Clinical Manifestations at Diagnosis in Japanese Patients with Systemic AL Amyloidosis: A Retrospective Study of 202 Cases with a Special Attention to Uncommon Symptoms

Masayuki Matsuda, Nagaaki Katoh and Shu-ichi Ikeda

Abstract

Objective  To retrospectively investigate the clinical manifestations at diagnosis in Japanese patients with systemic AL amyloidosis.

Methods  We reviewed the medical records of 230 Japanese patients who had visited our hospital and been diagnosed with AL amyloidosis, and abstracted those with the systemic type. The clinical data at diagnosis of systemic AL amyloidosis, including laboratory and imaging findings, were analyzed.

Results  Two hundred and two patients (mean, 58.7±9.5 years) were enrolled in this study. Immunofixation or immunoelectrophoresis was performed in 173 patients, 144 of whom were positive for M-protein in the serum and/or urine (κ:λ=30:114). The primary clinical manifestations at diagnosis were proteinuria and/or renal dysfunction (54.0%), congestive heart failure (24.8%), peripheral neuropathy (10.4%), hepatomegaly (7.9%) and arrhythmia (5.0%). The remaining patients developed unusual manifestations, such as solitary tumor, lymphadenopathy, gastrointestinal bleeding, intestinal pseudoobstruction, hemorrhagic tendencies and polyarthralgia. Dilatation of the intestine with marked thickening of the gastrointestinal wall on computed tomography and multiple nodular lesions with associated mucosal friability on endoscopy are characteristic findings of systemic AL amyloidosis.

Conclusion  The clinical pictures of Japanese patients with systemic AL amyloidosis are similar to those previously reported from the US and European nations; however, some patients with this disease develop uncommon symptoms. Conducting laboratory and histological examinations for systemic AL amyloidosis is necessary when making a differential diagnosis of these symptoms.

Key words: AL amyloidosis, systemic amyloidosis, amyloidoma, clinical manifestation, Japanese patients

(Intern Med 53: 403-412, 2014)
(DOI: 10.2169/internalmedicine.53.0898)

Introduction

Amyloidosis refers to a group of disorders with a heterogeneous pathogenic background that are now classified into many subtypes according to the chemical nature of the primary constituent amyloid fibril proteins (1). Amyloidosis derived from immunoglobulin light chains (AL) is a hematological disorder and a systemic form of the disease causes the dysfunction of multiple vital organs, including the heart, kidneys and gastrointestinal (GI) tract (2, 3). Abnormal plasma cells in bone marrow play a central role in the pathogenesis of systemic AL amyloidosis as a source of amyloidogenic monoclonal immunoglobulin (M-protein). Kyle and Gertz as well as Falk et al. independently described detailed clinical pictures of systemic AL amyloidosis based on data obtained from large sets of patients (2-4); however, since their reports, it has gradually become apparent that this disease can present with more varieties of clinical manifestations than previously thought (5). Amyloidosis has long been considered to be an incurable disorder. Nevertheless, it is now recognized that amyloid deposits can regress and organ dysfunction is reversible if the synthesis of the amyloid precursor protein is halted (6-8). Intensive che-
mortality data and/or radiological examinations suggestive of multiple organ involvement. Immunofixation or immunoelectrophoresis was performed in 173 patients, 144 of whom were positive for M-protein (κ/λ=30:114) in either the serum alone (n=15), urine alone (n=41) or both (n=88). Immunohistochemistry was performed on the biopsied tissues of 122 patients treated at our institute, and tissues of 38 and 82 patients were found to be positive for ALκ and ALλ, respectively. Two patients showed negative results on immunohistochemistry; however, microextraction and biochemical characterization identified their amyloid fibrils as being of immunoglobulin light-chain origin (14). The remaining 80 patients whose biopsy samples were not available for our immunohistochemical analysis were considered to have systemic AL amyloidosis based on the presence of potassium permanganate-resistant amyloid deposits in the biopsied tissues with positive M-protein in the serum and/or urine (15).

Fourteen patients were classifiable as having the myeloma-associated type with regard to exhibiting 10% or higher plasma cells in the bone marrow according to the diagnostic criteria proposed by the International Myeloma Working Group (16). Nevertheless, none of these 14 patients demonstrated any abnormal lesions suggestive of myeloma cell infiltration on either X-ray examinations or bone scintigraphy. Other myeloma-associated manifestations, such as anemia and a prominent increase in M-protein, were also unremarkable in these patients.

The age of onset and clinical manifestations at diagnosis in the 202 systemic AL amyloidosis patients are demonstrated in Fig. 1. The disease developed most frequently in patients in their 60s; however, one and six patients showed the onset of symptoms in their 20s and 30s, respectively. Proteinuria and/or renal dysfunction (n=109, 54.0%) was the most common manifestation, and 90 patients fulfilled the criteria for nephrotic syndrome. Congestive heart failure (n=50, 24.8%) was the second most common comorbidity. Data for echocardiograms were available in 36 of the 50 patients, and the thickness of the interventricular septum, percent fractional shortening (%FS) and E-wave deceleration time (DT) were 16.2±3.1 mm (normal <12 mm), 28.2±7.6% (normal >28%) and 145.2±38.7 ms (normal 180-250 ms), respectively. Ten patients underwent scintigraphy using 99mTc-technetium-pyrophosphate, which is sensitive for cardiac amyloidosis (17); however, only five showed a positive uptake. The third most frequent manifestation was peripheral neuropathy (n=21, 10.4%), including somatic and autonomic nerve dysfunction and carpal tunnel syndrome. Four patients exhibited bilateral carpal tunnel syndrome without obvious polynuropathy, three of whom also had other organ involvement, such as congestive heart failure. The fourth most frequent manifestation was hepatomegaly with or without liver dysfunction (n=16, 7.9%).

Fourteen patients displayed marked increases in the levels of alkaline phosphatase (1,285.4±1,092.2 IU/L, normal 124-367 IU/L) and γ-glutamyl transpeptidase (277.0±339.7 IU/L, normal 6-30 IU/L) in the serum in addition to hepatomegaly. Abdominal CT

### Results

We found 202 patients to have systemic AL amyloidosis (121 men and 81 women; 28 to 81 years; mean, 58.7±9.5 years). All of these patients showed amyloid deposits in at least one biopsy site with some abnormal findings in labora-
protrusion from the circumferential mucosa characterized amyloidomas showed nodular expansion with or without themselves or were found to have tumors on annual health while the remaining five patients happened to notice tumors as gross hematuria and/or melena (Fig. 3A) and one patient nary bladder or rectum manifested recurrent bleeding, such patients. Two patients with amyloidomas in either the uri-

The sites of the amyloidomas included the lungs, Solitary tumor manifestations:

The remaining patients developed the following unusual experienced Stokes-Adams attacks due to marked bradycardia.

Eight patients exhibited solitary tumors, so-called amyloi-
doms. The sites of the amyloidomas included the lungs, stomach, urinary bladder, prostate, rectum, tongue, epipharynx and anterior mediastinum in one patient each. The de-

Some patients complained of any serious symptoms, such as dysp-
nea, even though the lymph nodes were enlarged on both sides of the neck (20). CT often demonstrated a clear en-
hancement effect of the lymph nodes with or without calcifi-
cation (Fig. 4) showing remarkable uptake in one patient on positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) (20). Histopathology of the lymph nodes demonstrated massive deposition of amyloid with no obvious evidence suggestive of lymphoproliferative disorders (22). On immunohistochemistry, these amyloid de-

Lymphadenopathy

Six patients manifested lymphadenopathy. Three of them exhibited an enlargement of several lymph nodes in localized areas, primarily in the cervical region, in addition to other symptoms ascribable to visceral organ involvement, such as nephrotic syndrome, while the remaining three pa-
tients manifested systemic lymphadenopathy alone. In the latter patients, swollen lymph nodes were seen in the cervi-
al, axillar and inguinal regions and in the mediastinum as well as the retroperitoneum; some of these findings have been previously described (20, 21). On physical examina-
tions, these lymph nodes usually had a size of 1 to 3 cm in diameter, good mobility, a smooth surface, an elastic-firm consistency and no tenderness. As the lymph nodes adhered to the neighboring soft tissue in parallel with increases in size, their mobility was often decreased. The lymph nodes gradually became enlarged, some of which reached 4 cm or larger in diameter within several years. Nevertheless, no pa-
tients complained of any serious symptoms, such as dysp-
nea, even though the lymph nodes were enlarged on both sides of the neck (20). CT often demonstrated a clear en-
hancement effect of the lymph nodes with or without calcifi-
cation (Fig. 4) showing remarkable uptake in one patient on positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) (20). Histopathology of the lymph nodes demonstrated massive deposition of amyloid with no obvious evidence suggestive of lymphoproliferative disorders (22). On immunohistochemistry, these amyloid de-

GI bleeding and intestinal pseudoobstruction

GI bleeding without solitary tumors and/or intestinal pseudoobstruction were observed in eight patients consisting of the former alone in three patients, the latter alone in three patients and both in two patients. Among those with GI dence of associated malignancy except for those observed in either the stomach or lungs. The gross appearance of the gastric amyloidoma revealed an irregularly- shaped small le-
sion slightly depressed from the circumferential mucosa that resembled early-stage carcinoma classifiable as type IIc (Fig. 3B). Histopathology demonstrated ALκ-positive amyloid deposition with no associated malignancies. In contrast, the lung amyloidoma in another patient contained a round nodule with marginal spicular formation on CT that was compatible with the radiological findings of malignancy, and the histopathology of the surgically removed tissue revealed ALκ-positive amyloid deposition around the adenocarcinoma. Immunohistochemistry revealed the tumor cells in this patient to be positive for cancer-associated surface anti-
gens, such as receptors for advanced glycation end-
products (19). All eight of the patients also showed amyloid deposition in the vascular walls in areas around the amyloi-
domas and other biopsied tissues, particularly the gastroin-
testinal mucosa and renal glomeruli.

Figure 1. Age of onset (A) and clinical manifestations at di-
gnosis (B) in 202 Japanese patients with systemic AL amyloi-
dosis. The preferential age of onset was in the 60s; however, one and six patients developed the disease in their 20s and 30s, respectively. Proteinuria and renal dysfunction were the most common manifestations, followed by congestive heart failure. Some patients developed unusual manifestations, such as soli-
tary tumors, lymphadenopathy, gastrointestinal bleeding, intesti-
nal pseudo-obstruction, polyarthralgia and hemorrhagic tendencies.

demonstrated hepatomegaly and heterogeneous attenuation of the parenchyma with peripheral predominance (Fig. 2). Arrhythmia, such as sick sinus syndrome, was the fifth most common manifestation (n=10, 5.0%), and three patients ex-

GI bleeding and intestinal pseudoobstruction

GI bleeding without solitary tumors and/or intestinal pseudoobstruction were observed in eight patients consisting of the former alone in three patients, the latter alone in three patients and both in two patients. Among those with GI
bleeding, three patients had tarry stools suggestive of upper GI tract bleeding (Fig. 5), while the remaining two patients manifested melena. All of the patients with intestinal pseudo-obstruction complained of abdominal distension and anorexia ascribable to decreased bowel motility. Abdominal CT demonstrated dilatation of the intestines, particularly from the duodenum to the ileum, and marked thickening of the GI wall sometimes with an air-fluid level (Fig. 6). Endoscopy revealed multiple nodular lesions and erosions often with associated mucosal friability, exhibiting easy bleeding against mechanical stimuli in the GI tract, particularly in the stomach and duodenum (Fig. 7A). No lesions specific for bleeding were present. Histopathology of the biopsied mu-
cosa demonstrated massive amyloid deposition frequently with infiltrations of plasma cells and lymphocytes indicative of polyclonality (Fig. 7B, C and D). On immunohistochemistry these amyloid deposits were positive for ALλ and ALκ in five and three patients, respectively.

**Hemorrhagic tendency**

Two patients manifested a remarkable hemorrhagic tendency as the initial symptom. One patient developed massive hemorrhage in the peritoneal cavity after cholecystectomy with no obvious cause. Histopathology of the removed gallbladder and biopsied liver specimen demonstrated deposition of ALκ amyloid primarily on the vascular walls...
Figure 4. A representative case of systemic lymphadenopathy [22] showing recurrence of multiple enlarged lymph nodes with a clear enhancement effect (arrows) in the bilateral neck on CT two years after surgical removal (A: horizontal section, B: frontal section).

(Fig. 8A). Subcutaneous massive hemorrhage often occurred with no precipitating cause in various sites of the body, particularly in the trunk and lower extremities (Fig. 8B), which are likely to receive exogenous stimuli such as pressure. The laboratory data demonstrated no abnormal findings in either platelets or coagulation factors. The other patient also developed frequent subcutaneous hemorrhages in the extremities. A skin biopsy demonstrated ALκ amyloid in the perivascular region.

Polyarthralgia

Two patients manifested polyarthralgia. The biopsied tissue from the gastroduodenal mucosa showed ALλ amyloid deposition, leading to the diagnosis of AL amyloidosis in both patients (23). One patient complained of bilateral gonalgia and cubitalgia, while the other exhibited symmetri-
Fig. 6. CT in a patient with intestinal pseudo-obstruction demonstrating marked thickening of the wall in the stomach, particularly the distal portion (A), bulbus (B) and descending portion (C, arrow) of the duodenum and transverse colon (D).

The physical findings in both patients resembled those of rheumatoid arthritis with regard to almost symmetrical involvement of multiple joints (Fig. 9). X-ray examinations revealed multiple irregularly-shaped areas of hyperlucency in the proximal epiphyses of the bilateral humeri and carpal bones, which coincided with low-intensity signals on both T1- and T2-weighted images of magnetic resonance imaging (MRI) (23). Bone scintigraphy using technetium-99m methylene diphosphonate (\(^{99m}\)Tc-MDP) demonstrated clear uptake in the swollen and tender joints (23). In both patients, C-reactive protein (CRP) was almost normal despite the presence of severe pain, and autoantibodies, including rheumatoid factor, anti-cyclic citrullinated peptide antibodies, anti-nuclear antibodies, and anti-neutrophil cytoplasmic antibodies, were all negative.

**Discussion**

**Age at onset and common manifestations**

AL amyloidosis is the most common form among the five major types of systemic amyloidosis (24); the remaining four consist of amyloid A (AA), dialysis-related β₂-microglobulin (Aβ₂M), hereditary and senile systemic transthyretin-derived (ATTR) amyloidosis. According to a recent report, the estimated prevalence of AL amyloidosis in Japan is 6.1 per million persons (25). In the present study of Japanese patients, systemic AL amyloidosis commonly affected people in their 50s or older, as previously shown in the USA (2); however, the disease can occur even patients in their 30s or younger. Proteinuria and/or renal dysfunction, including nephrotic syndrome, was the most frequent manifestation at diagnosis, followed by congestive heart failure. Approximately 80% of the patients manifested either or both of these two symptoms at diagnosis. The frequency of renal involvement at diagnosis was 28% in a previous report from the USA (2), compared to approximately 54% in the present study. This discrepancy may be in part due to the inclusion of patients with mild to moderate proteinuria in the present study in addition to those with nephrotic syndrome. Among the patients with congestive heart failure, the decrease in E-wave DT was more remarkable than that observed in %FS on echocardiograms, indicating that the diastolic function is more severely affected than the systolic function from the early phase of illness in patients with AL amyloid cardiomyopathy, as previously shown in several studies (26, 27). Peripheral neuropathy, including carpal tunnel syndrome, is occasionally seen in patients with systemic AL amyloidosis and the clinical picture is known to be very similar to that observed in ATTR-type familial amyloid polyneuropathy with elderly onset (28, 29). In the present study, there were no obvious relationships between clinical symptoms at diagnosis and either the type of deposited AL amyloid or circulating M-protein. Macroglossia, diffuse hard goiters and swelling of the salivary glands are well-known clinical
manifestations in patients with systemic AL amyloidosis (2, 3); however, the present study was unable to clarify the precise frequency of these symptoms.

**Uncommon manifestations**

The present study additionally found that some patients with this disease manifest unusual signs or symptoms at diagnosis, to which previous reports from the USA have paid little attention (2, 3). Whether these manifestations are characteristic of Japanese or Asian patients with systemic AL amyloidosis should be clarified in further multinational investigations, and technical advances in techniques used at diagnosis, such as biopsies and immunohistochemistry, may in part contribute to the detection of such features. The first

---

**Figure 7.** Endoscopy of the patient shown in Fig. 6 demonstrating multiple polypoid lesions in the duodenum (A). The biopsied mucosa shows massive deposition of amyloid (B, Congo red staining), which is positive for ALκ on immunohistochemistry (the insert in A). This patient often exhibited a subcutaneous massive hematoma on CT (B, arrows) with no precipitating cause.

**Figure 8.** Histopathology of a patient with a hemorrhagic tendency demonstrating deposition of amyloid in the small vessel walls of the gallbladder (A, arrows, Congo red staining), which is positive for ALκ on immunohistochemistry (the insert in A). This patient often exhibited a subcutaneous massive hematoma on CT (B, arrows) with no precipitating cause.

**Figure 9.** Symmetrical swelling of both shoulders, the so-called 'shoulder-pad sign' (A). MRI demonstrates low- and high-intensity signals in the shoulder joints, primarily in the capsule, on T1- (B) and T2-weighted (C) images, respectively, which suggests the deposition of amyloid.
uncommon manifestation is solitary tumors, so-called amyloidomas, which are, in general, characterized grossly by mass formation in various organs and microscopically by heavy deposition of AL amyloid. This manifestation usually occurs in patients with the localized type (30, 31) and is infrequently associated with the systemic form of AL amyloidosis (32, 33). In the localized form, amyloidogenic light chains are produced by local, tissue-based lymphoplasmacytic dyscrasias (34-36), while in the systemic type, a circulating monoclonal protein functions as an amyloid precursor and amyloid deposition on the vascular walls in the affected organ is a characteristic finding (6). M-protein in the serum and/or urine is therefore a potent clue to distinguish the systemic type from the localized type (37). Considering that all of the 8 patients with amyloidoma in the present study also showed marked vascular wall involvement in the biopsied tissues with M-protein in the serum and/or urine (18, 19), AL amyloid deposition may occur widely in visceral organs and severely in localized areas, leading to mass formation (38), although the precise mechanisms remain unclear. Some antigens or proteins on the cell surface may play a role in inducing locally accelerated deposition of circulating amyloidogenic immunoglobulin light chains (19, 39).

The second unusual sign is lymphadenopathy. Systemic amyloidosis affects lymph nodes in a frequency ranging from 17% to 37% (40); however, lymphadenopathy is rarely seen as an initial manifestation of this disease. As M-protein was present in the serum and/or urine with the clonal expansion of plasma cells or lymphoplasmacytoid cells in the bone marrow likely producing the precursor immunoglobulin, all of the patients with systemic lymphadenopathy alone in the present study were considered to be classifiable as having systemic AL amyloidosis, although three of them showed no clear evidence suggestive of visceral organ involvement. The most characteristic finding was that amyloid deposition developed primarily in the lymph nodes, particularly in the cervical and supraclavicular regions. In some patients, CT demonstrated a clear enhancement effect of the lymph nodes, as observed in malignant lymphomas. These findings are ascribable to damage to vascular walls caused by amyloid deposition. One patient also showed a positive result on FDG-PET (20). Massive deposition of amyloid may have induced the activation of lymphocytes, resulting in marked uptake of FDG.

The third uncommon manifestation is GI bleeding and intestinal pseudo-obstruction. As systemic AL amyloidosis often affects the GI tract from the early phase of illness even without clinical symptoms, the upper and/or lower portions are selected as a preferential site for biopsy when making a definitive diagnosis of this disease with regard to procedural safety and sensitivity (41). Amyloid fibrils gradually accumulate in the GI wall and cause mucosal impairment leading to bleeding and intestinal pseudo-obstruction in parallel with a decrease in bowel motility via direct pressure of the neighboring tissues and/or ischemic changes due to vascular involvement (42, 43). Endoscopically, mucosal poly-
membrane may have caused the polyarthralgia and swelling of the joints observed in the present patient.

In conclusion, systemic AL amyloidosis occasionally presents with more varieties of clinical symptoms than previously thought. The use of endoscopy with histopathological examinations, measurements of M-protein in both the serum and urine and a whole-body survey, including CT, should be actively considered as early as possible in order to make a definitive diagnosis of systemic AL amyloidosis, as the disease is recently becoming treatable in conjunction with the clinical use of intensive chemotherapy regimens targeting pathogenic plasma cells, such as HDM/SCT, dexamethasone and bortezomib (9, 10).

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors are grateful to Dr. J. Koyama, Department of Cardiology at Shinsyu University Hospital and Dr. Y. Murata, Department of Urology, Aizawa Hospital for providing us with echocardiographic data and a photograph of cystoscopy, respectively.

This work was supported by a grant from the Intractable Disease Division, the Ministry of Health and Welfare, Amyloidosis Research Committee, Japan.

References


