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ORIGINAL PAPER

Aggressive granulomatosis of the hip: a forgotten mode of aseptic failure

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Abstract

Purpose It has been acknowledged that implant wear correlates with the risk for periprosthetic osteolysis, being aggressive granulomatosis the worst expression of bone resorption. We sought to determine the clinical, radiological, and histological features of aggressive granulomatosis after primary total hip arthroplasty (THA).

Methods We included nine cases with aggressive granulomatosis of the hip around cemented stems. Indications for revision THA consisted of progressive signs of extensive bone resorption or implant loosening. Mean follow-up since revision THA was 143 months (SD ± 59.4). We analysed clinical outcomes, component loosening and gross as well as histological characteristics of the granulomatous lesions.

Results Overall mean time between primary THA and revision surgery was 81 months (SD ± 20.8). All of the cases evidenced multiple ovoid tumour-like lesions around the stem with extensive bone loss. Only one case reported thigh pain before revision surgery, with radiological evidence of stem loosening; the remaining cases were asymptomatic with well-fixed implants. Gross anatomy findings revealed metallosis in the femoral canal and inside the cystic lesions. Pathology analysis showed monocyte-macrophage-dominated adverse foreign-body-type tissue reaction with fibroblastic reactive zones and granulomatous inflammation.

Conclusions We found a prevalence of 1% of this aseptic mode of implant failure. Since most of the retrieved stems were not loose, we did not find any alarming clinical symptoms anticipating implant failure. In this scenario, surgeons should be aware of the rapidly progressive nature of this entity and propose a revision THA in a timely fashion.

Keywords Aggressive granulomatosis · Total hip arthroplasty · Osteolysis

Introduction

Biocompatibility has been a matter of concern since the early development of total hip replacement (THR). Being initially under-reported, lysis around total joint biomaterials was the first of many complications to be described [1]. Originally, the so-called cement disease had been associated with the poor performance of cemented stems [2]; but later on, several in vitro and clinical studies have exhaustively reported on a high correlation between implant wear and the risk for periprosthetic osteolysis and aseptic loosening [3]. Thus, it is the 'particle disease' the one that triggers inflammatory pathways in cell recruitment, causing ultimately bone resorption through cytokine-mediated macrophage activation [4].

Osteolysis is likely multifactorial, but it is mainly affected by wear volume, which increases with use and patient activity. Usually, it takes time to generate wear debris, and osteolysis is

Level of Evidence: 4 - Retrospective case series

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uncommon before five years after THR, while the risk rises after ten years. [5] However, lysis may seldom develop rapidly in a destructive fashion. Harris et al. were the first to describe four cases of extensive, tumour-like femoral bone resorption around cemented stems [6]. This condition, called aggressive granulomatosis, is histopathologically characterised by a large number of granulomas and histiocytes [7, 8].

Tallroth et al. [8] and Santavirta et al. [9] have fully described the gross anatomy and immunopathological findings of aggressive granulomatous lesions around both cemented and uncemented hip replacements. However, after their publications, little has been reported on the incidence of this peculiar mode of rapidly progressive implant failure. Therefore, we sought to describe the clinical, radiological and histological features of aggressive granulomatosis after primary THR.

Material and methods

After obtaining approval of the institution's Research Ethics Board, we retrospectively analysed 2524 revision THRs operated at our centre between 1990 and 2016. Throughout this period, we performed 1031 one-stage revisions, 1370 two-stage revisions and 123 resection arthroplasties. Of the 1031 one-stage exchanges, 902 corresponded to aseptic revisions and 129 to chronic periprosthetic joint infections.

Of the 902 cases with aseptic loosening, we only focused on 10 cases (1.1%) that underwent revision arthroplasty due to aggressive granulomatosis of the hip, as prior outlined by Santavirta et al.'s criteria [9]. The authors defined this pathologic entity as localised, multiple ovoid tumour-like bone cysts which grow rapidly around the stem of either cemented or cementless THR, producing extensive bone resorption in the absence of infection [10]. Excluded from the study was one case with less than two year follow-up with incomplete radiographic assessment on our digitalised database.

Seven cases were female and two were male. Mean age at the time of revision surgery was 70.3 years (SD ± 6.9), whereas mean body mass index (BMI) was 24.87 (SD ± 2.9). Index diagnosis was primary osteoarthritis in five cases, hip dysplasia in three cases and Perthes sequelae in the remaining case. Two of the dysplasia cases were classified as grade A and one as grade B of the Hartofilakidis classification [11]. Except for one case, all primary surgeries were performed at our institution. One of the cases with Perthes disease had been treated with in situ pinning during childhood whereas another case with a history of hip dysplasia had been originally treated with a proximal femoral varus and derotational osteotomy during infanthood. The rest of the cases had not undergone previous procedures (Table 1).

All patients underwent primary hip arthroplasty between April 1991 and July 2007. In all cases, the index surgery involved a cemented stem (five Charnley stems [DePuy, Leeds, UK], two Muller stems [Zimmer, Winterthur, Switzerland] and two C-Stem stems [DePuy, Leeds, United Kingdom]). Acetabular reconstruction was performed with a Duraloc uncemented cup (DePuy, Leeds, United Kingdom) in four cases, an Ogee cemented cup (DePuy, Leeds, United Kingdom) in three cases and a Muller cemented cup (Zimmer, Winterthur, Switzerland) in the remaining two cases. These stems were made of either Ortron 90 cold-worked high-nitrogen stainless steel (Charnley and C-Stem stems) or 316L (AISI316L) stainless steel (Muller stem). The articulation consisted of metal-on-polyethylene bearing surfaces in all but one case in which it was ceramic-on-polyethylene. In all cases, polyethylene was non-highly crossed linked.

General indications for revision THR consisted of progressive signs of extensive bone resorption or implant loosening. All revisions were performed by one of two experienced hip reconstructive surgeons (M.A.B., F.P.). Under spinal anaesthesia, five of the included revisions were performed through a posterolateral approach whereas the remaining four were done through a transtrochanteric approach, both with the patient positioned in lateral decubitus. The rehabilitation protocol consisted of protected weight bearing with crutches during the first two post-operative weeks, with fixed range of motion exercises at 90° flexion, neutral internal rotation, 30° external rotation, and 45° abduction for three to six weeks. Progressive weight bearing was indicated as tolerated depending on radiographic findings at 45 post-operative days.

Demographic characteristics as well as functional and radiologic outcomes were obtained from the medical records of the prospectively collected database, which had been digitalized since 2003. These data were reviewed by four investigators (P.A.S., R.B., G. F., M.B.), three of whom were not involved in the original patient care (P.A.S., R.B., G.F.). Mean follow-up since revision THR was 143 months (SD ± 59.4). We evaluated intra-operative and post-operative complications, regardless of whether they were related to the surgical procedure, as previously portrayed by Saleh et al. [12] Radiologic evaluation was performed through a detailed assessment of an anteroposterior radiograph of the pelvis, and a false profile view. We analysed component loosening and location of the granulomatous lesions according to DeLee and Charnley [13] and Gruen et al. [14]. Femoral bone loss was certified with the Paprosky classification [15]. We computed whether granulomatous lesions were unique or multifocal. Fixation of the revised THR was defined through Engh's [16] criteria with the radiograph obtained at last follow-up. The Merle D'Aubigné and Postel [17] score was used to assess clinical outcomes.

Continuous variables were expressed as mean and range or SD. The Mann-Whitney *U* test was used for continuous variables, and Fisher's exact test was used for categorical variables. $P < .05$ was considered as statistically significant. No survival analysis was performed because of the small size of

Table 1 Demographic characteristics of the series

Case number	Sex/ age	BMI	Primary diagnosis	Prior surgery	Primary prosthesis (stem/cup)	Head size (mm)	Bearing surfaces
1	F/60	27	Osteoarthritis	No	Charnley/Duraloc	28	MoP
2	F/54	26,8	Osteoarthritis	No	Muller/Muller	22	MoP
3	F/57	23	Dysplasia grade A	No	C-Stem CDH/Duraloc	22	MoP
4	F/70	22	Osteoarthritis	No	Charnley/Ogee	22	MoP
5	F/62	25	Dysplasia grade A	No	Charnley/Duraloc	22	MoP
6	M/53	29,6	Perthes disease	In situ pinning	C-Stem/Duraloc	32	CoP
7	F/66	20	Osteoarthritis	No	Charnley/Ogee	22	MoP
8	F/53	23	Dysplasia grade B	Femoral osteotomy	Charnley SNS/Ogee	22	MoP
9	M/69	27,5	Osteoarthritis	No	Muller/Muller	28	MoP

BMI body mass index, *MoP* metal-on-polyethylene, *CoP* ceramic-on-polyethylene

the series. Statistical analysis was conducted with R software, version 2.7.0 (GNU; PSPP, Auckland, New Zealand).

Results

Overall mean time between primary THR and revision surgery was 81 months (SD ± 20.8). All of the cases evidenced multiple ovoid tumour-like lesions around the stem with extensive bone loss, which progressively grew in size and extent since their initial diagnosis (Fig. 1). The location of those well-circumscribed cysts was alongside different Gruen zones, as shown on Table 2. Mean preoperative serum erythrocyte sedimentation rate (ESD) and C reactive protein levels were 15.11 mm/h (SD ± 7.44) and 5.63 mg/L (SD ± 3.33), respectively. None of the patients had clinical signs or symptoms of a periprosthetic joint infection. Except for one case that experienced mild and inconsistent pain with activity, all patients referred no pain. Mean preoperative Merle D'Aubigné and Postel [17] score was 15.44 (SD ± 1.57).

The indication of revision surgery yielded mainly on the massive osteolysis around the femoral stems seen on radiological assessment (Table 3). None of the acetabular components presented with radiological evidence of osteolysis. At revision surgery, only one stem was found to be loose, while eight were well fixed. Five cases were revised with an impaction grafting technique with cemented stems [18]; two cases were treated with a modular, cementless stem with distal fixation (ZMR, Zimmer, Warsaw, Indiana, USA), whereas one case was treated with a proximally modular cementless femoral prosthesis with metaphyseal fixation (SROM, Depuy, Leeds, UK). None of the cups evidenced intraoperative signs of loosening. In five cases, the acetabular component was also revised in order to match the new femoral head size, whereas in four, the old cup was preserved (Table 2). In none of the cases, the polyethylene was found with clinically important signs of wear. Four of the bone defects were classified as Paprosky IIIB whereas five of them were typified as Paprosky IV. As for intraoperative complications, we registered a distal lateral cortical perforation with the stem trial in a femur reconstructed with an impaction grafting technique, which was bypassed by inserting a larger cemented stem.

Intra-operative cultures were negative for infection in all cases. Gross anatomy findings revealed moderate to intense metallosis in the femoral canal and inside the femoral cystic lesions (Fig. 2), which were delimited by a fibrous synovia-like membrane. Pathology analysis showed monocyte-macrophage-dominated adverse foreign-body-type tissue reaction with fibroblastic reactive zones and granulomatous inflammation (type IV hypersensitivity) around cement and metal particles (Fig. 3). Through light microscopy, the activated histiocytes appeared as epithelioid cells with round to oval nuclei, with irregular contours and abundant granular eosinophilic cytoplasm, coalescing to form multinucleated giant cells, as shown on Fig. 3. Occasionally, small perivascular lymphocyte infiltrates were also present.

Following revision surgery, there were no cases of aseptic loosening registered at final follow-up, and there were no recurrences of aggressive granulomatosis as well. Three of the impaction bone grafting cases developed a trochanteric non-union. Of those, two presented with isolated episodes of posterior dislocation, which were conservatively treated with closed reduction and bracing during 45 days. No other complications were computed. Mean Merle D'Aubigné and Postel [17] score was 15.55 (SD ± 1.57) at final follow-up, with no differences when compared to pre-operative values ($p = 0.88$).

Discussion

We have described a small series of patients with aggressive granulomatosis of the hip around cemented stems, with a

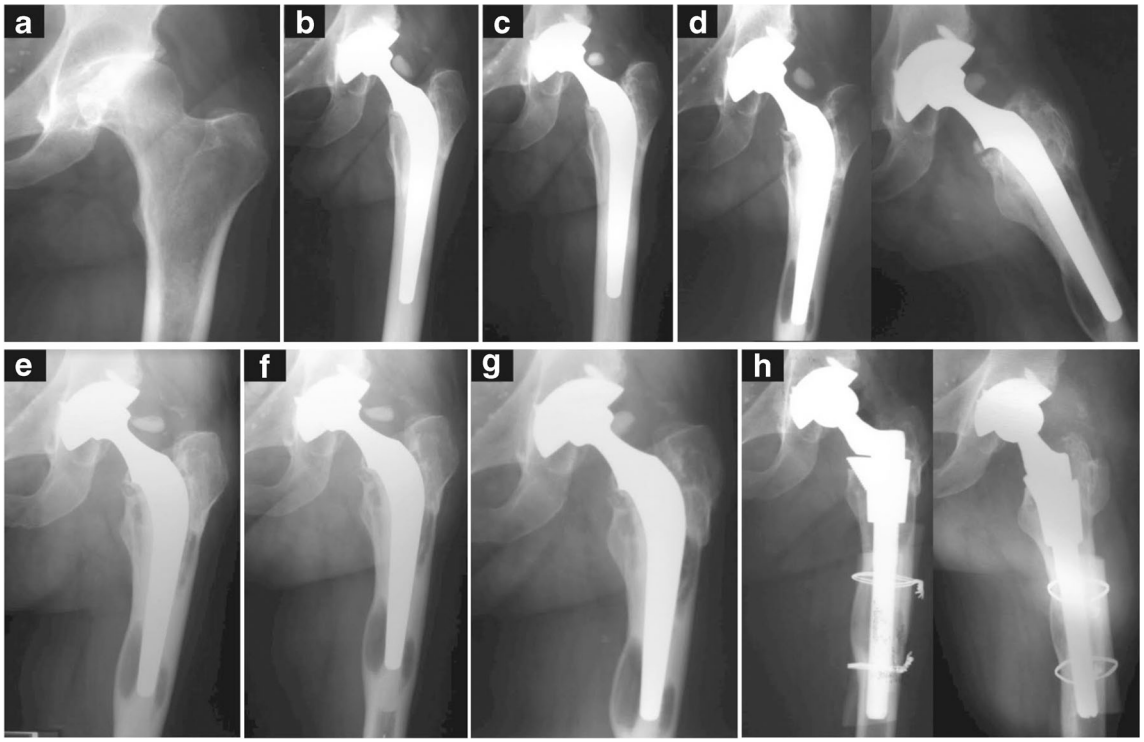

Fig. 1 **a** Anteroposterior left hip radiograph of a 69-year-old patient with subtle hip dysplasia showing secondary osteoarthritis and a coxa valga. **b** Immediate post-operative radiograph of the same patient's hip treated with a hybrid prosthesis (a 22-mm-Charnley femoral component and a Duraloc cup). **c** Post-operative radiograph at 1-year follow-up exhibiting a sound fixation of both components. **d** Post-operative anteroposterior and lateral radiographs of the same patient at 4 years of follow-up showing multiple ovoid tumour-like lesions around the stem located at Gruen's zones 2, 3 and 5; and initial bone resorption at zone 7. **e**–**g** Post-operative anteroposterior radiograph of the same patient's hip at 5 (**e**), 6 (**f**) and 7 years (**g**) of follow-up, depicting progressive bone loss associated with the growth in size with the ovoid lytic lesions, to the extent of producing thinning of the femoral cortex. Femoral bone loss was classified as Paprosky grade 3B. H. Although the patient was painless, a revision surgery was performed to prevent loosening and an eventual periprosthetic fracture. Revision total hip arthroplasty was performed with a proximally modular cementless femoral prosthesis with metaphyseal fixation (SROM, Depuy, Leeds, UK)

prevalence of 1% amongst all aseptic revisions performed at a single centre. Tallroth et al. [8] stated that less than 50 cases of aggressive granulomatous lesions around cemented stems had been reported by the early 90s. Since then, very few reports have been published on this unique type of implant failure [19–21]. Eskola et al. [22] pointed out that it should be considered as a separate pathologic entity since it differs clinically, radiologically and histopathologically from other types of loosening.

Table 2 Pre-operative clinical outcomes and intra-operative findings at revision surgery

Case number	Cysts (multiple/ solitary)	Site of granuloma (Gruen's zones)	Bone loss according to Paprosky	Metallosis (yes/no)	Pre-operative Merle D'Aubigné score
1	Multiple	2,3,5,6	3B	Yes	15
2	Multiple	1,2,3,5,6,7	4	Yes	14
3	Multiple	2,3,5,6	4	Yes	15
4	Multiple	2,6	3B	Yes	13
5	Multiple	2,3,5	3B	Yes	18
6	Multiple	3,4,5,6	4	Yes	18
7	Multiple	2,3,6	4	Yes	16
8	Multiple	2,3,5	4	Yes	15
9	Multiple	3,5	3B	Yes	15

Unlike these authors, we have found that only one of the included cases had radiological and intraoperative signs of loosening. In fact, we described that the mechanism of failure triggered by such tumour-like lesions was extensive osteolysis instead of loosening. In the series of 17 cases with granulomatous lesions described by Korovesis and Repanti [19], the histological findings of loose ($n = 13$) and non-loosened stems ($n = 4$) was exactly the same, suggesting that the mechanism of failure associated with cell macrophage-mediated osteolysis may be the same. Therefore, the advent of implant loosening seems to be a matter of time.

Actually, we described non-significant differences between pre and post-operative Merle D'Aubigné scores, adjudging this finding to the fact that, in general, loosening had not commenced at the time of revision. In this scenario, and different to what it has been reported, we have found a great clinicoradiological dissociation, since most of the cases were

Table 3 Type of revision total hip arthroplasty and post-operative clinical outcomes at final follow-up

Case number	Time to revision (months)	Revision technique	Revision prosthesis (stem/cup)	Cup revision? (Y/N)	Head size (mm)	Bearing surfaces	Follow-up (months)	Post-operative Merle D'Aubigné score	Complications
1	44	IBG	Revision C-Stem/Duraloc	N	32	MoP	102	16	Cortical perforation/TNU
2	73	IBG	C-Stem/Pinnacle	Y	32	MoP	128	17	–
3	55	IBG	CPT/Duraloc	N	22	MoP	100	16	TNU/dislocation
4	70	IBG	Revision C-Stem/Duraloc	Y	28	MoP	163	12	TNU/dislocation
5	91	Metaphyseal fixation	SROM/Duraloc	N	32	MoP	133	17	–
6	97	Distal fixation	ZMR/Duraloc	N	32	MoP	61	17	–
7	86	IBG	Revision C-Stem/Duraloc	Y	32	MoP	124	16	–
8	113	IBG	C-stem/Duraloc	Y	32	MoP	119	14	–
9	97	Distal fixation	MP/Delta	Y	36	MoP	24	15	–

IBG impaction bone grafting, *Y* yes, *N* no, *MoP* metal-on-polyethylene, *TNU* trochanteric non-union

painless when surgery was indicated. However, we believe that the indication of revision surgery must be as soon as the diagnosis of this entity is suspected, irrespective of implant fixation, as granulomas may grow to double their original size just in a few months [8]. Santavirta et al. reported on six cases with aggressive granulomatous lesions that, in the time period from diagnosis to revision, all granulomas had grown large in size; and while waiting for revision operation, two femoral stem components fractured [10]. Thus, it has been advocated that revision surgery should be indicated soon after diagnosis [20].

The underlying cause of aggressive granulomatosis remains as a matter of controversy. Polymethyl-methacrylate (PMMA) is fairly inert as long as implants remain well fixed [2]. However, the first reports of aggressive granulomatosis were related to fragmentation of the cement mantle and failure of fixation [6]. Surprisingly, the fact that most of the retrieved implants were considered as well fixed at revision THR seems to jeopardise this theory [8]. We found plenty of foreign-body granulomas around metal and cement particles, apparently mediated by activated macrophages. This issue suggests a mode of delayed-type (type IV) hypersensitivity, which had already been described as a result of metal-on-metal bearings [23]. In fact, it is a quite similar reaction to the one nominated as 'aseptic lymphocytic vasculitis-associated lesion' (ALVAL) [24], which was originally found in the soft-tissue pseudotumors around metal debris [25, 26]. Additionally, Goldring et al. [7] reported in the early 80s that the fibrous

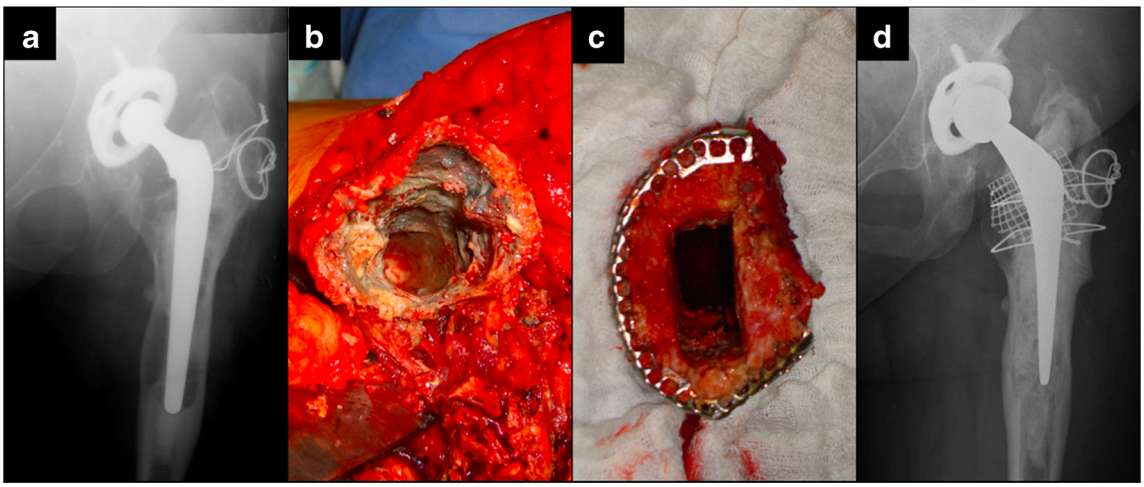

Fig. 2 **a** Post-operative radiograph of the 52-year-old female's left hip with a cemented Charnley Straight Narrow Stem (SNS) at 9 years following the surgical treatment of a dysplastic coxarthritis. Well-circumscribed tumour-like lesions are visible at Gruen's zones 2, 3, 5 and 6. **b** Intra-operative image after prosthesis and cement extraction evidencing extensive metallosis and a massive bone loss (Paprosky grade 4). **c** Intra-operative image showing reconstruction with impaction grafting technique. **d** Post-operative radiograph of the same patient's hip following revision surgery with a cemented short stem (C-Stem, Depuy, Leeds, UK)

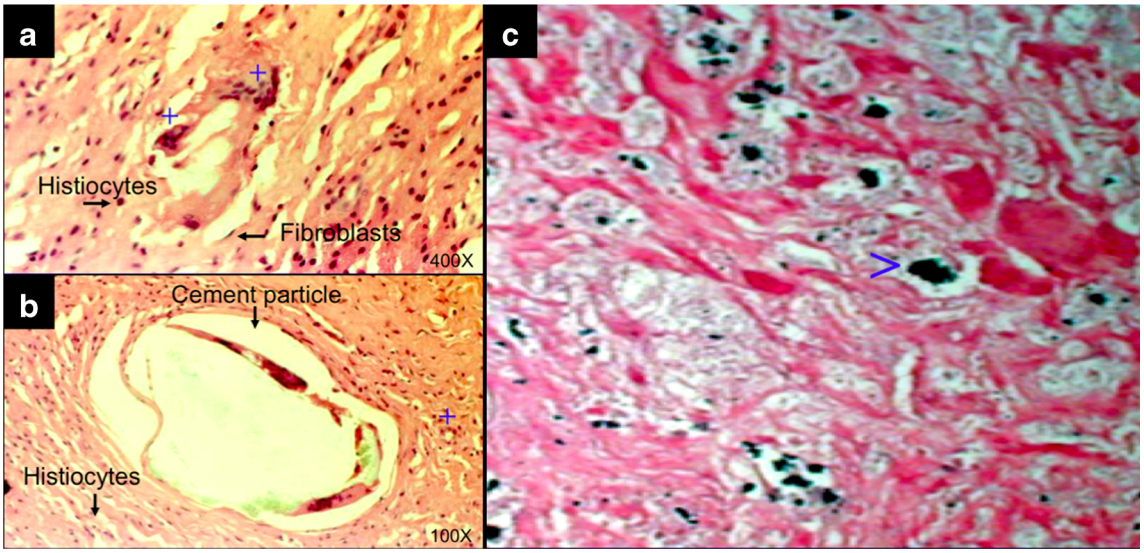

Fig. 3 Histological images of the biopsy obtained following revision surgery of a 69-year-old patient with aggressive granulomatosis of the hip. **a** Augmentation (× 400) image seen at the optical microscope, showing activated histiocytes as epithelioid cells with round to oval nuclei and granular eosinophilic cytoplasm, coalescing to form multinucleated giant cells (+). Abundant fibroblasts can be observed in contact with the histiocytes. **b** Augmentation (× 100) image displaying monocyte-macrophage-dominated adverse foreign-body-type reaction around a cement particle. Multinucleated histiocytes (+) can be observed around in the periphery. **c** Augmentation (× 600) image exhibiting multiple multinucleated giant cells with irregular contours (granulomas) in foreign-body reactions around metal particles (>)

membrane present at the bone-cement interface of loose implants had the ability to synthesise prostaglandin E2 and collagenase, which enhance bone resorption. Although speculative, the membrane seen around the tumour-like cystic lesions of aggressive granulomatosis is thought to be biologically active [27]. Nonetheless, we were unable to study the biochemical properties of this membrane at the time the prosthesis were retrieved.

The ideal metal alloy for cemented stem fixation has historically been a matter of concern. Stainless steel is rarely used in modern THR, since newer metal alloys of cobalt chrome are stronger and have more corrosion- and wear-resistance than the former [28]. In this series, we described three different stems made of either Ortron 90 cold-worked high-nitrogen stainless steel (Charnley and C-Stem stems) or 316L (AISI316L) stainless steel (Muller stem). Early work by Joshi et al. demonstrated that stainless steel stems were associated with a high rate (14.9%) of osteolysis at a minimum ten year follow-up, yet this incidence decreased with cement mantles of 3 mm in all femoral zones and with a stem/canal ratio of 60 to 70% [29]. Conversely, a post-mortem analysis of eight well-fixed Muller stems with a mean follow-up of 12 years revealed that although two cases developed femoral osteolysis, an incomplete cement mantle was found in all implants, being this issue non-essential for mid-term implant survival [30]. It is undeniable that stainless steel components undergo corrosion after implantation. Although corrosion is supposedly slow, it mainly depends on the impurities of the design and the size of the metal grain particles [28]. Additionally, stainless steel implants carry a higher modulus of elasticity (200 Gpa) than that of the bone (20 Gpa); thus, they must be implanted with a low-modulus cement (PMMA) to alleviate the potential stress-shielding effect of the high-modulus metal [31]. In this sense, it is not only the metal composition but also the structure of the cement mantle around the metal that enhances corrosion and metal debris, therefore triggering an inflammatory response [32]. Still, the exact cause of this quickly developed osteolysis around stainless steel stems remains unclear.

Despite its low prevalence, we consider aggressive granulomatosis as a rapidly devastating mode of implant failure. Given that it is impossible to know if all of the cemented stems inserted during the study period developed the same histological delayed-type hypersensitivity but without gross granuloma formation, we could speculate that some patient-related factors might be inherent. Currently, evidence suggests that metal hypersensitivity must be recognised since there might be an association between metallic total joint arthroplasty implants and hypersensitivity reactions that can potentially lead to aseptic implant failure [33]. Guenther et al. [34] concluded that allergic patients should be thoroughly educated about potential reactions resulting from implant choice, since in their study, 2% of cases were revised due to confirmed allergic reactions.

The current study had several limitations. First, its retrospective nature correlated with the biases exclusive to the study design. Despite studying a consecutive series of patients with aggressive granulomatosis, the series was small and did not include a control group of patients with ordinary loosening or osteolysis to compare radiological and histological

outcomes. Second, the small number of the series restrained the possibility of making categorical conclusions about the clinical and histological findings that can be found in this group of patients. Third, the histological examination carried out at the time of the retrieval analysis did not include more precise and thorough staining techniques such as immunochemical biomarkers. Santavirta et al.'s [9] immunohistological evaluation revealed that most of the cells in the aggressive granulomatous tissue were multinucleated giant cells and C3bi-receptor and nonspecific esterase-positive monocyte-macrophages. Likewise, we were also unable to study the biological potential of the synovia-like membrane circumscribing the pathologic cysts, which might have add valuable information about the pathogenesis of this unusual disease. Fourth, we did not study the retrieved prosthetic components with finite element analyses in order to inspect all metallic and polyethylene components for evidence of gross deformation, microfracture, and damage to articulating surfaces [35]. Finally, since the described phenomenon resembles the mode of failure of metal-on-metal bearings, it might have been useful to document serum metal ion levels in these cases, despite this issue being controversially associated with ALVAL and pseudotumour formation. [24]

In summary, we found a prevalence of 1% of this aseptic mode of implant failure. It was characterised by extensive bone loss produced by well-circumscribed tumour-like cystic lesions around well-fixed cemented stems. Since most of the retrieved stems were not loose, we did not find any alarming clinical symptoms anticipating implant failure. In this scenario, surgeons should be aware of the rapidly progressive nature of this entity and propose a revision THR in a timely fashion.

Compliance with ethical standards

Conflicts of interest Each author certifies that he has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article. No funding/grant was received for the development of this research. On behalf of all authors, the corresponding author states that there is no conflict of interest. Each author certifies that his institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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