Systemic AL Amyloidosis Mimicking Rheumatoid Arthritis

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Abstract

We report a patient with myeloma-associated systemic AL amyloidosis who showed chronic polyarthralgia as the main symptom. The clinical picture was similar to that of rheumatoid arthritis with regard to symmetrical swelling with tenderness in multiple joints, but inflammatory reactions were almost normal and autoantibodies were negative. He was diagnosed as having systemic AL amyloidosis based on deposition of κ-light chain-immunoreactive amyloid in biopsied tissue and Bence Jones protein in serum and urine. Magnetic resonance imaging and bone scintigraphy suggested this disease as the cause of the polyarthralgia. Systemic AL amyloidosis may be important in the differential diagnosis of chronic polyarthralgia.

Key words: bone scintigraphy, magnetic resonance imaging, polyarthralgia, systemic AL amyloidosis

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Introduction

Systemic AL amyloidosis is an intractable disorder characterized pathologically by deposition of insoluble fibrils derived from immunoglobulin light chains and clinically by dysfunction of multiple organs, particularly the heart and kidneys (1). This disease complicates multiple myeloma at a frequency of 6-15% (2). In this case report we describe a patient with myeloma-associated systemic AL amyloidosis who showed symmetrical swelling with tenderness in multiple joints as the main symptom. Polyarthropathy due to amyloid deposition occurs often in β2-microgloblin-derived amyloidosis but it is uncommon in AL amyloidosis (3-8). According to a cohort study in a large set of patients with multiple myeloma, amyloid arthropathy develops at a frequency of 3.5% (6). The clinical picture of the present patient was similar to that of rheumatoid arthritis (RA) except for negative results of autoantibodies and almost normal levels of inflammatory reactions, and we suggest that systemic AL amyloidosis may be important in the differential diagnosis of chronic polyarthralgia.

Case Report

A 64-year-old man with no chronic disease or significant family history gradually developed pain on motion and swelling in the right hand with no precipitating cause. These symptoms soon extended to the other hand and subsequently to the joints of the lower extremities, such as knees and ankles, within 3 months after onset. He became unable to raise both arms because of pain on motion in the shoulders, and his activity of daily living deteriorated quickly. Five months later he noticed numbness and a decrease in grasping power in both hands, and was successfully treated with surgical therapy on a diagnosis of bilateral carpal tunnel syndrome (CTS) in a neighboring hospital. Neither C-reactive protein (CRP) nor rheumatoid factor (RF) was positive in serum. Pain and swelling in systemic joints persisted, and he was admitted to our hospital 9 months after the onset of disease.

On admission, he was in an almost bedridden state with severe appetite loss and marked emaciation. Physical examination showed symmetrical swelling with tenderness in multiple joints, particularly in knees, shoulders, wrists and metacarpo-phalangeal (MCP) and proximal interphalangeal (PIP) joints (Figs. 1A, 1B). He complained of difficulty in walking and severe pain on passive movement with limited range of motion in all fingers. His grip strength was less than 1 kg on both sides. There were no abnormal findings in his chest or abdomen suggestive of involvement of visceral organs. Dysarthria and dysphagia ascribable to macroglossia were present (Fig. 1C), and other neurological findings were normal except for orthostatic hypotension and disuse muscle atrophy in the extremities. Routine laboratory
Figure 1. Photographs of the patient, showing swollen hands (A), symmetrical swelling of both shoulders, the so-called ‘shoulder-pad sign’ (B), and macroglossia (C) with teeth indentation (arrows).

tests demonstrated slight anemia (hemoglobin 10.9 g/dl, normal 12.9-17.4 g/dl) with hypoalbuminemia (albumin 3.6 g/dl, normal 4.2-5.1 g/dl), but hepatobiliary enzymes and renal indices in serum were within normal limits. CRP was almost normal (0.15 mg/dl, normal <0.1 mg/dl), and autoantibodies, including RF, the anti-cyclic citrullinated peptide (CCP) antibody, anti-nuclear antibody, and anti-neutrophil cytoplasmic antibody, were all negative. Serum immunoglobulin showed a slight decrease in IgA (48 mg/dl, normal 110-410 mg/dl) and IgM (14 mg/dl, normal 35-220 mg/dl) with normal levels of IgG (993 mg/dl, normal 870-1,700 mg/dl), IgD (0.4 mg/dl, normal <0.9 mg/dl) and IgE (108 IU/ml, normal <361 IU/ml). No significant proteinuria was seen in urinalysis. There were no abnormal findings in either chest X-ray or electro- and echocardiogram. Despite the lack of a monoclonal peak on protein electrophoresis, immunofixation demonstrated κ-type Bence Jones protein (BJP) in both serum and urine, and plasma cells with abnormal morphology were increased in smear specimens of the bone marrow (11% of total nucleated cells, normal 0.5-3.9%). Histopathology of the gastroduodenal mucosa and abdominal fat tissue showed massive deposition of ALκ-immunoreactive amyloid (Fig. 2). X-ray examinations revealed multiple irregular-shaped hyperlucencies in the proximal epiphysis of bilateral humeri (Fig. 3A) and carpal bones (Fig. 4A), which coincided with low-intensity signals on both T1- and T2-weighted images of magnetic resonance imaging (MRI) (Figs. 3B, 3C, Figs. 4B, 4C). Synovial tissues around flexor muscles at the wrist showed high-intensity signals on the T2-weighted image (Fig. 4C). Bone scintigraphy using technetium-99m methylene diphosphonate ("99mTc-MDP) demonstrated clear uptake in swollen and tender joints (Fig. 5). Gallium scintigraphy was negative.

The patient received two courses of VAD (vincristine 0.4 mg/day and doxorubicin 9 mg/m²/day by continuous infusion on days 1-4, and dexamethasone 40 mg/day by infusion on days 1-4, 9-12 and 17-20; all were repeated four weeks later) followed by oral hydrocortisone at a dose of 20 mg/day. His activity of daily living gradually improved in conjunction with a decrease in systemic arthralgia. M-protein was detectable in serum but not in urine. Bone marrow aspirations demonstrated a marked decrease in abnormal plasma cells. Further chemotherapy was not performed in this patient because of combined infection with pneumocystis ji- roveci and aspergillus.

Discussion

The present patient was diagnosed as having systemic AL amyloidosis based on deposition of ALκ-immunoreactive amyloid in the biopsied tissues as well as BJPκ-type M-protein in serum and urine. His macroglossia is a clinical finding characteristic of AL amyloidosis. Bilateral CTS treated 1 month prior to admission to our hospital can also be ascribed to this disease, although histopathological examination of soft tissue obtained from the carpal tunnel was not performed. Systemic survey demonstrated no obvious involvement of vital organs such as the heart and kidneys. According to the diagnostic criteria proposed by the International Myeloma Working Group, multiple myeloma was considered to underlie systemic AL amyloidosis in the present patient with regard to the presence of more than 10% plasma cells in the bone marrow (9).

The most interesting point in this patient is that his predominant symptom was systemic chronic polyarthralgia. There are three possible causes of the polyarthralgia in the present patient. The first is a complication of other disorders causing chronic polyarthralgia, particularly RA. The clinical picture of the present patient resembled that of RA with respect to symmetrical swelling with tenderness in multiple joints of extremities, including MCP and PIP joints, but serological markers, such as RF and the anti-CCP antibody, were negative. According to a recent report from Japan the
Figure 2. Histopathology of the gastric mucosa taken at biopsy, showing severe deposition of Congo red-positive substances mainly in the submucosal area (A, Congo red staining, bar=100 μm). On immunohistochemistry these substances were positively stained with anti-ALκ antibody (B, bar=100 μm).

Figure 3. X-ray demonstrates multiple irregular-shaped hyperlucencies in the proximal epiphysis of the right humerus (A, arrowheads), which coincided with low-intensity signals on both T1- (B, arrowheads) and T2-weighted images (C, arrowheads) of magnetic resonance imaging. Amyloid deposits are seen also in the periarticular soft tissue (B and C, arrows).

diagnostic specificity and positive predictive value of the anti-CCP antibody were 94.9% and 87.8% for RA, respectively (10). Inflammatory reactions were also almost negative in the present patient before and after admission to our hospital. CRP should have shown a marked increase if active RA was the cause of such pain and swelling of multiple joints as seen in the present patient. There were no symptoms or signs suggestive of other associated collagen dis-
Figure 4. X-ray demonstrates multiple irregular-shaped hyperlucencies in the right carpal bones (A, arrowheads), which coincided with low-intensity signals on both T1- (B, arrowheads) and T2-weighted images (C, arrowheads) of magnetic resonance imaging. Amyloid deposits with edema are seen also around the flexor muscles (B, C, arrows).

eases causing chronic polyarthralgia. The second possible cause of polyarthralgia is multiple myeloma. It is well known that this disease can cause osteoarthralgia due to infiltration of myeloma cells, particularly in the spine, but the present patient showed pain on motion in articular regions alone. Bone marrow aspirates demonstrated no remarkable increase of plasma cells, and $^{99m}$Tc-MDP scintigraphy showed obvious uptake localized to joints, suggesting that multiple myeloma was not the cause of the polyarthralgia in the present patient.

The third possible cause of polyarthralgia is AL amyloidosis itself. Among the amyloidoses, arthropathy preferentially occurs in the β₂-microglobulin-derived one, which complicates chronic renal failure with hemodialysis (3, 4). Amyloid deposition develops in the bone but also in the synovial membrane, leading to polyarthralgia and swelling due to destructive arthropathy (3, 4). This type of arthropathy can occur also in AL amyloidosis (5-7). The present patient showed symmetrical swelling of both shoulders, the so-called ‘shoulder-pad sign’, and limited range of motion in multiple joints from the early phase of illness, as is frequently seen in amyloid arthropathy due to AL amyloidosis (6, 11, 12). To detect amyloid deposition in joints, MRI and scintigraphy are useful (4, 13). In the present patient X-ray examinations of bones demonstrated multiple hyperlucencies in epiphyseal regions, which coincided with low-intensity signals on both T1- and T2-weighted images of MRI. Multiple myeloma usually shows low- and high-intensity signals on T1- and T2-weighted images of MRI, respectively, while amyloid deposition, including that in soft tissue, appears as low-intensity signals on both these images, as seen in the present patient (4, 6, 14, 15). Bone erosion in RA shows the same intensity pattern on MRI as in multiple myeloma (16, 17). Diphosphonate has a high affinity to amyloid fibrils irrespective of precursor proteins (12, 18, 19), and bone scintigraphy using $^{99m}$Tc-MDP demonstrated obvious uptake in swollen joints. These radiographical findings suggest that deposition of amyloid in the bone and synovial membrane may have caused polyarthralgia and swelling of joints in the present patient. Soft tissues around flexor muscles at the wrist showed high-intensity signals on the T2-weighted image in the present patient, and inflammatory edema may have been concurrent with amyloid deposition (6). Synovial biopsy is recommended in order to confirm deposition of amyloid (4, 6, 11-13), but in the present patient we did not perform this examination because of his poor general status.

Treatment of amyloid polyarthropathy in AL amyloidosis has not yet been established, but chemotherapy for multiple myeloma should be effective with regard to reduction of pathognomonic plasma cells producing precursor proteins of
amyloid. Because of the well-preserved function of vital organs, such as the heart and kidneys, we selected cyclic VAD as a chemotherapeutic regimen in the present patient (20, 21). Polyarthralgia quickly improved, probably in response to the dexamethasone in VAD, but his poor general status with infection did not allow us to perform more than 2 courses of this intensive chemotherapy. M-protein in urine disappeared after VAD in conjunction with a marked decrease in plasma cells in the bone marrow. Polyarthralgia has been well controlled with oral hydrocortisone alone.

In conclusion, systemic AL amyloidosis occasionally causes arthralgia and swelling in multiple joints, which are indistinguishable from polyarthritis due to active RA. When serological markers of RA, such as RF and the anti-CCP antibody, are negative in patients with polyarthralgia, amyloid arthropathy might be a possible diagnosis, and an intensive survey, including histopathological examinations and detection of M-protein, should be performed as early as possible.

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Figure 5. Bone scintigraphy using technetium-99m methylene diphosphonate demonstrates symmetrical uptake in swollen and tender joints (left: anterior view, right: posterior view).

References


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