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Pleomorphic clinical spectrum of metallosis in total hip arthroplasty

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Abstract

Purpose To summarize the biological effects of metal debris from hip arthroplasties which characterize a polymorphic clinical spectrum of local and remote manifestation.

Methods Retrospective study. Patient, implant, and surgical characteristics were collected, including implant survival, clinical manifestations, cause of arthroplasty revision or implant failure, and peri- and intra-operative complications. The primary endpoint was implant survivorship. Hip revision arthroplasty was decided considering clinical signs and symptoms, abnormal imaging (XR, MR, TC, echotomography, scintigraphy), and blood metal ion level. An ad hoc electronic form was used to collect demographic, epidemiological, and clinical variables. In-between group comparisons of quantitative variables were performed with the Student t test and the Mann-Whitney for parametric and non-parametric variables, respectively. Logistic regression analyses were carried out to assess the relationship between clinical and radiographic characteristics and stem and cup revision. Radiographic measurements of implant positioning validity and reliability were assessed using Krippendorff's alpha reliability coefficient. The statistical software STATA version 15 (StatsCorp, TX) was used to perform statistical computations.

Results In this MoM THA series, the most incident cause of implant failure was ARMD in 11 out of 14 (78.6%) patients. All clinical failure manifestations, revision surgery highlights, and intra-operative findings are reported.

Conclusions The local adverse reactions include lesions of different clinical relevance from small asymptomatic soft tissue lesions to dramatic osteolysis, necrosis, effusion, and growing masses which can cause secondary pathological effects. Symptoms of systemic toxicity are rarely described but may have been largely unreported in literature. Despite the extensive literature on the topic, the patient's management is still uncertain and challenging. Every metallic implant (e.g., screws, plates, spinal instrumentations) has a potential local or systemic adverse effect. Organizing a national registry of arthroplasty should be mandatory, in order to collect data about the patients, the surgery, the implanted device (with a careful post-marketing tracking), and the follow-up for all the procedures performed at a national level. The data collected in the registry will allow to analyze the implant survival and to better recognize the undesirable and sometimes unexpected effects of different biomaterials on the whole body.

Keywords Biomaterials · Metal ions · Metallosis · Pseudotumours · ARMD · ALVAL · Total hip arthroplasty

Introduction

Total hip arthroplasty (THA) is an extremely widespread and highly successful orthopaedic procedure. Over the years, a wide variety of materials have been used for bearing components and surfaces with the purpose of improving patient satisfaction and implant survivorship. At the end of the last century, the advances in metallurgy and manufacturing led to the development of a new generation of metal on metal (MoM) implants using cobalt-chromium-molybdenum alloys. The theoretical advantages were to produce less volumetric wear, thus reducing wear-induced osteolysis, and to have a thinner acetabular component, thus allowing larger femoral heads and increased ROM and stability [1]. Just like the awareness of the problems related with polyethylene wear particles after the first generation of Charnley implants, the serious complications with the MoM hips came to light when the international literature showed an unacceptable failure rate in MoM hip resurfacing arthroplasty (HRA) and THA. The use of MoM hip arthroplasty subsequently saw a quick decline [2–6]. Many medical device alerts were issued by national and international organizations and government regulatory agencies,

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leading to post-marketing surveillance and substantial discontinuation in the use of these implants. According to the American Academy of Orthopedic Surgeons, more than a million of total hip prosthesis with a MoM coupling have been implanted since 1996 [7, 8], and nowadays, the real challenge is to follow patient sequelae and fully understand the extent of a phenomenon that has not yet ended. The increased failure rate in MoM hip arthroplasty is associated with the release of metal products (biologically active particles, ions, metallo-organic compounds).

The biological effects of metal debris from hip arthroplasties characterize a polymorphic clinical spectrum of local or remote manifestation in the medium-long term [9–11].

Local effects

The local tissue response refers to metallosis, adverse reaction to metal debris (ARMD), adverse local tissue reaction (ALTR), aseptic lymphocytic vasculitis-associated lesion (ALVAL), and pseudotumours. The pleomorphic spectrum of local adverse reactions includes lesions of different clinical relevance from small asymptomatic soft tissue lesions to dramatic periprosthetic osteolysis, necrosis, effusion, and growing masses (cystic and/or solid) which can cause secondary pathological effects by pushing or displacing surrounding tissues. In case of wear with debris production, loosening, or infection, a soft tissue tumor-like mass with inflammatory characteristics, termed "pseudotumour" may appear. It is often asymptomatic and incidental but it can cause groin pain, hip discomfort, paresthesia, and sensation of mass or weight [12, 13]. In literature, the term pseudotumour is often used to indicate a wide spectrum of soft tissue lesions such as focal inflammatory reactions, necrotic regions, fluid collections of different compositions, wall thicknesses, and cystic or solid mass-like nodules of non-neoplastic and non-infectious origin. Pseudotumour is not exclusively observed with MoM interfaces, but formation also occurs in association with metal on polyethylene (MoP) and ceramic-on-polyethylene (CoP) THA prostheses [14–18] (Fig. 1).

Remote effects

In MoM hip arthroplasty, besides the local tissue damages, it is necessary to understand the entity of the systemic adverse effects induced by metal accumulation. The dissemination of metal particles and ions throughout the body has been associated with several systemic adverse effects, including immunotoxicity, organ toxicity (cardiomyopathy, polycythemia, hypothyroidism, neurological disorders, dermatological complications), cancerogenesis, and teratogenicity. Symptoms of systemic toxicity, sometimes referred to as "arthroprosthetic cobaltism," are rarely described in the literature and they are similar to those described in professional exposition to cobalt:

Fig. 1 Metallosis in MoP THA

cardiomyopathy, polycythemia, hypothyroidism, and neurological disorders (peripheral neuropathy, hand tremors, incoordination, cognitive decline, depression, vertigo, blindness and deafness) [19]. According to some studies, manifestations of systemic toxicity generally do not occur below a cobalt blood concentration of 100 μg/L, or even 300 μg/L, and appear first as haematological and thyroid disorders [20, 21]. From a systematic review of the literature, the established cases of arthroprosthetic-cobaltism well documented between 2001 and 2014 were 25; symptoms were diverse and involved cardiovascular system (60%), audiovestibular system (52%), peripheral motor-sensory system (48%), thyroid (48%), psychological functioning (32%), visual system (32%), and the haematological, oncological, or immune system (20%). In addition, almost all cases presented hip symptoms (84%). These adverse effects were observed on an average 41 months of period after implantation of the prosthesis and were associated with an average cobaltaemia of 324 μg/L, although four patients had a cobalt level of less than 20 μg /L. The authors underlined the tendency to a greater frequency of reports in recent years and also stressed that the problem may have been largely unreported in literature [22].

The adverse periprosthetic soft tissue response is influenced by implant, surgical, and patient factors. Peculiar implant factors can have influence on MoM hip arthroplasty failures, like the size of the head, the design of the components, the modularity, the coupling of different materials, the taper cone angle, the taper surface roughness, the taper geometry, the arc of cover, and the contact patch to rim distance [23–25].

Materials and methods

A retrospective study was carried out recruiting an original cohort of patients who underwent MoM bearing THA (126 hips) in the Orthopedic Unit of the University of Sassary,

Sassari, Italy, between June 2006 and March 2012. We included patients with uncemented MoM THA. MoM-implanted components were MITCH TRH System (standard acetabular cup, HAP coated, and modular head, taper V40) and anatomic femoral stem (monoblock or modular ABG II, Stryker, and Symax, Stryker). Our exclusion criteria were THA with bearing surfaces other than MoM. The total hip arthroplasty was implanted using the posterolateral approach to the hip. Patient, implant, and surgical characteristics were collected, including implant survival, clinical manifestations, cause of arthroplasty revision or implant failure, and peri- and intra-operative complications. In particular, patients' characteristics included diagnosis, gender, age, height, weight, BMI, age of intervention, and side. Implant characteristics were femoral head diameter, stem modularity, stem measure, and stem model. Surgical assessment included radiographic assessment of component positioning: acetabular cup abduction angle, lateral and vertical offset (measured with respect to the physiological hip joint centre), and lateral distance and vertical distance from the teardrop. Pelvic anteroposterior radiographs of post-operative patients were obtained and digitally recorded. A widespread spreadsheet software (Microsoft Excel for Windows) was used to analyze images and measure abduction angle and the vertical and lateral offset from the hip joint centre and from the teardrop. The physiological hip joint centre (HJC) was determined in the geometrical centre of the opposite unaffected hip; in patients with bilateral pathological deviation of the rotational centre (both affected hips or bilateral THA), the hip centre was determined following Fessy's method [26]. The component positioning was independently assessed by two experts. The primary endpoint was implant survivorship. Hip revision arthroplasty was decided considering clinical signs and symptoms, abnormal imaging (XR, MR, TC, echotomography, scintigraphy), and blood metal ion level.

Statistical analysis

An ad hoc electronic form was used to collect demographic, epidemiological, and clinical variables. Qualitative variables were described with absolute and relative (percentage) frequencies, whereas quantitative variables were summarized with means (standard deviations, SD) or medians (interquartile ranges, IQR) in case of parametric and non-parametric distribution, respectively. In-between group comparisons of quantitative variables were performed with the Student t test and the Mann-Whitney for parametric and non-parametric variables, respectively. Logistic regression analyses were carried out to assess the relationship between clinical and radiographic characteristics and stem and cup revision.

Radiographic measurements of implant positioning validity and reliability were assessed using Krippendorff's alpha reliability coefficient. A two-tailed p value less than 0.05 was considered statistically significant. The statistical software STATA version 15 (StatsCorp, TX) was used to perform statistical computations.

Results

A total of 120 patients were recruited. However, 28 were excluded for the following reasons: death not related to the intervention ($n = 5$), prosthesis revision for traumatic periprosthetic fracture ($n = 2$), missing data ($n = 21$). A total of 92 patients with 97 MoM THA were included in the final analysis. The median (IQR) age was 66 (59–72) years, and females were more prevalent (77%) with a mean (SD) BMI of 26.6 (4.6) kg/m^2 (Table 1). The most frequent pre-operative diagnoses were coxarthrosis (81.4%), hip dysplasia (5.2%), and aseptic necrosis of the femoral head (3.1%) (Table 2).

The most common prosthetic femoral head diameter was 44 mm (33/97 implants) (Chart 1a), and all the femoral stems were ABG II but 3 (Symax, Stryker size 5, 5, 6); the most common ABG II stem were size 4 (34/97) and size 5 (29/97) (Chart 1b); 17/97 ABG II stems were modular (long neck 5/17, short neck 12/17). Assessments of component positioning are summarized in Table 3.

Implant failure was observed in 14/97 (14.4%) total hip replacement (THR); revision hip arthroplasty was performed in 11 hips and three patients were scheduled for revision surgery. The mean (SD) implant survival before failure diagnosis was 6.6 (2.4) years.

The most incident cause of implant failure was ARMD in 11 out of 14 (78.6%) patients; a symptomatic pseudotumour was found in all ARMD cases; one patient showed ARMD associated with ALVAL, one case had a proven erythrocytosis caused by arthroprosthetic cobaltism, and one case had an associated aseptic loosening of the stem; in 3/14 (21.4%) cases, implant failure was not related with metallosis (aseptic loosening for mechanical failure). Clinical failure manifestations, revision surgery highlights, and intra-operative findings are described in Table 4. Krippendorff's alpha reliability coefficient values ranged from 0.74 (lateral distance from teardrop) to 0.97 (cup abduction angle). Logistic regression

Table 1 Patient characteristics

Male, n (%)		32/97 (33.0)
Median (IQR) age (years)		75 (68–80)
Median (IQR) height (cm)		164 (157–170)
Mean (SD) weight (kg)		70.9 (15.4)
Mean (SD) BMI (kg/m^2)		26.6 (4.6)
Median (IQR) age at intervention (years)		66 (59–72)
Side, n (%)	Right	58/97 (59.8)
	Left	39/97 (40.2)

Table 2   Pre-operative diagnosis. *FAI* femoro-acetabular impingement

Diagnosis, n (%)	Coxarthrosis	79/97 (81.4)
	Hip dysplasia	5/97 (5.2)
	Osteonecrosis of the femoral head	3/97 (3.1)
	FAI	3/97 (3.1)
	Post-traumatic coxarthrosis	2/97 (2.1)
	Juvenile rheumatoid arthritis	2/97 (2.1)
	Coxofemoral fracture	2/97 (2.1)
	Aseptic mobilization of hip prosthesis	1/97 (1.0)

analysis aimed to assess the relationship between clinical and radiographic characteristics and indication for acetabular cup and for femoral stem revision (14 failures) did not show any statistically significant associations. The inclusion of 97 implants did not show any statistically significant findings, with the only exception of vertical offset 1 (OR 1.2; *p* value 0.04) and hip dysplasia (OR 30; *p* value 0.009).

Discussion

The adverse periprosthetic soft tissue response is influenced by implant, surgical, and patient factors. Peculiar implant factors can have influence on MoM hip arthroplasty failures, like the size of the head, the design of the components, the modularity (Fig. 2), the coupling of different materials, the taper cone angle, the taper surface roughness, the taper geometry, the arc of cover, and the contact patch to rim distance. Above all, the head size is a critical factor. Small heads have little additional risk of ARMD when compared to conventional bearings, while many more problems are related with large-diameter (> 36-mm head size) MoM bearings. Large-diameter head should theoretically produce a smaller amount of metal debris because of enhanced fluid film lubrication, lower wear profiles, and lower risk of impingement and dislocation, but

some studies are on the opposite side, showing elevated risk of taper wear and rim loading leading to early aseptic loosening, adverse tissue reactions, high level of serum metal ions, and high revision rates [27]. The systematic review made in 2013 by Hartmann et al. shows that the maximum serum Co-levels are consistently higher at all post-operative assessments in patients who received MoM large-head THA and HRA in comparison with patient who received MoM small-head THA [28]. Nowadays, MoM large-head THAs are considered at greater risk of complications, and their use has been abandoned worldwide. Some selected surface replacements with larger heads (> 48 mm) are still used in young men because they allow high levels of physical activity and have good outcomes for long periods, but smaller head sizes have almost been abandoned. Surgical factors, as the acetabular cup inclination and the acetabular version, and patient factors like gender, dysplasia, metal sensitivity, and body mass index, can also contribute more or less significantly with clinical manifestations [29]. In the hip prosthesis treating hip dysplasia, there is the risk, for the surgeon, to maximize cup-host bone contact with excessive acetabular cup inclination and subsequent rim loading. In this type of patient, great attention must be used in avoiding excessive acetabular inclination. In this mid-term retrospective study, 5/97 hips were dysplastic and, despite an optimal component positioning, 2/5 needed revision surgery (statistically significant finding; OR 30; *p* value 0.009); only one failure in DDH was related to metallosis. No correlation between diagnosis and failure was observed in this study, probably due to small sample size and lack of a systematic follow-up (we only considered implant failure in cases of revision surgery and symptomatic patients). The early orthopaedic publications upon the assessment of pseudotumours were underestimating the entity of the phenomenon because MR imaging was not applied in the assessment of both symptomatic and asymptomatic patients, while in 2011, ultrasound studies in asymptomatic patients were demonstrating a prevalence of pseudotumours of 5% and 30% in symptomatic
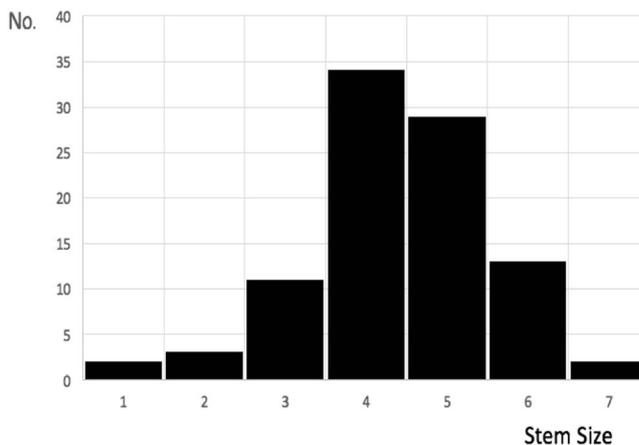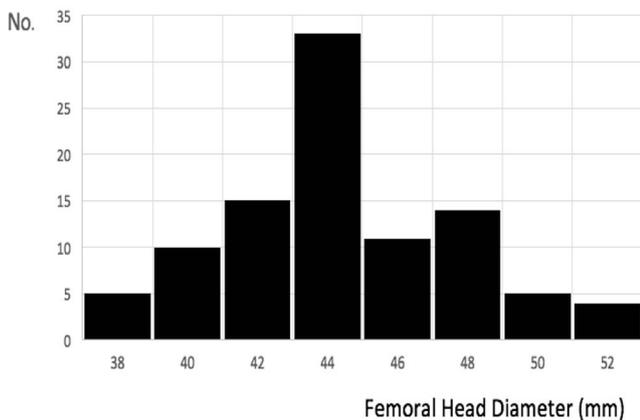
Chart 1 No. number of implants. **a** prosthetic femoral head diameter distribution. **b** ABG II stem size distribution

HRA and 40% in THA [30]. In MoP hip replacement, the incidence of pseudotumours is lower (13%) [31]. In 2012, an MR study showed a 59% of prevalence of pseudotumours with no significant difference in prevalence in between painful and well-functioning prosthesis [32]. In our series logistic regression, the analysis did not show any statistically significant correlation (p value < 0.05) when assessing the relationship between studied implant, surgical and patient variables (gender, age, height, weight, BMI, age at intervention, femoral head diameter, femoral head offset, stem size, acetabular cup abduction angle, lateral and vertical offset from HJC, and lateral and vertical distances from the teardrop), and indication for acetabular cup and femoral stem revision. This finding could be related to the poor statistical power of the sample. Krippendorff's alpha reliability coefficient values indicating radiographic measurements of implant positioning validity and reliability ranged from 0.74 (lateral distance from teardrop) to 0.97 (cup abduction angle) showing a good to excellent reliability.

In this 14 MoM THA failure series, we observed a protean clinical manifestation, especially referring to cases of metallosis (11/14). In all failures due to metallosis, we observed an ARMD with a symptomatic pseudotumour that causes groin pain at rest- or activity-related. Three cases complained about the presence of a painful mass (cases 1, 2, and 7); in two, the semi-cystic mass was extended towards gluteal muscles. The location of a fluid collection, considered the most common subtype of pseudotumour, can depend on the surgical approach because the reactive fluid often dissects preferentially through the surgical tract [33]. All patients of this series underwent THA through the posterolateral approach, and with this way, the capsular defect is posterior and the reactive fluid can leak posteriorly to the great trochanter and accumulates all over. A fluid collection can potentially extend posteriorly, sometimes compressing or irritating the sciatic nerve and causing neurologic symptoms (as observed in case 2), or can extend anteriorly into the iliopsoas muscle or bursa and then dissect cranially into the pelvis (cases 2, 3, and 6). The communication in between the joint space and the pseudotumour can be visible or impossible to identify because of the collapse of the connecting tract [34]. In case 6, a large retro-peritoneal intra-abdominal cyst adherent to the iliac vessels reached the pelvic cavity from the acetabular bone

Table 3 Acetabular cup component positioning. *HJC* hip joint centre

Mean (SD) abduction angle	41.9° (9.6)
Mean (SD) lateral offset from HJC, (mm)	− 2.5 (4.2)
Median (IQR) vertical offset from HJC (mm)	4.5 (2.5–7.5)
Mean (SD) lateral distance from teardrop (mm)	30.2 (3.8)
Median (IQR) vertical distance from teardrop (mm)	17.5 (15.0–22.0)

defects, so drainage was possible through the bone defects itself (Fig. 3). When there is a spreading of the lesion in the pelvic area along the psoas sheath, there can be neuro-vascular compression or ureteral compression, and the surgical procedure can become extremely challenging, often necessitating different surgical approaches (case 2 needed a double surgical approach: posterolateral to the hip and ilioinguinal: almost full drainage of the intrapelvic collections has been performed through the acetabular medial wall defect and an ilioinguinal approach was used to complete the resection of the lesions) and a multidisciplinary surgical team with the presence of the vascular surgeon. Algarni et al. reported a case of an iliopsoas bursal cystic lesion generating a venous obstruction and a unilateral lower-limb swelling 5 years after a MoM total hip arthroplasty. The bursal cyst was communicating with the hip joint and severely compressing the femoral vein, and the surgical treatment consisted in drainage of the cyst, synovectomy, and replacement with a ceramic-on-ceramic bearing interface [35, 36]. We observed a similar complication (case 2), with a recurrent omolateral lower-limb swelling which led to two intrapelvic collection drainage procedures for venous obstruction before revision surgery. A previous unreported clinical manifestation, consisting in prolonged, severe, and unexplained constipation and abdominal pain related to initially undetected massive retroperitoneal pseudotumor, led to intrapelvic collection drainage procedure after THR revision surgery (case 3).

If cystic or solid pseudotumours become large enough, they can compress of stretch the surrounding soft tissues and cause necrosis. An impairment of abductor mechanism, not a typical complication of posterolateral approach, was observed in 4/14 cases (cases 1, 5, 6, 10); 3/4 were ARMD-related. In one case, we observed acute abductor mechanism deficit due to a spontaneous trochanter fracture (case 5), and during revision surgery, we found a peritrochanteric cystic pseudotumour and abundant granulomatous tissue infiltrating the great trochanter and widely infiltrating the diaphysis at the bone-prosthesis interface. Only in one patient did we observe a minor systemic arthroprosthetic cobaltism manifestation (case 13 shows a mild erythrocytosis with haematocrit > 50%; the patient is now waiting for revision surgery and by herself undergoes chelation therapy).

In ARMD-related THA failure, the open resection of the lesions and the replacement of the MoM articulation still remains the treatment of choice. Other authors well described some technical difficulties of these surgical procedures [37]. In our series, we replaced 6/11 cups, one of them for aseptic loosening (case 11), and one patient is waiting for revision (in case 14 cup revision is strongly recommended for aseptic loosening with intrapelvic protrusion and blood metal level rising, despite the patient is now asymptomatic). All the revisions have been done with cementless components secured with additional bone screws except one. In case 6, because

Table 4 *C* case, *G* gender, *IMoMI* indication for MoM implant, *IS* implant survival, *IRev* indication for implant revision, *OA* osteoarthritis, *AL* aseptic loosening, *DDH* developmental dysplasia of the hip, *ARMD* adverse reaction to metal debris, *ALVAL* hypersensitivity to metal particles, *AC* arthroprosthetic cobaltism, *WfR* waiting for revision

| C	G	IMoMI	IS	IRev	Clinical signs and symptoms	Acetabular cup revision	Bearing	Stem revision	Pre-operative and intraoperative macroscopic findings
1	F	OA	7	ARMD	Symptomatic pseudotumour: groin pain, painful mass extended posteriorly towards gluteal muscles with worsening impairment of abductor mechanism and hip function.	No (liner for dual mobility)	MoP	Yes (cementless straight monoblock long stem + femoral shaft cerclage wiring).	Osteolysis in Gruen's zones 1 and 7. Intraarticular and periarticulargranulomatous tissue with dark fluid collection.
2	F	OA	5	ARMD	Symptomatic pseudotumour: activity-related hip pain, painful mass extended towards gluteal muscles; secondary mass effect due to neurovascular compression: (1) hypoesthesia and paresthesia due to sciatic nerve irritation; (2) recurrent omolateral lower-limb swelling that led to 2 intrapelvic collection drainage procedures for venous obstruction before revision surgery.	Yes: multihole hemispherical cup secured with 3 cancellous bone screws + bone grafting (autologous bone and synthetic bone graft substitutes). Almost full drainage of the intrapelvic collections through the acetabular medial wall defect.	MoP	Yes (cementless straight monoblock long stem).	Osteolysis in Gruen's zones 1 and 2; acetabular medial wall defect (intrapelvic medial cup migration < 1 cm). Intraarticular and periarticular granulomatous tissue (foreign body granulomas-like), fluid collection and grayish caseous necrosis, extended from trochanteric bursa to intrapelvic area along the psoas sheath (double surgical approach needed: posterolateral to the hip and ilioinguinal approach).
3	M	OA	6	ARMD + ALVAL	Symptomatic pseudotumour: constipation and abdominal pain related to massive retroperitoneal intrapelvic cystic collection that led to intrapelvic collection drainage procedure after revision surgery.	No (liner for dual mobility).	CoP	No (stable stem, no tribocorrosion at the taper junction).	No signs of osteolysis, no macroscopic wear, and correct position of the components. Semi-cystic pseudotumor with milky liquid content and periarticular gray and folded hyperplastic reactive tissue. Enlarged iliopsoas muscle with a cystic collection within the muscular structure.
4	F	OA	8	ARMD	Symptomatic pseudotumour: worsening groin pain.	No (liner for dual mobility).	MoP	Yes (cementless straight modular stem + plate and wiring fixation for proximal femoral Wagner's osteotomy).	Osteolysis in Gruen's zones 1 and 7. Partially cystic intracapsular pseudotumor with toothpaste-like caseous and corpusculated content

Table 4 (continued)

C	G	IMoMI	IS	IRev	Clinical signs and symptoms	Acetabular cup revision	Bearing	Stem revision	Pre-operative and intraoperative macroscopic findings
									extended in the bone gaps in Gruen's zones 1 and 7.
5	M	AL	8	ARMD	Symptomatic pseudotumour: groin pain, aseptic loosening of the stem and acute abductor mechanism breaking due to spontaneous trochanter fracture (tissue reaction noted during revision surgery).	No (liner for dual mobility).	MoP	Yes (cementless straight modular stem).	Periprosthetic interface osteolysis in all Gruen's areas. Mobilized Stem. Peritrochanteric cystic pseudotumor with a coffee-colored liquid content and abundant brownish-grayish granulomatous tissue infiltrating the large trochanter (which appears fractured) and widely infiltrating the diaphysis at the bone-prosthesis interface.
6	F	DDH	9	ARMD	Symptomatic pseudotumour: rest pain, instability and loss of abductor mechanism.	Yes (homologous bone graft and synthetic bone graft substitutes + Ganz anti-protrusion ring + cemented cup + liner for dual mobility).	MoP	Yes (uncemented tapered stem).	Catastrophic periacetabular bone loss with wide acetabular bone deficit and osteolysis of the ischium. Large retro-peritoneal intra-abdominal cyst adherent to the iliac vessels and semi-cystic pseudotumor with dark liquid content and folded hyperplastic reactive walls, which from the bone defects reaches the pelvic cavity. Severe degeneration of abductors tendons.
7	M	OA	4	ARMD	Symptomatic pseudotumour: rest hip pain and painful mass.	Yes (non-cemented hemispherical cup secured with 2 cancellous bone screws, liner for dual mobility).	CoP	No (stable stem, no tribocorrosion at the taper junction).	No osteolysis in Gruen's zones. Good bone stock. Peritrochanteric multicystic pseudotumor filled with grayish turbid liquid and necrotic tissue debris.
8	F	OA	2	ARMD	Symptomatic pseudotumour: groin pain.	Yes (non-cemented hemispherical cup secured with 3 cancellous bone	MoP	No (stable stem, no tribocorrosion at the taper junction).	One drainage procedures before surgery. No infection detected. Fibrosis and muscle-fascial scar

Table 4 (continued)

C	G	IMoMI	IS	IRev	Clinical signs and symptoms	Acetabular cup revision	Bearing	Stem revision	Pre-operative and intraoperative macroscopic findings
						screws, liner for dual mobility).			adhesions. Peritrochanteric cystic pseudotumor with dark liquid and grayish-blackish folded capsule hard fibrous in consistency and strident. Acetabular osteolysis and cup loosening.
9	F	OA	10	ARMD	Symptomatic pseudotumour: rest hip pain worsening with activity.	Yes: multihole hemispherical cup fixed with 2 cancellous bone screws + synthetic bone graft substitutes.	CoC	Yes (cementless straight monoblock stem).	Osteolysis in acetabular bone with small bone defect. Cup loosening. Solid grayish pseudotumor in continuity with the acetabular dome defect.
10	F	OA	5	AL	No pseudotumour. Groin and thigh rest pain; abductor mechanism deficit.	No (liner for dual mobility).	MoP	Yes (cementless straight monoblock stem).	No macroscopic signs of metallosis. Loosened stem. Subsidence of the stem, pedestal sign below the tip and periprosthetic radiolucent line.
11	M	OA	4	AL	No pseudotumour. Groin pain.	Yes (non-cemented hemispherical cup secured with 2 cancellous bone screws+ bone grafting (autologous bone and synthetic bone graft substitutes).	MoP	No (stable stem, no tribocorrosion at the taper junction).	Cup loosening. Intrapelvic medial cup migration >1 cm. Bone deficit at the bottom and at the posterior wall of the acetabulum.
12	F	OA	7 WfR	ARMD + AL	Symptomatic pseudotumour: rest hip pain worsening with activity.	Not expected; cup appears stable at XR, CT, and scintigraphic imaging	Hard on soft	Recommended	Periprosthetic osteolysis in Gruen's zones 1, 2, 6, and 7, subsidence of the stem, periprosthetic cystic pseudotumor.
13	F	OA	7 WfR	ARMD +AC	Symptomatic pseudotumour: groin pain. Haematocrit >50%; chelation therapy in another hospital.	Not expected; cup appears stable at XR, CT and scintigraphic imaging.	Hard on soft	Probable: not clear implant loosening.	Periprosthetic osteolysis in Gruen's zones 1, 2, and 7, cystic pseudotumor.
14	F	DDH	10 WfR	AL	Asymptomatic patient. Blood metal level rising.	Recommended; intrapelvic protrusion and rotation of the cup.	Hard on soft/CoC	Not expected; not clear implant loosening.	Cup loosening: acetabular medial wall defect (intrapelvic medial cup migration <2 cm).

Fig. 2 Tribocorrosion in taper
and stem neck modular junctions
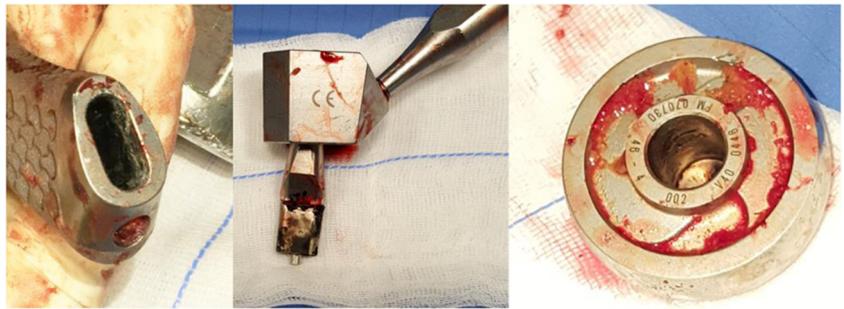
of a catastrophic periacetabular bone loss with wide acetabular bone deficit and osteolysis of the ischium, it was necessary to implant a Ganz anti-protrusion ring with a cemented cup and a liner for dual mobility in addition to homologous and synthetic bone graft. In other 3/5 ARMD-related cup revision, periacetabular defects made bone grafting necessary. Seven out of eleven femoral stem have been replaced (and two are waiting for revision). Additional procedures were performed: a femoral shaft cerclage wiring (case 1) and plate and wiring fixation for proximal femoral Wagner's osteotomy (case 4).

In all failure, MoM bearing has (or is waiting for) been replaced with hard on soft coupling.

The osteolysis is a widespread issue in metallosis-related failure. The osteolytic process is an immune response to the metallic debris triggering both the re-absorption of bone and particulate matter. Caicedo et al. suggested a monocyte-mediated mechanism towards a release of pro-inflammatory cytokines which contribute to metal-induced lymphocyte reactivity [38]. According to Tuan et al., there is an interaction among wear particles, macrophages, osteoblasts, bone marrow-derived mesenchymal stem cells, fibroblasts, endothelial cells, and T cells that contributes to the production of pro-inflammatory and pro-osteoclastogenic cytokines such as TNF-alpha, RANKL, M-SCF, PGE2, IL-1, IL-6, and IL-8. These cytokines not only promote osteoclast activation but can also interfere with osteogenesis [39]. The patients are complaining of joint pain and groin/buttock pain because of

compromission of the structural integrity of the bone and soft tissues. We observed bone defects in 11/14 cases. Six femur presented osteolysis, most commonly in great trochanter and calcar, and in six patients, we found a periacetabular bone loss ranging from small deficit to massive defects, which justified various intra-operative measures.

In one patient (case 3), we observed no blood metal level rising, no signs of osteolysis, no macroscopic wear or tribocorrosion at the taper junction, and correct position of the components but a massive retroperitoneal intrapelvic semi-cystic pseudotumor with milky liquid content and periarticular gray and folded hyperplastic reactive tissue. Histological examination showed a lymphocytic dominated reaction and an ALVAL was diagnosed. The hypersensitivity reaction (ALVAL) seems to represent an immune-mediated type IV delayed hypersensitivity reaction. It is manifested by surface ulcerations, leading to tissue inflammation, pain, abscess, and so on, and seems to result from activation by metallic nanoparticles of perivascular lymphocytes and macrophages. The wear debris is in the nanometric range and is phagocytosable by the cells of the immune system and may also form complexes with serum and tissue proteins and contribute to antigen presentation in the pathophysiology of metal hypersensitivity [40, 41]. This hypersensitivity phenomenon, not present in all patients, suggests that some patients may be more susceptible to metal debris. In support to this opinion, some articles showed implant failures in patients with correct positioning, non-pathologic levels of cobalt and chromium, and minimal wear rate of the components [42, 43]. So from one side, there can be an excessive wear of the bearing surfaces or the modular junctions causing a dose-dependent reaction to the accumulation of metal debris; from the other side, there can be hypersensitivity to metal particles that does not require substantial wear of the bearing surfaces.

The term pseudotumour is often used to indicate a wide spectrum of soft tissue lesions such as focal inflammatory reactions, necrotic regions, fluid collections of different compositions, wall thicknesses, and cystic or solid mass-like nodules of non-neoplastic and non-infectious origin. In our series, the description of macroscopic intra-operative findings greatly varies: intra-articular and periarticular granulomatous tissue with dark fluid

Fig. 3 Intrapelvic pseudotumour adherent to the iliac vessels

collection (cases 1 and 2); fluid collection and grayish caseous necrosis (case 2); semi-cystic pseudotumour with milky liquid content and periarticular gray and folded hyperplastic reactive tissue (case 3); semi-cystic intracapsular pseudotumour with toothpaste-like caseous and corpusculated content extended in the bone gaps (case 4); peritrochanteric cystic pseudotumour with a coffee-coloured liquid content and abundant brownish-grayish granulomatous tissue infiltrating all around the bone-prosthesis interface (case 5); peritrochanteric multicystic pseudotumour filled with grayish turbid liquid and necrotic tissue debris (case 7); fibrosis and muscle-fascial scar adhesions, peritrochanteric cystic pseudotumour with dark liquid and grayish-blackish folded capsule hard fibrous in consistency and strident to cut (case 8); solid grayish pseudotumour (case 9).

Considering the pleomorphic clinical spectrum of metallosis in total hip arthroplasty, a multimodal assessment of symptomatic and asymptomatic patients is obviously the most complete and sensitive way to detect the full spectrum of MoM-associated lesions. An annual (and eventually more frequent) monitoring of patients implanted is recommended and includes clinical examination, radiological examination, and metal ion level determination in blood.

The radiographic assessment is based on plain radiographs, which allows to identify implant loosening and major osteolytic areas but also to evaluate the positioning of the implant by measuring the inclination angle of the acetabular component and calculating the arc of cover, as well as eventual changes in serial controls. Cross-sectional imaging modalities are ultrasound (US) and metal artifact reduction sequence magnetic resonance imaging (MARS-MRI). US is mainly used to evaluate the superficial and peritrochanteric level. It is useful to identify tendon abnormalities and to well discriminates in between solid and cystic lesions but it is less useful in evaluating deep structures especially in obese patients and has limited function in the pre-operative planning [44]. CT scans are helpful in discriminating solid, cystic, and multicystic pseudotumours and in evaluating periprosthetic osteolytic areas in a better way than RX and MARS-MRI. The disadvantages are the non-optimal vision or the failure to detect many pseudotumours, the lack of reliability in the assessment of muscle atrophy, and the high amount of radiations. According to Robinson et al. [45], MARS-MRI is a modality that significantly reduces the susceptibility artifacts induced by metallic objects, thereby producing good quality images. It is superior to CT for the diagnosis and characterization of solid or cystic pseudotumours and muscle atrophy in order to decide the patient management and operative planning, but its use is limited by susceptibility artifacts that do not allow an optimal prosthesis-bone interface visualization. It requires an increased patient compliance because of increased scanning time. It is economically disadvantageous [43].

In our series, we only performed cross-sectional imaging in pre-operative assessment before revision surgery.

Metal ion measurement can be performed in blood, serum, and urine. Cobalt and chromium levels determination in whole blood has been widely used to monitoring MoM HA because of its practicality. We did not report blood ion levels because they were collected in an extremely inconsistent way (because of frequent lack of adequate laboratories, loss of many patients to follow-up, and refusal of many asymptomatic patients to undergo blood check).

The predictive value of metal ion blood levels for local and systemic effects is still controversial; nevertheless, in 2013, a European Consensus [46] suggested a regular metal ion monitoring in all patients (symptomatic and asymptomatic) with MoM bearing hip implants. In 2017, a Medical Device Alert from the Medicines and Healthcare products Regulatory Agency indicated in whole blood 7 ppb in one or both metals (chromium and cobalt) as the threshold values beyond which closer follow-up and cross-sectional imaging are needed. The device alert explains that the treatment and monitoring advices expressed do not include all clinical situations and each patient must be assessed individually [47]. Hart et al. provided additional information showing that the cut-off level of 7 μg/L provides a specific test but has a poor sensitivity (specificity 89% and sensitivity 52%) [48]. Considering these observations, the recommendation to set the threshold at 7 μg/L seems not anymore sufficient. According to these information, the European Consensus stated that cobalt-values without clinical concern are less than 2 μg/L and the threshold value for clinical concern is expected to be within the range of 2 to 7 μg/L even if the exact levels within this range have still to be determined [46, 48]. Every metal implant in the body can release metal ions [49]; therefore, the presence of multiple prostheses or even of less suspicious implants (such as partial resurfacing arthroplasty [50] with a less investigated metallo-organic compounds production from the metal on cartilage coupling) should be considered when interpreting metal ion blood levels.

Despite the extensive literature about the problem of metallosis, the patient's management is still uncertain and challenging. The surgical indication is strongly given only with severe pain, wide cystic or solid pseudotumour, or muscle damage. In other cases, there is not a clearly set management [51].

Conclusion

Every metallic implant has a potential local or systemic adverse effect, and low hazardous and biocompatible materials should be analyzed with in vitro toxicity studies and post mortem studies for safety evaluation. With regard to the risk of developing a metallosis, it is difficult to classify patients in

specific risk categories because of the presence of many variables (patient system, prosthetic system, patient-prosthesis composite system), some of which presumably still not known and some other unpredictable or unassessable (e.g., hypersensitivity reactions). Organizing a national registry of arthroplasty should be mandatory, in order to collect data about the patients, the surgery, the implanted device (with a careful post-marketing tracking), and the follow-up for all the procedures performed at a national level. The data collected in the registry will allow to analyze the implant survival and to better recognize the undesirable and sometimes unexpected effects of different biomaterials on the whole body.

Compliance with ethical standards

Conflict of interest   The authors declare that they have no conflict of interest.

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