CASE REPORT

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Acute cellulitis as local reaction to orthopedic implant – case presentation

OLIVERA LUPESCU[1,2)], MIHAIL NAGEA[2)], RĂZVAN SCURTU[3)], NICOLAE MARIAN CIUREA[2)], ALEXANDRU LISIAS DIMITRIU[1,2)], NARCIS MARCOV[4)], GHEORGHE ION POPESCU[1,2)], SIMONA BONDARI[5)]

[1)]*Department of Orthopedics, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[2)]*Clinic of Orthopedics and Traumatology, Clinical Emergency Hospital, Bucharest, Romania*

[3)]*Department of Pathology, Clinical Emergency Hospital, Bucharest, Romania*

[4)]*Department of Restorative Odontotherapy, Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[5)]*Department of Radiology and Medical Imaging, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

Due to increasing number of arthroplasties and osteosynthesis, foreign body reaction to implants is a major problem for orthopedic surgeons, since it is considered to be responsible for severe complications impairing the outcome of the treatment and requiring multiple surgery. Different mechanisms have been described as being involved, and research is focused on finding biomaterials with increased biocompatibility in order to minimize these complications. The clinical aspect of this reaction is usually dominated by chronic pain, with mild functional deficits, and the diagnosis results from excluding other causes of chronic pain, such as infection, osteoarthritis, peripheral neuropathies or angiopaties. The authors present a case with unusual clinical aspect, that of acute cellulitis, when early proper treatment, represented by implant removal, allowed healing without the onset of infection or other complications; histological evaluation confirmed the reaction to implant, thus concluding that surgical treatment when intolerance to implant is suspected is the only method to prevent future negative events.

Keywords: foreign body reaction, chronic inflammation, orthopedic implants, prosthesis.

Introduction

Two major types of implants are currently in use in orthopedics: prosthesis, for joint replacements, and osteosynthesis devices, for fracture fixation. Regardless the type of implant, studies have demonstrated that it interacts with the host and that, in different amounts, implant degradation can influence not only the surrounding tissues, but can also have a systemic effect. By different mechanisms, components of the implant induce local or general reactions, which can influence the stability of the implant, as well as the quality of bone healing [1, 2].

Even if systemic impact of the implants is rarely significant, excepting in patients with known hypersensitivity to metals, local interactions between the hosts and the implant are increasingly frequent described not only when implant removal is performed, but also when they become clinically obvious [3].

In some cases, this local reaction is aggressive, with severe pain, increased functional deficit, and the microscopic evaluation shows metallic impregnation of the surrounding tissues; in the most severe cases, inflammatory signs appear, requiring differential diagnosis with sepsis, but also immediate treatment so as to prevent its onset [4].

This article presents a case with an atypical cellulitis reaction to the implant, after osteosynthesis for a tibia fracture with plate and screws. The particularity of the case is the aspect of a cellulitis, with marked local signs of inflammation and general inflammatory syndrome, as well as local osteopenic aspects; the severe local inflammatory reaction could create confusions with acute infections, but due to the proper treatment, complete recovery was possible, thus proving the etiology.

Case presentation

The study was performed according to the European Communities Council Directive of 24 November 1986 (86/609/EEC) and the treatment of the patient followed the local Ethical Regulations, approved by the Ethical Committee. The patient has acknowledged and signed the Informed Consent for the treatment and for using this case for educational and scientific research purposes. The patient, female, 45 years old, employed, was operated in April 2013, in the Clinic of Orthopedics and Traumatology, Unit II, Clinical Emergency Hospital, Bucharest, Romania, after acute tibia pain onset; clinical and radiological exam showed a fracture of the distal tibia that occurred due to a progressive curving of the bone secondary to a bone cyst, revealed both by X-ray (Figure 1a) and magnetic resonance imaging (MRI) (Figure 1b). Surgery consisted in osteotomy of the peroneum, resection of the cystic area, reduction and bone restoration with a corticospongious graft; stabilization was performed as shown in Figure 2 using a paracortical implant (plate and screws).

The clinical outcome was favorable, with complete rehabilitation, full weight bearing, and no sequelae. Three years after initial surgery, without any traumatic event, the patient described progressive increasing pain, at the surgical site, followed by a cutaneous eruption, with no

systemic signs of infection. Dermatological examination was performed and the patient was advised to address to the hospital where she had been operated; when she was admitted in the same department (Clinic of Orthopedics and Traumatology, Unit II, Clinical Emergency Hospital, Bucharest), the foot, ankle and distal third of the shank were swollen, with shiny skin, hematic blisters and petechial eruptions localized on and between the fingers (Figure 2a), on the ankle – external aspect (Figure 2b) and internal (Figure 2c), as well as adjacent to the surgical incision, in the distal third of the shank (Figure 2c).

Radiological examination (Figure 4a) did not show any sign of implant failure or osteitis; compared to a previous examination, performed one year after surgery (when the clinical recovery was complete, the patient being asymptomatic), it revealed minimal changes within the fracture site, with discrete irregularities of the osseous structures due to two zones with diminished density. Inflammatory tests showed increased erythrocyte sedimentation rate (ESR) 30 mm/h (max. normal value 2 mm/h) and fibrinogen 560 mg% (max. normal value 400 mg%).

A dermatological evaluation was also performed, revealing infected *Tinea pedis* and cellulitis of the shank; the clinical and radiological aspect generated the diagnosis of acute dermatitis with cellulitis of the foot, ankle and shank; status post-distal tibia fracture on bone cyst – operated, healed, implant *in situ*; infected *Tinea pedis*.

Although the etiology of the acute inflammation had to be established, so to perform a complete treatment, the priority was to limit the risk of deep sepsis; as implants are highly attractive for bacteria (which rapidly develop biofilms on their surfaces), implant removal is recommended, but after acute phenomenon is suppressed.

Regarding the etiology, since no relevant traumatic or septic episode preceded the acute symptoms, a common fungal infection at the level of the fingers could be responsible for the aspect of the forefoot, but it could barely produce the dramatically aspect extended at the level of the ankle and distal shank; the absence of any infectious syndrome diminished the probability of a primary septic origin, but could not exclude it totally, because chronic osteitis can have an insidious aspect, with or without acute intercurrences.

After an interdisciplinary evaluation, orthopedics–dermatology, local (anti-inflammatory and anti-fungal) and general (anti-inflammatories and antibiotics) treatment was started, The outcome was favorable but no complete remission occurred not even after a month; minor cutaneous eruption persisted, as shown in Figure 3, adjacent to the incisions, on the internal (Figure 3a) and external (Figure 3b) aspect of the ankle, extending cranially (Figure 3c), demonstrating that, despite the anti-fungal and dermatological treatment, the triggering factor was persistent.

More than that, radiological evaluation performed one month after the initial episode (Figure 4b) showed that, at the level of the fracture, the two zones with diminished bone density not only persisted, but their density decreased furthermore, thus enhancing the irregularities of bone density.

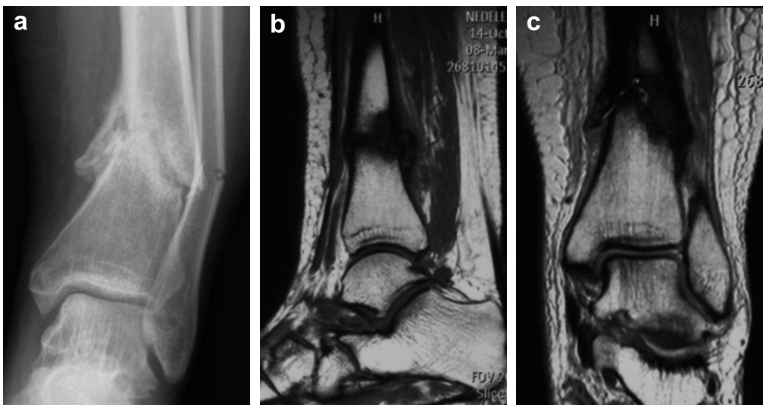

Figure 1 – ***(a) Preoperative X-ray showing fracture of the distal tibia and peroneum with angulation of the fragments, occurred on a bone cyst, limited by sclerotic bone; (b and c) MRI showing the limiting sclerotic bone and the benign aspect of the injury.***

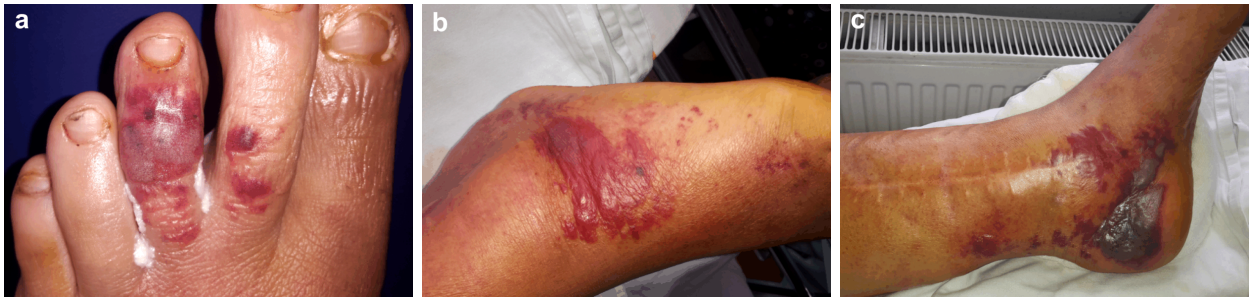

Figure 2 – ***(a) Acute cutaneous reaction with hemorrhagic blisters and petechiae; at the level of the forefoot, aspect of infected Tinea pedis; at the level of the ankle, the same aspect on the external (b) and internal (c) surface, accompanied by acute inflammatory signs.***

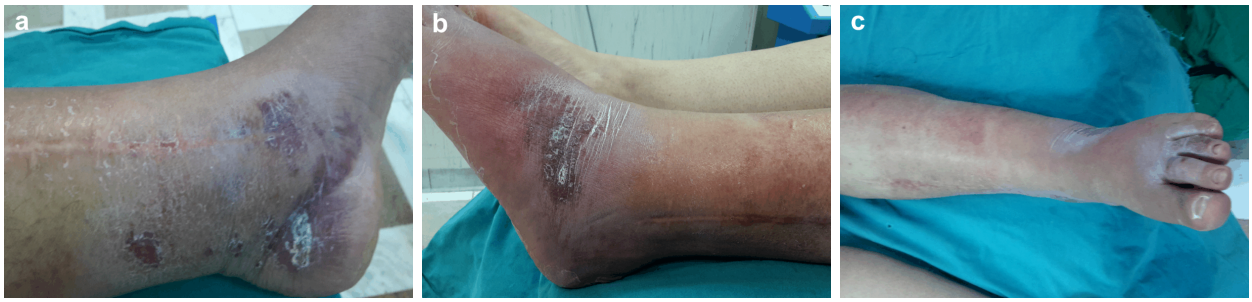

Figure 3 – ***Partial remission one month after the initial episode on the internal (a) and external (b) aspect of the ankle with cranial extension (c).***

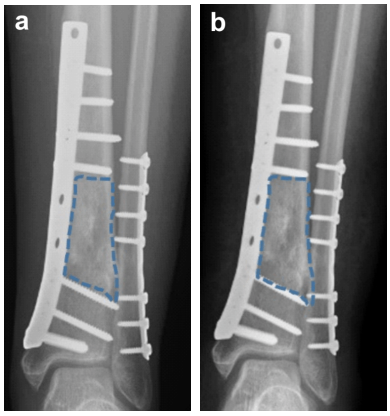

Figure 4 – ***Radiological aspect at the level of the former cyst, grafted with cancellous bone, area of bone density irregularities accompanying the inflammatory signs (a) and augmented one month after the initial episode (b).***

This aspect suggests the action of an osteolytic factor, which is strictly localized, otherwise its effects would have been visible on all of the bones; these aspects raised the suspicion of local infection, although no fistula or other specific signs for sepsis were found.

Under these circumstances, implant removal was the method of choice, for both the tibia and the peroneum, on the initial incisions. After incising the skin on the internal part of the ankle, marked edema of the subcutaneous tissue was obvious and two structures with granulomatous aspect and brown color suggesting metallic impregnation were excised (Figure 5a); at the level of the bone, after implant removal, the metallic color was revealed at the level of the peri-osseous covering soft tissues, of the reactive membrane beneath the implant and the cortex, as well as within the wholes of the screws (Figure 5b); at the level of the fracture, corresponding to the above-described radiological findings, a zone of avascular bony cortex was described (Figure 5c), adjacent to soft tissues with metallic impregnation and edema.

Due to this aspect, the tissular reaction to implant became highly probable as etiology of the inflammatory cellulitis; under these circumstances, thorough debridement was performed, including excision of the reactive soft tissues and the avascular bone, abrasion of the walls of those screw holes having metallic color and repeated lavage. Samples were taken for bacteriological testing.

The excised tissues were microscopically examined and revealed fibro-adipose, fascial and dense fibrous tissues, with particular features.

The fibro-adipose and fascial tissue contained congestive neoformation vessels with inflammatory perivascular tissues, nodules consisting of chronic inflammatory elements (lympho-plasmocytes) and vascular congestion (Figure 6, a and b); collections containing mono- and multi-nucleate histiocytes loaded with brown-yellow granular pigment (Figure 7) and lipophages with vacuolated cytoplasm, areas with hematic infiltrate, dense fibrotic areas with hyaline aspect, areas of liponecrosis, calcar salts depots (dystrophic calcifications) as different sizes nodules (Figure 8).

The dense fibrous tissue included amorphous material with nodular circumcised distribution, colored in brown-yellow or black-violaceous and inflammatory reaction with multinucleate cells specific for foreign body reaction and lymphoplasmocytary chronic elements with nodular distribution (Figure 9), as well as bone sequesters and bony fragments evolving to sequestration (Figure 10).

The histological aspect was therefore considered to be typical for a reaction to the implant, especially that all microbiological tests were negative (therefore excluding bacterial etiology), conclusion which was sustained by the clinical outcome. After implant removal, within three weeks, all the eruptions disappeared and within two months, the aspect of the shank was almost symmetrical with the other side, due to edema remission and skin healing.

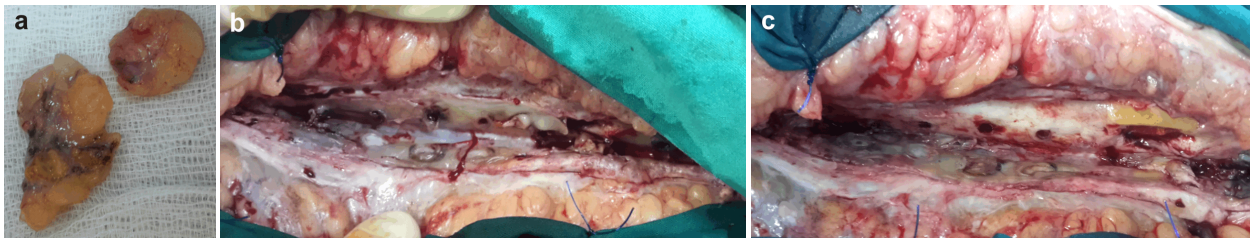

Figure 5 – ***Intra-operative aspect: (a) Within the adipose subcutaneous tissue, granulomatous structures with dark colored parts; Fibrous membrane adjacent to the bone with dark colors areas suggesting metallic impregnation (b), continuing in the holes of the screws, with a small area of avascular cortical bone (c).***

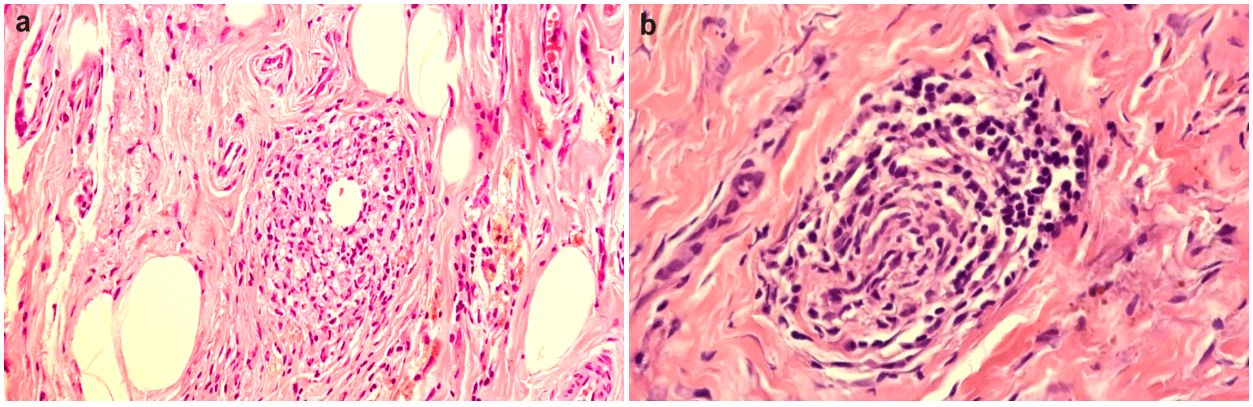

Figure 6 – *(a and b) Histiocytes loaded with lipidic pigment; adult adipose cells; chronic inflammatory elements with nodular distribution centered by a blood vessel; congestive neoformation vessels with inflammatory perivascular tissues. Hematoxylin–Eosin (HE) staining: (a) ×100; (b) ×200.*

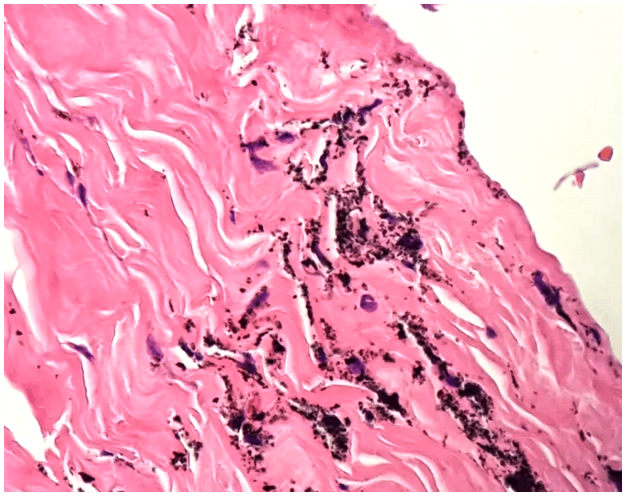

Figure 7 – *Dark brown exogenous pigmentary material impregnating the fibrous membrane, as well as inside the histiocyte cytoplasm, most probable due to corrosion. HE staining, ×400.*

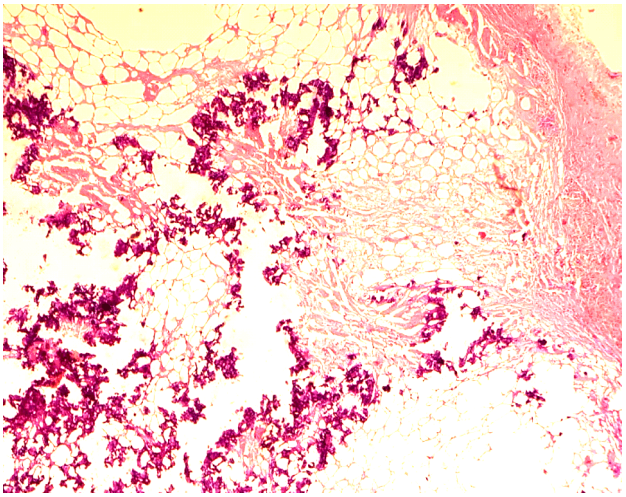

Figure 8 – *Areas of liponecrosis, which thus becomes susceptible to calcar salts intake, resulting in depots; mature adipose tissue; histiocyte agglutination loaded with lipidic pigment resulting from liponecrosis. HE staining, ×40.*

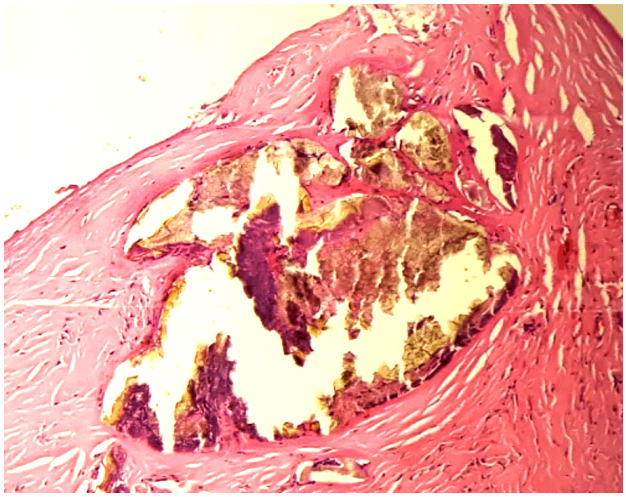

Figure 9 – *Within the peri-implant membrane, granulomatous reaction; bordering giant cells, induced by debris from corrosion – foreign body reaction surrounding amorphous material (pigmentary); bone sequestra inside and nearby the granuloma. HE staining, ×200.*

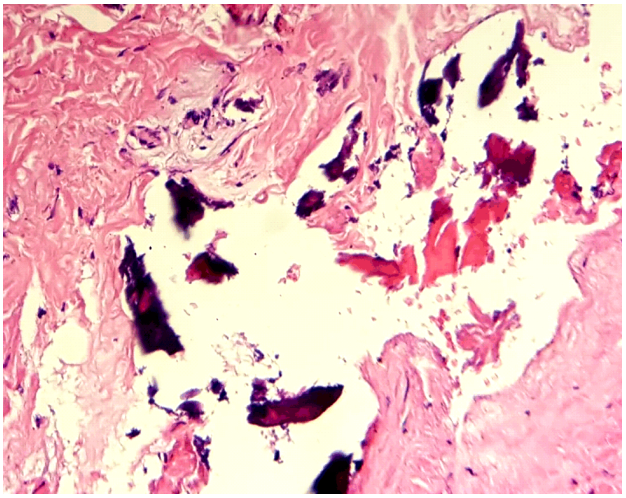

Figure 10 – *Dystrophic lamellar bone fragments evolving to complete necrosis, in different stages; complete necrosis – bone sequestra, dark purple. HE staining, ×200.*

Discussion

Due to the increasing number of orthopedic surgical procedures, the implant-associated pathology became of great interest, for it can affect, sometimes even dramatically, the outcome of the patients, even if initial surgery completely fulfilled its tasks. Besides implant breakage due to subsequent trauma and lack of bone healing, there are at least two other aspects, which need discussion: the first one is related to the interaction between the host and the implant, and the second to infections on implants. They are closely related, as any local foreign body reaction enhances the risk of infection, which dramatically diminishes the tolerance to implant [5].

Therefore, research focused not only on understanding the mechanisms of reaction to implant, but also on increasing the biocompatibility of implants, so as to minimize potentially negative effects [6]. Regardless its type and structure, a certain degree of implant degradation always exists, but the rates vary depending on the properties of the implant, as well as on the biological characteristics of the host.

Whilst degradation occurs only by wear in the case of polyethylene, metallic components deteriorate through wear and corrosion; depending on the contact surfaces and the sliding distance, wear degradation is more specific for prosthesis than for plates or nails, due to their reduced mobility, and results in particles with different sizes, smaller for metal than for polyethylene; the smaller the particles are, the greater their biological activity per mass is [7, 8].

Based on electrochemical processes, corrosion not only compromises the structure of the implant; generating metal oxides, hydroxides and phosphates, it results not only in local reactions, but also in systemic effects; although toxic actions have been reported for ions contained by orthopedic implants, especially for Co and Cr, the amounts usually released in the blood stream from these implants is far beyond the toxic one, thus considerably lowering the risk for systemic toxicity after orthopedic surgery [9–11].

Unlike this, local reactions to implant are not rare, and involve inflammation based on two types of mechanisms: the hypersensitivity mechanism and the macrophage-mediated reaction, each with specific histological characteristics: the hypersensitivity usually accompanies very small size debris and consists of a cell-mediated immune reaction, a lymphocytic response to metal products (as antigens), complexed with serum proteins (as antibodies), resulting in a lymphocytic perivascular infiltration accompanied by plasma cells, fibrin exudates and cellular necrosis [12, 13].

In the second case, the inflammation is usually triggered by phagocytosis of larger debris and involves mainly histiocytes, with minimal activity of B- or T-lymphocytes [14–16]. Regardless of the mechanism, inflammation triggers osteolysis, through direct action on osteoblasts and osteoclasts, therefore increasing the risk of implant loosening. Although the interaction between the tissues and the implant is always detectable using a histological evaluation, from a clinical point of view, it is usually undetectable, since most of the patients have no complains. In a small amount of cases, clinical signs of intolerance are described, mainly represented by chronic pain, with mild functional deficit [17–20].

It has been thoroughly described the affinity of bacteria for implants, with biofilm formation, thus diminishing the chance of diagnosing and destroying either Gram-positive and Gram-negative bacteria, for they live and multiply themselves in the biofilm, which represents a perfectly protective environment for them [21–23]. In such situations, implant removal is recommended, followed by sonication (for diagnostic purposes) and specialized surgical treatment; delayed diagnosis increases the bone destruction, thus requiring complicated grafting and stabilizing procedures. Due to increased risk of infection especially in aggressive forms of implant tissular reactions, early diagnosis followed by implant removal with thorough excision of all affected tissues is mandatory as prophylaxis of sepsis.

Diagnosis of tissular reaction to implant is sometimes difficult, due to non-specific clinical findings, such as chronic pain, which can have multiple causes. Cutaneous reactions are also non-specific, as this situation cannot be completely overlapped to skin hypersensitivity to metals and skin infections can have many other causes [24, 25].

More than that, the clinical aspect is rarely acute thus increasing the risk of confusion. Such a situation is the above-presented case, when the supposition of foreign body reaction was established based not on the initial cellulitis aspect, which could have been produced by the infected *Tinea pedis*, with secondary involvement of the ankle, but on the persistence of the eruption, despite the treatment, for a longer period of time (one month) with the implant as an alarm supplementary element. Two aspects were considered by the team treating this patient: either the implant is the one maintaining the cellulitis disturbances, either the implant will increase the chances that superficial cellulitis will induce deep sepsis; in both cases, the proper decision was the same – implant removal, as proven by the subsequent clinical outcome.

Since the microbiological evaluations (samples from the fracture site, as well as implant sonication) did not reveal any bacterial contamination, the only mean to establish a positive diagnosis was the histological exam. The elements described in this case where concordant to the data from the literature: according to Willert *et al.* [4], Thomas *et al.* [26] and Natu *et al.* [27], lymphocytes either infiltrating diffuse the perivascular space, either organized in a follicular manner, associated with tissular necrosis, macrophages and high endothelial venules were considered typical for tissular allergic reaction to implant and in part for tissue necrosis. The significance of sequestra in different stages is that of bone necrosis, resulting from direct osteolysis, due to activation of the osteoclasts by the metal debris and by chronic inflammation, as well [26].

According to Sansone *et al.* [28], tissular reaction to implant is characterized by unusual lymphocytic perivascular infiltration and plasma cells accumulation, as well as by diffuse and perivascular infiltrates of lymphocytes and plasma cells, massive fibrin exudation, accumulation of macrophages, infiltrates of eosinophilic granulocytes and necrosis, all these aspects being described in the

case presented in this paper, supporting the lymphocyte-dominated immunological response.

Analyzing the criteria proposed by Morawietz *et al.* [29], the histological findings described in this case are concordant to the type I – wear particle induced membrane, with foreign body particles; macrophages and multinucleated giant cells occupying at least 20% of the space, thus excluding the infection; the significance of these findings is crucial because in this particular case the histological exam was the only one able to establish the diagnosis, thus conducting the long term treatment.

It is important to underline that neglecting the presence of the implant as a supplementary risk factor could have resulted in considering the clinical aspect as only a cellulitis produced maybe by a resistant bacteria; in this situation, continuing the general and local treatment (without implant removal), might have resulted in multiple negative effects, such as dismicrobism, changes in bacterial resistance, and allergies, while the real cause, the foreign body reaction, would have continued to act, enhancing the bone and soft tissue injuries and the risk of infection.

Conclusions

Due to increasing number of procedures and gravity of symptoms, implant related pathology became of great interest not only for orthopedic surgeons, as an interdisciplinary approach, involving pathologists and infectionists is mandatory for a successful treatment. Understanding the histological mechanisms is crucial, since chronic inflammation is the basic process, generating mild clinical symptoms. Although acute symptoms are rare, reaction to implant must be always considered as a potential cause even for atypical findings. Histological evaluations are crucial for understanding the pathogenic mechanisms as well as for establishing the definitive diagnosis, especially in atypical situations, when other causes (infections, even tumors) must be excluded for the proper treatment to be performed.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding author
Nicolae Marian Ciurea, MD, PhD Student, Clinic of Orthopedics and Traumatology, Clinical Emergency Hospital, 8 Floreasca Avenue, 014461 Bucharest, Romania; Phone +4021–599 23 00 / 308, e-mail: dr.ciureanicolae@gmail.com

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