Atypical immunoglobulin light chain amyloidosis
Spontaneous vertebral compression fracture, liver involvement, and bone marrow involvement report of 3 cases and review of the literature

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Abstract
Background: Primary immunoglobulin light chain amyloidosis (AL amyloidosis) is a plasma cell disorder which mainly affects heart, kidneys, liver, and peripheral nervous system. Cases of atypical AL amyloidosis presented as spontaneous vertebral compression fractures have been rarely reported, and data about the management and clinical outcomes of the patients are scarce.

Methods: Herein, we present 3 new cases of AL amyloidosis with spontaneous vertebral compression fracture and review 13 cases retrieved from the literature.

Results: Moreover, we observed overrepresentations of liver involvement and bone marrow involvement in AL amyloidosis with spontaneous vertebral compression fracture.

Conclusion: We believe that better awareness of the rare clinical presentation as spontaneous vertebral compression fracture of AL amyloidosis can facilitate earlier diagnosis and earlier treatment.

Abbreviations: AL amyloidosis = primary immunoglobulin light chain amyloidosis, ALP = alkaline phosphatase, ASCT = autologous stem cell transplantation, CR = complete remission, cTnI = cardiac troponin I, dFLC = difference between involved and uninvolved serum immunoglobulin free light chain, FLC = free light chain, FLC-R = free light chain ratio, GGT = gamma-glutamyl transpeptidase, NT-proBNP = N-terminal of the prohormone brain natriuretic peptide, SPEP = serum protein electrophoresis.

Keywords: AL amyloidosis, plasma cell disease, vertebral fracture

1. Introduction
Primary immunoglobulin light chain amyloidosis (AL amyloidosis) is a plasma cell disorder characterized by overproduction and accumulation of insoluble amyloid fibrils composed of immunoglobulin light chains. The most commonly affected organs are the heart, kidneys, liver, and peripheral nervous system,[11] presenting as congestive cardiomyopathy, nephrotic-range proteinuria, hepatomegaly, and peripheral neuropathy, respectively.[2] A spontaneous vertebral compression fracture is a rare clinical presentation in patients with AL amyloidosis. Here we present 3 cases of AL amyloidosis with spontaneous vertebral compression fractures, liver involvement, and bone marrow involvement, with a review of the literature. All patients provided signed, informed consent, and the study was approved by Peking Union Medical College Hospital Institutional Review Board.

2. Case reports
Case 1 was a 64-year-old man who had his thoracic spine fractured accidentally 5 years ago. A computed tomography scan was performed and suggested a vertebral compression fracture of T11. The patient was treated with a percutaneous kyphoplasty and recovered well. He had a spontaneous lumbar compression fracture of L1 to L2 6 months later. Another 6 months later, he developed soy urine. An abdominal ultrasound showed that the liver edge was near the costal margin and 3.7 cm below the xiphoid process. The laboratory tests revealed the following: hemoglobin, 143 g/L (normal, 120–160 g/L); gamma-glutamyl transpeptidase (GGT), 656 U/L (normal, 10–60 U/L); alkaline phosphatase (ALP), 477 U/L (normal, 50–135 U/L); albumin, 34 g/L (normal, 35–52 g/L); creatinine, 89 µmol/L (normal, 59–104 µmol/L); 24-hour urine protein, 5.87 g (normal, 0.00–0.20 g); serum phosphate, 1.45 mmol/L (normal, 0.81–1.45 mmol/L); calcium, 2.17 mmol/L (normal, 2.13–2.70 mmol/L); serum cardiac troponin I (cTnI), 0.02 µg/L (normal, 0–0.04 µg/L); N-terminal of the prohormone brain natriuretic peptide (NT-proBNP), 213 pg/ml (normal, 0–125 pg/ml); serum protein electrophoresis (SPEP), negative monoclonal protein; serum free light chain (FLC) kappa, 51.6 mg/dL; serum FLC lambda, 10.5 mg/dL; serum FLC ratio (FLC-R), 4.91; difference between involved and uninvolved serum immunoglobulin FLC (dFLC), 40.1 mg/L; bone marrow biopsy, amyloid deposits with...
3.5% plasma cells; immune staining, predominant kappa light chains; and liver biopsy, amyloid degeneration with positive Congo red staining. He was treated with 6 cycles of bortezomib, cyclophosphamide, and dexamethasone, and reached hematologic complete remission (CR). At the follow-up examination 2 years later, the organ response was documented with a negative 24-hour urine protein, an ALP of 153 U/L, and a GGT of 322 U/L.

Case 2 was a 49-year-old woman who complained of progressive back pain for 5 years and was found to have multiple spontaneous vertebral fractures. Magnetic resonance imaging revealed old compression fractures involving T11 to T12 and L1 to L4. Biphosphonate therapy, calcium supplementation, and spinal surgery failed to relieve her pain. The physical examination was notable for macroglossia and liver enlargement with a liver edge palpable 6 cm below the costal margin and 4 cm below the xiphoid process. Laboratory tests indicated the following: hemoglobin, 117 g/L (normal, 110–150 g/L); albumin, 51 g/L; creatinine, 72 μmol/L (normal, 45–84 μmol/L); ALP, 165 U/L; GGT, 261 U/L; NT-proBNP, 309 pg/mL; cTnI, 0.00 μg/L; serum calcium, 2.30 mmol/L; serum phosphate, 1.4 mmol/L; serum parathyroid hormone, 31.7 pg/mL (normal, 12.0–63.0 pg/mL); 24-hour urine protein, 0.41 g; SPEP, no monoclonal protein; serum FLC kappa, 43.2 mg/L; serum FLC lambda, 13.2 mg/L; dFLC, 30 mg/L; FLC-R, 3.27; and bone marrow (plasma cells—1%), gingival, and tongue biopsies, scattered interstitial amyloid deposition with positive Congo red stain. The patient was treated with high-dose melphalan (200 mg/m²) followed by autologous stem cell transplantation (ASCT). A hematologic CR was achieved. At the 3-month follow-up examination, the ALP was 153 U/L, and the GGT was reduced to 80 U/L. Her general functional status improved.

Case 3 was a 48-year-old man who presented with lower back pain and increasing abdominal girth over the past year. The physical examination revealed hepatomegaly with the liver edge palpable 7 cm below the costal margin and 12 cm below the xiphoid process. A chest X-ray revealed multiple spontaneous vertebral and old costal fractures involving the right third and fourth ribs, as well as the left eighth rib. The patient was diagnosed with severe osteoporosis. The laboratory values were as follows: hemoglobin, 150 g/L; albumin, 47 g/L; creatinine, 75 μmol/L; ALP, 330 U/L; GGT, 445 U/L; serum calcium, 2.36 mmol/L; serum phosphate, 1.35 mmol/L; parathyroid hormone, 14.5 pg/mL; NT-proBNP, 108 pg/mL; cTnI, 0.00 μg/L; 24-hour urine protein, 0.36 g; SPEP, monoclonal protein (0 g/L); serum FLC kappa, 70.6 mg/dL; serum FLC lambda, 10.6 mg/dL; dFLC, 60.0 mg/dL; FLC-R, 6.66; bone marrow biopsy, 0.50% plasma cells, with amyloid fibrils deposited near vessels; and liver biopsy, large amount of amorphous amyloid deposits between hepatocytic blood vessels supporting vertebrae, which were positive in Congo red stain. The patient was treated with melphalan, dexamethasone, and daily thalidomide. During the past 6 months since he completed treatment, he achieved a hematologic CR, with a decrease in GGT (233 U/L) and ALP (224 U/L). The general functional status was largely improved with no additional vertebral fractures.

3. Discussion

Spontaneous vertebral compressions are rare manifestations in patients with AL amyloidosis. In our case series, spontaneous vertebral compression fractures were one of the initial presenting signs of AL amyloidosis. Interestingly, all 3 patients in this case series had liver involvement, as demonstrated by hepatomegaly and elevation in liver enzymes, especially ALP and GGT, as well as bone marrow involvement. In addition, none of the 3 patients had severe cardiac problems or involvement of other major organs. We reviewed the literature and found 13 reported patients with AL amyloidosis who presented clinically with spontaneous vertebral fractures; the characteristics of these cases are shown in Table 1.1–12 The median age of the 13 patients was 59 years (range, 29–76 years). There was a male predominance, with men accounting for 69% of affected patients. It is worth noting that of 11 reported cases, 8 (72.7%) also had liver involvement, 10 (90.9%) had bone marrow involvement, and 7 (63.6%) had both liver and bone marrow involvement, while only 1 patient had cardiac involvement, which was consistent with organ involvement in our case series.

In patients with AL amyloidosis who presented with vertebral compression fractures, the bone marrow and liver are frequently involved. The mechanism underlying the high frequency of coinvolvement of these organs is unknown. One possible explanation would be the potential kappa light chain dominance among the patients with vertebral bone involvement. According to Table 1, 8 of 11 patients (73%) were kappa-predominant. Of note, while kappa-predominance was observed in the patients with vertebral fractures and bone marrow involvement, the lambda-to-kappa light chain ratio in patients with AL amyloidosis is 3.8.11 This is in agreement with a former study indicating that the tropism of organ involvement in AL amyloidosis can be influenced by the light chain variable region, which supports the hypothesis that patients with kappa light chains are more likely to have hepatic involvement.12 In another study, soft tissue and bone involvement was considered, the kappa-to-lambda ratio was 1, and the major soft tissue and bone involvement included macroglossia and vertebral compression fractures.8

The mechanism underlying spontaneous vertebral compression fractures in AL amyloidosis has not been identified. In most cases with compression vertebral fractures, biopsies indicate nearly complete replacement of the bone marrow by amyloid fibrils. In addition, all patients reported with AL amyloidosis presenting with vertebral fractures had normal serum calcium, serum phosphatase, and serum parathyroid hormone levels, which was the same as our 3 cases. A possible explanation is that neither osteolytic lesions nor disorders of calcium phosphate metabolism cause multiple vertebral fractures in patients with AL amyloidosis. Instead, amyloid fibrils are first deposited near blood vessels supporting vertebrae, which may cause nutritional insufficiency in vertebrae, leading to progressive loss of bone density, and finally contributes to the compression fractures. Such a mechanism is different from that in amyloidosis associated with multiple myeloma, where lytic lesions are commonly associated and become the major cause of bone fractures.13

Treatment of the patients in this series was no more special than other cases with AL amyloidosis, except that surgery using bone cement was often used in managing vertebral fractures. Melphalan, bortezomib, thalidomide, cyclophosphamide, dexamethasone, and ASCT were used to treat our patients. Fortunately, all 3 patients responded well, with an improvement in symptoms and functional status. Such a favorable prognosis is largely attributed to the early diagnosis and early treatment of AL amyloidosis. During the past few decades, several patients with initial fractures in vertebrae have been reported to have died from AL amyloidosis due to delayed diagnosis as well as inappropriate treatment.14,15

Given our results and the reports in the literature, even though vertebral compression fractures are rare in AL amyloidosis, it is still important to consider AL amyloidosis in the differential diagnosis.
Table 1
AL amyloidosis with presentation of vertebral compression fractures in the literature.

| Study, y | Age, y/sex | Cardiac involvement | Renal involvement | Liver involvement | Bone marrow involvement | Bone involvement | Plasma cell dyscrasia | Treatment |
|----------|------------|---------------------|-------------------|------------------|------------------------|-----------------|----------------------|-----------|
| Axelsson (1970) | 64/M | + | + | | + | Progressive vertebral compression fractures, osteoporosis | Unknown | Unknown |
| Stavem (1980) | 55/M | + | + | | | Multiple spontaneous vertebral compression fractures | Unknown | Unknown |
| Kramer (1986) | 76/F | + | | | | Left femur and several vertebral fractures; osteoporosis | Kappa | Symptom-relief drugs |
| Willerjo (1994) | 29/F | | | | + | T6–7 vertebral compression | Unknown | Laminectomy |
| Prokaeva (2007) | 63/M | Unknown | Unknown | Unknown | Unknown | T4, T6, T7, and T12 compression fractures | Kappa | Unknown |
| | 59/M | Unknown | Unknown | Unknown | Unknown | T10–11 compression fractures | Lambda | Unknown |
| Botelho (2014) | 64/F | + | + | | | T8–11 and L1 vertebral compression fractures | Unknown | Unknown |
| | 47/M | + | + | | | Multiple compression fractures within the thoracic and lumbar spine | Unknown | Laminectomy |
| Sarosiek (2015) | 45/F | + | + | | | T12–L4 vertebral compression fractures | Kappa | Bortezomib, dexamethasone, bisphosphonates; and palliative radiation to vertebrae |
| Present case 1 | 64/M | + | + | | | Two spontaneous thoracic vertebral fractures | Lambda | Melphalan, prednison, and bisphosphonates |
| Present case 2 | 49/F | + | + | | | T7, T9–12, and L3–5 vertebral compression fractures | Lambda | Melphalan, prednison, and bisphosphonates |
| Present case 3 | 48/M | + | + | | | T4, T6–7, and T11–L1 vertebral compression fractures | Kappa | High-dose melphalan and ASCT |
| | 63/M | + | + | | | Multiple spontaneous vertebral compression fractures | Kappa | High-dose melphalan and ASCT |
| | 62/M | + | + | | | Two spontaneous thoracic vertebral fractures | Lambda | Melphalan, prednison, and bisphosphonates |
| | 56/M | + | + | | | Multiple spontaneous thoracic vertebral compression fractures | Lambda | Melphalan, prednison, and bisphosphonates |
| | 59/M | + | + | | | Two spontaneous thoracic vertebral fractures | Lambda | Melphalan, prednison, and bisphosphonates |
| | 56/M | + | + | | | T4, T6–7, and T11–L1 vertebral compression fractures | Kappa | High-dose melphalan and ASCT |
| | 63/M | + | + | | | Multiple spontaneous thoracic vertebral compression fractures | Kappa | High-dose melphalan and ASCT |
| | 64/M | + | + | | | T11 and L1–2 compression fractures | Kappa | Bortezomib, cyclophosphamide, dexamethasone, and kyphoplasty |
| | 49/F | + | + | | | T12 and L1–4 spontaneous fractures | Kappa | ASCT and kyphoplasty |
| | 48/M | + | + | | | T4–9 and T11–L1 compression fractures | Kappa | Melphalan, dexamethasone, thalidomide, and aspirin |

ASCT = autologous stem cell transplantation.
diagnosis of spontaneous vertebral compression fractures, especially in patients with hepatomegaly or elevated liver enzymes. Bone marrow biopsy is necessary, since most of the patients can have bone marrow infiltration of amyloid deposits. The functions of major organs are largely normal in most patients; thus, early diagnosis and early treatment are of great significance for such atypical cases of AL amyloidosis.

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