Systemic Amyloidosis Following Ankylosing Spondylitis
Associated with Congestive Heart Failure
A Case Report

Tsuneo Fujito, M.D., Teruo Inoue, M.D.,
Kazuhiro Hoshi, M.D., Hirokazu Hatano, M.D.,
Hirotoshi Kamishirado, M.D., Kan Takayanagi, M.D.,
Terumi Hayashi, M.D., Shigenori Morooka, M.D.,
Yutaka Takabatake, M.D.

and Yoshio Uehara, M.D.*

SUMMARY
We report the case of a 38-year-old man who developed fatal, systemic
amyloidosis following ankylosing spondylitis. He was admitted for symptoms of
congestive heart failure. Based on parotid gland biopsy and echocardiography,
he was diagnosed as having systemic amyloidosis following active ankylosing
spondylitis. However, the clinical course was rapidly progressive and eventually
the patient died of acute necrotizing pancreatitis. The association has been
reported thus far in a limited number of cases worldwide. The literature has
featured localized lesions and a benign clinical course of the amyloidosis. This
case, the first report from Japan, indicates that the amyloidosis associated with
ankylosing spondylitis might exhibit a rapidly progressive clinical course,
thereby suggesting that in such a case, meticulous treatment is required. (Jpn

Key words: Amyloidosis  Ankylosing spondylitis  Heart failure
Renal failure

MUCH knowledge has accumulated relating to the primary diseases
causing systemic amyloidosis, which include rheumatoid arthritis and
chronic tuberculosis. Ankylosing spondylitis might be associated with amyloidosis
of the kidney, rectum or liver vessels, however, since amyloid lesions are report-
edly localized to a limited area, the prognosis of this entity is believed to be
favorable.1–12 Despite the literature from other countries, there have been no case
reports thus far in Japan describing ankylosing spondylitis as a precursor of systemic amyloidosis. In this paper, we report the first Japanese case of amyloidosis following active ankylosing spondylitis, which had systemic lesions and a fatal outcome.

**CASE REPORT**

A 38-year-old man was admitted to our hospital because of dyspnea and palpitations. He had suffered from back pain since 18 years of age. Two years later he was diagnosed as having ankylosing spondylitis based on radiographic examinations and laboratory data. He had been treated with non-steroidal anti-inflammatory drugs since that time. Proteinuria and hypertension became overt one year before admission. In May 1989, he experienced dyspnea and palpitation, both of which became increasingly severe. He was admitted to our hospital on December 6, 1989. There was no family history of ankylosing spondylitis or amyloidosis. He was 170 cm in height and 63 kg in weight. Heart rate was 95 beats/minute and blood pressure was 200/100 mmHg. The conjunctivae were slightly anemic. The oral labia and mucosa were dry. The thyroid gland was diffusely enlarged and slightly firm. A grade III systolic ejection murmur was

![Figure 1. Two-dimensional and M-mode Echocardiogram. The left ventricle exhibits symmetric hypertrophy and granular sparkling in the interventricular septum, both of which strongly indicate deposition of amyloid fibrils. IVS = interventricular septum; PW = posterior wall.](image-url)
Figure 2. Morphology of parotid gland. Amyloid fibrils stained by Congo-red were deposited in the interstitium of the parotid gland (2-a) (×66). AA-type amyloid deposits were demonstrated, using anti-AA antiserum immunoperoxidase method (2-b) (×66).

Figure 3. Bone-radiography of vertebrae. Typical bamboo-like vertebrae, ilio-psoas joint sclerosis and calcification of the anterior longitudinal ligament were all demonstrated in the antero-posterior (left graph) and left to right lateral view (right graph).

found at the apical area. He exhibited a bent posture due to severe kyphosis.

Neurological examination was normal. Laboratory data revealed mild leukocytosis and anemia. Blood urea nitrogen was 28 milligrams/dl, serum creatinine 2.0 milligrams/dl, and total protein 5.9 grams/dl. Erythrocyte sedimentation rate (ESR) was 70 mm/hour. C-reactive protein (CRP) was 2.2 milligrams/dl. Rheumatoid factor and anti-nuclear antibodies were negative. Thyroid function was normal. Urinary protein excretion was 1.5 to 2.0 grams/day. Bence-Jones protein was not detected on immunoelectrophoresis. Human leukocyte antigen (HLA) B-27 was negative. Chest radiography showed mild cardiomegaly (cardiothoracic ratio 51%) and bilateral pleural effusions. Electrocardiograph revealed sinus tachycardia (heart rate 98/min) and a small R and deep S wave in
leads V2 to V4. Echocardiography showed symmetric thickening of the interventricular septum (19 mm in width) and the posterior left ventricular wall (20 mm in width) with mild hypokinesia and granular sparkling of the interventricular septum, indicating the occurrence of amyloid lesions and subsequent dysfunction in cardiac contractility. Aortic valve regurgitation was not evident on a color Doppler examination (Figure 1).

The right parotid gland was biopsied and histological examination showed Congo red-positive amyloid fibrils deposited in the interstitial tissue (Figure 2-a). More precisely, AA-type amyloid antigens were demonstrated in the deposits, using anti-AA amyloid-specific antibody and the immunoperoxidase method (Figure 2-b). Neither AL- nor AF- nor AE-type amyloid was observed in the tissue.

Bone radiography revealed typical lesions of ankylosing spondylitis: bamboo-like vertebrae, sacroiliac joint sclerosis (sacroiliitis), and calcification of the anterior longitudinal ligament of the vertebrae (Figure 3).

Because of massive proteinuria and intractable edema, the patient was treated with dimethylsulfoxide (DMSO) and non-steroidal antiinflammatory drugs; however, conventional treatment was ultimately found to be ineffective.
Thus, the medication was switched to 40 milligrams/day of prednisolone in order to suppress the activity of the underlying spondylitis. This treatment resulted in a marked decrease in the activity of ankylosing spondylitis as shown in the reduction of ESR and CRP and a decrease in plasma creatinine (Figure 4). However, he eventually died of acute pancreatitis on April 16, 1990.

Autopsy findings were as follows. The heart weighed 580 grams. The left ventricular wall was yellowish and showed concentric hypertrophy. Congo red-positive amyloid fibrils were diffusely deposited in the left ventricular wall. Amyloid deposits were also found in the kidney, liver, thyroid gland and pancreas. Moreover, marked destruction and diffuse coagulation necrosis were found in the pancreas, corresponding to the lesions seen in acute necrotizing pancreatitis. The hip, sacroiliac and intervertebral joints exhibited advanced changes corresponding to bony ankylosing spondylitis. The pathological diagnosis was 1) ankylosing spondylitis, 2) generalized amyloidosis and 3) acute necrotizing pancreatitis with peritonitis.

**DISCUSSION**

The patient had a history of lumbar back pain with limited movement of the lumbar spine. He exhibited severe abnormalities on bone radiography. These findings fulfilled the diagnostic criteria of definite ankylosing spondylitis, presented by WHO at the New York meeting held in 1967 and those by Calin et al in 1977. During the clinical course, he developed oral dryness, massive proteinuria, and various symptoms of congestive heart failure, suggesting the development of associated systemic amyloidosis. In fact, biopsy of the parotid gland revealed deposits of amyloid fibrils, strongly suggesting the diagnosis of systemic amyloidosis secondary to active ankylosing spondylitis.

Robert et al reported 229 cases of primary systemic amyloidosis, featuring the clinical case. Seventy-seven patients had congestive heart failure due to amyloidosis. The median survival of those patients was about 6 months, being much shorter than the overall median survival of 12 months in all 229 patients. These data suggest that primary systemic amyloidosis has a relatively poor prognosis, and that particularly when the heart is involved, the prognosis becomes much worse. That is also the case in secondary amyloidosis. Wright et al described secondary amyloidosis, concluding that half of the patients with secondary amyloidosis died of renal involvement, i.e. nephrotic syndrome or uremia.

Despite an increasing number of papers in the literature reporting a poor prognosis in primary and secondary amyloidosis, it has been noted that the prognosis of secondary amyloidosis following ankylosing spondylitis is fairly good. Teilum et al first reported two patients with amyloidosis following ankylosing
spondylitis. Since then, 28 patients have been reported in the world literature (Table). All patients but one had proteinuria and only 3 cases (cases No. 1, 3 and 28 in the Table) had signs and symptoms of congestive heart failure. Of the 28 patients; 5 died and 3 patients exhibited cardiac dysfunction. These reports demonstrate well the benign clinical course of secondary amyloidosis following ankylosing spondylitis. Intriguingly, however, it has also been shown that amyloidosis following ankylosing spondylitis potentially has a fatal clinical course when the cardiac muscle is involved. This was the case in our patient, and this relationship is in accordance with the outcome seen in primary amyloidosis.

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>Kidney</th>
<th>Heart</th>
<th>Amyloid lesions</th>
<th>Status</th>
<th>Cause of death</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>M</td>
<td>proteinuria</td>
<td>cardiac failure</td>
<td>kidney, adrenal, liver vessels</td>
<td>dead</td>
<td>cardiac disease</td>
<td>Tillem et al</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>kidney, spleen, adrenal, liver vessels</td>
<td>dead</td>
<td>uremia</td>
<td>Tillem et al</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>M</td>
<td>proteinuria</td>
<td>dyspnea</td>
<td>kidney, adrenal, spleen, liver vessels</td>
<td>dead</td>
<td>right cerebral hemorrhage</td>
<td>Halford et al</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>kidney</td>
<td>alive</td>
<td></td>
<td>Enevaa et al</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>rectum</td>
<td>alive</td>
<td></td>
<td>Enevaa et al</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>kidney</td>
<td>alive</td>
<td></td>
<td>Enevaa et al</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>kidney, rectum, spleen, adrenal, vessels</td>
<td>dead</td>
<td>uremia</td>
<td>Baywaters</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>M</td>
<td>proteinuria</td>
<td>aortic insufficiency</td>
<td>rectum</td>
<td>alive</td>
<td></td>
<td>Sorner et al</td>
</tr>
<tr>
<td>9</td>
<td>22</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>rectum</td>
<td>alive</td>
<td></td>
<td>Jayson et al</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>rectum</td>
<td>alive</td>
<td></td>
<td>Jayson et al</td>
</tr>
<tr>
<td>11</td>
<td>43</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>none</td>
<td>alive</td>
<td></td>
<td>Jayson et al</td>
</tr>
<tr>
<td>12</td>
<td>36</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>kidney, liver</td>
<td>alive</td>
<td></td>
<td>Tiku et al</td>
</tr>
<tr>
<td>13</td>
<td>30</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>rectum</td>
<td>alive</td>
<td></td>
<td>Haji et al</td>
</tr>
<tr>
<td>14</td>
<td>38</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>rectum</td>
<td>alive</td>
<td></td>
<td>Haji et al</td>
</tr>
<tr>
<td>15</td>
<td>34</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>rectum, synovia</td>
<td>alive</td>
<td></td>
<td>Lovy et al</td>
</tr>
<tr>
<td>16</td>
<td>45</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>kidney</td>
<td>alive</td>
<td></td>
<td>Gandhi et al</td>
</tr>
<tr>
<td>17</td>
<td>55</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>kidney</td>
<td>alive</td>
<td></td>
<td>Prakash et al</td>
</tr>
<tr>
<td>18</td>
<td>48</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>kidney</td>
<td>alive</td>
<td></td>
<td>Prakash et al</td>
</tr>
<tr>
<td>19</td>
<td>45</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>kidney</td>
<td>alive</td>
<td></td>
<td>Prakash et al</td>
</tr>
<tr>
<td>20</td>
<td>52</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>kidney</td>
<td>alive</td>
<td></td>
<td>Prakash et al</td>
</tr>
<tr>
<td>21</td>
<td>48</td>
<td>M</td>
<td>proteinuria</td>
<td></td>
<td>kidney</td>
<td>alive</td>
<td></td>
<td>Prakash et al</td>
</tr>
<tr>
<td>22</td>
<td>40</td>
<td>M</td>
<td>nephritis</td>
<td></td>
<td>kidney</td>
<td>alive</td>
<td></td>
<td>Goffraud</td>
</tr>
<tr>
<td>23</td>
<td>48</td>
<td>M</td>
<td>nephritis</td>
<td></td>
<td>kidney, liver, stomach</td>
<td>alive</td>
<td></td>
<td>Goffraud</td>
</tr>
<tr>
<td>24</td>
<td>58</td>
<td>M</td>
<td>nephritis</td>
<td></td>
<td>kidney, liver, thyroid</td>
<td>alive</td>
<td></td>
<td>Goffraud</td>
</tr>
<tr>
<td>25</td>
<td>40</td>
<td>M</td>
<td>nephritis</td>
<td></td>
<td>rectum, parathyroid, synovia</td>
<td>alive</td>
<td></td>
<td>Goffraud</td>
</tr>
<tr>
<td>26</td>
<td>42</td>
<td>M</td>
<td>nephritis</td>
<td></td>
<td>kidney, rectum</td>
<td>alive</td>
<td></td>
<td>Goffraud</td>
</tr>
<tr>
<td>27</td>
<td>33</td>
<td>M</td>
<td>nephritis</td>
<td></td>
<td>rectum</td>
<td>alive</td>
<td></td>
<td>Goffraud</td>
</tr>
<tr>
<td>28</td>
<td>38</td>
<td>M</td>
<td>proteinuria</td>
<td>cardiac failure</td>
<td>parotid gland, heart, rectum, liver, thyroid, parathyroid, pancreas</td>
<td>dead</td>
<td>acute pancreatitis</td>
<td>Fujito et al</td>
</tr>
</tbody>
</table>
Our patient exhibited an intractable clinical course on conventional treatment. Steroid treatment resulted in a marked decrease in the activity of ankylosing spondylitis. Despite this, the patient died of acute necrotizing pancreatitis. Long-term steroid treatment might cause acute pancreatitis, however, it is also reported that amyloidosis per se produces acute pancreatitis. In fact, amyloid fibrils were found in the pancreas of our patient. Although we could not draw a definite conclusion, it seemed probable that the acute pancreatitis was an amyloid-related event.

Finally, it should be noted that ankylosing spondylitis is one of the primary diseases related to systemic amyloidosis. Amyloidosis following ankylosing spondylitis may lead to congestive heart failure and dysfunction of various organs, thereby resulting in a poor prognosis. Much attention and meticulous treatment are required to prevent such a fatal outcome during the clinical course of ankylosing spondylitis.

ACKNOWLEDGMENT

The authors acknowledge Dr. Hideaki Satoh, M.D. for his morphological investigation using immunohistochemical techniques of amyloid deposition in the organs.

REFERENCES

10. Gandhi RM, Jacob CK, Kinbhakaran MG, Shasya JCM, Date A: Renal amyloidosis with ankylosing spondylitis. JAPI 32: 1069, 1988

