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CASE REPORT

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Successful treatment of osteoporosis in systemic mastocytosis with interferon alpha-2b

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Abstract Osteoporosis is frequently seen in systemic mastocytosis. Although diphosphonate therapy has been shown to be transiently effective, therapy options for this form of osteopenia are very limited. We have treated three patients with systemic mastocytosis and osteopenia successfully with interferon alpha-2b. Two patients had urticaria pigmentosa and two severe back pain due to vertebral compression fractures. All patients received a daily interferon dose of 3×5 mio units/week s.c. for a period of 6 months. Therapy was well tolerated, and back pain resolved in both patients. A marked decrease of mast cell numbers in the bone marrow and a significant increase of bone mineralization and bone density was observed in all patients. Our data suggest that alpha interferon may be a new treatment option for osteopenia in systemic mastocytosis.

Key words Systemic mastocytosis · Osteoporosis Alpha-interferon

Introduction

Systemic mastocytosis (SM) is a chronic stem cell disorder with increased numbers of mast cells in the skin, in parenchymatous organs, and in the bone marrow [8]. The clinical picture is influenced by release of mast cell mediators such as histamine, causing flushing, itching, headache, recurrent syncope, etc. Nearly all patients show bone marrow involvement, and clinical as well as radiologic evidence of osteopenia is present in 75% of cases [10]. Bone histology almost always shows a combination of osteosclerosis and osteopenia with a stippled radiographic pattern [3]. Symptomatic bone disease may manifest with severe bone or back pain due to vertebral compression fractures. Currently, an effective treatment of mastocytosis associated osteopenia is unknown, although a transient improvement has been reported with diphosphonate therapy [2]. Because a marked effect of interferon alpha-2b (IFN) was seen in a patient with malignant mastocytosis [5], we have treated three patients with SM and severe osteoporosis with IFN.

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Patients

Patient 1: a 39-year-old man. Diagnosis of SM with urticaria pigmentosa and severe osteoporosis with several vertebral compression fractures was made in 1984. Treatment was started with sodium fluoride, calcitonin, indomethacin, and cromolyn. Urticaria pigmentosa was stable, but osteoporosis progressed rapidly. Due to further vertebral fractures, his body height was reduced by 9 cm and he suffered from severe back pain. In September 1992, IFN-alpha-2b treatment was started (3×5 mio units/week s.c.). When he was re-examined in March 1993, his back pain had improved considerably. Bone density measured with quantitative computed tomography (Q-CT) had increased, and repeated bone biopsies showed improved bone mineralization and markedly reduced mast cell numbers, and IFN was stopped. In September 1993 he presented again with severe back pain. A progression of the osteoporosis with a reduced bone density was noted.

IFN-alpha-2b treatment was started again (3×3 mio units/week s.c.), and by July 1994 his condition, back pain, and bone density had improved again (Fig. 1). Urticaria pigmentosa had improved considerably with IFN-alpha-2b therapy when he was last examined in October 1995.

Patient 2: a 44-year-old man. Diagnosis of SM without urticaria pigmentosa was made in August 1993. He had severe osteoporosis with three vertebral compression fractures. In October 1993 IFN-alpha-2b treatment (3×5 mio units/week s.c.) was started. By May 1994 his back pain, bone density, and osteopenia had improved considerably (Fig. 1).

Patient 3: a 36-year-old woman. In 1982 a diagnosis of SM with urticaria pigmentosa was made. In October 1993, back pain and low-bone density values were noted. IFN-alpha-2b therapy

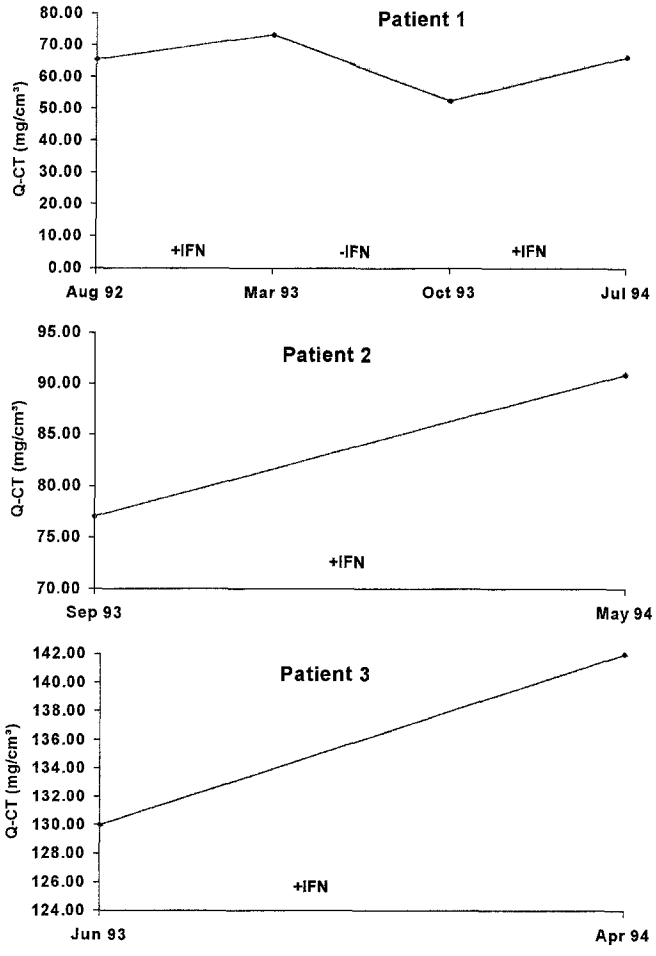

Fig. 1 Osteodensitometry determined by quantitative computer tomography (*Q-CT*)

was given from October 1993 to April 1994 (3×5 mio units/week s.c.). Urticaria pigmentosa showed only a minor response to IFN treatment, but bone density and back pain improved significantly (Fig. 1).

Methods

Osteopenia and mast cell numbers were determined with repeated bone marrow biopsies before and after 6 months of IFN treatment. Vertebral bone density was measured radiographically by dual-energy quantitative computed tomography (Q-CT), according to the method described by Kalender et al. [4]. Bone density was expressed as mg hydroxylapatite per cm^3 bone. Serum histamine levels were determined as described by Lorenz et al. [6] before and 1, 5, 10, and 25 min after the first IFN injection.

Results and discussion

Interferon-alpha-2b therapy was started at 1 mio units s.c. on day 1 up to 5 mio units s.c. on day 5 and then continued at 3×5 mio units/week sc for at least 6 months. Therapy was well tolerated; flue-like symptoms and arthralgias were treated successfully with paracetamol. Urticaria pigmentosa responded considerably in one patient and showed some improvement in another. Back pain improved markedly, so that analgetic therapy could be stopped. In all patients bone density increased (Fig. 1), whereas mast cell numbers and bone resorption decreased. Serum histamine levels increased after the first IFN-alpha-2b injection but decreased subsequently during the treatment (Fig. 1). It was noted that the clinical condition and all bone measurement parameters of patient 1 deteriorated when IFN-alpha-2b was stopped. This phenomenon of disease recurrence is well known in the interferon treatment of patients with other hematological diseases such as chronic myeloid leukemia [9], hairy cell leukemia, multiple myeloma, and non-Hodgkin's lymphoma. Little is known about the way mast cells influence bone formation. Mast cells release a wide range of factors including biogenic amines, chemotactic peptides, proteoglycans, and prostaglandins. Prostaglandins E_1 and E_2, for example, are powerful stimulators of bone resorption. Management of osteopenia due to systemic mastocytosis is difficult. Sodium fluoride, antihistaminics, and cromolyn have been reported to be ineffective. Chlorambucil and mithramycin have been advocated by several investigators but have been found inefficient by others [7]. Recently, diphosphonate therapy has been reported to be transiently effective [2, 7]. As reported by Kluin-Nelemans et al., IFN showed substantial antiproliferative effects in a patient with malignant mastocytosis [5]. They further showed that IFN reduces the liberation of cytokines such as IL-3 and IL-4. This inhibition of mast cell degranulation is supported by our data, because we demonstrated that IFN-alpha-2b reduces serum histamine levels considerably. Figure 2 shows the histamine liberation during and after IFN-alpha-2b treatment in patient 1. Interestingly, histamine levels increased to a value of 2.07 ng/ml when IFN-alpha-2b therapy was started. Although our patient developed no symptoms of anaphylaxis, histamine levels above 1.0 ng/ml have been made responsible for anaphylactic reactions in patients undergoing general anesthesia [6].

Although the exact mechanism of action is unknown, it is assumed that, as in other myeloproliferative diseases, IFN-alpha-2b inhibits mast cell prolifera-

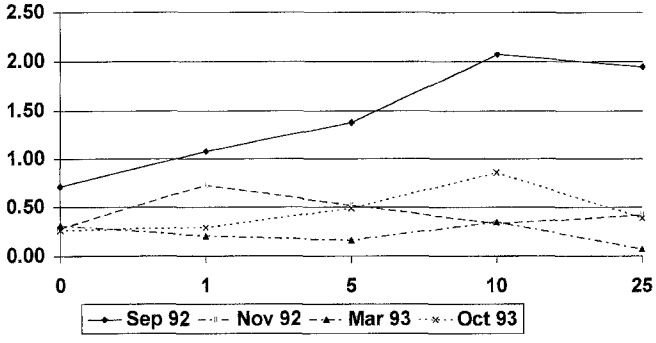

Fig. 2 Liberation of histamine after administration of IFN to patient 1. A value above 0.5 ng/ml is clinically relevant

tion and so reduces liberation of bone resorbing substances. This view is supported by the fact that high-affinity interferon receptors have been found on mouse bone marrow-derived mast cells [7]. We think that the marked improvement of osteopenia in our three patients after IFN-alpha-2b therapy was achieved via a direct inhibitory effect of IFN on mast cells. We conclude that IFN-alpha-2b seems to be an active agent that can improve osteopenia associated with systemic mastocytosis.

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