Recurrent and refractory lower limbs lymphedema in psoriatic arthritis: A case description and literature review

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Abstract

Lymphedema is an uncommon extra-articular complication of rheumatoid arthritis (RA), but it can also be associated with psoriatic arthritis (PsA), although rarely. While lymphedema associated with RA is well characterized in literature, only few cases have been described among patients with PsA. Upper limbs are the most common sites involved, with asymmetric pattern, even if some patients may present lower limb oedema, or progressive bilateral oedema.

Chronic established lymphoedema deriving from lymphatic vessel dysfunction should be clearly distinct from inflammatory distal pitting edema (IDPE), resulting from tenosynovitis and frequently encountered in PsA. In contrast to lymphedema, the latter condition generally presents an excellent response to steroid therapy, therefore it is essential to recognize the exact etiology of lymphoedema to approach the correct treatment. Here we report a case of lower limbs lymphedema in PsA and review the available literature upon the topic.

Introduction

Lymphoedema may occur as a rare complication of inflammatory joint diseases, such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA). While lymphoedema involving both upper and lower limbs is an unusual but well-recognized extra-articular feature of rheumatoid RA,[1] only few cases of lymphedema have been described in patients with PsA.[2]

Here we report a case of extremely disabling bilateral lymphedema of the lower limbs in a young woman with PsA. Furthermore, we conducted a literature review of studies in English to update and collect the described cases of lymphedema in PsA, highlighting its main clinical manifestations. We searched Pubmed and Embase databases from inception to December 1st, 2020. Lymphedema, psoriatic arthritis, psoriasis, spondylo-arthritis and their respective MESH terms were used as keywords. Emerging evidence on possible etiopathogenetic mechanisms and therapeutic options are also discussed.

Case Report

A 43-years-old Caucasian woman presented to our rheumatologic unit in 2006 for the recent onset of intense and persistent pain in both feet, associated with severe swelling of the left foot. Physical examination showed painful pitting oedema spread over the dorsum of the left foot, marked pain on palpation of the left metatarsophalangeal (MTF) joints, dactylitis of the left fourth toe and mild pain on palpation of the MTF of the right foot. Diffuse painless swelling of both legs, more evident at left lower limb, was also appreciated, with persistent indentation. The ultrasound (US) examination of the feet revealed the presence of active synovitis with altered power-doppler signal of the II-V left MTF and of the II-III right MTF. Besides, the instrumental examination of the left foot documented the presence of wide tenosynovitis of the extensor tendons of the dorsum and of the flexor tendon of the IV toe and intermetatarsal bursitis between II and III toes. US examination of legs confirmed diffuse subcutaneous oedema with numerous lymphatic lakes consistent of lymphoedema.

From her past medical history, it emerged that diffuse swelling of the lower limbs occurred even six months earlier, in the absence of concomitant joint or tendon inflammation and only recently worsened, concurrently with the onset of arthritis in the small joints of the feet. The patient since the onset of lymphedema has been regularly evaluated in the vascular surgery department of another hospital, where chronic relapsed idiopathic lymphedema had been diagnosed, partially responsive to conventional diuretic treatment undertaken. All main causes of lymphedema were excluded: chronic venous thrombosis, infections, allergic reactions, cellulitis as well as congestive heart failure, chronic kidney disease and pelvic masses.

From her past medical history previous episodes of right kidney cystopyelitis, non-erosive gastritis and esophagitis emerged. A family history of psoriasis (mother and sister) was associated.

Blood analysis showed increased C-reactive protein (CRP = 2.1 mg/dl). Autoimmunity panel tests such as ANA, ANCA, C3, C4, LAC, anti-cardiolipin, anti-beta2 glycoprotein antibodies, rheumatoid factor and anti-cyclic citrullinate antibodies were found all negative. Urinalysis, electrocardiogram and chest X-ray were all normal. Blood count, kidney and liver function were performed and found within normal ranges.

According to CASPAR criteria,[3] a diagnosis of PsA *sine* psoriasis associated with lymphedema was made and therapy with prednisone 7.5 mg/day plus local steroids injection of MTF was started. Within a month, distal pitting edema, synovitis and dactylitis completely remitted, and lymphedema almost completely resolved. Subsequently, steroids were gradually tapered and after 3 months the patient discontinued both steroids and diuretics.

In 2010 a sudden relapse of severe lymphedema in both lower limbs happened (Figure 1), once again more evident on the left leg and with extension to the dorsum of the left foot; no clinical or ultrasound signs of musculoskeletal inflammation were detected. A lymphoscintigraphy was then performed, which documented bilateral lymphatic insufficiency (Figure 2).

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Assuming an inflammatory lymphedema secondary to PsA, an effort with methotrexate up to 15 mg per week was made, in combination with heparin, diuretic therapy and steroid therapy (prednisone 25 mg/die), the latter gradually tapered and withdrawn over the next two months, during which no recurrence of lymphedema happened. Diuretics and heparin were also discontinued, and the patient continued only methotrexate.

In 2014 the patient experienced a new severe relapse of bilateral lymphedema, for which she was again hospitalized at our rheumatologic unit. The clinical and instrumental presentation was exactly comparable to the previous of 4 years earlier, with widespread bilateral lower limb lymphedema with extension to the dorsum of the left foot, without concomitant clinical or ultrasound signs of musculoskeletal inflammation. In this occasion, the patient reported the recent appearance of cutaneous psoriasis localized in the trunk, with nail psoriasis in both feet. All main causes of secondary lymphedema were once more excluded. Again, a therapeutic attempt with steroids and diuretics was proposed, this time without any benefit. Immunosuppressive therapy was then started with TNF-inhibitor as monotherapy (etanercept 50 mg/week) with excellent clinical results, conducting to a complete remission of lymphoedema within two months.

During the following 6 years, the patient continued the therapy with etanercept: only occasional transitory episodes of lower left limb swelling occurred, managed with benefit with short courses of steroids and diuretics.

Nonetheless, in March 2020 the patient experienced a new acute relapse of bilateral lymphedema, with severe functional impairment and inability to walk, therefore she was again hospitalized.

US confirmed diffuse bilateral lymphedema in the lower limbs and dorsum of the feet and ruled out signs of synovitis, enthesitis, dactylitis or tenosynovitis. Feet X-ray findings did not reveal any further significant osteo-structural changes and in particular no signs of erosions, areas of osteolysis, osteopenia or enthesopathy.

Serological tests for filarial infections were collected and found negative. Computed tomography of the abdomen and pelvis excluded suspected compressive masses. MRI of legs and feet confirmed abundant subcutaneous oedema, in the absence of articular or tendon inflammatory signs or bone oedema (Figure 3). A new lymphoscintigraphy confirmed bilateral lymphatic insufficiency. US examination of soft tissues, performed by the vascular

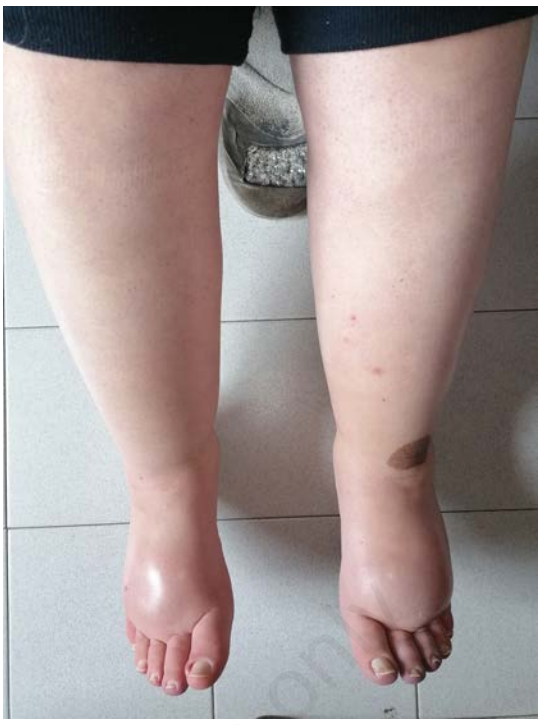

Figure 1. Diffuse lower extremity oedema.

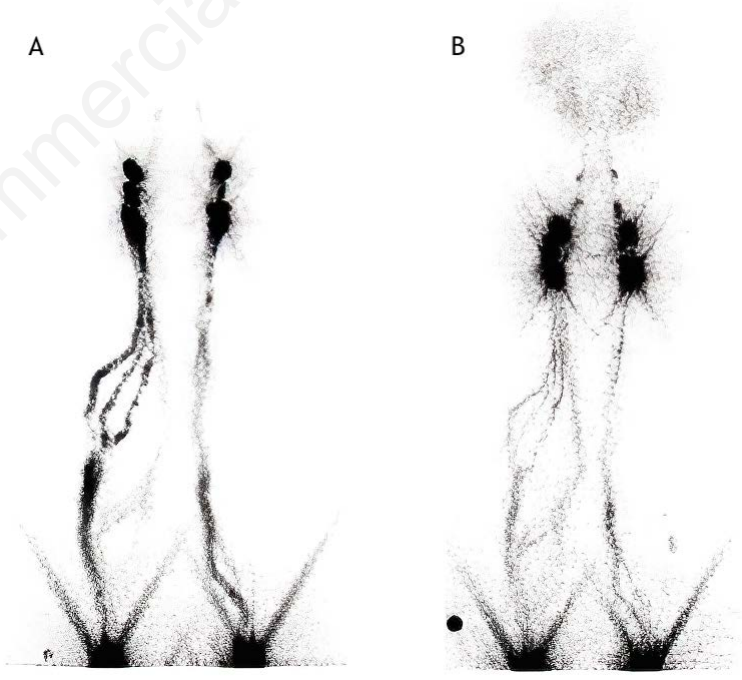

Figure 2. Lymphoscintigrams after injection with ^{99m}Tc-labelled nanocoll. Slow lymphatic drainage in both lower limbs, probably more evident on the right. No deficit of representation of the main femoro-inguinal and iliac lymph node stations. (A) Post-injection phase: normal visualization of the superficial lymphatic collectors of the right lower limb with the presence of visible collateral circles and minimal visualization of shunts in the deep pathway. On the left, only a deep lymphatic pathway is visible. Normal visualization of inguinal lymph nodes bilaterally. (B) Late phase: on the right, only the superficial lymphatic pathway is still visible; on the left, the deep lymphatic collector is still visible, with only minimal initial observation of the superficial pathway. The femoral-inguinal and iliac lymph nodes are visible bilaterally.

surgery consultant, confirmed the presence of a mainly organized oedema at the level of the medial region of the left leg, while in the lateral region and at the perimalleolar level the oedema still appeared fluid with the presence of numerous lymphatic lakes. The picture was referred to stage V lymphedema secondary to psoriatic arthritis. The patient was then treated with high dose steroids, diuretics and heparin, without substantial clinical improvement. Given the good clinical response obtained with the first attempt with anti-TNF, etanercept, a therapeutic switch to another anti-TNF molecule (adalimumab 40 mg/14 days) was decided in combination with low-dose steroids and diuretics. The patient was then discharged and in the following two months there was a moderate response to therapy with an improvement of the lower limbs swelling of about 50%.

In June 2020, however, a new severe recrudescence of lymphedema appeared, with marked functional impotence and nearly impossibility to walk. Methotrexate was then added to anti-TNF therapy at a dosage of 15 mg/week, unfortunately without substantial benefits.

In July 2020 the patient was hospitalized in the venous vascular surgery unit of our center where she began mechanical decongestant therapy with multilayer bandage and intermittent pneumatic compression (IPC),[4,5] manifesting in the following six months a significant clinical improvement with a remission of lymphedema of about 80%. Drug therapy with adalimumab 40 mg/14 days, methotrexate 15 mg/week, prednisone 5 mg/day, heparin and diuretics was then confirmed. The rehabilitation treatment using decongestant compression therapy was structured through weekly applications of lymphatic multilayer bandage (AD segment) according to the methods described in the literature for decongestant therapy.[6,7] Zinc oxide bandages, foam fixing bandages and non-adhesive inelastic bandages were applied. Given the impossibility of two bandages per week, due to the patient's distance from hospital, a protocol was adopted by our vascular centre with the application of a multilayer lymphatic bandage for 4 days and subsequent use of a flat therapeutic elastic stockings. To complete the therapy, given the problem of oedema in the patient's feet, a further specific compression was applied to the feet using a velcro-adjustable compression.[8] Every evening the patient underwent a home IPC cycle.[4] This synergy between elastic compression therapy and rheumatological therapy has led to a significant improvement in the quality of daily life and symptoms for the patient. Unfortunately, one month after the end of the decongestant phase, in the maintenance phase only with a flat elastic stocking, the patient's symptoms worsened. The patient's hypomobility, the lack of ambulation and the poor excursion of the ankle joint aggravated the lymphatic pathology and did not give way to the physiological muscular contraction of the leg muscles to activate the valve-muscular pump which would allow the physiological venous and lymphatic return.

In February 2021, one month after the end of the decongestant and rehabilitative treatment, a new worsening of the lymphedema in the left lower limb occurred, for which new compressive dressings were resumed and cycles of mesotherapy with intradermal injections of heparinoids were started, while drug therapy remained unchanged. In the following two months there was a satisfactory although not complete control of lymphedema. A periodic rheumatological and vascular follow-up of the patient has been then scheduled.

Discussion

Lymphoedema is a chronic and progressive condition characterized by a fluid accumulation in the skin and subcutaneous tissues resulting from impaired lymphatic drainage.[9] The main recognized causes of lymphoedema are cancer and its treatment (*e.g.* mastectomy), congenital abnormalities, chronic venous disease and infections (*e.g.* filariasis).[9] However, although more rarely, lymphedema can occur in other clinical conditions, among which allergic reactions, septic cellulitis, panniculitis, artefacts (Secretan's syndrome and Charcot's oedeme bleu) and chronic inflammatory arthropathies such as RA and PsA.[9,10] The early identification of lymphedema is of crucial importance to provide a correct differential diagnosis as well as a prompt and suitable therapy.

While lymphoedema involving both upper and lower limbs is a rare but well-recognized complication of RA[1,11-15] it has been rarely described in PsA with almost exclusive involvement of the upper limbs.[2]

To the best of our knowledge, 18 cases of lymphoedema have been described to date in patients with PsA, whose main clinical characteristics and the applied therapies are summarized in Table 1.[2,16-27] Among these, in 15/18 patients (83,3%) lymphedema was asymmetrical and involved exclusively the upper limbs; in 1/18 (5%) it

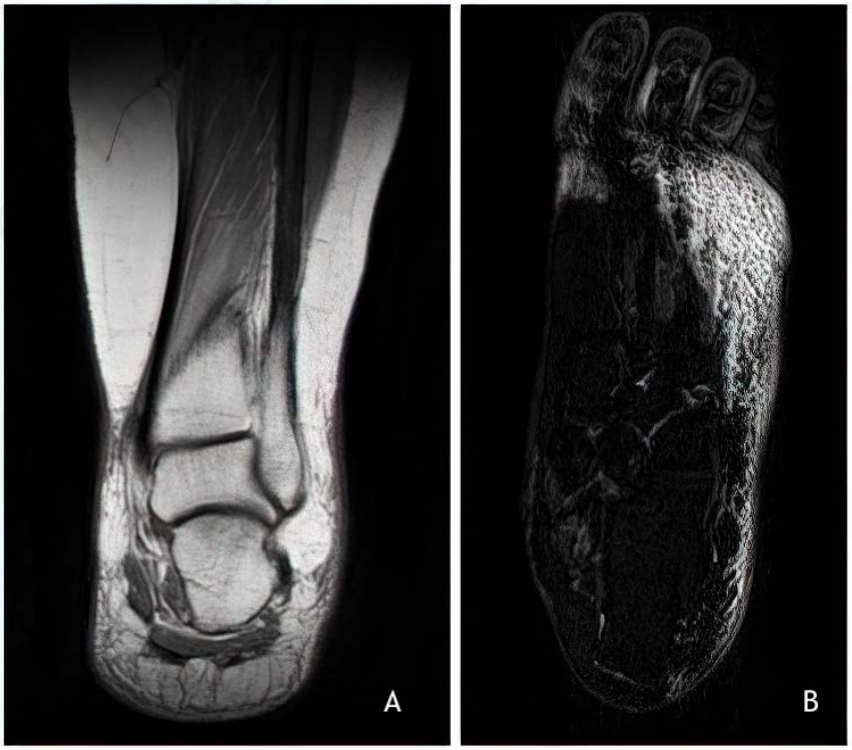

Figure 3. Magnetic resonance imaging (MRI) of left leg and foot: A) coronal T1-weighted MR image; B) axial short-term inversion recovery (STIR) image. Swelling and significant edematous imbibition of the soft tissues of the dorsum of the foot, extending to the lateral aspect. Modest edematous imbibition of the medial perimalleolar soft tissues, no signs of synovitis or tenosynovitis.

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Table 1. Clinical characteristics of the published case of psoriatic arthritis associated with lymphoedema.

Ref.	Pt,n.	Sex	Age (yrs)	Arthritis Distribution	Arthritis From yrs	LE site	Arthritis activity/ Therapy before LE	Arthritis activity at onset of LE	Therapy after LE	Improvement
16	1	F	46	Symmetrical polyarthritis	20	Upper/R	No/ NSAIDs	No	NSAIDs	No
17		F	30	Symmetrical polyarthritis+DIPs+ SI	9	Upper/ R>L	No/ NSAIDs	Yes	Cloroquine, physical	Slight (synovitis/LE)
		M	45	Asymmetrical polyartritis + DIPs	12	Upper/ R-L	No/ MTX, PDN	No	MTX, PDN physical	No
		F	62	Symmetrical polyarthritis +DIPs +cervical spine	9	Upper/R	No/ NSAIDs	No	Physical	No
	4	F	64	Symmetrical polyarthritis	6	Upper/L	No/ HC and NSAIDs	Yes	D-penicillamine physical	Complete (synovitis/LE)
18*	1	F	40	Symmetrical polyarthritis	15	Upper/R	No/ CyC/NSAIDs	Yes	CyC,PDN, physical	No (synovitis/LE)
19	2	F	54	Symmetrical polyarthritis	1	Upper/L>R	No/ PDN	Yes	Not known	Slight (synovitis/LE)
		F	44	Symmetrical polyarthritis	11	Upper/R>L	No/ NSAIDs	No	2nd line drug	No
2	1	M	41	Symmetrical polyarthritis+ DIP+SI	9	Upper/R>L	Yes/ SSZ,PDN	Yes	CyC physical	Slight (synovitis/LE)
20**	1	F	35	Symmetrical polyarthritis+ DIP	16	Upper/R	Not known/ Not known	Yes	MTX	No LE; Yes synovitis
21	1	M	52	Hands asymmetrical erosive arthritis	10	Upper/R Lower/L	Not known/ not-specified cDMARDs	Yes	Etanercept	Complete (synovitis/LE)
22	1	M	43	Asymmetrical polyartritis; dactylitis; SI;	9	Upper/L	Not known/Not Known	Yes	SSZ (7 months); MTX (33 months) ETA+MTX	Complete (synovitis/LE)
23	1	M	56	Symmetrical polyartrhritis; SI.	17	Upper/L	Yes/ MTX,SSZ,LFN,CYC)	Yes	Adalimumab	Significant (synovitis/LE)
24		M	38	Symmetrical polyartrhritis; DIP	17	Upper/R	Yes/MTX,PDN	Yes	ETA, MTX, PDN	No LE; Yes synovitis
	2	F	54	DIP; bilateral PIP, MCP	2	Upper/L	No / MTX, NSAIDs	No	ETA, MTX, PDN	No
25	1	F	42	Symmetrical polyartrhritis; DIP	22	Upper/R and L	No/ LFN,PDN,ABT	Yes	Physical	No (synovitis/LE)
26	1	F	44	Asymmetrical polyarthritis (knees,hands)	1,5	Lower/R>L (LE before synovitis)	---	Yes	ETA-ADA (both suspended for infection) MTX, PDN physical	No LE; Slight synovitis
27	1	M	52	Relapsing asymmetric polyarthritis	9	Lower/L	No/ NSAIDs	No	ETA	no

F, female; M, male; R, right; L, left; PIP, proximal interphalangeal; DIP, distal IP; LE, lymphoedema; ETA, etanercept; ADA, adalimumab; physical: limb exercise/compression/hosiery; * Two cases reported in the article, one excluded because clear inflammatory distal pitting oedema plus synovitis without lymphoedema. ** Two cases reported in the article, one excluded because a con sequence of heart failure

involved asymmetrically both upper and lower limbs;[21] and in 2/18 (11,1%) involved exclusively lower limbs, asymmetrically in one case[27] and symmetrically in the other one.[26] In our case, lymphoedema involved exclusively lower limbs in an asymmetrical manner, being more severe in the left leg. Therefore, in spite to what was previously stated,[2] in PsA lymphoedema can affect additionally lower limbs.

In Table 1 we have reported only the cases of established lymphoedema, excluding one of the two cases reported by Salvarani *et al.*[18] since referable to a clear inflammatory distal pitting oedema (IDPE) and one of the two cases reported by Yamamoto *et al.*, as caused by hearth failure.

Similar to patients with RA, the etiology of lymphoedema associated with PsA is rather complex and still unknown. In both RA and PsA it has been suggested that inflammatory products from the synovium are deposited in the adjacent lymphatics, leading to lymphangitis and lymphatic obstruction. A pre-existent abnormality of lymphatic function has also been suggested as a predisposing condition.[18,20,28] Actually, as appears from our literature review, the onset of edema is unpredictable and does not emerge a direct correlation between the presence and/or severity of arthritis and the appearance of lymphoedema (Table 1). Even in our case, lower limb lymphoedema began 6 months before the onset of arthritis, in a complete absence of joint or tendon inflammation, worsened with the onset of the first signs of arthritis, and subsequently flared regardless the concomitant presence of arthritis and/or tenosynovitis.

Moreover, quantitative lymphoscintigraphy disclosed abnormal lymphatic drainage of the affected limbs in all cases of PsA and lymphoedema in which lymphatic function has been examined, including our case. All these findings therefore suggest, albeit only on a speculative point of view, that lymphoedema of PsA is not only the consequence of the joint inflammatory process, but it has a more complex and multifactorial etiopathogenesis. Interestingly, the study of Kiely *et al.* examined with lymphoscintigraphy 10 patients (RA or PsA) with inflammatory arthritis and associated lymphoedema and 18 patients with inflammatory arthritis without lymphoedema: inflammatory arthritis alone did not cause impaired lymphatic flow, which suggested the presence of additional unrelated factors still unknown for the development of lymphoedema in PsA. From this point of view, it is interesting to note that also in other forms of chronic lymphoedema, *e.g.* postmastectomy oedema, it has been postulated that additional factors, besides those more clearly evident, such as the surgical or radiotherapy damage of the axillary lymphatic system, can contribute to the development of edema.[2,29] Venous flow abnormalities, such as loss of phasic variation, echogenic thrombi, narrowing with fixed vein walls, presence of collaterals and increased arterial inflow have indeed been detected by color Doppler imaging in a higher percentage of patients with postmastectomy oedema as compared with breast cancer patients without lymphoedema.[2,29-31] Although in PsA patients with lymphedema, including our case, major hemodynamic abnormalities have always been excluded by Doppler ultrasound, a large number of patients with edema and PsA should be examined compared with patients without edema to rule out similar vascular abnormalities.[2]

From a strictly clinical point of view, it is very important to bear in mind the two different pathologic mechanisms responsible for swelling in the setting of PsA, namely lymphatic vessel dysfunction which underlies the true lymphedema, and tenosynovial inflammation which underlies the IDPE of hands and feet.[18,24,26] In the latter, pitting edema is easily induced, more strictly localized along the tendon course of the dorsum of hands and feet and pain is often severe. In opposite, lymphedema is usually less painful, more diffused and extended to the forearm or leg and pitting oedema is less easily detectable.[18,24,26,32] These two conditions must be distinct and not confused for at least 2 important reasons. First, while lymphoedema in PsA is rare, IDPE is rather often observed in PsA as emerged from the case-control study of Cantini *et al.*[33] in which distal extremity swelling with pitting edema was recorded in 39/183 PsA patients (21%) and only in 18/366 (5%) outpatient rheumatic disease patients with other diagnosis. Furthermore, in 20% of PsA patients IPDE was the first manifestation of PsA.[33]

Second, unlike cases with typical lymphedema, in which the prevalence of lymphatic involvement may explain poor outcome to therapy, patients with IDPE due to tenosynovial involvement have a more favourable outcome to treatment, especially if there are not concomitant lymphatic changes.[32,33] In the reported cases of lymphoedema in PsA, three different situations can be observed: i) cases with exclusive lymphedema without concomitant inflammatory signs and no response to standard anti-inflammatory treatments;[16-19,24,26,27] ii) cases with limphoedema and concomitant IDPE and/or synovitis, in which a good or partial response to standard therapy has been observed;[2,17,19,21-23]; and iii) cases with limphoedema and concomitant IDPE and/or synovitis without response to standard anti-inflammatory therapy.[20,24-26] Our case appears emblematic of different situations: at the onset lymphedema was associated with clear inflammatory signs of the feet (IDPE, synovitis, dactylitis) and a remission of both inflammation and lymphoedema was recorded after steroid therapy. Subsequently there were 2 relapses of lymphedema (each one every 4 years after the previous one) in both cases without concomitant inflammatory signs of the extremities, but despite this, there was a good and prolonged response of lymphedema to specific anti-inflammatory and immunosuppressive therapy (steroids + methotrexate in the first relapse; anti-TNF etanercept in the second relapse). Finally, there was a third relapse of isolated lymphedema without concomitant inflammatory signs with loss of response to steroids and immunosuppressive drug therapy including TNF inhibitors. The good response of lymphedema at the onset and in the first two relapses seems to support the hypothesis of an inflammatory involvement of lymphatic vessels, while the complete loss of response on the occasion of the third relapse with chronic lymphedema underlines the likely intervention of other non-inflammatory factors in the maintenance of lymphedema.

Noteworthy, IDPE was first described in 1985 by McCarty *et al.* to describe a new syndrome characterized by remitting symmetrical synovitis of upper and/or lower limbs associated with pitting oedema of the dorsum of the hands and/or feet (RS3PE syndrome: remitting seronegative symmetrical synovitis with pitting edema) whose main clinical finding was severe tenosynovitis although synovitis of the underlying joints was also a possible component.[32]

Over the following years the clinical findings of RS3PE involving the upper or lower limbs in either symmetric or asymmetric fashion have also been observed in other rheumatic and non-rheumatic conditions such as polymyalgia rheumatic, late onset undifferentiated spondyloarthropaties, late onset RA, ankylosing spondylitis and acute sarcoidosis.[18,34-38] However, due to the exclusively inflammatory basis, all these conditions are promptly responsive to corticosteroids. Failure to respond to therapy may underline a paraneoplastic condition.[39,40]

Differentiating a real lymphedema from IDPE is therefore very important but not always clinically straightforward, especially if they coexist, therefore imaging studies are very useful. Lympho-scintigraphy is to date the diagnostic method of choice to

asses lymph function in the presence of lymphoedema,[41] while MRI and power-doppler US are able to highlight both the inflammatory fluid collection in the tenosynovial and synovial structures and the diffuse edema of soft tissues in lymphoedema.[18,24,42,43]

Finally, from a therapeutic point of view, interesting data emerged in literature on the use of anti TNF biological drugs in the treatment of lymphedema associated with PsA. Etanercept was not effective in two cases of pure lymphedema,[24,27] and in one case of lymphedema associated with arthritic manifestations,[24] while it was effective in two cases of lymphedema associated with active synovitis.[21,22] In one of these,[22] the benefit was prolonged (5 years). Similarly, adalimumab has been used successfully in one case of lymphedema associated with inflammatory manifestations.[23]

The use of TNF inhibitors seems not to give substantial added value in the treatment of chronic lymphedema in PsA when unrelated to active synovitis. In our case etanercept proved extremely effective even when used in the second relapse of isolated lymphedema without simultaneous inflammatory changes, with a prolonged benefit of about 6 years. However, with the appearance of a new severe relapse, etanercept was discontinued and adalimumab therapy proved ineffective. Even if data available so far do not allow definitive conclusions, it is however plausible to propose the use of immunosuppressive therapy as early as possible even in cases of isolated lymphedema associated with PsA (when all other causes of lymphedema have been ruled out) assuming that a form subclinical inflammation of joint or tendon may be the triggering cause. Obviously, a greater number of observations are essential to guide thorough a better understanding of the etiopathogenesis of lymphedema associated with PsA and to define the most suitable treatment needed. In cases of chronic unresponsive or poorly responsive lymphedema to therapeutic options, physical therapies, in particular mechanical decongestant therapy with bandage and sequential pneumatic pressotherapy, may be relevant, although not definitive, for the control of lymphedema.

So far in literature there are no strong available data on the effects of IL-17 or JAK inhibitors upon limbs lymphedema in psoriatic arthritis, nor in RA; further studies are required to elucidate possible benefits from these therapies.

Conclusions

Lymphoedema of both upper and lower limbs is a rare but possible complication of PsA that should be promptly recognized. Chronic established lymphoedema deriving from lymphatic vessel dysfunction should be clearly distinct from inflammatory distal pitting edema, resulting from tenosynovitis and frequently encountered in PsA.

In contrast to lymphedema, the latter condition generally presents an excellent response to steroid therapy.

Etiology of lymphoedema in PsA is to date unknown and presumably multifactorial, but a possible inflammatory origin has been hypothesized, leading to lymphangitis and lymphatic obstruction. The response to anti-inflammatory and immunosuppressive therapy is generally poor, which explains why a multifactorial genesis is more likely.

One of the key strengths of this study is the long duration of follow up, up to 15 years, extended more than the previously described cases in literature, allowing to observe additional longer term treatment effects and to better characterize the disease. Further studies are needed to verify long-terms effects of TNF-α inhibitors or other therapeutic options in isolated forms of lymphedema without concomitant signs of arthritis or tenosynovitis. Lymposcintigraphy, MRI and PDUS facilitate differential diagnosis between lymphatic edema and IDPE, proving useful in predicting prognosis. In the forms of PsA chronic lymphoedema unresponsive to a suitable therapeutic strategy, physical therapy appears an important option.

References

1. Joos E, Bourgeois P, Famaey JP. Lymphatic disorders in rheumatoid arthritis. Semin Arthritis Rheum. 1993;22:392-8.
2. Bohm M, Riemann B, Luger TA, Bonsmann G. Bilateral upper limb lymphoedema associated with psoriatic arthritis: a case report and review of the literature. Br J Dermatol. 2000;143:1297-301.
3. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665-73.
4. Tessari M, Tisato V, Rimondi E, et al. Effects of intermittent pneumatic compression treatment on clinical outcomes and biochemical markers in patients at low mobility with lower limb edema. J Vasc Surg Venous Lymphat Disord. 2018;6:500-10.
5. Maldonado TS, Rokosh RS, Padberg F, et al. Assessment of quality of life changes in patients with lower extremity lymphedema using an advanced pneumatic compression device at home. J Vasc Surg Venous Lymphat Disord. 2021;9:745-52.
6. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology. 2020;53:3-19.
7. O'Donnell TF, Jr., Allison GM, Iafrati MD. A systematic review of guidelines for lymphedema and the need for contemporary intersocietal guidelines for the management of lymphedema. J Vasc Surg Venous Lymphat Disord. 2020;8:676-84.
8. Borman P, Koyuncu EG, Yaman A, et al. The comparative efficacy of conventional short-stretch multilayer bandages and velcro adjustable compression wraps in active treatment phase of patients with lower limb lymphedema. Lymphat Res Biol. 2021;19:286-94.
9. Szuba A, Rockson SG. Lymphedema: classification, diagnosis and therapy. Vasc Med. 1998;3:145-56.
10. Badger C, Preston N, Seers K, Mortimer P. Physical therapies for reducing and controlling lymphoedema of the limbs. Cochrane Database Syst Rev. 2004:CD003141.
11. Dacre JE, Scott DL, Huskisson EC. Lymphoedema of the limbs as an extra-articular feature of rheumatoid arthritis. Ann Rheum Dis. 1990;49:722-4.
12. Dippy JE. Lymphoedema complicating rheumatoid arthritis. Ann Rheum Dis. 1991;50:658.
13. Kalliomaki JL, Vastamaki M. Chronic diffuse oedema of the rheumatoid hand: a sign of local lymphatic involvement. Ann Rheum Dis. 1968;27:167-9.
14. Lacroix HR, Gruwez JA, Casteels-Van Daele MC, Dequeker J. Lymphedema of the leg associated with rheumatoid arthritis. Lymphology. 1991;24:68-70.
15. Minari C, Cecconami L, Fioravanti A, et al. Lymphoedema of the limbs in rheumatoid arthritis. Clin Rheumatol. 1994;13:464-9.
16. Salvarani C, Macchioni PL, Veneziani M, et al. Upper limb lymphedema in psoriatic arthritis. J Rheumatol. 1990;17:273-4.
17. Mulherin DM, FitzGerald O, Bresnihan B. Lymphedema of the upper limb in patients with psoriatic arthritis. Semin Arthritis Rheum. 1993;22:350-6.
18. Salvarani C, Cantini F, Olivieri I, et al. Distal extremity swelling with pitting edema in psoriatic arthritis: evidence of 2 pathological mechanisms. J Rheumatol. 1999;26:1831-4.

19. Kiely PD, Joseph AE, Mortimer PS, Bourke BE. Upper limb lymphedema associated with polyarthritis of rheumatoid type. J Rheumatol. 1994;21:1043-5.
20. Yamamoto T, Nishioka K. Psoriasis arthropathy and lymphedema. J Dermatol. 2002;29:812-4.
21. Doffoel-Hantz V, Sparsa A, Verbeke S, et al. Lymphoedema: a rare complication of inflammatory rheumatism. Successful treatment with etanercept. Eur J Dermatol. 2007;17:337-8.
22. Lekpa FK, Economu-Dubosc A, Fevre C, et al. Efficacy of etanercept in lymphedema associated with psoriatic arthritis. J Rheumatol. 2009;36:207-8.
23. Tong D, Eather S, Manolios N. Psoriatic arthritis and chronic lymphoedema: treatment efficacy by adalimumab. Clin Rheumatol. 2009;28:1349-50.
24. Quarta L, Corrado A, d'Onofrio F, et al. Two cases of distal extremity swelling with pitting oedema in psoriatic arthritis: the different pathological mechanisms. Rheumatol Int. 2010;30:1367-70.
25. Martinez-Crespo G R-SF. [Linfedema bilateral en miembros superiores asociado a artritis psoriasica.][Article in Spanish]. Rehabilitacion. 2012;46:250-3.
26. Condit R. FG. Lower extremity swelling in a patient with psoriatic arthritis. Rheumatology Reports. 2013;5:1-3.
27. Fourgeaud C VS. [Lymphoedème des membres inférieurs:une manifestation rare des spondyloarthrites.][Article in French]. Rev Med Interne. 2019;40:837-40.
28. Kiely PD, Bland JM, Joseph AE, et al. Upper limb lymphatic function in inflammatory arthritis. J Rheumatol. 1995;22:214-7.
29. Stanton AW, Levick JR, Mortimer PS. Current puzzles presented by postmastectomy oedema (breast cancer related lymphoedema). Vasc Med. 1996;1:213-25.
30. Svensson WE, Mortimer PS, Tohno E, Cosgrove DO. Colour Doppler demonstrates venous flow abnormalities in breast cancer patients with chronic arm swelling. Eur J Cancer. 1994;30A:657-60.
31. Svensson WE, Mortimer PS, Tohno E, Cosgrove DO. Increased arterial inflow demonstrated by Doppler ultrasound in arm swelling following breast cancer treatment. Eur J Cancer. 1994;30A:661-4.
32. McCarty DJ, O'Duffy JD, Pearson L, Hunter JB. Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. JAMA. 1985;254:2763-7.
33. Cantini F, Salvarani C, Olivieri I, et al. Distal extremity swelling with pitting edema in psoriatic arthritis: a case-control study. Clin Exp Rheumatol. 2001;19:291-6.
34. Bhakta BB, Pease CT. Late-onset rheumatoid arthritis: is pitting oedema of the hands at onset a good prognostic indicator? Br J Rheumatol. 1997;36:214-9.
35. Cantini F, Niccoli L, Olivieri I, et al. Remitting distal lower extremity swelling with pitting oedema in acute sarcoidosis. Ann Rheum Dis. 1997;56:565-6.
36. Olivieri I, Padula A, Favaro L, et al. Dactylitis with pitting oedema of the hand in longstanding ankylosing spondylitis. Clin Rheumatol. 1995;14:701-4.
37. Olivieri I, Padula A, Pierro A, et al. Late onset undifferentiated seronegative spondyloarthropathy. J Rheumatol. 1995;22:899-903.
38. Salvarani C, Gabriel S, Hunder GG. Distal extremity swelling with pitting edema in polymyalgia rheumatica. Report on nineteen cases. Arthritis Rheum. 1996;39:73-80.
39. Cantini F, Olivieri I, Salvarani C. More on remitting seronegative symmetrical synovitis with pitting edema as paraneoplastic syndrome. J Rheumatol. 1998;25:188-9.
40. Tada Y, Sato H, Yoshizawa S, et al. Remitting seronegative symmetrical synovitis with pitting edema associated with gastric carcinoma. J Rheumatol. 1997;24:974-5.
41. Weissleder H, Weissleder R. Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. Radiology. 1988;167:729-35.
42. Agarwal V, Dabra AK, Kaur R, et al. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome: ultrasonography as a diagnostic tool. Clin Rheumatol. 2005;24:476-9.
43. Cantini F, Niccoli L, Nannini C, et al. Psoriatic arthritis: a systematic review. Int J Rheum Dis. 2010;13:300-17.