Alleviation of polyarticular syndrome in multicentric reticulohistiocytosis with intravenous zoledronate

C P Mavragani, K Batziou, K Aroni, D Pikazis, M N Manoussakis


A 67 year old previously healthy women presented with a 12 month history of generalised symmetric arthralgias and bilateral hand contractures. Her past medical history was unremarkable, except for heavy smoking.

On physical examination, she had tight incapacitating flexion contractures of both hands, and small cutaneous nontender well circumscribed nodules (3–6 mm diameter) on the dorsum of the fingers and over the proximal and distal interphalangeal joints (fig 1). A symmetric polyarthritis affecting the shoulders, elbows, proximal and distal interphalangeal joints, and the knees was prominent. Blood counts, biochemical profile and inflammatory markers, antinuclear antibodies, and rheumatoid factor were within normal limits. A hand x-ray examination showed erosive deforming arthropathy of the styloid processes. Biopsy samples of a skin nodule and of synovial membrane disclosed infiltrates of multinucleated giant cells and histiocytes, indicative of multicentric reticulohistiocytosis (MRH). The infiltrating histiocytes were macrophages, as illustrated by positive staining for CD68 marker and negative staining for S-100 (Langerhans’ dendritic cell marker) and HHF-35 actin (fibroblast marker).

The well described association of MRH with malignancies1–3 had prompted the screening for underlying malignancies, which disclosed a 10-fold increase of CA-125. A pelvic computed tomographic scan was normal; however, magnetic resonance imaging showed the presence of a small well circumscribed mass at the left parametrial space, which was subsequently removed by laparotomy and diagnosed as well circumscribed benign mass. After surgery the patient had a generalised painful stiffness of the trunk and extremities, which required the use of narcotic analgesics and confined her to bed. Intravenous methylprednisolone pulses were also administered, without response. Based on the recently reported effectiveness of intravenous alendronate for MRH,4 zoledronate (4 mg) was given intravenously, because alendronate was unavailable locally. Two weeks later, the stiffness and arthralgias were dramatically reduced. The patient is now completely free of pain and ambulatory.

DISCUSSION

MRH is a rare disorder of unknown cause, characterised by destructive symmetric arthritis associated with cutaneous papulonodular lesions. In about one third of patients, musculoskeletal symptoms may precede or follow an underlying malignancy (such as breast and ovarian cancer, melanoma or mesothelioma).5 MRH should be differentiated from fibroblastic rheumatism, which is also rare.6 Although strict differentiating histological criteria are lacking, multinucleated foreign body-type giant cells appear to denote MRH, whereas the predominance of myofibroblasts and excessive collagen production characterises fibroblastic rheumatism.5 The inclusion of fibroblastic rheumatism in the broader spectrum of non-Langerhans’ cell histiocytosis has been recently proposed.7

To date, the decision for systemic therapeutic intervention in MRH remains largely empirical. Treatment with steroids and various cytotoxic agents is of questionable efficacy,7 and in our patient it resulted only in resolution of the cutaneous nodules. Recently, the beneficial role of tumour necrosis factor blockers has been suggested; however, these are contraindicated in patients with concomitant neoplasia.

Intravenous alendronate has been recently proposed.8 In our patient, the administration of the parenteral bisphosphonate zoledronate, so far used for the treatment of osteoporosis and of hypercalcaemia of malignancy,9 dramatically alleviated the incapacitating joint symptoms. The precise mechanism of bisphosphonate action on MRH is unclear. However, after intravenous injection, bisphosphonates have been previously shown to deposit in the reticuloendothelial system,10 to inhibit the metalloprotease activity and matrix metalloproteinase-9 expression of infiltrating macrophages,11 and to induce apoptosis of macrophage-like cells.12 Therefore, one may speculate that their favourable effect in MRH is due to the inhibition of tissue infiltration by histiocytes, possibly through induction of apoptosis.

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Figure 1 Contraction flexures and cutaneous nodules in the dorsum of the fingers (arrows).

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Acetaminophen may act through β endorphin

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Acetaminophen, also known as paracetamol, is a non-steroidal anti-inflammatory drug (NSAID) with potent antipyretic and analgesic actions but with very weak anti-inflammatory activity. The mechanism of action of acetaminophen is still not clearly understood. It has no known endogenous high affinity binding sites. In addition, acetaminophen does not appear to share with NSAIDs the ability to inhibit peripheral cyclooxygenase (COX) activity. Although various biochemical studies point to inhibition of central COX-2 activity, the existence of a COX activity that is selectively susceptible to acetaminophen (COX-3?) is an alternative hypothesis. However, this may hold true only for the dog. Database analysis of human COX-1 showed a frame shift induced by intron 1, possibly showing COX-3 to be a virtual protein in humans.

Our studies in osteoarthritis provide evidence of a clear effect of acetaminophen on β endorphin levels in plasma (fig 1) compared with rofecoxib 25 mg/day. Plasma β endorphin levels decreased in 10 patients with osteoarthritis after 1 month of treatment with up to 4 g/day acetaminophen orally (p = 0.017) as well as after 3 months of treatment (p = 0.028). Whereas, there were no changes in the rofecoxib group after 1 month (p = 0.73) and 3 months (p = 1.00), respectively.

Acetaminophen may play a part in the delivery of peripheral β endorphin to their receptors and thereby relieve pain.

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