Mycotic vasculitis with repeated intracranial aneurysmal hemorrhage

Case report

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A case of repeated intracranial aneurysmal rupture occurring despite successful treatment of infective endocarditis is reported. While the valvular source of emboli was eradicated and serial angiograms documented no further aneurysms after resection of the primary lesion, the formation and rupture of multiple septic aneurysms occurred 9 months later in the opposite hemisphere. A relationship to damage of the cerebral vasculature by immune complexes is suggested as one possible explanation for this unusual occurrence. This implies that some patients with infective endocarditis may be at permanent risk for the formation and rupture of mycotic intracranial aneurysms, despite successful treatment of the primary cardiac lesion.

Key Words • mycotic vasculitis • intracranial aneurysm • infective endocarditis • Streptococcus viridans

The relationship between infective endocarditis and mycotic aneurysm formation appears clear: as many as 15% of patients with infective endocarditis harbor septic intracranial aneurysms. Yet, the pathogenesis, natural history, and management of these lesions remains controversial. Aggressive medical treatment of the underlying infected cardiac valve and surgical replacement, when indicated, have significantly reduced the morbidity and mortality rates associated with infective endocarditis. Mycotic intracranial aneurysms develop within days of the initial embolic event; however, experimental studies have shown that early initiation of antibiotic therapy delays the formation and rupture of these aneurysms. In spite of this, septic aneurysmal hemorrhage has been reported to occur while appropriate antibiotic treatment was in progress and, more infrequently, after the completion of such therapy.

The case described here represents an example of the formation of mycotic intracranial aneurysms after the initial hemorrhage was treated, the delayed formation of aneurysms is assumed to be the result of embolism from the initial valvular lesion. This suggests that, even with successful treatment of the primary focus or infection, patients with infective endocarditis may remain permanently at risk for mycotic intracerebral hemorrhage because embolic seeding may precede treatment of the primary infection. Their risk may also be related to low-grade vasculitic processes associated with the formation of immune complexes following the initial presentation or stimulated by multiple emboli too small to be detected with traditional studies.

Case Report

This 69-year-old white woman presented to the emergency room on December 29, 1985, with progressive decline in level of consciousness and difficulty in speaking over a 12-hour period. Eighteen months earlier, the patient had undergone oral surgery. Within 4 to 6 weeks following the dental procedure she noted the development of fatigue, weight loss, and night sweats. Fever was not documented. Outpatient evaluation at that time detected anemia of chronic disease, microscopic he-
maturia, and an erythrocyte sedimentation rate of 50 mm/hr. Several months later she developed a truncal macular rash that was interpreted as "vasculitis" from a biopsy specimen, and she was treated with oral prednisone, 20 mg/day. This stopped the weight loss, but fatigue and anemia persisted.

On March 9, 1985, the patient was involved in a minor motor-vehicle accident with minimal blunt trauma to the head; she did not lose consciousness. Three days later, she became confused and was admitted to the hospital. At that time, in retrospect, the family described a 1-month history of intermittent complaints by the patient of right-sided headache. Further questioning revealed that she had a known allergy to penicillin and had suffered from a heart murmur since childhood. The patient was unaware of ever being diagnosed as having rheumatic fever or heart disease.

**Examination.** Examination revealed normal body temperature and vital signs, conjunctival petechiae, a Grade III/VI pansystolic murmur, and numerous petechial lesions on the anterior tibial region. Neurological examination disclosed mentation somewhat less than expected for her age, with a markedly shortened attention span. The left nasolabial fold was somewhat flattened. She had good motor tone and strength, but exhibited marked dysmetria bilaterally. Sensation was intact except for difficulty with graphesthesia in both hands, more pronounced on the left. Reflexes were physiological and there were no pathological reflexes. Her gait was stable, but with difficulty in heel, toe, and tandem walking.

Laboratory studies showed mild anemia, leukocytosis, microscopic hematuria, and mild prerenal azotemia. Echocardiographic examination documented prolapse of the mitral valve. Six blood cultures were positive for *Streptococcus viridans*.

A computerized tomography (CT) scan of the head showed an intracerebral hematoma in the right parieto-occipital region (Fig. 1). Cerebral arteriography revealed a 2 x 4-mm aneurysm in the right posterior parietal region involving a distal branch of the right pericallosal artery (Fig. 2). In addition, several branch occlusions in the posterior distribution of the right middle cerebral artery were noted. No changes suggestive of vasculitis were found.

**First Operation.** A presumed diagnosis of mycotic aneurysm was made, and intravenous vancomycin therapy was started. On the 9th hospital day the patient was taken to surgery where a right parietal craniotomy was performed with obliteration and excision of the mycotic aneurysm and evacuation of the intracerebral hematoma. Her immediate postoperative care was uncomplicated. After 2 weeks of vancomycin therapy, the patient developed a diffuse macular rash and drug-induced hemolytic anemia. Because skin testing for allergy to penicillin was positive, the patient completed her 28-day course of antibiotics with clindamycin phosphate.

Follow-up echocardiography performed on the 18th hospital day revealed minimal mitral valve prolapse. Repeat blood cultures were negative. On April 17, 1985, the patient was discharged with minimal generalized weakness. Angiography 1 week following surgery and 6
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months later did not reveal any residual or additional lesions.

The patient showed no signs of recurrent neurological or endocarditis-related symptoms until December 28, 1985, when she awoke with a severe, generalized headache. Over the next 14 hours she became somnolent and began to slur her speech. Her physical examination revealed a Grade II/VI pansystolic murmur, but no evidence of peripheral embolization. She was oriented only to name and unable to perform complex commands. Testing of the cranial nerves was significant for a right homonymous hemianopsia and right central facial palsy. She also had an expressive dysphasia. Examination of motor function showed a right pronator drift. Her sensory examination was normal, and her reflexes were mildly brisk on the right. Laboratory studies were unremarkable except for the urinalysis which revealed 5 to 10 red blood cells/high-power field.

A hematoma in the anterior aspect of the left parietal lobe with spread into the sylvian fissure was seen on emergency CT scanning. A second hematoma in the left inferior frontal lobe was also present. Subarachnoid blood was noted in the basal cisterns and left sylvian fissure, and there was a moderate left-to-right shift (Fig. 3). An emergency angiogram of the left carotid artery revealed luminal narrowing of a midparietal convexity branch of the left middle cerebral artery, but there was no obvious aneurysm (Fig. 4).

Second Operation. The patient was immediately taken to the operating room where she underwent a left frontoparietal-temporal craniotomy. The dura was opened and a moderate amount of subdural blood was removed. The area of hematoma had dissected through the cortical surface of the parietal lobe above the sylvian fissure. This was followed intraparenchymally and a hematoma cavity was encountered. Upon evacuation of the hematoma, a finer area of thrombotic tissue was noted distally on a branch of the middle cerebral artery. The tissue was carefully dissected from the parenchyma and resected. A corticectomy was then performed over the inferolateral frontal lobe, where a second hematoma cavity was evacuated. The dome of a second aneurysm was identified and resected. Pathological examination of the excised tissue identified both specimens as mycotic aneurysms. A Gram stain of the tissue was negative. The preoperative and postoperative blood cultures were also negative.

Postoperative Course. The patient had been started on chloramphenicol during surgery. After a 6-day course, the antibiotics were discontinued and the patient remained afebrile and without other evidence endocarditis. Her steroid dosage was slowly tapered.

Four-vessel angiography on the 15th postoperative day showed no aneurysm, but did reveal multiple areas of apparent vasculitis both in the carotid artery distributions and in several branches of the verteobasilar system. By the time of the patient's discharge, her sensorium had cleared and the right pronator drift had resolved, but she was left with a receptive and expressive dysphasia which was improving. Subsequent angiograms at 2 weeks, 4 months, 9 months, and 15 months after the second hemorrhage were unremarkable for additional lesions.

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Discussion

Transient or permanent neurological manifestations occur in approximately one-third of patients with infective endocarditis, whether or not they receive antibiotic therapy. While the prognosis of patients with bacterial endocarditis is improved with antibiotic therapy, the incidence of neurological complications has not been significantly diminished. In the series of 385 patients reported by Jones, et al., those with infective endocarditis who suffered related neurological deficits experienced 1.5 times the mortality of patients who suffered no neurological sequelae. Generally, 2% to 10% of patients with infective endocarditis harbor a myotic aneurysm (with estimates as high as 15%). The mortality rate associated with myotic aneurysm without subarachnoid hemorrhage is 30% and rises to 80% if the aneurysm ruptures. Due to this often fatal presentation, the natural history and pathogenesis of the mycotic aneurysm in patients with infective endocarditis are obscure.

Experimental work by Molinari and coworkers demonstrated that septic aneurysm formation in animals not treated with antibiotics occurred at 1 to 3 days. With antibiotic therapy, development of aneurysms occurred at 7 to 10 days. In 1959, Alajouanine, et al., described a patient in whom a mycotic aneurysm developed 2 years after successful treatment of infective endocarditis. They suggested that "inapparent lesions may become established in the carotid and sylvian arteries during the course of bacterial endocarditis and that they may continue to develop independently after the endocarditis has been cured." In 1970, Hourihane reported the development of new aneurysms within 3 weeks following successful operative treatment of single septic aneurysms in two patients. Roach and Drake reported development of an aneurysm of the peripheral middle cerebral artery distribution 3 months after successful excision of an aneurysm of the distal anterior cerebral artery in a patient who was not treated with antibiotics. Because the patient in this report had no clinical manifestations of endocarditis in the 7½ months following completion of her antibiotic therapy, it can be assumed that her "secondary" lesions were actually the result of seeding during her initial embolic episode.

Due to the unpredictable course of the disease, it is difficult to identify the etiology and to explain the pathogenesis of delayed mycotic aneurysmal rupture. Infective endocarditis is well documented to cause a generalized vasculitis associated with circulating immune complexes. Thus, the patient's initial diagnosis of vasculitis is not surprising, nor even totally incorrect, as she had a proven vasculitis of the skin and probable involvement of the kidneys (microhematuria and mild azotemia). Immune complex-mediated processes have been associated with the development of aneurysms in the intracranial, coronary, and mesenteric circulations, as well as implicated as a possible cause for cerebral vasospasm following subarachnoid hemorrhage. Furthermore, the association of infective endocarditis and multiple mesenteric aneurysms without active infection has recently been described. It is tempting to speculate that immune complex formation resulting from infective endocarditis may contribute to the formation of mycotic intracranial aneurysms, and that corticosteroids may modify the natural history of the disease in a fashion similar to that suggested for antibiotics in the past. Further investigations are necessary to clarify these issues.

Animal studies and reported incidences of mycotic aneurysm in humans both imply that suspicion and early recognition of mycotic aneurysm will improve the likelihood of a successful outcome. Frazee, et al., examined 13 cases of bacterial intracranial aneurysm associated with cardiac disease and reported that the time from diagnosis of bacterial endocarditis to subarachnoid hemorrhage ranged from 0 to 35 days (average 18 days). They concluded that patients with bacterial endocarditis and possible intracranial aneurysm who had focal neurological signs or symptoms, severe headache, or seizures, could be expected to experience rupture of their aneurysms in approximately 10 days. When the possibility of mycotic aneurysm is seriously entertained, CT and four-vessel angiography should be considered mandatory in the work-up. There are no reported cases of magnetic resonance imaging of mycotic intracranial aneurysms.

While the use of CT has not been well defined, Simmons, et al., stated that focal areas of peripheral enhancement associated with hematoma may be classified as "characteristic" for septic aneurysm. This is, of course, not diagnostic, and angiography is required for the diagnosis of infective aneurysms. Development, enlargement, regression, and resolution of mycotic aneurysms have been demonstrated by this technique. Still, some investigators believe that only one-quarter of infective aneurysms are detected with a single angiogram.

The presence of a mass lesion often mandates immediate decompression. If the aneurysm occurs distally so that occlusion of the parent vessel and resection of the aneurysm can be accomplished without neurological injury, early operation has been recommended. On the other hand, if surgery is performed on patients with proximal lesions or lesions in the dominant hemisphere or who are neurologically stable, it carries the increased risk of intraoperative or perioperative complications associated with manipulation of acutely inflamed brain and a friable aneurysm wall. Bingham compared 45 cases of mycotic aneurysm managed medically and/or surgically and demonstrated that the mortality rate associated with operative treatment of mycotic aneurysm was quite low when deaths related to cardiac, infectious, or other medical problems, as well as subsequent hemorrhage from a second, previously undiagnosed aneurysm are excluded. This low incidence of mortality related to elective surgical therapy for mycotic aneurysm has been supported by others.
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While, in selected groups of patients, surgery can be performed with a low risk of morbidity, there is ample evidence that complete resolution of mycotic aneurysms can be effected with medical therapy. For multiple and proximally located lesions, medical treatment alone or in combination with an extracranial-intracranial bypass procedure may be advantageous. The mortality rate continues to be high, however, in patients treated medically. Some authors have suggested that patients undergo serial angiography every 7 to 10 days while on antibiotic therapy. Although aneurysms may develop or enlarge while the patient is on antibiotic therapy, this is not always considered a definite indication for surgery, which is sometimes reserved for aneurysms that remain unchanged or enlarge after completion of antibiotic treatment. Aneurysms followed medically have been shown to resolve as much as a year after cessation of antibiotic therapy, and some suggest serial angiography be performed at 6 weeks, 3 months, 6 months, and 1 year after termination of antibiotics to evaluate changes in the aneurysmal size. Whenever possible, however, treatment should consist of excision of the aneurysm in conjunction with antibiotic therapy. The possible role of vasculitis in exacerbation of intracerebral damage and symptomatology implies that steroids may be a useful addition to the standard bimodal regimen.

The patient described here raises serious questions regarding the pathogenesis and management of patients with mycotic aneurysms. Despite successful resection of her first mycotic aneurysm and effective treatment of the underlying endocarditis, she developed multiple contralateral lesions leading to catastrophic hemorrhage 8 months following her initial presentation. As there was no evidence of recurrence of her bacterial endocarditis between presentations, the recurrent hemorrhage implies that patients with successfully treated infective endocarditis may be at risk for formation of symptomatic mycotic aneurysms for extended periods of time or even throughout their lifetime.

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References