

CLINICO-PATHOLOGICAL CONFERENCE

A 38-year-old man with pulmonary hypertension, who had undergone atrial septal closure 26 years previously

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Abstract. The patient was a 38-year-old man. He underwent atrial septal closure at the age of 12 years at Yokohama City University Hospital, when he already had pulmonary vascular change and reduced left-to-right shunt with Qp/Qs of 1.55 and pulmonary artery pressure (PA) of 56/22 mmHg. Thereafter, he enjoyed running and skiing without any symptoms up until 32 years of age, when he developed syncope due to severe pulmonary hypertension and atrial flutter. PA was 116/57 mmHg and mRA was 13 mmHg on cardiac catheterization. He developed right heart failure and was referred to Keio University Hospital on May 12th, 2001. Home intravenous prostacyclin infusion therapy was introduced in addition to treatment for right heart failure. Echocardiography revealed a residual interatrial shunt (from right to left). He recovered and was discharged. His condition worsened again and he was readmitted to our hospital with chief complaint of visual disturbance due to digoxin intoxication, in addition to right heart failure. Despite aggressive treatment, he died of severe pulmonary hypertension, right heart failure and congestive hepatic failure on December 10th, 2001. The differential diagnosis, pathophysiology and necessary treatment of pulmonary hypertension are discussed in this paper. The clinical diagnosis was Eisenmenger syndrome due to atrial septal defect, and the pathological findings were compatible with this. (*Keio J Med* 52 (4): 250–262, December 2003)

Key words: right heart failure, Eisenmenger syndrome, prostacyclin, atrial septal defect, liver cirrhosis

Dr. Satoh (Moderator): Let's start the 1055th clinico-pathological conference (CPC). The patient was a 38-year-old man. He was born in January 1963, and died at the age of 38 last year. An ostium secundum type atrial septal defect (ASD) was first discovered at a medical check-up in 1975, when the patient was 12 years old, and he underwent atrial septal closure at Yokohama City University Hospital. Qp/Qs was 1.55, pulmonary artery pressure (PA) was 56/22 mmHg, and mean right atrial pressure (mRA) was 3 mmHg. The postoperative course was uneventful. Around 1978, the patient moved and stopped attending the hospital. Thereafter, he enjoyed running and skiing without any symptoms up until to 32 years of age.

In 1995, at the age of 32, the patient developed syncope and fell while climbing stairs on his way to work. He was admitted to Yokohama City University Hospital and found to have an intracranial hemorrhage. His cardiac function was diagnosed as normal.

In 1997, he suffered a common cold accompanied by cough, expectoration and difficulty in breathing and was re-admitted to Yokohama City University Hospital. PA was 116/57 mmHg on cardiac catheterization, indicating the recurrence of severe pulmonary hypertension, and mRA was 13 mmHg. There was no step-up of oxygen saturation in any cardiac chamber. Severe (grade III) tricuspid insufficiency was also noted. The symptoms were relieved by administration of beraprost, enalapril, furosemide and digitalis, and the patient was discharged from hospital.

In 1999, the patient developed syncope again with palpitations and was admitted to Yokohama City University Hospital, where atrial flutter was detected by electrocardiography (ECG). This was suspected as being responsible for syncope. Direct current cardioversion was performed. Digitalis was discontinued, and disopyramide and long-acting ISDN started.

The patient noted bilateral lower extremity edema

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and hepatomegaly in April 2001. He was referred to Keio University Hospital on May 12th and admitted on May 16th with the diagnoses of severe pulmonary hypertension (PH), tricuspid insufficiency and right heart failure. Prostacyclin was introduced for PH, and furosemide, dobutamine and digitalis for right heart failure. Atrial tachycardia was transiently observed for which amiodarone was started. Cardiac gated radionuclide ventriculography revealed low left and right ventricular ejection fractions (EF) of 49% and 41%, respectively. Echocardiography revealed a residual interatrial shunt (from right to left). His condition improved and he was discharged from hospital.

The patient was followed up in an outpatient clinic. He steadily gained weight, lost his appetite and developed abdominal swelling and general malaise. His symptoms gradually worsened and visual disturbance appeared. He was admitted to our hospital on November 7, 2001 for further treatment.

Ms. Takahashi (K.) (5th-year student): Both the left and right ventricular EF seem to have decreased on this admission. It is known that the EF of the left ventricle does not decrease in primary pulmonary hypertension (PPH). Does this imply that left heart failure had already occurred?

Dr. Satoh: It should be clear from the X-ray and physical examination findings on admission as to whether left heart failure was present or not. However, it is highly probable that the very low left EF was due to the deformation of the left ventricle caused by marked dilation of the right ventricle.

Mr. Tamura (5th-year student): Intravenous prostacyclin was introduced to treat the pulmonary hypertension and the patient was discharged from our hospital with an improvement in his condition. Were there any findings regarding the decline of pulmonary artery pressure?

Dr. Satoh: Several procedures can be used to tell any decline in pulmonary artery pressure such as catheterization, electrocardiography (ECG), physical examination and laboratory examinations. In fact, pulmonary artery pressure could not be recorded due to inability of the catheter to reach the pulmonary artery because of the marked dilation of the right atrium and right ventricle. Cardiac catheterization was not conducted after that. Neither physical examination, ECG nor X-ray findings showed any improvement in his pulmonary hypertension.

Mr. Tamura: Was any treatment other than intravenous prostacyclin tried, such as administration of nitric oxide (NO)?

Dr. Satoh: NO inhalation is certainly one method, and other drugs of choice include calcium blockers. Since NO administration is still exploratory, we must obtain permission for its use from the Ethics Commit-

tee. In the present case, permission had not been obtained at that time, and NO could not be administered.

Mr. Tamura: There was a residual shunt at the atrial level. Was the shunt responsible for the development of PH?

Dr. Satoh: There is a possibility that the residual shunt could have induced Eisenmenger syndrome, but the defect was very small, less than 1 cm in diameter. Therefore, the possibility that the shunt was responsible for pulmonary hypertension was considered to be low.

Mr. Oda (6th-year student): I would like to know the data on renal function and serum potassium level when he was admitted to Yokohama City University Hospital in 1999.

Dr. Satoh: According to this patient's referral letter, his renal function was normal and serum potassium level was within the normal range. What kind of ASD do you think this patient had, based on the hemodynamic data? Were the hemodynamic data typical of a patient with ASD?

Mr. Suzuki (5th-year student): This patient's Qp/Qs was more than 1.5, suggesting that ASD closure was indicated. His pulmonary arterial pressure was high, also supporting the indication for surgery.

Dr. Satoh: Patients with an ASD often have pulmonary hypertension because of increased pulmonary blood flow. This patient's Qp/Qs of 1.5 usually does not cause pulmonary hypertension based on increased pulmonary blood flow, although a Qp/Qs over 1.5 indicates a significant left-to-right shunt and the requirement for operation. This patient, however, had pulmonary hypertension of a moderate degree. What kind of pathophysiology do you think was present?

Ms. Takahashi: I think this patient had pulmonary hypertension from the beginning.

Dr. Satoh: Do you mean that his pulmonary hypertension had no relation to the ASD?

Ms. Takahashi: I don't think it was related.

Dr. Satoh: Then, you have to rule out diseases that can cause pulmonary hypertension other than ASD. The ASD may have been incidentally associated with one of them. There is, however, another possibility that his ASD had a large amount of shunt, which caused pulmonary arterial lesions, such as medial hypertrophy and intimal hyperplasia. The resultant high pulmonary arterial resistance would have reduced the amount of shunt. The latter possibility is more probable. Should shunt closure be performed when the pulmonary vascular lesions are advanced? The most typical indication for shunt operation is Qp/Qs over 1.5 without vascular lesions. When pulmonary vascular lesions are present and pulmonary vascular resistance is increased, the requirements for ASD closure are that Rp/Rs, the ratio

of pulmonary arterial resistance to systemic resistance, is less than 0.5 with Qp/Qs more than 1.5, accompanied by grade I or II of the Heath and Edwards classification of pulmonary vasculature or a good response to pulmonary arterial dilators, which increase Qp/Qs. This patient fulfilled these requirements and underwent surgery.

He suffered from syncope. What do you think caused this?

Ms. Takahashi: One possibility is that his pulmonary hypertension worsened further, with reduced cardiac output and the development of syncope. Arrhythmia is another possibility because he later experienced syncope due to atrial flutter.

Dr. Satoh: The causes of syncope are divided into four types. One is cardiac syncope. Patients with pulmonary hypertension develop syncope because of inability of the pulmonary arteries to dilate in response to an increase in cardiac output on exertion. The pulmonary arteries are normally very expandable and can increase their flow several fold. When patients with pulmonary hypertension exercise as a normal person would, they cannot achieve an increase in flow, resulting in reduced blood pressure and the development of syncope. The second possibility is arrhythmia. Are there any other causes?

Ms. Takahashi: Other causes are vasovagal syncope and syncope due to orthostatic hypotension.

Dr. Satoh: Those are other possibilities. The patient took two or three vasodilators, which might have caused a reduction in blood pressure and orthostatic hypotension. Patients with pulmonary hypertension are known to be prone to developing vasovagal reflex.

Ms. Takahashi: I think that cerebral emboli might have been the cause.

Dr. Satoh: If cerebral emboli had occurred, what kind of condition do you think he had?

Ms. Takahashi: I think that atrial fibrillation may have been responsible for that.

Dr. Satoh: Another possibility is that paradoxical emboli from the right to the left atrium were a source of cerebral emboli.

This patient was administered IV prostacyclin. It has been used for three years in Japan, and since 1991 in the USA. Do you know what kind of drug it is?

Mr. Takahashi (M.) (5th-year student): Prostacyclin dilates the pulmonary arteries and has an antithrombotic action.

Dr. Satoh: Prostacyclin is present in normal humans and can be synthesized through biotechnology. I would like to explain the characteristics of this drug briefly. This drug has to be constantly administered intravenously because of its short half-life. A catheter is inserted into the subclavian vein, passed subcutaneously, and exits through the chest wall skin. It is

connected to an ambulatory infusion pump, which delivers a determined amount of drug (Fig. 1). I have used this therapy in ten patients. Seven of them showed improvement, while the remaining three did not show a marked improvement and their condition deteriorated.

Dr. Yagi, I heard that a small opening was present in the operated atrial septum. What was the size of the opening?

Dr. Yagi (Cardiology): The size was not measured accurately. There are two methods of ultrasonographic examination of the heart; transthoracic echocardiography and transesophageal echocardiography. Transesophageal echocardiography yields more detailed information on the heart, but it was not conducted in this patient at our hospital. Only transthoracic echocardiography was conducted. The size of the atrial septal foramen was not measured. A shunt was observed, but the foramen seemed to be very small.

Dr. Satoh: Was it less than one centimeter in diameter?

Dr. Yagi: It was not actually measured, but possibly it was.

Dr. Satoh: Let's change the subject. I would like to return to the cause of syncope. Following the syncopal attack, he had an intracranial hemorrhage. What do you think were the causes of the syncope based on this fact?

Mr. Takahashi (M.): I think that the cerebral hemorrhage was due to embolism.

Dr. Satoh: Dr. Kataoka, from the Cardiopulmonary Division, what is your opinion?

Dr. Kataoka (Cardiology): The intracranial hemorrhage was caused by some injury. The existence of injury means that there was a very short time interval between the onset of the cause and the actual syncope.

Dr. Satoh: As explained by Dr. Kataoka, injury usually occurs when the patient cannot respond properly to an event when syncope is about to develop. Injury accompanied by syncope leads us to consider that the origin was cardiac.

By the way, the patient noticed visual disturbance just before admission. The main reason for this admission was actually worsening of right heart failure. However, his chief complaint was visual disorder. What do you think was the cause?

Mr. Takahashi (M.): He showed signs of right heart failure such as jugular venous distension with a prominent v wave. I think that venous congestion induced papilledema, resulting in visual disturbance.

Dr. Satoh: Dr. Takahashi, a pediatric neurologist, have you ever seen a patient with right heart failure accompanied by papilledema?

Dr. Takahashi (Pediatrics): I have never encountered such a case.

Dr. Satoh: That does not usually occur. Let's think about it later after looking at the laboratory data. Dr.



Fig. 1 Ambulatory continuous prostacyclin treatment. Left upper: The way the catheter is inserted. Left lower: The way a patient carries an ambulatory infusion pump for prostacyclin. Right: An ambulatory infusion pump. It is put inside the bag. A pump is compared to a felt marker.

Yagi, will you describe the findings of physical examination on admission and the laboratory data?

Dr. Yagi: On admission, the patient's height was 173 cm, weight 57 kg and the circumference of his abdomen was 89 cm. His blood pressure was 105/60 mmHg, with a pulse of 51 bpm. Positive findings were as follows. The conjunctivae showed mild jaundice, and the jugular vein was visible 20 cm above Louis' angle. The v waves of the jugular vein were prominent, and there was attenuation of the first heart sound and increased IIP. A third heart sound was audible and showed the Rivero-Carvalho sign. A fourth heart sound could not be heard. A III/IV murmur was heard at the 4th intercostal space and the left margin of the sternum, and showed the Rivero-Carvalho sign. A diastolic murmur I–II/VI was also heard at the 2nd intercostal space and the left margin of the sternum, but the Rivero-Carvalho sign was unclear. Right ventricular heave was palpable, and the lung fields were clear. The abdomen was considerably swollen, as already noted from its circumference.

A tympanic sound was heard on percussion, and fluctuations were also noted. The liver was palpable 2 finger-breadths below the right costal margin, with no tenderness. The spleen was not palpable. Edema was present in both legs.

In the laboratory data, the platelet count in peripheral blood was slightly low at 99,000. Prothrombin time (PT) was low at 36%. Clinical chemical data included total bilirubin (TB) of 2.9 mg/dl, showing an indirect dominance. Urea nitrogen (UN) was 39.2 mg/dl and creatinine (Cr) was 1.3 mg/dl. The UN/Cr ratio was increased. Alkaline phosphatase (Alp) level was 509 U/L and amylase (AMY) 721 IU/L, both elevated. Brain natriuretic peptide (BNP) was 1131 pg/ml, which was markedly elevated as compared to the normal value of approximately 30 pg/ml. As for thyroid function, free T₃ (FT3) and free T₄ (FT4) were slightly low. Thyrotropic hormone (thyroid stimulating hormone: TSH) was markedly elevated to 35.2 μ IU/l. Blood gas analysis showed partial pressure of carbon dioxide (pCO₂)

of 28.4 Torr and partial pressure of oxygen (pO_2) of 57.1 Torr, both decreased. There was no acidosis, and HCO_3^- was 19 mEq/L. Blood concentration of digoxin was elevated at 3.9 ng/ml.

Analysis of ascitic fluid on admission revealed a cell count of $334/mm^3$ and glucose concentration of 114 mg/dl, which were normal. The protein level was high at 2.1 g/dl, and lactate dehydrogenase (LDH) 991 IU/L. AMY was 411 IU/L, CEA 2.6 ng/ml, and CA19-9 8 U/ml. Antinuclear antibody (ANA) was negative and alcohol dehydrogenase (ADA) was 1.5 IU/L.

Mr. Tamura: I would like to confirm whether he was given coumadin because his INR increased to 1.91.

Dr. Yagi: The patient was taking warfarin on admission.

Mr. Tamura: Could you tell me whether he had liver dysfunction?

Dr. Yagi: Yes, he did.

Mr. Tamura: Chronic pulmonary thromboembolism has to be ruled out in the differential diagnosis of pulmonary hypertension. Did you perform any investigations to examine this?

Dr. Yagi: No, this was not possible because of the patient's poor general condition. I cannot say definitely, but since the patient was treated with warfarin, the possibility is considered to be low.

Dr. Satoh: It was ruled out based on the findings of pulmonary perfusion scintigraphy conducted earlier.

Dr. Sato (A.) (Internal Medicine resident): Was neurological examination done?

Dr. Yagi: There was no distinct hemiplegia or facial asymmetry. As for visual acuity disturbance, the patient complained of inability to focus properly.

Dr. Satoh: What kind of pathological condition do you think the patient had, based on the physical findings and laboratory data?

Ms. Takahashi: First I would like to refer to the physical findings. I think he had pulmonary hypertension because he had an accentuated P_2 on auscultation. He had right heart overload due to pulmonary hypertension and tricuspid regurgitation with Rivero-Carvalho sign. He had ascites judging from fluctuation on abdominal palpation. Jaundice of the conjunctivae and an engorged liver indicated liver congestion. All these findings as well as leg edema indicated that he had right heart failure. Laboratory data revealed liver dysfunction judging from increased bilirubin, LDH and ALP. An increase in KL6 indicated a pulmonary interstitial lesion. Reduced thyroid function may have been due to sick thyroid syndrome derived from severe right heart failure and progressive liver dysfunction. Hyperventilation was indicated by decreased PCO_2 . His digitalis level was far above the therapeutic range. It was concluded that he had liver dysfunction, thyroid hypofunction, pulmonary hypertension and right heart

failure.

Dr. Satoh: I appreciate your analysis. One thing I want to comment on is whether his hypothyroidism really was due to sick thyroid syndrome or not. The second comment is that his liver dysfunction was considered to be due to right heart failure. Is that true? Dr. Kato, from the Gastroenterology Division, would you comment on this patient's liver dysfunction? Can we attribute it to cardiac congestion?

Dr. Kato (Internal Medicine): I think there is no real problem with the interpretation. Some doctors may have some doubts about the GOT and GPT levels, which were not elevated in spite of hepatopathy. GOT and GPT are elevated in patients with heart failure when the hemodynamics suddenly worsen or the blood pressure suddenly rises. In other words, GOT and GPT are elevated in situations where hepatic necrosis occurs. When the liver becomes congested as a result of the gradual progression of right heart failure, GOT or GPT may occasionally not be elevated in a considerable number of cases. Concomitantly, bilirubin level is slightly increased in patients with liver congestion, and persists for a long period. In such cases, Alp level is also markedly increased. These findings of liver function tests may be characteristic of liver congestion.

Dr. Satoh: When biliary enzymes and bilirubin are elevated, but not serum GOT and GPT, liver dysfunction can be attributed to right heart failure.

Dr. Kato: The possibility of a congested liver being responsible for hepatopathy is also reasonably high. In this case, however, cholestasis due to drug-induced hepatitis etc. must be considered in the differential diagnosis. This is naturally taken into consideration in making the differential diagnosis, but if the time of its occurrence is consistent with the time of exacerbation of the pathological condition due to right heart failure, hepatopathy accompanying liver congestion should be considered the first choice.

Dr. Satoh: Thank you for your explanation. One of the students said that thyroid dysfunction was diagnosed as sick thyroid syndrome. Dr. Azuma, an endocrinologist, could you comment on the endocrinological abnormality?

Dr. Azuma (Internal Medicine): Euthyroid sick syndrome (low T3 syndrome) is a condition in which a low FT3 level is observed without thyroid abnormality in patients with systemic disease or malnutrition, and is considered a kind of biodefense mechanism. Naturally, it does not require supplementation of thyroid hormone. In some severe cases, FT4 may also be decreased, but it is rare that TSH exceeds 10. The present patient was certainly in a state of serious heart failure with liver cirrhosis, FT4 was low and TSH exceeded 20. Since thyroid hormone supplementation was considered necessary, the patient's condition should be clinically con-

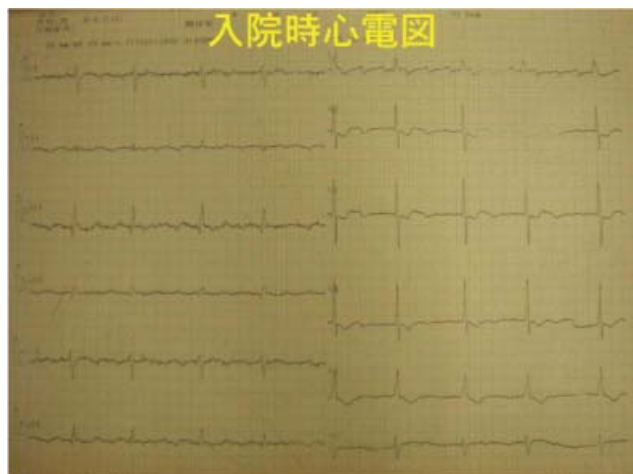


Fig. 2 An electrocardiogram on admission. Refer to the text for detail.

sidered to be hypothyroidism. As for whether or not the patient had Hashimoto disease, this would not be known, unless the appropriate autoantibody could be determined. Amiodarone may occasionally induce mild hypothyroidism because it contains a high level of iodine. However, it is believed that TSH rarely exceeds 10 in the absence of some disposition towards hypothyroidism.

Dr. Satoh: One of the chief side effects of amiodarone is hypothyroidism, but hyperthyroidism may also occur. So this patient's hypothyroidism may have been caused by amiodarone. Dr. Azuma argued that hypothyroidism of this degree may not have been caused by amiodarone alone, but may have been caused by Hashimoto disease from the start. This patient may have had primary pulmonary hypertension (PPH). A certain percentage of cases of PPH are complicated by Hashimoto disease.

Dr. Kato: Since amiodarone frequently induces hepatopathy, drug-induced hepatopathy also has to be considered in making the differential diagnosis. However, hepatic function showed a slight elevation of bilirubin and Alp about one year before the use of the drug. Therefore, these findings can be regarded as being attributable to chronic liver congestion.

Dr. Satoh: What were the electrocardiographic findings (Fig. 2).

Mr. Takahashi (Y.) (5th-year student): The rhythm looks like atrial flutter. The electrical axis is right judging from leads I and aVF. There is right ventricular hypertrophy because the R wave voltage in V₁ is more than 0.7 mV.

Mr. Suzuki: The RR interval is not strictly regular, but shows roughly 5 to 1 conduction. So I think it is atrial flutter.

Dr. Satoh: Well, the RR interval is almost regular, so



Fig. 3 Chest X-ray on admission. Refer to the text for detail.

isn't it sinus rhythm? If the RR interval is regular, the rhythm can be sinus rhythm or atrial flutter. Of course, ventricular tachycardia is another possibility. If this rhythm were sinus rhythm, a P wave would precede the QRS complex. When you look at lead II or V₁, you can find something like P waves. But they are more like sawtooths. You can also find them between the QRS complexes. These sawtooth-like configurations are flutter waves. There is one QRS complex among three flutter waves, suggesting 3 to 1 conduction of atrial flutter. Usually the rate of flutter waves is around 300 per minute. This patient's rate was 150, which was very slow. This may have been caused by amiodarone. Lead V₆ shows a deep S wave, suggesting that the patient had right ventricular hypertrophy.

Let's move to the roentgenographic findings. What were the findings (Fig. 3).

Mr. Tada (5th-year student): His cardiothoracic ratio (CTR) is 0.7, which is over the normal range of 0.5. The cardiac shadow is widened in a right to left direction, suggesting right ventricular enlargement.

Ms. Takahashi: The second cardiac arch, indicating the main pulmonary trunk, and the right second arch, which is the right atrium, are dilated.

Dr. Satoh: I will explain the additional findings. The left first arch is somewhat small, as reported in ASD. The pulmonary fields are very clear, indicating scanty



Fig. 4 Abdominal X-ray on admission. Refer to the text for detail.

pulmonary vessels. The vessels appear tapered, suggesting pulmonary hypertension. There also is pleurisy. The dilated left 4th arch shows right ventricular dilatation because it crosses the diaphragm in a right oblique and downward direction.

So what were the findings of abdominal roentgenography (Fig. 4).

Ms. Takahashi: There is a difference in lucency between the X-rays taken on standing and in the recumbent position, indicating the presence of ascites. Also intestinal gas appears dilated.

Dr. Kato: Increased intestinal gas, which is not explained only by the presence of ascites, was observed. Since a small amount of intestinal gas was observed, I would consider congestion of the small intestine from the plain roentgenographic findings of the abdomen. I suspect hypokinesia of the small intestine which is a kind of ileus in such cases.

Dr. Satoh: Dr. Yagi, will you explain the clinical course after admission?

Dr. Yagi: Digoxin was discontinued because the blood level of digoxin was high on admission. In order to improve his right heart failure, the dose of furosemide was increased, and dobutamine was administered. The patient's appetite subsequently improved. There was also an improvement in his visual acuity.

However, oxygen saturation was not improved. The amount of O₂ administered could not be reduced to less than 80%. Since the hematological data showed a tendency toward intravascular dehydration caused by diuretics, the diuretics were withdrawn on November 21. On around November 24, the abdominal swelling started to increase, together with a decreased blood oxygen saturation. Diuretics were started again at a lower dose. The ascites were drained by puncture when necessary to decrease abdominal swelling.

Heart-lung transplantation was considered and an attempt to improve the patient's general condition was made, but the blood oxygen saturation gradually decreased. On November 29, disturbance of consciousness developed. Since the blood ammonia concentration was elevated, the patient was diagnosed as having hepatic encephalopathy. The diuretics were withdrawn, and Aminoleban, Monilac, and Kanamycin were administered. The hepatic encephalopathy was temporarily relieved, but right heart failure and low output remained. The symptoms tended to gradually worsen. On December 4, FT3 was 0.9 pg/ml, FT4 40.4 ng/dl, and TSH 77 μ IU/ml, showing exacerbation of hypothyroidism. Although there was a risk of an increase in peripheral oxygen consumption, low-dose thyroid supplementation was started. On December 6, the urine volume started to decrease. Fluid infusion or administration of diuretics was conducted according to the patient's condition, but he did not respond favorably, and died on December 10.

Dr. Sato (A.): Could you show the potassium values?

Dr. Yagi: The potassium concentration was determined almost every day and was maintained at approximately 4.0 mg/L by intravenous potassium supplementation.

Dr. Kato: How about the nutritional state? I mean, how was feeding conducted? And one more point, how were his bowel movements?

Dr. Yagi: Bowel movements were stimulated with cathartics, Mentha fermentations, and so on, but were very infrequent. As you said, there may be a possibility that the decreased bowel movement triggered hepatic coma. The patient's nutritional state was not satisfactory, but he did not wish to receive intravenous hyperalimentation (IVH). Therefore, oral feeding was conducted with approximately 1/3 to 1/2 the amount of the normal daily diet.

Dr. Kato: In protein equivalents, how many calories were given, when feeding corresponding to about 1/2 the diet was conducted?

Dr. Yagi: A diet for heart failure patients was prepared. So, the patient was receiving half of 1800 Cal, i.e., 900 KCal or less, I think.

Dr. Satoh: How about the protein content?

Dr. Kato: In the diet for heart failure, the protein content is about 70 g. Since half of 70 g was ingested, the amount was not so high. However, was any procedure instigated for feeding such as amino acid transfusion by drip infusion or any other means?

Dr. Yagi: Amino acid transfusion was not conducted.

Dr. Satoh: He had a good appetite and ate at least half of every meal until he became unconscious.

Ms. Yamada (6th-year student): What kind of pathophysiology do you think was responsible for the arterial hypoxia? Could you show us the chest X-ray at that time?

Dr. Yagi: The chest roentgenogram revealed no remarkable change in the lung fields to account for the low oxygen saturation. CTR, however, had been gradually increasing. Identifying the cause of hypoxemia remains a problem. It may have been associated with pulmonary hypertension, or the following mechanism is a possibility. I believe that since severe tricuspid insufficiency was present, the blood did not flow toward the lungs but flowed toward the right atrium because of high pulmonary vascular resistance, even if the right ventricle contracted. For this reason, the low cardiac output state in the pulmonary circulation could have been responsible for hypoxemia.

Dr. Satoh: I would like to add that the ascites could have prevented diaphragmatic movement and caused alveolar hypoventilation, leading to hypoxia. The right to left shunt may have increased and induced hypoxia because of elevated right atrial pressure due to worsened pulmonary hypertension. Reduced pulmonary flow owing to severe pulmonary hypertension can cause ventilation-perfusion inequality, resulting in hypoxia.

He had visual disturbance just before admission. What do you think was responsible for it?

Dr. Yagi: The main cause of the visual disturbance may have been a side effect of digoxin, judging from the clinical course. Another possibility may have been cerebral dysfunction due to hypoxia. However, the main reason for the visual disorder can be considered to be digoxin.

Dr. Kato: Were any unusual findings observed in the ocular fundus?

Dr. Yagi: We consulted an ophthalmologist, but there were no specific abnormalities in the eyes themselves.

Dr. Satoh: I think the visual disturbance was almost certainly caused by digitalis intoxication, because his vision recovered to normal when the high dose of digitalis was reduced. He became unconscious on November 29th. What was the cause?

Mr. Takahashi (M.): I think that it was due to hepatic coma, because the serum ammonium concentration was markedly elevated due to reduced degradation of ammonium in the disordered liver, and this ammonium

would have entered the brain through the brain-blood barrier.

Dr. Satoh: What was the final diagnosis?

Ms. Takahashi: His main problem was right heart failure. When the diuretics were stopped because of dehydration and resultant hepatic coma, right heart failure ensued. If the diuretics had been continued, hepatic coma would have occurred. These conditions drove him into a corner and caused his death.

Dr. Satoh: You think that he died of right heart failure? What was the cause of right heart failure?

Ms. Takahashi: I think that his pulmonary hypertension caused right ventricular dysfunction and that it was already very severe when he underwent ASD closure, and worsened further after that.

Ms. Takahashi: If he had had Hashimoto disease or another autoimmune disease, it may have contributed to the pulmonary hypertension.

Dr. Satoh: We can conclude that he had Eisenmenger syndrome, can't we? What is your opinion on the cause of his pulmonary hypertension?

Dr. Yagi: It seems difficult to differentiate the causes of pulmonary hypertension in this patient. I am not sure whether Eisenmenger syndrome was really present or not, because he was not followed up frequently after his heart surgery. Therefore, we must examine whether the surgery was successful or not is a problem. There is another possibility; anomalous pulmonary venous drainage may have been associated with ASD, thereby inducing Eisenmenger syndrome. This possibility cannot be ruled out, either. However, it seems highly probable that PPH was responsible for his disease. Laboratory tests ruled out collagen diseases, chronic pulmonary thromboembolism, and angitis. Other tests ruled out angitis, aortitis syndrome, idiopathic portal hypertension, and liver cirrhosis. Therefore, diseases leading to secondary pulmonary hypertension were ruled out.

Dr. Satoh: PPH and Eisenmenger syndrome remain as the final differential diagnoses. ASD was the cause of Eisenmenger syndrome. Eisenmenger syndrome due to ASD is different from that due to VSD or PDA. A large shunt causes Eisenmenger syndrome in VSD or PDA, whereas in ASD, Eisenmenger syndrome occurs without a large shunt. The mechanism of pulmonary hypertension is considered to be different between those two types of congenital shunt. Some doctors think that Eisenmenger syndrome due to ASD is merely a combination of ASD and PPH. However, the duration of the clinical course seemed too long for PPH. In typical PPH, the 5-year survival is 27%.¹ Patients with Eisenmenger syndrome secondary to ASD develop the disease in their teens or 20s and usually live until their 40s or 50s.

We would like to discuss the treatment of hypo-

thyroidism and severe liver dysfunction in this patient. First, Dr. Kato, would you comment on the treatment of liver dysfunction?

Dr. Kato: Treatment of heart failure takes first priority over ascites, because ascites is considered to originate from congestion. I have another doubt about the occurrence of hepatic encephalopathy in this patient, because neither GOT nor GPT was markedly elevated on admission. Despite the fact that GOT and GPT were only very slightly elevated, hepatic encephalopathy rapidly worsened. At this point, what was the ammonia level?

Dr. Yagi: It was about 100.

Dr. Kato: It wasn't very high, was it? I don't think that this patient had acute hepatic failure, but I think he probably had hepatic fibrosis or was heading in that direction. The fact that GPT and GOT were only slightly elevated suggests the absence of liver necrosis. This may be different from hepatic failure with fulminant exacerbation. The presence of a chronically congested liver induces hepatic fibrosis and a decrease in hepatic function to some degree. In such cases, a massive amount of ammonia flows into the body from the intestine in the presence of congestion of the small intestine, resulting in failure of adequate treatment. This is the mechanism by which hepatic encephalopathy was considered to have developed in the patient.

Dr. Satoh: Do you consider that abnormality of the small intestine, rather than hepatic disorder, caused the coma?

Dr. Kato: The small intestine rather than the liver may be an important factor in hepatic encephalopathy. As far as the liver is concerned, an acutely deteriorating change such as necrosis may not have occurred widely during the course of this patient's disease.

Dr. Satoh: Is the treatment for coma caused by small intestinal disorder different from that due to liver dysfunction?

Dr. Kato: Let me see. Intestinal movement and enteral disinfection (as described here) are enumerated as treatment. It may be most important to induce defecation by intestinal movement with lactulose or lactitol.

Dr. Satoh: Thank you very much for your explanation. Regarding the treatment of hypothyroidism combined with heart disease, treatment of hypothyroidism or thyroid supplementation may sometimes aggravate heart failure because of increased oxygen consumption. Dr. Azuma, would you please comment on this?

Dr. Azuma: A recent review in the New England Journal of Medicine (Feb., 2001) has also shown that hormonal supplementation in hypothyroidism increases cardiac output and alveolar ventilation and decreases vascular resistance, and that it has beneficial effects on cardiac and pulmonary function. In the elderly and

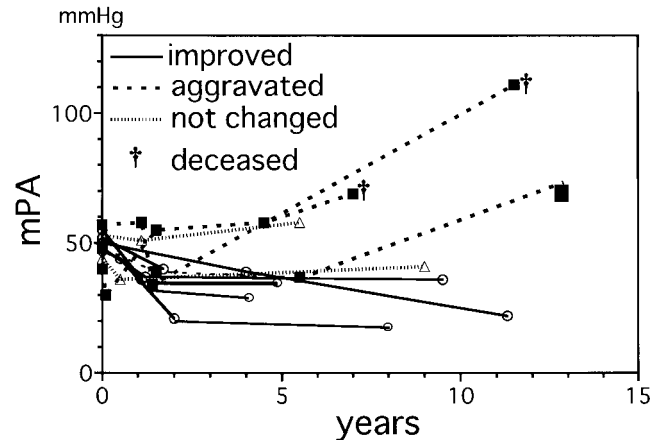


Fig. 5 Clinical course after the operation of the patients with atrial septal defect and pulmonary vascular disease. Ten patients, who had pulmonary hypertension defined as their mean pulmonary pressure of more than 40 mmHg after ASD operation, were followed. Three patients were aggravated. Two patients were not changed. The remaining 4 patients were improved. Two patients died.

patients with heart disease, however, hormonal supplementation should be started at a low dose, taking into consideration the increase in pressure on the heart along with the increase in oxygen consumption. The dose must be gradually increased under careful observation.

Dr. Satoh: What was the starting dose?

Dr. Azuma: There was no problem with 12.5 μ g as the initial dose.

Dr. Satoh: I would like to make a last comment. The patient's mean pulmonary arterial pressure was around 40 mmHg just before ASD closure. The prognosis of patients with an ASD and pulmonary vascular damage depends on the pulmonary pressure. From my research, patients with a mean pulmonary pressure of less than 40 mmHg have a very good prognosis. Some patients with a value of more than 40 mmHg had improved or not changed at ten years after the operation, while some died within ten years (Fig. 5). I could not find any good parameters to differentiate patients with these different prognoses. Dr. Ohkita, would you explain the pathological findings?

Dr. Okita (Pathology): The pathological diagnosis is shown in Table 1. The main lesion was pulmonary hypertension. The pathological finding in the lungs was plexogenic pulmonary arteriopathy. Such an arterial lesion forming a plexiform lesion is a pathological condition observed in PPH and pulmonary hypertension secondary to congenital heart disease including ventricular septal defect and patent ductus arteriosus, which are associated with increased pulmonary blood flow. Although rare, such an arterial lesion may be induced by drugs or observed in chronic hepatic disease, HIV infection, etc.

Table 1 Autopsy Findings

1. Pulmonary hypertension (380:380 g)
1) Plexogenic pulmonary arteriopathy
Heath and Edwards grade: V
Plexiform lesion,
chronic dilatation lesion with vein-like arteries,
hemosiderin deposition
2) Pulmonary artery atherosclerosis
3) treatment: prostacyclin
2. Core pulmonale (620 g)
1) Dilatation and hypertrophy of the right ventricle
right ventricular wall thickness: 7 mm
left ventricular wall thickness: 10 mm
2) Dilatation of the right atrium
3. Chronic and acute congestion of the liver + Hyperplastic nodule (1830 g)
1) Congestion and fibrosis in zone 3
2) Two hyperplastic nodules, left lobe, 12 mm, 6 mm
4. Ascites (5500 ml)
5. Atrial septal defect, 26 years after surgery
A slit-like defect in the posterior aspect of the sutured area

It is impossible to differentiate PPH from pulmonary hypertension accompanying congenital heart disease only from the histopathological findings in the lungs. In the present patient, differentiation of PPH from pulmonary hypertension secondary to ASD became an issue, but it is impossible to determine this only from the findings in the lungs. The clinical course also needs to be considered in the differentiation.

The lesions marked as 2) in No. 1, No. 2, No. 3, and No. 4 were associated with pulmonary hypertension, i.e., they showed atherosclerosis of the pulmonary artery, or pulmonale, chronic congestion of the liver, and ascites, respectively.

The Heath and Edwards Classification is essentially a classification of the severity of pulmonary vascular lesions accompanying congenital heart disease. Subsequently, it has been used to indicate the severity of PPH. The severity is classified as grades I through VI. This patient had grade V. Grade I and II are considered reversible. Grade III or higher is considered irreversible. Grade I lesions show thickening of the tunica media of arterioles and small arteries of the lungs. Grade II lesions show cellular hyperplasia of the small arteries and thickening of the tunica intima, which are due to the cellular hyperplasia. Grade III lesions show almost complete obliteration of small arteries, which is due to fibrous thickening of the tunica intima. Grade IV lesions show formation of plexiform lesions. Grade V lesions show plexiform lesions and dilatation of arteries, the walls of which become thin like the wall of a vein. Grade VI lesions show necrotizing vasculitis.

A plexiform lesion is defined as follows: A small pulmonary artery is dilated, in association with thickening of the tunica intima; and hyperplasia of heman-



Fig. 6 Cut surface of the lung. Pulmonary arteries were dilated and atherosclerosis was also observed.

gioendothelial cells and the smooth muscle in the thick tunica intima, forming a retiform structure. Concrete causes have not yet been identified, but necrotizing vasculitis has recently been believed to be responsible.

Both lungs weighed 380 g, showing a slight increase in weight. Macroscopic observation of the cut surface revealed that the pulmonary artery was dilated, and atherosclerosis was also observed (Fig. 6), secondary to pulmonary hypertension. The whole cut surface of the lung was slightly more reddish and brownish, reflecting hemorrhage and hemosiderosis.

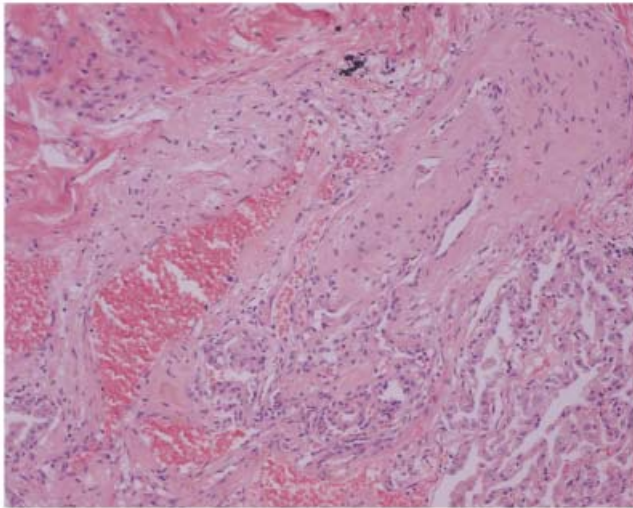
Microscopic findings of the lungs are shown in Fig. 7A. Small arteries (100–200 μ m in diameter), branching off from the pulmonary artery, show fibrous thickening of the tunica intima. There is a reticular slit-like or capillary-like space in the periphery. This is a plexiform lesion. In further peripheral areas, dilated blood vessels filled with erythrocytes are observed. In this region, the arterial wall has become thin like that of a vein.

EVG staining facilitates identification of fibrous thickening of the tunica intima of small arteries and plexiform lesions in the periphery (Fig. 7B). These lesions are characteristic of PPH and pulmonary hypertension accompanying congenital heart disease.

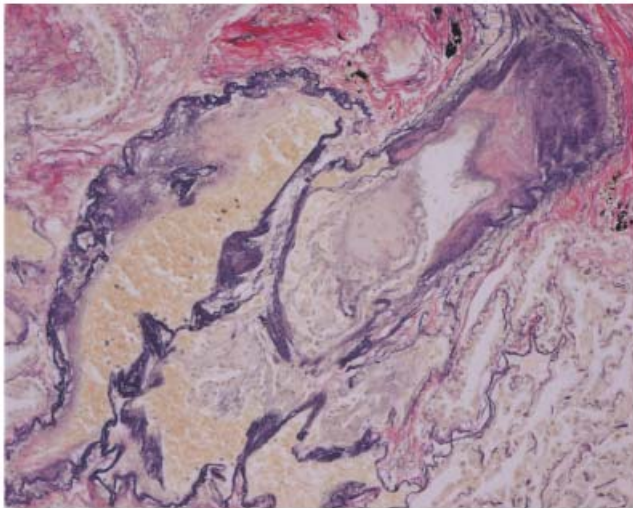
The pulmonary arteries around the lesions were dilated, and marked hemosiderosis was present in the parenchyma surrounding the pulmonary arteries. Some areas were hemorrhagic, and are considered to have resulted from hemorrhage from the dilated blood vessels.

Macroscopic observation of the heart showed that the right ventricular wall was about 7 mm in thickness (Fig. 8), showing marked thickening, and the right ventricle also showed luminal dilatation. The tricuspid valve and right atrium were also markedly dilated.

At the site where the ASD had been closed, the following were confirmed: The defect had been sutured in at least two points; it appeared to be closed but had a valvular form, and the left and right atria communicated with each other. However, the shape looked like



A



B

Fig. 7 Microscopic findings of the lung. Fibrous thickening of the tunica intima of a small artery, plexiform lesion, and dilated thin-walled arteries were observed. A) (H.E.) B) (Elastica van Gieson)

that observed in patent foramen ovale; when left atrial pressure was higher than right atrial pressure, there was no blood flow, while there was blood flow when right atrial pressure was higher than left atrial pressure. Therefore this slit-like communication between the left and right atria was not considered to be the cause of pulmonary hypertension.

The liver was a brownish color overall, with sites of marked hemorrhage and findings of chronic and acute congestion. Microscopically, hepatocytes were relatively preserved around portal areas, but erythrocyte pooling was observed in “zone 3”. The hepatocytes

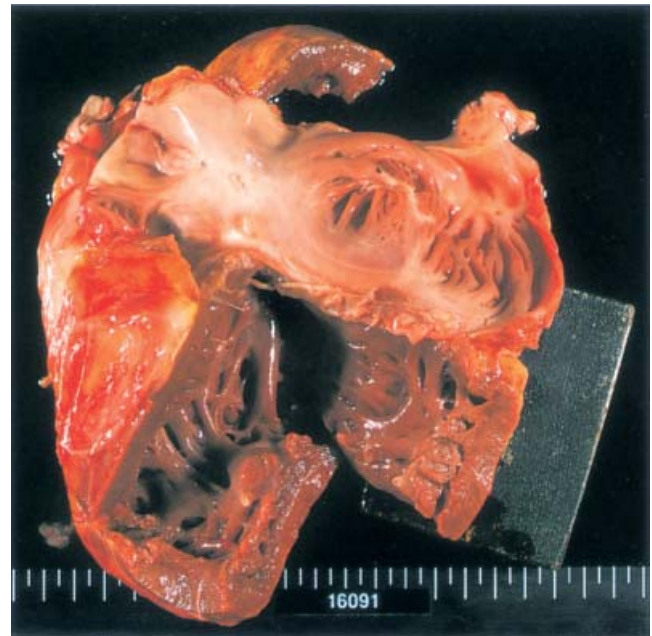


Fig. 8 Macroscopic observation of the right heart. The right ventricle was hypertrophied and dilated.

had mostly dropped out. Along with the chronic course of congestion, hepatocytes dropped out, and fibrosis was further associated with the congestion. The pathological findings confirmed hepatic congestion accompanying right heart failure.

There were hyperplastic nodules of 12 mm and 6 mm diameter in the left lobe of the liver, with a high possibility of their being focal nodular hyperplasia-like lesions, the presence of which is considered attributable to localized abnormality of blood flow in the non-cirrhotic liver. This type of lesion is characterized by the presence of fibrous cicatrices and abnormal blood vessels and has been incidentally detected on autopsy in many cases, though the frequency is believed to be low. Recently, however, the detection frequency of these lesions has been increasing owing to advances in diagnostic imaging.

Fig. 9 shows the microscopic findings of the nodule in the present patient. The liver with changes due to congestion is seen on the left, and a nodular lesion is shown on the right. Nodular hyperplasia of hepatocytes is observed, and they have lost their normal lobular structure, with trabecular proliferation. Large blood vessels are observed disproportionately at various sites. The hepatocytic atypia is not the type associated with hepatocellular carcinoma, but hyperplastic proliferation of hepatocytes may be observed. The lesion is considered to be similar to focal nodular hyperplasia.

Here we can see the pathological findings in the lungs, which are typical of pulmonary hypertension.

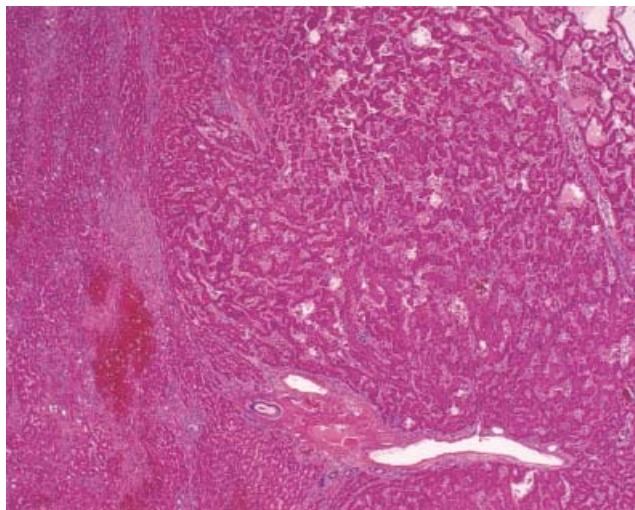


Fig. 9 Microscopic findings of a hyperplastic nodule of the liver. Hyperplastic hepatocytes proliferated in trabecular pattern.

They showed plexogenic pulmonary arteriopathy that corresponded to PPH or pulmonary hypertension associated with congenital heart disease. Lesions accompanying plexogenic pulmonary arteriopathy, which included cor pulmonale and hepatic congestion, were observed, and it is considered that the patient died from right heart failure associated with pulmonary hypertension.

Dr. Kato: How severe was the fibrosis of the liver?

Dr. Okita: The fibrosis was mild to moderate, and involved the central area of the lobules, although bridging fibrosis was not yet present.

Dr. Kato: Was hemorrhagic necrosis seen?

Dr. Okita: Hepatocytes gradually dropped out because of chronic congestion, resulting in zonal necrosis. Zone 3 showed zonal necrosis accompanied by chronic and acute congestion.

Dr. Kato: Were any necrotic cells detected?

Dr. Okita: The amount of recent necrosis was not large.

Dr. Satoh: Prostacyclin was administered to this patient. This drug is considered to reverse hypertrophy of pulmonary arteries. Did you detect any evidence of reversed remodeling such as relatively reduced medial or intimal hypertrophy or fewer plexiform lesions which are indicators of severe pulmonary hypertension?

Dr. Okita: I think it is hard to quantify any such findings, because the relation between the patient's status and the following conditions: histopathological severity of the plexiform lesion, symptoms of pulmonary hypertension, level of pulmonary arterial pressure, and severity of right heart failure remains unknown. Neither was there any histopathological description concerning lesions with restoration of a thick tunica intima

or tunica media. Therefore, it is difficult to evaluate any such findings possibly associated with beneficial effects of prostacyclin.

Dr. Satoh: Did you notice more recanalization of the pulmonary capillaries than usual?

Dr. Okita: There was no particular impression of an increased frequency of recanalization.

Dr. Satoh: You consider that the pathological findings in this patient who used prostacyclin were not different from those in patients without prostacyclin administration?

Dr. Okita: Certainly, the following aspects revealed no particular difference from the usual findings in PPH: vasoconstriction was present, plexiform lesions had formed, and dilated blood vessels were also present. However, what I did find unusual in the present case were the marked hemorrhage and hemosiderin deposition.

Dr. Satoh: I understand. Any other questions?

Dr. Yagi: This patient had very severe ascites. The blood data also strongly suggested intravascular dehydration. In spite of this, ascites persisted. It is also considered that ascites was diapedetic, but I wonder about the cause of ascites in the present patient. The pathological findings of the liver were not very severe. I can think of some other possibilities; for instance, I wonder if retention of such a massive amount of ascites occurred because of the hypothyroidism. Since very severe tricuspid regurgitation is associated with PPH, hepatic hypofunction with low output should also be considered.

Dr. Kato: I think the ascites cannot be explained by liver cirrhosis. Marked congestion of the liver and small intestine is considered to have been present. I wonder what the findings in the small intestine were; for instance, I wonder if severe edema or hemorrhage from the small intestinal mucosa was present. It is my interpretation that the ascites was secondary to congestion.

Dr. Yagi: In this case, finally, the amount of retained ascites may have reached about 5000 ml, but despite this amount, there was still a tendency toward intravascular dehydration. I wonder if the presence of a large amount of ascites can be explained only by congestion. I think there was another cause of the occurrence of ascites, related to the liver or abdominal organs, without edema of the legs.

Dr. Kato: Such a possibility varies on a patient-by-patient basis. As for ascites and edema due to liver cirrhosis, the main symptom is ascites in some patients while edema of the legs becomes severe in other patients. There also may be asymmetry of leg edema. It is impossible from the findings alone to rule out liver congestion as being responsible for the ascites, but in my opinion, congestion of the small intestine in this case was strongly related to the ascites.

Dr. Okita: With regard to the liver, it was much heavier than usual at 1830 g, indicating very severe congestion. As for findings in the small intestine, no organic lesion could be identified.

Dr. Kato: Occasionally, some reports have shown that portal hypertension is associated with nodular hyperplasia. Was there any finding indicating the presence of varices, for example?

Dr. Okita: I don't think that there was any finding indicating distinct portal hypertension. The spleen weighed 150 g, and slight congestion appeared to have been present, but not to a great extent. There was no dilatation of the portal vein or distinct varix.

Dr. Satoh: Are there any other questions? If not, I would like to conclude this CPC. Thank you for your attendance and contributions.