IDCases 27 (2022) e01386

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Type 2 leprosy reaction presenting as a monoarthritis post multidrug therapy

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ARTICLE INFO

Article history:
Received 14 December 2021
Accepted 5 January 2022
Available online xxxx

Keywords:
Leprosy
Mycobacterium leprae
Erythema nodosum
Arthritis

ABSTRACT

Type 2 leprosy reaction, or *erythema nodosum leprosum* (ENL), involves a complex interaction between the host's immune system and *Mycobacterium leprae*. It may occur before, during, or after treatment and have a variable clinical presentation involving different body systems, such as skin, osteoarticular, kidneys, and others. Thus, the differential diagnosis, depending on its clinical presentation, can be broad and challenging. The authors report a case of a severe monoarthritis during a type 2 reaction after the multidrug therapy (MDT) was discharged and the investigation of the differential diagnoses.

Introduction

Type 2 leprosy reaction, or *erythema nodosum leprosum* (ENL), is previously described in the literature as an immune response mediated by immune complexes that cause neutrophilic vasculitis [1,2]. Recent studies discussing the role of immune complexes in the pathogenesis of the disease reaction are still uncertain [3]. However, there is evidence of *in situ* increase of interleukin-6 (IL-6), interleukin-8 (IL-8), and transforming growth factor beta 1 (TGF-β 1). Peripheral increases of tumor necrosis factor-alpha (TNF-α), interleukin 1-beta (IL-1β), and TGF-β are also observed, showing that there is a series of complex interactions in the immune system related to the pathogenesis of this reaction [2–6].

Leprosy reactions can occur before, during, or after leprosy treatment with multidrug therapy (MDT) [2]. Among the risk factors related to its development are lepromatous leprosy and multibacillary disease, pregnancy, and lactation [7]. Some authors also relate an increased risk of developing reactions with the presence of other infections after vaccinations, some medications, and other factors [1,2]. The possibility of a Sars-cov-2 infection during the pandemic is an additional concern for leprosy centers, especially due to the possible increased risk for a type 2 leprosy reaction [8]. In general, studies show that reactions are more common in the first year of treatment, when there is a great bacillary destruction by an intense neutrophilic inflammatory infiltrate involving the regressing of the granuloma [7].

Clinical manifestations may include fever, asthenia, cutaneous and subcutaneous erythematous nodules, arthritis, synovitis, lymphadenopathy, neuritis, iridocyclitis, epididymo-orchitis, hepatitis, glomerulonephritis, among others [1,2].

The authors report a case of severe monoarthritis due to a type 2 reaction after the end of MDT for leprosy.

Case presentation

A 57-year-old male was diagnosed with lepromatous leprosy and treated with MDT. Treatment ended 4 months before the arthritis onset. The patient was closely monitored, during and after the treatment, due to a type 2 reaction state, presenting with erythematous nodules, tibial nerve neuritis, and previous necrotizing erythema nodosum scars on the skin surface.

In the first type 2 reaction episode, thalidomide (400 mg/day), prednisone (60 mg/day), and clofazimine (at an anti-inflammatory

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https://doi.org/10.1016/j.idcr.2022.e01386
2214-2509/

dose of 300 mg/day) were prescribed. A decrease in the number and severity of reaction episodes was observed after a year. Pentoxifylline (800 mg/day) was added to the therapy concomitantly with a gradual decrease in the use of corticosteroids.

At the end of the first year, there was a recrudescence of the type 2 reaction, with mild erythema nodosum, right knee arthralgia, and tibial nerve neuritis. Prednisone, thalidomide, and pentoxifylline were prescribed at the same previous doses. In some weeks, it was possible to observe an improvement of the cutaneous condition. After 2 months there was a worsening of pain and edema in the right knee joint, local inflammatory signs, and limitation to active and passive movement on the physical exam. Radiograph exam showed periarticular soft tissue edema, decreased medial joint space, mild osteopenia, and calcification of the tibial artery.

Three arthrocentesis were performed, with an average removal of 60–80 ml of purulent secretion. The material was sent for biochemical examination, which revealed the presence of group III synovial fluid (very inflammatory, > 20,000 cells). Gram, cultures for bacteria, fungi, and *Mycobacterium tuberculosis* were requested, and all results were negative. The patient underwent arthroscopy of the right knee, which visualized synovial membrane hypertrophy, chondromalacia with the destruction of cartilage tissue, and purulent effusion. Biopsy and continuous local irrigation were performed. The biopsy showed synoviocyte hyperplasia, increased subintimal cellularity, presence of polymorphonuclear cells, specific Virchowian infiltration with some granular bacilli in its interior, obliterative and necrotizing vasculitis, and intracavitary exudate, all characteristic of a synovitis of erythema nodosum leprosum.

Discussion

Arthritis associated with a type 2 reaction may precede, be concomitant with, or appear after ENL. It commonly manifests as polyarthritis or, oligo and monoarthritis in rare cases. This arthritis has an abrupt onset, intense pain, morning stiffness, and functional limitation. The most affected joints are knees, proximal interphalangeal joints, metacarpophalangeal joints, wrists, ankles, metatarsophalangeal joints, and elbows [9,10].

Treatment can be done with thalidomide (100–400 mg/per day), an immunomodulator derived from glutamic acid, and a potent selective inhibitor of TNF-α, in association with corticosteroids (1 mg/kg/day) for cases of neuritis, epididymo-orchitis, iridocyclitis, glomerulonephritis. Pentoxifylline (800–1200 mg/day) and clofazimine (300 mg/day, an anti-inflammatory dose) have been shown to help stabilize refractory reactions [1,11].

Joint involvement in leprosy can be very variable. Possible presentations are the occurrence of arthritis due to direct *Mycobacterium leprae* infection unrelated to the reaction, swollen hands, and feet syndrome, Charcot neuroarthropathy, tenosynovitis, enthesitis, cryoglobulinemic vasculitis, in addition to possible other infections when the patient is using immunosuppressive therapy [9,10]. The presentation may be similar to other connective tissue diseases, making differential diagnosis difficult, which may delay diagnosis and adequate therapy [12,13].

A high index of suspicion is required for cases of arthritis related to leprosy and leprosy reactions. In many cases, the differential diagnosis is difficult and extensive, especially when arthritis is included in the initial presentation of the disease [9]. The mycobacterium can be difficult to isolate, and some diagnostic techniques, such as PCR, are not always available. In such cases, extensive investigation to exclude other causes and histopathological analysis may be necessary. Tests, such as rheumatoid factor and antinuclear antibodies, can often be positive in leprosy and make the diagnosis difficult [9].

In the case reported, the patient presented with improvement in the erythema nodosum and worsening of joint symptoms, an atypical evolution. There was also a concern for possible immunosuppression due to the chronic use of prednisone. All those factors led to the diagnostic hypothesis of septic arthritis, which was less likely after the negative results. Exams for possible rheumatoid arthritis and acute gout were also ordered and came back negative. The diagnosis of arthritis related to a type 2 reaction was confirmed by studying the synovial fluid and histopathology of the synovial membrane. As the destruction of the synovia was intense, there was only clinical improvement after an invasive local approach with continuous irrigation and maintenance of the instituted systemic therapy.

The occurrence of monoarthritis in patients with type 2 leprosy reaction after the end of MDT is not well documented in the literature. Studies on leprosy reactional arthritis are related to the presentation of cases during an ENL outbreak in patients during leprosy treatment [14–16].

Some papers have reported the study of the synovial membrane in arthritis secondary to leprosy reaction [17,18] and have verified that the synovial fluid of arthritis can be from group I (inflammatory – < 2000 cells), group II (inflammatory – 2000–20,000 cells) or group III (very inflammatory – > 20,000 cells). *Mycobacterium leprae* may be present in approximately 1/3 of the analyzed fluids. It has been shown that patients present group I fluids in the first episode and group II or III fluids in later episodes, or vice versa [17,18]. In the reported case, there was a predominance of group III synovial fluid and specific Virchowian infiltrates with granular bacilli in its interior, probably because it was a case of recurrent ENL in a patient discharged from polychemotherapy more than 4 months ago when the episode of arthritis occurred. These findings corroborate with previous studies regarding the synovial membrane, which show more than half of the cases were mild reactional synovitis. The most constant acute change was intracavitary exudation with a strong neutrophilic component, often with vacuoles and positive bacilloscopy in its interior [18,19].

These studies have allowed us to explain the pathophysiology of arthritis in the type 2 reaction as a process identical to that of ENL of the skin. The synovial membrane of these patients is invaded by foci of Virchowian cells, and in these places there would be an antigen-antibody-complement reaction with the formation of insoluble complexes, triggering the inflammation in the synovia [18,19]. The intensity of arthritis would depend on the quantity and quality of specific infiltrate foci in the synovial membrane and would explain the different types of synovial fluid and histological aspects of the synovia [4,19].

Reactional arthritis in leprosy patients can simulate osteoarthritis, rheumatoid and rheumatic arthritis, acute gout, septic arthritis, and other rheumatic diseases [9]. Therefore, a careful differential diagnosis should be investigated to rule out the possibility of association with other rheumatic and infectious diseases. The presence of inflammation during an episode of ENL can affect the synovium of a large joint leading to severe reactional arthritis, even after drug discharge from MDT. It is important to have high diagnostic suspicion and prompt investigation to start drug treatment or invasive approach to avoid greater morbidity from this disease, which is already related to a high prevalence of disabling sequelae and great stigma.

CRediT authorship contribution statement

Isabela Maria Bernardes Goulart: Data collection, Writing – original draft, Writing – review & editing. **Marcela Araujo de Oliveira Santana:** Data collection, Writing – original draft, Writing – review & editing. **Willian Vargas Tenório da Costa:** Data collection, Writing – original draft, Writing – review & editing. **Matthew Martin Pavelka:** Writing – original draft, Writing – review & editing.

Bruno de Carvalho Dornelas: Data collection, Writing – original draft, Writing – review & editing.

Data Availability

The data used in this study can be accessed upon contact with the corresponding author.

Ethical approval

None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Funding Statement

This work was supported by: Projeto fortalecimento da rede de atenção integral e integrada aos pacientes com hanseníase da região do Triângulo Mineiro e Alto Paranaíba, TED: 157/2019 – FN.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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