Case Report

AN AUTOPSY CASE OF BEHÇET'S SYNDROME ASSOCIATED WITH PULMONARY ARTERITIS AND TUBERCULOSIS

Goroku Ohta†† Tomokatsu Nishino*, Kazuaki Onchi*, Gu Tsumura*, Kunihiro Ooe†, Tadayoshi Takegoshi*, Noboru Takekoshi**
Norio Iwaki**, Masayuki Tsuchiya**, Takashi Takada**
Mototaka Murakami††† Hiroshi Yoshizawa†† and Masanobu Kitagawa†††

Since Behçet described in 1937 a chronic recurrent triple-symptom complex, oral aphthous lesions, genital ulceration and ocular inflammation, evidence has been accumulated to support the concept that the disease may be a systemic vascular and connective tissue disorder involving large to small arteries and veins. Recent immunological observations indicated that circulating autoantibodies were demonstrated at a time of progression or recurrence during prolonged course of the disease.

A case presented here had a highly active necrotizing arteritis of the pulmonary arterial system with a systemic derangement of vascular walls and together with old tuberculous lesions in the right lung.

Case

A 34-year-old man was admitted to Kanazawa University Hospital because of high fever, cough and sputum, on 4 January 1969 (Fig. 1).

Key Words:

Since August 1965 he had been suffered repeatedly from aphthous stomatitis with or without fever. In My 1967 he was admitted to a municipal hospital with a temperature of 40°C with shaking chills and headache. The recurrence of pain and nodular cutaneous lesions resembling those of erythema nodosum on the left lower extremity and also redness and slight induration in the portions of venous injection were noted. His fever, rash and oral ulcers were improved but the skin lesions, mentioned above, and flu-like symptoms remained. A month later, he was discharged and continued his ambulatory treatment. On 17 January 1968 he was readmitted to the municipal hospital with a temperature of 39°C with shaking chills and oral aphthous ulcers. During the second admission, the same nodular cutaneous lesions in the extensor side of the lower limbs and ulcers on the scrotum. He had a recurrence of the fits once a week during subsequent 2 months and received glucocorticoid treatment. He was discharged on 1 July 1968. In December 1968 the same oral, respiratory signs and high fever developed again. He was admitted to Kanazawa University Hospital.

Physical examination on the admission
The temperature was 38.8°C. He had an oral aphthous ulcer in the mucosa of lower lip. There

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* : Dept. of Medical Zoology, School of Medicine, Kanazawa University
† : Dept. of Internal Medicine, Hokusoku Hospital
** : Dept. of 2nd Internal Medicine, School of Medicine, Kanazawa University
†† : Dept. of 1st Pathology, School of Medicine, Kanazawa University, Kanazawa City, Japan.

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Fig. 1. The clinical course.

Fig. 2. X-ray film of the chest indicates two abnormal shadows in a middle field of the right lung.

was no abnormal finding in his lung fields on percussion and auscultation. The percussion revealed normal cardiac border. There was the functional systolic murmur at the apex. The second was split and fixed. There were multiple erythema nodosum-like eruptions in crops in the extensor side of the left lower extremity and several brownish, small finger-sized pigmentation in the extensor side of the bilateral extremities. There was no difference in the blood pressure measured between in the upper and lower extremities. Neurological examination exhibited no abnormal signs. Ophthalmological examination exhibited a presence of bilateral serous iritis and a left corneal leucoma. Vision on the right was 0.1 and on the left 1.5, both uncorrected. Fundoscopic examination showed normal pattern.

**Laboratory Examination**

Urinalysis revealed no abnormality. Examination of the blood: Hb value was 74%, RBC count 3,720,000 and WBC count 10,400, with a differential count of 62% segmented neutrophils,
20% nonsegmented neutrophils, 2.5% eosinophils, 24% lymphocytes with some atypical lymphocytes. LE cells were negative. Thrombocytes count was 154,000, bleeding time 2 minutes, tourniquet test negative, prothrombin time 14.4 seconds, thrombotest 54%, and fibrinogen level 594 mg per cent. Blood chemistry: Serum proteins were 7.8 g per cent, which consisted of 34.5% albumin, 8% alpha-1 globulin, 14.8% alpha-2, 16.5% beta, and 26.5% gamma. with an albumin-globulin ratio (A/G) of 0.53. Icterus index was 4.5 units, ZTT 11.6 units, TTT 4.5 units, serum amylase 0.48 unit, alkaline phosphatase 2.0 units, SGOT 14 units, SGPT 2 units and LDH 380 units. Serological examination: CRP was 6 plus and RA plus-minus. ASLO was positive in a dilution of 1:100, cold agglutinin 1:8 and Paul-Bunnell's reaction 1:28. LE test was negative. Wasserman's reaction was negative, blood sedimentation rate 63 mm/1 hour and 104 mm/2 hours, Mantoux's reaction 12 mm x 5 mm. Serum electrolyte: Na was 135 mEq/L, K 3.6 mEq/L, Ca 4.4 mEq/L, Cl 105 mEq/L and P 3.5 mg/dl. Serum lipid: Beta-lipoprotein was 1395 mg/dl, total cholesterol 242 mg/dl, phospholipid 232 mg/dl and neutral fat 40 mg/dl. Viscosity was 2.06. Examination of sputum: Tubercle bacilli and other organism cultured from the sputum was found to be negative. Renal function test: PSP test showed 46.5% excretion of injected dye in 15 minutes and 67.0% total in 2 hours.

X-ray films of the chest showed two abnormal shadows in the middle field of the right lung and those were confluent and situated in 6 cm and 10 cm distance respectively in tomographic films (Fig. 2, 3). Bronchographic examination revealed no passage of the injected material into branches of the bronchial trees in the right lower lobe corresponding to the area showing abnormal

*Fig.3. Tomographic film shows two confluent shadows in 6 cm and 10 cm distance of the right lung.*
shadows demonstrated by the tomographic films in 6 cm distance.

A scintigram of the lungs revealed reduced blood supply in the field of the right lower lobe (Fig. 4).

Angiographic examination of the lungs indicated a presence of obstruction in branches of pulmonary arteries of the right middle and lower lobe (Fig. 5).

An intravenous pyelography revealed no abnormality.

Electrocardiogram was of normal limits.
Behcet Syndrome with Pulmonary Arteritis and Tuberculosis

Fig. 6. Electrocardiogram shows normal limits.

Fig. 7. The upper figure shows occlusions, tuberculosis and bleeding of the lung. The lower figure shows thrombosis of the renal and iliac veins.

(Fig. 6).

On the 3rd day's admission, he had severe hemoptysis with the total amount of approximately 400 ml blood, lasting over 30 hours. Improvement was obtained with treatment of glucocorticoid and the patient was discharged one year later. On 12 February 1971 he was admitted to Hokuriku Hospital because of bloody sputum, a high fever and oral aphthous ulcers. Sooner he was discharged with much improvement and followed by occasional check-ups in the out-patient clinic. On 29 August 1971 he noticed again bloody sputum, abdominal pain and diarrhea, and subsequently readmitted to our hospital. On the 5th day following the last admission black stools and coffee grounds-like vomittings occurred, followed by aggravated abdominal pain. Laparatomy was done and panperitonitis was noted with necked eye. He died several hours later.

Postmortem examination

The right lung weighed 600 g and the left 670 g and both were enlarged moderately. On cut surface of the left lung lumina of Artery 6 and 8 of pulmonary arterial branches revealed complete occlusion and their walls were thickened. Thrombotic materials were found in the many other medium-sized arteries. The right lung revealed the same thrombotic occlusion of lumina of many arteries (Artery 4 to 10). Despite of presence of widespread arterial occlusions there was no infarction throughout the lungs. Hilar region of both lungs was fibrotic and areas of hemorrhage was found in the right lung. Extrapulmonary portions of main pulmonary arteries were macroscopically intact and pulmonary vein system appeared to be normal. In the fields of Segment 6 and 10 of the right lung partially calcified tuberculous lesions were present. Pseudomembranous inflammation was noted in the ileum, and acute enteritis was seen in the jejunum, associated with a presence of panperitonitis without any evidence of perforation. Aphthous stomatitis and ulcer in the scrotum were present. Bilateral iliac and renal venous walls were remarkably thickened, associ-
ated with thrombotic materials.

All arterial lesions of the lungs detected with neked eye were histologically consistent with a diagnosis of necrotizing granulomatous arteritis (Photo 1). Some walls of large branches of the pulmonary arteries were replaced completely by granulomatous tissue and some of their lumina showed aneurysmal dilatation with a lack of elastic elements and to be filled with thrombi (Photo 2). Many of the medium-sized muscular arteries also were affected with active inflammation (Photo 3) but a majority of arteries with lesser caliber was intact except a presence of thromboembolic materials. Large thrombi ad-
herring to the affected arterial walls were partially organized and their non-organized areas of thrombi adjacent to the damaged walls appeared to be necrotic, giving an appearance of caseated mass. Ziehl-Neelsen's stain, however, revealed no acid fast bacilli in the thrombi and vascular walls. A few large arteries found in the right hilar region showed occlusion with granulomatous tissues and the walls had no inflammation, suggesting healing stage of arterial lesion. Bronchial arteries also were involved in much lesser degree and pulmonary veins were intact.

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Portion of the right lower lobe revealed a presence of partially calcified tuberculous lesions where acid fast bacilli were detected with conventional stain. Serial sections from the area showed that there were no affected vessels within and around the tuberculous lesions.

Extrapulmonary portions of the main pulmonary arterial walls revealed neither inflammatory nor sclerotic changes but a widespread disappearance of elastica interna and focal loss of the medial elastic elements, when stained with Verhoeff's method or Elastica Van Gieson (Photo 4). Such a derangement of elastic fibers was most striking in whole lengthening of the aorta with a complete loss of elastica interna (Photo 5). And A. brachialis, A. subclavia, A. carotis interna, A. renalis, A. mesenterica superior and inferior and A. iliaca communis also were involved with fragmentation and/or swelling of the elastica interna and focal loss of elastic elements in their media. All arteries, mentioned above, exhibited and increase in amount of medial connective tissue fibers and PAS positive materials with an absence of inflammatory or sclerotic changes. Thrombi of the iliac and renal veins were replaced by granulomatous tissues with protrusion into the lumina and fibro-granulomatous thickening of their intima was predominant (Photo 6). A presence of perivascular cell infiltration in their adventitia and outer part of the media indicated that the venous changes were resulted from inflammation.

Many small vessels in the areas of the ileum showing pseudomembranous changes were affected with either arteriolitis or severe thrombophlebitis. In the areas of the submucosa displaying much lesser intensity of exudative inflammation amyloid-like substances were deposited in many walls of arterioles (Photo 7). Yellow fluorescence was demonstrated in these vascular walls under fluorescence microscope when sections were treated with thioflavint. Particular fluorescence also was noted in the same vessels, when stained with Congo red.

Ulcerated areas of the skin from the scrotum revealed highly active inflammation in the dermis with necrotizing arteriolitis and thrombophlebitis, both with obstruction of their lumina (Photo 8).

Pathological diagnosis
1) Necrotizing and granulomatous arteritis of pulmonary artery, associated with thromboembolism.
2) Thrombophlebitis of bilateral renal and iliac veins.
3) Pseudomembranous enteritis with panperitonitis.
4) Ulceration of the scrotum and the oral mucosa.
5) Healed tuberculosis of the right lung.

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DISCUSSION

Recent statistical observations indicated that an incidence of patients with Behçet's disease reported was highest in Japan and Shimizu et al. implied approximately 50 thousands people were now suffered from the disease in our country. Recurrent aphthous stomatitis, scrotal ulceration and serous iritis seen in the present case fulfilled the criteria described by Behçet as the triple-symptom complex. Since the original description, many other manifestations have been reported in this disease; encephalopathy, arthritis, enterocolitis, thrombophlebitis of large and medium-sized veins, arteritis and/or aneurysmal dilatation of large arteries, endocarditis, myocardial degeneration, epididymitis, pancreatitis and subungal infarction. Although all the mani-
festations have been assumed to be resulted from vasculitis or angitis, a few reported cases revealed no evidence of vasculitis and only perivascular cell infiltration or interstitial edema. Nevertheless, a emphasize has been made to a damage to large vascular walls in certain cases of the disease by France in 1951 and Boolukos in 1960 and Shimizu et al. described a term of vasculo-Behcet’s syndrome in which large and medium-sized arteries and/or veins were affected predominantly together with the mucocutaneous-ocular lesions; aorta, renal artery (A.) and vein (V.), common iliac A. and V., femoral A. and V., radial A., coronary A., pulmonary A. and V., brachial A., carotic A., subclavian A. and Vena cava inferior or superior. Common lesion of the arteries, mentioned above, was a aneurysmal dilatation with or without rupture which was occasionally a cause of death. Luminal obstruction of the trunks arteries rarely occurred to produce a pulseless syndrome, which might be produced by multiple factors. Budd-Chiari syndrome or subclavian steal syndrome sometimes were encountered to be caused by thrombotic occlusion of vena cava system. Thrombophlebitis of either large or small veins was known to be more often in this disease than the lesions of the arterial system was.

According to Urayama involvement of the pulmonary arteries in the disease was not so rare in Japan and a few cases experienced by himself revealed an aneurysm formation of the vessels. However, severe necrotizing lesions of larger and medium-sized branches of the pulmonary arteries, as seen in the present case, has not been reported hitherto. Vascular inflammation, if present, of the affected large arterial walls tended to be non-specific and chronic in reported cases. Destruction of the walls in the present case was very much extensive and old lesions of not only the walls but attached thrombi were found at postmortem. Thrombophlebitis, however, of the iliac and renal veins was in completely healed stage. These indicate that unknown agents, presumably endogenous, giving a damage to large vascular walls seem to be differed in intensity of their toxic activities, acting duration and time during a prolonged course of the illness depending upon individuals of the affected vessels. This also will give an explanation to the fact that there was no infarction throughout the lungs despite of a presence of widespread thromboembolism in the lungs.

It is well known that there was a systemic derangement of elastic elements in the walls of elastic type arteries even with a lack of inflammatory and sclerotic changes. In addition to this finding, mentioned above, PAS positive materials and connective tissue fibers were seen to increase diffusely and in contrast smooth muscle cells appeared to decrease in number in the media of the same type of arteries of the present case. Mechanism to cause such vascular changes in an absence of inflammation remained unknown,
though many investigator still assumed their inflammatory origin. Pseudomenbraneous enteritis found in the present case was severe in particular in the lower part of the ileum and extended into the serosa to produce panperitonitis which was accerated by laparotomy performed several hours before death. Morphological examination of the intestine suggests that necrotic lesions of the mucosa might be secondary to vascular disease which was consisted of severe necrotizing arteriolitis, deposition of amyloid-like substances in the arteriolar walls and highly active thrombophlebitis of venules in the submucosa. The fact that similar vasculitis was found in ulcerated areas of the scrotum indicates that the intestinal vascular lesions may be a part of manifestations of Behçet’s disease. Possibility may exist that cellular hypersensitivity to tuberculous bacilli would play some role in pathogenesis of pulmonary arteritis, as suggested by a presence of old tuberculous lesions in the right lung, though there was no evidence of any morphological relationship between the lesions and pulmonary arteritis.

REFERENCES