CLINICO-PATHOLOGICAL CONFERENCE

IgD myeloma with systemic amyloidosis with chest discomfort as an initial symptom

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Abstract. A 53-year-old man was admitted to Keio University Hospital because of serious dyspnea and edema of the lower extremities. Eighteen months previously, the patient had complained of chest discomfort, and was then admitted for the first time to our hospital for evaluation of chest pain. Electrocardiography showed poor R wave progression in leads Vl through V4, and diffuse nonspecific ST-segment and T wave abnormalities with low voltage. However, no definitive diagnosis could be made at this initial admission and a calcium-channel blocker was prescribed. Despite this treatment, the patient was readmitted with worsening dyspnea and lower extremity edema. The diagnosis of heart failure and nephritic syndrome was made at the second admission. In addition, immunoelectrophoresis showed a monoclonal IgD (λ) M protein and increased plasma cells in the bone marrow, suggesting a diagnosis of multiple myeloma. The patient was thus given dexamethasone (20 mg per day for 4 days) intravenously, but his symptoms did not improve. Two weeks later, the patient deteriorated further with congestive heart failure and renal failure, and subsequently died of cardiac arrest with ventricular fibrillation. On autopsy, IgD (λ)-positive plasma cell proliferation was found in the bone marrow, confirming the diagnosis of multiple myeloma. In addition, amyloid deposition was detected in various organs including the heart, kidneys, esophagus, duodenum, ileum, colon, tongue, and lungs. In particular, the weight of the heart was 650 g demonstrating a hypertrophic septum and amyloid deposition in the myocardium and even coronary arteries. In summary, the final diagnosis was IgD (λ) multiple myeloma associated with systemic amyloidosis. (Keio J Med 53 (3): 178–191, September 2004)

Key words: multiple myeloma, IgD, amyloidosis, cardiomyopathy, angina

Dr. Kizaki (Moderator): I am going to start the class by introducing Professor Rao. I also have a special guest from the Division of Nephrology, Dr. Kumagai, and two hematologists, Dr. Awaya and Dr. Hattori, from Keio University School of Medicine. They are going to give us some comments. Professor Rao is not at all familiar with today's case, and has none of the details.

The doctor in charge is Dr. Ieda, a cardiologist. Could you please start today's case presentation?

Dr. Ieda (Internal Medicine): This case is a 53-year-old male, whose chief complaints were dyspnea and edema of the lower extremities.

Onset and course: The patient was in his usual state of health until about 18 months prior to the current admission, when he began feeling exertional chest discomfort. Seven months later, he was admitted to our hospital. This was his first admission. The electrocardiogram (ECG) showed poor R wave progression in leads V1 through V3 and diffuse nonspecific ST-segment and T wave abnormalities. We performed coronary angiography during this initial admission, and discovered minimal atherosclerotic disease. Left ventricular function was normal. Examination of the microscopic specimens from a right ventricular endomyocardial biopsy showed only mild edema. The patient was released with inconclusive findings and given a calcium channel blocker, amlodipine, for presumed variant angina, thus concluding his first visit.

Dr. Kizaki: Dr. Ieda has explained the first part

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of this patient's history. Are there any questions so far?

Dr. Rao (Pittsburgh University): I have a question. Please forgive me if this sounds like a criticism, but I am not sure I would have done a coronary angiogram in a patient who presented in this way, with signs of heart failure. I would like to know what the indication was for a coronary angiogram in this patient. That is question number one.

The second question is for the cardiologist. If you are going to do a coronary angiogram in a patient who presents with clear clinical signs of right heart failure, why was just a left heart catheterization done? Why did you not also do a right heart catheterization?

Dr. Ieda: Before his first admission, as an outpatient, we did an exercise stress test using scintigraphy. From this test, we found that he had diffuse cardiac ischemia. His complaint was typical angina, so we performed cardio-angiography.

Dr. Rao: May I ask a follow-up question to that? If you saw generalized ischemia on a nuclear study – that is what you are saying, aren't you? – and he was quite symptomatic, are you sure that he was able to achieve a degree of stress that would adequately test the myocardium? So, if he had a generalized uptake of the radionuclide, could it have been something else? What I am trying to point out is this: when you see global uptake of the radionuclide, it does not necessarily mean that there is generalized ischemia. I do not want the students to infer from your comment that generalized myocardial uptake of radionuclide always implies generalized ischemia. There is another possibility that I am alluding to. If you have not really stressed the heart, you will not be able to identify areas of poor uptake compared to normal uptake. Under those conditions, generalized nuclide uptake really has little or no significance.

Dr. Ieda: We recognized a broad reversible defect on scintigraphy. We thought he had angina involving a broad area, such as left main trunk stenosis or three vessel disease, or cardiomyopathy, like hypertrophic cardiomyopathy (HCM). We thought we had to rule out cardiomyopathy.

Dr. Rao: The suspicion of a cardiomyopathy is exactly why I said I would not have done an angiogram. My first choice for this patient would be an echocardiogram to determine what pattern of cardiomyopathy is present: is it dilated, restrictive, or hypertrophic obstructive? Only if the echo shows that he has dilated cardiomyopathy, would I proceed to a coronary angiogram. On the other hand, if the patient turns out to have restrictive cardiomyopathy, I would want to do a double catheterization, *i.e.*, both right and left heart catheterization. Lastly, if the patient has hypertrophic cardiomyopathy, then I would do a left heart catheterization, with particular attention to the outflow tract of the left ventricle. So, I think it is essential to first get an echocardiogram in order to make the correct decision regarding heart catheterization.

Dr. Ieda: Before this admission, we did also get an echocardiogram. I will show you the data.

Dr. Rao: So that was done! Until this moment, no one said that an echocardiogram had been obtained.

Dr. Kizaki: At this stage, a 53-year-old man was admitted to our hospital because of chest discomfort. The cardiologist did several examinations: an echocardiogram (ECG), and so on. The tentative diagnosis is angina with inconclusive findings, and the patient is given a calcium blocker. In this early period, what is the diagnosis of this patient?

Ms. Ono (5th-year student): These findings are suggestive of cardiomyopathy and variant angina. Infection is one of the causes of cardiomyopathy; therefore, we would like to know whether or not he had an infection.

Mr. Oyanagi (5th-year student): I thought the diagnosis was cardiomyopathy.

Dr. Kizaki: At this time, we had relatively few examinations. We had only ECGs, chest X-rays and echocardiograms.

Dr. Ieda: This figure shows the first ECG and chest X-ray on the first admission (Fig. 1). The left panel shows the ECG, as you can see. On the right side, you can see from V1 toV3, the poor R wave progression and diffuse nonspecific ST changes. The right panel is the chest X-ray, showing only mild cardiac hypertrophy and no pulmonary congestion or effusion.

This is the parasternal view of the long axis and this is a color Doppler image. As you can see, there is mild mitral valve regurgitation. Here is the left atrium and left ventricle; here the aorta and right ventricle.

This is the short axis in the parasternal view. As you can see, this is the left ventricle and here's the right heart. There is only mild concentric hypertrophy but left ventricular wall motion is normal. This provides a four chamber-view from the apex.

Dr. Rao: Do you have an E to A measurement from the echo?

Dr. Ieda: Yes, we do.

Dr. Rao: And what was the left ventricle wall thickness?

Dr. Ieda: The left ventricular septum was 1.2 cm, and the posterior wall was also 1.2 cm.

Dr. Rao: And what about E to A? In other words, early vs late diastolic wall motion?

Dr. Ieda: E was 113 and A was 56. Dct was 192 msec.

Dr. Kizaki: What did you conclude from these findings?

Dr. Ieda: From this echocardiogram, we recognized only mild MR due to thick MV leaflets and mild con-

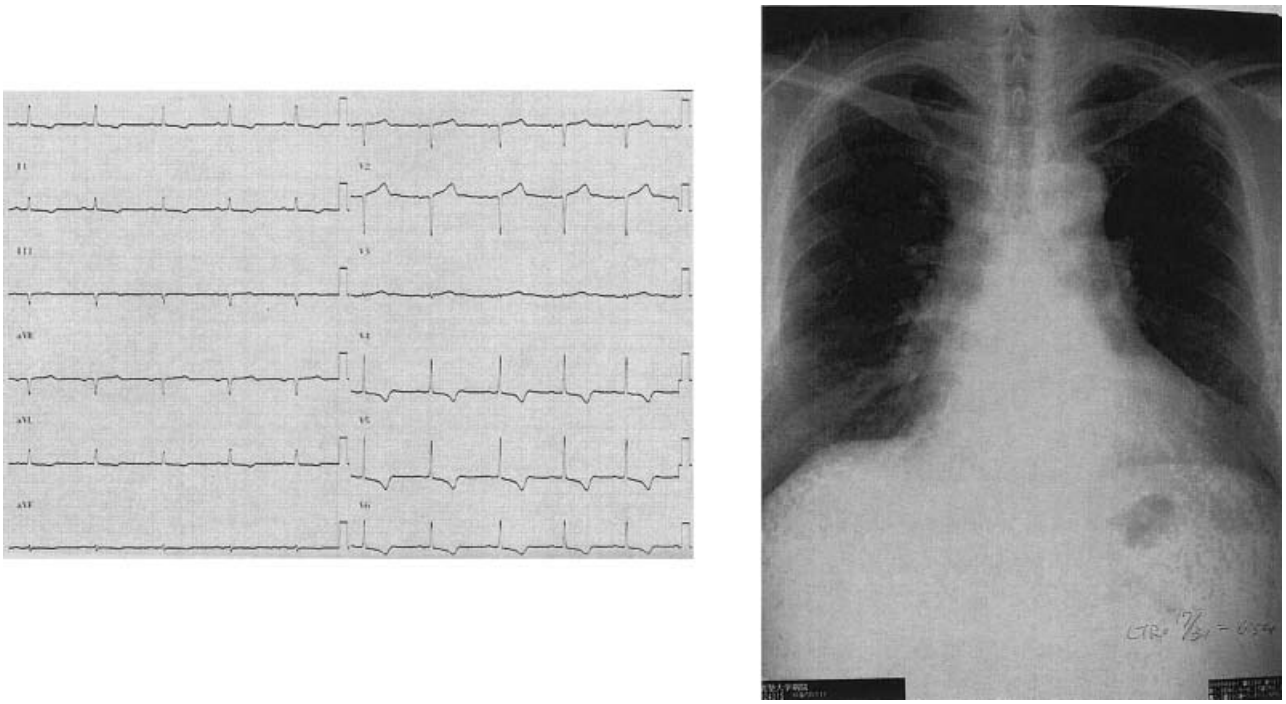


Fig. 1 The ECG and chest radiography at the 1st admission. The ECG showed poor R wave progression in leads V1 through V3, and diffuse nonspecific ST-segment and T wave abnormalities. Cardiomegaly was apparent in the chest radiography.

centric LVH. There was no discernible abnormality in the hemodynamic system.

Dr. Kizaki: The students are suggesting that in this case the diagnosis is cardiomyopathy due to some infection. What do you think about that?

Dr. Ieda: It is possible, but he had no fever and the time course is not typical. I think this presentation differs from those of myocarditis or pericarditis.

Dr. Rao: There are a couple of things here. First, I am assuming from what you have said, that he does not have a dilated myocardium.

Dr. Ieda: That's correct, he did not.

Dr. Rao: Although you have not mentioned it, it appears from the images that the left ventricular chamber size is not increased. To me, it does not look like a case of dilated cardiomyopathy at all, because the left ventricular end diastolic volume appears normal. You did not give me a number, but just looking at it, it does not seem to be particularly increased.

The second point I want to make is regarding left ventricle wall motion. It is difficult to tell unless you are actually at the bedside of the patient while it is being done, but it does not look at all reduced. Nor does it look like there is any diastolic dysfunction. There seemed to be reasonable movement, but that is hard to tell from the short view we are being shown. So I have to ask the cardiologist who was there, because sometimes it can be more subjective and visual: Was there any diastolic dysfunction from concentric hypertrophy? Was there any diastolic dysfunction in your opinion, Dr Satoh?

Dr. Satoh (Internal medicine): I think it is difficult to evaluate diastolic dysfunction. I saw this patient at that time, and I could not find any jugular vein abnormality. In restrictive hemodynamics, descent of the jugular vein is exaggerated. The apex beat was felt to be prolonged, suggesting left ventricular diastolic dysfunction. I think he had left ventricle hypertrophy, but there was no restrictive left ventricular abnormality. I do not feel that he showed that restrictive pattern.

Dr. Rao: I want to explain something here to the students. Does anyone know why I am asking all these questions? No one knows, right?

Let me tell you. What we are trying to decide is, what is the pattern of cardiomyopathy that the patient had? I am in the same position as you; this case is new to me; so we all have no idea what is going on in this case. The patient came in with heart failure. So our first question is: Does the patient have congestive heart failure? It certainly looks like we have right heart failure as evidenced by the elevated jugular venous pressure. But there appears to be no clinical evidence to this point of left heart failure, because I cannot see any congestion in the lungs on the chest x-ray. So, I think we have evidence to suggest that he has a failing right heart.

When you see that, the next question is: What pattern of cardiomyopathy does the patient have? Is this a dilated cardiomyopathy? Is it a restrictive cardiomyopathy? Or is it an obstructive cardiomyopathy? You have to find out before you can investigate what is causing the cardiomyopathy, because the causes of the three patterns are very different. It is very important that you do not jump ahead to investigate the cause before you even know what it is you are investigating!

In trying to determine the pattern, you look for some things on the echo, which is what I have been trying to determine through all the questions I have been asking. In a patient with dilated cardiomyopathy, what you have essentially is a flabby bag of a heart that is not contracting. So you will see enlarged chambers with feeble wall motion.

In a patient with restrictive cardiomyopathy, on the other hand, you see increased wall thickness. This means that the myocardium is also very stiff and does not move appropriately to either contract or relax the ventricle. The first result of this stiffness is resistance to entry of blood into the ventricle. Initially, this affects the early, passive phase of ventricular filling in diastole (called E on the echo). The late phase of filling, which is dependent on atrial contraction (called A), is initially spared, and actually may be exaggerated, so that the normal E to A ratio is reversed. Later on, when the ventricle stiffness is so great that atrial contraction cannot overcome it, the ratio becomes ''normal'' again. This is the typical pattern of restrictive cardiomyopathy.

Finally, in obstructive cardiomyopathy you might see asymmetric septal hypertrophy or a pattern of progressive reduction in flow through the outflow tract as systole progresses.

Having said that, though, I must concede that it is sometimes very hard to tell in the early stages what kind of cardiomyopathy a patient has. So, you have to respect the opinion of the cardiologist who has seen the patient and who does the echocardiogram. And if he says he did not see wall motion abnormalities, or he did not see abnormal relaxation, then you must accept it. So, in this case, where we are told that there were no wall motion abnormalities on echocardiography, a diagnosis of restrictive cardiomyopathy is difficult to sustain. But it does appear from all the clinical evidence that the patient has a restrictive cardiomyopathy.

Ms. Matsuki (6th-year student): I am just confused, because this patient had chest discomfort; I think we just jumped to the conclusion that he had a heart disorder. I was wondering whether this patient might have renal dysfunction that is causing edema and all these other symptoms. Besides that, he had a history of a heart condition. Would that be a possibility?

Dr. Ieda: On the first admission, blood to urine nitrogen was 9.9 and the creatine level was 0.9, which is normal.

Dr. Kizaki: I think we should move to the second stage. The patient developed many more complaints. So Dr. Ieda, could you explain?

Dr. Ieda: Later, the patient again presented, this time three months before the final admission, with complaints of paroxysmal nocturnal dyspnea, constipation and edematous legs. Upon admission, laboratory tests revealed prominent proteinuria, a low albuminemia and renal insufficiency, suggesting nephritic syndrome. Immunoelectrophoresis detected a gammaglobulin peak in serum and urine samples of the IgD(λ) type. A bone marrow biopsy specimen showed a monoclonal increase in plasma cells, leading to the diagnosis of multiple myeloma. A radiograph of the chest, which I will show you later, was interpreted as showing cardiomegaly with a moderate increase in bilateral pleural effusions.

A transthoracic echocardiogram revealed increased echogenicity and symmetric hypertrophy of the myocardium, and wall motion was decreased, suggesting an infiltrative process like amyloidosis. In addition, unsustained VT, atrial fibrillation, hypotension and hypothyroidism were subsequently detected. Several cycles of furosemide infusions followed by a conversion to oral therapy partially resolved his dyspnea and lower extremity edema. We consulted with the hematologist and started dexamethasone intravenously to treat the multiple myeloma. The patient was discharged after one month with instructions to follow the oral medication regimen and to make appropriate lifestyle changes. Despite this treatment, the patient was readmitted two weeks later with worsening dyspnea and edema.

Dr. Kizaki: Regarding the second admission, do you have any questions for Dr. Ieda? During this second admission, various symptoms were observed – for example, those of the nephrotic syndrome, of multiple myeloma and of cardiomegaly suggesting amyloidosis.

Mr. Ogura (5th-year student): I think these are typical symptoms of heart failure and nephrotic syndrome, but it is not clear whether he had symptomatic amyloidosis at this time. I would like to know about the past history of this patient.

Dr. Kizaki: As you can see below, his only previous illness was hepatitis which was virus antigen positive. He was a carrier.

Mr. Inokuchi (5th-year student): We have started considering amyloidosis, so was there any biopsy or congo red staining to clarify the assumed mitotic activity?

Dr. Ieda: Yes, we did such tests. As you can see above, we performed an endomyocardial biopsy, and during the second admission we performed a gastrointestinal biopsy in the duodenum, but no amyloidosis or

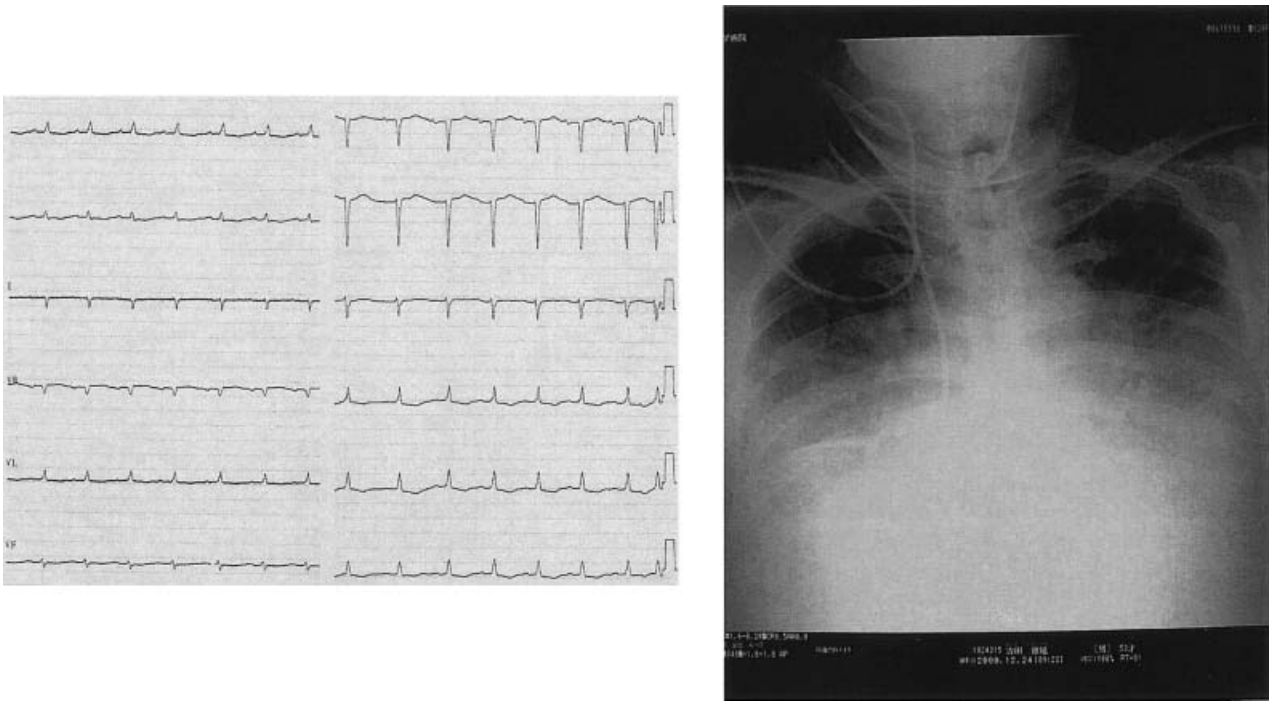


Fig. 2 The ECG and chest radiography at the 2nd admission. Low voltage in hind limbs was revealed in the ECG. There is pulmonary congestion and moderate increase in bilateral pleural effusions.

amyloid protein was detected in either specimen (Fig. 2).

Dr. Kizaki: I think the histology was rechecked several times but no amyloidosis was found.

Dr. Rao: Did you do a fat biopsy?

Dr. Ieda: No, we did not.

Dr. Rao: It is my understanding that either the fat pad or gingival biopsy gives you the highest yield for confirming the presence of primary amyloid, also known as AL amyloidosis. The second point to make is that a symmetrically hypertrophied myocardium does not imply that the amyloid deposition is diffuse. In fact, endomyocardial biopsy, more often than not, fails to pick up the presence of cardiac amyloid. This is because (a) the sample is so small that the yield is very low in conditions where involvement is not diffuse, and (b) even though we tend to think of amyloid as involving the whole myocardium; it is actually very patchy involvement. So, it might require several biopsies – far more than can be safely taken without making a hole in the heart! – if you really want to find amyloid deposition in the myocardium. Of course, that is completely different in a postmortem study, where you have the advantage of making serial sections through the heart, and can almost always find the amyloid deposition.

But that is why the diagnosis of amyloidosis in this case, based on what we have seen so far, must depend on the overall clinical picture. The first clue to the diagnosis is a pattern of restrictive heart disease with concentric ventricular hypertrophy and limitation of wall motion on echocardiography. In contrast to the first echo, now we do see diastolic dysfunction with a failure of the myocardium to relax. The most common cause of this pattern of restrictive cardiomyopathy is cardiac amyloidosis. The second clue, which is almost diagnostic, is a classic pattern of nephrotic syndrome associated with multiple myeloma. There can be no other diagnosis than cardiac amyloidosis in this context, even if you do not show me a congo red positive biopsy. In my opinion then, there is no other diagnosis at this point. And that brings up a very interesting problem: the calcium-channel blocker was probably the worst thing to use.

Why is a calcium channel blocker the worst drug you could have used to treat this patient, if you suspect cardiac amyloidosis, in retrospect?

Dr. Ieda: For amyloidosis, calcium channel blockers are contra-indicated.

Dr. Rao: For the sake of the students, again, can you please explain why a calcium channel blocker is contra-indicated?

Dr. Ieda: Calcium antagonists or beta blockers are contra-indicated in amyloidosis because the toxic side effect is prominent in cardiac amyloidosis. Even if the

level of the medication is at the normal treatment target, side effects could possibly occur, so we do not use it.

Dr. Rao: And that toxicity occurs because calcium channel blockers bind irreversibly to amyloid fibers. So once they are bound, the calcium channels are permanently blocked, and myocardial contractility will become profoundly impaired. That is why you must not use a calcium channel blocker if you suspect amyloidosis.

Dr. Kizaki: Dr. Rao, now back to the diagnosis of this second admission. I will ask Mr. Ogura. What do you think of the diagnosis of nephrotic syndrome in this patient? What is the cause of the nephrotic syndrome? Is the diagnosis of nephrotic syndrome correct?

Mr. Ogura: Yes, it is.

Dr. Kizaki: If it is correct, then what is the cause of the nephrotic syndrome in this patient?

Mr. Ogura: Amyloidosis is one of the most attractive candidates.

Dr. Kizaki: How about other causes?

Mr. Ogura: Other causes are globular nephritis, diabetes mellitus or hepatitis B, and so on.

Dr. Kizaki: Dr. Kumagai, could you comment on the diagnosis of nephrotic syndrome at that time?

Dr. Kumagai (Internal medicine): The most probable genesis of the nephrotic syndrome of this patient was, as he said, amyloidosis, and/or what is shown below. Nephrotic syndrome is a very typical manifestation of amyloidosis in this patient because the position of amyloid growth in the monitor destroys protein selectivity, which prevents a protein molecule from moving out of the capillary into the urinary space. So, nephrotic syndrome is a very difficult syndrome. It is a typical sign of amyloidosis.

Dr. Kizaki: In the first admission, we could not detect the deposition of amyloid. We could not diagnose this patient as having amyloidosis, or confirm its absence, during this period. Then, in the second period, he developed nephrotic syndrome, so the nephrologists suggested that it may have been due to amyloidosis. But even in these terms, we cannot prove there is amyloid, right? We performed biopsies, but no amyloidosis was found. However, from the clinical symptoms, amyloidosis is the most likely diagnosis at this time.

He was also diagnosed with multiple myeloma. Dr. Awaya, as a hematologist, what do you think? There is a diagnosis of nephrotic syndrome, multiple myeloma and amyloidosis. What do you think?

Dr. Awaya (Internal Medicine): Obviously the patient had proteinuria and I assume this is a combination of nephrotic syndrome and paraprotein. Although we did not see the electrophoresis pattern, it seems the patient had paraprotein in his urine. I am not sure about the description of the increase in plasma cells, but if it was compatible with plasmacytoma, based on these two pieces of evidence, I think it is reasonable to make a diagnosis of multiple myeloma. Thus, the underlying disease of this patient was multiple myeloma and he developed the amyloidosis due to the multiple myeloma. The nephrotic syndrome was also secondary to the amyloidosis. I think it is reasonable to combine the three issues.

Dr. Rao: May I just ask what criteria you used to define an increase in plasma cells? Was it at least ten percent?

Dr. Awaya: Yes. It seems that an aspiration was performed.

Dr. Rao: So, was it a core biopsy or was it an aspiration?

Dr. Kizaki: Both, in the bone marrow. Also, I can show you the results of protein analysis. Dr. Awaya, I have a question. During the first admission, there was no evidence of multiple myeloma. Then, the patient was diagnosed with multiple myeloma one year later. What do you think about the time elapsed until the diagnosis of multiple myeloma? It was only one year.

Dr. Awaya: Do you mean that you would like an explanation of why we did not make the diagnosis of amyloidosis at the initial presentation?

Dr. Kizaki: Yes.

Dr. Awaya: Probably the answer to that question is this. Now we know he was diagnosed with IgD myeloma. And with IgD myeloma, as you know, it is hard to make the diagnosis because the M peak level is relatively low, compared to IgG or IgA. So, I speculate that the patient might have had multiple myeloma at the initial presentation.

Dr. Kizaki: I think the key point for the diagnosis was the results of the bone marrow biopsy. As shown by immunoelectrophoresis, Bence-Jones protein was seen in the urine only on the second admission. Only the IgD(λ)M protein was detected in serum. The diagnosis of multiple myeloma may have been definitive at this time.

Dr. Rao: There is little further to say! The patient had a multiple myeloma: there were Bence-Jones proteins in his urine, which are nothing other than the lambda light chains we have identified, he had a single immunoglobulin spike on plasma immunoelectrophoresis, and he had an increase in plasma cells in the bone marrow. And that makes the diagnosis certain. And it also means that cardiac amyloidosis was a result of a multiple myeloma.

Dr. Kizaki: We do not have much experience with IgD myeloma. How about you?

Dr. Rao: I have none. So, I will wait for the hematologist to tell us.

Dr. Kizaki: Ms. Ono, what are the characteristics of IgD myeloma? What are the clinical manifestations?

Ms. Ono: Extra nodal plasmacytoma and amyloidosis are more frequently seen than in other types of myeloma.

Dr. Kizaki: Dr. Hattori, what do you think of the choice of dexamethasone at this point?

Dr. Hattori (Internal Medicine): I think it was a good choice. Firstly, because dexamethasone has less nephro and cardiac toxicity, secondly because there is no bone marrow suppression, and thirdly because dexamethasone works very quickly compared with melphalan and prednisone.

Dr. Kizaki: But at this time, the patient's diagnosis was amyloidosis. Was there any evidence of the effectiveness of dexamethasone on amyloidosis?

Dr. Hattori: No. Basically, there is no effective therapy against established amyloidosis. One paper shows melphalan plus prednisolone to be an effective treatment for prevention of progression of amyloidosis. So, dexamethasone is good for the treatment of multiple myeloma, but I do not know how effective it is for amyloidosis.

Dr. Kizaki: Ms. Okishio, do you think the choice of dexamethasone was good for this patient or not? If not, do you have any comments on the treatment?

Ms. Okishio (5th-year student): I think the dexamethasone was chosen for the patient's quality of life because other therapies may have considerable toxicity. So, I think the choice was good.

I have a question. In this case, maybe thalidomide was available. The toxicity of thalidomide is mild and it can improve the patient's quality of life.

Dr. Kizaki: This is a very old case, so thalidomide was not available at that time.

Dr. Hattori: I looked for papers describing the efficacy of thalidomide for amyloidosis, but found only one. Sixteen patients were enrolled in this study, 14 had renal involvement, and 4 had cardiac involvement. Thalidomide was effective for reducing Bence-Jones proteins. However, there was no comment on the improvement of amyloidosis. More importantly, the article also emphasized an unexpectedly high frequency of severe toxicity. Grade 3 or 4 toxicity was observed in 50% of the patients, which also reinforces the idea that even if thalidomide had been available, it should have been used with special caution in this patient.

Dr. Kizaki: Professor Rao, what do you think of the choice of dexamethasone, and what do you think of thalidomide?

Dr. Rao: First of all, there is no evidence to show that any treatment makes a difference in amyloidosis: not a single study shows that anything works. As for treating his multiple myeloma, that is equally futile, because his heart is going to give out long before anything else. Once this degree of cardiac failure develops, the prognosis is extremely bad for most patients with cardiac amyloid. So, if he had presented with multiple myeloma without the cardiac amyloid, I would have pursued aggressive chemotherapy with melphalan-prednisolone. But at this point in the patient's course, the prognosis is really grim. In terms of survival, he has weeks, or maybe months at the most to live. So, it would really make no sense, as already mentioned by one of the students, to ruin what little quality of life he might have left to him by using toxic alkylating agents. And because he has CHF, a steroid without a significant mineralocorticoid effect, like dexamethasone, is a good idea.

Dr. Kizaki: I think this discussion is very difficult for everyone. Could someone summarize the diagnosis of the second admission to the students? Ms. Ogawa? What was the diagnosis at the second admission? Amyloidosis or multiple myeloma? Nephrotic syndrome? Heart failure? Please summarize what happened in the second admission.

Ms. Ogawa (5th-year student): The major diagnosis is multiple myeloma, accompanied by amyloidosis. The nephrotic syndrome is also attributable to the amyloidosis.

Dr. Kizaki: If so, what do you think of the first admission? You say this is multiple myeloma, associated with amyloidosis which possibly induced the nephrotic syndrome. But in the first admission, only angina was detected. Do you think multiple myeloma was already present at that time?

Ms. Ogawa: Yes, I believe it was.

Dr. Kizaki: We are going to discuss this later, after the pathologists make some comments. Now, we will look at the patient's last admission.

Dr. Rao: I think this patient had multiple myeloma from the time when the symptoms began. At that time, maybe, the only clue may have been the presence of some light chains in the urine. But that would be missed unless an immunoelectrophoretic analysis of the urine was performed. And that is certainly not warranted for every patient with CHF who walks in the door. Without that, though, you will not pick up light chains in the urine. And those light chains would be deposited continually in the tissues and the patient will eventually end up with amyloidosis. So, in my opinion, the patient had multiple myeloma at his first presentation.

Dr. Kizaki: All right. This is the basic summary of this case.

Ms. Matsuki: If the patient, in fact, had multiple myeloma from the beginning, and if we want to confirm this retrospectively, for instance as you mentioned, if the patient only had Bence-Jones protein at the time he presented with angina, do we see a difference in the total protein level at the time as an increase in total protein, which might suggest that he had multiple myeloma at that time?

Dr. Rao: The answer to your question is 'no'. Bence-

Jones proteins are not measured in total plasma proteins. These are only light chains. And, as previously mentioned, in IgD myeloma there is usually a very small increase in IgD. For reasons that are not clear, IgD appears to be a much more toxic form of myeloma.

Dr. Kizaki: Actually, at the first admission, the total protein level was normal.

Dr. Kumagai (Internal Medicine): Dr. Ieda, is there a possibility that the deposition of amyloid molecules on the coronary arteries is a genesis of angina or the ST depression seen on EKG?

Dr. Ieda: Yes, it is possible. About 10 or 20 percent, a small fraction, of amyloidosis patients have vessel amyloid deposition, and our patient had typical angina pectoris, so this might be the case. But he also had cardiac hypertrophy due to amyloidosis, so both findings were present.

Dr. Kumagai: Did you find any amyloid deposition in the cardiac septum? I recognized some, looking at your first echocardiogram. I also think amyloid deposition existed.

Dr. Rao: I do not think I saw any evidence of cardiac amyloid in that first echo. Clearly in the second echo, you give a very striking description of a classic pattern of the granular appearance of cardiac amyloid.

Dr. Kizaki: In this discussion, from the beginning this patient had multiple myeloma and amyloidosis.

Dr. Ieda: This is the second admission echocardiogram. As you can see, this is a parasternal view, long axis. This is the left ventricle. The left ventricle echo density was a little bit higher than on the first admission and contractility was significantly decreased compared to the first admission. You can see here a small amount of pericardial effusion.

This is a short axis view. This is the left ventricle and it is not clearly seen in this video. You can see the pericardial fusion here and the thickness appears to be increased significantly. The echo density was very high, higher than on the first echocardiogram. Decreased contractility is apparent. The calculated IVS diameter is 1.4, that of the posterior wall 1.4, and of the ejection fraction 50%. We did not check E to A here, but the IVC value was determined to be 2.1 cm and respiratory change markedly decreased. This is the four-chamber view.

Dr. Rao: Now you can see it very clearly. If you look in the region of the interventricular septum, you can see the bright spots going through it. That is what is called a speckled granular pattern. The words that are sometimes used to describe it are ''like stars in the night.''

Dr. Kizaki: So shall we move to the last admission? And Dr. Ieda, could you explain the clinical course?

Dr. Ieda: The patient was thought to have worsening congestive heart failure. Here, this is the third admission. The left panel is the ECG and the right panel is the chest X-ray. As you can see, premature ventricular contraction can be seen here and the poor R progression was not changed much, but the voltage of the precordial leads, and you can see it in the limb leads, was significantly lower than at the first admission. As you can see in the right panel, this is, as you know, the heart and here are the lungs. Clearly, the heart was enlarged and you can see that pulmonary effusion and pulmonary congestion have appeared at this time.

The patient was thought to have worsening congestive heart failure due to cardiac amyloidosis. He underwent Swan-Ganz catheter placement. The mean right atrial pressure was 9 mmHg, the right ventricle pressure was 43/11 mmHg, that in the pulmonary artery 43/22 mmHg and mean pulmonary capillary wedge pressure 36 mmHg with a cardiac index of 1.6. We thought he had very severe congestive heart failure. First of all, we administered low dose dopamine, furosemide and a PDE III inhibitor intravenously. The next day, sudden-onset spontaneous ventricular fibrillation occurred but was converted back to a sinus rhythm with DC shock treatment.

Although initial basic blood chemistry results were unremarkable, the serum CRP rose to 20 and bilateral pulmonary edema increased. So, we started ten-day treatment with antibiotics and immunoglobulin infusion, which reduced the inflammation as the heart failure subsided. By the 20th hospital day, however, his blood pressure dropped as low as 70/40 mmHg and multiple syncopal episodes were recorded. The patient's renal failure and constipation also worsened. Cardiac function continued to deteriorate. The cardiac index was 0.7 and the pulmonary capillary wedge pressure was now 20 mmHg. On the 23rd hospital day, his rhythm again deteriorated into ventricular fibrillation, but on this occasion he could not be resuscitated (Fig. 3).

Dr. Kizaki: At the third admission, congestive heart failure worsened and very serious arrhythmia occurred. In addition, further renal failure was noted. Then, I think the attending doctor attempted multiple resuscitations but to no avail and the patient died. We should discuss the last part, which is the cause of death. Mr. Ogura, what was the cause of death in this patient?

Mr. Ogura: The immediate cause of death was thought to be acute deterioration of his heart failure.

Dr. Kizaki: We should sum up the clinical diagnosis of this patient. We have discussed several points since the beginning of this session. I will ask Mr. Oyanagi to summarize the diagnosis of this patient. After a great deal of discussion, the diagnosis was multiple myeloma.

Mr. Oyanagi: In this case, who typified the clinical course of amyloidosis associated with multiple myeloma, common manifestations of multiple myeloma,

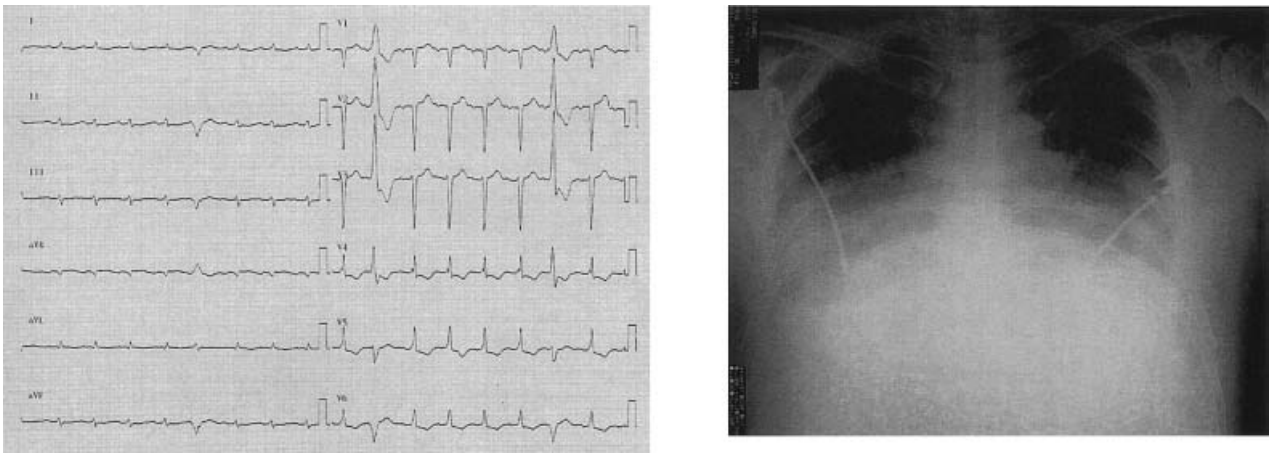


Fig. 3 The ECG and chest radiography at the 3rd admission. There is sinus tachycardia and PVCs in the ECG. There is severe bilateral pleural effusion in the chest radiography.

such as myeloma kidney and bone lesions, could not be identified. The major symptom, which was cardiac, resulted mainly from amyloidosis. But neither ventricular myocardial biopsy nor gastrointestinal biopsy revealed any apparent amyloid deposition. The cause of death might thus have been a bacterial infection, or possibly congestive heart failure, but we still as a group do not have a definitive conclusion.

Dr. Rao: At this time, after being on a high dose of dexamethasone for so many days, was he administered stress dose steroids while he was sick? Could he have gone into hypotensive shock because he did not get steroids after his adrenals were suppressed for months with high dose dexamethasone?

Dr. Ieda: No, in the third admission, we did not use dexamethasone.

Dr. Rao: The reason that it is important is because he was getting dexamethasone as an out-patient.

Dr. Ieda: No, we did not prescribe it.

Dr. Rao: But you said he was given dexamethasone.

Dr. Ieda: In the second admission.

Dr. Rao: You said he was told to follow the oral medication regimen. After the second admission, the patient was discharged after one month with instructions to follow the oral medication regimen, which was dexamethasone. I am assuming that means that he was on dexamethasone when he came in for his admission the third time.

So, assuming that he was taking it until he got admitted, and it was no longer given, it is possible that this patient collapsed because of an adrenal crisis precipitated by the fact that he was not given ''stress dose'' steroids after admission. His own adrenals were suppressed from high dose steroids as an outpatient, and unless he was given steroids in hospital, he would collapse and die.

Dr. Kizaki: I think the patient was given only one course of dexamethasone for four days at the second admission. After that, no dexamethasone.

Dr. Ieda: That is correct. We could not continue dexamethasone.

Dr. Rao: So what ''oral medication regimen'' was the patient given when he was discharged with the diagnosis of multiple myeloma after the second admission?

Dr. Kizaki: It says in the first page: ''a regimen of oral medication, and to make appropriate lifestyle change.''

Dr. Ieda: This was not dexamethasone. It was another medication.

Dr. Kizaki: Do you have any opinions on the diagnosis? The students say it was multiple myeloma, that is, amyloidosis associated with multiple myeloma, and then worsened heart and kidney failure.

Dr. Ieda: We thought so but the biopsy did not show a clear view of amyloid deposition, making a diagnosis of amyloidosis difficult in this case.

Dr. Kizaki: From the clinical symptoms, you can diagnose amyloidosis.

Ms. Matsuki: Since his CRP rose to 20, did you not take blood or any types of culture?

Dr. Ieda: You mean during the third admission?

Dr. Kizaki: Is your concern about sepsis?

Ms. Matsuki: Yes.

Dr. Kizaki: I believe several blood cultures were performed.

Ms. Matsuki: Since they were not mentioned, I presume they were all negative.

Dr. Kizaki: The results were consistently negative. The blood cultures were repeated but they were negative. Do you have any other opinions or questions?

Dr. Rao: Were any treatments given for the patient's hyperthyroidism?

Dr. Ieda: Hyperthyroidism was managed starting from the second admission. Thyradin S was prescribed. Are you familiar with this?

Dr. Rao: But hyperthyroidism will not give you light chains in the urine. It will not give you an immunoglobulin spike. And if you are treating hypothyroidism with thyroid hormone therapy, the patient is not going to die. This patient was dying of multiple myeloma and cardiac amyloidosis.

Dr. Kizaki: Are there any other opinions on the clinical diagnosis of this patient? Is the multiple myeloma diagnosis right? Dr. Awaya, what do you think? The students say the diagnosis of multiple myeloma was associated with the amyloidosis. What do you think about their diagnosis? Is it right?

Dr. Awaya: As I said before, I think the diagnosis of multiple myeloma was definite. We were not able to obtain evidence by biopsy, which could prove the existence of amyloidosis. From the clinical perspective, however, the patient had macroglossia, nephrotic syndrome and so forth. So, the clinical course was highly suggestive of amyloidosis. I think it is reasonable to make a diagnosis of amyloidosis in this case.

Dr. Kizaki: What do you think about the cause of death? The students think it was heart failure due to amyloidosis, perhaps with some infection, hyperthyroidism or an adrenal crisis.

Dr. Awaya: I think an adrenal crisis is very unlikely in this case because we treated him with a very short course of dexamethasone. A typical clinical course of cardiac amyloidosis, like Dr. Rao said, is very rapid and progressive, so I think the cause of death in this case is obviously cardiac amyloidosis.

Dr. Rao: That was my impression right from the start, so I am in no position to change it now; multiple myeloma with cardiac amyloidosis. The only reason that it was not seen on biopsy was because the wrong tissue was biopsied. It should have been the gums or the fat.

Dr. Kizaki: Dr. Mori, could you explain the autopsy findings?

Dr. Mori (Pathology): I will now show you the bone marrow biopsy findings. First, I would like to show the histology of the bone marrow biopsies. As you can see, the bone marrow shows hypercellularity, with a typical plasmacytoid cell proliferation at high magnifications. These cells stained positively for anti-EMA and VS38C. Based on these findings, we made a diagnosis of multiple myeloma.

This slide shows biopsy specimens from the duodenum and myocardium. Although amyloidosis was clinically suspected, we could not demonstrate amyloid deposition in these tissues. You can see some congo red staining in this section, but we could not see green birefringence under polarized light microscopy. Thus, amyloidosis was concluded to be negative. In addition, we did not examine gingival or fat tissue.

I will now show you the autopsy findings. These are the gross findings of the vertebrae. As you can see, bone lysis was present in this area.

This slide shows the bone marrow in the area of bone lysis. You can see hypercellular bone marrow at low magnifications and at high magnification particular plasmacytoid cells, indicating multiple myeloma.

These are the immunohistochemical findings from the plasmacytoid cells. There is positive staining for both anti-VS38C antibody and anti λ, κ chain, but the κ chain was negative. This is kappa chain; this is lambda chain (Fig. 4).

Figure 5 shows the patient's heart. The horizontal section of the heart shows a hypertrophic septum with a packed, waxy appearance. The weight of the heart was 650 g.

The myocardium had amyloid deposition. You can see amorphous, eosinophilic material in the myocardium. The congo red staining is positive here. Under the polarized light microscope, there is green birefringence.

Dr. Rao: Could you just point out to the students the spotty nature of involvement? So, if you take a biopsy of the heart, it will not be positive for amyloid.

Dr. Mori: This epicardial region has a small number of amyloid deposits. Almost all the amyloid depositions were in this other area.

This slide shows microscopic findings of the kidney. As you can see, amyloid deposition is apparent in the perivascular area and interstitial areas. Glomerular basement membranes also show deposition.

Here is a hyalinized cast in the tuberous area, but in this case there were only a few amyloid deposits, so I think the kidneys could not be defined as harboring amyloid.

Amyloid deposition was also found in other organs. This slide shows amyloid in the esophagus. This area demonstrates green birefringence.

The lungs also had amyloid deposits.

This patient had a persistent infection with hepatitis B virus. The liver weighed 1,600 g and showed a nodular appearance. These are microscopic and macroscopic findings.

The patient's pathologically marked congestion was confirmed and with elastica van Gieson staining. Periportal fibrosis was also observed. This shows periportal fibrosis and congestion.

At high magnification, lymphoid cell infiltration was seen in the portal area and piecemeal neo-necrosis was identified. Thus, I made a diagnosis of chronic active hepatitis.

This is the final pathological diagnosis for this patient (Fig. 6). The main disease was multiple myeloma. The

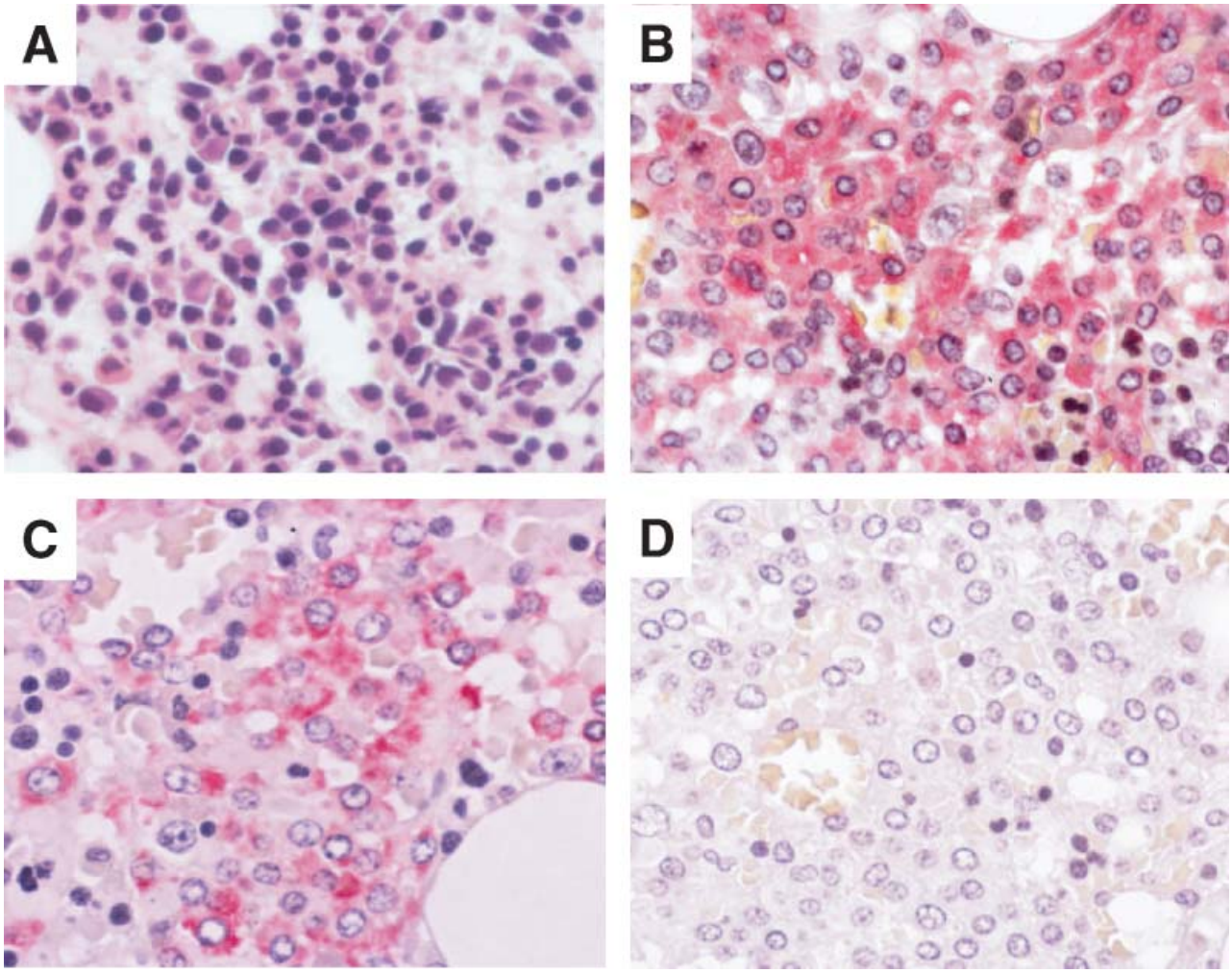


Fig. 4 Autopsy findings of the bone marrow. Shown are atypical plasmacytoid cells proliferation H-E (A) and Vs38c (B). Immunohistochemical staining of λ chain protein (C) and κ chain protein (D).

autopsy findings were myeloma cell infiltration and invasion, particularly proliferation of a typical plasmacytoid cells.

Invaded areas included the vertebrae and costae. Deposition of amyloid light chains, *i.e.* lambda chains, was seen in the visceral organs; the heart, kidney, duodenum, stomach, ileum, colon, tongue and lungs. Systemic congestion and edema were seen in many organs including the liver, spleen and kidneys, and the lower extremities. There was pleural effusion, ascites, and pericardial effusion. Chronic active hepatitis was present, and additionally, there were no septic findings.

I prepared one more figure illustrating amyloidosis (Fig. 7). Amyloidosis is defined as a disease of abnormal deposition of insoluble amyloid microfibers which are characterized under electron microscopy as 10 to 15 nm microfibers. This is a microscopic finding. With H-E staining, amyloid fibers stain as eosinophilic amorphous materials and are positively stained with congo red. Under a polarizing microscope, amyloid shows green birefringence, as you can see here. Biochemically, they are formed from protein comprised of many materials and amyloid fibers are classified into several groups according to the amyloid light chain, the AL, which is derived from plasma cells. AA (amyloid associated) is not associated with immunoglobulin proteins, which are made by the liver. β_2 microglobulin is a normal serum protein that complicates the course of patients on long-term hemodialysis. Amyloidosis is grouped into generalized and localized forms. As you can see from this figure, this case fits into the category in which the major fiber protein is AL and lambda chains.

Dr. Kizaki: Thank you, Dr. Mori. I think it is quite possible that the pathological diagnosis is compatible

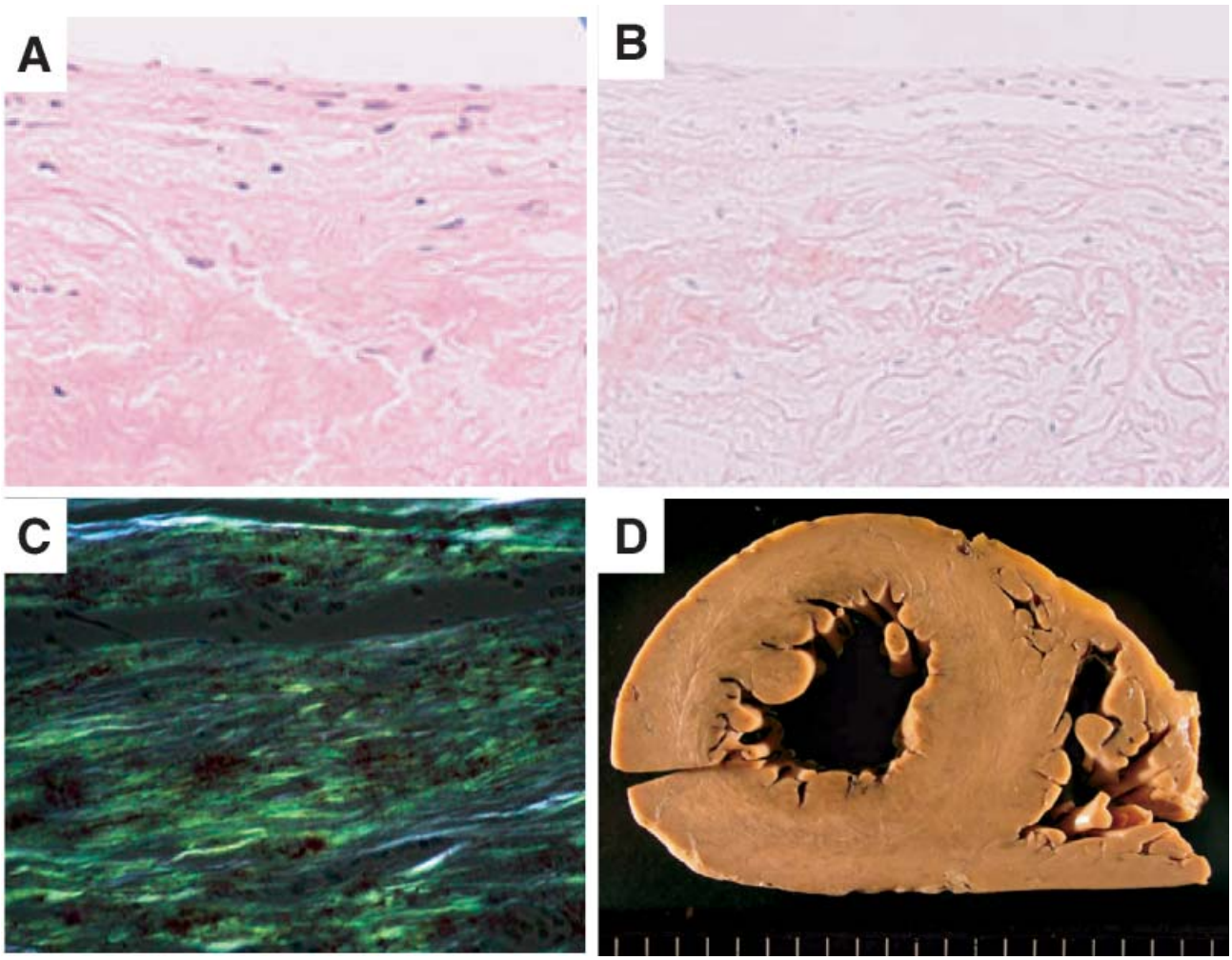


Fig. 5 Autopsy findings of the heart. H-E (A) and congo-red (B) staining shows myocardium deposition of amyloid and apple green birefringence is observe under polarized light microscopy (C). Horizontal section of the heart: Hypertrophic and packed appearance was observed (D). The heart weight was 650 g.

with our clinical diagnosis. The students here were excellent. I think your diagnosis is right. But we should ask some questions of the pathologist. Do you have any questions for Dr. Mori?

Dr. Kumagai: Did you find amyloid deposition in the coronary arteries and thyroid gland?

Dr. Mori: We found coronary arterial deposition of amyloid.

Dr. Kumagai: How about the thyroid gland?

Dr. Mori: The thyroid probably did not have prominent deposition.

Dr. Kumagai: Thank you so much.

Dr. Kizaki: That means the reason for the patient's first admission, the angina, was ultimately the amyloidosis. How about other questions?

Dr. Satoh: Some reports have stated that if you perform an electron microscopic study of the cardiac biopsy specimen, you can obtain a diagnosis of amyloidosis. We suspected amyloidosis at the first admission. We then asked pathologists to perform congo red staining. If we had asked you to do an electron microscopic study, could we have obtained the correct diagnosis?

Dr. Mori: Yes, I think so.

Dr. Rao: I am sorry. I have to disagree with you. Cardiac amyloid is a patchy disease, and that is why you do not see it on endomyocardial biopsy. My recommendation, if I would have thought of amyloidosis in this patient and if the endomyocardial biopsy came back negative, would have been to do a gingival biopsy or a fat pad biopsy. In fact, I would go for three fat pad biopsies, or even four, one from each quadrant of the abdomen. Alternatively, I might ask the oral surgeon to do a gingival biopsy. If all of those specimens were negative, only then would I say there is no amyloidosis.

Can I just add one more point? The new classifica-

Pathological diagnosis

1. Multiple myeloma
- i) **Diagnostic biopsy of the bone marrow:**
  Plasmacytoid cell infiltration, marked, compatible with multiple myeloma
  (Keio Univ. Hosp. P202-01) VS38c (+), EMA (+), AL (λ), Bence-Jones protein (+)
- ii) **Myeloma cell proliferation and invasion: vertebrae, costae**
- iii) **Post status of steroid therapy**
- iv) **Amyloidosis:**
  Deposition of amyloid light chain (AL) in the visceral organs including heart (650g), kidneys (220, 200g), esophagus, stomach, duodenum, ileum, colon, tongue and lungs.

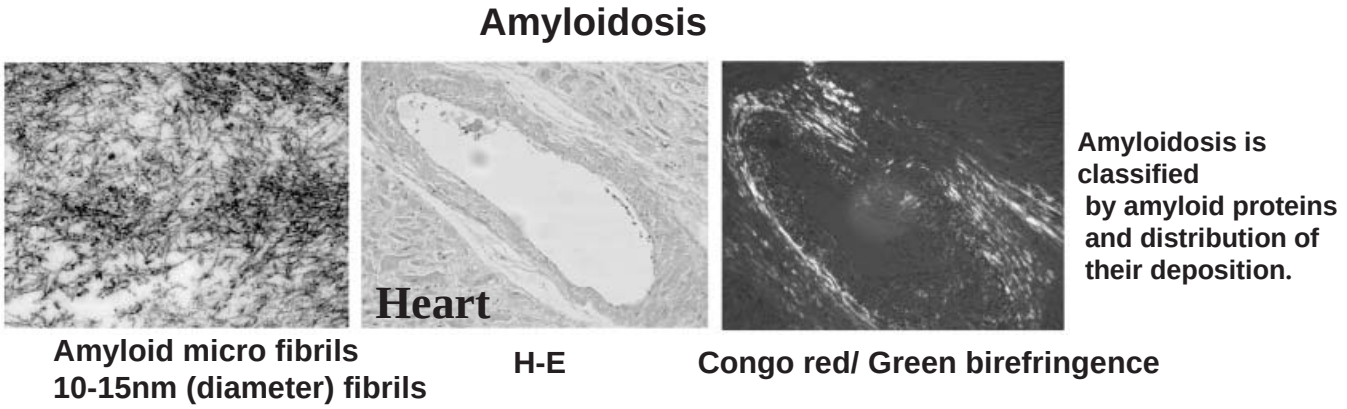
2. Systemic congestion and edema:
Liver (1600g), spleen (100g), and lower extremities

3. Pleural effusion (1300, 1200ml), ascite (small amount) and pericardial effusion(45ml)

4. Chronic active hepatitis
HBV-Ag(+), Inuyama classification (A2, F1)

5. Atherosclerosis of the aorta, moderate

Fig. 6 Pathological diagnosis of the autopsy.



Clinicopathologic Category	Associated Diseases	Major Fibril Protein	Chemically Related Precursor Protein
Systemic (Generalized) Amyloidosis			
Immunocyte dyscrasias with amyloidosis (primary amyloidosis)	Multiple myeloma and other monoclonal B-cell proliferations	AL	Immunoglobulin light chains, chiefly λ type
Reactive systemic amyloidosis (secondary amyloidosis)	Chronic inflammatory conditions	AA	SAA
Hemodialysis-associated amyloidosis	Chronic renal failure	β_2-microglobulin	β_2-microglobulin
Hereditary amyloidosis			
(1) Familial Mediterranean fever	—	AA	SAA
(2) Familial amyloidotic neuropathies (several types)	—	Transthyretin*	Transthyretin
Localized Amyloidosis			
Senile cardiac	—	Transthyretin	Transthyretin
Senile cerebral	Alzheimer's disease	$A\beta_2$	APP
Endocrine (e.g., medullary carcinoma of thyroid)	—	Procalcitonin	Calcitonin

Fig. 7 Summary of amyloidosis.

tion of amyloidosis is basically split into three – AL amyloid, AA amyloid and other. AL amyloid is the one that is composed of amyloid light chains. On the other hand, AA amyloid is due to the deposition of fibrils of a protein called serum amyloid protein A. This is an acute phase reactant, but we have no idea why it gets deposited in situations associated with chronic inflammation. The last form is familial amyloid. In one variant, the amyloid protein consists of transthyretin, which is an abnormal thyroid binding protein, but there is no thyroid disorder.

Dr. Kizaki: At first admission, Dr. Ieda, the doctor in charge, suspected amyloidosis and he performed cardiac biopsies but he could not detect amyloid. So, your recommendation would be to perform another biopsy just using fat or some other tissue specimens?

Dr. Rao: That is where we rely on the pathologist to tell us that they could not find it in the endomyocardial biopsy, and that the only way to make the diagnosis is from a fat pad or from the gingival tissue.

Dr. Kizaki: Any questions for Dr. Mori, the pathologist? Or, any comments on the diagnoses of this patient? No further comments or opinions?

Dr. Awaya: I think this case can be summarized in two points. First, it is very difficult to make a diagnosis of IgD myeloma. Secondly, as Dr. Rao stressed, when you elect to make a diagnosis of amyloidosis, you need to choose the proper tissue, which is basically fat.

Dr. Rao: In defense of whoever was taking care of this patient, making the diagnosis would have changed nothing at all. You would not have been able to do a thing to prevent this patient from dying.

Dr. Hori (Emergency Medicine): My question is not regarding the cause of his death but I am thinking about his clinical course during the second admission. Clinicians probably were able to predict his clinical outcome would be grave. As such, what kind of diagnosis was made? Did the doctor in charge announce it to the patient himself? My second question is, in the United States, Dr. Rao, if your patient has a similar clinical entity with a grave clinical cause such as cardiac amyloid, how do you deal with such a patient, regarding the presentation of the diagnosis to them?

Dr. Ieda: In the second admission, we thought he had cardiac amyloidosis and myeloma, so his prognosis was very bad. Previously, I told his family his survival would be about six months. After consulting with his family, we presented this information as fully to the patient as we had to his family. Perhaps he died suddenly.

Dr. Kizaki: Dr. Rao, suppose you have the same patient in the United States, what would you do?

Dr. Rao: Basically, I would break the news to the patient very kindly, very gently. The students should recognize that this is one of the most delicate of all functions that you will ever perform as a physician. You must be very, very understanding, very gentle, and very compassionate. Look at it this way: you are signing the patient's death warrant. You have given the patient a sentence of death. There is no more serious task you will ever perform in your lives than telling a patient, ''I can do nothing for you and you are going to die.'' You do not take that responsibility lightly. Just think about it, there is not a thing you can do and the patient knows that he is going to die. You need to be very sensitive to that situation.

And you need to involve the family. In most situations, you cannot tell the family without telling the patient, unless there is a reason the patient cannot comprehend or cannot understand the significance – for example, if there is some CNS involvement, or if you think the patient will not understand the significance of what you are telling them. That is a different story. But as a general rule, the patient is the first to know. You have to tell the patient, and then have a family conference.

If there is a silver lining to this dark cloud, it is that most patients who are this sick know they are going to die. They are not stupid. This patient probably knew. But it was just a question of someone confirming it for him. So, when you do that, you have to be understanding. I know that the students are still very young and inexperienced, but rest assured that when you do it often enough you will really get a sense of how to do it. Only by doing it will you learn. No one can tell you how to do it. If you are a kind person and you really care for your patients, you will find your own way to tell them.

Dr. Kizaki: Thank you. That is a very difficult problem; how we should treat dying patients. Any questions or comments? If not, then this CPC is over. Thank you very much to the participating doctors and thank you very much, Dr. Rao.