Bone involvement in patients with systemic AL amyloidosis mimics lytic myeloma bone disease

The definition of organ involvement in systemic AL amyloidosis has been recently published and a consensus conference has defined major criteria for 7 main organ systems.[1] However, bone disease was not included in the list of affected organs and has not yet been systematically studied. It has been diagnosed rarely after emergency surgery of the spine.[2,3]

Using the Salmon and Durie classification[4] patients with monoclonal gammopathy (MG) and osteolytic bone lesions in X-ray are diagnosed as multiple myeloma (MM) stage III. Differentiation between MG or MM as the underlying disease of AL amyloidosis might have significant therapeutic consequences.

Since 2004, we have systematically evaluated 330 patients with systemic AL amyloidosis admitted to our Amyloidosis Clinic for the underlying plasma cell disorder, organ involvement and the presence of bone lesions. Diagnosis of AL amyloidosis had been made using Congo-red staining and immunohistochemical confirmation of the light chain type of amyloid. Conventional bone X-ray was performed as usual in MM. Magnetic resonance imaging (MRI) of the whole body or regions of interest was also performed if osteolyses had been diagnosed or suspected in bone X-ray.[5] Biopsy of the bone lesions had been confirmed in MRI was performed prior to starting chemotherapy. Patients gave their informed consent and the study was approved by the Ethics Committee of the University of Heidelberg.

Four patients with newly diagnosed systemic AL amyloidosis and osteolytic lesions due to amyloid deposits were identified. Two patients had involvement of the spine with spinal cord compression and underwent emergency surgery due to imminent paraplegia. The two other patients had large bone lesions in X-ray and MRI. Figure 1 shows X-ray (digital radiography) of the right proximal femur with osteolytic lesions in the diaphysis of the femur without sclerotic reaction and no alteration of the cortical bone. The corresponding coronal MR-Image (T2 STIR) delineates large areas of increased T2-intensity in the diaphysis of both femurs suggesting bone marrow infiltration by MM. In all 4 patients, biopsy material showed extensive depositions of amyloid in the bone, as well as monoclonal plasma cells and giant cells only at the margins. Patient characteristics and outcome are shown in Table 1.

Patient 3 presented with advanced cardiac involvement. It must be noted that admission for high urgency cardiac transplant was delayed for three months because initially she was considered to suffer from MM stage III, which is an exclusion criterion for solid organ transplantation.[6] She died of progressive heart failure before a donor could be identified. Patient 1 also died of progressive cardiac disease. Two patients are alive after chemotherapy without evidence of progression into advanced MM, although the follow-up period is still relatively short.

Amyloid bone disease is rare and presents a challenge for diagnosis. *Amyloidoma* of the bone has only been reported in a few cases.[7-9] Pambuccian described 3 new cases and 34 cases from the literature, and discussed solitary plasmocytoma with local amyloidosis as the cause of the bone destruction.[7] The description of the histological picture is similar to that observed in our patients. However, at least one of the 3 patients in their report also had systemic organ involvement. Lipper and Lai describe *bone amyloidoma* patients with a long-term follow-up of up to 12 years without progression into advanced MM.[8,9] Apart from MM, bone involvement has also been described in other hematologic malignancies, such as Hodgkin's disease or non-Hodgkin's lymphoma. However, biopsies in these cases showed tumor infiltrates in the bone similar to those in plasmocytoma. The histomorphological description in our patients implied that bone involvement was the result of local amyloid production and deposition because monoclonal plasma cells have only been detected at the margins

Table 1. Characteristics of 4 patients with AL bone involvement.

Patient	*1*	*2*	*3*	*4*
Age at diagnosis	54	73	45	52
Sex	Male	Male	Female	Female
Underlying plasma cell disorder	MG	MG	MM stage I	MG
Monoclonal protein	κ	κ	IgA κ	κ
Immunohistochemistry	rectum biopsy, κ	bone biopsy, κ	bone marrow biopsy, κ	bone biopsy, κ
Level of monoclonal protein in serum at diagnosis	FLC 185 mg/L IF negative	FLC 48 mg/l IF negative	FLC 1840 mg/L IF positive, IgA 3,2 g/L	kappa 286 mg/L IF negative
Level of monoclonal protein in urine at diagnosis	123 mg/d	IF negative	2300 mg/d	655 mg/L
Amyloid deposition in pelvic BM bx	no	yes	yes	no
Plasmacells in BM cytology %	7	17	35	7
Number of lesions in MRI/X-ray	3/3	0/0	>20	18/6
Localization of lesions in MRI	extremities	spine	diffuse	spine, pelvis, scapula, extremities,
Diagnosis of bone involvement	X-ray, MRI, biopsy	MRI, surgery	X-ray, MRI, biopsy	ribs, MRI, surgery
Major involved organ	heart	bone (multiple fractures)	heart	bone (multiple fractures)
Other involved organs	gastrointestinal tract	liver, lung, kidney	polyneuropathy	none
Chemotherapy	CAD	12x MP	5x MDex	3x VAD, CAD, HDM
Current status	died of heart failure +8 months	alive in CR +21 months	died in PR of heart failure +5 months	alive in PR + 16 months

AL: amyloidosis; bx: biopsy; BM: bone marrow; CAD: cyclophosphamide/adriamycin/dexamethasone; CR: complete remission; F: female; FLC: free light chain; HDM: high-dose melphalan; IF: immunofixation; M: male; MDex: melphalan/dexamethasone; MG: monoclonal gammopathy; MM: multiple myeloma; MP: melphalan/prednisone; MRI: magnetic resonance imaging; PR: partial remission.

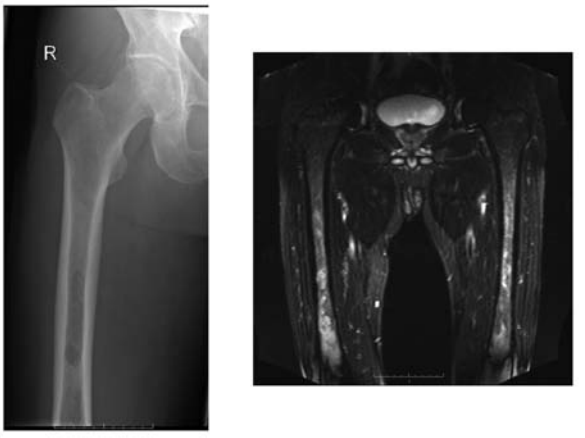

Figure 1. X-ray (digital radiography) of the right proximal femur and corresponding coronal MR-Image (T2 STIR). The X-ray shows osteolytic lesions in the diaphysis of the femur without sclerotic reaction. No alteration of the cortical bone. MRI delineates large areas of increased T2-intensity in the diaphysis of both femurs suggesting bone marrow infiltration by multiple myeloma.

of amyloid deposits. This is a characteristic phenomenon of local amyloidosis[10] in which amyloid is deposited extracellularly at the site of the monoclonal light chain production. The amyloid in the bone might replace the normal bone structures and lead to destruction mimicking MM bone disease in X-ray and MRI.

Our study has two limitations. Whether diffuse amyloid bone marrow involvement might cause osteopenia cannot be answered and needs further investigation. Secondly, there is a risk that we have overlooked concomitant MM bone disease in patients 3 and 4 who presented approximately 20 bone lesions in MRI.

In our opinion, amyloid bone disease must be considered in patients with a monoclonal gammopathy and osteolytic bone lesions. In our institution, X-ray as well as MRI and bone biopsy for suspicious lesions are now included in the evaluation of newly diagnosed patients with systemic AL.

To summarize, amyloid involvement of the bone leading to osteolyses is rare. It might be the result of local amyloid production even in patients with systemic amyloidosis and can mimic lytic myeloma bone disease. Importantly, the diagnosis of advanced MM could mean the physician does not take into consideration cardiac[11] or renal transplant[12] as an effective treatment option prior to high-dose chemotherapy and blood progenitor cell transplantation in these patients.

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