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Research Article

Osteomyelitis and other forms of osteitis in need of surgery between 2012-2019 in an Orthopedic Center in Romania. Scarce cases of late onset metal-on-metal implant failure still emerging

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Abstract. Aim: The main objective of this paper is to evaluate the number of metallic implant failure due to aseptic complications in need of revision surgery between the given years. Material and methods: We retrospectively analyzed patients over the age of 18 with osteomyelitis that required surgery between the years of 2012 and 2019, in an Orthopedic Center in Romania. The main objective of this paper is to evaluate the number of MoM implant associated osteomyelitis due to long-term complications in need of revision surgery. As a secondary end point, we aim to contextualize this data by analyzing the total amount of osteomyelitis in need of surgery regardless of etiology, the comorbidities that could have a role in this pathology and the infectious pathogens responsible. Results: After the selection process 52 patients were included in the study: 18 patients with implant related osteomyelitis and 34 with osteomyelitis in need of surgery unrelated to MoM orthopedic implants. The mean age of the patients at time of surgery (n = 52) was 50.12±13.87. While the cause of most implant related events (e.g., osteitis and/or osteomyelitis in need of revision surgery) was of infectious nature, in some cases the infectious etiology was excluded and a late immune reaction was confirmed. While in 17 out of the 18 patients which had an implant related event, an infectious agent was isolated, 1 patient with a MoM total hip replacement system presented a long-term implant failure. The patient presented with an irreducible dislocation of the right hip where the implant was placed. Based on the blood work results, radiographic findings and the histopathological report we concluded that this was a case of long-term implant failure due to a chronic immune response to the implanted metal-on-metal total hip replacement system. In the group with osteitis/osteomyelitis unrelated to orthopedic implants most had a positive medical history of trauma or fractures: 41.17%, and/or other severe comorbidities that predisposed them to such infections: 55.88%. Only 4 patients didn't have an obvious cause or declared predisposing factor. The main bacteria identified in these cases were: Staphylococcus aureus (62.5%) and less frequent Staphylococcus epidermidis (18.7%), Pseudomonas aeruginosa (6.2%), bacteria from the Proteus family (3.1%) and MRSA (9.3%). Conclusion: While the number of aseptic implant failures in recent years is fairly low, the need for recognizing and understanding this pathology so we can provide proper screening and treatment for patients with MoM implants is of current interest.

Key Words: Type IV hypersensitivity, orthopedic metallic implants, aseptic osteolysis, metal-on-metal arthroplasty

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Introduction

The incidence of metal sensitivity, especially nickel, chromium and cobalt, is on the rise. Although difficult to assess, dermatological hypersensitivity to metals is said to be between 10% and 15% within the general population (Basketter et al 1993, Cramers et al 1977, Gawkrodger et al 1993, Merritt et al 1996). However, the sources of sensitization are often not easy to detect. A study by Basketter and colleagues (Basketter et al 1993) analyses the existing literature related to the presence of these metals in consumer products, defined as personal items, personal care items and detergents/cleaning products. This analysis revealed that so-called consumer products are a minor source of contact with nickel, cobalt and chromium. Thus, it can be argued that traces of these elements found in consumer products are either insignificant, or the period of exposure to them is too low to induce sensitization. Moreover, the same analysis revealed that a sensitized person usually has more significant sources of contact with such metals, such as jewellery (e.g., earrings) and other metallic objects. Thus, our attention needs to be shifted away from consumer products, which, as it has been shown, contain insignificant amounts of these substances, to other sources of exposure to such metals.

Metallic orthopaedic implants can be such a source of sensitization. However, specific data regarding the mechanisms involved

are incomplete due to several reasons: the difficulty of assessing the incidence of this condition, the symptoms involved, the role of metal sensitization in long term implant failure due to the intricacies of innate immune response, acquired immune response and the role of concurrent metal sensitization with implant related infections.

Metal implants are used in various ways in orthopedic surgery, while this type of implant is usually well tolerated (Codosch et al 2009) e.g., orthopedic plates and screws, other types of metal devices have their usage limited by aseptic long-term complications that lead to device failure. With regards to metal-on-metal (MoM) total replacement implants and metal-on-metal total resurfacing implant systems their usage has seen a steady decline (www.fda.gov 2021) since there have been multiple reports of long-term implant failure (Bahraminasab et al 2012, www.ec.europa.eu 2021). In this context there are a number of patients that have MoM systems implanted in previous years and require active surveillance in order to determine if complications may arise.

This paper aims to evaluate the number of aseptic complications of orthopedic implants that required revision surgery between the years of 2012-2019 in the Clinic of Orthopedics and Traumatology "Alexandru Radulescu" Cluj-Napoca. The main objective of this paper is to evaluate the number of metallic implant failure due to aseptic complications in need of revision surgery between the given years. As a secondary end point, we aim to contextualize this data by analyzing the total amount of osteitis/osteomyelitis in need of surgery regardless of etiology.

Material and methods

This retrospective study included patients over the age of 18 with osteomyelitis that required surgical intervention. The patients were treated in the Clinic of Orthopedics and Traumatology "Alexandru Radulescu" Cluj-Napoca between the years of 2012 and 2019.

This study brought to attention of the Ethics Committee of the Clinic of Orthopedics and Traumatology "Alexandru Radulescu" Cluj-Napoca for approval but considering the fact that all patient's data has underwent a process of anonymization no special approval was deemed necessary.

Exclusion criteria for participation in the study: incomplete, damaged or lost patient files, lack of consent for surgical treatment, surgery performed in other hospitals.

Data extracted from the patient's files consisted of: age, gender, diagnosis of admission and discharge, type of orthopedic device extracted, complete blood count and microbiological tests results.

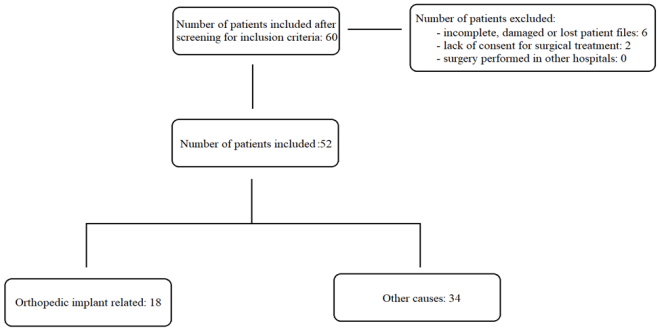

Figure 1. Patient selection criteria and inclusion process

Sixty patients met the initial inclusion criteria. From the total number of patients 8 patients were excluded (Figure 1). IBM SPSS Statistics ver. 26 was used to determine the age: mean, standard deviation (S.D.), standard error of mean (S.E.M), confidence interval (C.I.), median age with quartile 1(Q1) and 3(Q3). The homogeneity of sex and age distribution in the two groups was verified with Levene's Test for Equality of Variances. The normal distribution of age of the included patients was tested with the Kolmogorov-Smirnov (KS) and Shapiro-Wilk (SW) normality test.

Results

After the selection process, a number of 52 patients were included in the study. Age mean at the time of revision surgery for the included patients (n = 52) was 50.12 years [min = 22.08, max = 82.24] [S.D.=13.877, S.E.M. = 1.924], the age of the population was significantly older than the average age of Romania, 41.3 years (www.statista.com) [one sample T test, CI 95% LL = 4.956, UL = 12.6839, $p < 0.01$; Test value = 41.3]; median age 51.625 [Q1 = 41.112, Q3 = 59.1175].

Number of males treated 40 (76.92 %) and number of females treated 12 (23.08%). The distribution of gender/age in the implant related and the event unrelated to orthopedic implants was homogenous: gender/implant F (1,50) =0.044, p=0.834; age/implant F (1,50) =0.433, p=0.513. The age in both groups was normally distributed, no implant group [df = 34, KS p = 0.200, SW p = 0.837] and implant group [df = 18, KS p = 0.163, SW = 0.728] as seen below.

The main categories of comorbidities present in both groups were cardiovascular, diabetes, skin diseases (Table 1). Other comorbidities that were present were: gastroenterological, urological (e.g., benign prostatic hyperplasia), psychiatric (e.g., anxiety disorder spectrum: 1, alcoholism: 3, persistent depressive disorder:1), neurological (e.g., spastic paraplegia: 1, one-sided hearing loss: 1, unspecified polineuropathy:1, spastic hemiplegia:1, epilepsy with "grand mal" seizures: 1) and ophthalmologic comorbidities.

Infectious versus non-infectious events

From the 52 patients that were included in our study most events were unrelated to implantable devices: 34 patients. This subset of patients had a positive medical history of trauma or fractures: 41.17%, and/or other severe comorbidities that predisposed them to such infections: 55.88%. Only 4 patients didn't have an obvious cause or declared predisposing factor. The common denominator of the patients whose orthopedic event was not related to implantable devices was the presence of the septic component. The main bacteria identified in these cases were: *Staphylococcus aureus* (62.5%) and less frequent *Staphylococcus epidermidis* (18.7%), *Pseudomonas aeruginosa* (6.2%), bacteria from the Proteus family (3.1%) and MRSA (9.3%).

The patients who had an implant related event in need of surgery represented 34.6% out of all patients included. While the cause of most implant related events (e.g., osteitis and/or osteomyelitis in need of revision surgery) was of infectious nature, in some cases the infectious etiology was excluded and a late immune reaction was confirmed. Out of the 18 patients which has an implant related event in 17 an infectious agent could be isolated. The main bacteria isolated were: *Staphylococcus aureus*

Table 1. Main comorbidities of the patients that required an orthopedical surgical intervention

Type of comorbidity	Number of patients with set comorbidity type in the implant related event group	Number of patients with set comorbidity type in the implant related event group
Cardio-vascular	1	3
Type 1 /Type 2 Diabetes	4	2
Skin conditions	1	2
Others	3	13

(73.7%), *Staphylococcus epidermidis* (10.5%) and less frequent germs from the Klebsiella species, Proteus species and MRSA (Methicillin-resistant *Staphylococcus aureus*), 5.3% each.

The case in which an infectious pathogen could not be isolated was the case of a patient with a metal-on-metal total hip replacement system. The patient presented with an irreducible dislocation of the right hip where the implant was placed. The blood work revealed an inflammatory syndrome with high levels of fibrinogen and C-reactive protein (CRP) but the complete blood count (CBC) did not indicate a systemic active infection as both leukocyte and neutrophil count was normal. A normocytic hypochromic anemia was discovered and it was interpreted in the context of chronic inflammation that was present at the interface of the joint implant. The plain radiography confirmed the suspicion of dislocation (Figure 2) and the presence of osteolysis, periprosthetic osteoporosis and the presence of a pseudotumor at the implant site. Taking the investigations into consideration and after a complete physical examination the decision for revision surgery was taken. The histopathological report revealed a cystic lesion that presented an outer wall comprised of a simple cuboidal epithelium with fibrin deposits and granulation tissue. The outer wall also presented microhemorrhage zones, siderophage cells and an important inflammatory cell infiltration. Withing the cystic formation fibrin aggregates that organize conjunctively.

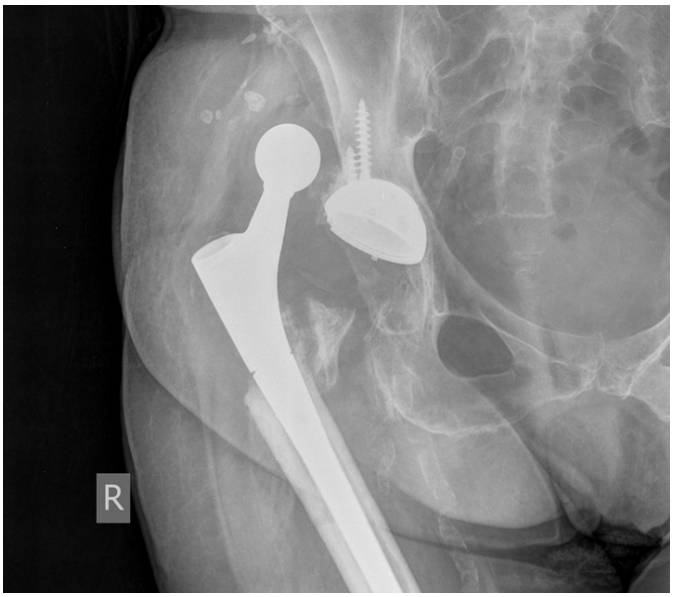

Figure 2. Patient presenting a metal-on-metal total hip replacement system with an irreducible dislocation in need of revision surgery

Based on the blood work results, radiographic findings and the histopathological report we concluded that this was a case of long-term implant failure due to a chronic immune response to the implanted metal-on-metal total hip replacement system.

Discussion

As suggested in other studies (Ribeiro et al 2012, Carek et al 2001) diabetes and other infectious comorbidities (e.g., infectious skin conditions) predispose the patient to infectious related orthopedic events (in our case: infectious osteomyelitis and infectious complications of orthopedic implants).

With regard to other comorbidities while both groups presented patients with cardiovascular diseases with varying degrees of severity it is important to note that all patients with cardiac afflictions were over the age of 65 years. The cardio-vascular afflictions present in both groups had no hemodynamic impact upon the limbs in need of surgery, thus for our patients we can eliminate the cardiovascular factor as a predisposing condition. The group with implant unrelated osteomyelitis presented a patient with debilitating neurological disease and decubitus eschar in which the cause for the infectious osteomyelitis was clearly related to the prior mentioned pathology.

We must note that there are multiple reasons for the infectious nature of most implant related osteitis in need of surgery: 1) low number of patients included in the study, 2) most implantations of metal-on-metal implant systems in our center took place between 2005 and 2015 thus the time frame of the analysis was too short to capture the time period in which most implants will fail (Neumann et al 2010) and 3) this study included all orthopedic implants which contained metal components in their structures including those that are used in a surgical context with high bacterial load e.g., external fixators. We expect that in a future analysis of the patients with the same characteristics the number of cases of non-infectious metal-on-metal implant failure to increase slightly.

Another interesting aspect of infections related to metal alloy orthopedic implants is the co-existence in some cases of a foreign body immune reaction with the inflammatory infiltrate specific to infections. In our study a patient presented in the histopathologic report the presence of fused macrophages (giant cells) in the zone juxtaposed to the orthopedic implant scattered through the dominant mixt inflammatory infiltrate comprised mostly of neutrophilic cells. Considering from a quantitative stand point the main cellular infiltrate was comprised from neutrophilic cells, thus the question of an infection favorizing metal alloy degradation and exacerbating the immune response to the orthopedic implant can be taken into consideration, but further research is needed.

Conclusion

To sum up, while the number of aseptic implant failures in the given years was fairly low in comparison to the infectious related implant failure of orthopedic implanted devices, the need to understand this type of long-term orthopedic implant failure is essential in order to try to detect this type of event as early as possible thus the importance of regularly screening the patient with metal implants is of outmost importance.

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