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MINIREVIEWS

Lymphedema and rheumatological disorders

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Abstract

In the literature, although the prevalence of lymphedema is low in inflammatory rheumatological diseases, rigorous approaches to diagnosis and treatment have led to significant improvement in patients' quality of life. Lymphedema is observed more frequently in patients with rheumatoid arthritis with respect to case presentations, but it is also observed in psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, and childhood inflammatory rheumatological diseases. Other rheumatological diseases and tumor-related secondary causes should also be kept in mind in the diagnosis of lymphedema. Complex decongestive therapy-skin care, manual lymph drainage, compression and exercise are the primary treatment approaches. Both basic drugs and tumor necrosis factor-α inhibitors have been tried in addition to complex decongestive physiotherapy programs. However, the success of alternative medical treatments is controversial in the literature. It may be useful to include the disease in post-diagnosis complex decongestive physiotherapy program and to use the drugs mentioned in the literature. However, more data are needed to reach conclusive results.

Key words: Lymphedema; Rheumatoid arthritis; Psoriatic arthritis; Ankylosing spondylitis; Systemic sclerosis

Core tip: Coexistence of inflammatory rheumatological diseases and lymphedema is an under-recognized subject. Drawing clinicians' attention to this issue is important for improving patients' quality of life. In patients with inflammatory rheumatological disease and lymphedema, although the complex decongestive therapy method is the primary approach, tumor necrosis factor-α inhibitors mentioned in the literature, whose efficacy requires explanation, may also be tried.

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INTRODUCTION

Lymphedema (LE) may be defined as an accumulation of protein-rich interstitial liquid as a result of congenital or acquired disruption of the lymphatic circulation. It occurs as a consequence of increased lymphatic load and/or reduced lymphatic transport. LE is a chronic, progressive condition that impairs mobility and joint movement: the swollen areas increase in size and weight, often causing postural alterations and pain as the individual struggles to perform daily living activities. It eventually leads to impairment of physical and psychosocial functions, accompanied by a change in body image and thus affects quality of life[1].

In the literature, although the coexistence of inflammatory rheumatological diseases and lymphedema is rare, attention is drawn to the difficulties in its diagnosis and treatment. The most frequent inflammatory rheumatological disease that accompanies lymphedema is reported to be rheumatoid arthritis (RA)[2-11]. However, other cases have been reported where LE is accompanied by psoriatic arthritis (PsA)[4,12-15], ankylosing spondylitis (AS)[16], systemic sclerosis (SS)[17,18] and childhood inflammatory rheumatologic diseases[19-21], in addition to RA[22].

PATHOGENESIS

Lymphedema associated with RA was first described by Kalliomaki and Vastamaki in 1968[12], and it appears to be a relatively rare complication of RA. Several reports indicate that lymphedema as a complication of RA is not restricted to seropositive arthritis, but also occurs in other forms of inflammatory arthropathy[12,16,18,20]. Few cases of lymphedema associated with PsA have been described[12-15]. As in patients with RA and lymphedema, the etiology of edema associated with PsA remains puzzling.

Associated arterial and venous disease can be found in approximately half of patients in SS[17,18]. Leg ulcers have been described in SS, often revealing a multifactorial etiology. In scleroderma, skin biopsies showed fibrosis of the lower two-thirds of the dermis and the subcutaneous fibrous trabeculae. Its presence in sclerodermatous skin has also been described and may partially account for the early edematous phase of the disease. One study using fluorescence microlymphography (which allows visualization of the superficial cutaneous lymphatic capillary network) found that lymphedema in SS could, at least in part, be a result of lymphatic microangiopathy[18]. By contrast, significant chronic lymphedema, leading to the development of elephantiasis nostras verrucosa, is extremely rare[18].

In those cases of PsA and lymphedema in which lymphatic function was examined, quantitative lymphoscintigraphy disclosed abnormal lymphatic drainage of the affected limb. There are several reports that suggest lymphatic vessels are altered in both inflammatory arthritis and psoriasis. No lymphatic vessel staining in the manner of normal lymphatics was found in rheumatoid arthritic synovium. Based on morphological examination of psoriasis skin lesions, several authors have described abnormalities of the lymphatics, such as dilatation, lack of fenestration or dermal distal blind loops. Other authors were unable to confirm such findings. Patients with chronic plaque psoriasis revealed a greater network of lymphatics in perilesional skin compared with lesional skin, as demonstrated by fluorescence microlymphography[12]. To determine whether inflammatory arthritis itself leads to impaired lymphatic function, Kiely *et al*[23] examined 10 patients with inflammatory arthritis (RA or PsA) and edema and 18 patients with inflammatory arthritis without edema using lymphoscintigraphy. Inflammatory arthritis alone was not associated with impaired lymphatic flow, suggesting the presence of additional unrelated factors for the development of lymphedema in patients with inflammatory arthropathy.

We are unaware of any studies addressing the macromolecular composition of the interstitial fluid from swollen extremities of patients with lymphedema and PsA. In RA, conflicting data have been reported regarding the protein content of the edematous fluid. In at least some of these reports, protein levels of the interstitial fluid of patients with edema and RA were compared with the protein contents of the interstitial fluid of patients with congestive heart failure and edema. Future studies on directly testable microvascular parameters, such as interstitial fluid pressure, interstitial colloid osmotic pressure and interstitial plasma protein content in swollen limbs of patients with PsA, as well as the careful design of proper controls may shed more light on the pathophysiology of PsA and lymphedema[12].

Some cases have been reported of lymphedema development in patients with AS[16] and juvenile rheumatoid/idiopathic arthritis[19-21].

In addition, scleroderma-like skin changes during lymphedema development induced by taxanes (docetaxel) treatment have been observed[17]. Improvement was reported shortly after the discontinuation of medication. Histological examination of skin biopsies showed diffuse infiltration of histiocytes and macrophages in the superficial dermis associated with lymphangiectasia without vasculitis. Although its mechanism is unknown, an autoimmune or paraneoplastic origin has been considered[17]. It is difficult to comment on the relationship between docetaxel and early lymphedema-associated scleroderma-like skin changes, yet it should be taken into consideration.

The etiology is unknown in inflammatory arthropathy. This uncertainty in etiology and pathogenesis may be explained by the lack of data on lymphedema in inflammatory rheumatological pathologies. The available data are based on limited information mostly from case presentations; therefore, it is limited mostly to clinical practice. Several hypotheses have been suggested for its pathogenesis in patients with inflammatory rheumatological disease, such as lymphangitis, lymphatic obstruction caused by fibrin, capillary permeability increase, fluid retention associated with immobilization, venous obstruction, lymph vessel obstruction, lymphatic obstruction associated with coagulation system abnormalities, abnormal fibrinolysis and potential fibrosis of the superficial lymph vessels[2-10]. Some cases presented with an increase in plasma fibrinogen degradation products or hypoalbuminemia[9]. Diffusion of inflammatory processes into lymphatic vessels is thought to be a possible cause of chronic lymphangitis and edema[24].

In any of these diseases, there was no correlation with positivity for the rheumatoid factor or with the severity of the disease[9-12].

CLINIC PRESENTATION AND DIAGNOSIS

The duration of lymphedema after the onset of RA varied from the simultaneous onset to 37 years (mean duration: 7.7 years). The most affected sites were the upper limbs, especially the hands. Only six cases showed lower limb involvement. Positivity for the rheumatoid factor was noted in 61.3% of the patients[9]. The majority of previous reports described the lymphedema as persistent. In some patients with RA, an extension of the inflammatory process to include lymphatic vessels may cause the chronic lymphangitis responsible for the

edema[6]. This would interfere with normal lymph flow and lead to local tissue edema. It is possible that some treatments may reverse lymphangitis before permanent damage to structure or function can occur[15]. In PsA, lymphedema exclusively affects the upper limbs, with the right more frequently affected than the left. In most of these patients the metacarpophalangeal and interphalangeal joints, followed by the wrist and carpal joints, were involved[12].

The diagnosis is clinical, as one or more limbs have been observed to undergo painless swelling. Ultrasonography, Doppler ultrasonography, magnetic resonance imaging (MRI), lymphoscintigraphy and histopathological examination are used to confirm the diagnosis of lymphedema[13,14]. Ultrasonography helps the diagnosis by imaging of the lymph nodes, diagnosing secondary lymphostatic edema (tumor, metastasis), distinguishing adipose tissue (distinguishing lipedema), and imaging of joint and/or soft tissue (Baker's cyst rupture). Doppler ultrasonography is an illuminating tool, especially in terms of venous insufficiency and thrombosis. Computed tomography and magnetic resonance imaging are very important in the diagnosis of tumors and metastases. In addition, MRI may be used to identify and determine the location of circumscribed fluid accumulations. These analyses are particularly helpful for differential diagnosis. Qualitative lymphoscintigraphy discloses abnormal lymphatic drainage of the affected limb[11].

Lymphedema due to RA or PsA must be distinguished from a number of other conditions, including remitting seronegative symmetrical synovitis with pitting edema syndrome. Distal extremity swelling with pitting edema has also been described in polymyalgia rheumatica and giant cell arteritis. Primary lymphedema usually affects women, has an earlier onset and involves the lower extremities in the majority of cases. All forms of secondary lymphedema, including those caused by lymphatic compression or obstruction by tumors, infections (*e.g.*, filariasis) or artifacts (SecreÂtan's syndrome and Charcot's oedeme bleu) must be distinguished from lymphedema associated with PsA[2-10,12]. In differential diagnosis, venous stasis, deep vein thrombosis, congestive heart failure, vasculitis, hypoalbuminemia and nephrotic syndrome should be considered[23,25].

Rarely, rheumatological disorders can cause chronic lower extremity swelling in children. Lymphedema and other conditions are ruled out by lymphoscintigraphy and magnetic resonance imaging. If there is no history of trauma and no other potential cause of the swelling can be identified, children are referred for rheumatological consultation. A patient thought to have a condition other than lymphedema on history and physical examination usually undergoes MRI evaluation to confirm the suspected diagnosis and/or to define the extent of the disease. MRI also is commonly used as a secondary imaging study if lymphoscintigraphy is negative. Correct diagnosis is important, because the natural history and management of lymphedema are very different to other lower extremity diseases in children[19-21].

TREATMENT

Treatment for lymphedema is inefficient and is usually limited to symptomatic treatment. The intervention for lymphedema-complex decongestive therapy-CDT-consists of four main components: skin care, manual lymph drainage, compression and exercise, and remains the cornerstone of therapy in all patients suffering from lymphedema associated with inflammatory rheumatic diseases[1]. Skin care (moisturizing the skin; protection from infection and trauma), manual lymph drainage, short stretch bandage technique and exercise steps are applied in an intensive treatment program until the difference in arm circumference is reduced in patients. Manual lymph drainage is a sensitive massage technique applied using special techniques for lymph circulation stimulation, taking body lymph circulation into consideration. The person who applies this technique must receive special training. Short stretch bandage compression, as the name suggests, is a multi-layered bandage applied using short stretch bandage materials and special techniques. When the difference in arm circumference is reduced and when this decrease is stabilized, we proceed with maintenance treatment and the patient is given a special lymphedema compression garment. Skin care, manual lymph drainage and exercise steps are also continued during this process. Patient education (diet and protection) is one of the most important treatment steps. Although it is a challenging treatment, patient compliance to this treatment is generally favorable.

In most cases of RA or PsA, introduction of disease modifying drugs does not improve the edema. In some cases, intra-articular injection of corticosteroids into the joint proximal to the swollen area resulted in prompt resolution of the edema, whereas in other patients, intra-articular corticosteroids had little effect[12].

The literature includes publications indicating that tumor necrosis factor (TNF)-α inhibitory drugs used in the treatment of rheumatological diseases may be effective for lymphedema treatment[15,16,26]. Ostrov[11] reported that etanercept dramatically reduced the lymphedema in a patient with RA. Almodóvar *et al*[16] described the first case of a patient diagnosed with ankylosing spondylitis that was complicated with lymphedema who, after receiving treatment with infliximab, showed complete disappearance of the lymphedema. The mechanism by which TNF-α inhibitor therapy acts on lymphedema is not known, but the drugs are believed to act on the inflammatory response of the lymphatic vessels. Assuming that synovitis causes adjacent lymphatic inflammation and, ultimately, fibrosis, maximal control of active rheumatoid synovitis could abrogate this reaction. Therefore, TNF-α inhibitor therapy can be considered for the treatment of extra-articular manifestations in rheumatic diseases, such as lymphedema.

On the other hand, the temporal relationship suggest-

ed a link between the initiation of TNF-α inhibitors and the development of lymphedema[25]. Many authors have reported paradoxical effects of TNF-α inhibitors, such as new onset or exacerbation of psoriasis or psoriasiform skins. This is a class effect, as it has been associated with all the three TNF-α inhibitors. In some cases, the lesions completely resolved after the drug was discontinued, but returned on re-challenge either with the same agent or a different TNF-α inhibitor, whereas, in other cases, the lesions subsided after topical treatment. The underlying mechanism for these paradoxical effects is not well understood. Anti-TNF-α-TNF-α immune complexes may be deposited in small capillaries, triggering a type Ⅲ hypersensitivity reaction. Another theory is that TNF-α blockade may interfere with the maintenance of tolerance by inhibiting apoptosis[25]. Lymphedema after initiation of TNF-α inhibitors remains a diagnosis of exclusion. A temporal relationship points toward a possible linkage; however, the actual pathophysiology remains unclear. In inflammatory rheumatological conditions, disease modifying drugs are not very effective; however, some favorable results have been reported for TNF-α inhibitors. These data, on the other hand, are very confusing. Based on current data, it is not possible to say that TNF-α inhibitors are effective or ineffective. When this kind of case is encountered, complex decongestive therapy (CDT) treatment can be initiated and other drugs may be tried in addition to the principal treatment, depending on the patient's response. There is no sufficient explanation of how CDT works in these case presentations; therefore, it is difficult to say if the treatment response is associated with CDT or with the drugs. It may be beneficial to provide more explanatory information on treatment in future case presentations.

In a conclusion, lymphedema may be observed, although rarely, in inflammatory rheumatological diseases. The pathology of this occurrence, which presents as extra-articular involvement of the disease, is not fully established; therefore, the likelihood of successful treatment is low. The efficacy of TNF-α inhibitor drugs reported in case studies also seems to be contradictory. Based on these results, it may be useful to include the disease in post-diagnosis complex decongestive treatment program and to use the drugs mentioned in the literature. However, more data are needed to reach conclusive results.

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