

Symptomatic Peripheral Mycotic Aneurysms Due to Infective Endocarditis

A Contemporary Profile

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Abstract: Peripheral mycotic aneurysms (PMAs) are a relatively rare but serious complication of infective endocarditis (IE). We conducted the current study to describe and compare the current epidemiologic, microbiologic, clinical, diagnostic, therapeutic, and prognostic characteristics of patients with symptomatic PMAs (SPMAs). A descriptive, comparative, retrospective observational study was performed in 3 tertiary hospitals, which are reference centers for cardiac surgery. From 922 definite IE episodes collected from 1996 to 2011, 18 patients (1.9%) had SPMAs. Because all SPMAs developed in left-sided IE, we performed a comparative study between 719 episodes of left-sided IE without SPMAs and 18 episodes with SPMAs.

We found a higher frequency of intravenous drug abuse, native valve IE, intracranial bleeding, septic emboli, multiple embolisms, and IE diagnostic delay >30 days in patients with SPMAs than in patients without SPMAs. The causal microorganisms were gram-positive cocci (n = 10), gram-negative bacilli (n = 2), gram-positive bacilli (n = 3), *Bartonella henselae* (n = 1), *Candida albicans* (n = 1), and negative culture (n = 1). The median IE diagnosis delay was 15 days (interquartile range [IQR], 13–33 d) in the case of high-virulence microorganisms versus 45 days (IQR, 30–240 d) in the case of low- to medium-virulence microorganisms. Twelve SPMAs were intracranial and 6 were extracranial. In 10 cases (8 intracranial and 2 extracranial), SPMAs were the initial presentation of IE; the remaining cases developed symptoms during or after finishing parenteral antibiotic treatment. The initial diagnosis of intracranial SPMAs was made by computed tomography (CT) or magnetic resonance imaging in 6 unruptured aneurysms and by angiography in 6 ruptured aneurysms. The initial test in extracranial SPMAs was Doppler ultrasonography in limbs, CT in liver, and coronary angiography in heart. Four (3 intracranial, 1 extracranial) of 7 (6 intracranial, 1 extracranial) patients treated only with antibiotics died. Surgical resection was performed in 7 (3 intracranial, 4 extracranial) and endovascular repair in 4 (3 intracranial, 1 extracranial) patients; all of them survived.

In conclusion, we found that SPMAs were a rare complication of IE that developed only in left-sided IE, and especially in native valves.

Intracranial hemorrhage, embolism, multiple embolisms, and diagnostic delay of IE were more common in patients with SPMAs. The microbiologic profile was diverse, but microorganisms of low-medium virulence were predominant, and had a greater delayed diagnosis of IE than those caused by microorganisms of high virulence. SPMAs were often the initial presentation of IE. The most common location of SPMAs was intracranial. Noninvasive radiologic imaging techniques were the initial imaging test in intracranial unruptured SPMAs and in most extracranial SPMAs. Surgical and endovascular treatments were safe and effective. Endovascular treatment could be the first line of treatment in selected cases. Mortality was high in those cases treated only with antibiotics.

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Abbreviations: CT = computed tomography, CTA = computerized tomographic angiography, DSA = digital subtraction angiography, IE = infective endocarditis, IQR = interquartile range, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, PMAs = peripheral mycotic aneurysms, SPMAs = symptomatic peripheral mycotic aneurysms.

INTRODUCTION

Peripheral mycotic aneurysms (PMAs) in infective endocarditis (IE) result from septic embolization of vegetations to the arterial vasa vasorum with subsequent spread of infection throughout the vessel wall.⁴⁴ They are mainly located in the branches of intracranial arteries,⁴ but have also been described in intraabdominal arteries,^{2,3,18,25–27,35,41,43,56,61,63} coronary arteries,^{39,46,47,54,62} and limbs.^{6,17,19,24,30,32,33,37,40,45,48,52,57,58}

PMAs are often diagnosed in the course of IE, but may be the first manifestation of the disease.^{4,14,66} The main reported causal microorganisms are *S. aureus*, *Streptococci*, and *Enterococcus*.^{4,12,13,50,55} The most common presenting symptoms are fever, chills, malaise, or weight loss that can precede the onset of focal events.^{49,50,55} Patients with an intracranial aneurysm may develop focal neurologic symptoms, severe headache, altered sensorium, meningitis, or seizures.^{48,50,55} The clinical presentation of extracranial aneurysms is highly variable; they may appear as a pulsatile and painful mass in an extremity, as myocardial infarction, or as visceral hematoma, among other clinical manifestations.

Diagnosis requires imaging tests. Conventional angiography or digital subtraction angiography (DSA) have been the gold standard techniques to diagnose PMAs. But other radiologic imaging tests are acceptable to screen for PMAs. Management includes conservative treatment with antibiotics or surgery, although endovascular treatment has lately emerged as a new option.^{4,11,12,49,66}

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In the last 2 decades there have been changes in the epidemiology and microbiology of IE,^{9,22} especially in industrialized nations. IE affects older patients; there is an increasing incidence of IE associated with prosthetic valves and degenerative valvular disease, while underlying rheumatic valve is decreasing. An increase in health care-associated IE has been documented.²² Microbiologically, oral streptococci have fallen behind staphylococci as the leading cause of IE.²² Echocardiographic techniques allow an earlier diagnosis of IE, and there has been progress in imaging diagnostic tests, and microvascular, neurosurgical, and endovascular therapies. All these changes may have modified the profile of patients with PMAs. Therefore, we conducted this study to describe the current epidemiologic, microbiologic, clinical, diagnostic, therapeutic and prognostic characteristics of patients with symptomatic PMAs (SPMAs).

PATIENTS AND METHODS

Patient Sample

We conducted a retrospective, descriptive, comparative study of patients with and without SPMAs secondary to IE. From 1996 to 2011, 922 episodes of definite IE³⁴ were prospectively and consecutively collected in a computerized register of IE.

We found 18 episodes (1.9%), corresponding to 18 patients who developed symptoms related to PMAs, and they were subsequently confirmed on imaging tests. A prospective search of PMAs in patients without clinical symptoms related to PMAs was not performed. Because all SPMAs developed in patients with left-sided IE, we performed a comparative study between 719 episodes of left-sided IE corresponding to 694 patients without SPMAs and 18 episodes with SPMAs.

The study was conducted at 3 tertiary hospitals in Spain: Hospital Clínico Universitario de Valladolid, Hospital Universitario de La Princesa, and Hospital Clínico Universitario San Carlos de Madrid; all were referral centers for cardiac surgery.

Epidemiologic, microbiologic, clinical, and echocardiographic variables were analyzed using a computerized and standardized protocol. We analyzed the treatment and diagnostic methods used for SPMAs and the clinical course.

Procedures

Microbiologic procedures were extraction of at least 3 blood cultures at the time of clinical suspicion of IE. Other samples such as valvular tissue, septic metastases, and prosthetic material were sent for culture and histologic examination. Only 2 SPMAs were cultured. Serology of *Brucella*, Q fever, *Legionella*, *Mycoplasma*, and *Chlamydia* was performed in 2 patients with negative blood cultures, and *Bartonella* serology in 1.

As for diagnostic radiology procedures, the initial imaging test for detection of SPMAs was chosen by the corresponding physician. Angiography was performed in all patients who underwent surgical or endovascular repair (n = 11).

For follow-up, patients were evaluated in the outpatient clinic at 1, 3, and 6 months after discharge, and subsequently once a year. Most patients were followed for at least 1 year: 415 (82%) patients without SPMAs and 11 (79%) with SPMAs. None of them developed SPMAs during follow-up.

Definitions

We used the following definitions: diagnostic delay of IE was the time from the onset of symptoms to the diagnosis of IE. Microorganisms isolated in 17 patients with SPMAs were classified in relation to their virulence; those capable of producing rapid tissue destruction were considered the most virulent. High-virulence microorganisms were *S. aureus*, *S. pneumoniae*, *Escherichia coli*, and *Serratia* species. Low- to medium-virulence

microorganisms were *Enterococcus*, *S. viridans*, gram-positive bacilli, and *Candida* species.

Statistical Analysis and Ethical Review

Qualitative variables are provided with their frequency distributions; the Fisher exact test was used for comparisons. Quantitative variables are expressed as the mean \pm standard deviation and range or a median and interquartile range (IQR). Quantitative variables were compared using the Mann-Whitney U test. In each hypothesis contrast, the null hypothesis was rejected when the type I or α error was below 0.05. Statistical analyses were performed using SSPS v. 15.0 software.

The investigation did not require approval from the hospital ethics board.

RESULTS

Epidemiologic, Microbiologic, and Clinical Characteristics of IE Episodes

The epidemiologic and clinical characteristics of the IE episodes with and without SPMAs are shown in Table 1. Globally, patients had an elevated mean age that was lower in patients with SPMAs (51 \pm 19 vs. 66 \pm 14 yr); IE occurred more frequently in males. There was a higher frequency of intravenous drug use (16% vs. 3%) and native valve IE (77% vs. 60%) in patients with SPMAs. The most common location of IE in patients with SPMAs was native mitral valve.

Clinically, fever was the most common symptom, followed by cardiac manifestations, and there were no differences between the groups. There was a higher occurrence of cutaneous manifestations (27% vs. 13%), intracranial bleeding (33% vs. 5%), and septic emboli (77% vs. 28%) among patients with SPMAs than in those without. Ten patients (56%) with SPMAs versus 20 patients (3%) without SPMAs had septic emboli in 2 or more different regions; 5 of them involving several areas (see Table 1). Diagnostic delay of IE \geq 30 days was greater among patients with SPMAs than those without (61% vs. 36%).

The causal microorganisms in patients with and without SPMAs are described in Table 2. Globally, the most common bacteria isolated were *S. aureus*, followed in decreasing order by coagulase-negative staphylococci, *S. viridans*, and *Enterococcus*. In patients with SPMAs, *Enterococcus* was the predominant microorganism. Because of the small number of patients with SPMAs, we could not perform a statistical analysis to compare the differences between the type of microorganisms isolated in patients with and without SPMAs. The relationships between the virulence of the microorganisms and the diagnostic delay of IE in patients with SPMAs are shown in Table 3. The median diagnostic delay of IE was 15 days (IQR, 13–33 d) for high-virulence microorganisms versus 45 days (IQR, 30–240) for low- to medium-virulence microorganisms (p = 0.000). Time to diagnosis was >15 days in 15% of patients with high-virulence microorganisms versus 90% of patients with low- to medium-virulence microorganisms (p = 0.028). In 13 patients (72%) the causal microorganism was isolated in blood cultures, in 3 of them the same microorganism was cultured in other samples: 1 in cerebrospinal fluid, 1 in urine, and 1 in the SPMA. Etiologic diagnosis was made in 3 (16%) by culture of surgical material (2 heart valve, 1 splenic abscess plus heart valve) and in 1 (5%) by serology (*Bartonella*). Cultures and serology were negative in 1 patient.

Mycotic Aneurysms

SPMAs were intracranial in 12 patients (66%), all in the region of the middle cerebral artery, and extracranial in 6 (34%): popliteal arteries (n = 2), ulnar artery, humeral artery, hepatic artery, and coronary artery (1 each). None of the patients with

TABLE 1. Epidemiologic and Clinical Features of Left-Sided IE in 719 Episodes Without and 18 Episodes With SPMA

Feature	Without SPMA No. (%)	With SPMA No. (%)	P
Number	719 (97)	18 (3)	
Age, yr: Mean±SD/range	66 ± 14/12–98	51 ± 19/19–98	<0.001
Male sex	452 (62)	11 (61)	>0.999
Nosocomial endocarditis	189 (26)	2 (11)	0.181
Underlying heart disease:	480 (67)	11 (61)	0.619
Hypertrophic cardiomyopathy	6	2	0.009
Congenital	31	2	0.191
Rheumatic valve disease	56	2	0.646
Degenerative	94	0	0.150
Valve prosthesis	303	4	0.333
No heart disease	233 (32)	7 (39)	0.619
Previous IE	60 (8)	3 (16)	0.194
Intravenous drug user	21 (3)	3 (16)	0.019
Valvular location			
Native	415 (60)	14 (77)	0.097
Aortic	192	3	0.427
Mitral	149	7	0.078
Multivalvular	74	4	0.113
Prosthetic	304 (40)	4 (33)	0.097
Aortic	113	3	>0.999
Mitral	124	0	0.055
Multivalvular	67	1	>0.999
Clinical features:			
Fever	623 (86)	17 (94)	0.493
New murmur	408 (56)	13 (72)	0.233
Heart failure	407 (56)	9 (50)	0.635
Renal failure	276 (38)	6 (34)	0.808
Septic shock	118 (17)	5 (27)	0.202
Cutaneous manifestations	93 (13)	5 (27)	0.078
Ischemic stroke	92 (13)	7 (39)	0.006
Intracranial hemorrhage	35 (5)	6 (33)	<0.001
Constitutional syndrome	219 (30)	6 (33)	0.800
Septic emboli	198 (28)	14 (77)	<0.001
Multiple septic emboli	20 (3)	10 (56)	<0.001
Localization:			
Spleen	61	8	0.001
CNS	139	6	0.141
Kidney	13	2	0.049
Axilo-humeral	16	1	0.346
Diagnostic delay of IE ≥30 d	256 (36)	11 (61)	0.044
Cardiac surgery	404 (56)	10 (55)	>0.999
Elective	211	8	0.193
Emergency	193	2	0.179
Hospital mortality	217 (30)	4 (22)	0.606

Abbreviation: CNS = central nervous system.

intracranial SPMA had multiple intracranial PMAs; 1 of them developed a popliteal SPMA 4 years later. One of the patients had bilateral popliteal SPMA.

Symptoms related to SPMA were the initial presentation of IE in 8 patients with intracranial SPMA: 2 presented as meningoencephalitis with notoriously decreased conscious level, 3 as ischemic stroke, 3 as hemorrhagic stroke secondary to the rupture of SPMA (1 subarachnoid hemorrhage, 1 intraparenchymal hemorrhage, and 1 with both types of hemorrhage). Four patients

developed symptoms during hospitalization while receiving correct parenteral antibiotic therapy: 1 had an ischemic stroke in the first week and 3 had intraparenchymal hemorrhagic strokes due to the rupture of PMA; 2 in the second week and 1 in the fifth week of treatment (Figure 1). Thus 6 (50%) intracranial SPMA became ruptured.

Two extracranial SPMA were the initial presentation of IE, 1 in the popliteal artery with pain and palpable throbbing mass, and another located in the liver with abdominal pain

TABLE 2. Causal Microorganisms of Left-Sided IE in 716 Patients Without and 18 Patients With SPMA

Microorganism	Without SPMA (n = 716) No. (%)	With SPMA (n = 18) No. (%)
<i>S. aureus</i>	118 (16)	2 (11)
<i>Enterococcus</i>	68 (9)	3 (16)
<i>Streptococcus viridans</i>	93 (12)	2 (11)
<i>Streptococcus bovis</i>	34 (4)	0
Other <i>Streptococci</i>	50 (7)	1 (5.5)
Coagulase-negative <i>Staphylococci</i>	118 (16)	1 (5.5)
Gram-negative bacilli	33 (4)	2 (11)
Fungus	14 (2)	1 (5.5)
Anaerobes	14 (2)	1 (5.5)
Polymicrobial	49 (7)	1 (5.5)
Other*	22 (2.5)	2 (11)
Negative cultures	103 (14)	1 (5.5)

*Other: Gram-positive bacilli, HACEK organisms, *Bartonella*, *Bruceella*, *Coxiella*, *Chlamydia*, *Legionella*, *Mycoplasma*.

secondary to hematoma and hepatic ischemia due to aneurysm rupture (Figures 2 and 3). The other extracranial SPMA did not rupture. Three began to show symptoms during parenteral antibiotic therapy: 1 in the ulnar artery, 1 in the humeral artery, and 1 in both popliteal arteries with peripheral neuropathy and painful pulsatile masses (Figure 2 and 4). The patient with SPMA located in the coronary artery developed an acute coronary syndrome with acute pulmonary edema 3 weeks after finishing IE treatment (see Figure 2). Two of 8 patients who developed SPMA during hospitalization still had fever in the second week of antibiotic treatment.

Fifteen patients (83%) showed neurologic symptoms at some stage, either due to other central nervous system septic emboli (n = 3) or to SPMA (n = 12). In 9 patients the neurologic symptoms were the debut of IE, and in the other 6 they appeared while the patients were receiving antibiotic therapy.

The diagnosis was made by computed tomography (CT) in 4 cases (22%); 1 ruptured in the liver and 3 unruptured intracranial SPMA; by magnetic resonance imaging (MRI) in 3 (16%)

unruptured intracranial SPMA; and by Doppler ultrasonography in 4 (22%) (2 popliteal, 1 humeral, 1 ulnar). In 7 patients the first diagnostic technique for SPMA was angiography (38%): 1 coronary, 6 ruptured intracranial SPMA; CT did not detect 5 ruptured intracranial SPMA. In 4 patients (22%) angiography was done as an additional test before performing surgical or endovascular treatment (1 popliteal, 1 humeral, 1 ulnar, 1 hepatic).

Seven patients with SPMA (39%), 6 intracranial and 1 popliteal, received only antibiotic treatment. Three patients with intracranial SPMA died during hospitalization: in 2 patients SPMA were not ruptured and the cause of death was septic shock, in the other patient the SPMA was ruptured and the patient died due to cardiogenic shock. The patient with the popliteal SPMA was first designated for cardiac surgery and died during the procedure. The other 3 patients had nonruptured intracranial SPMA and were cured by antibiotics (mean duration, 6.3 ± 5 wk); they had no follow-up after hospital discharge.

Surgical resection was performed in 7 cases (39%): 1 coronary, 1 humeral, 1 ulnar, 1 popliteal, and 3 intracranial; all of them were cured, and in 6 patients with long follow-up there were no complications (mean, 4.5 ± 2.8 yr). The mean duration of antibiotic treatment in these patients was 7 ± 2.9 weeks.

Endovascular treatment was performed in 4 (22%) cases: 1 hepatic and 3 intracranial; all patients were cured. Occlusion of the SPMA was performed using coils in 1 patient, with cyanoacrylate in another, and with cyanoacrylate plus coils in 2 patients (see Figures 3 and 5). All patients underwent control angiography between the third and seventh day after the procedure; in 2 SPMA a contrast leak was observed and consequently a second endovascular procedure had to be performed. The 4 patients were discharged after completing a minimum of 6 weeks (mean, 8 ± 0.8 wk) of intravenous antibiotic treatment, and 2 of them in whom coils were implanted (1 intracranial, 1 hepatic) remained on oral antibiotic treatment for another 12 weeks. Patients with endovascular treatment were followed for a mean of 30 ± 20 months. After discharge, magnetic resonance angiography (MRA) was performed in all patients with intracranial SPMA treated by endovascular procedures, although in 1 of them the initial control was with arteriography. There was not any local postprocedural complication or recurrence of IE. One patient had neurologic sequelae related to the intraparenchymatous hemorrhage. The patient, who had *Bartonella* IE with an intracranial SPMA, developed pain during exercise and swelling of

TABLE 3. Causal Microorganisms in 17 SPMA Classified in Relation to the Virulence of the Organism and the Diagnostic Delay of IE

High Virulence (N)	Diagnostic Delay (d)	Low-Medium Virulence (N)	Diagnostic Delay (d)
MSSA (n = 2)	15	<i>Enterococcus</i> (n = 3)	1
			30
	15		30
<i>S. pneumoniae</i> (n = 1)	15	CNS (n = 1)	90
<i>E. coli</i> (n = 1)	30	<i>Bartonella henselae</i> (n = 1)	365
<i>Serratia marcescens</i> (n = 1)	10	<i>S. viridans</i> (n = 2)	100
Polymicrobial (MSSA & <i>Streptococcus spp.</i>) (n = 1)	45	<i>Bacillus circulans</i> (n = 1)	31
		<i>Corynebacterium striatum</i> (n = 1)	21
		<i>Propionibacterium acnes</i> (n = 1)	390
		<i>Candida albicans</i> (n = 1)	45
Median	15	Median	45
IQR (p25–p75)	13.75–33.75	IQR (p25–p75)	30–240

Abbreviations: CNS = coagulase-negative *Staphylococci*, MSSA = methicillin-susceptible *Staphylococcus aureus*.

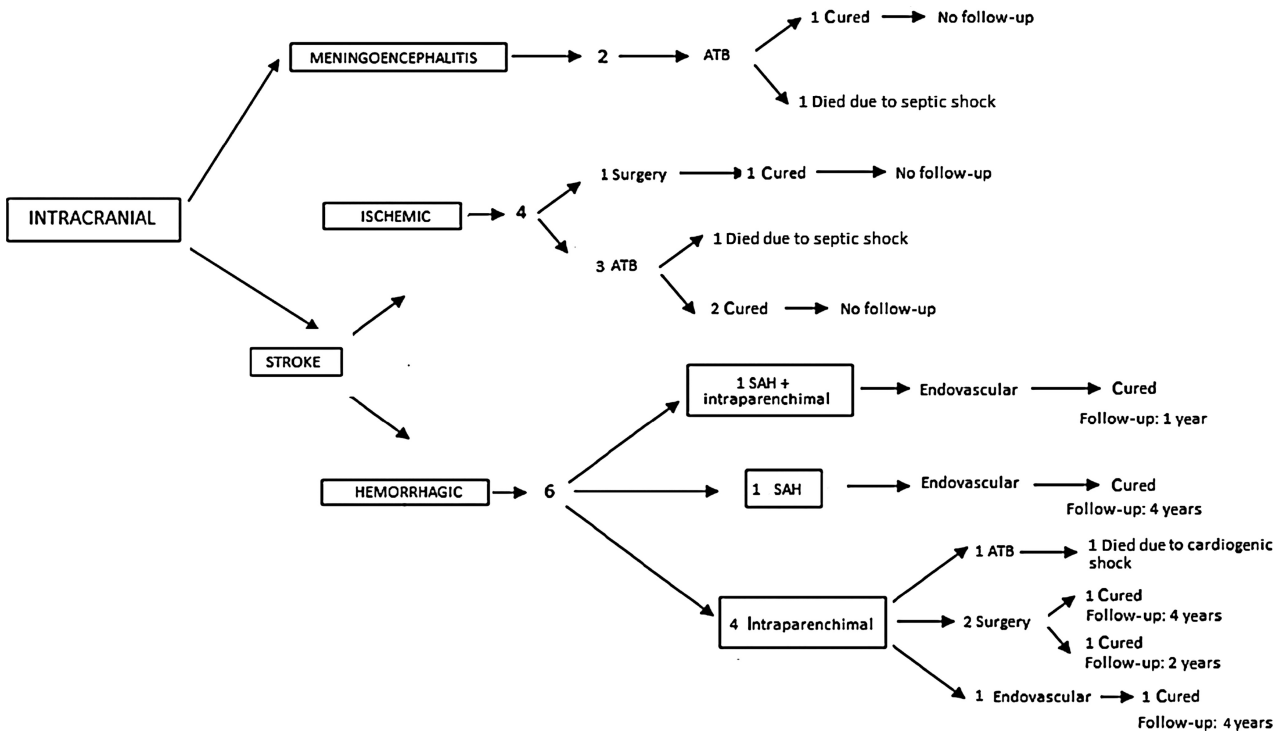


FIGURE 1. Treatment and outcome of 12 patients with intracranial SPMA. Abbreviations: ATB = antibiotics, SAH = subarachnoid hemorrhage.

the left calf 4 years after the intracranial SPMA was resolved. A Doppler ultrasonography did not detect any abnormality, but a computerized tomographic angiography (CTA) disclosed an aneurysm in the popliteal artery fistulized to the popliteal vein. We note that the *Bartonella* serology of this patient had previously

converted to negative, but when the popliteal aneurysm appeared an increase in the titers was observed.

Ten patients (55%) underwent cardiac surgery in the active period of IE. Urgent surgery was indicated for 2 patients who had subarachnoid hemorrhage due to rupture of SPMA; 1 for

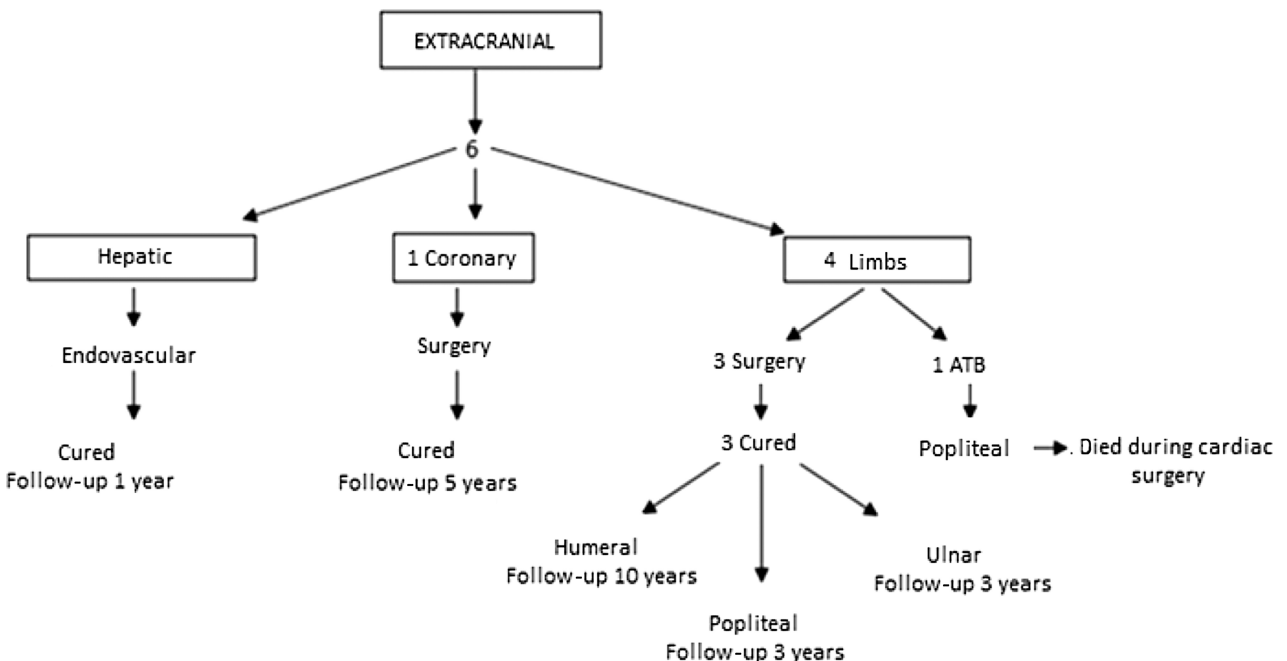


FIGURE 2. Treatment and outcome of 6 patients with extracranial SPMA. Abbreviation: ATB = antibiotics.

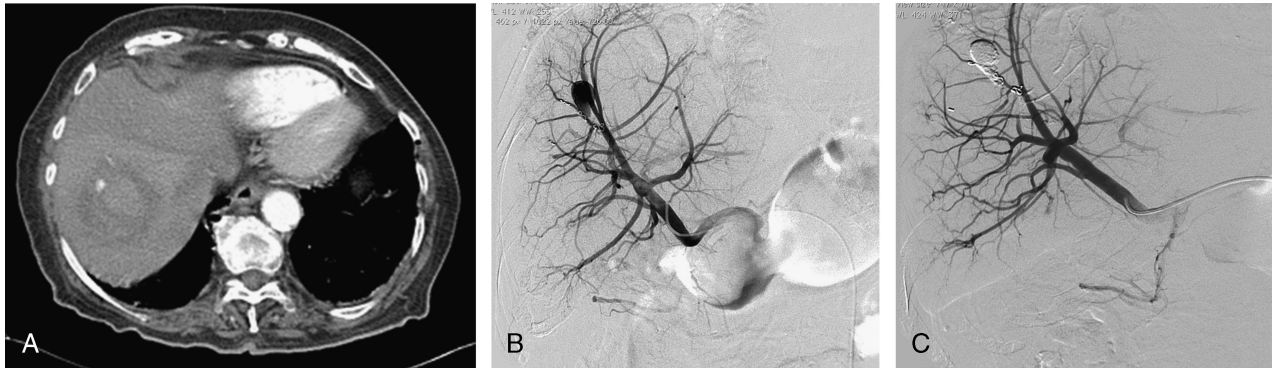


FIGURE 3. A, CT scan image in arterial phase showing a hematoma in the right hepatic lobe and a small hyperdense image corresponding to a small aneurysm with extravasation of intravascular contrast. B, Hepatic arteriography showing an aneurysm in a branch of the right hepatic artery. C, Final result after combined embolization of the aneurysm and the branch of the hepatic artery from which coils and cyanoacrylate originate.

heart failure with severe mitral and aortic valve regurgitation and another because of persistent signs of infection. In both cases endovascular treatment of the SPMA was performed, allowing valve replacement at 5 and 6 days from the effective embolization. Elective surgery was indicated in 8 patients.

DISCUSSION

Epidemiologic, Microbiologic, and Clinical Characteristics of IE Episodes

SPMAs developed only in patients with left-sided IE, something reported in the literature^{6,49,55} and coherent with the pathogenesis of PMAs that result from septic embolization of vegetations. The occurrence of SPMA found in the current study is in the lower range reported by other authors: 1.2%–5%.⁴ The true prevalence of PMAs is unknown because some remain asymptomatic and resolve with antimicrobial therapy. The prevalence has been reported to be higher when PMAs have been actively searched for in patients with neurologic symptoms by means of CT scan and arteriography (31%)⁶⁰ or by CT/CTA and MRI/MRA (magnetic resonance angiography) (13.3%).²¹

Our SPMA population reflected some of the epidemiologic changes detected in patients with IE in developed countries, such as predominance of male sex, older age, lower frequency of rheumatic heart disease and a higher occurrence of prosthetic valve, or absence of underlying heart disease.^{8,9,16,22} Older publications showed a higher frequency of female sex and rheumatic heart disease and a minor occurrence of prosthetic valve or of absence of underlying heart disease.^{13,55} What remained unchanged from previous studies to the current study is the lower mean age and the preponderance of native valve location, particularly of native mitral valve in patients with SPMA.⁵⁵ According to our findings intravenous drug use could be a risk factor for developing SPMA.

Fever and constitutional syndrome have been referred to as the most common presenting symptoms of SPMA,^{49,50,55} but we did not find any differences in their frequency between patients with or without SPMA. As is well known, intracranial hemorrhage was more common in patient with SPMA. The fact that multiple embolisms were more common among patients with SPMA suggests that this population might also have an increased risk of developing PMAs. Other authors have also reported that patients with PMAs usually have a history of previous embolism.⁶⁵

In most series the etiologic microorganisms most often implicated are *S. aureus*, *S. viridans*, and *Enterococcus*,^{11–13,29,49,55}

but in the current study the microbiologic profile was more diverse and did not show such dominance for these microorganisms. Probably the predominance of *S. aureus*, viridans streptococci, and *Enterococcus* is because these bacteria are the most common causative microorganisms of IE, and not because they have a higher predisposition to cause PMAs. Salgado et al⁵⁵ compared intracranial SPMA due to IE, collected in the English-language literature, with 150 consecutive patients with IE admitted to the Cleveland Clinic, and did not find any microbiologic association. Some authors have stated that PMAs occur more often with low-virulence organisms such as *S. viridans*,⁶⁸ and that many patients may have a prolonged history of systemic prodromal symptoms antedating the onset of neurologic symptoms.⁵⁵ In an experimental canine model, Molinari found that both types of microorganisms, low and high virulence, can cause SPMA; whereas high-virulence types will cause them in a short time, low-virulence types will need a longer time. We had similar results: the IE delayed diagnosis was longer in patients with SPMA, low-medium virulence microorganisms were predominant, and had a greater delayed diagnosis of IE than those caused by high-virulence microorganisms. Delayed diagnosis of IE could increase the risk of SPMA by 2 mechanisms: a prolonged exposition to embolization and a postponement in the introduction of antibiotic therapy that would avoid the enlargement and rupture of PMAs. Since 1990 the improvement in microbiologic and echocardiographic techniques has allowed an earlier diagnosis of IE. IE caused by virulent microorganisms may be



FIGURE 4. Popliteal aneurysm in a patient with infective endocarditis.

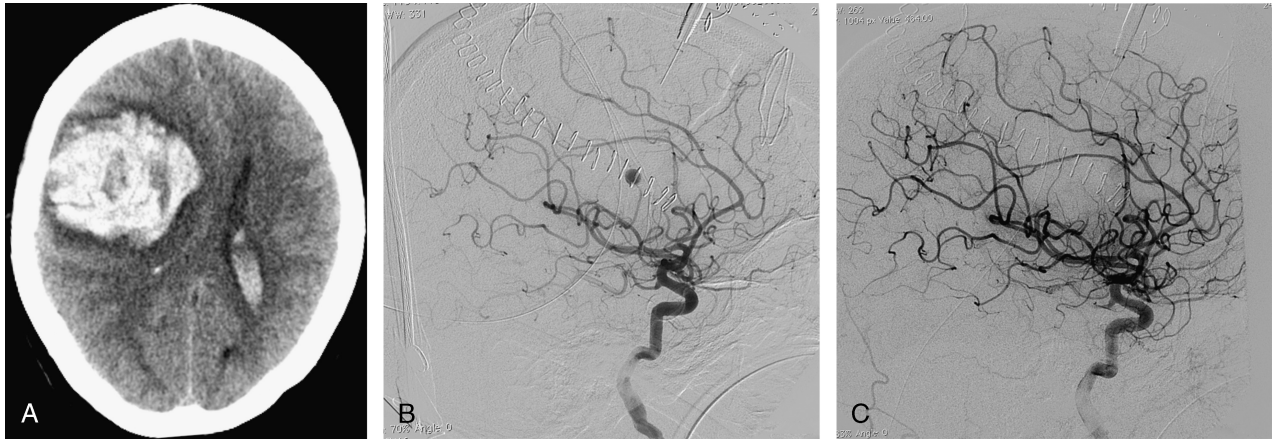


FIGURE 5. A, CT scan image showing large right frontal intraparenchymal hematoma open to ventricular system with ipsilateral ventricular system collapse and herniation subfascial with midline shift. B, Arteriography showing mycotic aneurysm of a frontal branch from the anterior division of the right middle cerebral artery. C, Right internal carotid arteriography showing occlusion of the aneurysm after embolization with cyanoacrylate.

benefiting the most from this earlier diagnosis, whereas some IE caused by low-medium virulence microorganisms, with lower clinical expression, may still have a long delayed diagnosis. This could explain the different distribution of microorganisms in the current series compared to the distribution in earlier studies.

Mycotic Aneurysms

The location of the SPMA in our sample is consistent with previous reports;⁴ intracranial was the most frequent location, and the branches of the middle cerebral artery were the most commonly affected. Other intracranial locations such as anterior or posterior cerebral arteries are reported with variable frequency in the literature. Multiple intracranial PMAs have been reported in patients with IE,^{11,13,64} and simultaneous association with extracranial PMAs has also been described in up to 35% of the patients.^{5,26} Both situations were uncommon in our population.

SPMAs at intracranial locations can cause neurologic symptoms such as severe headache, altered sensorium, meningitis, and focal neurologic deficits. Unruptured PMAs often initially present with minor focal deficits due to septic embolization to the intracranial vasculature. Local compression from an expanding aneurysm can also cause cranial nerve palsy. The clinical presentation for ruptured SPMA includes severe unremitting localized headaches, dizziness, seizures, altered mental status, and focal neurologic deficits.^{4,15,49,50,55} Following aneurysm rupture the occurrence of subarachnoid hemorrhage ranged from 25% to 100%,^{11–13,20,50,55} and the occurrence of intraparenchymal hemorrhage ranged from 40% to 100%.^{11–13,50} Our patients with unruptured SPMA presented with focal deficits due to ischemic stroke or meningitis; whereas patients with ruptured SPMA presented with intraparenchymal (83%) or subarachnoid hemorrhage (33%). In other series ruptured SPMA constituted 72%–85% of the reported cases.^{11,13,50,66}

Manifestations of SPMA at the extremities include pulsatile painful masses, ischemia secondary to thrombosis or rupture, splinter hemorrhages or ischemic lesions due to digital embolization,^{6,17,19,24,30,32,33,37,40,45,48,52,57,58,67} and neurologic symptoms and signs due to direct compression or occlusion of the vasa nervorum.^{30,40,51} Presentation may also mimic a deep vein thrombosis in popliteal SPMA.¹⁴ None of our patients experienced ischemia or rupture. Rupture of a popliteal or infrapopliteal aneurysm is extremely uncommon.⁵⁷ PMAs of the hepatic artery

are rare now. The clinical presentation included abdominal pain in 80% of cases reported; rupture of these aneurysms is frequent and usually has a fatal outcome.^{3,12,56} The development of a coronary artery mycotic aneurysm is unusual. They can be asymptomatic or can cause an acute coronary syndrome with extensive ventricular dysfunction, as in our patient. They have a great tendency to distal embolization, myocardial infarction, and rupture that may result in cardiac tamponade and sudden death. They are most frequently seen at the left anterior descending or circumflex artery and may resolve with antibiotic therapy or enlarge and eventually rupture.^{10,39,46,47,54,62} Most PMAs of the superior mesenteric artery branch present with significant abdominal pain, sometimes a pulsatile abdominal mass can be appreciated, but physical examination is rarely diagnostic because most lesions are small.^{26,35,61}

As noted in the current series, PMAs may be the first manifestation of IE,^{13,14,55} may be diagnosed in its course,^{4,27,30,38–40,46,66,68} or may appear even long after completion of antibiotic treatment.^{54,57} In a case of *Bartonella henselae* IE, cerebral SPMA developed 9 months before IE was diagnosed.¹⁴ There is currently no clinical, analytical, or microbiologic marker to indicate which PMA will rupture. Intracranial PMAs have the highest risk for a patient's life. According to data reported in the literature, actively searching for these is justified in patients with previous neurologic symptoms,^{13,21,24,49,60} in patients with extracranial PMAs,^{11,26} or in patients who are going to start anticoagulant treatment.⁷ The results of the current study point out that PMAs must also be investigated in patients with multiple embolisms, especially if they had a long delayed diagnosis of IE.

The initial test for evaluating a patient with a cerebrovascular accident is CT/CTA or MRI/MRA in order to rule out PMAs in patients without evidence of intracranial bleeding.⁷ CT scanning may discern not only subarachnoid and intracerebral hemorrhage but also edema and infarction, which are commonly associated with PMA rupture.^{15,49} Although a normal CT does not rule out a PMA,⁴⁹ usually patients with PMAs have an abnormal brain CT.⁶⁰ Recently, CTA has reported specificity rates of 90%–94% for detecting aneurysms smaller than 3 mm and up to 100% for aneurysms larger than 4 mm, and sensitivity rates of 96%–98%.²³ MRA also can detect aneurysms as small as 3–4 mm.^{4,15,23,28} CTA and MRA have the advantage of being noninvasive procedures that render the aneurysms in 2 or 3 dimensions in relationship to the bony landmarks. The major drawback of CTA is its

low sensitivity to detect aneurysms that are very small and those located close to the base of the skull. To our knowledge no studies have compared arteriography, CTA, and MRA in the diagnostic accuracy of PMAs. Currently, angiography, either conventional or DSA, is the gold standard for diagnosis of PMAs but it is an invasive procedure that carries a small risk of complications (<1%) or neurologic deficits (<0.5%).^{28,49} It must be performed in patients with bleeding or for prior assessment before invasive treatment.^{4,7,15,23,30,48} A newer CTA technique like multidetector CT may improve the detection of smaller aneurysms and may possibly replace DSA in the management of PMAs.²⁸ In our patients without intracranial bleeding, SPMAs were diagnosed by noninvasive radiologic imaging techniques, but in 5 of 6 patients with intracranial bleeding, angiography was essential.

In PMAs of the limbs, noninvasive procedures such as color-duplex ultrasonography, CTA, and MRA can establish the diagnosis.^{30,40,57,58} Angiography is important to demonstrate the status of the inflow and outflow vessels, hence guiding any operative approach. CTA and MRA can be satisfactory when clinical conditions preclude angiography.³⁰ Coronary arteriography is the test of choice for coronary PMAs.^{10,39,46,47,54,62} CT/CTA and MRI/MRA are the initial imaging tests for intra-abdominal PMAs, but angiography is the most reliable procedure for confirming the diagnosis, as well as for demonstrating the presence of anatomic variations.²⁷ Contrast-enhanced multidetector CT provides prompt detection and characterization of mesenteric PMAs,⁶¹ although angiography is still recommended.³⁵

Decisions regarding the most appropriate therapy for PMAs must be individualized. When an intracranial PMA is diagnosed, if asymptomatic, antibiotic treatment for 6 weeks and close assessment of the evolution of its size with serial angiography has been recommended; this is how 30%–52% of PMAs will resolve.^{4,5,13,15,28} Cerebral angiography should be repeated every 1–2 weeks during intravenous antibiotic therapy.^{1,4,28} CTA and MRA have been used to monitor PMAs under antibiotic therapy.^{1,4,28} PMAs that are large in size (≥ 8 mm) may be at increased risk of bleeding, since it has been reported that PMAs that tend to grow or do not decrease have a greater diameter than those that resolve (8.3 mm vs. 6 mm). Nevertheless, it has been observed that even small PMAs can rupture and bleed fatally. PMAs that increase in diameter, which are symptomatic or ruptured, require invasive treatment. In some cases, the aneurysm may persist after a 6-week course of antibiotics. Disappearance of PMA can take an average of 14.4 weeks during conservative management.³¹ Thus, some authors suggest continuing the follow-up for 3 months⁶⁴ and surgery if the PMA remains unchanged, whereas others recommend surgical resection if a large residual aneurysm persists at the end of treatment.⁵⁰ With this management the mortality is low, but greater than when antibiotic and surgery are combined, because fatal ruptures or permanent neurologic deficits have been reported.^{13,28,49,64} Therefore, a proactive early surgical intervention or endovascular treatment irrespective of the PMA size, provided it is technically feasible, has to be considered.^{11,28} This management has to be specially recommended in patients who will require anticoagulation. In 5 of the 6 current patients with unruptured SPMAs, conservative treatment with antibiotics was elected; 2 patients died because of septic shock and 3 were cured, but as they were not followed, the final outcome after discharge is unknown. In the current series, all patients with intracranial SPMAs who had rupture with bleeding, except 1 patient who had very poor hemodynamic status, received surgical or endovascular treatment (see Figure 1). Ruptured SPMAs have the worst prognosis, and they have been generally managed by surgery. In the series published since the 1970s, patients treated with surgery and antibiotics had a good

prognosis with very low mortality,^{28,49} although a bias in favor of surgery has been suggested because of the selection of patients, maybe excluding patients judged to be too sick to tolerate surgery, and the propensity to publish positive surgical results.²⁸ The commonly used procedures are clipping, trapping, anastomosis, and proximal ligation. Patients with a ruptured aneurysm with hematoma and mass effect would require urgent surgery. Surgery has the advantage that the distal vessels could be spared in eloquent areas. It may be possible to do anastomotic procedures in eloquent areas. There is no clear advantage for delayed surgery after antibiotic therapy compared to early surgery.²⁸ But cranial surgery due to its contraindication to the use of anticoagulation can delay cardiac surgery. A waiting period of 2–3 weeks on antibiotics after craniotomy for a ruptured aneurysm has been recommended before undergoing cardiac surgery.⁴⁹ In the last 2 decades the use of endovascular treatment of noninfectious intracranial aneurysms has been associated with less morbidity and mortality than surgery.²³ Endovascular treatment of ruptured and nonruptured SPMAs due to IE has been reported in case reports and small series with successful results: no mortality related to the procedure, low morbidity reported with transient complications, and no permanent neurologic disabilities.^{11,12,15,66} Morbidity generally has been related with initial stroke.¹¹ After the procedure, monitoring of these patients has been performed using arteriography.^{11–13,66} Experience using CTA or MRA in PMAs due to IE is scarce,⁶⁶ but these have often been used in noninfectious aneurysms.^{22,69} Endovascular treatment has the advantage of being able to advance cardiac surgery when it is urgent,^{11,15,66} as in 2 of our patients; it is less invasive and thereby minimizes the risks associated with general anesthesia in patients with impaired cardiac valvular function. The main disadvantage is that endovascular treatment will sacrifice the parent vessel. Nevertheless, previous selective amobarbital injection in a conscious patient can determine if occluding the aneurysm will infarct additional eloquent neural tissue.^{11,28,49} There still is the question of whether placing a coil or cyanoacrylate in infected SPMAs could result in an infectious recurrence and weakening of the vessel with delayed rupture. None of these events occurred in patients in the current or in previously reported series.^{11,15,66} Because of the theoretical high risk of recurrence of infection we use long-term suppressive oral antimicrobials in patients who undergo endovascular repair. Consequently, endovascular treatment could be the first-line of invasive treatment in intracranial SPMAs except for patients who need surgery for decompression of intracranial hemorrhage, or in those in whom there are technical difficulties for carrying out endovascular procedures. Management of multiple intracranial PMAs should be dictated by the most dangerous aneurysm. If both ruptured and unruptured aneurysms are present, management should be dictated by the ruptured one.⁴⁹

Extracranial PMAs have been associated with a high mortality rate.⁴ Conservative treatment with antibiotics has been considered only in a minority of patients with intra-abdominal^{2,11,18,61} or coronary⁴⁶ PMAs. Although some resolved with this approach,^{11,18,61} PMAs can enlarge, rupture, or cause complications as late as 3–9 months after ending antibiotic treatment.^{2,46,63} The outcome of our patient with *Bartonella henselae* IE is remarkable because he developed a new peripheral SPMA in the popliteal vein 4 years later, after the cure of the intracranial SPMA. Although it is possible that this PMA was already present 4 years before and it was not recognized until it fistulized to the arterial vein, the elevation of the serology titers, when previously they had become negative, arouses doubt that a persistent endothelial infection became symptomatic later. *Bartonella henselae* has the ability to infect endothelial cells and has mechanisms to maintain persistent infection, and relapse

of IE has been reported.^{42,53} Most of the intraabdominal,^{26,27,35,41} coronary,^{39,46,47,54} or limb^{6,17,24,30,33,38,40,45,48,52,57,59} PMAs have been treated by surgery. The commonly used procedures are excision with ligation or revascularization with an autologous vein graft to restore the flow. In the literature published since the 1980s, the outcomes have been favorable with low mortality or morbidity. Lost limbs have been rarely reported, and deaths have been related to other complications of IE.^{6,17,36} Percutaneous endovascular management of noninfectious visceral artery aneurysms is now considered a safe and effective alternative to conventional surgery, with lower procedural morbidity and mortality and high technical success rates, but its role in infectious aneurysms has yet to be defined. In the last decades endovascular repair of PMAs due to IE has been reported in intraabdominal PMAs by embolization associated with stent implantation,^{2,18,25,56} in limbs generally by embolization plus stent grafting,^{19,32,52} and in coronary PMAs using stent.⁶² The outcomes were favorable with no relapse or rebleeding, as in the current patient with hepatic SPMA. In 1 patient the procedure failed and required surgery.⁴⁸ Antibiotics should be given for at least 6 weeks, but we suggest that oral suppressor antibiotics be maintained for 3 months. The management of extracranial PMAs has to be individualized, but an interventional approach has to be recommended if they are symptomatic or if they are located in limbs or coronary arteries. In our opinion, surgery is the first option for limb or coronary PMAs in the active phase of IE, if there are no contraindications. Endovascular repair could be the first approach for intraabdominal PMAs, and for other extracranial locations only when surgery is not feasible and the IE is microbiologically eradicated. Endovascular or surgical repair should always be considered at the time of diagnosis, even when PMAs are asymptomatic.

Hospital mortality in patients in the current study with intracranial SPMA (25%) is lower than that described in older series (mortality rate approaches 60%),⁴ and similar to that reported by other authors who also provide their experience with patients treated only with antibiotics or combined with surgical or endovascular repair (19%–22%),^{12,50,64} Mortality in series where the patients were exclusively treated with antibiotics and endovascular techniques has ranged between 0 and 40%.^{11,66} Sepsis or cardiac complications were the cause of death irrespective of the type of treatment. Rebleed of the same SPMA was only noted in the group treated conservatively.^{11,12,50,64,66} Morbidity was related with the initial stroke. Hospital mortality in patients with extracranial SPMA was 17% and was not related to SPMA.

Study Limitations

The current study was performed in tertiary hospitals, a setting that biases the type of patients included in the database. Our samples do not reflect the characteristics of all patients with IE in the general population, but rather the population of patients with IE admitted to dedicated hospitals. This bias cannot be avoided, but it must be recognized.

On the other hand, the current study cannot give information about the real incidence of PMAs in our population because 1) only the features in patients with SPMA are described, since a prospective protocol to detect PMAs in patients with IE was not performed; and 2) all patients did not have follow-up, so we cannot exclude that other PMAs became symptomatic and ruptured after discharge.

Conclusions

We found that SPMA were a rare complication of IE and only developed in patients with left-sided IE. Some epidemiologic characteristics in patients with SPMA remain the

same as in older studies, but other characteristics reflected the changes detected in patients with IE in developed countries. Intracranial hemorrhage, multiple embolisms, and a longer delayed diagnosis of IE were more common in patient with SPMA. The microbiologic profile was diverse and showed no preference for any organism, but low-medium virulence microorganisms were predominant, and cases related to these had a greater delayed diagnosis of IE than cases related to high-virulence microorganisms. SPMA were often the initial presentation of IE. Intracranial location was the most common. Unruptured SPMA presented with focal deficits due to ischemic stroke or meningitis; whereas ruptured SPMA presented with intraparenchymal hemorrhage or subarachnoid hemorrhage. Active search for intracranial SPMA is justified in patients with previous neurologic symptoms, extracranial PMAs, multiple embolisms, or when anticoagulant treatment has to be initiated. In patients without intracranial bleeding, SPMA were diagnosed by noninvasive radiologic imaging techniques, whereas in those with intracranial bleeding, angiography was essential. CT/CTA and MRI/MRA are the initial imaging tests to rule out brain PMAs in patients without evidence of intracranial bleeding. Angiography must be performed in patients with intracranial bleeding. CT/CTA and MRI/MRA are the initial imaging tests for intraabdominal PMAs, and color-duplex ultrasonography for PMAs of the limbs. Angiography should be performed before invasive treatment. Surgical and endovascular treatment were safe and effective procedures with no mortality. Endovascular treatment could be the first line of invasive treatment in intracranial SPMA except for patients who need surgery for decompression of intracranial hemorrhage, or in those in whom there are technical difficulties for carrying out endovascular procedures. A proactive approach to an unruptured PMA with early interventional treatment irrespective of its size should be considered, especially when the patient will require anticoagulant treatment. In extracranial PMAs an interventional approach at the time of diagnosis has to be considered, if feasible. In our opinion, surgery is the first option for limb or coronary PMAs, and endovascular treatment for intraabdominal PMAs. The prognosis of patients with SPMA has improved, but mortality is still high.

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