British Journal of Rheumatology 1996;35:898–900

CASE REPORT

SEVERE OSTEOPOROSIS DUE TO SYSTEMIC MAST CELL DISEASE: SUCCESSFUL TREATMENT WITH INTERFERON ALPHA-2B

T. LEHMANN, C. BEYELER, B. LÄMMLE,* T. HUNZIKER,† P. VOCK,‡ A. J. OLAH,§ C. DAHINDEN¶ and N. J. GERBER

*Divisions of Rheumatology, *Haematology, †Dermatology, ‡Diagnostic Radiology, §Anatomy and ¶Immunology, University Hospital, 3010 Berne, Switzerland*

SUMMARY

We describe a 33-yr-old man suffering from severe vertebral osteoporosis and urticaria pigmentosa due to systemic mast cell disease (SMCD). Because i.v. clodronate therapy could not prevent further vertebral fractures, an additional treatment with interferon alpha-2b was initiated. During 24 months of treatment, our patient had no further pain episodes, no new vertebral fractures were discovered, trabecular bone mineral density (BMD) increased significantly and urticarial symptoms improved. Nevertheless, the extent of skin lesions remained unchanged. On histological examination, a remarkable decrease of mast cells was observed in the bone marrow, but not in the skin. Five months after discontinuation of interferon alpha-2b, trabecular BMD decreased and urticarial symptoms deteriorated. These findings illustrate a beneficial effect of interferon alpha-2b on SMCD-induced osteoporosis as well as urticarial symptoms, and raise the question whether this treatment may have a diverse impact on mast cell populations in different tissues.

KEY WORDS: Osteoporosis, Systemic mast cell disease, Interferon alpha.

SYSTEMIC mast cell disease (SMCD) is an uncommon disorder characterized by an abnormal proliferation of mast cells with infiltration of skin, bone marrow, spleen, liver and lymph nodes [1, 2]. Typical symptoms include flushing, diarrhoea, vomiting and a skin rash called urticaria pigmentosa. In addition, bone pain, radiographic bone lesions and generalized osteoporosis, occasionally the only manifestation of SMCD, have been described [3–11].

There is no cure for SMCD and prospects in the treatment of SMCD-associated osteoporosis are poor [11–15]. The bisphosphonate clodronate may have a transient efficacy in reducing bone turnover [14] and interferon alpha might be helpful in the treatment of life-threatening SMCD [16, 17].

We report on a patient suffering from severe vertebral osteoporosis and urticaria pigmentosa due to SMCD. After i.v. clodronate therapy for 2 yr had failed in every respect, we established additional injections of interferon alpha-2b.

CASE REPORT

In February 1991, a diagnosis of SMCD with urticaria pigmentosa and osteoporosis was made in a 33-yr-old man with severe back pain.

The skin showed a widespread typical maculopapular rash with Darier's sign and an intense urticarial reaction. On biopsy, there was a perivascular mast cell infiltration in the corium. Thoracic and lumbar spine radiographs revealed fractures of most thoracic and lumbar vertebral bodies 4 and 5. Mean lumbar trabecular bone mineral density (BMD) of vertebral bodies 1–3, measured by single-energy quantitative computed tomography, was 30.4 mg calcium hydroxyapatite (Ca-HA)/ml, equivalent to 4.3 S.D. below the age- and sex-related reference value [18]. A massive infiltration by mast cells was found in a bone marrow aspirate specimen taken from the posterior iliac crest. Histomorphometry of a tetracycline double-labelled iliac bone biopsy revealed: (1) reduced recruitment and/or life span of osteoblasts, as indicated by decreased osteoblast surface; (2) diminished synthetic activity of individual osteoblasts, deduced from the marked decrease in osteoid volume, surface and thickness, and confirmed by non-measurable bone formation rate; (3) normal bone resorption (Table I) [19]. All blood tests for other causes of osteoporosis, including cortisol, free testosterone, intact parathormone, 25-hydroxyvitamin D_3, thyroid-stimulating hormone, growth hormone, calcitonin, and urinary excretion of calcium and hydroxyproline, were within normal limits. Urinary excretion of *N*-methylhistamine was only slightly elevated and serum tryptase was undetectable.

Treatment with clodronate

During i.v. treatment with clodronate, 600 mg every other month, pain improved only temporarily. Urticarial symptoms and lesions remained unchanged with persistent Darier's sign. After 2 yr, new fractures of lumbar vertebral bodies 4 and 5 were noticed, and trabecular BMD was slightly decreasing (Table II). Mast cell infiltration of the bone marrow remained pronounced.

Treatment with interferon alpha-2b

In August 1993, additional treatment with s.c. injections of interferon alpha-2b (Intron A®; Essex SA, Switzerland) was initiated at a daily dose of 0.5 million U and increased every 3 weeks by 0.5 million U to a maximum of 5 million U/day. In August 1994, the dose was reduced to 3×3 million U/week.

Submitted 5 September 1995; revised version accepted 29 April 1996.

Correspondence to: Christine Beyeler, Department of Rheumatology, University Hospital, CH-3010 Berne, Switzerland.

TABLE I
Histomorphometric parameters of bone formation

Histomorphometric parameters of bone formation	Patient's data	Normal values (mean ± S.D.)
Osteoid volume/total volume (%)	0.6	4.9 (2.8)
Osteoid surface/bone surface (%)	3.1	11.6 (6.0)
Osteoid thickness (μm)	5.5	11.1 (2.5)
Osteoblast surface/bone surface (%)	0.5	5.0 (3.2)
Bone formation rate/bone surface ($\mu m^3/\mu m^2$/day)	NM*	0.023 (0.018)
Wall width (μm)	31.3	51.0 (5.6)

*Not measurable.

Urticarial symptoms decreased remarkably and Darier's sign became negative 4 months after the introduction of interferon alpha-2b. Skin lesions, however, were still present to the same extent and perivascular mast cells in biopsy of lesional skin even increased slightly after 12 months. The patient had no further pain episodes and no new fractures were discovered. Lumbar trabecular BMD increased significantly within 1 yr and remained stable after dose reduction of interferon (Table II). Bone marrow aspirate and biopsy specimens showed a remarkable decrease of mast cells after 6 months, and a further reduction after 12 months.

Side-effects

A dose reduction due to adverse effects of interferon alpha-2b was never necessary. Quality of life in general was good throughout the treatment, although a slight tendency to depression, an increased need for sleep and a slight loss of hair were reported, beginning at a daily dose of 3.5 million U. These effects improved after a dose reduction to 3 × 3 million U/week. A mild myelosuppression of all three cell lines was noted, starting at a daily dose of 3 million U and resulting in minimal values for haemoglobin of 12.9 g/dl, white blood cells of 3.0×10^9/l and platelets of 127×10^9/l at a daily dose of 5 million U. All other laboratory parameters did not change throughout the observation period.

Follow-up

Clodronate was stopped in January 1995 and interferon alpha-2b in July 1995 due to well-being of the patient and stable trabecular BMD. However, urticarial symptoms deteriorated 1 month later and trabecular BMD decreased significantly until December 1995 (Table II).

TABLE II
Trabecular bone mineral density (BMD). The *Z*-score is defined by the number of standard deviations below the age- and sex-related reference value. From February 1991 until January 1995, i.v. clodronate infusions were given every other month. From August 1993 until July 1995, s.c. interferon alpha-2b injections were added

Date	Trabecular BMD (mg Ca-HA/ml)	*Z*-score	Per cent change from baseline
February 1991	30.4	−4.3	+16.9
August 1991	21.5	−4.6	−17.3
February 1992	22.0	−4.6	−15.4
September 1992	21.3	−4.5	−18.1
April 1993	19.6	−4.9	−24.6
August 1993	26.0	−4.6	0
December 1993	33.7	−4.3	+29.6
April 1994	47.3	−3.8	+81.9
August 1994	41.5	−4.0	+59.6
February 1995	39.7	−4.1	+52.7
December 1995	29.3	−4.4	+12.7

DISCUSSION

To our knowledge, this is the first report on the beneficial effect of interferon alpha-2b on SMCD-associated osteoporosis.

SMCD is a clonal disorder derived from early pluripotent stem cells of the bone marrow [2, 20] and in some respect resembles myeloproliferative diseases that respond to treatment with interferon alpha [21]. In chronic myelogenous leukaemia, doses up to 9 million U/day are administered, whereas in hairy cell leukaemia 9 million U/week have proven to be effective. In our patient, treated with increasing doses up to 5 million U/day, a clinical and radiological effect emerged after 4 months at a daily dose of 3 million U and no worsening occurred after a dose reduction to 3 × 3 million U/week, suggesting that low doses might be sufficient in the treatment of osteoporosis due to SMCD.

In analogy to two other case reports [16, 22], we noticed a marked decrease of mast cells in the bone marrow, but in our patient this effect emerged without concomitant treatment with corticosteroids. We are well aware of the possibility of a sampling error due to the fact that mast cells gather in clusters. Although urticarial symptoms improved, lesional skin of our patient showed a slight increase of mast cells, confirming the finding of another report [23]. These observations suggest that interferon alpha-2b inhibits proliferation of mast cells in the bone marrow, whereas it may merely interfere with mast cell activity in the skin. Conclusions drawn from the change in cutaneous symptoms, which are easily evaluated, thus cannot necessarily be applied to the course of osteoporosis. As laboratory parameters of bone metabolism did not change during treatment, the bone process could only be judged by measurement of trabecular BMD. This is a considerable impediment in the assessment of interferon's therapeutic efficacy in osteoporosis.

In summary, we document a beneficial effect of interferon alpha-2b treatment in a patient suffering from severe osteoporosis due to SMCD, a potentially disabling disease, for which no other effective treatment is known. More reports are needed to confirm our finding. Whether the response to interferon alpha-2b is dependent on the mast cell phenotype remains to be assessed in further studies.

ACKNOWLEDGEMENTS

We thank Essex Chemie SA, Switzerland, and the private health care insurance Konkordia, Switzerland, for the provision of Intron A®.

REFERENCES

1. Webb TA, Li CY, Yam LT. Systemic mast cell disease: a clinical and hematopathological study of 26 cases. *Cancer* 1982;49:927–38.
2. Travis WD, Li CY, Bergstralh EJ, Yam LT, Swee RG. Systemic mast cell disease: analysis of 58 cases and literature review. *Medicine* 1988;67:345–86.
3. Tharp MD. Southwestern Internal Medicine Conference: the spectrum of mastocytosis. *Am J Med Sci* 1985; 289:119–32.

4. De Gennes C, Kuntz D, De Vernejoul MC. Bone mastocytosis: a report of nine cases with a bone histomorphometric study. *Clin Orthop* 1992;**279**: 281–91.
5. Lidor C, Frisch B, Gazit D, Gepstein R, Hallel T, Mekori YA. Osteoporosis as the sole presentation of bone marrow mastocytosis. *J Bone Miner Res* 1990; **5**:871–6.
6. Lidor C, Hallel T, Oren VO. Migratory multiple bone involvement in a patient with systemic mastocytosis. *Clin Nucl Med* 1990;**15**:640–3.
7. Chines A, Pacifici R, Avioli LA, Korenblat PE, Teitelbaum SL. Systemic mastocytosis and osteoporosis. *Osteoporos Int* 1993;**3**(suppl. 1P):147–9.
8. Floman Y, Amir G. Systemic mastocytosis presenting with severe spinal osteopenia and multiple compression fractures. *J Spinal Disord* 1991;**4**:369–73.
9. Andrew SM, Freemont AJ. Skeletal mastocytosis. *J Clin Pathol* 1993;**46**:1033–5.
10. Harvey JA, Anderson HC, Borek D, Morris D, Lukert BP. Osteoporosis associated with mastocytosis confined to bone: report of two cases. *Bone* 1989;**10**:237–41.
11. Schoenaers P, DeClerck LS, Timmermanns U, Stevens WJ. Systemic mastocytosis, an unusual cause of osteoporosis. *Clin Rheumatol* 1987;**6**:458–62.
12. Metcalfe DD. The treatment of mastocytosis: an overview. *J Invest Dermatol* 1991;**96**:55S–59S.
13. Camus JP, Prier A, Lièvre JA, Stephan JC, Laveant C. L'Ostéoporose mastocytaire. *Rev Rhum Ed Fr* 1979; **46**:29–35.
14. Cundy T, Beneton MNC, Darby AJ, Marshall WJ, Kanis JA. Osteopenia in systemic mastocytosis: natural history and responses to treatment with inhibitors of bone resorption. *Bone* 1987;**8**:149–55.
15. Conrad ME, Carpenter JT, Toddn JN, Murat TM. Mithramycin in the treatment of systemic mastocytosis. *Ann Intern Med* 1975;**83**:659–60.
16. Kluin-Nelemans HC, Jansen JH, Breukelman H *et al.* Response to interferon alfa-2b in a patient with systemic mastocytosis. *N Engl J Med* 1992;**326**:619–23.
17. Austen KF. Systemic mastocytosis. *N Engl J Med* 1992;**326**:639–40.
18. Kalender WA, Felsenberg D, Louis O *et al.* Reference values for trabecular and cortical vertebral bone density in single and dual-energy quantitative computed tomography. *Eur J Radiol* 1989;**9**:75–80.
19. Schenk RK, Olah AJ. Histomorphometrie. In: Kuhlencordt F, Bartelheimer H, eds. *Handbuch der Inneren Medizin VI/1A*. Springer, 1980:438–94.
20. Metcalfe D. Classification and diagnosis of mastocytosis: current status. *J Invest Dermatol* 1991;**96**:2S–4S.
21. Talpaz M, Kantarjian H, Kurzrock R, Trujillo JM, Gutterman JU. Interferon alpha produces sustained cytogenetic responses in chronic myelogenous leukemia Philadelphia chromosome-positive patients. *Ann Intern Med* 1991;**114**:532–8.
22. Delaporte E, Pierard E, Wothers BG *et al.* Interferon-α in combination with corticosteroids improves systemic mast cell diseae. *Br J Dermatol* 1995;**132**:479–94.
23. Czarnetzki BM, Algermissen B, Jeep S *et al.* Interferon treatment of patients with chronic urticaria and mastocytosis. *J Am Acad Dermatol* 1994;**30**:500–1.