

Intractable Bone Pain in Myelofibrosis

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Abstract

Myelofibrosis is a rare pre-malignant hematological disease. The aim of treatment is disease control and relief of symptoms. We report a case where disease control was acceptable for 10 years, but with very poor symptom control; in the last 9 months the patient was alive, and he suffered from bone pain that was resistant to any known medical, analgetic therapy. In order to identify plausible differential diagnoses the patient was excessively examined, but only myelofibrosis was found.

Keywords: Myelofibrosis; Bone pain; Extremity pain

Introduction

Primary myelofibrosis (MF) is a clonal disease arising in a hematopoietic stem cell. The expanding clone leads to reactive replacement of bone marrow by collagen fibrosis, osteosclerosis and neo-angiogenesis. Thirty percent of MF patients will develop acute leukemia, and average survival is 5 - 7 years [1]. Extramedullary hematopoiesis causes hepatosplenomegaly, which burdens the MF patient with abdominal pain, early satiety/dyspepsia and diahorrea, and in late phase leads to ascites, portal hypertension and esophagus varices. Anemia, thrombosis, bleeding or infections, by means of inefficient hematopoiesis, are common clinical features of MF, and along with hyper-metabolic symptoms this leaves the MF patient with severely reduced quality of life.

Additionally, some MF patients experience severe extremity/bone pain. The origins of these pains are generally

accepted to be a result of the expanding bone marrow, periostitis or osteosclerosis [2-4]. Autopsies showed osteoporosis, leukemic infiltration in bones and micro-fractures in a case of severe bone pain in MF [5]. Severe bone pain is not a common symptom, and most patients respond to standard analgetics.

We report a case of a man, who had MF for at least 10 years, was treated with hydroxurea (HU), and developed intractable bone pains during the last 6 months of life.

Case Report

A 52-year-old man debuted in 1998 with apoplexia in capsula interna sinistra resulting in dysaesthesia and hemiparesis dextra. Peripheral blood analysis showed high hemoglobin and thrombocytosis. Bone marrow aspirate showed hyperplasia in erythropoiesis, granulopoiesis and thrombopoiesis, but not enough to fulfill diagnostic criteria for MPN. He was treated with venesection and aspirin, though HU treatment was discussed, primary to reduce thrombocyte count in this patient with prior thrombosis, but the patient rejected this.

In 2004 thrombocyte count reached $931 \times 10^9/L$ and a new bone marrow aspirate showed progression to early state MF with suppressed erythropoiesis and hyperplastic thrombo- and granulopoiesis. HU 10 g weekly was initiated with significant effect on peripheral blood count, and treatment was tolerated well. He continued venesection once in a while to maintain hematocrit below 45%. After 4 years he needed venesection more frequently to maintain hematocrit, and increasing HU dose was discussed. Since the patient tolerated venesection well, he did not wish to have more HU.

Peripheral blood picture changed media 2012 as thrombocytes rose to $812 \times 10^9/L$. HU dose was discussed, but the patient had a lot of respect for medicine in general and did not want to have more HU. For 6 months his peripheral hematology indicated sub-optimal treatment, as thrombocytes were $700 - 800 \times 10^9/L$ and leukocytes $14 - 18 \times 10^9/L$. HU was increased to 12 g weekly in December 2012 with good effect on peripheral blood count, and no adverse effects. During winter 2012/13 the patient had accelerating problems in walking because of pains in hips and femurs, and had of-

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ten infection, treated in primary sector. He was examined by orthopedic colleagues because of accelerating pains in legs, arms and columnna, especially in the hip/lumbar region, but only finding was minor degree of arthrosis. Prostate specific antigen (PSA) was normal. Combination therapy with morphine, gabapentin, paracetamol and ibumetin had some effect on the pains. In June 2013 peripheral hematological parameters decreased and HU was paused. New bone marrow aspirate showed chronic phase MF, no dysplasia. MR-scan of columnna showed diffuse marrow infiltration in lumbar corpora, os sacrum and os ileum, and there was no radiologic findings indicating discus prolapse or caudaequina. Bone biopsy from the affected area in os ileum showed MF similar to the bone marrow sample. Pegasys 90 µg weekly was started, initially with some effect on bone pain, but after 1.5 months the pains accelerated, now also affecting thorax and costae, and constitutional symptoms (night sweat and weight loss) occurred. There were no new radiologic findings, and a new bone marrow aspirate showed unchanged MF status. Pegasys doses were increased to 135 µg/week, and prednisolon was added, but gave only limited effect. Daily morphine doses was 160 mg, and insufficient. Analgetic therapy was changed to fentanyl patch releasing 50 µg/h initially, increased to 125 µg/h, but still inefficient. The patient died a few days after the last increase in morphine dose, but still in severe pain.

Discussion

This case demonstrates a rare history of MF, where disease control was acceptable for many years, but the patient developed severe bone pains in the last 9 months of his life. He was treated with high doses of morphine without significant and lasting effect. Several radiologic examinations and bone marrow aspirates showed nothing but MF, and PSA was normal.

The literature is sparse regarding treatment of resistant extremity pain in MF. One study describes five MF patients with intractable extremity pain treated with low-dose single fraction radiation. In four of these patients radiation therapy

did release pain within days. The fifth patient did not respond to therapy for a month, but after physical therapy he had pain relief for several years. Remission lasted from a few weeks in two cases, to several years. Short remission was associated with accelerated disease or transmission to AML [6]. In our case the patient had pain in all four extremities, hip, back and thorax. Low-dose radiation therapy involving such a large treatment area could cause intractable hematological toxicity.

Bone pain in MF seems to have many causes; our knowledge comes from a few case reports and general assumptions. Until we understand more about the genesis of severe bone pain, treatment must be based on trial-and-error with great regrets for the patient.

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