

CLINICO-PATHOLOGICAL CONFERENCE

A 73-year-old man with confusion, fever, and positive MPO-ANCA

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Abstract. A 73-year-old man was admitted to the hospital because of progressive lethargy and fever. He had a history of hypertension since the age of 40, and was diagnosed as having a testicular tumor at the age of 50. On admission, he looked pale and stuporous. Laboratory examination revealed microscopic hematuria. The erythrocyte sedimentation rate was 110 mm/hr, and the serum CRP was 14.3 mg/dl. The titer of myeloperoxidase-antineutrophilic cytoplasmic antibodies (MPO-ANCA) was higher than 1:1000. On the sixth hospital day, he required ventilatory assistance because of aspiration pneumonia and was connected to a respirator. He was treated with intravenous corticosteroids, to which he responded in the short term with resolution of the fever and decrease in the serum CRP level, however, the consciousness disturbance persisted and the fever recurred soon thereafter. He developed gross hematuria and the renal function deteriorated. He eventually died of renal failure and pulmonary hemorrhage. Although his clinical course and laboratory findings were consistent with those of microscopic polyangitis, the pathological diagnosis was crescentic glomerulonephritis with no evidence of vasculitis. (Keio J Med 53 (2): 103–114, June 2004)

Key words: vasculitis, microscopic polyangitis, confusion, ANCA, hematuria

Dr. Nagata (Moderator): We shall now start the 1072nd Clinico-pathological Conference (CPC) of our institution. Dr. Teramoto, the physician-in-charge of the patient, will give us a clinical presentation of the patient.

Dr. Teramoto (Internal Medicine): The patient was a 73-year-old man with the chief complaints of pyrexia and consciousness disturbance.

Concerning the history of present illness, the patient had suffered from occasional arthralgia, low grade fever, and generalized malaise since around 1999, but he had been able to continue to keep house until October 2000. On October 31, 2000, he was vaccinated against influenza and three days after the vaccination he developed generalized muscle aches and easy fatigability. He became unable to carry on with his household activities, and visited Johsai Hospital for examination on November 14, 2000. Hematological examination at that hospital revealed an increase in the serum C-reactive protein (CRP) level to 5.20 mg/dl, and a high serum γ -globulin level. Thereafter, he visited a

family physician on November 28, where he was suspected as having senile depression. Hematological examination at this clinic revealed a further increase in the serum CRP level to 8.60 mg/dl, and the hemoglobin (Hb) level was 10.2 g/dl. He became unable to carry on with the activities of daily living (ADL), and tired easily, even while talking or eating meals. When it became difficult for him to be understood by others, his wife who was herself suffering from schizophrenia and was a regular outpatient at the Department of Psychiatry of our hospital, took him to the department for examination on December 22, 2000. He was admitted to the psychiatry department on the same day, and was immediately started on intravenous hyperalimentation to improve his nutritional status. Despite this, however, his consciousness disturbance persisted and his general condition remained unchanged. Pyrexia of 38.0–38.9°C was also recorded. Since malignant tumor, collagen disease, or infection, rather than a psychiatric disease, was suspected as the cause of the consciousness disturbance, the patient was referred to the Department of

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Gastroenterology on December 28, 2000, for further investigation and management.

Concerning the patient's past history, he had had pulmonary tuberculosis at about 20 years of age, appendicitis at about 30 years of age, and was diagnosed as having a gastric ulcer and hypertension during the fourth decade of life. However, detailed information regarding the treatment of the hypertension could not be obtained. He was diagnosed as having a testicular tumor at about 50 years of age. Finally, at the age of 72, he had undergone excision of a colonic polyp.

In regard to his personal history, he was not a habitual smoker or drinker.

Concerning his family history, both his wife and daughter suffered from schizophrenia. There was no family history of allergy.

Mr. Inokuchi (6th grade student): Was there any history of weight loss? Were any purpuric rashes observed at any point of time during the clinical course?

Dr. Teramoto: No details regarding weight loss or observation of purpuric rashes were available at the time of admission, but both the clinical signs were noted during the patient's stay after admission to the hospital.

Dr. Nagata: We can probably assume that the patient had weight loss, since he became unable to eat daily meals. His general condition at the time of admission was extremely poor, and he looked tired and emaciated. Under these circumstances, he could certainly be assumed to have lost considerable weight.

Dr. Teramoto: As for purpura, FOY was used during the course of treatment, and purpura appeared at around the time that it was started.

Dr. Nagata: The purpura appeared after admission, and I suppose we can assume that it was absent at the time of admission.

Dr. Suwa (Internal Medicine): This patient had a past history of hypertension; do you know any details of his medication at the time of admission?

Dr. Teramoto: When he was admitted to our hospital, he was receiving oral Nifedipine.

Dr. Nagata: Did he have asthma or any symptoms of bronchitis?

Dr. Teramoto: He had no clinical features of any infection, of pneumonia in particular, or of asthma.

Dr. Nagata: Did he give you a history of tooth extraction before admission?

Dr. Teramoto: No.

Dr. Nagata: So, in this patient, we must first resolve the issue of time of onset of the disease. Since 1999 or so, he had had arthralgia, low grade fever, and generalized malaise. However, his ADL were maintained. It is difficult to say whether the symptoms were triggered by the prophylactic vaccination against influenza that he received on October 31, 2000, but he developed serious constitutional symptoms, including muscle aches,

easy fatigability and generalized malaise from November 3, about 3 days after the vaccination, and was found to have elevated serum levels of inflammatory markers. When do you think the present disease process set in?

Dr. Teramoto: I would not be able to comment on the precise time of onset of his disease, but in view of his age, the symptoms that appeared 3 days after the vaccination may be assumed to be related to pyrexia following the vaccination. I believe it is possible that the patient developed acute disseminated encephalomyelitis (ADEM). We shall discuss this further while we talk about the differential diagnosis in this patient.

Dr. Nagata: Three days after the vaccination against influenza, he developed severe generalized malaise and muscle aches, much like the symptoms of a common cold, am I right?

So, Dr. Teramoto, will you now please tell the audience about the patient's condition on admission?

Dr. Teramoto: The patient's examination findings on admission were as follows: His height was 172 cm and body weight was 65 kg. His consciousness was I-3 on the Japan Coma Scale (JCS). His blood pressure was 160/64 mmHg at the time of being referred to the Department of Internal Medicine; the pulse rate was 84 per minute, and the body temperature was 37.2°C. Mild anemia was present, but there was no jaundice. No significant abnormalities were found on oral examination. The heart sounds were regular, and lung examination did not reveal any abnormalities. There was edema over the lower extremities. Nuchal rigidity was \pm . There was no tremor at rest. The pupils were equal, and 3.0–3.9 mm in diameter. There was no nystagmus or double vision. The papillary light reflex was normal on both sides. There were no significant abnormal findings on neurological examination. Babinski's sign was negative. Neither Chaddock's reflex nor Hoffmann's reflex was observed. Manual muscle testing (MMT) revealed a slight reduction of power, but it was assumed to be mostly within the normal range. There were no sensory abnormalities, including pain perception. The muscle strength was slightly decreased.

Dr. Nagata: Was there a right-left difference in the blood pressure of this patient?

Dr. Teramoto: No, there was no significant right-left difference in the blood pressure.

Dr. Nagata: Were there any heart murmurs?

Dr. Teramoto: No, there was no heart murmur.

Dr. Nagata: Was any bruit heard over the abdomen or chest?

Dr. Teramoto: No, there were no bruits over the abdomen.

Dr. Nagata: According to your presentation, the patient did not have any purpura. Were there any skin rash or subcutaneous nodes?

Dr. Teramoto: There were no significant abnormal

Table 1 Laboratory Test Results during Admission

[Laboratory findings on admission] (On admission) [Occult blood] 3+, [Urinalysis] pH 6.5, Glu 1+, Pro ±, Bld 3+, Ket –, Nit –, Leu –, Bil –, Uro ±, Many RBCs, WBC classification <2, CAST neg., E-C neg., Bac. neg., [Peripheral blood] WBC 8,500/μl (Band. +, Seg. 84.5%, Lymph. 12.7%, Mono. 1.6%, Eosino. 0.8%, Baso. 0.4%), RBC 27,900/μl, Hb 7.5 g/dl, Ht 24.3%, Plt 264,000/μl, MCV 87 fl, MCH 26.9 pg, MCHC 30.9 g/dl, Retics 12%, [Coagulation system] APTT 30.3 sec., PT-sec. 14.0 sec., PT-% 51%, PT-INR 1.45, FNG 421 mg/dl, FDP 692 ng/ml, D-dimer 8.3, ESR ≥ 110 mm/h, [Biochemistry] TP 8.0 g/dl, ALB 2.9 g/dl, TC 143 mg/dl, TB 0.8 mg/dl, DB 0.2 mg/dl, Cre 1.1 mg/dl, UA 5.6 mg/dl, Na 135.2 mEq/l, K 3.6 mEq/l, Cl 99 mEq/l, Ca 7.7 mg/dl, LDH 384 IU/l, GOT 36 IU/l, GPT 18 IU/l, Alp 156 IU/l, γ-GTP 17 IU/l, ChE 126 IU/l, Glu 139 mg/dl, CRP 14.30 mg/dl, ferritin 1090 ng/ml, Fe 17 μg/dl, TIBC 171 μg/dl, UIBC 154 μg/dl, measurement of protein demarcation Alb 38.3% ↓, α1 5.3% ↑, α2 12.8% ↑, β 9.4%, γ 34.2% ↑, A/G 0.62 ↓, IgG 1940 mg/dl, IgA 378 mg/dl, IgM 67 mg/dl, C3 74 mg/dl, C4 29 mg/dl, CH50 6.0 U/ml, VB12 1012 pg/ml ↑, FA 7.6 ng/ml, [Tumor markers] CA 19-9 U/ml, CEA 3.2 ng/ml, SCC 1.3 ng/ml, PA 1.8 ng/ml, PAP 0.8 ng/ml, [Others] HbsAg (–), HCV Ab (–), 40-fold positive ANA, Pattern SPE, RF <11, anti-DNA antibody <10.0, MPO-ANCA 1000<, IC-C1q <1.5, IC-C3d 14.5, negative CRYO-G, ASO <53, IGG-RF 0.3, anti-RNP antibody 8.1, anti-SSA antibody 4.8, S.II-2R 1420 U/ml ↑, negative lupus anticoagulant, [Urinary cytodiagnosis] Class II, [Lumbar puncture] Cell count 1, mono 1, poly 0, protein 52 mg/dl, Cl 129 mEq/l, glucose 89 mg/dl, IgG 13.6 mg/dl, negative general bacterial culture, negative tubercle bacillus culture

findings on dermatological examination at the time of admission.

Dr. Nagata: You mentioned that the patient had been diagnosed as having a testicular tumor; was there any enlargement of the testicles at the time of admission?

Dr. Teramoto: No, no testicular enlargement was noticed in the patient at the time of admission.

Dr. Nagata: Will you then please explain the laboratory findings of the patient on admission (Table 1).

Dr. Teramoto: The laboratory findings of this patient on admission were as follows: Stool tested positive (+++) for occult blood. Urinalysis revealed the presence of many red blood cells (RBCs) and less than 2 white blood cells (WBCs) per high power field. There were no casts. Peripheral blood examination revealed a WBC count of 8,500/μl, with marked predominance of neutrophils. The Hb was 7.5 g/dl and the platelet (Plt) count was 264,000/μl. All the values were within normal limits. As for the blood coagulation profile, the activated partial thromboplastin time (APTT) was 30.3 sec., within the normal range.

On the other hand, the serum fibrinogen level was slightly elevated. The serum level of fibrin degradation products (FDP) was also elevated. The serum D-dimer level was elevated to 8.3. The erythrocyte sedimentation rate (ESR) was markedly increased at 110 mm/

h. Blood biochemical examination revealed a slightly decreased serum albumin level. Other tests revealed the following significant findings: the serum ferritin level was increased to 1,090 ng/ml, and the serum Fe concentration was decreased to 17 μg/dl. The serum vitamin B₁₂ (VB12) level was elevated. There was no significant increase in the level of any of the tumor markers. The antinuclear antibody titer was 1:40, with a SPEC pattern, suggesting that it was slightly above the normal range. The serum titer of MPO-ANCA was markedly increased to more than 1:1000. The serum immune complex (IC)-C1q level was less than 1.5, and that of IC-anti-C3d was 14.5, suggestive of a slight increase over the normal range. The serum was negative for cryoglobulins (CRYO-G), as well as for lupus anticoagulant. A lumbar puncture was also conducted, and CSF examination revealed a cell count of 1, which was a mononuclear cell. The protein level was 52 mg/dl, within the normal range. Glucose was also within the normal range. As for culture of the CSF, both cultures for pyogenic organisms and for tubercle bacilli were negative.

Mr. Ito (Y: Yujiro) (6th-grade student): Both the serum albumin and serum cholinesterase levels were decreased. The patient might have had liver dysfunction – is that possible?

Dr. Teramoto: The patient meal intake was very poor because he got extremely tired while eating. So, he was assumed to have had malnutrition.

Ms. Ueda (6th-grade female student): How about the level of BUN?

Dr. Teramoto: It (BUN) was 25.6 mg/dl, slightly high.

Dr. Suwa: Did you conduct testing for HBsAg and hepatitis C virus (HCV) antibody? When was the MPO-ANCA measured?

Dr. Teramoto: Yes, we did the tests for HBsAg and HCV antibody – both were negative. The MPO-ANCA was measured soon after the patient's condition suddenly deteriorated early in the following year. The results were obtained around mid-January.

Dr. Nagata: You mentioned that the ESR was high on admission. It was markedly elevated, wasn't it?

Dr. Shibata (Pathology): Was the serum titer of anti-basement membrane antibody measured?

Dr. Teramoto: No, it was not measured at the time of admission.

Mr. Ito (Y.): Examination of the cerebrospinal fluid (CSF) revealed an increase in the IgG level. What do you think of that?

Dr. Abe (Internal Medicine): The normal level of IgG in the CSF is approximately 5–6 mg/dl. Based on this, the IgG level in this patient can be considered as being elevated. In the presence of infections, for instance, including meningitis, the CSF IgG level is

increased. As for other diseases, it may occasionally be elevated in cases of autoimmune angiitis, systemic lupus erythematosus (SLE) and central nervous system (CNS) lupus, which are all collagen vascular diseases, and in multiple sclerosis (MS), a disease of the CNS. Since there was no increase in the CSF cell count, the increased IgG level may have reflected an autoimmune pathological condition.

Dr. Teramoto: Let me now explain to you the X-ray findings in this patient. A chest X-ray revealed no abnormal findings, including no evidence of pneumonia. No cardiomegaly was noted either. This is an X-ray taken on December 23, 2000, the day after his admission to the hospital. This X-ray was taken on February 5, 2001, just before the patient died. It shows haziness of both lung fields. Since bloody sputum was aspirated from the endotracheal tube, the haziness of the lung fields was attributed to pulmonary hemorrhage.

This is an X-ray of the abdomen taken in the prone position. It revealed a slight increase in the large intestinal gas shadow, but there were no other findings, such as an increase in the small intestinal gas shadow, which would have been indicative of ileus.

Dr. Nagata: Dr. Abe, could you comment on the findings on magnetic resonance imaging (MRI) of the head of this patient?

Dr. Abe: The patient had consciousness disturbance and pyrexia of at least 38°C. There seems to have been no distinct focal neurological deficit, but the patient did have mild nuchal rigidity. He was suspected of having an inflammatory lesion of the CNS, and a lumbar puncture was conducted. No increase in the CSF cell count was found. Therefore, MRI was conducted to exclude inflammatory or space-occupying lesions in the head.

No space-occupying lesion is observed in any of the images. Diffuse cerebral atrophy is observed, but there is no distinct diagnostic pattern that would allow precise determination of the cause of dementia on this image, and the atrophy is not localized, which is a typical finding in Alzheimer's disease or Pick's disease. Coronal sections were also obtained, but no definite lesions were identified.

Dr. Teramoto: These are computed tomographic (CT) images of the abdomen, showing a transverse section across the epigastric region of the abdomen. Mild pleural effusion is observed bilaterally. Other findings include the presence of ascitic fluid around Gerota's fascia anterior to the kidney. Since ascitic fluid has more or less the same CT density as blood, hemorrhage cannot be ruled out. A left renal cyst is also present. The CT revealed no evidence of massive hemorrhage, as a particular cause of the anemia.

Dr. Nagata: So, there were no specific imaging findings that might help us to make a diagnosis; no space-

occupying lesions and no signs of chronic inflammation. Right?

Dr. Teramoto: Yes.

Dr. Nagata: Here was a patient who was a 73-year-old man – a man of fairly advanced age. What was the general clinical course of this patient?

Mr. Ito (C: Chihiro) (6th-grade student): From the findings, the course may be assumed to be subacute.

Dr. Nagata: There was a relatively distinct onset of symptoms on October 31, 2000, and the patient died in February, 2001. The patient was of fairly advanced age, and his overall clinical course was subacute in nature, although after admission, he appears to have had a rather fulminant course. The patient was referred to the Department of Internal Medicine on December 28, 2000, after which his general condition rapidly deteriorated. The physician-in-charge may have administered symptomatic therapy for this patient.

What was the differential diagnosis considered at the Department of Internal Medicine? What were the distinctive clinical features of the patient?

Mr. Ito (C:): The patient had a history of arthralgia, low grade fever, generalized malaise, persistent fever of unknown cause, consciousness disturbance, and his stool was positive for occult blood.

Dr. Nagata: The clinical presentation was characterized by nonspecific systemic symptoms of a subacute nature, but eventually the patient followed a fulminant clinical course. What were the positive signs? What were the positive findings on laboratory examination and the condition on admission?

Mr. Inoue (6th-grade student): Laboratory findings indicated the presence of anemia, and the patient had mild consciousness disturbance, and mild hypertension.

Dr. Nagata: The clinical features were not so distinctive on admission, but after admission, the patient developed severe resistant hypertension.

Mr. Inoue: Stool occult blood was positive, and urinalysis also revealed the presence of occult blood and RBC.

Dr. Nagata: Urinalysis revealed not only an occult blood reaction of the urine, but also RBC on microscopic examination. Microscopic hematuria is a significant finding. Microscopic hematuria may occasionally be observed even in healthy women, but in male patients, hematuria is an important morbid finding. The balloon of self-retaining catheters can damage the tissue of the urinary bladder. Can this possibility be considered in this patient? Was hematuria persistent?

Dr. Teramoto: The hematuria was persistent from the time of admission.

Dr. Nagata: There was microscopic but no macroscopic hematuria. Right?

Dr. Teramoto: Gross hematuria was not observed in this patient until the terminal stage.

Dr. Nagata: You mean hematuria was detected consistently whenever urinalysis was conducted?

Dr. Teramoto: Yes. The hematuria was not attributed to trauma associated with insertion of the self-retaining balloon catheter in the bladder.

Mr. Inoue: Urinalysis revealed \pm urinary protein. Peripheral blood examination revealed a mean corpuscular volume (MCV) indicative of normocytic normochromic anemia. The serum FDP was elevated, indicating activation of the fibrinolytic system.

Dr. Nagata: Did the patient have eosinophilia, Dr. Teramoto?

Dr. Teramoto: The patient never had eosinophilia.

Dr. Nagata: Was the serum IgE measured?

Dr. Teramoto: No.

Dr. Nagata: How about other significant findings in the patient?

Mr. Inoue: There was elevation in the serum levels of inflammatory markers, including an elevated ESR and increase in the serum CRP level to 14.3 mg/dl.

Dr. Nagata: These are remarkable abnormal findings. The ESR was as high as 110 mm in the first hour.

Mr. Inoue: The serum albumin and serum cholinesterase levels were decreased.

Dr. Nagata: These findings may be reflective of malnutrition.

Mr. Inoue: The serum iron level was low, while the serum ferritin level was high. The total iron-binding capacity (TIBC) and the unsaturated iron-binding capacity (UIBC) were slightly low. These findings may be suggestive of chronic inflammation. Other laboratory findings included an increase of the serum level of IgG, decrease of the 50% hemolytic unit of complement (CH50), and increase of the serum level of VB12. In addition, MPO-ANCA (P-A NCA was positive (+), although this was not detected immediately after admission. These are all the significant findings in this patient, I suppose.

Dr. Nagata: Is the MPO-ANCA titer slightly high or very high?

Dr. Teramoto: It is very high.

Dr. Nagata: It is very difficult to make a diagnosis in this patient, isn't it? Such diverse clinical features and abnormal laboratory findings are observed. It is difficult to determine which features might be relevant and which can be ignored while making a diagnosis. At the time when the patient was referred to the Department of Internal Medicine, I suppose Dr. Teramoto thought that the patient had a disease falling under the category of internal medicine rather than psychiatry. Positive findings, from which the presence of an organic disease can be distinctly suspected, namely, pyrexia and weight loss, were also present. Should the differential diagnosis include malignant tumor, collagen vascular diseases, and infections? Many of the symptoms and findings

observed in this patient may occur in malignant tumors, collagen vascular diseases, as well as infections. Thus, it is impossible to make a precise diagnosis based on the clinical findings alone.

Shall we now discuss the differential diagnosis of this patient?

Dr. Teramoto: Gastroscopy and computed tomography (CT), conducted as screening tests for malignant tumors, did not indicate the presence of any malignant tumor.

Dr. Nagata: So, screening of the whole body by diagnostic imaging and endoscopy revealed no tumor or tumor-like lesions. We are conducting a diagnosis of exclusion. How about infectious diseases?

Dr. Teramoto: The presence of an infectious disease was repeatedly examined for by chest roentgenography and bacterial culture.

Dr. Nagata: Do you mean that there was no positive evidence of infection as determined by bacterial on cultures?

Dr. Teramoto: Yes, the bacterial cultures were all negative.

Dr. Nagata: Then, the CSF and urine were examined. Was any inflammatory mass found on CT?

Dr. Teramoto: No, no inflammatory mass was found.

Dr. Nagata: At this time-point, consciousness disturbance was a prominent clinical feature. Clouding of consciousness was observed, with a JCS score of I-3.

Dr. Teramoto: This score corresponds to the stage at which simple responses to questions are possible.

Dr. Nagata: The vaccination against influenza weighs on my mind here. Generally, this patient had no focal neurological deficit, but he had disturbance of consciousness. Dr. Abe, what diagnoses would you consider in such a case? Would you comment on whether or not the patient had any neurological disease?

Dr. Abe: Since the patient's speech could not be understood by others, it was very difficult to evaluate the neurological findings. However, the patient's eyes were open, and there were no laterality in spontaneous movements.

The mild nuchal rigidity may also be attributable to poor general condition and contracture. Disturbance of consciousness without any focal neurological deficit indicates diffuse disturbance of cerebral function, but it can occur from various causes. The differential diagnosis in this patient was as follows: Meningoencephalitis; slow virus infection, such as Creutzfeldt-Jakob disease (CJD), and ADEM, when the subacute course is taken into consideration; The other diagnoses that must be considered include metabolic diseases, such as pulmonary encephalopathy, hypoxic encephalopathy, hepatic encephalopathy, uremia, Wernicke encephalopathy, and avitaminoses, e.g., pellagra, electrolyte imbalances, including hyponatremia, hypernatremia, and hyper-

calcemia, systemic diseases such as collagen vascular diseases, vasculitis, and epilepsy.

There was some reference to malignancy. Limbic encephalopathy as a remote association may be enumerated as a differential diagnosis in this context. Examination conducted at our department ruled out meningoencephalitis and ADEM.

In this context, one patient who developed ADEM following prophylactic vaccination against influenza has been reported.

Dr. Nagata: Could it be possible that the patient had Guillain-Barré syndrome after the vaccination?

Dr. Abe: Yes, Guillain-Barré syndrome-like symptoms were present and the diagnosis could be considered, however, the patient also had disturbance of consciousness, which is rather suggestive of a central nervous system disorder rather than peripheral neuropathy.

Dr. Nagata: This syndrome can hardly be considered in this patient, because motor neuropathy was absent.

Dr. Abe: This syndrome must be suspected if decreased muscle strength of all the four extremities occurs acutely. Central neuropathy indicates the presence of ADEM, or infection may also have been caused by prophylactic vaccination, although the probability (for infection to be caused by vaccination) is considerably low. In any event, while it is very rare for infections to be related to prophylactic vaccination, the possibility was entirely ruled out by laboratory examination. Slow virus infection can hardly be considered in the differential diagnosis, and hepatic encephalopathy and pulmonary encephalopathy may be ruled out by the absence of any abnormal laboratory findings.

Dr. Nagata: Since uremia was absent before admission, it is ruled out as the cause of the consciousness disturbance in this patient. Vasculitis may still account for the patient's condition. The possibility of malignant tumor associated with the paraneoplastic syndrome is low, isn't it? ADEM was suspected, but it was ruled out by imaging. The vaccination against influenza can hardly be regarded as being related to the patient's condition, right?

Ms. Ueda: While it remains unclear if the consciousness disturbance can be correlated with the other symptoms, which included pyrexia and general malaise, and with the laboratory findings, based on the laboratory findings and diagnostic findings, I consider vasculitis to be one of the differential diagnoses, based on the presence of chronic inflammatory markers, anemia, and elevated MPO-ANCA titers. Among these, drug-induced vasculitis, e.g., microscopic polyangiitis (MPN) and Churg-Strauss syndrome, must be strongly considered in the differential diagnosis.

Dr. Nagata: You consider the possibility of vasculitis caused by drugs. That is why you asked about the

details of the treatment received by this patient, is that right?

Ms. Ueda: Yes.

Dr. Nagata: Mr. Iguchi, what made you wonder about the presence or absence of purpura?

Mr. Iguchi: I suspected vasculitis too.

Dr. Nagata: Henoch-Schönlein purpura may also be suspected.

Mr. Iguchi: Since weight loss and purpura are included in the diagnostic criteria of vasculitis, I assumed that the presence of these symptoms may be useful pointers for making a diagnosis.

Dr. Nagata: In the present patient, it would appear that it would have been terribly difficult to make a definitive diagnosis early after admission. Many differential diseases were enumerated, but the decisive diagnostic factor was considered to be the elevated titer of MPO-ANCA. Perhaps, Dr. Teramoto also thought so, and he may have considered vasculitis syndrome as a disease associated with positivity for MPO-ANCA. Now, among the diseases enumerated, Mr. Inoue, which do you think would be characterized by positivity for ANCA (Table 2) in vasculitis syndrome (Table 3)?

Mr. Inoue: I considered MPN. Positivity for MPO-ANCA is associated with MPN. It has been believed that the antibody is rarely present in classic cases of PN.

Dr. Nagata: Wegener's granulomatosis may be characterized by a positive test for ANCA?

Table 2 ANCA-associated Small-vessel Vasculitis

Wegener's granulomatosis
Microscopic polyangiitis
Churg-Strauss syndrome
Pauci-immune renal-limited glomerulonephritis

Table 3 Vasculitis Syndromes

I. Systemic necrotizing vasculitis
A. Polyarteritis nodosa (PAN)
1. Classical PAN
2. Microscopic polyangiitis
B. Allergic angitis and granulomatosis of Churg-Strauss
C. Polyangiitis overlap syndrome
II. Wegener's granulomatosis
III. Temporal arteritis
IV. Takayasu's arteritis
V. Henoch-Schölein purpura
VI. Predominantly cutaneous vasculitis (hypersensitivity vasculitis)
A. Exogenous stimuli proven or suspected
1. Drug-induced vasculitis
2. Serum sickness and serum-sickness-like reactions
3. Vasculitis associated with infectious diseases
B. Endogenous antigens likely involved
VII. Other vasculitis syndromes

Mr. Inoue: No. This is a weak possibility, because Wegener's granulomatosis is characterized by CANCA positivity.

Dr. Nagata: How about other types of vasculitis?

Ms. Ueda: In Churg-Strauss syndrome, the number of eosinophils is usually believed to be increased. This condition does not seem to match with the patient's condition, because no eosinophilia or asthmatic symptoms were observed.

As for the drug-induced types of vasculitis, the drugs commonly known to cause this syndrome are propylthiouracil and hydralazine (hydrochloride). Since the patient had no past history of medication with these drugs, this type of vasculitis was excluded from the diagnosis.

Dr. Nagata: Is it impossible to include Henoch-Schönlein purpura in the differential diagnosis?

Mr. Inokuchi: Henoch-Schönlein purpura was included in the differential diagnosis. However, since the serum test for MPO-ANCA was positive, we more strongly considered the other two diseases mentioned above, MPN and Churg-Strauss syndrome, in the differential diagnosis.

Dr. Nagata: You mean that classical PN need not be considered in the differential diagnosis because the patient with classical MPN was MPO-ANCA positive?

Mr. Inokuchi: Yes. As MPO-ANCA is positive, classical PN is not included in the differential diagnosis. Moreover, MPN rather than Churg-Strauss Syndrome is assumed to be more consistent with the absence of asthmatic symptoms and eosinophilia in this patient.

Dr. Nagata: This 73-year-old man who had a subacute-fulminant course also had anemia and hypertension. Is this consistent with the diagnosis of MPN?

Mr. Inokuchi: Hypertension is caused by acute progressive glomerulonephritis (GN) associated with MPN. MPN may also lead to gastrointestinal hemorrhage, which could explain the occult blood positivity of the stools. Hematuria may also be associated with nephropathy in cases of MPN.

Dr. Nagata: Hematuria may be an important feature for making a diagnosis in this patient. Hematuria is associated with GN.

Mr. Inokuchi: How about a renal biopsy in this patient? Was it conducted?

Dr. Nagata: Dr. Teramoto, please explain the diagnostic approach and the treatment administered to this patient, including the indications for renal biopsy.

Dr. Teramoto: Yes, I shall explain the course of the patient post-admission.

After the patient was referred to the Department of Gastroenterology, the pyrexia persisted and the hypertension became severe and resistant to treatment. To determine the cause of the fever of unknown origin and the consciousness disturbance, the patient was exam-

ined by both a rheumatologist and a neurologist. On January 2, the patient developed airway obstruction because of secretions, and developed cardiorespiratory arrest. A renal biopsy could not be performed because of the poor general condition of the patient. There were no particular regions of angiitis that could be biopsied. As for confirmation of the diagnosis of vasculitis, the patient was already intubated by the time this diagnosis was considered, because the patient was found to be positive for MPO-ANCA in early or mid-January. The general condition of the patient did not permit any invasive examination.

Dr. Nagata: If either of the testes had been enlarged, it could have been biopsied. If skin rash had been present, a skin biopsy might have been performed. However, neither was observed, and the patient's general condition did not allow any invasive examination to confirm the diagnosis of vasculitis.

Then, Dr. Suwa, could you comment on the important clinical signs in this case, the diagnostic approach employed, and the treatment options?

Dr. Suwa: It was very difficult to make a diagnosis in this patient. Treatment was also difficult and the clinical course took an acute turn, resulting in death.

The most remarkable abnormalities in this patient, observed before he developed terminal respiratory and circulatory failure, included pyrexia, neuropathy, hypertension, anemia, nephropathy (hematuria), high levels of inflammatory markers (ESR 110 mm/h, CRP 14.30 mg/dl), hyper γ -globulinemia, and high serum titers of MPO-ANCA. A particularly noteworthy finding useful for making a precise diagnosis was the elevated serum MPO-ANCA titer to as high as 1,000 EU. The past history of arthralgia, myalgia, and testicular tumor must also be considered. The most probable differential diagnostic possibility that can one-dimensionally explain the complicated morbid condition of the patient is MPO-ANCA-associated vasculitis. Histopathological evidence of vasculitis would have confirmed the diagnosis of microscopic polyangitis. However, in the absence of evidence of MPN, the patient's condition may be diagnosed as ANCA-associated vasculitis, including the pulmonary-renal syndrome that leads to pulmonary hemorrhage and acute progressive GN.

An interesting issue that must be considered at this point is the relationship between drugs and infections. For instance, some reports have shown that hydralazine administration for hypertension can be associated with positive ANCA positivity, and that proton pump inhibitors, i.e., remedies for peptic ulcers, may conversely induce gastrointestinal hemorrhage. In the present case, however, the condition was not assumed to be drug-related. Some studies have shown that MPO-ANCA is produced in some cases of infections, e.g., hemolytic

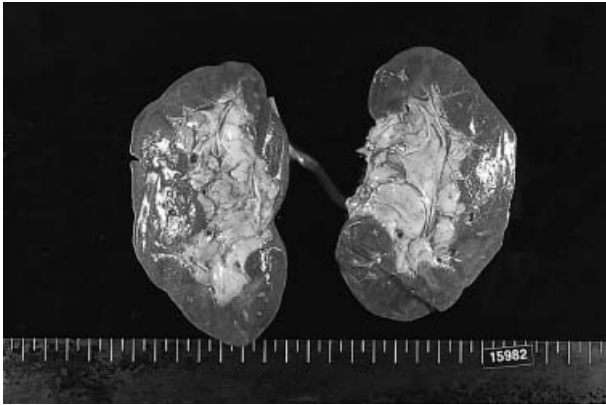


Fig. 1 Kidney. Macroscopic findings (A cut was made at the hilum of the kidney). It is deeply red on the whole.

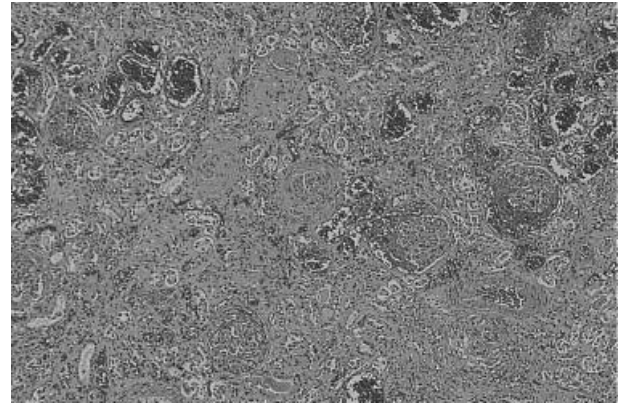


Fig. 2 Kidney. A low magnification view. Mostly normal glomeruli are also present, but crescent-forming glomeruli and hyalinized glomeruli are remarkable.

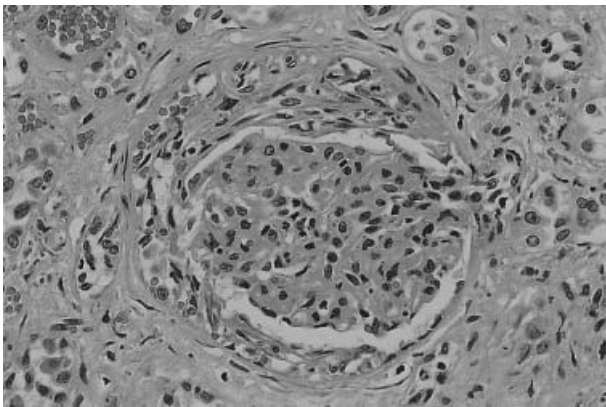


Fig. 3 A magnified view of the glomeruli. Crescent formation is observed.

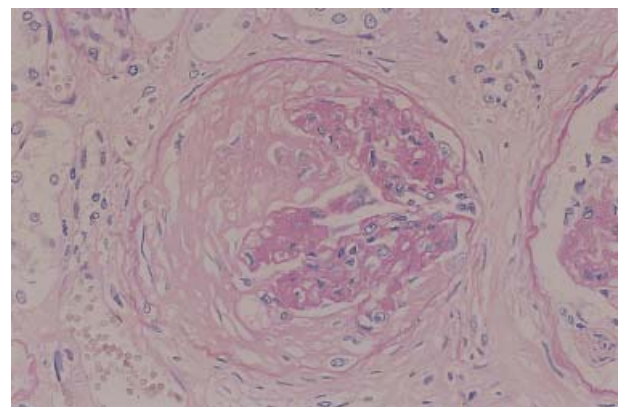


Fig. 4 PAS staining of the kidney. Crescents formed along the Bowman's capsule stain pink and become distinct.

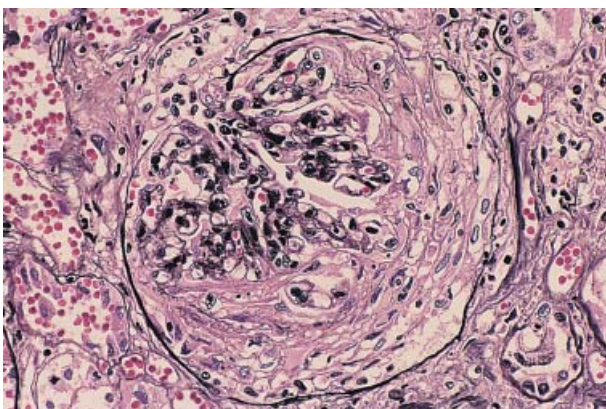


Fig. 5 PAM staining of the kidney. There is no marked change in the basement membrane of the glomerular capillaries.

streptococcal infection, GN, and subacute endocarditis, to induce vasculitis. We have also encountered a patient in whom the MPO-ANCA titer increased after the occurrence of hemolytic streptococcal infection and the patient went on to have ANCA-associated vasculitis. In the present patient, it is also possible that the vaccination against influenza caused some kind of imbalance of cytokines, followed by a series of morbid events.

Dr. Nagata: What was the direct cause of death, Mr. Chihiro Ito?

Mr. Ito (C.): The direct cause of death was assumed to be renal failure or pulmonary hemorrhage.

Dr. Nagata: Pneumonia was also suspected from the radiographs. Was there an acute process that led to death?

Dr. Teramoto: Two or three days before his death, the patient started having bloody sputum, and progressive deterioration of his respiratory status. Thus, pulmonary hemorrhage was assumed to have occurred about two days prior to the patient's death.

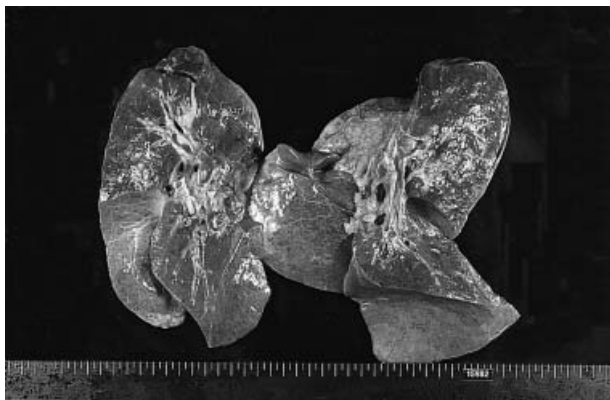


Fig. 6 Lung. Macroscopic findings (A cut was made at the hilum of the lung). The cut surface shows dark red.

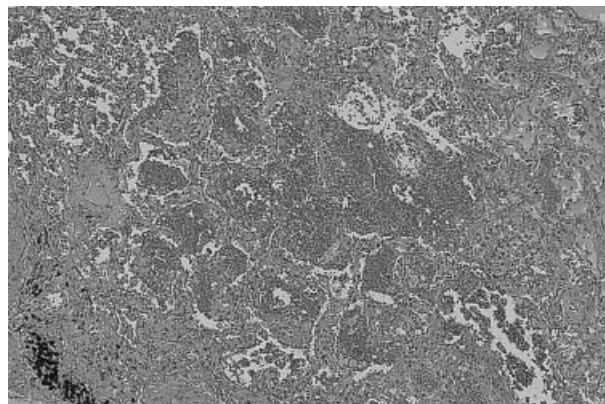


Fig. 7 Lung. A low magnification view. Alveolar hemorrhage is generally remarkable.

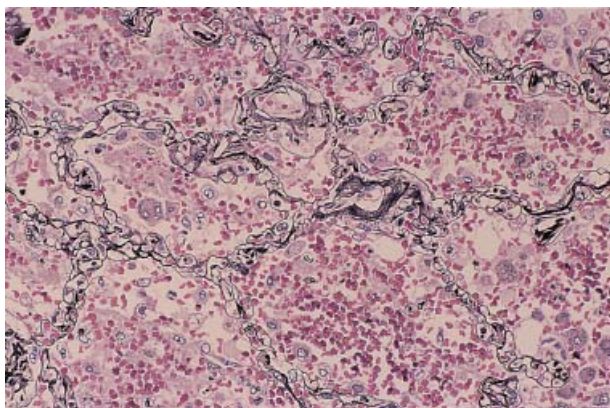


Fig. 8 PAM staining of the lung. There is no marked change in basement membrane of the pulmonary capillaries.

Dr. Nagata: Could you explain the histopathological findings of this patient, Dr. Shibata?

Dr. Shibata: As we have just heard, various differential diagnostic possibilities were considered clinically in this patient. From the histopathological standpoint as well, MPN was considered as the first possibility, based on the patient's clinical course. However, a detailed systemic histopathological screening did not reveal any evidence of vasculitis. (Fig. 1)

Autopsy findings of the kidney are shown first. This is a cut section of the kidney at the level of the hilum. Macroscopically, the kidney appears slightly enlarged, with a slightly congested appearance. (Fig. 2)

This is a low-magnification view of the kidney. It shows marked congestion. Most of the glomeruli observed show hyalinization, and crescent formation can also be visualized. These findings indicate a generally damaged kidney. (Fig. 3)

This is a highly magnified view of the glomeruli. So-called crescent formation is observed with abundant cellular components adhering to the wall of Bowman's

capsule. Crescent formation is seen in approximately 80% of all the glomeruli. (Fig. 4)

This is a slide showing the periodic acid Schiff (PAS) staining reaction. Crescents are seen along the wall of Bowman's capsule. In this region, the nuclei are mostly lost, and a fibrous crescent is formed. (Fig. 5)

This is a slide showing the periodic acid methenamine silver (PAM) staining reaction. Crescents are seen along Bowman's capsule. PAM staining is very useful for examining whether or not some deposits are present in the basement membrane. PAM staining did not reveal thickening of the basement membrane of the capillary vessels, duplication of the basement membrane, or any deposits on the basement membrane.

As we have seen, crescentic GN was present in the kidney, but there was no evidence of vasculitis. No deposits were confirmed on the glomerular basement membrane, either. We investigated whether or not immune complexes were present, although the data are not shown in this presentation. There was no immune complex deposition along the basement membrane. (Fig. 6)

These are the autopsy findings of the lungs. Here is the hilum of the left lung, along which a transverse section was cut, and here is the right lung. The whole lung looks red. Alveolar hemorrhage and congestion and/or edema were clearly observed in the upper lobe. (Fig. 7)

This is a low-magnification view of the lung. In regard to the alveolar structure, they usually appear clear because of intra-alveolar air. Unlike the normal structures, hemorrhage is widely observed in the alveoli and there is no space for air. (Fig. 8)

Since the patient had alveolar hemorrhage, we looked for the presence or absence of vasculitis-like changes. This is a slide stained with PAM, showing alveolar capillaries. In the presence of vasculitis, the basement membrane of the alveolar wall capillaries

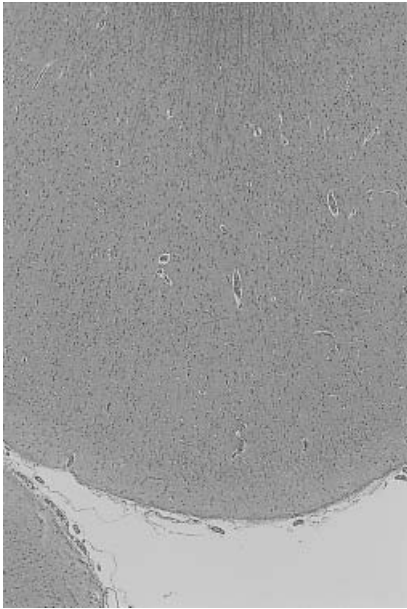


Fig. 9 A low magnification view of normal cerebral cortex.

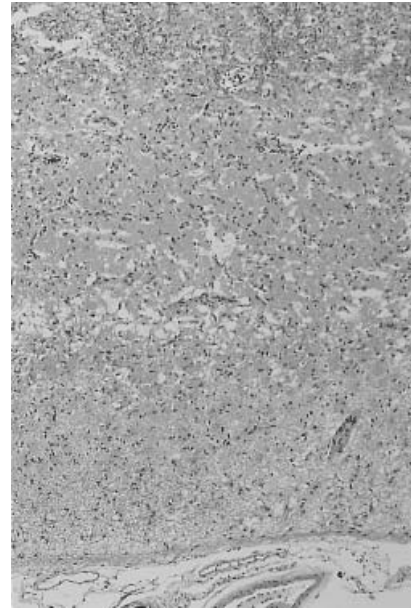


Fig. 10 A low magnification view of the cerebral cortex of this patient. The regions corresponding to 3–5 layers of cerebral nerve cells show coagulative necrosis.

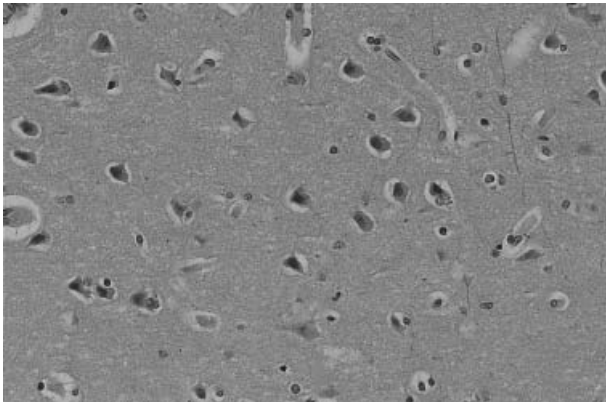


Fig. 11 A high magnification view of normal cerebral cortex. Nerve cells are present.

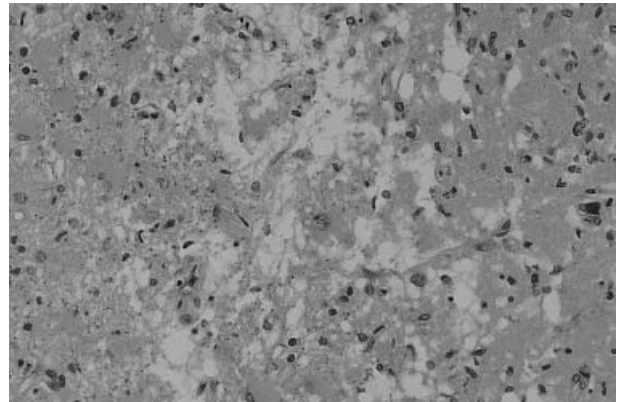


Fig. 12 A high magnification view of the cerebral cortex of this patient. Deficits of medium to large nerve cells are observed.

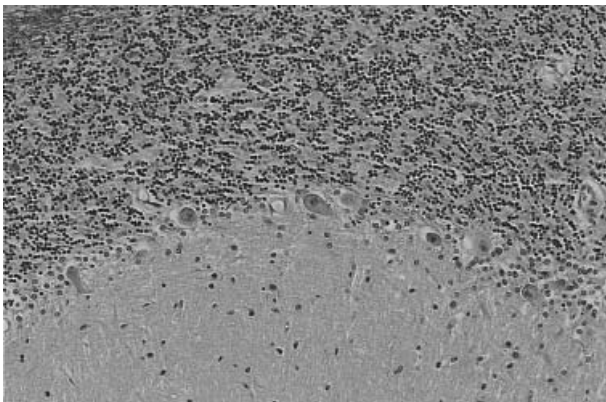


Fig. 13 Normal cerebellum. Purkinje cells are present in areas bordering the molecular layer and granular layer.

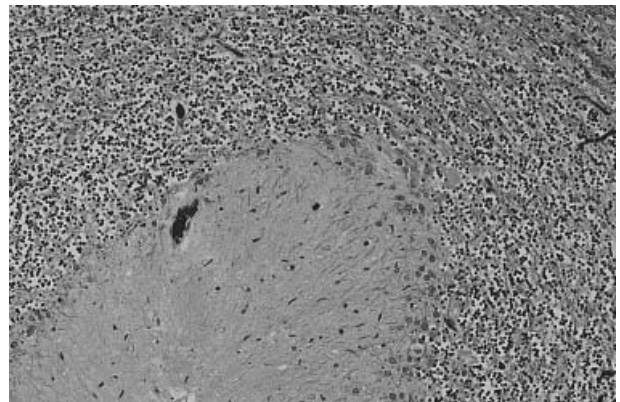


Fig. 14 The cerebellum of this patient. Deficits of Purkinje cells are observed.

Table 4 Glomerular Diseases That Clinically Show Findings of Acute Progressive GN and Histologically Accompany Crescent Formation

1. Primary glomerular disease (crescent-forming nephritis)
Type I: Anti-GBM disease [pulmonary hemorrhage (–)]
Type II: Immune complex type [anti-GBM (–), ANCA (–)]
Type III: Pauci-immune type [ANCA (+)]
2. Conditions accompanying systemic diseases
General vasculitis
Microscopic polyangiitis [ANCA (+)]
Wegener's granulomatosis [ANCA (+)]
Churg-Strauss syndrome [ANCA (+)]
Goodpasture disease [anti-GBM (+), pulmonary hemorrhage (+)]
SLE
Henoch-Schönlein purpura
3. Diseases accompanying infections
Acute poststreptococcal GN
Infective endocarditis
MRSA-related nephritis

often show distinct rupture or tears, but the alveolar structures and the structure of the basement membrane of the alveolar capillaries is maintained. Thus, no evidence of vasculitis was confirmed in the lungs either. (Fig. 9)

These are the findings of the brain. This is the surface of a normal cerebrum, which is densely packed with nerve fibers and (nerve) cells. (Fig. 10)

This is an image showing some vacuolar layers that are present in the brain, as compared with the dense packing with nerve fibers and cells mentioned above. (Fig. 11)

This is a magnified view of the normal cerebral cortex. Many pyramidal nerve cells are present, and there are no vacuolar spaces. (Fig. 12)

In this patient, nerve cells are severely degenerated. Histopathological examination revealed the presence of laminar cortical necrosis, in which the cerebral cortex is partially destroyed by coagulative necrosis. This finding may be associated with the ischemic changes that might have occurred when the patient had cardiopulmonary arrest one month before his death. (Fig. 13)

This is the normal cerebellum, showing round Purkinje cells in areas bordering the granular layer and the molecular layer. (Fig. 14)

In this patient, no Purkinje cells were present in the boundary between the layers. This is also a change that might be associated with ischemia caused by the cardiopulmonary arrest that occurred approximately one month before the patient's death.

Only ischemic changes could be confirmed on autopsy of the brain. That is as far as the tissue slides are concerned. (Table 4)

For cases of acute progressive GN, histopathologically characterized by crescent formation, three main

etiological possibilities are considered; primary glomerular disease, changes associated with systemic diseases, and changes associated with infectious diseases.

Primary glomerular disease is mainly classified into three types, type I with anti-basement membrane antibody, type II caused by immune complex deposition, and type III which is positive for ANCA and has no relation to immunoglobulin at all. Types I and II were ruled out in this case, because precipitation of immunoglobulins could not be confirmed at all in any tissue examined. The possibility of crescent-forming nephritis associated with ANCA positivity was therefore considered.

Crescentic GN is known to be associated with some systemic diseases. In connection with Goodpasture's syndrome, however, no evidence of vasculitis was observed in any tissue. As for the diagnosis of Wegener's granulomatosis, no granulomas could be confirmed. In relation to Churg-Strauss syndrome, granulomatous vasculitis could not be confirmed. Anti-basement membrane antibody was not detected in the serum. These diseases are therefore ruled out, because they are hardly supported by the histological and clinical findings.

In relation to infectious diseases, GN following hemolytic streptococcal infection, infectious endocarditis, and methicillin-resistant *Staphylococcus aureus* (MRSA)-related nephritis is associated with crescent formation. However, these conditions were ruled out based on the clinical features.

So, the etiological diseases were, thus, the case was histopathologically diagnosed as a case of primary glomerular disease with crescent-forming MPO-ANCA-associated nephritis not related to immunoglobulin.

With that, I end my presentation.

Dr. Nagata: Thank you, Dr. Shibata.

Dr. Suwa: The present patient had severe anemia, with a Hb level of 7.3 g/dl, and the stool was positive (+++) for occult blood. From these findings, gastrointestinal hemorrhage was suspected. Was there any gastrointestinal lesion observed histopathologically that would warrant a special mention?

Dr. Shibata: There were no lesions that could lead to gastrointestinal hemorrhage.

Dr. Kimura (Pathology): Is MPO-ANCA a pathogenic antibody, or an antibody that is merely elevated in patients with the disease?

Dr. Suwa: I shall talk a little more about ANCA first. ANCA, i.e., anti-neutrophil cytoplasm antibody, is briefly classified into P-ANCA and C-ANCA, according to the pattern of staining of the cytoplasm. The main antigen for P-ANCA, also abbreviated as MPO-ANCA, has been found to be myeloperoxidase. The corresponding antigen for C-ANCA, also abbreviated as PR 3-ANCA, observed in cases of Wegener's gran-

ulomatosis is proteinase 3. As for the etiological significance of MPO-ANCA, MPO-ANCA is produced by immunization or (external) injection of antibodies to secondarily induce vasculitis in animal experiments. These experiments are based on the following hypothesis: neutrophils and endothelial cells, which are activated by inflammatory cytokines, adhere to each other; ANCA acts on the adhering cells to release MPO and PR 3 granules, which cause histological changes. This hypothesis is called the "ANCA cytokine sequence theory". Furthermore, from the fact that the ANCA titer varies in parallel with the clinical disease activity,

it is assumed that ANCA may directly participate in tissue damage in a way similar to anti-DNA antibodies and anti-phospholipid antibodies in SLE. Thus, strong etiological significance is attached to ANCA, but further study is required.

Mr. Iguchi: I wonder why the reticulocyte count was not increased despite the presence of severe anemia. What were the bone marrow findings?

Dr. Shibata: The bone marrow showed slight hypoplasia at autopsy, but there were no distinctive findings.

Dr. Nagata: I shall now declare the CPC closed. Thank you very much for your participation.