References

1. CUTOLO M, ACCARDO S: Sex hormones, HLA and rheumatoid arthritis. *Clin Exp Rheumatol* 1991; 9: 641-6.
2. MASI AT: Sex hormomes and rheumatoid arthritis: cause and effect relationship in a complex pathophysiology? *Clin Exp Rheumatol* 1995; 13: 227-40.
3. CUTOLO M, BALLEARI E, GIUSTI M, MONACHESI M, ACCARDO S: Sex hormone status of male patients with rheumatoid arthritis: evidence of low serum concentrations of testosterone at baseline and after human chorionic gonadotropin stimulation. *Arthritis Rheum* 1988; 31: 1314-17.
4. MASI AT, JOSIPOVIC DB, JEFFERSON WE: Low adrenal androgenic-anabolic steroids in women with rheumatoid arthritis (RA): gas-liquid chromatographic (GLC) studies of RA patients and matched normal control women indicating decreased 11-deoxy-17-ketosteroid excretion. *Semin Arthritis Rheum* 1984; 14: 1-23.
5. QUIGLEY CA, DE BELLIS A, MARSCHKE KB, EL-AWADY MK, WILSON EM, FRENCH FS: Androgen receptor defects: historical, clinical and molecular perspectives. *Endocr Rev* 1995; 16: 271-321.
6. CHAMBERLAIN NL, DRIVER ED, MIESFEID RL: The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. *Nucleic Acids Res* 1994; 22: 3181-6.
7. KAWASAKI T, USHIYAMA T, UEYAMA H *et al.:* Polymorphic CAG repeats of the androgen receptor gene and rheumatoid arthritis. *Ann Rheum Dis* 1999; 58: 500-2.
8. ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 3: 315-24.
9. YEN JH, CHEN JR, TSAI WJ, TSAI JJ, LIU HW: HLA-DRBI genotyping in patients with rheumatoid arthritis in Taiwan. *J Rheumatol* 1995; 22: 1450-4.

Systemic mast cell disease: a rare cause of osteoporosis

Sirs,

We present a case of a 53-year old woman with a history of a recent onset of weakness, widespread joint and muscle pain, iching, urticaria and lower back pain. A diagnosis of urticaria pigmentosa was performed 10 years previously by skin biopsy. After surgical menopause (49 yrs) the woman had rib fractures without major trauma; she had no anaphylactic episodes, stomach pain or diarrhoea; occasionally she suffered from diffuse iching when sunned. On examination she presented brownish pigmented skin nodules of a few centimetres in diameter, predominantly on trunk and proximal parts of legs. Darier's sign was positive and there was tenderness to finger pressure over the spinal processes of the lumbar spine. Laboratory tests were normal except for markers of bone turnover that were increased (Table I), urine and serum calcium and phosphate levels were normal. Total body scintigraphy with Tc^{99} showed increased radionuclide uptake in some areas of the skull and pelvic girdle, but radiography did not show bone lesions. Bone mineral density (BMD), (DEXA with Hologic 4500 equipment), showed rarefaction of the lumbar spine with normal femoral neck (Table I).

Table I. Values of the parameters examined before and after neridronate therapy.

	BMD L1-L4 g/cm^2	T score L1-L4	BMD femoral neck (g/cm^2)	T score femoral	PYR	D-PYR	u NTX	AP
Before therapy	0.770	-2.5	0.991	0.4	45	9.8	59	285
After therapy	0.824	-2.0	1.013	0.6	32	6.7	38	120

u NTx: urine crosslinked N telopeptides of type I collagen (nM BCE/mM Creatinine) (normal female range 3-51) competitive inhibition enzyme linked immunosorbent assay; PYR: urine pyridinoline (nM/mM creatine) (normal female range 16-37) competitive enzyme immunoassay; DPYR: urine deoxipyridinoline (nM/mM creatine) (normal female range 3.0-7.4) competitive enzyme immuno assay; AP: alkaline phosphatase (UI) (normal range 0-270).

A bone marrow biopsy taken from the iliac crest was compatible with medullary mastocytosis : paraosteal and centromedullary sites showed rounded cell aggregates formed of lymphocytes (CD3 positive), plasma cells (CD79 positive), eosinophils and histiocytes, abundant mast cells with metachromatic cytoplasmic granules in a fine reticulin network; the megakaryocytic and eythropoietic lines were normally represented.

According to the above data the diagnosis of systemic mast cell disease was performed (1-4). The patient was treated with neridronate: 25 mg i.m./month for 6 months; skin lesions were managed with ketotifen (10 mg/die). Ten months later BMD was increased and markers of bone turnover returned into normal ranges (Table I).

Our patient has clearly been affected for years by systemic form of mast cell disease, not by cutaneous mastocytosis: indeed, bone marrow biopsy showed mastocytosis bone localization. Mast cells infiltrating bone marrow release several substances affecting bone metabolism that seem to be related to the extent and the severity of the disease (5, 6).

Radiological lesions occur in 60-80% of cases of systemic mast cell disease; generally bone lesions are widespread: osteosclerotic lesions predominate in the axial skeleton and are sometimes present in the long bones; generalised rarefaction with vertebral fractures occurs in 16% of cases (6, 7). Several cases of osteoporosis secondary to mastocytosis have been reported without skin manifestations or other extraosseous symptoms associable with systemic mast cell disease (3, 6, 8)

There is still no specific treatment for systemic mast cell disease. Ketotifen, inhibiting histamine release, acts on the pathogenetic mechanism of mastocytosis and would therefore affect bone remodelling without altering bone mineral density. Bisphosphonates, inhibiting bone resorption, could potentially be useful in management of systemic mast cell disease, although few data are available in the literature; however, clodronate and pamidronate might have positive effects on bone mineral density and bone pain (9). Owing to high levels of bone resorption markers we prescribed to our patient intramuscular neridronate 25 mg/-month for 6 months. Neridronate is a third generation bisphosphonate with high antiresorptive activity whose main indication is treatment of osteogenesis imperfecta but also used in management of post-menopausal osteoporosis.

In our patient, the increase in bone mineral density and the normalization of bone turnover markers after 6 months of neridronate therapy can be related to the strong antiresorptive effects of this drug and suggests that neridronate could be an effective treatment for osteoporosis caused by systemic mast cell disease.

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References

1. TRAVIS WD, LI CY *et al.*: Systemic mast cell disease: analysis of 58 cases and literature review. *Medicine* 1988; 67: 345-68.
2. WHITE MP: Infiltrative disorders of bone. In *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 4th ed. American Society for Bone and Mineral Research, 1999.
3. CHINES A, PACIFICI R *et al.*: Systemic mastocytosis and osteoporosis. *Osteoporos. Int* 1993; 3 (Suppl. 1):147-9.
4. LIBOR C, FRISCH B *et al.*: Osteoporosis as the sole presentation of bone marrow mastocytosis. *J Bone Min Res* 1990; 5: 871- 6.
5. GRIESER T, MINNE HW *et al.*: Systemic mastocytosis and skeletal lesions. *Lancet* 1997; 350: 1103-4.
6. JOHANSSON C, ROUPE G *et al.*: Bone density, bone markers and bone radiological features in mastocytosis. *Age Ageing* 1996; 25: 1-7.
7. DELLING G, RITZEL H *et al.*: Histological characteristics and prevalence of secondary osteoporosis in systemic mastocytosis. A retrospective analysis of 158 cases. *Pathologe* 2001 Mar; 22:132-40.
8. BIARES V, RAVIOLO P *et al.*: Systemic mastocytosis: a case with diffuse bone involvement. *Minerva Med.* 1996; 87: 33-9.
9. MARSHALL A, KAVANAGH RT *et al.*: The effect of pamidronate on lumbar spine bone density and pain in osteoporosis secondary to systemic mastocytosis. *Br. J. Rheumatol* 1997; 36: 393-6.