



Original contribution

Osteoclast differentiation and bone resorption in multicentric reticulohistiocytosis

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Summary Multicentric reticulohistiocytosis (MR) is a systemic disease of unknown cause characterized by the presence of a heavy macrophage infiltrate in skin and synovial tissues and the development of an erosive polyarthritis. The synovial fluid in MR is known to contain numerous mononuclear cells. In this study, we have determined whether these cells contribute to joint destruction in MR by differentiating them into osteoclasts. Synovial fluid mononuclear cells were isolated from the knee joint of a 44-year-old male with MR. These cells were cultured with various combinations of macrophage–colony stimulating factor, receptor activator for nuclear factor κ B ligand (RANKL), tumor necrosis factor α , interleukin-1 α , osteoprotegerin, and zoledronate. Osteoclast differentiation was assessed by expression of tartrate-resistant acid phosphatase, vitronectin receptor, and the extent of lacunar resorption. Most MR synovial fluid mononuclear cells expressed a macrophage phenotype (CD14⁺, CD68⁺, HLA-DR⁺, CD11b⁺). Extensive osteoclast formation and lacunar resorption were noted in macrophage–colony stimulating factor/RANKL–treated cell cultures. MR synovial fluid contained increased tumor necrosis factor α and decreased osteoprotegerin compared with osteoarthritis synovial fluid. Lacunar resorption was inhibited in cultures containing zoledronate. Pamidronate treatment of the patient also reduced the number of synovial fluid macrophages and resulted in less osteoclast formation and lacunar resorption. MR synovial fluid contains numerous macrophages that are capable of differentiating into osteoclasts by the RANKL signaling pathway. Inhibitors of osteoclast formation and resorption activity may be of use in preventing the severe joint destruction that commonly occurs in MR.

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1. Introduction

Multicentric reticulohistiocytosis (MR) is a rare systemic disease of unknown cause characterized by the presence of a heavy macrophage infiltrate in the skin and synovial tissues

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[1,2]. Although the natural course of this disease is variable, a progressive symmetric erosive polyarthritis occurs in approximately 60% of cases. This arthritis can resemble rheumatoid arthritis with small joints of the hands and feet often being affected. Marginal erosions commonly occur, and there is progressive joint destruction. Approximately one half of patients exhibit extensive phalangeal resorption with shortening of the fingers and end-stage arthritis mutilans [3,4]. Response to corticosteroid and immunosuppressive treatment is variable and unpredictable, but recent reports have suggested a promising therapeutic role for bisphosphonates and anti-tumor necrosis factor α (TNF α) biologics [5,6].

The characteristic cutaneous nodules in MR contain numerous plump mononuclear and multinucleated cells that are believed to contain phospholipids, glycoproteins, and neutral fat. A number of studies have shown that these inflammatory cells have a macrophage phenotype [7-10], although one study suggested that these cells have a dendritic cell origin [11]. Similar collections of mononuclear and multinucleated cells are found in joint tissues [12-15]. However, the precise origin and nature of the infiltrating mononuclear cells found in MR synovial tissues and synovial fluid have not been defined, and some studies have noted a predominance of lymphocytes [15,16].

It has previously been shown that macrophages in the synovial membrane and synovial fluid of inflamed joints are capable of differentiating into osteoclasts, the multinucleated cells that are specialized to carry out lacunar bone resorption [17,18]. To determine the nature of mononuclear cells in MR joint fluid and to examine whether these cells play a role in the joint destruction, we have analyzed the phenotype of the mononuclear cells obtained from the synovial fluid of a patient with MR and cultured them under conditions required for mononuclear phagocyte-osteoclast differentiation. In this way, we have defined the humoral conditions by which osteoclast differentiation occurs in MR and examined the effect of anti-resorptive and anti-inflammatory agents on osteoclast formation and resorption as well as changes in MR synovial fluid cytology.

2. Materials and methods

2.1. Case report

A previously healthy 44-year-old man presented with a 6-week history of fevers, drenching night sweats, weight loss, and widespread asymmetric polyarthropathy affecting virtually all his peripheral joints. He developed an itchy rash maximal over the ears, hairline, and shoulders, which subsequently spread to the extensor surface of all the fingers as well as the lips and buccal mucosa. Initial investigations showed an elevated C-reactive protein (200 mg/L), normal chest radiograph, negative rheumatoid factor, and normal

blood white cell count. The diagnosis of MR was suspected from the clinical presentation and confirmed by the histology of biopsies taken from skin lesions on the left arm and right hand (see below). Synovial fluid was aspirated from the knee joint when the patient first presented and on 5 subsequent occasions during treatment.

The patient was treated initially with 3 pulses of 1 g methylprednisolone intravenously on alternate days followed by an oral maintenance dose of prednisolone 10 mg daily. In the light of the encouraging reports of the use of bisphosphonates in this condition [5], treatment with pamidronate was started (60 mg intravenously at monthly intervals for 6 months). On this regimen, there was substantial benefit in his joint symptoms, and repeat radiographs showed only early erosive change in the third right proximal and distal interphalangeal joints. However, there was deterioration in the severe skin disease during this time. Consequently, he received 4 infusions of the anti-TNF α chimeric monoclonal antibody, infliximab (3 mg/kg); 12 weeks later, his skin had greatly improved, and there was further improvement in his joints.

All synovial fluid samples taken at presentation and during treatment were sent for analysis of synovial fluid cytology and microbiological culture. The total nucleated cell count, differential, and preparation of cytocentrifuged specimens for hematoxylin-eosin, periodic acid-Schiff (PAS), and immunohistochemical staining were carried out as previously described [19]. Cytospin preparations were also examined by transmission electron microscopy. These were fixed with 2.5% glutaraldehyde/0.1 M cacodylate buffer, pH 7.2, postfixed in osmium tetroxide, dehydrated by passing through graded alcohols, and then embedded in epoxy resin. Serial thin sections were cut and then stained with uranyl acetate and lead citrate before examination in a JEOL 1200EX transmission electron microscope (JEOL Ltd, Tokyo, Japan).

2.2. Reagents

All cell incubations were performed in α minimal essential medium (α MEM) (Invitrogen, Paisley, UK) and glutamine (2 mmol), benzyl penicillin (100 IU/mL), streptomycin (10 μ g/mL) (Gibco, Paisley, UK), and 10% heat-inactivated fetal bovine serum (FBS) (Sigma, Dorset, UK). Synovial fluid cell cultures were incubated in a humidified atmosphere with 5% carbon dioxide at 37°C. Human soluble receptor activator for nuclear factor κ B ligand (RANKL) and osteoprotegerin (OPG) was kindly provided by Amgen Inc (Thousand Oaks, Calif). Human macrophage-colony stimulating factor (M-CSF), TNF α , and interleukin-1 α (IL-1 α) were purchased from R&D Systems Europe (Abingdon, UK), dexamethasone (Sigma) was dissolved in absolute alcohol and stored at -20°C, and zoledronate was supplied by Novartis Pharma (Basel, Switzerland) dissolved in a stock solution of water at a concentration of 100 mmol and stored at -20°C.

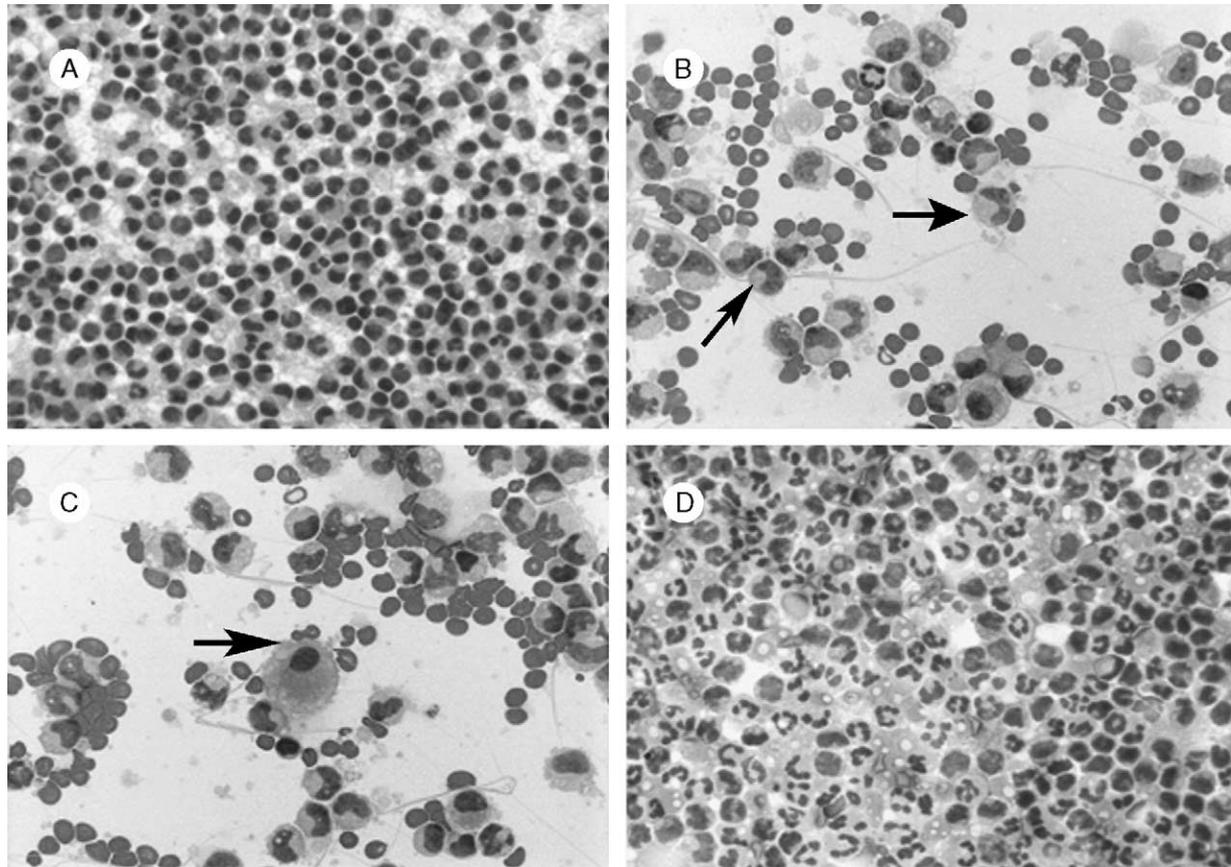


Fig. 1 Cytological findings of knee joint synovial fluid at the time of presentation showing in numerous mononuclear macrophage-like cells (A and B), many of which have an indented nucleus (arrows), and in scattered plump cells with foamy cytoplasm (C). (D) After treatment with infliximab, in addition to scattered macrophage-like cells, there are also large numbers of polymorphs (hematoxylin-eosin, original magnification $\times 40$ [A], $\times 200$ [B,C], and $\times 100$ [D]).

2.3. Isolation and culture of MR synovial fluid cells

Aspirates of synovial fluid taken at initial presentation, 10 and 20 days posttreatment with corticosteroids and pamidronate were used for isolation of MR synovial fluid cells. Synovial fluid was collected in sterile universal tubes and centrifuged at 2250 rpm for 25 minutes at 4°C . The cell pellet was removed and washed in α MEM and then resuspended in α MEM/FBS. The number of synovial cells in the cell suspension was counted in a hemocytometer after lysis of red cells with a 5% vol/vol acetic acid solution. Synovial fluid cells (1×10^5) were added to 4-mm-diameter dentine slices and 6-mm-diameter glass coverslips and incubated for 2 hours at 37°C in 5% carbon dioxide. After 2 hours incubation, nonadherent cells were removed by washing. Dentine slices and glass coverslips were then transferred to 16-mm-diameter wells of a 24-well tissue culture plate and incubated for up to 14 days in α MEM/FBS in the presence of the following cytokines/growth factors: (1) no factor; (2) M-CSF (25 ng/mL); (3) RANKL (30 ng/mL); (4) M-CSF (25 ng/mL) + RANKL (30 ng/mL); (5) M-CSF (25 ng/mL) +

TNF α (20 ng/mL) + IL-1 α (10 ng/mL); (6) M-CSF (25 ng/mL) + TNF α (20 ng/mL) + IL-1 α (10 ng/mL) + OPG (100 ng/mL); (7) M-CSF (25 ng/mL) + RANKL (30 ng/mL) + zoledronate (10^{-8} mmol). The culture medium and humoral factors were replaced every 3 days.

2.4. Cytochemical assessment of MR synovial fluid cells and osteoclast formation

Cell preparations on coverslips at 24 hours, 7 days, and 14 days were assessed histochemically for the expression of the osteoclast-associated enzyme, tartrate-resistant acid phosphatase (TRAP), using a commercially available kit (Sigma) [20]. Cell preparations on coverslips were also stained immunohistochemically by an indirect immunoperoxidase technique with the monoclonal antibody 23C6 (Serotec, Oxford, UK), which is directed against CD51; the vitronectin receptor (VNR), a highly osteoclast-associated antigen [21]; and, JML-H14, directed against CD14, a monocyte/macrophage-associated antigen that is not expressed by osteoclasts [22,23].

2.5. Functional evidence of osteoclast differentiation

Functional evidence of osteoclast differentiation was determined by a lacunar resorption assay system using cell culture on dentine slices [17]. Dentine provides a smooth-surfaced mineralized substrate for the assessment of lacunar resorption. After cells had been cultured on dentine slices for either 24 hours, 7 days, or 14 days, the slices were removed from the wells and fixed in 4% glutaraldehyde and 10% Triton-X-100. The dentine slices were dehydrated by passing through graded alcohols and then through graded hexamethyl-disilazane (Sigma) before being air-dried. Dentine slices were then mounted on to aluminum stubs (Agar Scientific Ltd, Stansted, UK) using double-sided sellotape, sputtered with gold, and examined using a Philips SEM 505 scanning electron microscope (Philips Electron Optics, Eindhoven, The Netherlands). The extent of lacunar resorption on each dentine slice was measured using a computer image analysis system and expressed as the percentage of surface area resorbed \pm standard error of the mean.

2.6. Detection of cytokines in MR synovial fluid

Levels of TNF α and OPG in the synovial fluid were measured using enzyme-linked immunosorbent assay (ELISA) kits following the manufacturer's instruction (Quantikine; R&D Systems). Synovial fluids aspirated from the knee joints of 5 osteoarthritis (OA) patients (4 men, 1 woman; average age, 67 years) were used as controls. The ELISAs of synovial fluid were done at the same time with the same standards and were read off the same standard curve.

2.7. Immunocytology of MR synovial fluid and skin lesions

Cytospin preparations of synovial fluid and paraffin-embedded sections of the skin biopsies were stained by an indirect immunoperoxidase technique using monoclonal antibodies directed against CD3, CD4, CD8, CD20, CD45, CD68, S100, and HLA-DR (all obtained from Dako, Cambridge, UK) as well as with the aforementioned anti-CD14 and anti-CD51 antibodies.

2.8. Statistical analysis

Each experiment was carried out in triplicate. Statistical significance was determined using Student *t* test, and *P* values less than .05 were considered significant.

3. Results

Histopathology of lesions on the left arm and right hand showed essentially similar features with a diffuse infiltrate of plump macrophages with foamy or ground-glass (PAS⁺) cytoplasm and a few scattered giant cells in the superficial

dermis. These cells expressed CD68 and were negative for CD3, CD4, CD8, CD20, CD45, and S100. Morphological features of these lesions were typical of MR.

3.1. Cytopathology and ultrastructure of MR cells in synovial fluid

The synovial fluid of the knee joint obtained at the time of diagnosis was of low viscosity, slightly pink, and showed poor mucin clot formation. It contained numerous white blood cells (7400-8900/mm³); these included numerous

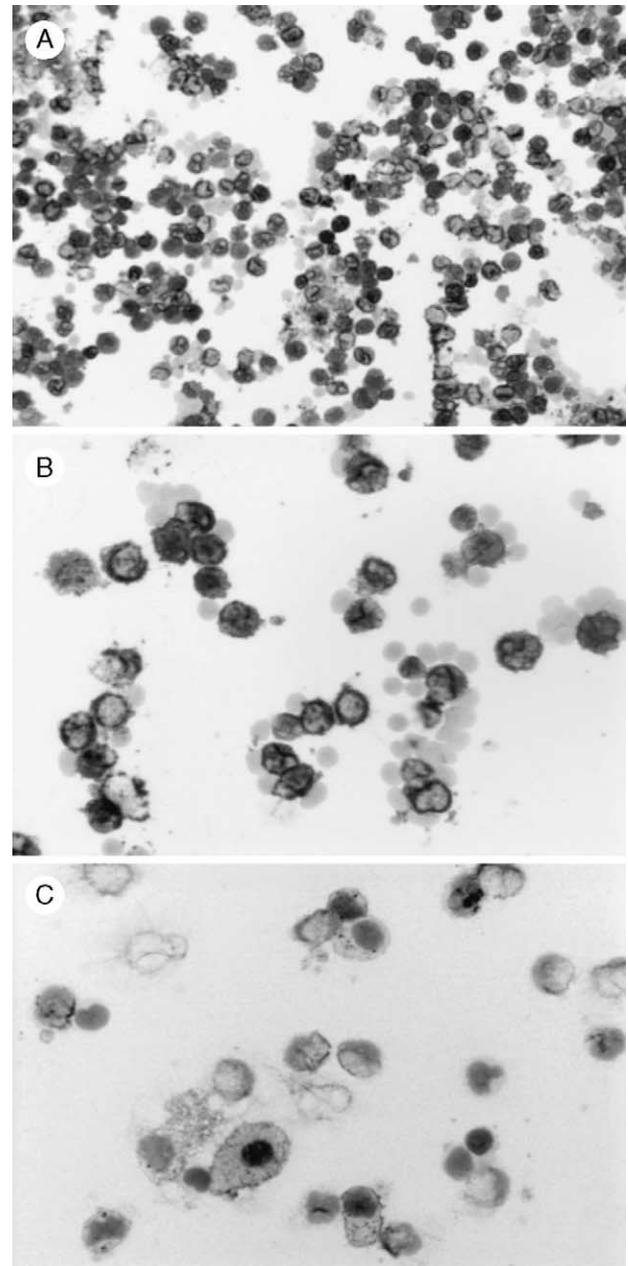


Fig. 2 Indirect immunoperoxidase staining of knee joint synovial fluid cells showing expression of (A) HLA-DR, (B) CD14, and (C) CD45 (original magnification, $\times 40$ [A], $\times 200$ [B], and $\times 400$ [C]).

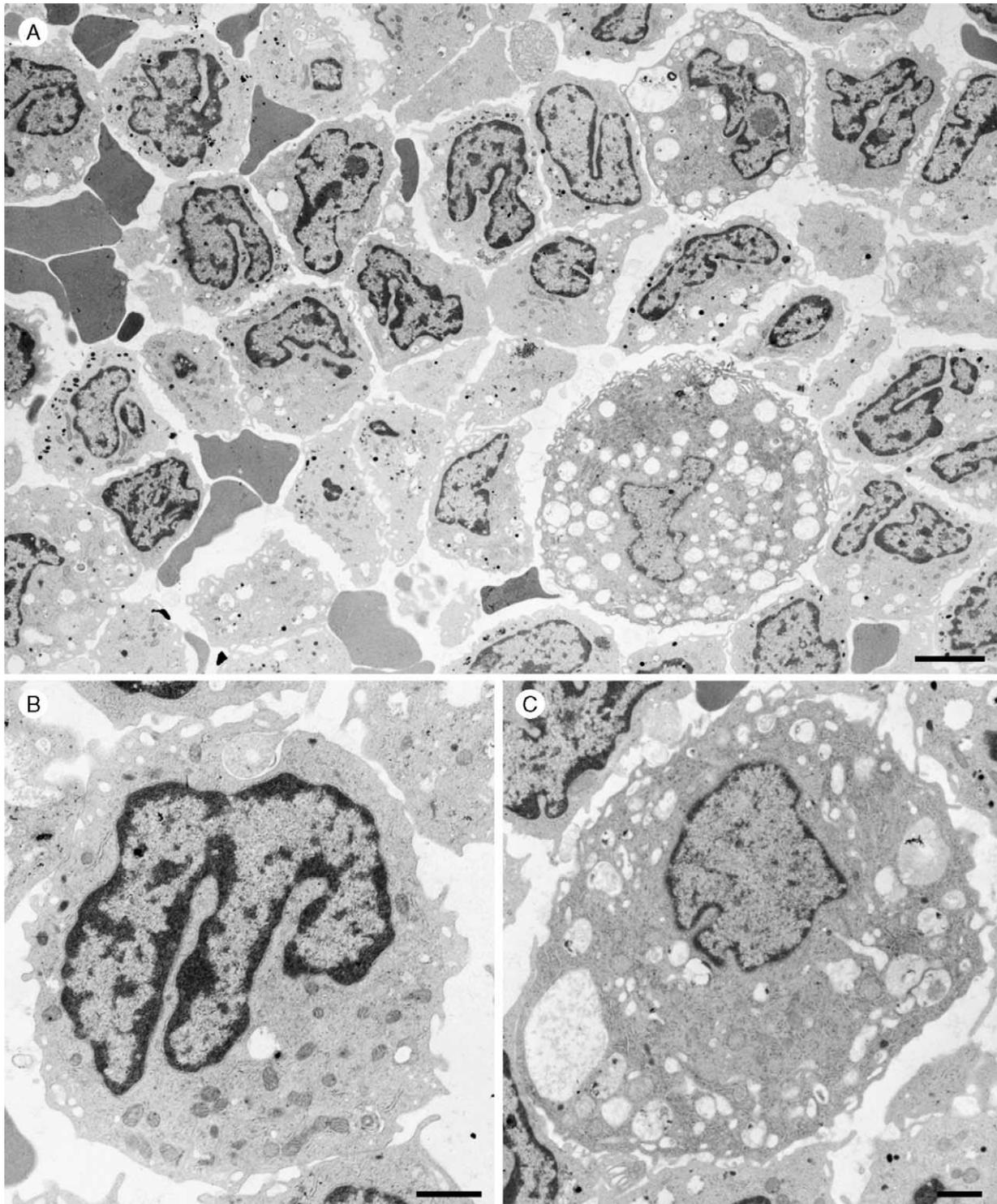


Fig. 3 A, Low-power photomicrograph showing the ultrastructure of synovial fluid mononuclear cells (bar represents 10 μm). B, Detail of a macrophage-like mononuclear cell showing invagination of the nucleus. The cytoplasm contains a few mitochondria, vacuoles, and dense granules (bar represents 1 μm). C, Detail of a large mononuclear cell in which the cytoplasm is vacuolated and contains lipid droplets (bar represents 1 μm).

macrophages (90%) with scattered polymorphs (8%) and other nucleated cells (2%). Most cells had a macrophage-like morphology with an indented, kidney-shaped nucleus and abundant eosinophilic cytoplasm (Fig. 1A, B). There

were also scattered plump mononuclear and multinucleated cells with abundant foamy cytoplasm (Fig. 1C). Immunohistochemistry showed that the mononuclear and multinucleated cells expressed CD14, CD45, CD68, and HLA-DR

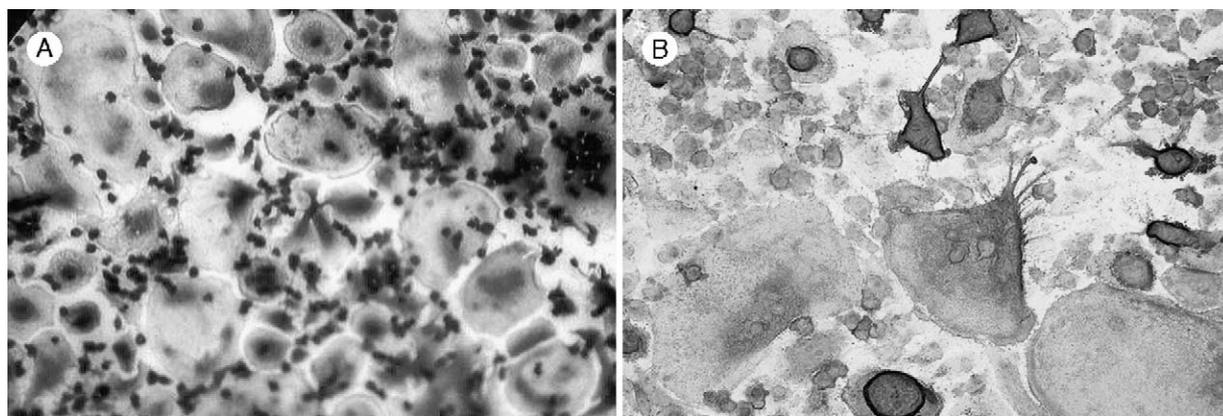


Fig. 4 The 14-day culture of MR synovial fluid cells treated with RANKL and M-CSF resulted in the formation of numerous large multinucleated (A) TRAP⁺ and (B) VNR⁺ cells (original magnification, $\times 200$).

and were negative for CD3, CD20, and S100 (Fig. 2); these cells were also negative for the osteoclast-associated markers, TRAP and VNR (CD51).

Ultrastructural examination of the synovial fluid cells by transmission electron microscopy showed large numbers of macrophage-like mononuclear cells (Fig. 3). Most mononuclear cells were small (10–30 μm), although a few larger mononuclear cells and scattered multinucleated cells measuring up to 100 μm were noted. The nuclei of mononuclear

and multinucleated cells were large and irregular in shape and had deep invaginations. The cytoplasm contained abundant Golgi apparatus, a few small mitochondria, strands of rough endoplasmic reticulum, and a variable number of dense granules, probably lysosomes, and lipid vacuoles. There were a few cytoplasmic surface processes.

In the synovial fluid aspirates taken after treatment was commenced with methylprednisolone and pamidronate, the nucleated cell count fell to 5200/mm³ (10 days) and

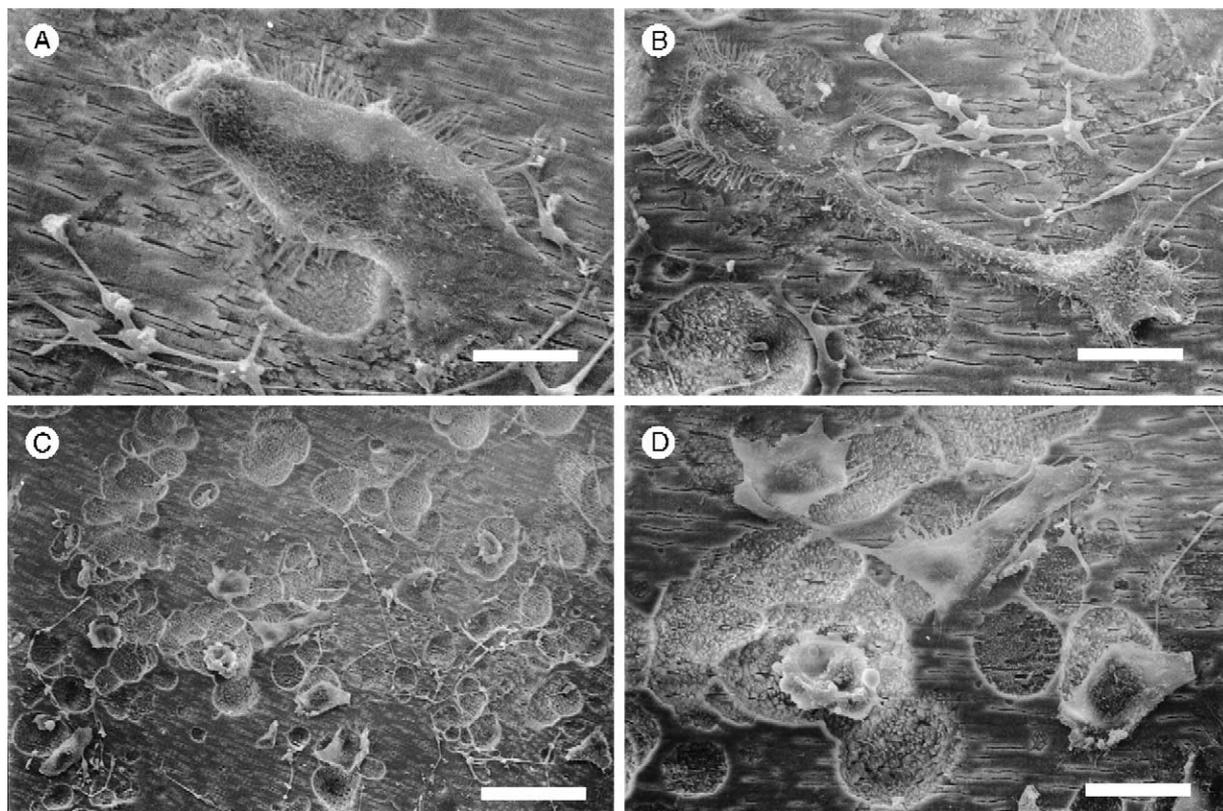


Fig. 5 Scanning electron micrographs of 14-day culture of RANKL/M-CSF-treated MR synovial fluid macrophage-like cells on dentine slices showing osteoclast-like cells on the dentine surface and associated lacunar resorption (bar represents 30 μm for [A], [B], [D] and 100 μm for [C]).

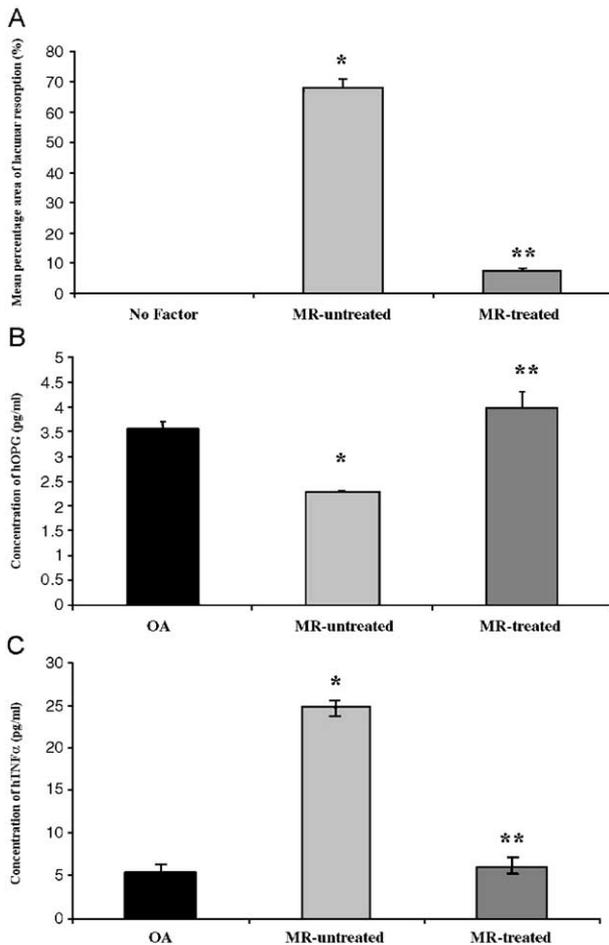


Fig. 6 A, Mean percentage lacunar resorption (\pm SEM) seen in 14-day cultures of MR synovial fluid cells that were isolated when the patient first presented and after treatment with pamidronate ($*P < .005$, $**P < .01$ relative to no factor). The concentration of OPG and TNF α in synovial fluid before and after this treatment is shown in (B) and (C). Error bars represent the standard error of the mean. The statistical differences between treated and untreated groups relative to OA is given on the figure ($*P < .005$, $**P < .001$).

4700/mm³ (20 days); a similar range of cell types was noted with relatively few polymorphs and most of the cells (>85%) showing the macrophage-like morphology noted above; there were scattered plump mononuclear and multinucleated cells with foamy cytoplasm. In the synovial fluid aspirate taken after infliximab was commenced, the cell count had increased slightly to 6500/mm³, but the proportion of polymorphs had greatly increased to 45% of the nucleated cells (Fig. 1D).

3.2. Phenotypic characteristics of isolated synovial fluid macrophages

Isolated synovial fluid macrophages incubated for 24 hours on glass coverslips, in the presence or absence of M-CSF and RANKL, expressed the monocyte/macrophage markers CD14 and CD68 and were negative for the osteoclast markers TRAP and VNR. Cultures of the

synovial fluid macrophages on dentine slices showed no evidence of lacunar resorption after 24 hours incubation. Isolated cells thus expressed the cytochemical and functional phenotype of macrophages and not osteoclasts [23].

3.3. Osteoclast formation from synovial fluid macrophages

In synovial fluid macrophage cultures incubated for up to 14 days with 10% FBS in the presence of M-CSF and RANKL, numerous TRAP⁺ and VNR⁺ cells were present in cultures on coverslips (Fig. 4). Numerous resorption pits were also noted in cultures on dentine slices, where over 60% of the dentine slice was resorbed (Figs. 5 and 6A). Large osteoclast-like cells were found overlying or adjacent to typical lacunar resorption pits, which were well-defined areas of excavation containing exposed mineralized collagen fibers. Osteoclasts exhibited broad pseudopodia and fine filopodia at the cell periphery; these processes made contact with the resorbed and unresorbed dentine surface. Treatment with either M-CSF or RANKL alone was not sufficient to stimulate osteoclastogenesis in 14-day synovial fluid macrophage cultures. Synovial fluid macrophages incubated with TNF α and IL-1 α in the presence of M-CSF and OPG, but without RANKL, did not stimulate osteoclast formation as evidenced by the fact that TRAP⁺ and VNR⁺ multinucleated cells were not present in 14-day cultures on coverslips, and resorption pits were not formed in cultures on dentine slices. The addition of zoledronate to the synovial fluid macrophage cultures treated with M-CSF and RANKL abolished osteoclast formation and resorption.

Synovial fluid macrophages incubated for up to 14 days with 10% FBS in the presence of M-CSF and RANKL after the patient had received treatment with methylprednisolone and pamidronate were still able to differentiate to form TRAP⁺ and VNR⁺ multinucleated cells, although fewer TRAP⁺ and VNR⁺ multinucleated cells were seen in the cultures. However, the extent of lacunar resorption in these cultures was significantly less than that seen in cultures of synovial fluid macrophages isolated from the patient before treatment (Fig. 6A).

3.4. OPG and TNF α in MR synovial fluid

ELISA analysis of the knee joint synovial fluid before treatment was commenced showed that the concentration of TNF α was 5 times higher than the mean of 5 samples of OA knee joint synovial fluid. After treatment with prednisolone and pamidronate, the TNF α concentration fell to levels comparable to those seen in OA samples. In contrast, the OPG concentration was slightly lower than that of samples of OA knee joint synovial fluid (Fig. 6B, C).

4. Discussion

In this study, we have shown that macrophages are the main inflammatory cell component of both cutaneous lesions

and inflamed joints in MR. Ultrastructural and immunohistochemical features of MR synovial fluid cells indicate that these cells are macrophage-like and not dendritic cells or lymphocytes as previously reported [11,14,16]. Our findings show for the first time that the numerous inflammatory macrophages that are present in MR synovial fluid may contribute to the erosive arthritis of this condition by differentiating into mature functional osteoclasts by a RANKL-dependent mechanism. We found that MR synovial fluid contains an increased amount of TNF α , which is known to promote osteoclast formation. A decrease in the number of MR cells was seen following treatment of the patient with bisphosphonates; this also decreased synovial fluid macrophage-osteoclast differentiation and resorption. Our findings indicate that treatments directed at inhibiting osteoclast differentiation and resorption may be useful in controlling the joint destruction of MR.

Although previous studies have shown that MR skin lesions contain numerous cells that express mononuclear phagocyte markers, such as CD68, lysozyme, α -1-antitrypsin, MAC 387, and CD15 [8-10], marked differences in the number and nature of cells in MR synovial fluid have been reported in the few case reports that have carried out synovial fluid cytoanalysis. Our findings most closely match those of the early study of Ehrlich et al [4], which found a very large number of leucocytes in MR synovial fluid. The synovial fluid of the case examined by Spadaro et al [24] also contained numerous leucocytes including PAS⁺ (diastase-resistant) macrophage-like cells with a ground glass cytoplasm; these cells were similar to those found in the cutaneous lesions. Spadaro et al also noted scattered binucleated giant cells and undifferentiated cells undergoing mitosis. The synovial fluid of the case studied by Freemont et al [13] had a low nucleated cell count (200-800 cells/mm³) wherein macrophages were the predominant cell type. They noted the presence of large cells that appeared to represent very large PAS⁺ mononuclear macrophages (up to 70 μ m in diameter); these cells stained positively for the macrophage markers lysozyme and α -1-antitrypsin. Freemont et al also noted that lymphocytes, predominantly of B-cell lineage, and immunoblasts accounted for approximately 10% of all cells. Samaan et al [16] reported that cells in synovial fluid from a case of MR did not express the monocyte marker CD14 and on this basis suggested that these cells had a lymphocyte rather than a macrophage origin.

In the present case, the nucleated cell count was high at presentation with over 90% of the cells being macrophage in phenotype. These cells expressed several mononuclear phagocyte markers, including CD14, CD68, and HLA-DR. There were also scattered larger macrophage-like cells with plump cytoplasm that were mononuclear or multinucleated. These large cells were morphologically similar to those present in the skin nodules of the patient. The mononuclear cells in MR synovial fluid also exhibited the ultrastructural characteristics of macrophages, having an indented nucleus and possessing lysosomes that contained

lipid droplets [4,11-14]. Like monocytes and macrophages, these synovial fluid cells did not express the osteoclast markers TRAP and VNR but were capable of differentiating into osteoclasts when cultured with RANKL and M-CSF [17,18]. There was no expression of the dendritic cell marker S100, either in skin lesions or in synovial fluid, and MR synovial fluid cells did not express CD20 or CD3, B and T cell markers, respectively. Our results indicate that MR synovial fluid cells are predominantly macrophage in phenotype, and that they do not represent activated lymphocytes or dendritic cells as previously suggested [11,14]. We noted a fall in the number of white cells in synovial fluid after treatment with corticosteroids and pamidronate, and it is possible that, in the 2 previously reported MR cases where a low white cell count was found in synovial fluid, the treatment that the patients received before synovial fluid cytoanalysis may have influenced the extent of leucocyte infiltration.

Osteoclasts form part of the mononuclear phagocyte system and are known to be derived from the CD14⁺ monocyte fraction in peripheral blood [25,26]. In the combined presence of M-CSF and RANKL, these cells are capable of differentiating into mature osteoclasts that can carry out lacunar resorption [27]. In this study, we found that CD14⁺ MR synovial fluid cells, which did not express the osteoclast markers TRAP and VNR, were capable of differentiating into multinucleated TRAP⁺ and VNR⁺ cells that were capable of lacunar resorption. This osteoclast differentiation occurred only in the presence of both RANKL and M-CSF. We and others have recently shown that synovial fluid macrophages are capable of differentiating into osteoclasts and that in inflammatory joint conditions, where there is an increase in the number of synovial fluid macrophages, there is increased osteoclast formation and resorption activity [18,28]. It is thus probable that the large macrophage population in MR synovial fluid contains a large number of osteoclast precursor cells that are capable of differentiating into bone resorbing osteoclasts. These cells are likely to contribute to the bone and joint destruction, which is characteristic of this condition. Treatment with the bisphosphonate, pamidronate, had a beneficial clinical effect on the affected joints with decreased joint pain and apparent arrest of joint destruction. This was reflected by the complete inhibition of lacunar resorption seen in synovial fluid macrophage cultures treated with zoledronate. Bisphosphonates are known to act in several ways to inhibit osteoclast resorption [29]. These include decreasing osteoclast resorption activity as well as reducing the number of osteoclasts formed from marrow precursors and limiting osteoclast survival by stimulating apoptosis. Thus, the beneficial clinical effect of pamidronate in our patient may have been to reduce both the number and activity of osteoclasts formed from mononuclear phagocyte precursors in MR synovial fluid.

In our study, we found that TNF α but not OPG, a decoy receptor for RANKL, was markedly increased in MR

synovial fluid (compared with noninflammatory OA synovial fluid). TNF α could be operating in a number of ways to promote osteoclast formation and resorption. TNF α is known to induce RANKL expression by bone stromal cells and to induce osteoclast formation by direct stimulation of macrophages exposed to permissive levels of RANKL [30,31]. Thus, the increase in synovial fluid TNF α in our MR patient may have shifted the RANKL: OPG balance in favor of increasing osteoclast formation and resorption activity. TNF α is also known to stimulate osteoblasts to promote osteoclast resorption activity. TNF α is known to produce osteoclast formation by a RANKL-independent mechanism [32], but no evidence of a RANKL-independent mechanism induced by this inflammatory cytokine was noted in this study. Treatment with infliximab, a TNF α antagonist, appeared to benefit both joint and skin disease in our patient, although it was noted that the proportion of neutrophil polymorphs in synovial fluid increased after this treatment was introduced.

There have been isolated reports of improvement in MR with anti-TNF α therapy, and our case provides some support for this type of treatment [6]. Our case also supports the use of bisphosphonates that have previously been recommended. However, although pamidronate suppressed synovitis and bone destruction, it did not influence the severity of the skin disease. Bisphosphonates bind strongly to bone, and this would localize the therapeutic effect of these drugs to osteoarticular tissues rather than skin. We propose that combinations of corticosteroids, methotrexate, bisphosphonates, and/or anti-TNF α biologics should be considered early in the treatment of this potentially devastating disease.

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