In Behçet's disease, pulmonary involvement is uncommon, with a prevalence of less than 5%.¹ Pulmonary artery aneurysms (PAAs) are the most common form of pulmonary involvement in Behçet's disease, followed by pulmonary artery thrombosis, pulmonary infarction and pulmonary parenchymal disorders.² Thrombosis usually develops as a consequence of the underlying extensive vasculitis.^{3,4} Currently, pulmonary artery aneurysms are the second most common type of arterial involvement in Behçet's disease, preceded by aortic aneurysms.² Hemoptysis of varying degrees up to 500 ml was the most common symptom of PAAs, observed in 79%.^{2,5} Hemoptysis can sometimes be massive and lethal, when PAAs rupture into the adjacent bronchus.⁶ Other manifestations of PAA include cough, dyspnea and chest pain.⁶

Hughes-Stovin syndrome is a combination of pulmonary artery thrombosis and aneurysms with peripheral thrombophlebitis and is considered an incomplete variant of Behçet's disease. Characterized by an association of multiple PAAs and peripheral venous thrombosis, Hughes-Stovin syndrome shares identical pulmonary manifestations with Behçet's disease.⁷ Thrombophlebitis, formation of large pulmonary and/or bronchial aneurysms and aneurysmal rupture leading to massive hemoptysis and death are the three phases of the clinical paradigm of Hughes-Stovin syndrome.⁸

Previous reports have described the clinical features of PAAs in Behçet's disease.^{2,9-11} However, the relationships between the clinical features and prognosis have not been sufficiently evaluated and thus remain to be identified. This article presents a comprehensive literature review of the subject.

■ MATERIALS AND METHODS

Search strategies

A comprehensive literature search was conducted on MEDLINE, Highwire Press and Google for the year range 1990-2013. The search terms included "Behçet's disease", "Hughes-Stovin syndrome" and "pulmonary artery aneurysm" or "pulmonary artery pseudoaneurysm". Data were extracted from the text, figures and/or tables, with details of the study population, demographics, duration of Behçet's disease, characteristics of PAAs, management strategies and pertinent indications, follow-up duration and main outcomes (survival, recurrence, complication, reintervention and mortality).

Definitions

Severity of hemoptysis was defined as: mild <5 ml in 24 hours; moderate 5-600 ml/24 hours and massive >600 ml/24 hours, or 100 ml/<24 hours to 1000 ml/several days, or >50 ml per expectoration,¹² and sudden recurrent massive hemoptysis was defined as life-threatening hemoptysis. Onset of action was defined as the time for the immunosuppressive agents to take effect (including symptom relief, decreased inflammatory mediators, reduced pulmonary or intracardiac thrombus and reduced PAA) after administration; and cure time was the time interval from drug administration to complete resolution of the PAA and pulmonary or intracardiac thrombus.

Statistical analysis

Quantitative data were presented as mean \pm standard deviation with range and median values, and intergroup differences were compared using the unpaired *t* test. Frequencies were compared using Fisher's exact test. Univariate and multivariate analyses were conducted to evaluate predictive risk factors. Results with $p < 0.05$ were considered statistically significant.

■ RESULTS

The literature search yielded 107 reports^{5, 10,13-118} covering 199 patients. Five case reports, each describing the case of one patient, diagnosed Hughes-Stovin syndrome.^{37,49,51,54,99} Among the patients whose gender could be ascertained, there were 166 (85.6%) males and 28 (14.4%) females, giving a male-to-female ratio of 5.93:1. Patients were aged 31.0 ± 10.9 (range: 10-69; median: 30) years ($n=150$). Male patients were aged 31.6 ± 11.4 (range: 10-69; median: 30) ($n=122$) and females were aged 28.6 ± 8.5 (range: 14-48; median: 27) ($n=24$). There was no significant difference in patient age between male and female patients ($p=0.2249$). Patients had presented symptoms of Behçet's disease for 5.0 ± 4.8 (range: 0.25-26; median: 3) years ($n=52$) and their diagnoses of Behçet's disease had been established for 4.7 ± 2.9 (range: 0.83-10; median: 5) years ($n=34$). No difference was detected between the time since onset and time since Behçet's disease diagnosis ($p=0.7522$). On admission, 156 (78.4%) patients presented with hemoptysis, while 43 (21.6%) patients did not exhibit hemoptysis ($\chi^2=128.3$, $p < 0.0001$). Hemoptysis was the only symptom at onset in 109 (69.9%) patients, while hemoptysis was present in combination with other symptoms in 47 (30.1%) patients ($\chi^2=49.3$, $p < 0.0001$). In

addition to hemoptysis, fever, dyspnea, cough and chest pain were also common symptoms in the PAA patients. Comparison of the secondary symptoms of hemoptysis patients with those of hemoptysis-free patients revealed a significant intergroup difference in prevalence of cervical or pedal edema (Table 1). Hemoptysis volume was reported for 69 patients. Hemoptysis was mild in 5 (7.2%) patients,^{28,48,55,65,68} moderate in 9 (13.0%),^{37,50,57,70,71,76,95,112,118} (1 patient with increasing hemoptysis volumes⁷⁶), massive in 51 (73.9%)^{5,10,14,15,21,23,24,29,34,43,45,51,53,55,56,58,59,64,74,81,84,85,87,96,98,99,109-111,115} (2 patients with increasing hemoptysis volumes^{84,85}) and life-threatening in 4 (5.8%) patients^{25,34,41,42} ($\chi^2=118.5$, $p<0.0001$). Frequency of hemoptysis was reported for 17 patients, as follows: recurrent/repeated/iterative in 9 (52.9%),^{14,21,54,58,59,63,65,72,79} intermittent in 6 (35.3%)^{21,27,57,81,113,118} and persistent in 2 (11.8%) patients.^{18,63} Additionally, one patient was described as having hemoptysis of unknown origin on admission.⁴⁷ Overall, duration of the PAA patients' symptoms was 2.6 ± 4.1 (range: 0.03-24; median: 1.5) months ($n=35$). One exceptional patient exhibited clinical manifestations 14 days after admission.²⁶

Erythrocyte sedimentation rate was tested for 43 patients. Results were elevated in 39 (90.7%) patients^{13,14,17,18,21,26,35,38-40,43,45,47,50,56,57,59-61,65,68-70,73,76,81,83,88,92,93,95,98,104,106,108,111-113,116,118} and normal in 4 (9.3%) patients^{21,35,37,43} ($\chi^2=57.0$, $p<0.0001$). The quantitative erythrocyte sedimentation rate for these patients was 72.2 ± 34.9 (range: 10-152; median: 71.5) mm/h ($n=38$). Seventeen patients had C-reactive protein tested and results showed normal C-reactive protein in 1 (5.9%) patient³⁵ and elevated C-reactive protein levels in 16 (94.1%) patients, with a quantitative value of 8.7 ± 5.7 (range: 1.5-19.7; median: 7.6) mg/dl ($n=15$).^{13,21,38,39,61,62,66,76,81,92,104,106,107,116,118}

Pulmonary artery aneurysms developed on the right side in 111 patients (39.4%),^{5,10,14,16,29,32-34,36-38,56,60,61,75,76,79,85,86,107,109,112,114-116,118} on the left side in 91 patients (32.3%)^{5,10,13,14,16,17,30,33,35,46,48,51,55,56,64,69,72,78,87,88,94,98,100,102,109,111,118} and on both sides in 72 patients (25.5%)^{14-16,18,20-28,33,34,39-45,47,49,50,52-55,57-59,62,63,65,68,70,73,74,77,78,80,81,83,84,89-91,93,95-97,100,101,104,105,106,108,109,113,115} ($\chi^2=12.5$, $p=0.00194$). In 43 patients (30.1%) PAAs were single, in 97 (67.8%) they were multiple, and in 3 patients (2.1%), PAAs extended from the main pulmonary branch to lobar (segmental) arteries ($\chi^2=140.1$, $p<0.0001$). With regard to singularity versus multiplicity, the most common type of PAA were multiple bilateral PAAs (Figure 1). Detailed locations in the pulmonary zones were provided for 381 PAAs in 146 patients described in a total of 82 different reports,^{5,10,13-18,20-29,32-35,37-46,48,49,51,52-54,56-62,64,65,68-70,72,74-76,78-81,83,87-89,91,93,95,96,98,102,104-107,109-116,118} showing that 293 (76.9%) PAAs originated from the lobar arteries, 45 (11.8%) from the segmental

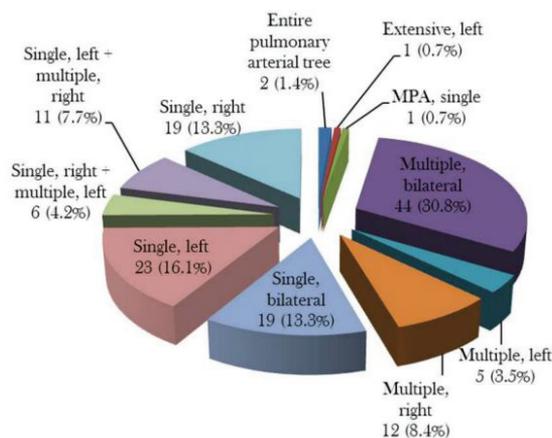


Figure 1. Singularity and multiplicity of pulmonary artery aneurysms. MPA: main pulmonary artery.

Table 1. Comparison of symptoms of 47 hemoptysis patients and 43 patients free from hemoptysis.

Symptom	Hemoptysis patients (n=81)	Hemoptysis-free patients (n = 67)	χ^2	p value
Fever, n (%)	22 (27.2) (1 [4.5] was fever of unknown origin)	26 (38.8) (1 [3.8] was fever of unknown origin)	2.3	0.13196
Dyspnea, n (%)	17 (21.0)	13 (19.4)	0.1	0.81134
Cough, n (%)	15 (18.5)	15 (22.4)	0.3	0.55998
Chest pain, n (%)	13 (16.0)	8 (11.9)	0.5	0.47579
Weight loss, n (%)	9 (11.1)	2 (3.0)	3.5	0.06066
Edema, n (%)	3 (3.7) (1 [33.3] was cervical and 2 [66.7] were pedal edema)	0 (0)	3.9	0.04855
Loss of vision, n (%)	1 (1.2)	0 (0)	1.3	0.25688
Cardiac arrest, n (%)	1 (1.2)	0 (0)	1.3	0.25688
Palpitation, n (%)	0 (0)	1 (1.5)	1.8	0.18407
Epilepsy, n (%)	0 (0)	1 (1.5)	1.8	0.18407
Stroke, n (%)	0 (0)	1 (1.5)	1.8	0.18407

arteries, 40 (10.5%) from the main pulmonary arteries and 3 (0.8%) extended from the main pulmonary branches to the lobar (segmental) arteries ($\chi^2=744.6, p<0.0001$). Analysis of the distribution of the PAAs across pulmonary zones revealed that the right lower lobar arteries predominated, followed by the left lower lobar arteries (Figure 2).

The mean dimension of PAAs was 4.0 ± 2.4 (range: 0.5-13; median: 3.6) cm (n=60). The PAAs were pseudoaneurysms in 5 (2.5%) patients,^{72, 87,88,91,118} while all the remaining PAAs were true aneurysms ($\chi^2=359.0, p<0.0001$). A significant difference in diameter was detected between false and true aneurysms (8.0 ± 3.5 [range: 4-13; median: 4] cm vs. 3.7 ± 2.0 [range: 0.5-9; median: 3.1] cm, $p<0.0001$). Ten patients (5.0%) suffered from PAA

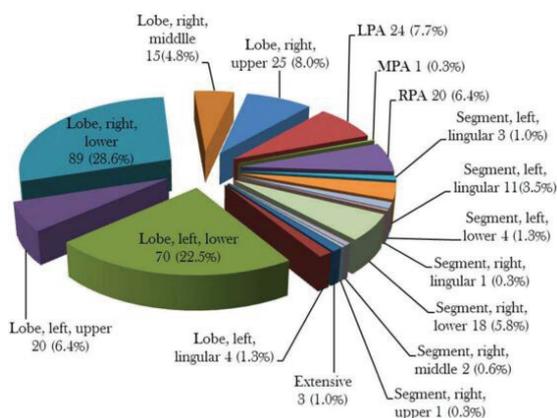


Figure 2. Distribution of pulmonary artery aneurysms. LPA: left pulmonary artery; MPA: main pulmonary artery; RPA: right pulmonary artery.

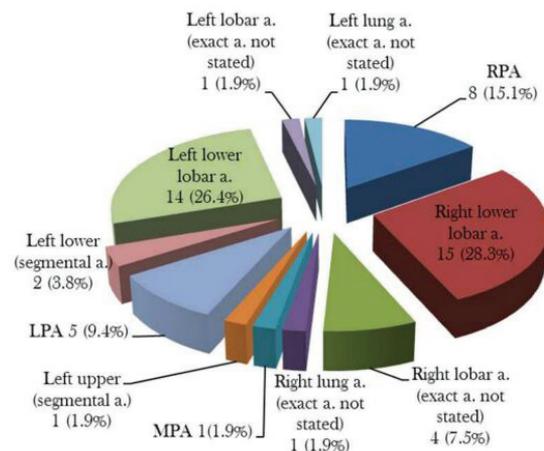


Figure 3. Distribution of concurrent intramural thromboses of pulmonary artery aneurysms. a: artery; LPA: left pulmonary artery; MPA: main pulmonary artery; RPA: right pulmonary artery.

rupture.^{38,55,62,64,75,84,109,115,118} In two large PAA patient cohorts, concurrent pulmonary artery thrombus accounted for 15/46 PAAs in 13 patients¹¹⁰ and 8/96 PAAs in 43 patients.^{5,109} In another 35 reports,^{5,10,13, 14,16,18,21,23,27,33,34,38,46-49,56,58,60,63,68-70,74,79,81,84,94,108-111,114-116}

concurrent intramural thrombus was present in 53 PAAs in 41 (28.7%, 41/143) patients. Thrombi were located in right, left and bilateral PAAs in 18 (43.9%), 12 (29.3%) and 10 (24.4%) patients, respectively, and in a main pulmonary artery aneurysm in 1 (2.4%) patient. Concurrent PAA and intramural thrombosis was most often seen in the right lower lobar and left lower lobar arteries (Figure 3).

Excluding pulmonary arterial thrombus, intrapulmonary complications were present in 10 (5.0%) patients, including 5 (50%) pulmonary infarcts, 4 (40%) pulmonary emboli and 1 (10%) pulmonary emboli and infarct. Extrapulmonary cardiovascular events occurred in 56 (28.1%) patients, including thrombus formation in 52 (92.9%), and arterial aneurysm and vein dilation in 2 (3.6%) patients, each (Table 2).

Management strategies for the PAAs were not described for 70 patients. Of the remaining 129 patients, 82 (63.6%) were treated conservatively,^{10,13-15,17-19,22, 23,25,27-29,31,37,38,40,41,46,49-56,61-63,65,68-70,73,75,78,81,83,84,86,91,94,95, 97,99,100,102-104,105,108,112-116,118} 22 (17.1%) were treated interventionaly^{10,24,32,34,42,47,60,64,71,72,74-76,79,87,89,92,96} and

Table 2. Extrapulmonary cardiovascular events in 56 patients.

Extrapulmonary cardiovascular events	n (%)
Arterial aneurysm	2 (3.6)
Femoral artery	1 (1.8)
Coronary artery	1 (1.8)
Dilated veins	2 (3.6)
Azygous vein	1 (1.8)
Hepatic vein	1 (1.8)
Thrombus formation	52 (92.9)
RV	18 (32.1)
DVT	11 (19.6)
IVC	4 (7.1)
RA	3 (5.4)
Dural sinus + DVT	3 (5.4)
RA + RV	2 (3.6)
Dural sinus + RV	2 (3.6)
SVC	2 (3.6)
Dural sinus	1 (1.8)
Dural sinus + RV + DVT	1 (1.8)
IVC + DVT	1 (1.8)
RV + DVT	1 (1.8)
RV + SVC	1 (1.8)
Dural sinus + jugular vein	1 (1.8)
SVC + innominate vein	1 (1.8)

DVT: deep venous thrombosis; IVC: inferior vena cava; RA: right atrium; RV: right ventricle; SVC: superior vena cava.

25 (19.4%) were treated surgically with concurrent immunosuppressive agents^{21,26,30,35,36,43,55,58,59,78,85,88,98,100,106,107,110,111,115,118} ($\chi^2=79.7$, $p<0.0001$). Two patients given conservative treatment were eventually treated for PAA interventionally because of PAA progression^{40,41} and one patient who originally underwent interventional embolization of the PAA was later subjected to emergency pulmonary artery ligation because of PAA recurrence with severe hemoptysis and respiratory distress.²⁴ There were a total of 24 interventional and 26 surgical procedures for PAAs. Additionally, one patient underwent resection of endomyocardial fibrosis plus tricuspid valve repair¹⁰¹ and one patient underwent surgical excision of intracardiac mass.⁵⁶

Of the whole patient sample, immunosuppressive treatment strategies were described in 114 patients. Steroids were administered to 101 (88.6%), cyclophosphamide to 62 (54.4%), azathioprine (150 mg/day or 2 mg/kg/day) to 25 (21.9%), colchicine (0.5-1.5 mg/day) to 36 (31.6%), anticoagulants to 22 (19.3%), methotrexate to 3 (2.6%) and cyclosporine A was administered to 2 (1.8%) patients. Alternative conservative treatments included infliximab, a tumor necrosis factor neutralizing agent, 5 mg/kg at 0, 2, 6, 14 and 22 weeks in 3 (2.6%) cases, adalimumab, a human monoclonal antibody against tumor necrosis factor- α , in 2 (1.8%), hematopoietic stem cell transplantation in 2 (1.8%) and mycophenolate mofetil in 1 case (0.9%). Onset of action was soon after drug administration in 5 (4.4%) patients.^{22,52,58,104,118} In another 31 patients,^{13,15,17,18,20,25,37,46-48,50,51,61,65,69,81,94,97,103,109,116} onset of action took 13.6 \pm 23.5 (range: 0.25-120; median: 6) months (n=44). Cure time was 6.4 \pm 5.5 (range: 2-24; median: 5) months (n=18).^{14,25,34,38,46,47,54,56,59,61,63,65,73,81,91,95,113,116} In 11 cases PAA embolization materials were described, as follows: N-butyl cyanoacrylate

(n=3, 27.3%),^{34,41} Nester® Embolization Coils (n=3, 27.3%),^{74,76} Amplatzer devices (n=3, 27.3%),^{64,66,72} Ethylene Vinyl Alcohol Copolymer (n=1, 9.1%)⁷¹ and Guglielmi detachable coils (n=1, 9.1%).⁶⁰ In patients with multiple PAAs, the number of embolization coils deployed in a single patient varied from 2,⁷⁴ through 6,⁷⁴ to 10.⁷⁶ Details of surgical operations performed on PAA patients are listed in Table 3, showing that lobectomy was the most common surgical operation, accounting for 42.3% of surgical procedures.

The indications for conservative treatment in severe patients were extensive PAA locations,^{55,97} failed interventional embolization⁹⁵ and patient reluctance to undergo interventional embolization or surgical operations.^{29,68,114} Hematopoietic stem cell transplantation⁸⁶ and tumor necrosis factor- α plus infliximab²⁵ were indicated for patients refractory to conventional immunosuppressive therapy. Indications for interventional embolization included bilateral pulmonary artery involvement,⁷⁴ giant pulmonary artery pseudoaneurysm,⁸⁷ ruptured PAAs,⁶⁴ failed conservative treatment,³⁴ to avoid potential surgical complications⁶⁰ and patients' reluctance to undergo surgical operations.⁷² Patients with rapidly expanding pulmonary artery (pseudo)aneurysms^{24,26,107} or with recurrent PAA following successful percutaneous embolization²⁴ usually warranted surgical operations; while patients with uncontrolled massive hemoptysis with impending PAA rupture often required an emergency operation.^{55,59,106,110} A total of 9 patients received intervention/surgery for the treatment of PAA on an urgent basis including 1 interventional embolization⁴¹ and 8 open thoracic operations.^{24,35,55,85,110,115,118} In all 9 of these patients an urgent procedure was indicated for massive hemoptysis, and 4 (44.4%) patients of whom suffered from a PAA rupture.^{55,110,115,118} Patients were followed-up for 22.5 \pm 33.5 (range:

Table 3. Surgical operations for pulmonary artery aneurysms in 26 patients.

Surgical operation	n (%)
Lobectomy	11 (42.3)
Pneumonectomy	3 (11.5)
PAA excision	2 (7.7)
Pulmonary artery ligation	2 (7.7)
Pulmonary artery aneurysmorrhaphy	1 (3.8)
Pulmonary artery aneurysmorrhaphy + pneumonectomy	1 (3.8)
Pulmonary artery aneurysmectomy + pneumonectomy	1 (3.8)
Thoracotomy (patient died during thoracotomy with no time for further interventions)	1 (3.8)
Lobectomy + pulmonary arterioplasty	1 (3.8)
Left pulmonary artery replacement under cardiopulmonary bypass	1 (3.8)
Left and right pulmonary artery operations (details not stated)	1 (3.8)
Surgical operation (details not stated)	1 (3.8)

0.75-204; median: 15) months (n=94). Outcomes were not described for 24 patients. Of the remaining 175 patients, 108 (61.7%) were event-free survivals and 44 (25.1%) patients died. Time to death was reported for 30 patients, 11 (36.7%) of whom were early deaths and 19 (63.3%) of whom were late deaths ($\chi^2=4.3$, $p=0.03887$). Mean time to death was 6.1 ± 7.2 (range: 0-24; median: 3) months after intervention or after discharge (a "0" indicates that one patient died of uncontrolled massive bleeding during the operation⁸³). Cause of death was described for 27 patients: massive hemoptysis in 20 (74.1%), PAA rupture in 4 (14.8%), pulmonary hemorrhage as evidenced by bronchoscopy in 2 (7.4%), postoperative bleeding in 1 (3.7%) patient and septicemia in 1 patient (3.7%) ($\chi^2=47.2$, $p<0.0001$).

Outcomes were reported for 175 patients and comparison of outcomes across different treatments revealed that conservatively treated patients were prone to suffer from PAA progression, that interventional embolization was associated with higher risks of recurrence and reintervention for PAAs, and that surgically treated patients had the highest overall and early mortality rates. However, there were no significant differences in late mortality between these three groups (Table 4). The time to death of surgically treated patients was much shorter than among conservatively treated patients (2.3 ± 5.9 months vs. 7.8 ± 6.4 months, $p=0.04650$). There were 24 interventional procedures, 23 (95.8%) of which were elective including 1 (4.3%) postoperative death, while 1 (4.2%) was an emergency intervention and the patient survived. There were 26 surgical procedures, 21 (80.8%) of which were elective, including 9 (42.9%) deaths; whereas 5 (19.2%) were emergency surgeries, including 3 (60%) deaths ($\chi^2=0.5$, $p=0.48953$). Ten patients suffered PAA rupture. Four of them had been managed

conservatively, 4 had been managed surgically and 2 had been managed interventionally, with only 2 surgically-treated patients surviving, giving an overall survival rate of 20% and an emergency surgery survival rate of 50% ($\chi^2=5.0$, $p=0.08416$).

Univariate analysis revealed that presence of hemoptysis ($p<0.0001$), lobar artery involvement ($p=0.00200$) and PAA rupture ($p=0.00900$) were statistically significant adverse prognostic factors indicative of poor prognosis in PAA patients, whereas intramural pulmonary artery thrombus ($p=0.16000$), surgical intervention ($p=0.20900$), emergency operation ($p=0.23100$) and PAA multiplicity ($p=0.97400$) were not predictive. Attempts to identify independent risk factors for mortality using multiple logistic regression employed hemoptysis, lobar arterial aneurysm, multiplicity, concurrent intramural thrombus and surgical/interventional therapy as input variables, overall model fit parameters were: $\chi^2=14.1580$, $df=5$, $p=0.0146$. Mortality correlated significantly with lobar artery involvement, and there was a quasi-correlation with hemoptysis (Table 5).

DISCUSSION

The pulmonary vasculitis seen in PAA associated with Behçet's disease is primarily located in the vasa vasorum. Histopathological observations revealed pulmonary vasculitis involving all layers of pulmonary arteries and veins,³ resulting in thrombosis, stenosis, aneurysm formation and rupture. Mononuclear inflammatory cells, predominantly lymphocytes, are responsible for inflammatory infiltration in and around the vessel wall. Additionally, impaired natural killer cell activity and immune system dysregulation have also been observed in patients with Behçet's disease and pulmonary manifestations.¹¹⁹ Marked intimal thickening with degenerative changes in the

Table 4. A comparison of the outcomes of 173 patients with pulmonary artery aneurysm: patients treated conservatively versus surgically versus interventionally.

Outcome	Conservative (n=83)	Surgical (n=25)	Interventional (n=24)	Treatment not indicated (n=66)	χ^2	p value
Event-free survival, n (%)	47 (56.6)	10 (40)	12 (50)	39 (59.1)	9.3	0.00970
Progression, n (%)	7 (8.4)**	0 (0)	0 (0)	1 (1.5)	6.7	0.03473
Recurrence, n (%)	4 (4.8)	1 (4)	5 (20.8)†	4 (6.1)	8.4	0.01464
Complication, n (%)	2 (2.4) ‡	1 (4)	2 (8.3) †	0 (0)	2.1	0.34975
Reintervention, n (%)	0 (0)	0 (0)	7 (29.2)	0 (0)	42.1	<0.00001
Outcome not stated, n (%)	6 (7.2)	1 (4)	2 (8.3)	14 (21.2)	--	--
Death, n (%)	20 (24.1)	12 (48)	3 (12.5)	8 (12.1)	8.0	0.01872
Early death	2 (10)	5 (41.7)	1 (33.3)	1 (12.5)	10.4	0.00548
Late death	18 (90)	7 (58.3)	2 (66.7)	7 (87.5)	2.7	0.26446

* One patient died due to the refusal of all treatments and was not therefore a member of any of the above groups; ** Two patients eventually died; † Reintervention was required in all patients; ‡ One patient died.

Table 5. Odds ratios and 95% confidence intervals for multivariate regression analysis of risk factors predictive of mortality.

Variable	Odds ratio	95% confidence interval	p value
Hemoptysis	2.6030	0.9573-7.0779	0.0609
Lobar arterial involvement	0.3025	0.1062-0.8614	0.0251
Multiplicity of the pulmonary artery aneurysm	1.4231	0.6332-3.1986	0.3931
Concurrent pulmonary artery aneurysm and intramural thrombus	0.7596	0.2986-1.9323	0.5638
Surgical/interventional therapy	1.6011	0.7041-3.6408	0.2614

medial layer from the lobar branches to the arterioles can explain hemoptysis and PAA rupture.¹²⁰ Bronchopulmonary fistulas found during autopsies of patients who died of sudden hemoptysis⁴³ and in surgical specimens resected from patients with massive hemoptysis^{10,110} were apparently the causative etiology of life-threatening hemoptysis.

Aneurysms may be single or multiple, unilateral or bilateral, saccular or fusiform, and may be located in the main pulmonary artery or lobar or segmental arteries.² Pulmonary vasculitis in Behçet's disease may also result in thrombosis, stenosis or occlusion of lung vessels, but thrombosis rather than embolism was usually associated with PAAs.¹²¹ Other pulmonary problems seen in Behçet's disease patients, including pleural effusion and chylous pleural effusions, are the result of vascular complications.¹¹ Focal hemorrhages or infarct areas can present in the lung parenchyma adjacent to the aneurysms.¹²⁰ Thrombosed aneurysms cause ischemia and infarction in the pulmonary parenchyma.⁶ Pulmonary artery aneurysms may manifest as hilar enlargement or round, lobulated opacities on chest radiographs.¹⁶ Computed tomography has largely replaced angiography as the diagnostic tool and magnetic resonance imaging can also be useful for diagnosis of PAAs, but appears to be less sensitive than computed tomography for diagnosis of small PAAs.²

Erkan et al.² reported that PAAs are most often located in the right lower lobar arteries, followed by bilateral main pulmonary branches. Tunaci et al.¹⁰⁹ proposed that the pulmonary arteries of the lower lobe were the most common site of involvement, and a mural thrombus was observed in 85% of PAAs. Aneurysms were most frequently located in the lobar artery in the right lower lobe (35%), followed by the lobar artery in the left lower lobe (19%) and right main pulmonary artery (17%), and 33% of aneurysms had partial or total thrombus within the aneurysm itself.¹⁰⁹ The present study showed similar results to those published by Tunaci et al.¹⁰⁹ Another important finding of Tunaci et al.¹⁰⁹ was complete or partial

PAA resolution in response to immunosuppressive treatments: 76% of PAAs completely disappeared in 3-42 (mean: 21) months and 24% of PAAs regressed in 4-28 (mean: 17) months after treatment.¹⁰⁹ It was reported that the largest aneurysm was 7 cm,¹⁰⁹ and the mean diameter of aneurysms was 2.3±1.1 cm.¹²² The present study, however, revealed much larger dimensions of PAAs with a mean diameter of 4.0 cm.

In Behçet's disease, immunosuppressants should be the first line treatment of choice and provoke regression of the PAAs and associated thrombus in a majority of the patients.²¹ Pulse methylprednisolone followed by oral prednisolone is one routine regimen for Behçet's disease.^{48,50,59} Monthly intravenous cyclophosphamide 1 g, and azathioprine 2.5 mg/kg/day may also be employed.⁸⁸ Tumor necrosis factor-neutralizing monoclonal antibody infliximab was an effective treatment for a case of potentially lethal PAA in Behçet's disease.²⁵ Two patients with resistant PAA were treated with hematopoietic stem cell transplantation.⁸⁶ Other tumor necrosis factor- α blockers, which include etanercept and adalimumab, would also be effective for the treatment of PAA in Behçet's disease patients.⁷⁷ Pulmonary artery aneurysm patients with thrombophlebitis and/or pulmonary emboli who are on anticoagulants are at risk of massive bleeding and so anticoagulants should be used with great caution, especially in patients with hemoptysis.⁷⁶

Alternative management strategies to conservative treatment include surgical and transcatheter interventions. Diseased lung tissue resection is preferred to pulmonary artery reconstruction in surgical treatment of PAAs. Surgical treatment mostly consists of major anatomical resection rather than preserving lung tissue. Immediate operation for PAAs should be performed when systemic inflammation is under control after short-term immunosuppressive therapy.²¹ Patients with recurrent or massive hemoptysis, in particular patients with ruptured PAAs, warrant emergency surgery, which is often associated with very high mortality.²¹ Endovascular embolization has been shown to be

effective at controlling PAA hemorrhage.³⁴ The Amplatzer duct occluder is currently the most commonly used device for management of large aneurysms.⁸⁸ It can be employed in most cases and recurrent PAAs may be curable with reintervention.³²

Pulmonary artery aneurysms were the major contributing factor to overall mortality from Behçet's disease.¹²¹ In the early years, short-term survival of patients with PAAs associated with Behçet's disease was only 50%.³ A decade later, 5-year survival had increased to 62%.⁴ The present study displayed an overall survival of 76.9% at a mean follow-up of 21.6 months.

The present study revealed that PAAs have predilections for hemoptysis manifestations, right lower lobar locations, multiplicity and concurrent intramural thrombus formation. Surgical intervention therapy is warranted in most of the patients. All these variables were shown to be predictive risk factors for higher mortality in PAAs. For refractory cases that respond poorly to conservative treatment, endovascular embolization and Amplatzer occluder device are good choices for PAA management. Hemorrhaging PAAs can also be controlled by pneumonectomy, lobectomy, pulmonary artery aneurysmectomy, or pulmonary arterial ligation, but these options may be associated with higher mortality compared with interventional and conservatively treated patients.

The most important limitations of this review are related to the non-availability of numbers, locations and dimensions of the arteries involved by PAAs in a large proportion of the references cited. Further prospective studies with more detailed information of PAAs are essential if more precise conclusions are to be drawn.

In conclusion, PAAs in Behçet's disease are characterized by a predilection for hemoptysis manifestations, right lower lobar location, multiplicity and concurrent intramural thrombus formation. Both the condition itself and the surgical operations it warrants are linked with high mortality due to PAA hemorrhage.

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