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A man from Morocco and chronic hip pain

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PRESENTATION OF CASE (DR. JOSÉ RAMÓN PAÑO)

The patient was a 52-year-old male, born in Morocco, and living in Spain for the last 25 years. He was diagnosed with Diabetes Mellitus more than 25 years before and was a heavy smoker until he quit 6 years ago.

At the age of 25, he suffered a closed hip fracture after am uncertain intensity occupational accident while working as a farmer and required surgery with placement of osteosynthesis material that apparently consisted in an intramedullary nail. Hardware had to be removed after a short time (2-3 months) due to infection, as endorsed by the patient, although he did not provide any information on the nature of the infection or the antimicrobial treatment received.

The patient was a native of northern Morocco, a shoemaker by profession, in an inactive situation at the present time and awaiting a disability concession. He lived with a friend and receives habitual treatment with long-acting insulin glargine and acetaminophen.

Chief complaint. He was admitted from the outpatient Orthopedic Clinic due to pain in the right hip that was pointed at fingertips. The pain had intensified in recent years and the patient had progressive gait limitation that prevented him from walking without the help of a cane. Over the past 12-15 years, he had occasionally experienced "holes" that opened and closed repeatedly and ooze. The appearance of those sinus tracts did not relieve symptoms.

He did not refer associated sensitivity disturbances. He did not complain of shortness of breath, chest pain, palpitations, leg edema, abdominal pain, bowel rhythm disturbances or urinary symptoms. Upon request, fever, asthenia, anorexia or weight loss were denied.

Physical examination. Temperature was 36.6º C; Blood pressure 125/90 mmHg; Heart rate 88 bpm; Respiratory rate 16 rpm. The patient was conscious, oriented, eupneic at rest and not sweaty. Skin and mucous membranes were well colored and the patient was well hydrated. Yugular pulse was normal. There were no heart murmurs or extra tones. Lung examination was normal. The abdomen was soft, with no masses or organ enlargement and normal bowels sounds. On the external side of the right proximal femoral region, there was an old scar of approximately 25 cm, with no signs of erythema or active exudate.

Initial laboratory data. Haemoglobin 9.6 g/dL, Mean Corpuscular Volume 87.6. Platelet count 173,000 uL, White Blood Count 14,800/uL (Neutrophiles 92%). Coagulation tests without abnormalities. ESR 15, first hour. CRP 0.2 mg/dL. Glucose 319 mg/dL, ALT 20 U/L, AST 12 U/L, total billirubin 1 mg/dL, GGT 19 U/L, CPK 105 IU/L. HbA1c 7.2. Ferritin 271 IU/L (30-400), Na 139 mmol/L, K 4.07 mmol/L.

Images. Posteroanterior and lateral chest X-ray (Day 0) are shown in figures 1 and 2. Simple hip X rays are displayed in figure 3. A CT scan of both hips was reported as follows:

"Very important morphological alteration of the right hip with almost complete bone destruction of the femoral head and neck and marked erosion of the acetabulum with cortical disruption in its anteromedial portion. The lesion extends to the proximal femoral diaphysis with bone fragmentation of the major trochanter, forming a bony protrusion. The femoral diaphysis shows sclerosis and cortical insufflation on the lateral side. All the described findings suggest chronic evolution in relation to a previous process (traumatic, necrotic...).

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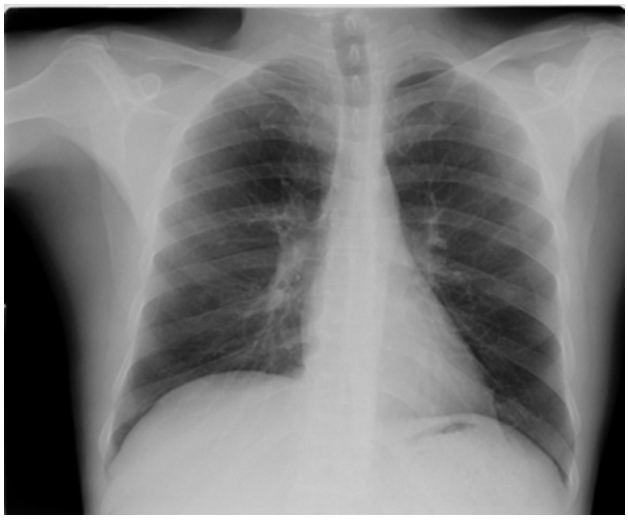

Figure 1 | **Posteroanterior chest X ray on admission**

Due to extensive bone destruction it is not possible to rule out the presence of active osteomyelitis, however secondary signs such as soft tissue edema or collections are not seen."

Orthopedic surgery. The orthopedic surgeons decided to perform a scheduled intervention to carry out an extensive debridement with necrotic bone resection (not curettage) and active cleaning, with the intention of future prosthesis in this region with technical difficulties given the patient's anatomy. At this point a consultation to Infectious Diseases, asking the proper perioperative antibiotic prophylaxis was placed.

DIFFERENTIAL DIAGNOSIS OF THE PATIENT (DR. CARLOS PIGRAU)

I am totally unaware of the diagnosis of this patient. In my opinion, this patient who refers an spontaneous hip fracture, with postoperative infection and multiple episodes of fistulization and with the images provided, has, without a doubt, an osteomyelitis and chronic arthritis with an important extension and with very serious consequences. My main question, therefore, is to speculate on the causal microorganism. I was not told if the patient had been subjected to infiltrations in the hip or if he had ingested non-pasteurized dairy products that could suggest brucellosis.

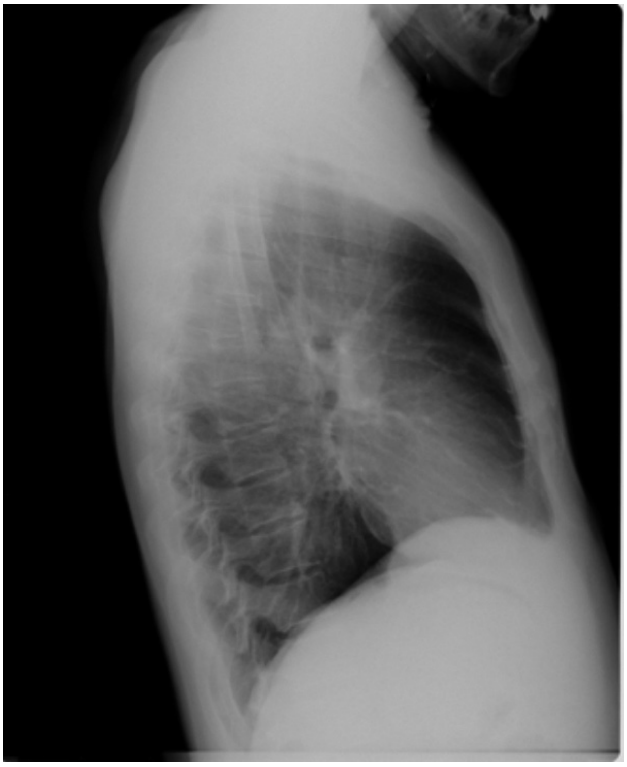

Figure 2 | **Lateral Chest X ray on admission**

I will first discuss the hypothesis that the patient's condition is the result of intramedullary nail infection, trying to

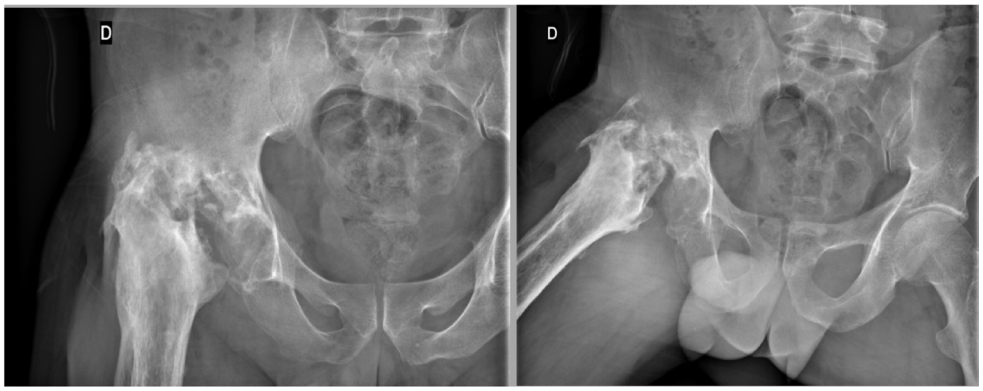

Figure 3 | **Right Hip X rays**

clarify the risk of infection from this procedure, the microorganisms that cause it and also the possibility of a mycetoma. I will refer later to an approach based on the fact that this patient has had a pathological fracture at a very early age and I will discuss infections such as brucellosis, or infections from other bacteria such as actinomycosis and tuberculosis. Finally, and in case this patient has suffered repeated infiltrations, I will discuss chronic *Candida* spp. infection.

Trampuz and Zimmerly [1] reported that 5% of the devices used as fixators in fractures get infected, the proportion is lower if they have been used to fix closed fractures (1-2%) than if they are used to reduce open fractures (30%). Infections can occur early (within the first two weeks after implantation), delayed (2-10 weeks) or late (more than 10 weeks after fixation). The infection can be acquired during the operation, contiguously or by the hematogenous route. In a very recent meta-analysis, the risk of infection following a closed fracture reduced by an intramedullary nail was 5.9% [2]. The most frequent microorganisms are *S. aureus* and coagulase negative *Staphylococcus* (CNS), followed by Gram-negative bacilli. Although chronic *S. aureus* osteomyelitis (OM) can relapse 40 to 50 years after the initial infection, as we have observed in some adult patients who suffered an hematogenous *S. aureus* in its youth this condition is infrequent. Although I cannot exclude absolutely this possibility, or due to other non aggressive microorganism such as CNS or *P. acnes*, in this patient it seems unlikely that it is an intramedullary nail infection, because I expected that with 15 year chronic fistulization the diseases probably would have had an acute relapse earlier.

Micetomas are skin and soft tissue infections with the ability to penetrate deep into tissues, including bone. They produce local invasion that does not respect anatomical structures and invade deep tissues, producing multiple sinus tracts. They are divided into eumycotic mycetomas (caused by fungi) that may be dark (e.g. *Curvularia* spp.) or caused by clear fungus (hyalohiphomycetes). Alternatively, "Mycetomas" may be caused by bacteria particularly of the genus *Actinomyces*, *Nocardia* and *Streptomyces spp.* Mycetomas are much more common in pressure-stressed areas such as the feet and in tropical and humid countries, where people often walk barefoot [3-5]. In this patient, the invasion of superficial soft tissue does not seem to be noticeable at the time of admission and this, together with the epidemiological reasons mentioned above, makes me reject, in principle, this aetiology.

With regard to the possibility of this patient having tuberculosis, we reviewed our experience with osteo-articular tuberculosis a few years ago [6]. In Spain, 5.8% of all tuberculosis cases have an osteo-articular focus. Pre-existence of concomitant pulmonary tuberculosis occurs in only 23-30% of cases and should not be used to rule out this possibility. Fever is also rare and the etiological diagnosis is sometimes confirmed years after the onset of clinical manifestations of the process [7]. The hip occupies a relatively intermediate position among the most frequent locations of bone and joint tuberculosis. Our group reported as early as 2004 that hip tuberculosis often begins as a pertrochanteric bursitis and then spreads in depth [8]. Occasionally, osteo-articular tuberculosis is multifocal and this is particularly common in patients from Asia and Africa [9, 10]. I suppose that during surgery samples were sent for traditional mycobacterial cultures in this patient, including samples for histology assessment and request of a PCR for *Mycobacterium tuberculosis*. In our experience bone PCR for *M. tuberculosis* has a high diagnostic yield (unpublished data) and shortens the time to administer an adequate antituberculous therapy. Treatment, if the disease is confirmed, should, in my opinion, be carried out for 9-12 months, although the Clinical Practice Guidelines recommend only six months. In this patient, with his background and clinical presentation, tuberculosis will be at the forefront of my preferred diagnoses.

Actinomycosis is another possibility in this patient, given the chronic nature of the disease and the frequency of sinus tracts, but its most frequent locations are the jaw, lung and abdomen and hip involvement is extraordinarily rare [11-13,14]. Undoubtedly, histology would be a key element for this diagnosis and I also believe that a long incubation in anaerobic atmosphere should be requested for samples sent to the microbiology laboratory. In any case, it seems to me a remote possibility and I place this diagnosis at the bottom of my list.

Finally, I would like to discuss the possibility that we are dealing with a fungal infection and particularly with an osteomyelitis or arthritis caused by *Candida* spp. [15,16]. In a review of Gamaletsou et al., which covers their experience between 1964 and 2014, patients with *Candida* arthritis are on average 40 years old, mostly male (62%) and usually not immunosuppressed. The vast majority are acquired by hematogenous spread although only 29% had concomitantly demonstrated candidemia. Pre-injection of corticosteroids may be an important predisposing factor and hence my initial question as to whether this patient had received repeated infiltrations due to hip pain at any time. In the Spanish series of patients with candidemia (CANDIPOP), in 752 episodes of Candidemia there was no late arthritis episodes comparable to the one we are discussing today [17,18]. Fever is rare in these cases, and systemic leukocytosis is frequently lacking, but there is usually leukocytosis in the synovial fluid. The treatment has traditionally been done with amphotericin B and for a very long time with a median of 64 days. One of the doubts, in this patient is the necessary therapeutic advice, not being septic, not having prosthetic material and not being an immunosuppressed patient, I believe that he does not need a wide spectrum empirical treatment before having the results of the samples taken during the surgery. However, it seems advisable to always cover methicillin-susceptible *S. aureus* and SCN with amoxicillin/clavulanic acid (2g IV every 8 hours).

DR. CARLOS PIGRAU'S DIAGNOSIS

In my opinion, the first diagnostic possibility for this patient is that of a hip tuberculosis and in this sense I expect stains, cultures or PCR tests for *M. tuberculosis* to be positive in the surgical samples.

I find less attractive the possibility of other bacterial infections such as those caused by *S. aureus* or CNS.

Finally, I can dismiss the possibility of an invasive fungal infection, particularly caused by *Candida* spp.

EVOLUTION OF THE PATIENT (DR. JOSÉ RAMÓN PAÑO)

The patient was operated on without peroperative antimicrobial prophylaxis and underwent extensive surgical debridement. Seven intra-operative tissue samples were sent to Microbiology and Pathology Departments. After the samples were taken, a treatment with vancomycin and cefepime IV was started in the operating theatre and continued in the immediate postoperative period.

The postoperative period was without significant incidents and at 72 hours the intra-operative cultures showed no growth in culture, with the exception of a CNS isolation in one of the 7 culture samples. Serology for Brucella, including Rose Bengal and Brucella Capt. were also negative. The sample tested positive for *M. tuberculosis* by PCR but cultures never turned positive in any of the samples. Samples were not sent to Pathology.

Antibiotic treatment was discontinued and anti-tuberculous (INH/RIF/PZD/ETB) treatment was initiated and continues today, with good clinical and analytical tolerance.

DISCUSSION

Tuberculosis of the hip accounts for 15% of all osteo-articular tuberculosis, and is the second leading cause of bone involvement, after vertebral tuberculosis. It is more frequent in the second or third decade of life and requires a differential diagnosis with transitory tenosynovitis, rheumatoid arthritis or osteonecrosis processes [19]. It causes pain and functional impotence and often leads to cold abscesses and sinus tracts. There are 4 evolutionary stages that begin with synovitis, early arthritis, established arthritis, and advanced arthritis. The latter, in our opinion, is the situation of our patient.

The clinical suspicion of tuberculosis must be established first and foremost in the context of hip destruction and in the appropriate epidemiological context. Histology usually shows the presence of granulomas and finally the diagnosis should ideally be confirmed by culture but both the presence of a stain with resistant acid-alcohol bacteria and a positive PCR in this context would be sufficient confirmatory tests [20]. In a recent review of the value of PCR for tuberculosis in different forms of extrapulmonary disease, an enormous variability of targets and test results is demonstrated but the authors conclude that the results of a PCR, with clinically compatible and histologically compatible results are more than sufficient to initiate etiologic treatment [21].

Conventional treatment includes the use of anti-tuberculous agents, combined with rehabilitative treatment and stages III and IV debridement and synovectomy, with proximal femoral osteotomy, arthrodesis or Girdlestone procedure [19].

In recent years, however, a systematic review of published studies on Total Hip Replacement (THR) in patients with tuberculosis of the hip [22], collected thirteen articles, comprising 226 patients, showing that THR in tuberculosis of hip is a safe and efficient way to save the joint function. Antituberculous treatment was given for at least 2 weeks pre-operatively and continued post-operatively for between six and 18 months after total hip replacement. Only 3 patients had reactivation of infection after more tan 5 years mean follow up. A two-stage THA is an alternative treatment option for patients with advanced active tuberculosis of the hip particularly when sinus tracts or extensively destroyed tissue is present [23-25].

FINAL DIAGNOSIS

Chronic hip osteomyelitis due to osteo-articular tuberculosis.

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