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Ankylosing Spondylitis and Right Lower Limb Lymphoedema A Rare Association: A Case Report and Review of the Literature

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Abstract **Case Report**

Introduction: Ankylosing spondylitis or rheumatic pelvispondylitis is a chronic inflammatory rheumatism characterized by an axial localization predominantly in the spine and sacroiliac joints, an involvement of the entheses and a tendency to bone ankylosis by ossification of these entheses. We report an observation of right lower limb lymphedema associated with ankylosing spondylitis. ***Observation:*** This was a 63-year-old patient with a history of inflammatory rheumatism (his older sister) and osteoporosis (his mother), He was diagnosed with ankylosing spondylitis based on enthesis involvement (bilateral tilted gluteal pain and low inflammatory back pain) with a positive HLA-B27 antigen by the 8-point Amor criteria for spondyloarthritis (right unilateral sacroiliitis, low inflammatory back pain, bilateral tilted gluteal pain, HLA-B27+ and NSAID sensitivity). The unilateral lymphedema with positive Stemmer's sign affected the lower 2/3 of the right lower limb. It occurred one year after the onset of ankylosing spondylitis. The echo-Doppler scan showed no signs of thrombosis or venous infiltration of the lower limbs, and diffuse infiltration of the subcutaneous tissue of the right leg without inflammatory character. Treatment of ankylosing spondylitis gradually improved the lymphedema. ***Conclusion***: Lymphedema is a rare complication of ankylosing spondylitis. Dermatologists should be alert to early swelling of the extremities in patients with ankylosing spondylitis so as not to delay specific multidisciplinary treatment and measures to avoid irreversible lymphatic damage.

Keywords: Ankylosing spondylitis, lymphedema, Senegal.

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INTRODUCTION

Ankylosing spondylitis or rheumatic pelvispondylitis is a chronic inflammatory rheumatism characterized by a predominantly axial localization in the spine and sacroiliac joints, an involvement of the entheses and a tendency to bone ankylosis by ossification of these entheses with a strong association with HLA-B27 (90% of cases) and an absence of autoantibodies [1, 2]. It is the leading spondyloarthritis and occurs particularly in young adult males. It is the second most common chronic inflammatory rheumatic disease after rheumatoid arthritis [3]. Apart from ankylosing spondylitis (APS), the most common form, of spondyloarthritis includes psoriatic arthritis, reactive arthritis and rheumatism associated with inflammatory bowel diseases. Lymphoedema of the limbs is due to dysfunction of the lymphatic system responsible for lymph stasis [4, 5]. Lymphoedema can be classified schematically into primary lymphoedema (isolated, complex malformation syndromes, genetic anomalies), i.e., without any notion of intervention on the lymphatic system, in particular, the lymph node areas, and secondary lymphoedema due to lesions of the lymphatic system, mainly after treatment of cancers including lymph node dissection associated or not with irradiation, breast for the upper limb, cervix, endometrium, ovaries, prostate, bladder, rectum, anal margin, melanoma, Hodgkin lymphoma or not for the lower limb [6, 7]. It is a chronic disease, whose main risks without treatment are the progressive increase in volume, the occurrence of infectious complications (erysipelas) and the impact on the quality of life [5, 8]. Treatment aims to stabilize the volume over the long term and to avoid possible complications. Lymphedema is a rare extra-articular manifestation that has been described in rheumatoid arthritis and spondyloarthritis.

We report an observation of HLA B27 positive ankylosing spondylitis associated with lymphedema of the right lower limb with an analysis of the clinical, echo-Doppler and evolutionary characteristics.

OBSERVATION

This was a 63-year-old patient with a history of inflammatory rheumatism (his older sister) and osteoporosis (his mother), in whom ankylosing spondylitis was retained based on enthesis involvement (bilateral tilted gluteal pain and low inflammatory back pain) with positive HLA-B27 antigen by the classification criteria Amor Criteria for 8-point spondyloarthritis (right unilateral sacroiliitis, low inflammatory back pain (VAS: 6/10), bilateral tilted buttock pain, HLA-B27+ and NSAID sensitivity). One year later, oedema of the right lower limb appeared progressively, starting at the foot and then moving up to the level of the lower 1/3 of the right leg. No erysipelas episode with positive Stemmer's sign, which is the impossibility of wrinkling the skin of the dorsal surface of the base of the second toe (Fig 1). The venous echo-doppler showed no signs of thrombosis or venous insufficiency of the lower limbs, and the presence of diffuse infiltration of the subcutaneous tissue of the right leg without an inflammatory character with regular lymphatic drainage (Fig 2). The inguinal and bilateral iliac retro crural lymph nodes were absent on the left and present on the right. Thus the diagnosis of ankylosing spondylitis and lymphedema of the right lower limb was retained, the treatment was based on 15mg of methotrexate per week (Monday), 5mg of folic acid per week (Wednesday), and the outcome was favorably marked by the regression of lymphedema and low back pain (VAS : 1/10) with a more or less significant recurrence after 2 months of treatment.

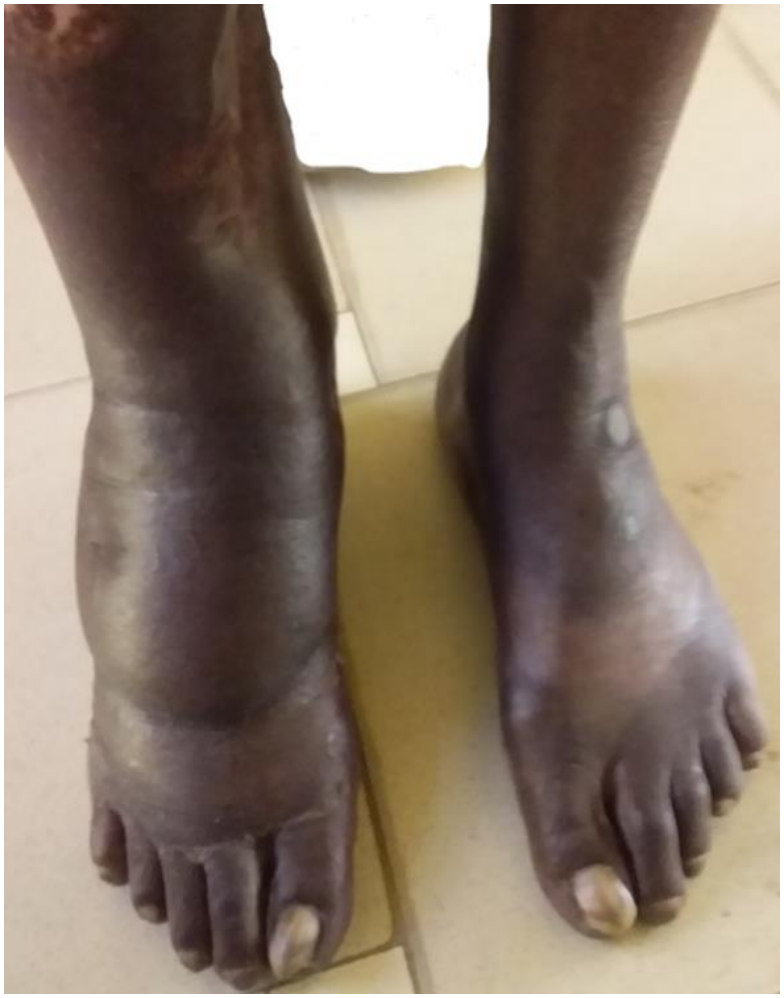


Figure 1: Lymphedema of the right lower limb during ankylosing spondylitis, accentuation of the flexion folds of the dorsum of the foot

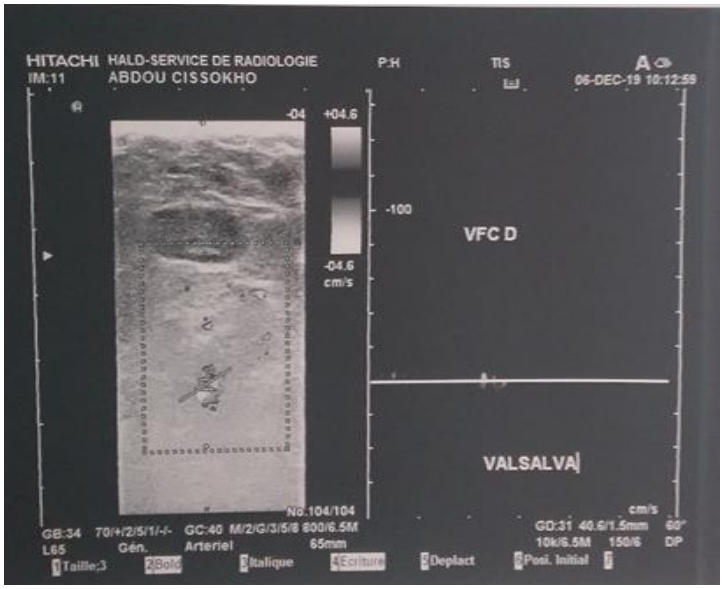
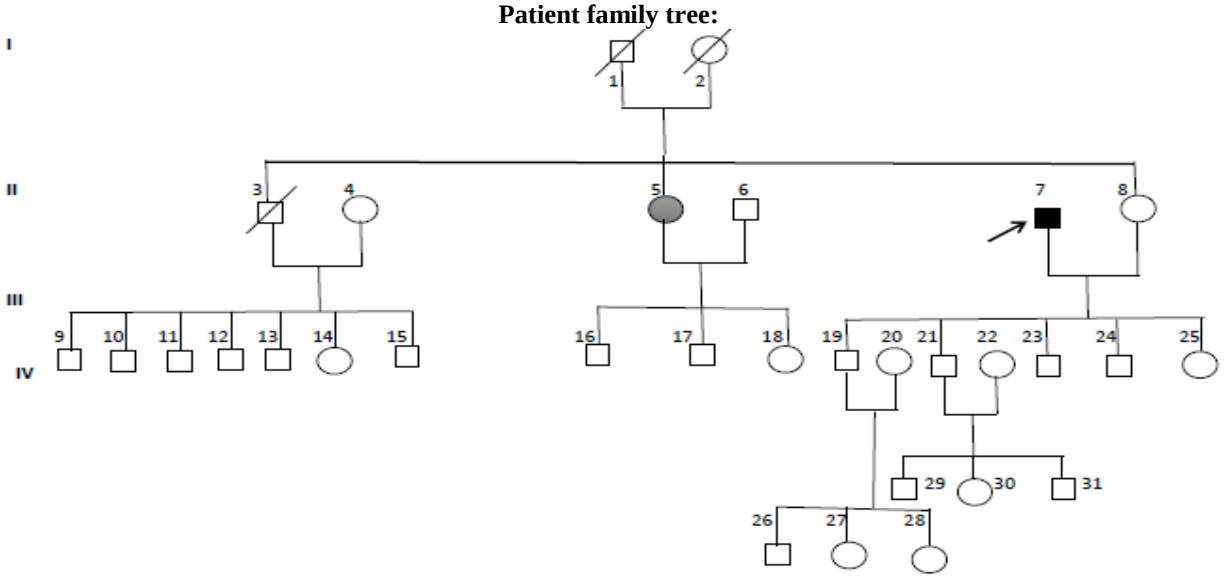


Figure 2: Venous echo-doppler of the lower limbs showing diffuse infiltration of the subcutaneous tissue of the right leg without inflammation

Patient family tree:



1. Kaye Cissokho
2. Coumba Toure
3. Nouha Cissokho (décédé)
4. Djenaba Diaw
5. Aminta Cissokho (rhumatisme inflammatoire)
6. Khousse Ndieye
7. **Abdou Cissokho (SPA+Lymphoedeme)**
8. Dabo Camara
9. Yaya Cissokho
10. Amy Conde
11. Lamine Cissokho
12. Mohamed Cissokho
13. Ndeye Gueye Cissokho
14. Massa Cissokho
15. Moustapha Cissokho
16. Yakouba Nddiaye
17. Grand Ndeye
18. Hawa Ndiaye
19. Mohamed Cissokho
20. Salemata Camara
21. Idrissa Cissokho
22. Hawa Coulibaly
23. Hamidou
24. Souleymane Cissokho
25. Moustapha Cissokho
26. Hawa Cissokho
27. Penda Cissokho
28. Ndaye Cissokho
29. Aziz Cissokho
30. Absatou Cissokho
31. Abdel-karim Cissokho

DISCUSSION AND COMMENTS

Our observation is that of an HLA B27 positive ankylosing spondylitis associated with lymphedema of the right lower limbs. Lymphedema is a rare complication that occurs during ankylosing spondylitis [9-11]. To our knowledge, only 42 cases have been reported exclusively in the literature, 30 of which were associated with rheumatoid arthritis and the other 11 with spondyloarthritis, including 4 cases of HLA B27 positive ankylosing spondylitis. All patients were middle-aged adults with a female/male ratio of 2 :1. Lymphedema affected exclusively the lower and sometimes the upper limbs, on the right more often than on the left and in contrast to patients with rheumatoid arthritis [12, 13]. This association does not appear to be coincidental and has been previously reported in psoriatic arthritis and rheumatoid arthritis [14, 15]. There was no direct correlation between the severity of arthritis and the development of oedema. As in patients with rheumatoid arthritis and lymphedema, the etiology of the oedema associated with spondyloarthritis remains unclear. Several hypotheses have been advanced regarding its pathogenesis in patients with rheumatoid arthritis and spondyloarthritis, such as lymphangitis, lymphatic obstruction, increased capillary permeability, abnormal fibrinolysis, and other disorders related to lymphatic function and structure. In the cases of spondyloarthritis and lymphedema in which the lymphatic function was examined, the Doppler ultrasound revealed an absence of signs in favor of thrombosis and venous insufficiency of the lower limbs and the presence of diffuse infiltration of the subcutaneous tissue of the right leg without inflammatory character. The observed quantitative colloid motion abnormalities in both branches paralleled the clinical severity of our patient's oedema as much as the extent of oedema, pitting and inability to grasp were more apparent on the right side [16, 17].

These findings indicate that lymphedema in ankylosing spondylitis is a direct consequence of disrupted lymphatic transport in the affected limb. For example, histological analysis of synovial lymphatic capillary structure obtained during synovectomies in patients with rheumatoid arthritis and juvenile idiopathic arthritis has shown there is an accumulation of lymphocytes, monocytes, ma crophages, and cellular debris within the lumen of lymphatic capillaries [10,16].

Based on morphological examination of psoriasis skin lesions, several authors have described lymphatic abnormalities such as dilatation, lack of penetration, or distal dermal blind loops, while other authors have been unable to confirm. A more recent study in patients with chronic plaque psoriasis revealed a larger network of peri-lesional lymphatics compared to lesional skin. To determine whether inflammation during spondyloarthritis itself leads to impaired lymphatic function, Kiely et al examined 10 patients with inflammatory arthritis such as rheumatoid arthritis and ankylosing spondylitis and oedema and 18 patients in inflammatory arthritis without edema13 by lymphoscintigraphy [13].

The results of histological analysis and capillary structure suggest that local synovitis and the accumulation of inflammatory cells may be the cause of obstruction of small-caliber synovial lymphatic vessels. Other authors have suggested that increased capillary permeability, abnormal development of fibrosis, or abnormalities in lymphatic vessel function or structure may be involved [10,11].

However, lymphedema sometimes occurs in areas that are poorly affected by spondyloarthritis, suggesting a systemic rather than local mechanism. Indeed, inflammatory mechanisms involving various cytokines (IL1, IL3, IL4, IL13, IFN) and growth factors (VEGF-C) have also been demonstrated in the development of lymphedema [18]. Systematic inflammation in rheumatologic disease could then be the factor favoring the occurrence of lymphedema in a possible predisposing terrain.

To the best of our knowledge, we are not aware of any studies investigating the macromolecular composition of interstitial fluid in swollen extremities of patients with lymphedema and spondyloarthritis. In rheumatoid arthritis, conflicting data have been reported regarding the protein content of oedema fluid. In some of these reports, the protein levels in the interstitial fluid of patients with oedema and rheumatoid arthritis were compared with the protein contents of the interstitial fluid of patients with congestive heart failure and oedema. Future studies on directly verifiable microvascular parameters such as interstitial fluid pressure (Pi), interstitial colloid osmotic pressure (pi), and interstitial plasma protein (Ci) content in swollen limbs of patients with spondyloarthritis, as well as careful design of appropriate controls, can elucidate the pathophysiology of spondyloarthritis and lymphedema [16, 18].

The presence of soft, asymmetrical, scooping oedema of the lower limbs and feet has been described in elderly patients with atypical and late forms of HLA B27-positive ankylosing spondylitis [13]. The oedema was then associated locally with peripheral oligoarthritis. Similarly, Marquart-Elbaz *et al*., [18] described a case of HLA B27-positive ankylosing spondylitis, revealed by soft oedema of the forefeet and distal hyper fixation of the feet on bone scans, as in our patient's case. In the articles published in the literature, it is difficult to affirm that these oedemas are true lymphoedemas because of the lack of precision in the clinical descriptions and their long-term evolution. Lymphedema due to spondyloarthritis must be distinguished from many other conditions, including symetrical seronegative synovitis with pitting oedema

syndrome (RS3PE) and giant cell arteritis. In another case, Bohm, M *et al*., [19] reported that forearm lymphedema was due to a multilobulated olecranon bursa with inflamed leaks, which is not the case in our patient. All forms of secondary lymphedema, including those due to lymphatic compression or obstruction by tumors, infections (e.g., filariasis), or artifacts (Secrétant syndrome and Charcot blue oedema), must be distinguished from lymphedema associated with spondyloarthritis. Indeed, lymphedema is an increase in the volume of a limb linked initially to a "liquid" oedema composed of an excess of lymph with the more or less rapid appearance of tissue changes (increase in adipose tissue and skin thickness, true skin fibrosis), which becomes the majority, making lymphedema chronic and largely irreversible [3]. Similarly, the lack of hindsight and follow-up of these patients does not allow us to confirm this diagnosis. Doppler ultrasound is used as a diagnostic tool to confirm the clinical diagnosis of lymphedema. However, in almost all cases reported in the literature, the diagnostic tool used was lymphoscintigraphy and the Doppler ultrasound did not reveal any particularity. Almodovar R *et al*., [21] stated that lymphoscintigraphy in patients with ankylosing spondylitis and lymphedema was "abnormal" without detailing the results of the examination. When the diagnosis of lymphedema is uncertain, MRI can also be performed to rule out tenosynovitis, associated with reversible oedema after treatment [11].

In our observation, the delay in the onset of lymphedema with rheumatologic disease was variable, ranging from a few months to 1 year. In the literature, this delay is often not specified, nevertheless, Almodovar, R *et al*., reported a case of ankylosing spondylitis in a 58 year old patient who developed a typical picture of ankylosing spondylitis at the age of 15 years and whose diagnosis was only revealed at the age of 51 years with development of oedema [21]. This shows us that the delay in the onset of oedema in this patient was 43 years, which is not the case in our patient.

The treatment of lymphedema associated with spondyloarthritis is ineffective and is usually limited to symptomatic treatment. In most cases of rheumatoid arthritis or ankylosing spondylitis, the introduction of disease-modifying drugs does not improve the oedema. It is sometimes based on low-elastic bandages that act on the fluid component to obtain maximum reduction and then on the wearing of an elastic compression whose objective is to maintain the reduced volume over the long term. It is useful for the patient to learn, as part of a therapeutic education program, how to apply self-bandages to be autonomous and to encourage long-term compliance [17]. Complications may occur, in particular erysipelas, the risk of which is increased in the presence of lymphedema. In some cases, intra-articular injection of corticosteroids into the joint proximal to the swollen area resulted in rapid resolution of the oedema, whereas in other patients intra-articular injection of corticosteroids had little effect. A beneficial effect was also reported with penicillamines. A partial improvement of upper limb lymphedema in ankylosing spondylitis was noted upon reintroduction of chloroquine phosphate according to Dacree *et al*., [25]. Regarding anti-TNF-α therapy, infliximab, recently approved for the treatment of ankylosing spondylitis (AS), is effective on peripheral joint manifestations and the axial skeleton. However, there is little information available on its efficacy for extra-articular manifestations In addition, Grillet and Dequeker described a case in that resulted in an early pulsed therapy with methylprednisolone that resulted in a marked decrease in oedema [26]. In our patient, 3 months of conservative treatment with methotrexate, prednisolone, and hydrochloroquine resulted in partial resolution of oedema and improvement in lymph flow parameters. Fernando K *et al*., showed that methotrexate 7.5mg/week, prednisolone 10mg/day combined with etanercept administered subcutaneously at 50mg once a week complemented improvement in arthritis and oedema [27]. Almodovar *et al*., Showed that in patients with axial forms of ankylosing spondylitis, infliximab led to an improvement as early as the second week and then to a complete disappearance of lymphoedema of the limbs, confirmed by lymphoscintigraphy before the 12th week of treatment [21]. The main hypothesis put forward is an anti-inflammatory action on the lymphatic vessels [18]. In rheumatoid arthritis and psoriatic arthritis, the evolution of lymphatic disease under specific treatment (corticosteroids, anti-TNF-α, monoclonal antibodies) differs according to the authors, some noting an improvement or even a disappearance of lymphoedema under specific treatment [11, 16], others noting its persistence in the long term despite the continuation of the treatment. Indeed, Tong D *et al*., had shown an improvement in lymphedema in patients treated with tumor necrosis factor alpha antagonists for psoriatic arthritis (Etanercept), rheumatoid arthritis (Etanercept) and ankylosing spondylitis (Infliximab). However, regular use of compression hosiery, manual lymphatic drainage, and initiation of an upper extremity exercise program remains the cornerstone of therapy in all patients with lymphedema associated with spondyloarthritis and rheumatoid arthritis [28].

CONCLUSION

Ankylosing spondylitis or rheumatic pelvispondylitis is a chronic inflammatory rheumatism of which lymphedema is a rare complication of APS dermatologists should be attentive to early swelling of the extremities in patients with APS in order not to delay multidisciplinary treatment and measures to avoid irreversible lymphatic damage.

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Declaration of Interest: No interest.

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