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# Multicentric reticulohistiocytosis and fibroblastic rheumatism

Francesco Trotta, Professor of Rheumatology<sup>a,1</sup>, Matteo Colina, MD, PhD<sup>b,\*</sup>

<sup>a</sup>Section of Rheumatology, Department of Clinical and Experimental Medicine, University of Ferrara, Via Savonarola 9, 44121 Ferrara, Italy

<sup>b</sup>Rheumatology Service, Section of Internal Medicine, Department of Medicine. Ospedale "Santa Maria della Scaletta", Via Montericco 4, 40026 Imola, Italy

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Multicentric reticulohistiocytosis (MRH) and fibroblastic rheumatism (FR) are uncommon disorders with similar joint and skin manifestations. They are usually included among the non-Langerhans histiocytoses, but recent insights drive some criticism. The diagnosis is often challenging and must be confirmed by the histological typical features. If the skin manifestations are missing, the arthritic complaints may be confused with those of other rheumatic disorders. In these cases, only a careful clinical and radiological evaluation leads to the correct diagnosis. The natural course of the diseases may rapidly develop into disabling manifestations, making an aggressive treatment strongly recommendable. There is emerging evidence that anti-tumour necrosis factor- $\alpha$  agents and bisphosphonates are promising drugs for MRH, while a course of methotrexate and steroids seems to be the best option for FR. Finally, the clinician should be aware that in many cases MRH, but not FR, is associated with a large number of systemic manifestations and with malignancy. This eventuality must be accurately ruled out.

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Multicentric reticulohistiocytosis (MRH) and fibroblastic rheumatism (FR) are two uncommon dermato-arthropathies sharing some clinical and radiologic features. Both the diseases are characterised by a destructive polyarthritis with similar erosive aspects and by cutaneous involvement with papules and nodules. However, the histopathological features are clearly different, a multinucleated

\* Corresponding author.

E-mail addresses: [trf@unife.it](mailto:trf@unife.it) (F. Trotta), [matteo.colina@gmail.com](mailto:matteo.colina@gmail.com) (M. Colina).

<sup>1</sup> Tel.: +39 (0) 532 201379; fax: +39 (0) 532 978889.

giant cell with 'ground glass' appearance of the cytoplasm being the hallmark of MRH and myofibroblasts in a network of thickened collagen being that of FR.

## Classification

MRH and FR are usually classified among the non-Langerhans histiocytoses. Histiocytoses comprise a heterogeneous, confounding group of disorders in which various tissues, including skin and other organs, are infiltrated by overgrowing cells of the mononuclear phagocytic system arising from the common CD34 + precursor cell. These disorders are currently identified by histopathology and by immunohistochemical differentiation of their component cells.

According to the Histiocyte Society recommendation, the histiocytoses have been categorised in Langerhans cell histiocytoses (class I), non-Langerhans cell histiocytoses (non-LCH) (class II) and malignant histiocytoses (class III) [1]. Based on the ontogeny of the cells, class II was further subdivided into class IIa, in which there is a predominance of dermal dendritic cells, and class IIb involving cells other than Langerhans cells and dermal dendrocytes. In this last subgroup were included MRH and FR. [2]

In the right clinical context, lesional cells that are CD1a+/Langerin +/S100+ can be identified as Langerhans cell. The non-LCH are defined by the accumulation of histiocytes that do not meet the phenotypic criteria for the Langerhans cells. These cells can develop either into the interstitial/dermal dendrocyte (S100-/CD68+/CD14+/Factor XIIIa+) or into the monocyte/macrophage lineage (S100±/CD68+/CD1a-), depending on the cytokine environment. Even after a cell has differentiated, often an intimate relationship remains with many functional, morphological or phenotypical overlaps showing that the demarcation between the groups is not always well defined [3,4].

From the clinical point of view, it has been proposed to divide the non-LCH into three groups: those that affect predominantly the skin (including juvenile xanthogranuloma and other disorders of the juvenile xanthogranuloma family), those that affect skin but have a major systemic component (among them MRH) and those that primarily involve extra-cutaneous sites (such as Erdheim–Chester and Rosai–Dorfman disease) [5].

Recently, another hypothesis arising from the evidence of the osteoclastic-like activity of the MRH cells has been proposed. These cells exhibit properties of osteoclast markers staining positively with tartrate-resistant acid phosphatase (TRAP) and cathepsin K. Moreover, by a receptor activator of nuclear factor kappa-B ligand (RANKL)-dependent mechanism, MRH synovial fluid macrophages may differentiate into mature functional osteoclasts that can carry out bone resorption and erosive arthritis. The therapeutic efficacy of bisphosphonates further implicate that the osteoclasts have a pathogenetic role. Although not completely specific, these data suggest that MRH may be considered a 'systemic osteoclastic disease' [6–8].

In the attempt to formulate a unifying concept for the non-LCH, Zelger et al. [2] described five major morphological type of histiocytes, namely scalloped, vacuolated, xanthomatised, oncocytic and spindle cell, the last being the more mature type very resistant to treatment. Following this concept, FR has been included among the spectrum of the non-LCH, the presence of spindle-cell macrophages suggesting that they are another phenotypic expression of pluripotential histiocytes. Other arguments supporting this opinion were the clinical similarities with MRH as well as with other diseases comprised in this group.

However, histiocytic origin of the cells involved in FR is nowadays in doubt. In fact, recent immunohistochemical data have shown that most of the spindle-shaped cells of the FR nodules are calponin and smooth muscle actin (SMA) strongly positive, but clearly negative for most histiocytic/dendrocytic markers. Moreover, the spindle-shaped cells have the ultrastructural features typical of myofibroblasts, not of macrophages, failing to confirm an histiocytic origin of the disease. Therefore, FR should be considered a distinct clinic-pathologic entity that, given the clinical course and the biological data, could be properly added to the group of fibromatoses instead of histiocytoses [9]. With further immunophenotypic studies, greater clarity should be achieved on this topic.

## Multicentric reticulohistiocytosis

MRH is an uncommon disease characterised by prominent skin and joint manifestations. Systemic complaints are frequently present. An association with an underlying malignancy and an autoimmune

disease is reported in about 30% and 15% of the cases, respectively. Therapeutic options continue to be a challenge and remain largely empirical. Histologically, the lesions show a characteristic infiltrate of histiocytes and multinucleated giant cells with eosinophilic 'ground-glass' cytoplasm. The cells are usually positive for CD45 and CD68, but they lack S100 and CD1a expression which characterise Langerhans cells, and therefore are thought to be of monocyte/macrophage lineage.

Apart from earlier vague reports, the first adequately described case of MRH was provided in 1937 by Weber and Freudenthal [10], while the term 'multicentric reticulohistiocytosis' was introduced in 1954 by Golz and Laymon [11]. This designation has gained general acceptance over the years during which the disease has emerged as a definite clinical and pathological entity, replacing many other nowadays obsolete synonyms.

So far, about 250 cases have been reported, mostly as isolated cases or small series. For several reasons, it is very likely that this is an under representation of the disease. In the past, some reviews have appeared summarising the majority of published cases in the world literature [12–15].

Due to its rarity, data on the incidence and prevalence of MRH are unavailable. The disease has a worldwide distribution, the highest concentration in Europe and USA reflecting simply an increased awareness of this disorder in these countries.

MRH has not been shown to have a familial component. A very rare variant – familial histiocytic dermatoarthritis – characterised by familial occurrence of MRH associated with glaucoma, uveitis and cataracts was seldom described [16]. MRH usually starts in patients in their fourth decade of life; however, cases in paediatric and in elderly people have been reported [17,18]. Females are affected two–three times more often than males [12,14]. Cases have been observed also in pregnant women [19].

## Clinical aspects

The onset of the disease is usually insidious: in the majority of patients the joint symptoms occur first, followed by skin manifestations. The latency from the articular onset of the disease and the cutaneous manifestations ranges from a few months to 6 or more years, with a mean of 3 years, making correct diagnosis difficult. Less frequently skin involvement occurs before or simultaneously with joint manifestations [12,14,20]. Some patients with prominent dermatologic manifestations and minimal articular complaints have been described [21].

### Arthritis

From the beginning, the arthritis tends to be symmetrical, maximally affecting interphalangeal joints of the hands. As with other more common inflammatory joint diseases, stiffness, swelling and moderate pain are the other prominent clinical features. Without the accompanying skin lesions, the arthritis is commonly misdiagnosed until the more evocative radiographic features and skin lesions appear.

Distal interphalangeal (DIP) joints are frequently involved (75% of patients), representing one of the clinically distinguishing features as well as a disparity between severity of joint destruction and subjective symptoms. In the absence of the typical skin manifestations, this clinical picture may be confused with Heberden's nodes or with the articular manifestations of other rheumatic diseases [22]. Knees, shoulders, wrists, hips, ankles, elbows and feet are the other most commonly affected areas, but any other joint may be involved, including occasionally temporo-mandibular and atlanto-axial [12,15,20].

In the past, the progression of the MRH arthropathy has been described as 'rapidly destructive' evolving into a severe and incapacitating disease; the younger the patient, the more likely the propensity for joint destruction. An end-stage 'arthritis mutilans' has been detected in about half of the patients [12,13]. In recent years, when more aggressive therapies have been introduced, the progression tends to be described as 'very slow' with a lower incidence of disabling arthropathy than in the past (12% vs. 45%) [12,14,20]. Either spontaneously or in response to therapy, the disease tends to wax and wane, gradually losing its activity, although the period of inflammatory activity may last 2–10 years or more. Obviously, the destructive sequelae lead to a chronic disability.

### Cutaneous manifestations

Skin involvement consists of multiple flesh-toned to reddish-brown papules and nodules, most commonly located on the face, neck and hands (Fig. 1). Sometimes itchy, they vary in size from a few mm to 2 cm, ranging in number from a few to a hundred. The facial distribution tends to include the ears, bridge of the nose and scalp. Vermicular lesions bordering the nostrils are considered pathognomonic [14]. On the hands, they are particularly distributed to the dorsum and sides of the fingers. Around the nail folds, small papules represent a typical sign (so-called ‘coral beads’). The lesions have a tendency to a cephalo-caudal distribution with a decreasing number on the lower trunk and legs. They may occasionally coalesce to form large plaques giving a cobblestone appearance. In the worst cases, severe involvement of the face leads to a visually impressive disfigurement referred to as ‘leonine facies’ [12,20,23]. Xantelasma-like patches involving the eyelids are evident in about 20% of patients. Nail changes including longitudinal ridging and hyperpigmentation result from involvement of the DIP joints or the nail bed matrix [12,23]. A diffuse, irritable erythema or severe pruritus presenting as a photosensitivity dermatitis may precede the appearance of the nodules [24].

With increasing frequency has been reported, cases of MRH presenting with skin features closely mimicking those of dermatomyositis [25–27]. Confusing features may be the erythematous rash in a fashion of photodistribution, papular lesions on the dorsum of the hands simulating Gottron’s sign and the periungueal telangiectasia. In a review of the published cases of MRH, these features have been revealed as the presenting symptoms more commonly than previously thought (about 10% of the patients). Therefore having dermatomyositis-like features did not have an increased association with malignancy. Histological examination of skin biopsies allows the definite diagnosis.

Due to the distribution over the sun-exposed areas, it has been suggested that the skin eruptions of MRH are closely associated with a sunlight-induced Kóbner’s phenomenon [12,24,27]. This hypothesis has been confirmed in a patient in whom repeated irradiation of ultraviolet B on the uninvolved skin resulted in the induction of the typical lesions [28].



**Fig. 1.** Typical cutaneous manifestations in a case of MRH. Firm reddish-brown multiple papulo-nodules are evident over the dorsum of the hand and in the fingers, with the classical “coral beads” appearance around the nailbeds.

Mucosal surfaces of the lips, tongue, gingiva or nasal septum are involved in over half of the cases. Vulvar and perianal lesions are described in isolated reports [14]. Both the cutaneous and mucosal lesions repeatedly appear and regress spontaneously or with therapy.

#### *Other systemic manifestations*

Even if articular and cutaneous manifestations are prominent, it is now clear that MRH is a systemic disorder in which many tissues may be affected. In fact, the typical histology has been observed in biopsy and autopsy tissues from many organs. Sometimes the systemic involvement of the disease may be widespread.

Pulmonary symptoms were reported in 20% of the cases. Several authors have observed non-specific pathologic findings including pleural effusions, hilar adenopathy, pulmonary infiltrates and fibrosis in a background of usual interstitial pneumonia, but only in few cases the relationship with MRH was based on results of tissue examination [29–31]. Constrictive pericarditis is the more frequent complication for the heart [32,33], and progressive heart failure due to myocardium involvement has been also described. Other manifestations include salivary gland enlargement, dysphagia, splenomegaly and involvement of submucosal tissue underlying a gastric ulcer [34,35]. Muscle weakness with minimal non-specific chronic inflammation on biopsy has been suggested to be a typical finding of muscle disorder in MRH. In a few cases, symptoms of muscle disease were myositis like and dominated the clinical picture [26,36].

Fever, weight loss, general weakness and fatigue may be other constitutional accompanying features.

#### *Associated diseases*

MRH has been described in association with various conditions. Hyperlipidaemia and a positive tuberculin skin test have been identified in 30–58% and 12–50% of cases, respectively [12–15,20]. As first noted by Barrow and Holubar in their review [12], a concomitant autoimmune disease has been reported in a significant percentage of cases (5–20% of the cases) (Table 1). Although concurrence could be pure coincidence, a common autoimmune aetiology has been suggested [37–40].

#### *MRH and malignancy*

In different series and in the available review, a significant association of MRH with malignancy is reported in 15–31% of the retrieved cases. The association was observed with several carcinoma, breast and ovarian being the most often identified, but including also stomach, cervix, lung, colon, pancreas as well as mesotelioma, malignant melanoma, sarcoma, malignant lymphoma and leukaemia or even metastasis from an unknown primary tumour [12,15,41–43]. MRH may occur also around the time of recurrence of metastasis of a previously diagnosed and treated cancer [44,45].

That high association rate has led some authors to indicate MRH as a paraneoplastic syndrome, but this deserves some criticism because no specific malignancy has been consistently reported in

**Table 1**

Autoimmune diseases associated with multicentric reticulohistiocytosis [37–40].

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Sjögren's syndrome
Hypothyroidism
Primary biliary cirrhosis
Systemic sclerosis
Systemic vasculitis
Myositis
Celiac disease
Systemic lupus erythematosus
Rheumatoid arthritis
Diabetes mellitus

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association with MRH, together with the fact that in all cases but one, [46], the evolution of the two diseases do not run a parallel course.

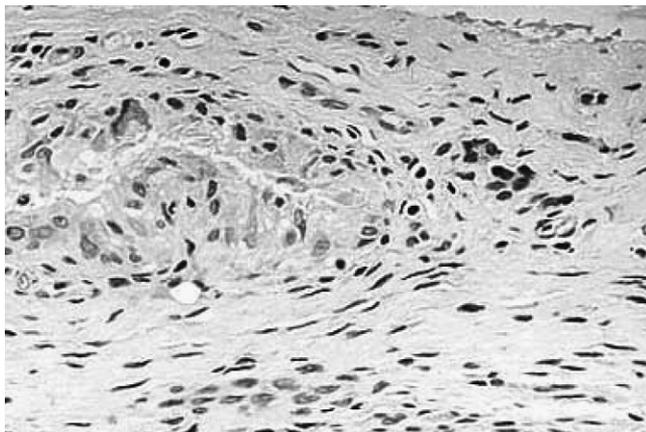
Notably, it is of the utmost clinical importance that the onset of MRH may be concurrent as well as precede the onset of the neoplasm [41,42,46]. Even if MRH does not fulfil the criteria for a paraneoplastic disease, any patient with a diagnosis of MRH should undergo a thorough investigation to exclude malignancy.

## Histopathology

The diagnosis of MRH is performed on the basis of the characteristic histopathologic findings of nodules in skin and/or synovial tissue. The typical infiltrate is composed of many mononuclear histiocytes and multinucleated giant cells 50–100 mm in diameter. Their cytoplasm is eosinophilic, periodic acid-Schiff (PAS) positive, finely granulated or with a 'ground-glass' appearance (Fig. 2). The nuclei may be arranged haphazardly or may align along the periphery or cluster in the centre. Other inflammatory cells are also present, but in lesser numbers. In the earlier lesions, fewer giant cells and more eosinophils, lymphocytes and histiocytes have been reported. In the later stages, an increasing number of giant cells have been emphasised. Finally, lymphocytes and giant cells decrease in number, fibroblasts appear and there is fibrosis. Some authors reported features of collagen phagocytosis in the cytoplasm of the cells [12,47–49].

Various histochemical studies have been performed in attempts to elucidate the nature of the material deposited in the cells. With different methods, the results suggest a non-specific accumulation of lipids (mainly neutral fat substances and phospholipids) and other PAS-positive diastase-resistant material, indicating the presence of a polysaccharide component other than glycogen or acid mucopolysaccharide. Electron microscopy studies confirmed the presence of dense granules with the morphology of lysosomes in the cytoplasm. Synovial lesions parallel those seen in the skin, but giant cells have been reported to be less numerous [48,49].

Immunohistochemical findings are variable and conflicting but, in more definitive reports, the data support the notion of monocyte/macrophage origin of both mononuclear and multinucleated giant cells. In fact, CD68 and CD45 expression are the most constant and reliable markers identified in these cells, being reported positive in all studies in which it was tested [50]. Together with the negativity of S100, CD1a and Factor XIIIa, these data are consistent with a non-Langerhans histiocytic disorder. Moreover, has been found that the proliferating cells stained for cytokines produced by activated macrophages – in particular tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$  and IL-6 – that are also elevated in the serum, decrease after treatment [50,51]. These data support the concept that MRH



**Fig. 2.** A synovial membrane biopsy in another case of MRH showing infiltrates of large histiocytes and multinucleated giant cells with abundant granular eosinophilic cytoplasm.

is a macrophage-reactive process where pro-inflammatory cytokines may be released locally and in the blood, which may account for the systemic symptoms.

Finally, it has been reported that the multinucleated giant cells exhibit an osteoclastic differentiation staining strongly with osteoclast tissue markers (TRAP and cathepsin) and are positive for CD10, a cell surface metallo-protease, which activity could account for the joint destruction [8,52].

### Laboratory investigations

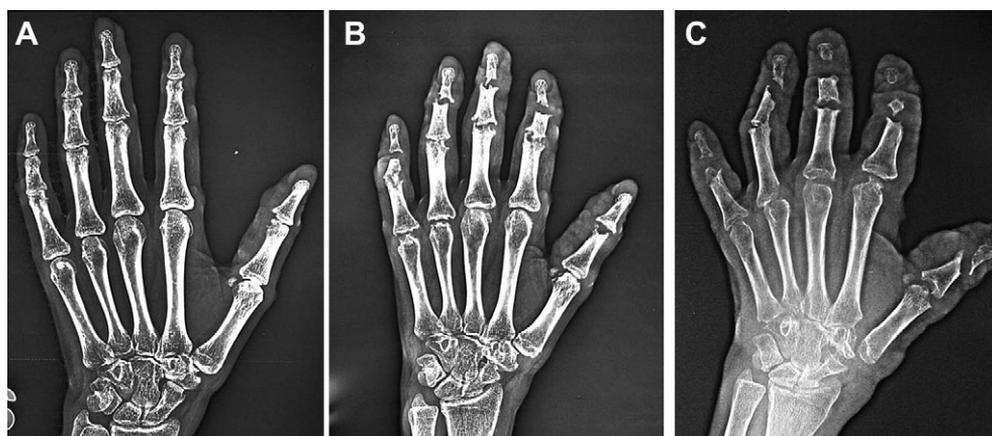
There are no specific or diagnostic laboratory tests for MRH. About half of the patients have a moderate increase in erythrocyte sedimentation rate (ESR) and a mild anaemia. Hyperlipidaemia is inconstant, and 5–30% of the cases have slight to moderate hypercholesterolaemia. A positive rheumatoid factor, anti-cyclic citrullinated antibodies, hypergammaglobulinemia and positivity for anti-nuclear antibodies have been noted only rarely, excluding the cases with an associated autoimmune disease [53].

Synovial fluid analysis has been performed on a few patients with highly variable results: synovitis may be present, with a wide range of cellularity from mild to highly inflammatory, with different types of cell populations. Mononuclear cells and lymphocytes are usually prominent in cases of moderate activity and polymorphonuclear granulocytes in the more inflammatory synovial effusions [12,20,48].

### Radiology

Imaging plays a crucial role in the diagnosis of MRH and a careful radiological reading together with an accurate clinical examination is the key to the right identification of the disease [22].

The arthritis associated with MRH is typically erosive (Fig. 3). The erosions, which reflect the evolution of the infiltrative granulomatous process, are initially well circumscribed and progress rapidly, spreading from the margins to the entire joint surface. These changes result in a widening of joint space, loss of cartilage and resorption of subchondral bone. Remarkably, osteoporosis and periosteal new bone formation are absent in the majority of cases, in contrast with other forms of inflammatory arthritis [22,54]. The most characteristic sites of involvement are the interphalangeal joints (IP) particularly distal (DIP) of the hands, which can be affected in as many as 75% of the cases. The arthritis may progress very aggressively, leading to the disabling ‘opera glass’ deformity. An associated involvement of the wrists can be apparent. In the feet, the abnormalities resemble those of



**Fig. 3.** Dramatic progression of the joint damage in a case of MRH that date back to eighties when the therapeutic capabilities were limited. Well circumscribed marginal erosions are prominent in the bare areas of PIP and DIP (A). After 2 years (B) a progression occurred with widening of the joint space. Ten years later (C) a severely deforming *arthritis mutilans* dramatically developed (so-called “opera glass” feature). In the soft tissues are present multiple cutaneous nodules.

the hands, and all the appendicular skeletal joints may present similar changes. In the spine, bilateral, symmetrical erosions may affect the sacroiliac and costovertebral joints and bony ankylosing may develop without subchondral bony sclerosis. An atlanto-axial involvement with severe destructive abnormalities has been reported [55].

## Differential diagnosis

In the absence of cutaneous manifestations, the diagnosis can be challenging and the patients with MRH are often misdiagnosed. The differential diagnosis of MRH must include all other causes of erosive polyarthritis, in particular FR, psoriatic arthritis, erosive osteoarthritis, elderly gout and rheumatoid arthritis (Table 2) [20,22,54,56]. A detailed analysis on this topic has been reported in our previous reports [20,22].

## Aetiopathogenesis

Aetiology and pathogenesis of MRH remain unknown. Its pathological features and disease course appear indicative of a 'reactive disorder' to an unidentified initiating agent inducing the histiocytic proliferation. Because many associated conditions have been reported – including autoimmune diseases, malignancy and mycobacterial infection – it has been also suggested that MRH is an immunological process related to an underlying autoimmune or neoplastic disease.

MRH is currently listed in the group of the histiocytoses. In these diseases, an uncontrolled macrophage activation is evident with a release of many cytokines and other secretory products that promote macrophage activation and proliferation [50,51]. In MRH, an increase in macrophages and endothelial cell of IL-12 has been described, as well as a prominence of IL-1 $\beta$ , IL-6 and TNF- $\alpha$  [50,57]. These cytokines have a variety of pro-inflammatory activities, and the differing 'cytokine microenvironments' are likely to explain the different clinical and pathological picture of the disease. Moreover, they are indirect inducers of bone resorption. The finding that some mononuclear cells of the MRH infiltrate stain positive for osteoclast markers may support the hypothesis that they may induce histiocytes to differentiate into osteoclast-like multinucleated giant cells [6–8,57]. This attainment of knowledge on the immunopathogenesis of the disease has induced consideration of stimulating new therapeutic approaches.

## Treatment

Owing to the rarity of the disease and the unfeasibility of controlled trials, treatment of MRH remains largely empirical. Although MRH may be considered as a 'self-limiting' disease, the permanent sequelae of the active phases can be physically and psychologically disabling. For these reasons, it has been recommended that the disease should be treated more aggressively.

**Table 2**

Radiological features of other erosive arthropathies compared to multicentric reticulohistiocytosis.

	DIP involvement	Symmetrical distribution	Erosions	luxta-articular osteoporosis	Joint space
MRH	Present	Yes	Marginal	Absent	Widened
Fibroblastic rheumatism	Present	Yes	Marginal/central	Present	Widened
Psoriatic arthritis	Present	No	Marginal (with periosteal new bone formation)	Absent	Widened/narrowed
Erosive osteoarthritis	Present	Possible	Central	Absent	Narrowed
Gout (elderly)	Present	Possible	Marginal (with overhanging margins)	Absent	Preserved/ narrowed
Rheumatoid arthritis	Unusual	Yes	Marginal	Present	Narrowed

Non-steroidal anti-inflammatory agents, hydroxychloroquine (200–400 mg/day) and corticosteroids may be useful as symptomatic drugs, but they do not seem to induce remission or modify the outcome of the disease. In some cases, remission has been achieved with methotrexate (MTX) (7.5–25 mg weekly), chlorambucil (0.1 mg/kg/day) or cyclophosphamide (up to 2.2 mg/kg/day, 6–18 months of treatment), particularly when they are introduced early [58–60]. Few cases of MRH responsive to azathioprine and a case responsive to leflunomide have been also reported [61,62]. In general, the combination of corticosteroids and MTX seems to be effective in controlling arthritis, whereas the addition of cyclophosphamide or chlorambucil seems to be more effective for the skin lesions.

Recently, some authors reported excellent responses to anti-TNF- $\alpha$  agents. A dramatic clinical and radiographic improvement has been observed with etanercept (25 mg twice weekly), infliximab (5 mg/kg) and adalimumab (40 mg every other week) in patients who were refractory to numerous therapies [63–68]. However, anti-TNF agents have not been uniformly effective, in particular for the joint manifestations of MRH. In these cases, a switch between the different compounds may provide another opportunity [67]. On review of the relatively small reported cases treated with TNF blockade, there appears to be a trend toward success treating simultaneously with TNF inhibition, prednisone and MTX. An early treatment may bring further improvement, representing the early phases of the disease a sort of ‘window of opportunity’. The clinician may be aware that TNF- $\alpha$  blocking agents should be used with great caution considering the high incidence of co-existing malignancies and purified protein derivative reactivity associated with MRH.

Skin and joint disease improvements have also been obtained with amino-bisphosphonates, namely alendronate (10 mg intravenously for 6 weeks then reduced to 10 mg once a month) and zoledronic acid (4 mg, repeated infusions) [6,8,51]. The efficacy of bisphosphonates might be due to their negative effects on the osteoclast-like macrophages by inducing their necrosis and/or apoptosis and thus preventing skin and synovial tissue infiltration by these cells.

Moreover, sun-protection clothing and sunscreens may be useful for the treatment of skin lesions.

### **Fibroblastic rheumatism**

Even more rare than MRH is FR. First described by Chaouat et al. in 1980 [69], there have been about 30 reported cases to date, nine of them involving paediatric patients [9,70–76]. Although earlier literature suggested a female predominance, based on the recent data, about 60% have occurred in males. The clinical features are similar to MRH that can be considered as the closest principal differential diagnosis. In short, FR is a dermato-arthropathy characterised by a rapid onset of symmetric polyarthritis and cutaneous lesions typically involving the hands. The course is variable and joint deformities with severe destructive changes on radiography similar to that of MRH may develop. However, from the histological point of view, these two conditions are clearly differentiated.

### **Clinical aspects**

The clinical spectrum of the disease can be only provided from single case report description. FR has been worldwide reported, mostly in Europe (more frequently originating from France), but recently cases from Brazil [74], Asia [75,76] and from India [77] have also been described. The presenting symptoms may be rheumatological and/or cutaneous: the occurrence of both joint symptoms and skin nodules is pivotal for the diagnosis. Usually, clinical presentation is brutal, with suddenly developing arthralgias and symmetrical polyarthritis mainly of the upper limbs. Rheumatologic manifestations may be heralded by generalised morning stiffness. Only a case without rheumatologic manifestation has been described [78]. Diffusely swollen hands with warmth erythema, palm thickening and sclerodactyly limiting finger extension is a frequent feature (approximately 80% of the cases) [73,79]. Less frequently, skin thickening may involve forearm, arm and trunk [77]. Raynaud’s phenomenon has been described in less than 50% of the cases. Fever may occur, described at onset in a case with skin eruptions and inflammatory arthropathy [80].

Cutaneous manifestations start as small maculo-papules, developing into nodules in few days. Skin nodules, which range in size from 2 mm to 20 mm, are always present and may either precede or –

more frequently – erupt after the onset of joint symptoms. They are firm, flesh coloured to purplish, tender or indolent on palpation, typically involving the hands, located over the extensor surface of metacarpophalangeal (MCP) and IP as well over other para-articular sites (ankles, elbow, knees or feet) (Fig. 4). Mimicking MRH, the papules may involve periungueal areas [78]. Skin nodules flattened and regress usually in 6 months to few years. Keloid hypertrophy of scar tissue may be present.

The course of the disease is variable and has been described as insidious or rapidly progressive [79]. A severe functional disability of the hands is common with permanent flexion contracture of the finger and MCP joints and with range of motion reduction of the affected joints producing the '*main en griffe*' appearance.

Differently from MRH, no association with malignancy or visceral involvement has been reported ever in the cases with long-term observation. Up to date only one patient was found to have lung adenocarcinoma [81].

### Laboratory investigations

For FR, no specific diagnostic test exists. All laboratory investigations are usually normal, including acute phase reactants, rheumatoid factor, anti-cyclic citrullinated peptide and anti-nuclear antibodies. During the acute phases, ESR may be elevated.

### Radiology

In the initial phases, joint radiography shows no abnormalities, except for soft-tissue swelling. In few cases, magnetic resonance imaging showed tenosynovitis of the hand flexors [73,74,82]. In the few cases with a long follow-up, a destructive and aggressive arthropathy with remarkable joint damage may develop [69,79,83,84]. In such cases, radiography may reveal highly destructive bone lesions affecting carpus, MCP, IP joints and forefeet with erosions marginal and central resembling that of MRH.



**Fig. 4.** Fibroblastic rheumatism. Skin nodules on the dorsal side of the hand with concomitant finger retraction (courtesy by Dr. Sylvie Fraitag, Hôpital Necker-Enfants Malades, Paris).

## Histopathology

Diagnosis is demanded to histological examination of skin nodules. Synovial membrane specimens may be also informative. The skin histopathology is unique for the disease, the lesions being purely fibrotic. They are characterised by thickened papillary dermis with intense proliferation of densely packed uniform 'spindle-shaped' fibrocytic-fibroblastic cells – in some case with plump morphology [85] – within a background of thickened collagen fibres occasionally arranged in a 'whorling' pattern. These cells have a greater proliferative rate *in vitro*. The fibroblastic proliferation occurs without increased synthesis of collagen [81]. The elastic fibres disappear almost completely. This is a characteristic but not specific finding, as other disorders have shown loss of elastic fibres highlighting the critical relevance correlating biopsy results with the clinical presentation [86]. In a few cases, a minimal perivascular, lympho-histiocytic cell infiltrate has been noted.

Immunohistochemical staining of the expanded cells are typical for myofibroblasts. In fact staining for desmine,  $\alpha$ -SMA and calponine, characterising myofibroblasts, are positive whereas histiocytic markers are negative. Ultrastructural aspects confirm their nature of myofibroblasts, recognisable by intracytoplasmic vesicles containing collagen fibres and large amount of well-developed rough endoplasmic reticulum [79,80,83,87].

Synovial membrane has been studied only in few cases [71,87,88] showing synovial cell hyperplasia, no inflammatory cells infiltrate, marked proliferation of fibroblasts exhibiting, as in the dermis, ultrastructural features of myofibroblasts, in a matrix of vascular granulation tissue.

## Aetiopathogenesis

FR is a unique fibro-proliferative disease. The origin is unknown and the pathogenetic mechanisms leading to increased dermal fibroblasts have yet to be elucidated. Both exogenous and endogenous factors may drive the observed fibroblast proliferation. Histological features suggest an overwhelming myofibroblastic response to an unidentified (infectious?) stimulus, at least in some cases [80,86]. Transforming growth factor  $\beta$  and granulocyte-macrophage colony-stimulating factor may play a role. They are among the cytokines known to induce phenotype switch of fibroblasts in myofibroblasts, promoting collagen phagocytosis leading to joint destruction [79].

## Treatment

Despite multiple treatments having been employed, including acetylsalicylate, antimalarial, colchicine, D-penicillamine and interferon, at present there is no known effective treatment to arrest the disease. Corticosteroids have been widely used but the efficacy is unpredictable. A course of prednisone (1 mg/kg/day) may result in improvement of joint pain, but complete resolution is rare. In a single case long-term treatment with MTX low dosage seems to control the disease [80]. In other cases, MTX employed in higher dose (until 30 mg weekly) was able to induce improvement suggesting that this drug may be highly beneficial in FR, also in paediatric age [9,70,73,89]. Infliximab has also demonstrated efficacy in inducing improvement of scleroderma-like alterations and joint mobility in a case with exuberant clinical findings [90]. To date, the association of prednisone with MTX in the early phases of the disease seems to be the best option, but other studies are warranted to confirm the efficacy. Intensive physiotherapy with passive mobilisation of the involved joints may be associated.

## Summary

MRH and FR are rare disorders of unknown aetiology sharing some clinical and radiological features. They primarily affect the skin with multiple nodules and papules and joints with a poly-arthritis often rapidly destructive. From the histological point of view, the two diseases can be clearly differentiated.

The arthropathy of MRH can be unresponsive to treatment leading to a disabling 'arthritis mutilans' and the skin lesions can be particularly disfiguring. Moreover, MRH is associated with concomitant malignancies in up to 30% of cases suggesting that the disease could be a paraneoplastic disorder. The

aetiology is still unknown, but there is recent evidence that pro-inflammatory cytokines have a pathogenetic role. To achieve the remission, the therapeutic trend is to initiate treatment early and aggressively. MTX and cyclophosphamide, alone or in association with corticosteroids, have been shown to be the first line most useful treatments. More recently, TNF- $\alpha$  blockade and bisphosphonates have been demonstrated to be other promising therapeutic options. In the future, treatment with new anti-cytokine agents and/or new anti-bone resorption drugs should be considered in the treatment of this potentially devastating disease.

FR is even more rare than MRH also characterised by cutaneous and joint symptoms. Differently from MRH, no association with malignancy or visceral involvement has been reported. The origin of this unique fibro-proliferative disease is unknown and the pathogenetic mechanisms leading to increased dermal fibroblasts have yet to be elucidated. To date, there is no known effective treatment to arrest the progression of the disease. The association of prednisone with MTX in the early phases of the disease seems to be the best option. As the pathogenesis of the disease becomes more fully understood, better treatment strategies should emerge.

### Practice points

- MRH and FR are very rare diseases most commonly affecting people in their middle age, but cases in paediatric and in elderly age can occur.
- Lacking any specific laboratory test, histology is necessary to confirm the diagnosis.
- At the onset of the diseases cutaneous manifestations may be absent, making the diagnosis challenging. In these cases, a careful clinical examination and radiological reading may be the key.
- Marginal erosions and widening of joint space are the most indicative radiological aspect of MRH.
- In the late stages, radiological features of FR are similar to that of MRH.
- The skin manifestations of MRH may mimic that of dermatomyositis.
- Sclerodactily and Raynaud's phenomenon may be a feature of FR.
- Malignancies are associated with MRH in more than 25% of cases and must be accurately ruled out.
- Early treatment could prevent devastating consequences.
- Anti-TNF- $\alpha$  agents and bisphosphonates represent the approach with more promising results in MRH.
- For the treatment of FR, MTX and steroids in the early phases of the disease represent the best option.

### Research agenda

- Additional studies for a clear understanding of the aetiopathogenesis of the diseases and for a better classification of them are needed.
- Therapeutic role of new biologic agents and new osteotropic drugs must be tried.
- The efficacy of MTX should be clarified, and at which dosage.
- Predictive criteria for a poor clinical outcome remain to be analysed.
- The relationships of MRH with malignancy and autoimmune diseases must be better defined.

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