Report on Two Cases of Takayasu's Disease, Complicated with Tuberculide- or Tuberculoderma-like Exanthemas

HIDEO TAKEZAWA, TAKEHIKO SAKAKURA, MICHIKO KOMADA*,
YOSHIMARO KOTANI AND TSUGUO HAMAGUCHI**

* The 1st Medical Clinic (Director: Prof. H. Takasaki), School of Medicine, Mie Prefectural University, Tsu

** The Dermatology Clinic (Director: Prof. T. Hamaguchi), School of Medicine, Mie Prefectural University, Tsu

SO FAR, more than 350 cases of so-called pulseless disease have been reported in this country, since the first report of a case with reduction in retinal arterial pressure, arteriovenous anastomosis and "wreath-like" arterial anastomosis around optic nerve papillae by TAKAYASU¹⁾, in 1908. Although the exact pathogenesis of this syndrome is not yet known, immunopathologic approaches are getting more and more concentrated on the possible role of immunoallergic reactions playing in establishing the characteristic disease.

We have recently experienced two cases of TAKAYASU's disease, which developed tuberculide-like or tuberculoderma-like eruptions with positive tuberculin skin reaction.

The purpose of this paper is to describe these two cases and to discuss the possible responsibility of tuberculosis-allergy for the development of this clinical syndrome.

CASE I

Case 1: 33 year-old drug store employee and the mother of a child had been admitted in our clinic on February 24, 1964, complaining of continued slight headache with occasional episodes of vertigo and palpitation by moderate physical exertion since last five years.

She had also been aware of the presence of abnormally cold upper extremities since her age of around 20. Five years prior to the data

of admission, she was incidentally found to have absent pulses on both radial arteries. According to her statement, she had been prone to have "chillbrains" since her late childhood. The above mentioned headache was rather milder in its grade and protracted in its duration. Transient attacks of vertigo was easily provoked by sudden rise from the supine position or by sudden erection of her head upright or to backward, although no episode of spells of loss of consciousness has been experienced. Since the time when she noticed cold extremities, gradually increasing fatigue in her upper extremities, especially in the left side has been recognized, until she begun to have "claudication of her left arm". In the past, she had no episode of visual impairment. Menstruation has been normal. Tuberculin skin reaction was positive on her age of eight. Seven years prior to the data of admission, she suffered from right-sided tuberculous pleurisy and was treated by antituberculous chemotherapy for about one year.

On admission, she was found to be 152 cm high and weighing 41 kg, which is about the normal average size in this country. Skin was normal at this time. Pulse was inappreciable in both radial arteries, although small sized pulse was clearly felt on both carotid arteries with moderate systolic thrill. Pulsations of abdominal aorta, both femoral arteries and dorsal

(Received for Publication, June 11, 1966)

pedal arteries were all felt well. Blood pressures by cuff method were 130/98 mmHg and 130/100 mmHg in right and left brachial arteries, and 184/98 mmHg and 186/100 mmHg in right and left popliteal arteries, respectively. Carotid sinus rubbing caused transient vertigo with significant decrease in heart rate. Oculocardiac reflex was also positive in reducing pulse rate significantly. Eye ground findings were remained within normal range, although cloudiness of cornea due to parenchymal keratitis was observed in both eyes. Retinal arterial pressures were 55/32 mmHg and 76/42 mmHg in right and left side, respectively. Left ventricular heave was felt on midclavicular line at the fifth intercostal space. Evident ejection click was heard in apical region and the aortic second sound was much accentuated. On both carotid arteries and on both sternoclavicular joints, no specific vascular bruit was heard. Liver and spleen were not palpable and all the neurological signs were within normal range.

Laboratory findings: Urinalysis and examination of the feces revealed no abnormality. Some grade of anemia was noted, hemoglobin content being 9.3 gm/dl, hematocrit being 31

per cent, leucocyte count was 4800/cmm, in which 42 per cent neutrophilic cells, 1 per cent basophilic cells, 1 per cent eosinophilic cells, 7 per cent monocytes and 49 per cent of lymphocytes were included. Serum protein content was 8.4 gm/dl and thera tio of albumin to globulin was 0.8. Cephaline cholesterol flocculation test was significantly positive. S-GPT and BUN were normal. Serum Na was 141 mEq/L, K 4.6 mEq/L and iron was 20 r/dl. Renal function study has revealed normal PSP excretion, normal concentrating power and normal creatinine clearance as 1031 dl/hour. Serological reaction for syphilis was negative. ASLO titer was 250 Todd units, RA test was negative. Erythrocyte sedimentation rate was 58 mm and 104 mm during the first and second hour. Tuberculin skin reaction was strongly positive. Chest X-ray film is shown in Figure 1, which indicates no definite abnormality. Figure 2-A shows the angiography, indicating

Fig. 1. Posteroanterior chest X-ray film of Case No. 1.

Fig. 2. Angiogram of Case No. 1
In the lower part, schematic illustration is shown.
(see text)

the presence of characteristic narrowing of main branchings from the aortic arch as have schematically shown in Figure 2-B. EKG findings are within normal range. After around one month's clinical check-up, she was discharged from the ward and had been engaging in her daily work as an employee of a drug store until the end of September 1965, when she developed papulonecrotic tuberculide-like exanthema in her forearms and extensor side of wrists as have shown in Figure 3-A. At the same time, she also noticed erythema nodosum-like eruptions with neuralgic pain and tenderness to pressure in her extensor side of the legs, as have shown in the picture in Figure 3-B. After two week's treatment by oral administration of Oxyphenbutazone (Tanderil), erythemas have disappeared and she had been feeling better until April of 1966, when developed the same type of papulonecrotic tuberculide-like exanthema in her both arms. Skin biopsy has been done on both type of eruptions. Scattered pale pink or pink brown papules of 1 to 4 mm diameter were found from extensor side of the forearms through the back of hands, some of which have shown an appearance of serous papule and some are presenting central necrosis with dark brown crust. Microscopically, epidermis has been thickened and the border of each cells are obscure. Pycnosis and vacuolation are also present. In the uppermost layer of the corium, massive leucocyte infiltration with leucocytosis is seen, which is surrounded

by cone-shaped lesion of small round cell and fibroblast infiltration, with its tip down. Connective tissue in this lesion appears to be edematous or reticular. As have shown in Figure 4-A, the tip of cone-shaped infiltration reached down to the subcutaneous tissue and indicating the picture of so-called proliferation atrophy of fatty cells. Wall of medium or small sized vessels is thickened and proliferation of intimal layer with leucocyte infiltration is so marked as in some of these vessels are obliterated. The vessels in more superficial layers especially at the site of cell infiltration are markedly destructed. Microscopic findings of the erythema nodosum-like eruption are shown in Figure 4-B, in which thickening of the wall of vessels in subcutaneous tissue through deep corium and the protrusion of the thickened wall into the lumen are observed. In parts, proliferation of intimal cells and edema are seen, although no fibrinoid degeneration is found. Although less, some grade of small round cell and fibroblast infiltration are observed. Culture of tubercle bacilli from these eruptions were all negative.

CASE 2

Case 2: 40 year-old female farmer had been admitted in the dermatology clinic on July 12, 1965, because of intractable pyodermic eruption in her both forearms. The eruption begun to appear on December 1963, when she got bruise on her extensor side of the left forearm.

Fig. 3. Papulonecrotic tuberculide-like eruption (A) and Erythema nodosum-like eruption (B).

The skin trauma did not show any tendency to heal and despite the repeated therapeutic attempts by dermatologists, steadily developed pyodermic eruptions spreading over whole skin of left forearm with moderate pruritus, which was followed by succeeding spread of the eruption on both shins. These skin lesions had been remaining unhealed until the date of admission.

She was born normally after uneventful pregnancy, and her physical development had been normal. According to her statement, she had easily developed SOB or palpitation by severe physical exertion in her primary school days, although she had no episode of syncopal attack nor cyanosis. On her age of 30, she was incidentally diagnosed as "cardiomegalic" through X-ray examination. Around this time, she began to feel vertigo or fainting by sudden erection of her head upright or backward and cold left arm with fatigue. These symptoms had been persisted until August of 1962, when she began to feel vague compression on her left precordium and increased intensity of palpitation, and she was admitted in a medical clinic for detailed clinical check-up, which revealed the presence of cardiac murmur and cardiac hypertrophy with absence of the left radial pulse. The dermatologic diagnosis at the time

of this admission was tuberculosis verrucosa cutis and she had been put on antituberculous chemotherapy with streptomycine and para-amino-salicylic acid for about three months, which resulted in some improvement of the skin lesions. As the cardiovascular symptoms aggravated on October of 1965, she came to the medical clinic for through examination. At the time, she was found to be 144 cm high and weighing 46 kg with medium body frame. She tilted her head down when in erect position, giving impression of "shyness" (Figure 5-A). Pulse was well palpable on the right radial artery, while left radial pulse was absent. Right carotid artery was forcefully felt, whereas left carotid arterial pulsation was much weaker. Pulsations of both femoral, popliteal and dorsal pedal arteries were all full sized and collapsing. Marked systolic thrill was felt on the right carotid artery and on left carotid artery, although less in its intensity. Pulse was rated up to 100 per minute. Skin appeared to be rather pale and no cyanosis was noted. Pyodermic eruptions were found in her left arm and both lower extremities as have shown in Figure 5-A and B. Jugular vein is distended 5 cm above the clavicular level. Left ventricular heave was felt far out to the left anterior axillar line in the sixth intercostal space. In the third inter-

Fig. 4. Microscopic finding of paponecrotic tuberculide-like eruption (A) and erythema nodosum-like eruption (B). (see text)

costal space left to the sternal border, marked diastolic thrill was felt. On auscultation to the heart, LEVINE's grade 3 to 4 ejection systolic murmur with its point of maximum intensity in third intercostal space right to the sternum and high pitched grade 4 early diastolic murmur with diastolic thrill in second intercostal space left to the sternum were obtained. Blood pressures by cuff method were 150/110 mmHg in right arm, while in left arm KOROTOKOF sound was almost inaudible, 240/40 mmHg in right and 250/40 mmHg in left popliteal arteries, respectively. Evident DUROZIEZ's double sounds were audible on both femoral arteries. Liver was felt 2 cm below the rib arch on the right midclavicular line. Spleen was not palpable. Carotid sinus rubbing caused marked diminution of pulse amplitude and heart slowing accompanied by syncopal attack.

Laboratory findings; Urinalysis has revealed no abnormality, except strongly positive urobilinogen reaction. In the peripheral blood, erythrocyte count was 353×10^4 cmm, white cell count was 4660/cmm, in which 55 per cent neutrophilic cells, 2 per cent eosinophilic cells, 8 per cent monocytes and 35 per cent lymphocytes were included. Hematocrit was 34 per cent and hemoglobin content was 10.1 g/dl. Erythrocyte sedimentation rate was 88 mm

during the first one hour. ASLO titer was 125 Todd units. CRP and RA test were negative. Total serum protein was 6.6 g/dl with albumin to globulin ratio of 0.8. TTT and ZST were 4 and 3 units, respectively. S-GOT and S-GPT were all normal. Alkaline phosphatase was 1.7 units. Choline esterase was 0.5 pH. NPN and BUN were 24 mg/dl and 14 mg/dl, respectively. Creatinine, uric acid, Na and K content were all within normal range. Electrophoretic pattern of serum protein indicated the following fractions; albumin 40.9 per cent, α_1 -globulin 5.6 per cent, α_2 -globulin 12.5 per cent, β -globulin 9.8 per cent and γ -globulin 31.3 per cent, which clearly showed the increase in globulin fraction. Serological reactions for syphilis were all negative, whereas tuberculin skin reaction was definitely positive. Results of renal function studies were all within normal range and the creatinine clearance was estimated as 1816 dl/24 hours. Renal biopsy was also performed in this case, which revealed no significant anomaly. Right heart catheterization was performed on December 10, 1965, which revealed the presence of moderate pulmonary hypertension; pulmonary arterial pressure was 38/14 mmHg with mean of 23 mmHg. No systolic pressure gradient was observed between pulmonary artery and right ventricle, RV

Fig. 5. Lateral view of case No. 2, showing pyoderma in left forearm and both shins (A) and pyoderma in left shins of case No. 2 (B). (see text)

pressure was 39/2 mmHg. Pulmonary arterial

Fig. 6. EKG of case No. 2, showing LVH and ST-T depression in left precordial leads. (see text)

Fig. 7. Microscopic finding of tuberculoderma-like pyoderma in left forearm of case No. 2. (see text)

wedge pressure was 10 mmHg in mean. Right femoral arterial pressure was 230/40 mmHg with mean of 110 mmHg, and its pressure contour has shown rapid rising and falling pattern with no appreciable dicrotic notch, which strongly suggests the presence of aortic regurgitation. Cardiac index by direct Fick method was estimated as 4.8 l/min./M².

Ophthalmologic examination revealed the presence of significant dilation of retinal vein with narrowing of arteries. Optic nerve papillae were appeared normal. Central retinal arterial pressure were 48/24 mmHg and 44/24 mmHg in right and left eyes, respectively. No

Fig. 8-A. Angiogram of case No. 2, schematically illustrated in the lower part. (see text)

arteriovenous anastomosis was noted at this time. EKG has been shown in Figure 6, which indicates frequent occurrence of nodal premature beats and left ventricular hypertrophia with systolic overloading pattern. Phenolsulphophthalein excretion was 25 per cent during the first 15 minutes and 65 per cent during 120 minutes. Endogenous creatinine clearance was 1.816 dl/24 hours. Specific gravity of urine has ranged between 1.021 and 1.004 by FISH-BERG's test. Microscopic finding of the skin biopsy specimen obtained from her left forearm eruption is shown in Figure 7, which revealed nonspecific chronic suppurative inflammation; epidermis is diffusely thickened and marked parakeratosis with exocytosis of neutrophilic leucocytes are observed, although no significant change of epidermis cell proper. Small round cells and histiocytic infiltration mingled with smaller number of neutrophilic cells are found diffusely throughout whole layers of the corium. In the same part, bunch of fibrosis are found. No giant cell is seen and the sign of vasculitis is not recognized. Culture of tuberculosis bacilli from the skin specimen

was negative.

She is still under our observation, and she has been treated by oral administration of beta-methazon since November 1965, which giving marked improvement of the skin lesion. Angiocardiographic studies has shown characteristic narrowing of the main branchings from the aortic arch with significant dilation of pulmonary main trunk as have been shown in Figure 8-A and B. Plain chest X-ray film is shown in Figure 9, which indicates the presence of left ventricular hypertrophia with marked dilation of pulmonic knob.

DISCUSSION

In 1948, SHIMIZU and SANO²⁾ have reported six cases of TAKAYASU's disease and analyzed this characteristic symptom complex with a literal review on 24 reported cases. They have summarized the clinical picture of these patients as 1) absence of pulse in arms, 2) characteristic eye findings and 3) marked exaggeration of carotid sinus reflex. In this study, they named the disease as "myaku-nashi-byo", which is translated as "pulse-less-disease". Histologically, they recognized the findings as thromboarteritis obliterans subclavio-carotica

Fig. 8.-B. Angiocardiogram of case No. 2, indicating marked dilation of main pulmonary artery trunk. (see text)

Fig. 9. Postero-anterior chest X-ray film of case No. 2.

or panarteritis brachiocephalica cardinalis, and etiologically, from the basis of the presence of tuberculoma-like granuloma in the diseased arterial wall, they have suspected this syndrome as being most likely due to tuberculosis. Ross and McKusik⁸⁾ have made extensive review of the aortic arch syndrome in 1953. Pulseless disease appeared to be included in the category of "young female arteritis" variety of aortic arch syndrome, so mentioned in their paper.

In our two female cases, characteristic conditions including absent radial pulse, high incidence of syncopal attacks, hemodynamic feature of so-called "reversed coarctation" i.e. hypertonic and collapsing pulse in lower extremities, increase in erythrocyte sedimentation rate and positive tuberculin skin test etc. were clearly observed and the clinical diagnosis of pulseless disease by SHIMIZU and SANO or "young female arteritis" variety of aortic arch syndrome by Ross and McKusik are well compatible with these clinical findings, furthermore, convincing finding of aortic arch syndrome was obtained through aortographies, which indicated pathognomonic narrowing of main branchings from aortic arch. Interesting to us is that both two cases developed tuberculide-like or tuberculoderma-like exanthemas, case No. 1 repeatedly developed during her clinical course papulonecrotic tuberculide on her both forearms and erythema nodosum on her shins, while case No. 2 first complained of verrucous tuberculoderma-like pyoderma on her left forearm and both shins before she was diagnosed as pulseless disease through medical examinations because of the development of cardiovascular symptoms two months later.

Although higher incidence of loss of scalp hair or thin and delicate skin have been reported²⁾ in this syndrome, the number of reports on pulseless disease combined with skin lesion is lacking. FURUYA and ISHIHARA⁴⁾ have recently reported a case of pulseless disease occurred in 19 year-old female, who had repeated outbreaks of papulonecrotic tuberculide-like skin eruption on her whole skin other than neck, scalp and face. ASK-UPMARK^{5), 6)} has reported in his extensive clinical survey of this syndrome a occasion of erythema multiformis

and two cases with erythema nodosum. In this country, there are three other reports combined to WEBER CHRISTIAN's syndrome⁷⁾, nodal tuberculous phlebitis plus temporal arteritis⁸⁾ and papel plus pustel⁹⁾, respectively. In our two cases, culuture of tubercle bacilli from the skin specimen was negative. Papulonecrotic tuberculide and erythema nodosum seen in case No. 1 is appeared to be appropriately included into the category of allergic angitis most likely based on tuberculosis, while verrucous tuberculoderma-like pyoderma observed in case No. 2 appears to be rather similar to SCHWARTZMAN's phenomenon in its pathogenesis¹⁰⁾. In the recent report, NASU¹¹⁾ has studied the morphogenesis of this syndrome on the ground of histology of the arterial wall lesion. He has suggested 1) infection or allergy following to infection of the arterial wall would be the most probable etiologic factor, or may act at least as a trigger in the early morphogenesis. 2) immunopathological mechanism of a rheumatoid nature also play a role in the pathogenesis. ITO¹²⁾ has detected anti-aorta anti-body in the serum of patients of this syndrome and suggested the possible participation of autoimmune mechanism in the development of this syndrome. MAEKAWA and ISHIKAWA¹³⁾ have named the syndrome as "occlusive thromboaortopathy" and demonstrated the increase in mucopolysaccharides, chiefly consisted of hyaluronic acid and secondly, using OUCHTERLONY procedure, observed significant development of precipitating boundary between patient's sera and group A type 1 partially purified streptococcal M protein. These reports indicates the possible role of immune allergic phenomenon in the development of the syndrome triggered by microorganism invasion, including tubercle bacilli.

The skin lesions, seen in our two cases manifested as papulonecrotic tuberculide and erythema nodosum or verrucous tuberculoderma-like pyoderma are supposed to be due to hyperergic status to tubercle bacilli and this same condition could be responsible for the development of the characteristic inflammatory occlusive condition instituted in the aortic wall. Additionally, we have also been interested in

the fact that in case No. 2, marked dilation of the main pulmonary artery was observed. As have been stated above, mucopolysaccharide accumulation in the arterial wall has been observed and furthermore, NASU has stressed the close relationship between MARFAN's syndrome and pulseless disease of cicatrized type after diffuse productive inflammation. The enormous dilatation of the main pulmonary artery in case No. 2 could well possibly be a MARFAN's type aneurysmal dilatation.

SUMMARY

We have reported two cases of TAKAYASU's syndrome, in which skin complication of tuberculide- or tuberculoderma-like eruptions are observed. Thirty-three and 40 year-old female patients with characteristic clinical picture of "pulseless disease" have developed during their clinical course, papulonecrotic tuberculide-like exanthema on her forearms and erythema nodosum-like eruptions in her shins in the former and tuberculoderma-like pyoderma on her left forearm and both shins in the latter. Skin biopsy has been done on these eruptions, which indicated nonspecific proliferative inflammation and the culture of tubercle bacilli from these specimen was negative.

It has been suggested that the immunoallergic reaction would be well responsible in pathogenesis of both aortic lesion and skin eruptions, most likely based on tuberculosis allergy.

Acknowledgement

We are grateful for Prof. Dr. H. Takasaki for his kind reviewing of the manuscript.

REFERENCES

- 1) Takayasu, M., *Acta Soc. Ophthalm. Jap.* **12**; 554, 1908. (in Japanese)
- 2) Shimizu, K. and Sano, K., *Rinsho Geka* **3**; 377, 1948. (in Japanese)
- 3) Ross, R. S. and McKusik, V. A., *A. M. A. Arch. Int. Med.* **92**: 701, 1953.
- 4) Furuya, T. and Ishihara, F., *Hihuka no Rinsho* **6**; 83, 1964. (in Japanese)
- 5) Ask-Upmark, E. and Fajers, C., *Acta Med. Scand.* **149**: 161, 1954.
- 6) Ask-Upmark, E. and Fajers, C., *Acta Med. Scand.* **155**: 275, 1956.
- 7) Nagai, D., *Kyudaidomonkai Kaiho* **69**; 31, 1956. (in Japanese)
- 8) Yamakawa, K., Kitamura, K., Ota, H. and Anazawa, Y., *Respiration & Circulation* **6**; 539, 1958. (in Japanese)
- 9) Kobori, T. and Ishihara, M., *Jap. J. Dermat.* **71**; 1237, 1961 (in Japanese)
- 10) Rostenberg, A., *Brit. J. Dermat.* **65**; 389, 1953.
- 11) Nasu, T. and Mamiya, N., *Jap. Circulation J.* **30**; 68, 1966.
- 12) Ito, I., *Jap. Circulation J.* **30**; 75, 1966.
- 13) Maekawa, M. and Ishikawa, K., *Jap. Circulation J.* **30**; 79, 1966.