The menacing pulmonary artery aneurysms of Behçet's syndrome

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Introduction

A man in his thirties has a history of deep vein thrombosis and starts to suffer from haemoptysis. At the top of the list of diagnostic possibilities will be pulmonary tuberculosis, especially if this patient lives in an area that is endemic for tuberculosis or pulmonary thromboembolism in the light of his history of thrombophlebitis. However if this patient also has Behçet's syndrome (BS), every effort should first be made to exclude a diagnosis of bleeding pulmonary aneurysm, since the prognosis of this most lethal complication of BS seems to depend rather heavily on the swiftness with which the diagnosis is made once haemoptysis, almost invariably the first symptom, appears (1). BS is unique among the vasculitides in that one of its manifestations may be the development of pulmonary artery aneurysms (PAA). There have been isolated reports of patients who developed pulmonary aneurysms during the course of microscopic polyangiitis (2) and polyangiitis overlap syndrome (3). However, these were microaneurysms detected during angiographic studies and involving the small and medium branches of pulmonary arteries. In contrast, pulmonary aneurysms in BS predominantly occur in the large proximal branches of the pulmonary arteries, thus leading to lethal bleeding. There is also the so-called Hughes-Stovin syndrome. First described by the English physicians Hughes and Stovin in 1959 (4) Hughes syndrome is

the combination of pulmonary thrombosis and aneurysms in association with peripheral thrombophlebitis. As discussed elsewhere in this issue (5) it is probably nothing more than a different clinical presentation of BS, especially in the light of their similar demography and histology.

Pathologic findings

Pulmonary vasculitis related to BS typically occur in the vasa vasorum of the pulmonary arteries, but can be seen in vessels of all sizes. Inflammatory infiltration in and around the vessel wall consists mostly of mononuclear inflammatory cells, predominantly lymphocytes. Some cases show neovascularization of the vasa vasorum. These changes in the vasa vasorum lead to ischemic changes in the vessel wall. These in turn lead to the loss of elastic fibers and of muscle cells in the media layer or to transmural necrosis ending in the formation of true aneurysms. This is accompanied by marked intimal thickening with degenerative changes in the medial layer from the lobar branches down to the arterioles. There may be fibrotic changes on the adventitial side of aneurysm (Fig. 1). The presence of adventitial fibrosis and thrombotic occlusion seem to prevent the early rupture of these aneurysms into the bronchial wall in some cases. Thrombotic occlusion and recanalization are observed in some medium sized arteries. The weakening and loss of integrity of the vascular layers also cause dissection of the vessel wall alongside the occlusion of the vessel lumen. Finally, focal hemorrhages or infarct areas can present in the lung parenchyma adjacent to the aneurysms. If all of these structural changes result in the disruption of the anatomical integrity of the vessel wall, a so-called pseudo-aneurysm is formed. This differs from a true aneurysm where all 3 layers are diseased, weakened and out pouched, but not yet disrupted. It is not uncommon to see a true and a pseudo-aneurysm in BS side by side (Fig. 2).

Although the first descriptions of PAA in BS appeared in the early 1930s (6), the diagnosis of PAA in BS had been



Fig. 1. Adventitial fibrosis and neo-vascularization adjacent to the pulmonary artery eneurysm. There is inflammatory infiltration around the vessels (H+EX40).

mainly a postmortem finding until the early 1980s (7). However, PAAemerge as the most frequent type of arterial involvement in BS today. According to retrospective studies these aneurysms occur in 1% of BS patients (8), but the actual figure is probably higher. We recently surveyed 387 BS patients who had been registered in our center between the years 1977 and 1983 (9). After 20 years we could obtain information about the outcome in 346 (90%). Ten of these 387 patients (2.6%) had developed PAA. Also all of these aneurysms had developed solely among 262 men, given a frequency of 3.8% in this sex. It should also be noted that we have seen only one woman among our 50 patients with PAAsince 1977, when we first started our dedicated clinic (1). This is not unexpected since BS is known to run a more severe course among men in almost all respects (10). PAA show a close association with the presence of venous disease elsewhere. Although venous involvement occurs in about one-third of BS patients (11), more than 80% of patients with PAA



Fig. 2. This lobectomy specimen shows a lower lobe pulmonary artery aneurysm (thin arrow) which has ruptured, resulting in a large intraparenchymal pseudoaneurysm (thick arrow).

have this association (7, 12). This association is mainly with deep vein thrombosis of the lower extremities, but accompanying thromboses of the venae cavae and/or intracardiac thromboses are not unusual (13,14). On the other hand, the recent outcome survey among our patients also suggested that this association was not restricted only to PAA. Eight out of 10 patients with abdominal or peripheral arterial aneurysms also had accompanying deep vein thrombosis of the lower extremities (9). What makes these patients prone to venous thrombosis is currently not clear, but endothelial injury rather than intrinsic coagulation defects seems to be operative in the pathogenesis (15, 16). It is also not known why pulmonary artery aneurysms are often multiple and bilateral whereas peripheral aneurysms are as a rule, single.

Outcome and management

PAA constitute the leading cause of mortality in BS. In a previous retrospective study we reported a 50% mortality among 24 BS patients with PAA within 1 year following the onset of haemoptysis (8). Similarly, 9 of 10 patients with PAA in our outcome survey died during follow-up (9). PAA were also the main cause of mortality among 262 male BS patients, being responsible for 9 of the 39 deaths. On the other hand, our current experience suggests that this dismal outcome is somewhat improving. We recently collected data on 26 BS patients who had been diagnosed in our center as having PAA between 1992 and end of 2001. We have seen that 16 patients (62%) have been followed by us for a mean of 4 years after the diagnosis of PAA (1). This outcome was significantly better than what we had reported before (8). The significantly shortened time for diagnosing PAA and the prolonged immunosuppression with cyclophosphamide and steroids appeared to play the major roles in this improved outcome.

The PAAsometime present with a very profuse haemoptysis and the attending physician judges that there simply is no time for any medication to work. The experience with surgery (emergency or selective) in PAA, unfortunately, has

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been very disappointing (17). An alternative course in such cases is emergency embolization and the results from a dozen or more reported cases are not as discouraging as emergency surgery (18).

Finally, the question remains as to whether one can diagnose PAA before the telltale symptom of haemoptysis starts. In this regard the young male patient with peripheral thrombophlebitis is surely the most suspect. Our rather salutary, nevertheless admittedly informal, experience suggests that periodic screening of all such patients with pulmonary imaging in the asymptomatic stage would not be fruitful. We maintain, however, such formal studies are still needed in the light of the extreme gravity of the pathology at hand.

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