# Histopathology of the ruptured pulmonary artery aneurysm in a patient with Behçet's disease

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*Clin Exp Rheumatol 2009: 27 (Suppl. 53): S91-S95.* 

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**Key words:** Behçet's disease, pulmonary artery aneurysm, thrombosis, angiogenesis.

Competing interests: none declared.

# ABSTRACT

**Objective.** Vascular involvement (vasculo-Behçet's disease) is relatively common in Behçet's disease. Although pulmonary artery aneurysm (PAA) is rare, it is the most serious and sometimes fatal complication. However, the mechanism of the development of PAA is unclear. In the present study, we carried out immunohistological examination of the ruptured pulmonary aneurysm in a patient with vasculo-Behçets disease.

**Methods.** Light microscopic examination was carried out on paraffin-embedded sections of autopsied pulmonary arteries of a Behçet's disease patient who died of the rupture of the left pulmonary artery aneurysm.

Results. Histopathology of the ruptured aneurysm revealed the formation of thrombus and recanalization. In addition, there was proliferation of small vessels in the vascular wall, as if the recanalization was extended to the vascular wall. Of note, marked perivascular cuffing of mononuclear cells, consisting of CD45RO+ T cells and CD68+ monocytes, were observed around the recanalizing capillaries as well as around the proliferating small vessels in the wall of the pulmonary artery. Of note, pericapillary infiltration of CD20+ B cells was noted exclusively in the vascular wall. The ruptured portion of the aneurysm lacks the lamina elastica, indicating that the aneurysm was so called pseudo-aneurysm.

**Conclusion.** It is likely that the first event might be the formation of inflammatory thrombus in the pulmonary artery. During the process of recanalization of the thrombus, the basic inflammatory process of Behçet's disease caused marked angiogenesis as well as perivascular cuffing of inflammatory cells in the thrombus and the wall, leading to fragility of the wall.

## Introduction

Behçet's disease is a chronic relapsing inflammatory disease of unknown etiology, presenting recurrent aphthous stomatitis, uveitis, genital ulcers, and skin lesions (1). The prominent histopathological features in the inflamed tissues are infiltration of lymphocytes and monocytes, and sometimes polymorph nuclear leukocytes, through small veins without microscopic changes in the vessel walls (1, 2). Thrombophilia or thrombophlebitis involving small and large veins is also common, whereas arteritis is rare (1, 2). In these regards, Behçet's disease is unique compared with other vasculitides (1).

Vascular involvement in Behcet's disease, usually called vasculo-Behçet's disease is one of the most serious complications of the disease (1). It is well known that venous thrombosis represents 85-93% of vasculo-Behçet's disease (2). There have been increasing numbers of reports on pulmonary artery aneurysm (PAA), which is the most serious and sometimes fatal complication (3, 4). Although the role of vasculitis in the pathogenesis of PAA has been suggested (4), the precise sequelae have not been delineated due to the paucity of autopsy studies. In the present study, we carried out immunohistological examination of an autopsied patient who died of the ruptured PAA.

# Patients and methods

# Case report

A 39-year-old man, who had presented recurrent oral aphthous stomatitis, folliculitis, and genital ulcer for several years, was admitted due to repeated hemoptysis on August 17, 1995. He had had recurrent episodes of hemoptysis for several months prior to admission. On admission, his blood pressure was 104/78mmHg with pulse rate

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102 per minute. Physical examination revealed oral and genital ulcers, and marked venous dilatation on his abdominal wall. Pathergy test was positive. Laboratory studies showed red blood cell count  $386 \times 10^4$ /mm<sup>3</sup>, hematocrit 33.2%, hemoglobin 10.6 g/dl, white blood cell count 12,600/mm<sup>3</sup>, platelet count  $34.1 \times 10^4$ /mm<sup>3</sup>, and elevation of C-reactive protein 12.7 mg/dl. Arterial blood gas analysis at FiO<sub>2</sub> 32% showed PaO<sub>2</sub> 71.0Torr and PaCO<sub>2</sub> 32.1Torr. HLA-B51 was negative. Chest CAT scan revealed ground glass opacity lesions in the left lower

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lobe of the lung (Fig 1). Abdominal CAT scan disclosed the occlusion of the inferior vena cava. He was diagnosed as pulmonary hemorrhage due to vasculo-Behçet's disease. In spite of treatment with prednisolone, methotrexate and colchicine, he died of recurrent massive hemoptysis on September 18, 1995. Autopsy findings showed massive bleeding in bilateral lower lobes of the lung due to rupture of aneurysms of lower branches of bilateral pulmonary arteries. Organized thrombus in the inferior vena cava was also noted.

#### Light microscopy.

Lung tissues were fixed in formalin and embedded in paraffin. Sections were subjected to a variety of stain procedures including hematoxylin and eosin, elastica van Gieson staining, and immunohistological staining for endothelial cells (HC1/6, CD31), B cells (L26, CD20), T cells (UCHL1, CD45RO), and monocytes (KP-1, CD68).

## Results

Histopathology of the ruptured aneurysm revealed the formation of thrombus and recanalization (Fig. 2). In



Fig. 1. Chest CAT scan showing pulmonary infiltration on the left lower lobe.



**Fig. 2.** The wall of aneurysm in the left pulmonary artery (elastica van Gieson [EVG]). Original magnification x25.



**Fig. 3.** Immunohistological examination of the left pulmonary artery with CD31 staining. The border between the thrombus and the vascular wall is indicated by a dotted line. Original magnification x25.



**Fig. 4.** The left pulmonary artery, showing the recanalization in the organizing thrombus and the angiogenesis in the vascular wall, accompanied by perivascular cuffing of mononuclear cells (H&E). Original magnification x25.

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Fig. 5. High magnificent view of the wall of the left pulmonary artery, showing the perivascular cuffing of inflammatory cells around capillaries the (EVG). Infiltrating cells are disrupting elastic fibers. Original magnification x50.

HE

CD45RO



**Fig. 6.** Immunohistological examination of inflammatory cells infiltrating around the recanalizing capillaries in the thrombus. Original magnification x50.

addition, there was proliferation of small vessels in the vascular wall, as if the recanalization was extended to the vascular wall (Fig. 3). Of note, marked perivascular cuffing of mononuclear were observed around the recanalizing capillaries as well as around the proliferating small vessels in the wall of the pulmonary artery (Fig. 4). It appears that perivascular cuffing of mononuclear cells resulted in the disruption of elastic fibers in the vascular wall (Fig. 5). Perivascular infiltrating mononuclear cells consisted of CD45RO+ T cells and CD68+ monocytes with very few CD20+ B cells in the organizing thrombus (Fig. 6). By contrast, infiltration of significant numbers of CD20+ B cells, in addition to T cells and monocytes, were noted around the capillaries in the vascular wall (Fig. 7). The ruptured portion of the aneurysm lacks the lamina elastica, indicating that the aneurysm was so called pseudo-aneurysm (Fig. 8). Taken together, these results indicate that thrombus formation followed by recanalization is the primary event preceding the formation of aneurysm. Thus, extended recanalization into the vessel walls followed by infiltration of inflammatory cells appears to result in fragility of the vessel walls, leading to the formation of pseudoaneurysm. Finally, it is suggested that activation of B cells in the vascular wall might also participate in the development of the PAA.

#### Discussion

Venous thrombosis appeared to be the major vascular involvement in 7-33% of patients with Behçet's disease, and represents 85-93% of vasculo-Behcet's disease (1, 2). Among vascular manifestations, PAA is an important complication of Behcet's disease (3, 4). Previous studies showed that 24(1.1%)out of 2179 patients with Behçet's disease were diagnosed as having pulmonary arterial aneurysms (5). Deep vein thrombosis was significantly associated with the male gender and a positive pathergy test (2, 4). Consistently, our case was a male patient with positive pathergy test. It is therefore suggested that male gender and positive pathergy test might also be risk factors for PAA. Our case was complicated with thrombosis in the inferior vena cava, which is consistent with previous reports. Thus, the striking clinical feature of patients with PAA has been shown to be the presence of other large extrapulmonary vessel lesions, including deep and subcutaneous venous thrombi and arterial aneurysms and/or occlusions. The previous cumulative analysis from many countries/regions showed that 78% among patients with Behçet's disease and PAA had other large extrapulmonary vascular lesions (4). Close correlation of thrombophilia with PAA is underscored by several clinical reports on patients with PAA and intracardiac thrombi (6-8). Of note, thrombi within PAA are also common. Total or partial occlusion of pulmonary arteries is shown in more than 100 PAA cases (4). In addition, Tunaci et al. demonstrated mural thrombotic changes during regression of PAA (9). Consistently, thrombotic occlusion of pulmonary arteries was found also in our patient.

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Hamuryudan et al. have reported detailed descriptions of histopathological examination findings (10). Thus, there were adventitia fibrosis and thrombotic occlusion with recanalization (10). The results in the current studies strongly suggest that the first event might be the formation of inflammatory thrombus in pulmonary arteries, followed by recanalization. During the process of recanalization of the thrombus, the basic inflammatory process of Behçet's disease appear to facilitate excessive angiogenesis, extending from the thrombus into the wall of pulmonary arteries. Subsequently, perivascular cuffing of inflammatory cells, which is also a characteristic feature of Behçet's disease (11-13), might lead to fragility of the wall, resulting in the development of pseudoaneurysm. Consistently, Hamuryudan et al. also reported that there was inflammatory infiltration around the vessels generated through neo-vascularization (10). The data therefore indicate that PAA developed due to the massive cellular infiltration through recanalizing capillaries and proliferating small vessels in the wall, but not due to the necrotizing or granulomatous inflammation of the wall of pulmonary arteries.

Similar findings have been noted in the perforated ileocecal lesions in patients with Behçet's disease. Thus, there was marked angiogenesis with perivascular cuffing of CD45RO+ T cells and CD68+ monocytes in submucosal layer and muscularis propria layer. In addition, it appeared that in muscularis propria layer, smooth muscle fibers were segmented by infiltrating CD45RO+ T cells (14). Moreover, histopathological characteristics of the central nervous system lesions in neuro-Behçet's disease have been shown to be perivascular cuffing of CD45RO+ T cells and CD68+ monocytes with few CD20+ B cells (13). Of note, perivascular cuffing of CD20+ B cells was observed, not in the recanalizing thrombus, but in the vascular wall in our patient. It is therefore suggested that the natures of immune reactions might be different depending on the site of inflammation within the pulmonary arteries. Further studies to delineate such differences in



**Fig. 7.** Immunohistological examination of inflammatory cells infiltrating around the capillaries in the vascular wall. Original magnification x50.

**Fig. 8.** The wall of aneurysm in the left pulmonary artery, showing no lamina elastica (EVG). Original magnification x25.



detail would be helpful for a complete understanding of the pathogenesis of PAA in Behçet's disease.

The precise sequelae of accelerated angiogenesis and perivascular cuffing remain unclear. Of note, however, previous studies disclosed that the serum levels of vascular endothelial growth factor (VEGF) as well as monocyte chemoattractant protein 1 (MCP-1) were significantly elevated in patients with Behçet's disease and acute thrombosis (15). VEGF is a stimulant of angiogenesis secondary to ischemia while MCP-1 is induced by shear stresses leading to vascular collateral development (15). Moreover, MCP-1 has been also shown to contribute to the recanalization of venous thrombi (15). It is therefore suggested that these cytokines might play a role in the pathogenesis of PAA. Since VEGF has been found in patients with active Behçet's disease irrespective of the presence of acute thrombosis and VEGF itself is a potent stimulator of NO production

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with endothelial cell effects (16), it is likely that it plays a central role in the development of perivascular cuffing of inflammatory cells. Further studies are also required to delineate this point.

#### References

- 1. HIROHATA S, KIKUCHI H: Behçet's disease. *Arthritis Res Ther* 2003; 5: 139-46.
- HOUMAN MH, BEN GHORBEL I, KHIARI BEN SALAH I, LAMLOUM M, BEN AHMED M, MILED M: Deep vein thrombosis in Behçet's disease. *Clin Exp Rheumatol* 2001; 19 (Suppl. 24): S48-50.
- YAZICI H, ESEN F: Mortality in Behçet's syndrome. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S138-40.
- UZUN O, AKPOLAT T, ERKAN L: Pulmonary vasculitis in Behçet's disease: a cumulative analysis. *Chest* 2005; 127: 2243-53.
- HAMURYUDAN V, YURDAKUL S, MORAL F et al.: Pulmonary arterial aneurysms in Behçet's syndrome: a report of 24 cases. Br J Rheumatol 1994; 33: 48-51.

- ERNAM D, ATALAY F, ALP A, HASANOĞLU HC: A Behçet's disease patient with intracardiac thrombus, pulmonary artery aneurysms complicating recurrent pulmonary thromboembolism. *Tuberk Toraks* 2006; 54: 168-71.
- ENDO LM, ROWE SM, ROMP RL, BUCKMAS-TER MA: Atkinson TP. Pulmonary aneurysms and intracardiac thrombi due to Behçet's disease in an African-American adolescent with oculocutaneous albinism. *Clin Rheumatol* 2007; 26: 1537-9.
- YAKUT ZI, ODEV K: Pulmonary and cardiac involvement in Behçet's disease: 3 case reports. *Clin Appl Thromb Hemost* 2007; 13: 318-22.
- 9. TUNACI M, OZKORKMAZ B, TUNACI A et al.: CT findings of pulmonary artery aneurysms during treatment for Behçet's disease. *AJR Am J Roentgenol* 1999; 172: 729-733
- HAMURYUDAN V, OZ B, TÜZÜN H, YAZICI H: The menacing pulmonary artery aneurysms of Behçet's syndrome. *Clin Exp Rheumatol* 2004; 22 (Suppl. 34): S1-3.
- 11. MÜLLER W, LEHNER T: Quantitative electron microscopy microscopical analysis of leuko-

cyte infiltration in oral ulcers of Behçet's syndrome. *Br J Dermatol* 1982; 106: 535-44.

- KANEKO F, TAKAHASHI Y, MURAMATSU Y, MIURA Y: Immunological studies on aphthous ulcer and erythema nodosum-like eruptions in Behçet's disease. *Br J Dermatol* 1985; 113: 303-12.
- HIROHATA S: Histopathology of central nervous system lesions in Behçet's disease. *J Neurol Sci* 2008; 267: 41-47.
- KIKUCHI H, HIROHATA S: Histopathological analysis of intestinal involvement in Behçet's syndrome. EULAR 2007, Barcellona, Ann Rheum Dis 2007; 66 (Suppl. 2): FRI0330.
- 15. BOZOGLU E, DINC A, ERDEM H, PAY S, SIMSEK I, KOCAR IH: Vascular endothelial growth factor and monocyte chemoattractant protein-1 in Behçet's patients with venous thrombosis. *Clin Exp Rheumatol* 2005; 23 (Suppl. 38): S42-8.
- CEKMEN M, EVEREKLIOGLU C, ER H et al.: Vascular endothelial growth factor levels are increased and associated with disease activity in patients with Behçet's syndrome. Int J Dermatol 2003; 42: 870-5.