LESSON OF THE MONTH

Multicentric reticulohistiocytosis: a rare cause of erosive arthropathy of the distal interphalangeal finger joints

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Background: Multicentric reticulohistiocytosis (MRH) is a rare systemic disease, presenting with typical skin abnormalities and erosive polyarthritis, which is often associated with malignancy.

Case report: A case of MRH arthropathy, in which the typical nodular skin manifestation of the disease was absent, is described in a patient with a past history of breast cancer and no evidence of recurrent or new malignancy.

Results: Careful clinical and roentgenological evaluation disclosed important clues to differentiate this condition from other more common distal interphalangeal arthritides—namely, osteoarthritis and its “erosive” variant, rheumatoid arthritis, psoriatic arthritis, tophaceous gout, dialysis related hand arthropathy, and from the rarer fibroblastic rheumatism, all of which can be mimicked by MRH. Histopathology showed the characteristic histiocytic and multinucleated giant cell infiltrate with ground glass cytoplasm, and immunohistochemical analysis showed markers evocative of a monocyte/macrophage origin of MRH.

CASE REPORT

A 70 year old non-insulin dependent diabetic white woman was referred to us for a progressive deformity, only slightly painful, affecting the 2nd and 3rd distal interphalangeal (DIP) joints of both hands, which she had complained about for one year. In 1986 the patient underwent left mastectomy for breast cancer. In 1988 and in 1991, respectively, axillary nodes clearance and irradiation of superclavicular lymph nodes were further required owing to metastatic disease. No evidence of disease recurrence was subsequently shown during clinical, laboratory, and instrumental follow up.

Physical examination showed a bilateral mild swelling (fig 1A) of the 2nd and 3rd finger DIP joints resembling Heberden's nodes, usually found in osteoarthritis (OA), together with joint instability and decreased range of motion. Accurate skin examination and palpation for breast masses and lymphadenopathy were negative. Laboratory findings showed a raised erythrocyte sedimentation rate (52 mm/1st h; normal <38) and C reactive protein (8 mg/l; normal <6 mg/l), mild normochromic-normocytic anaemia (haemoglobin 114 g/l) and leucopenia (white blood cells $3.7 \times 10^9/l$). C3 and C4 complement levels were within normal limits and routine biochemistry was otherwise normal. An x ray examination of the hands showed a destructive arthropathy with prominent subchondral bone osteolysis, leading to joint space widening and severe malalignment of the 2nd and the 3rd DIP joints of both hands (fig 1B). The unexpected radiographic pattern, quite unusual for nodal OA, prompted us to perform a synovial biopsy, which showed a histological picture consistent with a histiocytic granuloma: the synovial membrane showed a nodular infiltrate of plump histiocytes with abundant finely

Figure 1 (A) Absence of skin nodules is coupled with deformity and mild swelling resembling Heberden's nodes of the 2nd and 3rd finger DIP joints of the right hand. (B) The corresponding right hand x rays show the presence of large erosions of the 2nd and 3rd DIP joints. Note the markedly enlarged joint space and the absence of heterotrophic new bone formation.

granular eosinophilic cytoplasm, multinucleated giant cells, and fibrosis (fig 2). The cytoplasm of histiocytes and giant cells showed a striking periodic acid-Schiff (PAS) diastase resistant positivity and CD68 immunoreactivity, which failed to stain with anti-S100 and anti-CD1a. A diagnosis of multicentric reticulohistiocytosis (MRH) was established and, when further diagnostic investigation had ruled out the presence of primary or metastatic cancer, treatment with

Abbreviations: DIP, distal interphalangeal; MRH, multicentric reticulohistiocytosis; OA, osteoarthritis; PAS, periodic acid-Schiff; PsA, psoriatic arthritis

Figure 2 Synovial membrane cellular infiltrate mainly composed of large histiocytes with eosinophilic ground glass cytoplasm, sparse multinucleated giant cells, and fibrosis (haematoxylin and eosin stain).

prednisone (5 mg daily), low dose methotrexate (10 mg intramuscularly weekly), and bisphosphonates (clodronate 100 mg intramuscularly weekly) was started. After a 12 month follow up no skin rash and no apparent neoplasia were noted, but hand x rays showed progression of the disease with further erosive involvement of both thumb interphalangeal joints, the left 5th proximal interphalangeal joint, and the right trapezio-metacarpal joint.

DISCUSSION

MRH is a rare systemic disease of unknown cause characterised by flesh coloured to reddish-brown papules and nodules over the skin (giving a so-called “coral beads” appearance around the nailfolds) and oropharyngeal and nasal mucosal surface, associated with a destructive and mutilating polyarthritis. Constitutional complaints such as fever, malaise, weight loss, and itching are commonly present.¹ Data on its incidence and prevalence are unavailable. Fewer than 200 patients are described in the literature and, except in the work by Barrow and Holubar,² they are reported mostly as small sized series or isolated cases. This report is the second of two cases³ seen at our clinic over 30 years.

The arthropathy of MRH is a destroying, symmetrical, and relatively painless process usually localised but not confined to the interphalangeal finger joints.⁴ Cutaneous involvement occurs first in only 18% of patients, and in 21% it develops simultaneously with the arthritis, while in the remaining cases the typical skin lesions are missing at the onset, and follow arthritis after an average of three years.² A diagnosis of MRH can easily be suspected when a patient is seen with the typical skin lesions associated with the erosive arthritis characteristic of the disease in its full presentation. On the other hand, the arthropathy of MRH, as the sole manifestation of the disease, can scarcely be differentiated from other more common arthritides by clinical and radiological methods alone.

Our patient presented with swelling limited to DIP finger joints, resembling Heberden's nodes (fig 1A). Such a sign might have pointed to a diagnosis of nodal OA of the hands. However, the history, dating back only one year, and x rays of the hands, disclosing a bilateral symmetric involvement of the 2nd and 3rd finger DIP joints with a gross erosive process coupled with remarkable enlargement of the joint space (fig 1B), were against OA. The characteristic radiological changes of interphalangeal finger OA, such as subchondral bone sclerosis, joint space narrowing, and marginal osteophytic bone outgrowths, were absent.

Subchondral sclerosis, osteophytes, joint space narrowing and, moreover, a tendency to ankylosis are typically noted also in the “erosive” variant of OA, which is considered by some authors⁵ merely as a phase in the evolution of finger OA. It is distinguished for the superimposition of erosions, commonly beginning as sharply margined defects in the central portion of the joint giving a so-called “gull wing” appearance.⁶ Moreover erosive OA is usually heralded by marked inflammatory complaints (pain, redness, and warmth),⁷ whereas MRH is a relatively painless arthritis.

In our patient the distribution of articular lesions ruled out a diagnosis of rheumatoid arthritis, in which severe erosions of finger DIP joints occur less commonly (in about 3% of patients)⁸ and are usually associated with changes at more proximal joints of the hands. The absence of periarticular osteopenia and of joint space reduction further distinguishes MRH from rheumatoid arthritis.

DIP finger joints involvement is common in psoriatic arthritis (PsA), in which it may even occur in the absence of psoriatic skin abnormalities which can appear only later in the course of the disease in 15–20% of cases.⁹ Extensive erosions in PsA may produce a mutilating arthritis with an “opera-glass” appearance of the hands,¹⁰ but enthesal and periosteal new bone production and an asymmetrical pattern of articular involvement are additional radiographic features which help in differentiating PsA from MRH.^{4,11}

Chronic tophaceous gout may present as a destructive arthritis potentially mimicking MRH. Tophaceous gout with prominent involvement of the interphalangeal finger joints is associated with diuretic use, particularly among elderly women,¹² and often involves joints that are already affected by nodal OA.¹³ However, tophaceous gout often also affects joints other than the finger DIP joints, mostly asymmetrically, showing prominent soft tissue swelling (tophi) and a non-demineralising arthritis with either central, marginal, or peri-articular erosions with overhanging edges and reactive changes of bone. Remarkably, in gouty arthritis the joint space is well preserved in width until the late stages of the disease, when joint space narrowing and even bony ankylosis have been seen.¹⁴

A destructive DIP arthropathy with radiological evidence of subchondral osteolysis and widening of the joint space, with scant complaints of joint pain and inflammation, has been reported also in patients undergoing dialysis for chronic renal failure.¹⁵ Radiological evidence of an extensive subchondral cystic involvement, located especially in the carpal bones, of chondrocalcinosis and of periarticular calcifications as well as the frequent coexistence of other dialysis related osteoarticular disorders of the hand, such as carpal tunnel syndrome and flexor tendinopathies,¹⁶ clearly distinguish dialysis hand arthropathy from MRH.

Romas *et al* reported a noteworthy case of fibroblastic rheumatism,¹⁷ a disease even rarer than MRH, which can mimic MRH itself for the presence of skin nodules and a symmetrical destructive arthropathy characterised by erosive changes with prominent involvement of interphalangeal finger joints, particularly the DIP joints. However, the usual occurrence of Raynaud's phenomenon and sclerodactyly and the presence of juxta-articular osteoporosis in fibroblastic rheumatism, the latter being disproportionately mild with respect to the erosive changes in MRH, are valuable features which enable differentiation between the two diseases.

Biopsy of pathological skin or synovial tissue is usually required to achieve a definite diagnosis, and the finding of mononuclear and multinucleated giant cells with eosinophilic “ground glass” PAS positive cytoplasm is typical of MRH. In our patient the positive reaction for anti-CD68, coupled with a negative staining with anti-CD1a and anti-S100, supports a monocyte/macrophage origin of MRH as in most of previous reports.¹⁸

MRH has been reported to occur simultaneously with primary breast cancer,¹⁹ and in association with recurrent,

metastatic breast carcinoma²⁰ and with a lymph node metastasis of an unknown primary carcinoma expressing the immunohistological phenotype of breast cancer cells.²¹ In our patient the diagnostic investigation showed no evidence of primary or recurrent neoplastic disease. On the other hand, MRH is associated with malignancy in about 30% of the cases reported,^{2,22-23} and it is considered by some authors to represent a paraneoplastic manifestation.²¹ Nevertheless, the wide spectrum of malignancies seen in association with MRH (breast, cervix, colon, stomach, lung, pleura, larynx, ovary, lymphoma, leukaemia, sarcoma, melanoma, and metastasis of unknown primary cancer), together with the fact that the two diseases do not always run a parallel course, makes the paraneoplastic nature of this entity questionable.^{19,24}

Owing to the unfeasibility of controlled trials because of the rarity of the disease, there is no consensus about drug treatment of MRH. Hence, the treatment of this disease remains largely empirical. Nevertheless, remission or at least stabilisation of MRH has been achieved by treatment with corticosteroids, alkylating agents, methotrexate, and hydroxychloroquine, as single drugs or in combination regimens.²⁵⁻²⁷ In our patient the initial therapeutic attempt with low dose steroids, pulse methotrexate, and anti-bone resorptive agents did not improve the erosive changes, which rather extended to affect other finger joints.

In conclusion, although the definitive diagnosis of MRH rests upon histological examination of biopsy specimens, careful roentgenological reading and analysis of clinical features are the keys to the early diagnosis of this disease and enable differentiation of this rare disease from other more common erosive DIP finger arthropathies; the pathogenesis of this condition is unknown but, owing to the frequent association of MRH with cancer, it is mandatory to consider such a possibility during diagnostic investigation.

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