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CASE REPORT

Rare complications of osteolysis and periprosthetic tissue reactions after hybrid and non-hybrid total disc replacement

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Abstract
Purpose Few complications have been reported for lumbar total disc replacement (TDR) and hybrid TDR fixations. This study evaluated retrieved implants and periprosthetic tissue reactions for two cases of osteolysis following disc arthroplasty with ProDisc-L prostheses.
Methods Implants were examined for wear and surface damage, and tissues for inflammation, polyethylene wear debris (polarized light microscopy) and metal debris (energy-dispersive X-ray spectroscopy).
Results Despite initial good surgical outcomes, osteolytic cysts were noted in both patients at vertebrae adjacent to the implants. For the hybrid TDR case, heterotopic ossification and tissue necrosis due to wear-induced inflammation were observed. In contrast, the non-hybrid implant showed signs of abrasion and impingement, and inflammation was observed in tissue regions with metal and polyethylene wear debris.
Conclusions In both cases, wear debris and inflammation may have contributed to osteolysis. Surgeons using ProDisc prostheses should be aware of these rare complications.

Keywords Chronic inflammation · Hybrid fixation · Metal wear debris · Osteolysis · Polyethylene wear debris · Total disc replacement

Introduction

TDR is an established alternative to lumbar fusion for the treatment of back and leg pain that is associated with degenerative disc disease (DDD). In cases of 2-level DDD, hybrid fixation is a new approach that involves combining the advantages of TDR with spinal fusion at the adjacent level. This approach preserves motion at one level and maintains stiffness in the lower segment to prevent adjacent segment degeneration. Although the majority of patients attain clinically significant pain reduction after 1-level TDR or hybrid fixation, foreign-body response to wear debris and rare osteolysis instances have been noted for other devices. Historical generations of polyethylene-core TDRs such as the CHARITÉ (originally Waldemar Link, Hamburg, Germany, later fabricated by DePuy Spine, Raynham, MA, USA and currently discontinued) have shown evidence of polyethylene wear debris in periprosthetic tissues, accompanied by histological changes, the presence of histiocytes and multinuclear giant cells [2, 3]. As a consequence of adhesive/abrasive wear mechanisms, polyethylene wear particles are released and then ingested by resident macrophages initiating a chronic immune

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response that can lead to osteolysis [4]. Evidence of lumbar periprosthetic osteolysis appeared in 1 of 21 implant revisions from 18 patients who received a CHARITÉ in a previously reported study, but little is known about osteolysis around ProDisc-L implants [3].

Interestingly, in the aforementioned study, osteolysis occurred in a patient that underwent hybrid fixation. This raises the question of whether the combination of TDR and fusion may create a loading and kinematic environment conducive to potential osteolysis. Another potential factor that may contribute to osteolysis in the spine is the use of bone morphogenic protein (BMP) during fusion. McKay et al. [5, 6] noted that resorption rates around the implant increase with the use of BMP-2, presumably due to BMP-induced enhancement of osteoclast activity, which results in vertebral osteolysis.

The purpose of this study was to report two unusual osteolysis cases after ProDisc-L lumbar disc replacement—one in which the patient underwent TDR at the level superior to BMP-induced interbody fusion at L5-L6 and another who had similar osteolytic lesions after 1-level TDR without any exposure to BMP-2. Both patients underwent TDR with ProDisc-L (Synthes, West Chester, PA, USA) prosthesis, which consists of an ultra-high molecular weight polyethylene (UHMWPE) core and two metallic endplates made of a cobalt-chromium (CoCr) alloy, similar to the CHARITÉ [7]. However, unlike the CHARITÉ, the UHMWPE core of ProDisc-L is locked into the inferior endplate, thus allowing relative motion only between the core and the superior endplate. To our knowledge, there have been no previous reports of osteolysis with the use of ProDisc-L.

Materials and methods

Two patients who suffered from lumbar disc herniation and radiculopathy underwent surgery. One patient required multi-level treatment and opted for hybrid fixation with ProDisc-L TDR and fusion, while the other received 1-level ProDisc-L TDR. Both TDRs were extracted during revision surgery and periprosthetic tissue specimens selected from regions adjacent to the implant were obtained. Retrievals, operative notes and radiographs were de-identified and collected in accordance with an IRB-approved protocol.

Implant retrieval analysis

The two sets of retrieved components were cleaned in 10 % bleach and examined under a stereomicroscope equipped with a digital camera (Leica DFC490) to assess for surface damage and gross fracture. All components were inspected to identify surface damage mechanisms (plastic deformation, scratching, burnishing, pitting, and embedded debris). Damaged regions of the implants were analyzed using scanning electron microscopy (SEM; Supra 50 VP, Zeiss Peabody, MA, USA), energy-dispersive X-ray spectroscopy (EDS) and x-ray fluorescence (XRF).

Tissue Preparation and Histological Analysis

Tissues collected from revision surgeries were fixed in Universal Tissue Fixative (Sakura Finetek USA, Inc., Torrance, CA, USA), and decalcified based on the presence of heterotopic ossification determined by microCT (μCT 80, Scanco Medical, Brüttisellen, Switzerland). One to two 4-mm punches from each tissue, considering variations in color, texture, and size of specimen, were embedded in paraffin blocks for 6-μm serial sectioning and staining with Alcian blue (Electron Microscopy Sciences, Hatfield, PA, USA), hematoxylin, and eosin (H&E) (ThermoFisher Scientific, Waltham, MA, USA). Entire tissue sections were imaged under transmitted light microscopy using a Motic BA300POL microscope (Motic, Richmond, British Columbia, Canada), equipped with an elliptically polarized light imaging system and ProgRes SpeedXT core 5 (Jenoptik, Jena, Germany) microscope camera. Inflammatory cells were confirmed using the Wright-Giemsa stain (Electron Microscopy Sciences, Hatfield, PA, USA). Tissues with notable chronic inflammation were examined using environmental scanning electron microscopy (ESEM; XL-30 ESEM-FEG, FEI Company, Hillsboro, OR, USA) with backscatter and were analyzed with EDS.

Case reports

Case 1

A 40-year-old male suffering from discogenic collapse with lower back pain and radiculopathy at L5-S1 underwent anterior discectomy at L5-S1 and interbody arthrodesis with 17×24 mm titanium-threaded fusion cages filled with BMP-2. A few months later, a posteriorly displaced cage, along with osteophyte formation and foraminal stenosis, required the patient to undergo revision of the cage. Segmental pedicle screws were used to stabilize the cage on the right side; 6.5 mm Xia (Stryker Spine, Allendale, NJ, USA) pedicle screws were inserted at L5 and S1. Once the cages were locked, posterior interbody arthrodesis was then implemented at L5-S1 with the use of BMP-2 in two small sponges placed between each cage. One year later, with continued back pain and disc herniation at L4–L5, the patient opted for hybrid fixation and underwent anterior interbody placement of 12 mm-large and 6-degree

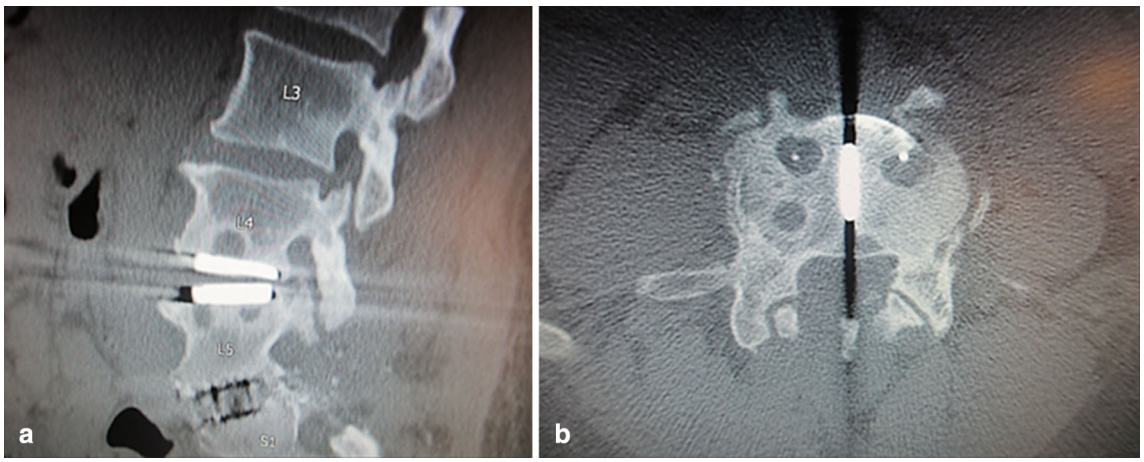


Fig. 1 Sagittal (**a**) and axial (**b**) CT scans from case 1 illustrating discogenic herniation and osteolytic cysts at inferior L4 and superior L5. The axial scan also shows that there may be facet osteophytes and nerve root compression at the foramen

Table 1 Clinical information for the hybrid (case 1) and non-hybrid (case 2) cases

Implant	Level	Sex	Age at implantation	Age at revision	Primary diagnosis	Revision reason	Previoussurgeries	Implantation time
Case 1	L4–L5	M	41	46	Lumbar disc herniation, radiculopathy	Pain, osteolysis	11	5 years
Case 2	L4–L5	M	56	59	Lumbar disc herniation, radiculopathy	Pain, subsidence, osteolysis	4	3 years

ProDisc-L at L4–L5. The following year, the pedicle screw instrumentation at L5-S1 was removed and there was solid fusion at the level. The patient also required mass resection of osteophytes, other bony spurs and scar tissue.

Three years after fusion, persistent patient pain and severe arthropathy and degeneration was noted at right L4–L5. Posterior fusion was undertaken; 6.5 mm screws were inserted and a PEEK rod was implemented at L4–L5, followed by posterolateral arthrodesis using local bone autograft, BMP-2, and DBX Demineralized Bone Matrix Allograft (Musculoskeletal Transplant Foundation, Edison, NJ, USA). However, computed tomographic (CT) scans in the following year revealed osteolytic cysts at L4–L5 (Fig. 1). The PEEK rod stabilization system and artificial disc were removed and sent for retrieval analysis. Preoperative work up and intraoperative cultures ruled out infection. Tissue samples adjacent to the disc were also removed for histological analysis. An overview of clinical information is provided in Table 1.

Device retrieval analysis

The ProDisc-L prosthesis was retrieved 5 years after implantation. Due to iatrogenic damage, we could not determine if the core's rims experienced impingement with the superior endplate (see Online Resource Fig. 1). While the backside surface also experienced iatrogenic damage, there was evidence of burnishing and scratching that occurred in vivo. There were no obvious signs of impingement on the metallic endplates, and the abrasive scratches were not patterned in any physiological manner, suggesting they occurred during device removal. Analysis using SEM and EDS revealed no abnormal surface deposits on the metallic endplates. As expected, XRF scans consistently detected cobalt-chromium ratios matching ASTM F-75 cobalt alloy weight-standards in the interior of the endplates, and the exterior plasma-coated elements consisted of alloy compositions seen in commercially pure titanium.

Tissue analysis

Periprosthetic tissues from this patient were obtained from two unclassified regions around the implant. One region was identified as predominantly fibrocartilage and the other region was mature trabecular bone. One isolated region in the fibrocartilage tissue contained hemosiderin deposits and macrophages, consistent with an innate response to hemorrhage prior to explantation. Large areas of the surrounding tissue were also necrotic due to inflammation. There was no evidence of metal wear debris in any tissues and only minor polyethylene debris was detected in

Table 2 An overview of tissue morphology for the two cases

Implant	Tissue location	Degeneration	Bone/cartilage	Hemosiderin	Innate/adaptive inflammation	PE Wear debris (particles/mm^2)	Metal wear debris
Case 1	*Region 1	No	No/yes	Minor	Minor/no	None	No
	*Region 2	Yes	Yes/none	None	No/No	1.13	No
Case 2	Lateral annulus I	No	No/isolated	None	No/no	None	No
	Lateral annulus II	Yes	Isolated/yes	None	No/no	None	No
	Left lateral	Yes	No/yes	Moderate; isolated	Moderate/no	None	No
	Lateral spur I	Yes	Yes/isolated	None	No/no	None	No
	Lateral spur II	Yes	Yes/no	None	No/no	None	No
	Posterior lateral	Yes	Yes/no	Mild	Moderate/yes	2.74	No
	Superior end plate	No	Yes/no	None	No/no	None	No
	Left cyst	No	Isolated/no	Mild	Severe/yes	2.96	Yes
	Right cyst	Isolated	Isolated/no	Moderate	Severe/yes	2.88	Yes
	Inner cyst	Yes	No/no	Moderate	Severe/yes	2.90	Yes
	Intradiscal	Isolated	Isolated/isolated	Moderate; isolated	Severe/yes	None	Yes
	Right intradiscal	No	No/no	Severe	Moderate/yes	None	Yes
	Posterior intradiscal	Yes	No/no	Mild; isolated	Moderate/yes	1.01	Yes
	Anterior intradiscal	Yes	Yes/yes	None	No/no	1.25	No

* Exact tissue region of extraction is unknown

isolated regions of the trabecular bone at a mean density of 1.13 particles/mm^2. In bony tissue samples, the fatty marrow in the intertrabecular spaces contained only a small number of viable cells; isolated regions of these samples consisted of necrotic bone marrow along with necrotic bone with empty osteocyte lacunae (see Online Resource Fig. 2). An overview of tissue morphology is provided in Table 2.

Case 2

A 56-year-old male with a herniated disc and radiculopathy at L4–L5 underwent anterior TDR with a 10 mm-large and 6-degree ProDisc-L. Three years after, subsidence of disc was noted at L4 on the right side, along with the formation of osteolytic cysts in CT scans at L5 that appear similar to the lesions seen in case 1 (Fig. 2). Progressive back pain led to removal of ProDisc-L, followed by placement of 22 mm PEEK interbody graft filled with BMP-2 for interbody fusion at L4–L5. Preoperative workup and intraoperative cultures were negative for infection.

Device retrieval analysis

The ProDisc-L prosthesis was retrieved 3 years after implantation. There was clear evidence of chronic impingement between the endplates and burnishing at the core's edge; microscopic scratches of fan-shaped pattern were found on the interior of the metallic plates and a glossy appearance on the polyethylene core, respectively (Fig. 3). SEM images of the impinged regions showed a polished appearance in comparison to the as-manufactured texture seen in non-impinged regions of the metallic plate. The unidirectional and circumferential wear patterns seen on the endplates suggest the wear may have occurred during axial rotation and/or lateral bending of the articulating surfaces. The impingement was most likely due to implant subsidence which was observed by the surgeon during surgery. The dome of the core also had evidence of multi-directional scratches and burnishing. There were no indications of fatigue wear or fracture of the polyethylene core. No abnormal surface deposits were observed by SEM/EDS analysis. XRF scans showed the metallic surface-constituents on the interior of the endplates consistently matched CoCr ratios seen in ASTM F-75 cobalt alloy standards, and the exterior of plates consisted of weight compositions seen in commercially pure titanium.

Tissue analysis

The periprosthetic tissues in this patient showed several abnormalities such as progressive degeneration, varied inflammation levels, and metal and polyethylene wear debris (Table 2). While degeneration was observed in tissues from various regions, inflammation was predominantly in the intradiscal and cyst tissue; there were no signs of inflammation in tissues from the lateral annulus, left lateral, lateral spur, superior end plate and anterior intradiscal regions. Cyst tissue from L5 regions showed signs of

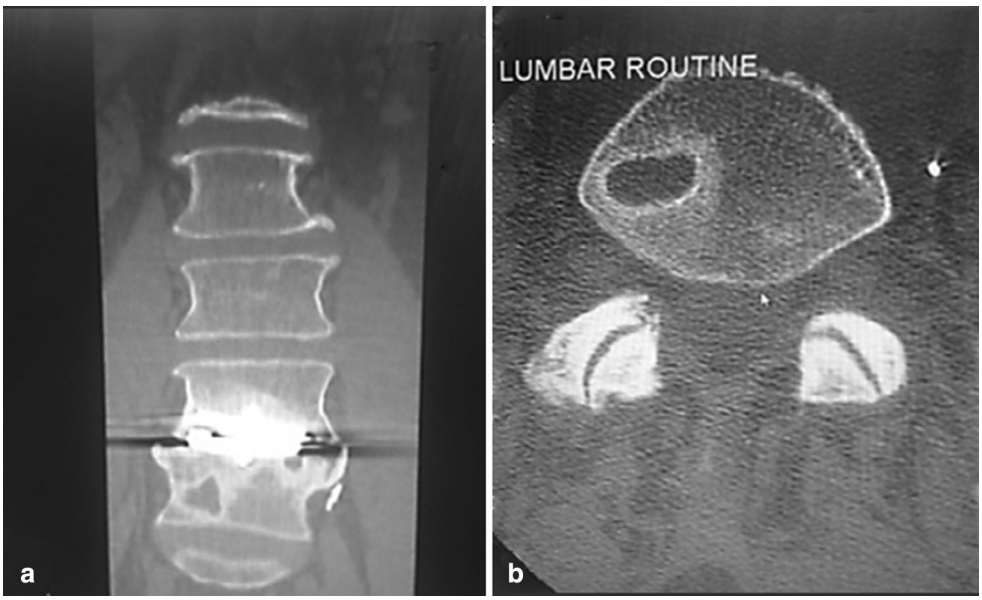


Fig. 2 Sagittal (**a**) and axial (**b**) CT scans from case 2 showing L4 subsidence on the right side of the vertebra and one large osteolytic cyst in L5. Smaller osteolytic formations are also evident at superior L5

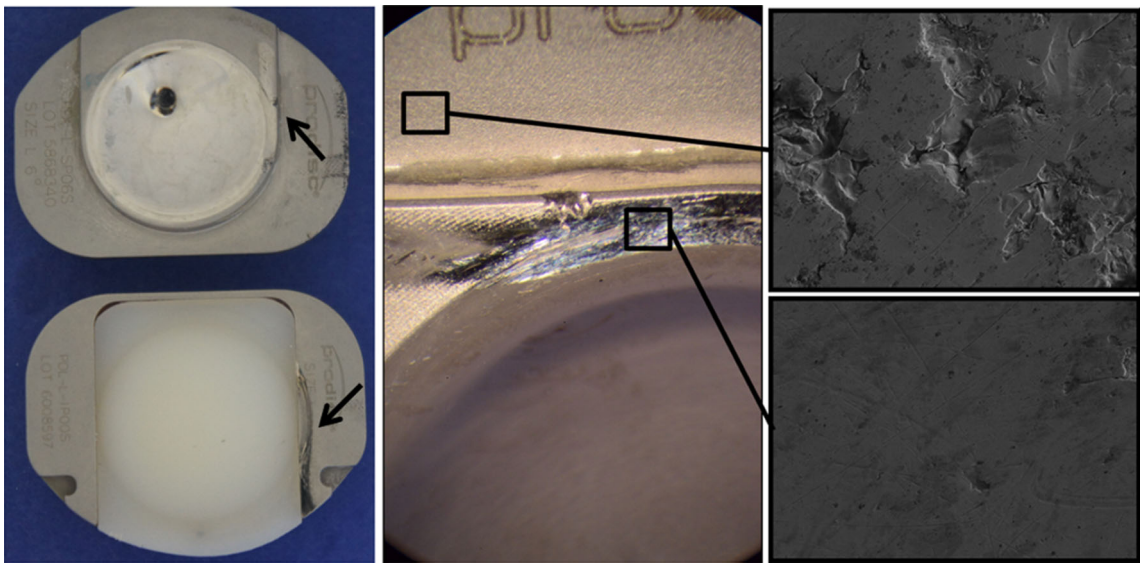


Fig. 3 Retrieved ProDisc-L TDR, 3 years after insertion. Note the signs of impingement on both endplates (*arrows*). The impinged region on the metallic plate (*lower right*) has a smooth surface compared to the unimpinged region (*upper right*)

both innate and adaptive immune response; macrophage ingested metal-wear-debris was present throughout the tissue and isolated areas of lymphocytes were also present (Fig. 4). Cyst and intradiscal tissues also contained hemosiderin deposits (not shown), suggesting a prior hemorrhage that may have contributed to or exacerbated the chronic inflammation. To confirm metallic wear debris, tissues with notable inflammation were examined by ESEM using backscatter and were analyzed with EDS. The particles from cyst and intradiscal tissues were predominantly cobalt and chromium, however, titanium was also detected (Fig. 5). Polyethylene wear debris was present in relatively low numbers in all cyst, posterior-intradiscal, anterior-intradiscal and posterior-lateral tissues. The mean polyethylene particles in these tissues was 2.08 particles/mm^2. These particles varied from oval to amorphous in shape and were localized to regions of chronic inflammation (Fig. 6).

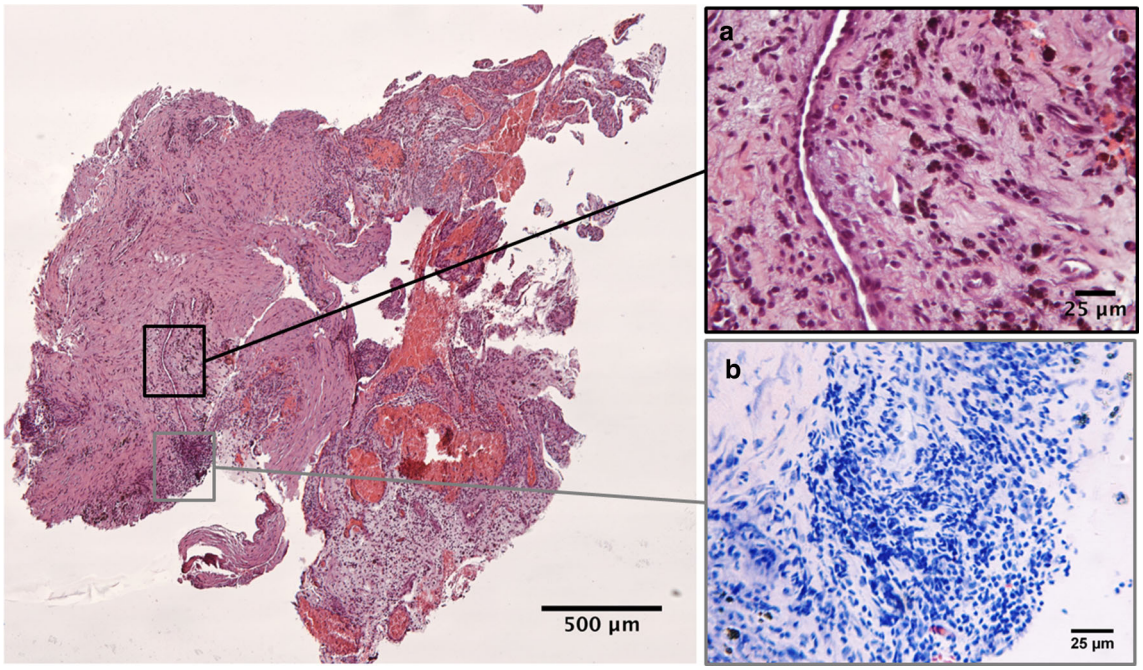
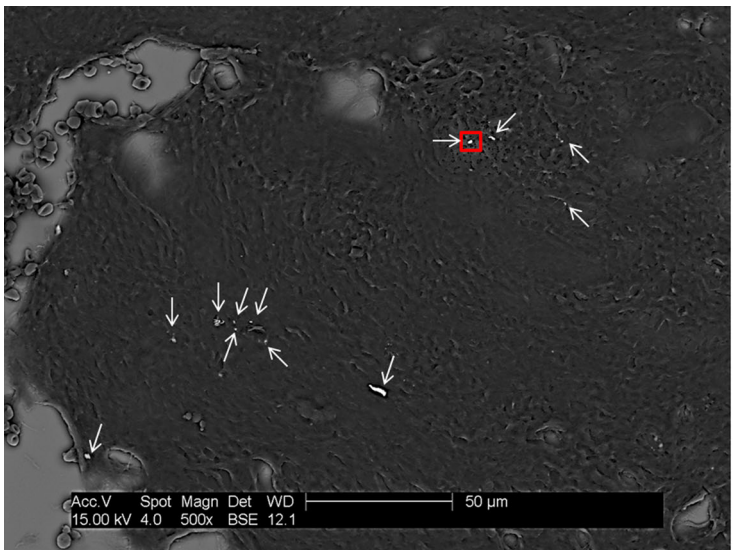
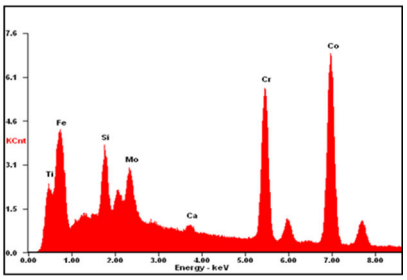


Fig. 4 Histology of inner-cyst tissue with H/E stain showing mixed inflammation throughout. *Inset* A shows presence of macrophage-ingested metallic debris (H/E, 400×). Inset B shows presence of lymphocytes in the tissue (Wright-Giemsa, 400×)





Element	Wt%	At%
TiL	17.09	19.46
FeL	20.09	19.61
SiK	01.94	03.77
MoL	03.56	02.02
CaK	00.35	00.48
CrK	15.75	16.52
CoK	41.22	38.14
Matrix	Correction	ZAF

Fig. 5 Titanium alloy and cobalt-chrome particles (*arrows*) were confirmed by use of backscatter scanning electron microscopy with elemental dispersive spectroscopy. Analysis of a region of interest (*square*) evidenced cobalt as the most abundant metal visualized by scanning electron microscopy. *Wt* weight, *At* atomic weight

Discussion

This study reported two unusual cases of osteolysis in TDR patients with a ProDisc-L. The first patient suffered from multi-level DDD and opted for hybrid fixation, while the second had a 1-level TDR. Both patients developed osteolytic lesions in vertebrae adjacent to the prostheses. Infection was ruled out in both cases. Retrieval and histological analysis of the hybrid case showed minor amounts of wear, however, tissue responses included fibrocartilage generation, heterotopic ossification, and necrosis due to inflammation. The second case showed signs of endplate impingement and adverse local tissue reactions (ALTRs) in intradiscal and cystic tissues. In this

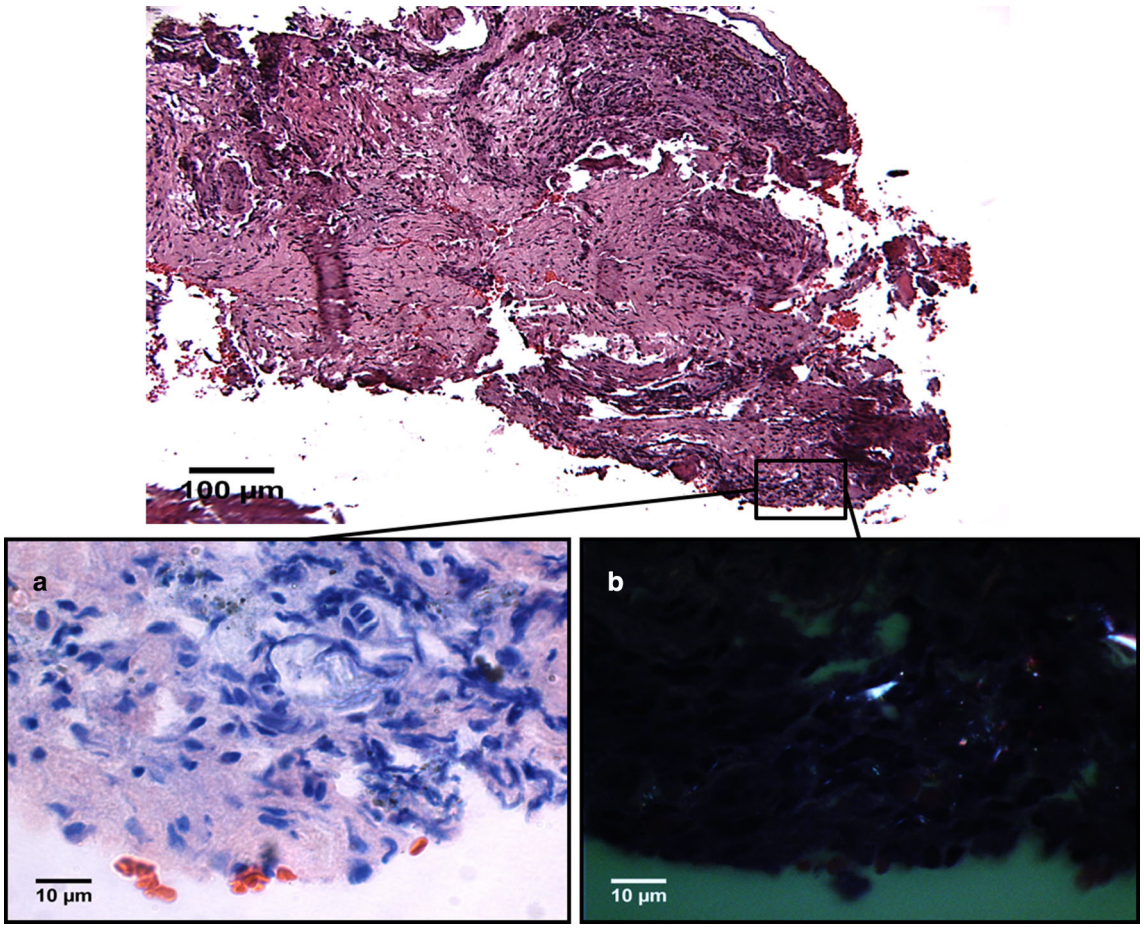


Fig. 6 An H/E stained region of left-cyst tissue was stained with Wright-Giemsa (A, 1000×) and observed under polarized light (B, 1000×), showing evidence of mixed inflammation and polyethylene particles, respectively

second, impingement case, the amount of polyethylene wear debris was relatively low, but there was CoCr wear debris and associated inflammation. In both cases, inflammatory tissue responses may have contributed to the osteolytic lesions.

One difference between the hybrid and non-hybrid case was the use of BMP-2. The hybrid patient was exposed to BMP-2 on five occasions, in comparison to the patient that had a 1-level TDR who received none. Although osteolysis was a late observation after BMP-2 application, the hybrid patient only sought medical attention due to pain. A number of tissue responses to BMP-2 have been noted after spine surgery including heterotopic ossification observed in the hybrid patient's retrieved tissue [8–10]. Although previously believed to be asymptomatic, heterotopic ossification can lead to delayed neural compression and pain [10]. Furthermore, recent studies reported increased resorption rates with the use of BMP-2 around implants, raising the question whether BMP-2 contributes to osteolysis in regions adjacent to the fused segment [5, 6]. Authors have reported asymptomatic osteolysis after interbody fusion and attributed bone loss to endplate violation during disc space preparation and/or to overdosing of BMP-2 [11–13]. Whether BMP-2 has a dose-responsive effect on the activation of osteolytic pathways remains unclear, since an optimal BMP-2 dose for fusions is still not agreed upon.

Osteolysis, along with tissue reactions involving mixed immune responses have been previously reported in a CHARITÉ by Kurtz et al. [3], but these devices consisted of polyethylene cores that were gamma-air-sterilized. ProDisc devices utilize conventional gamma-inert-sterilized polyethylene that has been previously reported in total joint replacements to significantly lower oxidation, wear debris generation and inflammation [16, 17]. ProDisc TDRs have been approved by the Food and Drug Administration, and only a limited number of complications have been documented with the use of either ProDisc-L or ProDisc-C. While hybrid fixation with ProDisc-L and fusion remains under clinical evaluation, there have been no previous reports of osteolysis with the use of ProDisc-L. However, with use of ProDisc-C for cervical TDR, one exceptional case of progressive osteolysis was reported and

attributed to a possible immune-mediated metal sensitivity reaction [18].

In contrast to the minimal immune reaction in the hybrid case, there were substantial ALTRs in the intradiscal and cyst tissue of the non-hybrid case. Wear debris-induced inflammation is known to mediate osteolysis; thus, impingement and subsequent pro-inflammatory processes may explain the clinical symptoms and radiographic progression seen in the non-hybrid case [19]. All samples of cyst tissue showed signs of chronic inflammation and lymphocytic infiltration which were similar to ALTRs to metal ions from implant corrosion of metal-on-metal total hip replacements (THRs) [20]. These findings suggest that ALTRs from THRs share some characteristics with the cyst tissue from the non-hybrid case.

The present study reported two rare osteolysis cases following implantation of the Prodisc-L. In one case, wear-debris induced inflammation; in the second case, inflammation induced heterotopic ossification. As surgeons incorporate ProDisc technology into their clinical practice, the rare complication of osteolysis and its occurrence should be taken into account when defining contraindications for spinal arthroplasty.

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