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Necrotizing Fasciitis As the First Manifestation of Tuberculosis in an Immunocompromised Patient

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Disseminated tuberculosis is a process that mainly affects immunocompromised hosts. Its initial appearance as necrotising fasciitis is exceptional especially if it is not associated to a bone disorder. The diagnosis of this rare complication requires a high degree of suspicion and the evidence of *Mycobacterium tuberculosis* in the muscular tissue, since the symptoms may mimic the underlying illness itself, for this reason the most sensitive method for demonstrating tuberculous infection is a muscular biopsy. Here we present the case of a patient who was receiving immunosuppressant therapy for nephrotic syndrome by minimal lesion glomerulonephritis and who developed this rare complication, where diagnosis was made by muscular biopsy. So we do a review of similar case reports in the literature.

Key words: Necrotizing fasciitis. Tuberculosis. Immunosuppressive Agents. Minimal lesion glomerulonephritis.

Fascitis necrosante como primera manifestación de tuberculosis en un paciente inmunodeprimido

La tuberculosis diseminada es un proceso que suele afectar a pacientes inmunodeprimidos. Su manifestación inicial como fascitis necrosante es excepcional, sobre todo si no se asocia a tuberculosis ósea. El diagnóstico de esta rara complicación requiere un alto índice de sospecha por parte del clínico y el aislamiento del *Mycobacterium tuberculosis* en el tejido muscular, ya que los síntomas pueden remedar a la enfermedad de base, por lo que la biopsia muscular se presenta como la principal herramienta diagnóstica. Presentamos el caso de un paciente que recibía terapia inmunodepresora por síndrome nefrótico asociado a nefropatía por cambios mínimos y que desarrolló esta rara complicación, donde el diagnóstico se hizo basándose en los hallazgos de la biopsia muscular. También se realiza una revisión de los casos similares encontrados en la literatura médica.

Palabras clave: Fascitis necrosante. Tuberculosis. Agentes inmunodepresores. Nefropatía por cambios mínimos.

Introduction

Necrotizing infections of the skin and soft tissue have been known by the medical community since centuries ago and have received different denominations: progressive bacterial synergistic gangrene, Meleneys' Gangrene, Fourniers', etc. It was Wilson[1] in 1952 who coined the term necrotizing fasciitis to define a group of these processes that were characterized by inflammation and necrosis of the reticular dermis and the superficial aponeurotic fascia, with a relative preservation of subjacent musculature; so, diagnosis is established when these findings are demonstrated in the biopsy or under surgical exploration.[2] It is an uncommon nosologic entity, but extremely serious and if not treated precociously an an adequate manner, it has a mortality rate that can reach 74%.[3] It is usually caused by virulent microorganisms of the *Streptococcus* genus, anaerobic bacteria or enterobacteria and can affect both previously healthy patients as well as patients with chronic disease of immunocompromised. In this last group there are few cases described of this complication in the literature, in patients with connective tissue diseases,[4-6] even though the great majority of them receive immune suppressant drugs. Though the incidence of tuberculosis infection in patients with systemic illness is approximately 3%,[7] presentation as necrotizing fasciitis is exceptional, especially if there is no bone affectation.[8]

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We describe the case of a patient that, after starting treatment with prednisone and cyclophosphamide for a minimal change nephropathy, developed necrotizing fasciitis that was unresponsive to conventional antibiotic treatment, and that improved after initiating anti-tuberculosis drug therapy, when tuberculosis infection was demonstrated both in muscle and bronquial tissue. The diagnosis of this rare complication requires a high suspicion index and the demonstration of *Mycobacterium tuberculosis* in the muscle tissue, due to the fact that the symptoms can imitate even the underlying pathology.

Figure 1. *Images obtained during the first hospitalization were heliotrope erythema is visible on the eyelids (left) and Gottrons' papules are found on the hands (right).*

Case Presentation

We present the case of a 50 year old male patient with nephrotic syndrome due to glomerulonephritis secondary to minimal change nephropathy and bilateral interstitial pneumonia diagnosed 18 months before. Because of this, treatment with prednisone at 1 mg/kg/day was started 12 months before and 2 months before, in another hospital, cyclophosphamide (2 mg/kg/day) was initiated due to the presence of cryoglobulinemia, skin vasculitis and a descent in the creatinine clearance under 24 mL/min. When the patient was visited the first time in our hospital he showed skin lesions that suggested dermatomyositis: heliotrope erythema and Gottrons' papules (Figure 1). Nonetheless, the muscle studies (enzymes, EMG, biopsy, and autoantibodies) were negative.

There was no evidence of occult neoplasia or amiloidosis in the complementary studies. After the initiation of treatment with cyclophosphamide, 2 months before, the patient presents intense fatigue, as well as pain of moderate intensity and hardening of the posterior thigh region muscles that did not improve upon rest and that had increased in intensity during the last week, impeding gait.

Upon physical exploration he was found to be normotensive, with a body temperature of 38.5°C and eupneic. Of interest the patient presented malaise, the neurologic exam did not show any focal signs, muscle strength was diminished globally 4/5 in the extremities. Deep tendon reflexes were discreetly diminished in a symmetric manner. There was no evidence of a sensory level deficit or alterations in sensibility. Peripheral arterial pulse was present and symmetric. There was atrophy and skin ulcers on the hands. The extension and external rotation, both active and passive, of the left hip were painful, and there was sensitive induration with a discreet increase in temperature of the underlying soft tissue but with no skin lesions, nor fluctuation in the posterior region of the left thigh. The complete blood count showed leucopenia (3.4 10^9/L), linphopenia (0.04 10^9/L), and hemoglobin of 101 g/L. The blood chemistry showed: creatinine, 141.4 µmol/L (040); Na, 127 mmol/L (135-145); albumin, 32 g/L (4060); erythrocyte sedimentation rate (ESR), 101 mm (<20); ferritin, 4.470 µg/L (80-300); polymerase Cain reaction (PCR), 35 U/I (<5); glutamicoxalacetic transaminase (GOT), 67 U/I (30-50); gammaglutamiltranspeptidase (GGT), 122 U/I (3060). The rest of the parameters (creatinkinase [CK], aldolase, glutámic piruvic transaminase [GPT], alkaline phosphatase, lactatodeshidrogenase [LDH], inmunoglobulins, complement) were within normal limits. Human immunodeficiency virus (HIV) serology, hepatitis C virus (HCV), hepatitis B virus (HBV), luetics, and the antinuclear antibodies were negative. The chest x-ray showed a alight bibasilar interstitial pattern. Left thigh ecography showed soft tissue edema that affected both muscle groups and intermuscular space as well as subcutaneous soft tissue. Magnetic resonance imaging (MRI) results were similar (Figure 2). Upon the diagnostic suspicion of pyogenous myositis of the internal muscle compartment of the left thigh in an immunocompromised patient, needle aspiration biopsy was performed on the indurated zone, with a sterile culture, and treatment was initiated with imipenem/cilastatine 1 g every 6 h; in spite of this, the patient persisted with fever 7 days after the start of antibiotics and the blood culture done at admission was negative. A closed muscle biopsy with no tissue debridement was undertaken, observing the presence of a chronic inflammatory infiltrate without clear granulomas, fascia necrosis (Figure 3) and abundant acid-fast bacilli in the Ziehl-Neelsen stain (Figure 4). A bronchoscopy was performed, and the culture of the bronchial aspirate showed *M tuberculosis*. Imipenem was suspended and treatment with pyrazinamide (1750 mg/day), ethambutol (1200 mg/day), riphampin (600 mg/day), and isoniazide (300 mg/day) was initiated, with improvement both of the local inflammatory signs as of the general symptoms. This treatment was completed after 2 months with 4 drugs and after a total of 1 year for isoniazide and riphampin. Presently the patient is asymptomatic.

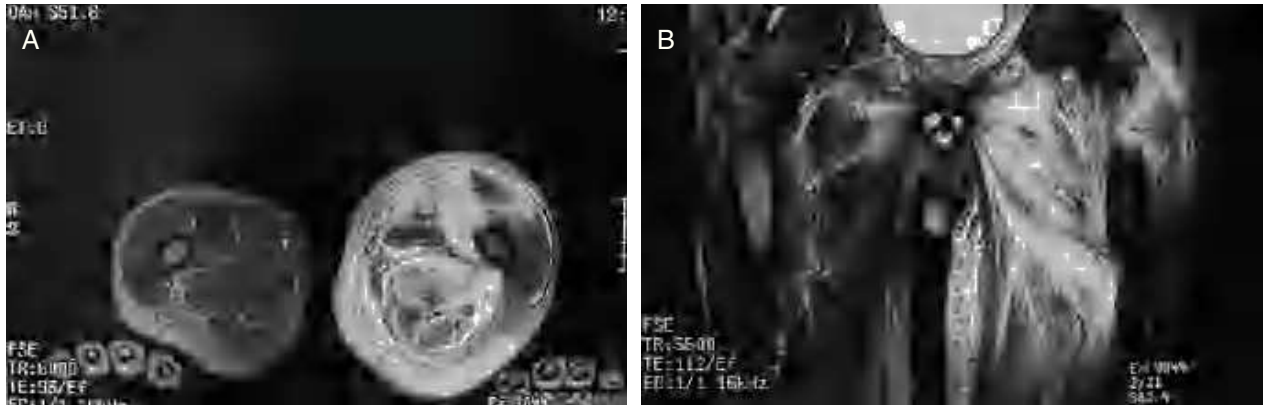

Figure 2. *Magnetic resonance images in the axial (A) and coronal (B) projections in the medial thigh zone on T2 phase, where hyperintense signal changes are appreciated, affecting both the subcutaneous fat as well as the interna muscle compartment of the left thigh, with edema that affects muscle groups, intermuscular spaces and subcutaneous soft tissue.*

Discussion

Our case illustrates a rare presentation of disseminated tuberculosis in an immunocompromised patient. This diagnosis is established when confronted with the presence of a polymorphonuclear infiltrate with muscle fascia necrosis and the isolation of *M tuberculosis*, both in muscle biopsy (Figure 4) and afterwards in the Löwestein bronchial aspirate culture. After the initiation of tuberculostatic treatment, the clinical evolution of the patient was excellent, with a significant improvement, both of the local symptoms and the general ones, excluding the necessity of surgical debridement or complications such as fistulas or osteomyelitis.

Approximately 3% of patients with tuberculosis present osteomuscular complications,[9,10] so these extrapulmonary manifestations can be considered exceptional when excluding bone infection. In our literature review, it is evident that the characteristics of the referenced patients (Table) are similar to the ones described in our case. The affected patients come from areas with a high prevalence of tuberculosis[10-13] or are immunocompromised due to chronic illness or the use of immunesupressant drugs,[9,12-14] conditions that our patient presented taking into account that the prevalence of tuberculosis in our county is 14 per 100 000 inhabitants. The chest x-ray is normal in half the patients. We must remember that immunosupression attenuates the inflammatory response and, secondary to this, diminishes the presence of infiltrates, adenopathy, cavitation, etc, that tends to be less in these cases. The start of tuberculostatic treatment can be delayed for months because it is necessary a high degree of suspicion by the physicians part and conventional cultures are usually negative. Besides this, the patients with connective tissue disease can have alterations in their muscle tissue because of the underlying illness[15] and hide an additional process, as we thought was happening in our case, when treatment with imipenem failed, until we got the biopsy result.

For this motive, the most practical method to demonstrate tuberculosis infection is the muscle biopsy, with a sensibility of 80%.[9] Nonetheless, as indicated previously, granulomas may be absent from the infected tissues of immunocompromised patients, and for that reason it is necessary to include stains that demonstrate the presence of Koch's bacillus.[15] The need for surgical treatment is high in the reviewed series,[9,10] but in the present as well as in other sporadic published cases,[12,14,16] it was not necessary. In the same manner, the mortality observed in these patients is low, which contrasts to the elevated rate that is evidenced in the fascitis caused by other, more virulent types of agents.[2,3] Patients that die due to tuberculous fasciitis tend to be immunocompromised, have a greater delay in the start of specific treatment and have multiple muscle groups affected.[10]

Treatment with immunosuppressive drugs and steroids is every day more common in the clinical setting. Their use makes the patients receiving them more susceptible to infections that are regulated by the cellular immune response. This way, Hernández Cruz et al[7] have estimated that the prevalence of tuberculosis infection in patients with systemic illness in México is of 2.5%, being the extrapulmonary complications the most frequent ones. Notwithstanding this, not all drugs carry the same risk, so in a recent review done in patients with rheumatoid arthritis, drugs associated to a higher risk of tuberculosis infection were, in this order, cyclophosphamide, infliximab and azathyoprine.[17] This leads to reflect upon the assumption of the risk of tuberculosis infection in patients that receive anti-tumor necrosis factor therapy, bot not so much in patients on other kinas of immunosupressants.

Figure 3. *Muscle biopsy that shows intense inflammatory infiltrate of polymorphonuclear cellls around muscle fibers and their preservation.*

Figure 4. *Zhiel Neelsen stained muscle that shows acid-fast bacilliform formations.*

The low incidence of tuberculosis infection in striated muscle is due to physiologic conditions (high concentrations of lactic acid, rich vascularization, low quantities of the mononuclear-phagocytic system cells), that are less than favorable for the growth of *M tuberculosis.*[8] The mechanisms of striated muscle invasion are, in order of frequency, by contiguous transfer, by hematogenous dissemination or direct inoculation.[10] In our case there was no antecedent of trauma or adjacent bone affectation and mycobacteria were found in the bronchial aspirate, leading to think in the hematogenous spread as the most plausible mechanism of dissemination. Muscle affectation of the thigh, as the one in our patient, is the most frequent localization in cases of hematogenous spread, though the reasons for this are unknown.[10] As was indicated in the introduction, the diagnosis of necrotizing fascitis is based on the surgical exploration or the anatomopathologic study o the subcutaneous soft tissue. The role of imaging techniques is centered on the evaluation of extensión and local complications, such as the formation of absesess or bone affectation.
MRI seems the technique with the best diagnostic definition in this kind of processes. Nonetheless, its validity for topographic or ethiologic diagnosis is a matter of controversy. To some, this technique permits the delimitation of blood vascularity, the lack of celullitis cells in a fascitis or to distinguish polymyositis

TABLE 1. Characteristics of Cases Described in the Referentes of Muscle Infections Due to Mycobacterium Tuberculosis

Author (Reference)	Number of Cases	Chronic Underlying Illness	Use of Immunosupressive Drugs	X-Ray Findings	Symptom Duration	Diagnostic Method	Surgical Treatment	Mortality
Puttick et al[9]	11	7 (63.6%)	6 (54.5%)	4 (36.3%)	4 months	Biopsy (72.7%)	9 (81.8%)	0
Wang et al[10]	35	10 (28.5%)	3 (8.5%)	18 (51.4%)	2 months	14* (40%)	29 (82.9%)	5 (14.3%)
Kabani et al[11]	1	No	No	Yes	2 months	Yes	Yes	0
Trikha end Guptah[12]	1	No	No	No	2 months	Biopsy	No	0
Stebbings et al[13]	1	Yes	Yes	Yes	2 weeks	Culture	Yes	0
Indudhara et al[14]	1	Yes	Yes	No	3 months	Culture	No	0
Jonson y Herzig[16]	1	Yes	Yes	No	1 week	Biopsy	No	0

*The other 21 were by culture, but it is not specified if it was by leedle aspiration or biopsy.

from a septic pyomyositis, because the latter one shows a brilliant muscle border.

To others, the absence of gadolinium uptake alter injection is characteristic of necrotizing fascitis.[18] Lastly, some authors suggest that the presence of venous throbosis or cellulitis distinguishes pyogenous pyomyositis from tuberculosis.[19] We didn't use paramagnetic contrast in the MRI, and although there were no signs of trombosis Esther in echo-Doppler or in the MRI, there appeared to be cellulitis (Figure 2), though this was not confirmed in the biopsy. To conclude, and as a contribution of interest to the presented case, we relieve that immunocompromised patients with fascitis or pyomyositisw that do not respond to convencional treatment must undergo a muscle biopsy, processing it with oportunistic germ cultures such as mycobacteria and fungi.[13]

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