Virchows Arch (2008) 453:529–534
DOI 10.1007/s00428-008-0659-9

CASE REPORT

Necrotic granulomatous pseudotumours in bilateral resurfacing hip arthoplasties: evidence for a type IV immune response

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Received: 29 March 2008 / Revised: 21 July 2008 / Accepted: 18 August 2008 / Published online: 4 September 2008

Abstract Clinical, radiological and histological findings were analysed in four patients who developed bilateral pseudotumours following metal-on-metal (MoM) resurfacing arthroplasties of both hips. Using a panel of monoclonal antibodies directed against HLA-DR, macrophages (CD14, CD68), dendritic cells (DC-SIGN, S100, CD11c), B cells (CD20), and T cells (CD3, CD4, CD8), the nature of the heavy inflammatory response seen in these cases was examined. Bilateral masses developed in periprosthetic soft tissues following the second MoM arthroplasty; these were characterised histologically by extensive coagulative necrosis, a heavy macrophage infiltrate and the presence of granulomas containing macrophages and giant cells; there was also a diffuse lymphocyte and variable plasma cell and eosinophil polymorph infiltrate. Immunohistochemistry showed strong expression of HLA-DR, CD14 and CD68 in both granulomatous and necrotic areas; lymphocytes were predominantly CD3+/CD4+ T cells. The clinical, morphological and immunophenotypic features of these necrotic granulomatous pseudotumours, which in all cases develop following a second resurfacing hip arthroplasty, is suggestive of a type IV immune response, possibly to MoM metal alloy components.

Keywords Metal-on-metal (MoM) resurfacing hip arthroplasty · Pseudotumours · Immunohistochemistry · Type IV immune response

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Introduction

Resurfacing hip arthroplasties containing second-generation cobalt–chromium–molybdenum alloy metal-on-metal (MoM) components are now being increasingly employed in the treatment of arthritic disease. This component combination is particularly useful for the treatment of end-stage osteoarthritis of the hip in relatively young patients when conventional total hip replacement (THR) may not last a lifetime and the patient is likely to require revision surgery. The advantages of MoM resurfacing hip arthroplasty include relative conservation of bone, improved wear characteristics, lower dislocation rate and the ability to meet the higher demands and expectations of more active patients.

MoM articulations produce a high concentration of metal ions and wear particles that induce a foreign body macrophage response as well as a variable but often heavy infiltrate of lymphocytes and plasma cells, many of which are found around small vessels [5, 11, 18]; this inflammatory reaction has been termed an "aseptic lymphocyte-dominated vascular associated lesion" (ALVAL), and is considered by some investigators to develop as a result of a delayed hypersensitivity response to wear debris derived from the metal implant components [5, 9, 10]. However, several features characteristic of a type IV immune response, including a history of previous exposure to the antigen prior to development of the reaction and a granulomatous response [14], have not been documented in these cases.

In this study, we report a series of four patients who presented with an identical history of development of granulomatous pseudotumours following bilateral MoM resurfacing hip arthroplasty. The clinical, morphological and immunohistological findings in these cases would appear to provide evidence for a type IV hypersensitivity response being associated with the pathogenesis of these lesions.

Clinical history

Patient 01 This 50-year-old female patient presented with bilateral osteoarthritis (OA) secondary to hip dysplasia. She underwent staged hip resurfacings 34 months apart (left Birmingham hip resurfacing and right Conserve +). The patient experienced significant pain in her first hip resurfacing 6 weeks after the second hip resurfacing and subsequently sustained a fracture of the neck of the femur on that side after a trivial fall. At the time of revision surgery, a large mass was noticed posterior to the joint. The lesion was cystic; it contained fluid within thickened walls and communicated with the hip joint. The failed resurfacing was revised to a conventional THR and the patient made an uneventful recovery. The pain on the revised side settled completely. The patient has started experiencing pain on the right side for several months and magnetic resonance imaging (MRI) scans have confirmed the presence of a pseudotumour (similar to the contralateral side) posterior to the hip joint.

Patient 02 This 64-year-old female patient with bilateral primary OA underwent simultaneous bilateral resurfacings (Birmingham Hip Resurfacings). She was asymptomatic for 58 months, at which time she developed intermittent groin pain in the left hip and noticed a lump under the scar. This lump was a large fusiform cystic mass which was non-tender to touch and was not associated with any lymphadenopathy. Ultrasound examination confirmed bilateral pseudotumours—partly solid, partly cystic with thickened wall and a large fluid collection. Repeated aspirations of the hip joints have kept the symptoms under control but the patient may need revision surgery in future. Percutaneous biopsy has confirmed typical features of pseudotumour associated with MoM hip resurfacing (see below).

Patient 03 This 47-year-old female patient with bilateral OA secondary to trauma underwent staged hip resurfacings (both Birmingham hip resurfacings) 10 months apart. Following the second hip resurfacing, within 2 months the patient developed bilateral hip pain worse in the first hip resurfacing. An MRI scan of the pelvis revealed the presence of bilateral pseudotumours anterior to the hip joint. There was a fluid collection as well as the presence of thickened synovium. The patient underwent revision surgery on one side with uneventful recovery and complete resolution of symptoms. She is awaiting revision surgery on the other side.

Patient 04 This 65-year-old female patient with bilateral primary OA underwent staged resurfacings (bilateral Birmingham hip resurfacings) 4 months apart. Six months after the implantation of the second resurfacing, she presented with pain and femoral nerve palsy on the first hip resurfacing side. An MRI scan confirmed the presence of pseudotumour on both sides posterior to the hip joint. She underwent staged revision, which relieved her pain, but the nerve palsy did not recover. Subsequently, she developed pain on the contralateral side with inability to bear weight, this was also revised to a conventional THR and the patient made an uneventful recovery.

Materials and methods

The clinical, radiological and investigative findings in four female patients who had osteoarthritis and underwent bilateral MoM resurfacing arthroplasty employing second-generation metal components are summarised in Table 1.

Samples of the pseudotumour, the pseudocapsule and acetabular and femoral pseudomembrane were examined histologically. All samples were fixed in 10% neutral buffered formalin prior to processing and embedding in paraffin wax. Five-micrometer-thick tissue sections were stained with haematoxylin and eosin and examined by light microscopy.

Representative sections of the pseudotumours were analysed by immunohistochemistry using a large panel of antibodies to T lymphocytes (CD3, CD4, CD8), B lymphocytes (CD 20), macrophages (CD14, CD 68), plasma cells (VS38c), dendritic cells (DCSIGN) and HLA-DR to characterise the immunophenotype of inflammatory cells. Details of monoclonal antibodies used are shown in Table 2.

Results

With the exception of a raised ESR and CRP in one patient and a slight eosinophilia (0.5×10^9/l) in another patient, the white cell count, immunological and other investigations were normal. Radiological investigations, including MRI, computed tomography (CT) and ultrasound, showed the presence of a mass located posterolateral to the joint in three of the four patients; the other patient had a mass anterior to the joint, involving the psoas bursa and muscle (Fig. 1). Further imaging revealed a similar mass abnormality around the contralateral hip implant. No reactive lymph nodes were noted on imaging or at operation.

Three of the four patients (four hips, one being revised on both sides) underwent excision of the mass and revision to a conventional total hip replacement. Histology of these masses showed a number of common features. There was extensive (>50%) coagulative necrosis of periprosthetic connective tissue and muscle in which the ghost-like outlines of large numbers of infiltrating macrophages were evident; many of these macrophages appear to lie in small (granuloma-like) aggregates in the necrotic areas (Fig. 2). Focal areas of cystic degeneration were noted in the necrotic areas.

Table 1 Clinical, radiological and investigative findings in bilateral pseudotumour patients

	Age	Gender	Pre-operative diagnosis	Interval between surgeries	Type of implant	Timing of onset of symptoms	Symptoms	FBC, inflammatory markers	Immunological tests[a]	Plain X-rays	Ultrasound	MRI
P01	50	Female	OA secondary to dysplasia	34 months	BHR, conserve+	6 weeks post 2nd surgery	Hip pain, swelling	Normal	Normal	Loose femoral component, femoral neck narrowing	Not done	Cystic mass
P02	64	Female	Primary OA	0 months simultaneous	BHRs	60 months post surgery	Hip pain, swelling	Normal	Normal	No loosening/lysis	Cystic mass	Cystic mass, synovial hypertrophy
P03	47	Female	OA secondary to trauma	10 months	BHRs	2 months post 2nd surgery	Hip pain	Mild Eosinophilia	Normal	No loosening/lysis	Cystic mass	Cystic mass, synovial hypertrophy
P04	65	Female	Primary OA	4 months	BHRs	6 months post 2nd surgery	Hip pain, femoral nerve palsy	Raised ESR, CRP	Normal	Acetabular erosion	Solid mass	Solid mass, synovial hypertrophy

All patients developed symptoms after the second surgery and the symptoms developed in the hip which was resurfaced first.
OA Osteoarthritis, *BHR* Birmingham hip resurfacing (Smith & Nephew), *Conserve* + Conserve Plus (Wright Medical)
[a] Immunological tests included Rheumatoid Factor Test, IgG, IgA and IgM levels, anti-nuclear and anti-centromere antibodies.

Table 2 Monoclonal antibodies employed in this study

Antigen	Mouse monoclonal antibodies	Source
CD3	F7.2.38	Dakopatts (UK)
CD4	NCL-L-CD4-368	Novocastra (UK)
CD8	C8/144B	Dakopatts (UK)
CD20	L26	Dakopatts (UK)
CD14	CD14-223	Novocastra (UK)
CD68	KPI	Dakopatts (UK)
DC SIGN	120507	R&D (UK)
HLA-DR	CR3/43	Dakopatts (UK)
Plasma cell	VS38c	Dakopatts (UK)

Surrounding the necrotic areas, there was a very heavy macrophage infiltrate; this took the form of a pseudotuberculoid granulomatous response with aggregates of macrophages and giant cells forming a mantle around the large areas of necrosis (Fig. 2). There were also small discrete granulomas which appeared to represent a viable counterpart of the collections of non-viable macrophages found in necrotic areas of the lesion. There was a diffuse, focally heavy lymphocytic infiltrate and scattered lymphoid aggregates around the necrotic areas. There were also occasional plasma cells and eosinophil polymorphs in two of three cases (Fig. 3). Scattered tiny black particles, presumed aggregates of metallic wear particles, were seen in necrotic connective tissue, but this was not a prominent feature in any of the cases examined.

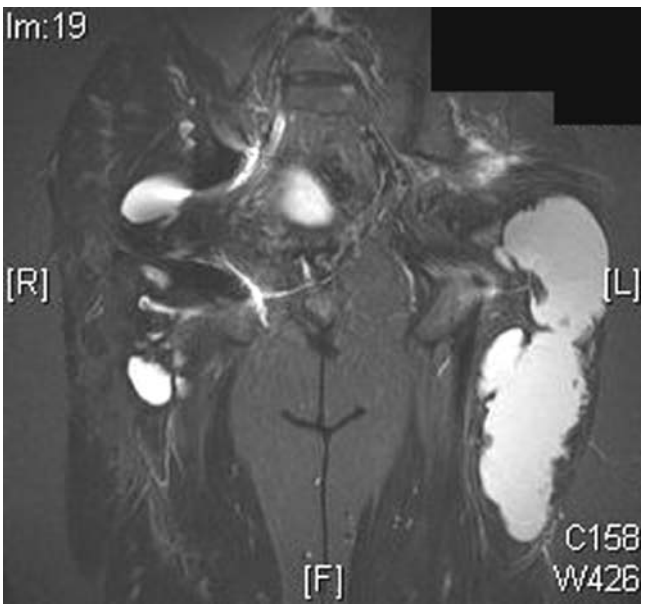

Fig. 1 Coronal T2 STIR-weighted image showing bilateral cystic masses, more extensive on the *left side*. The left-sided mass has a markedly irregular inner wall and extends from the posterior aspect of the hip into the region of the hamstrings, the lateral compartment and the adductors

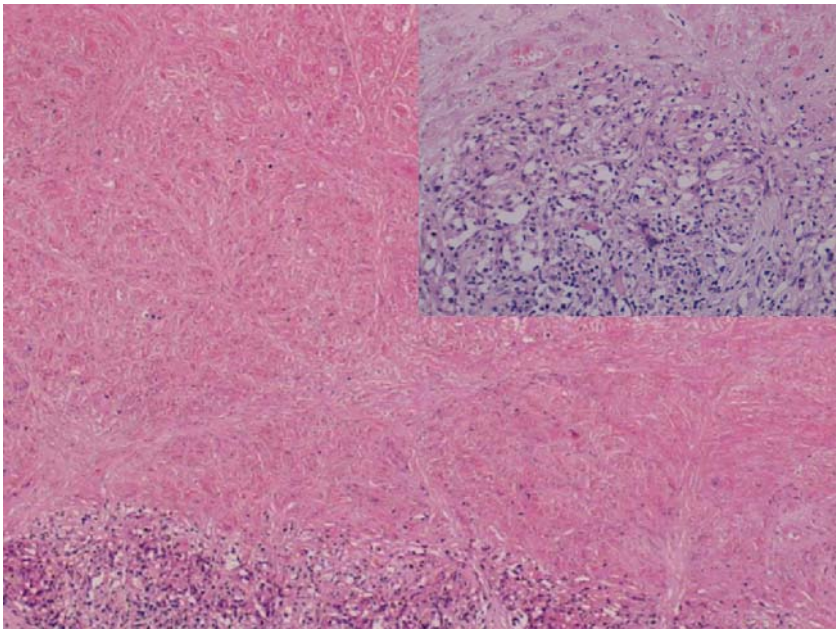

Fig. 2 There is extensive coagulative necrosis which is rimmed by granulomas. The *inset* shows a high power view of the granulomas which contain macrophages and giant cells

No organisms were isolated on microbiological culture of periprosthetic tissues or identified on Ziehl-Neelsen, Grocott, PAS and Giemsa staining. Immunohistochemistry showed prominent HLA-DR expression in both the necrotic and viable (granulomatous) areas of the tumours in which there were numerous CD14+/CD68+ macrophages. Lymphocytes were mainly CD3+/CD4+ T cells (Fig. 4); there were scattered CD20+ B cells, and a few dendritic cells (CD11c+, S100+, DC SIGN+).

Discussion

All four cases in this series presented with an identical history of a large pseudotumoural mass developing after a second bilateral hip resurfacing arthroplasty employing second-generation MoM components. CT, MRI and ultrasound imaging showed that the masses were partly solid and partly cystic. The masses were largely composed of areas of coagulative necrosis in which there were large numbers of macrophages; these areas were surrounded by macrophage and giant cell granulomas as well as T lymphocytes, plasma cells and eosinophil polymorphs. This necrotic granulomatous response and inflammatory infiltrate is typically seen in the context of a delayed hypersensitivity reaction and, taken with the strikingly similar chronological history in all cases of the lesions developing after implantation of a second MoM resurfacing

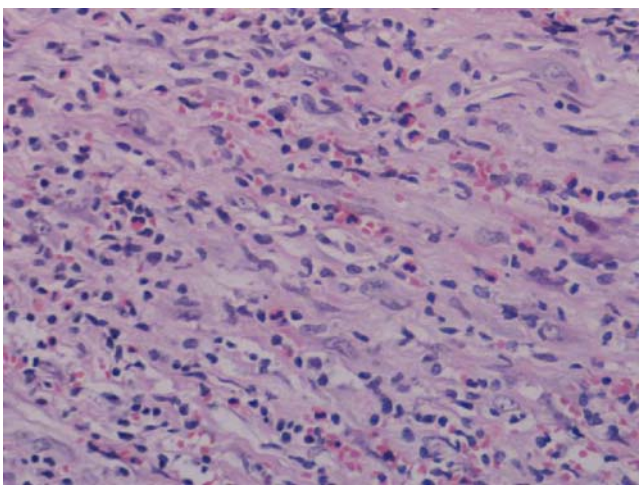

Fig. 3 Eosinophil polymorph infiltrate in inflammatory tissue of the pseudotumour

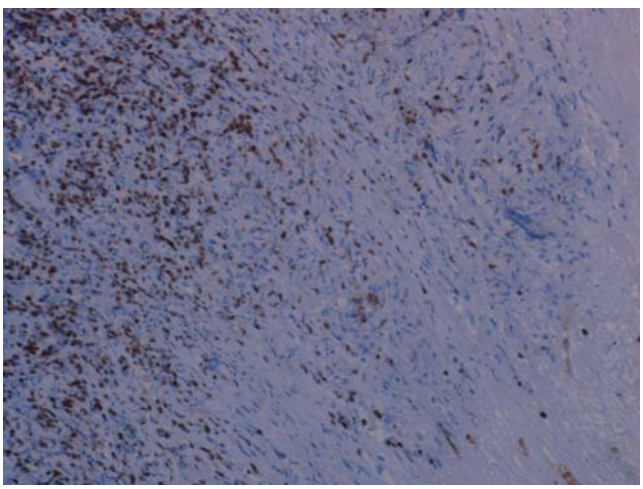

Fig. 4 Immunohistochemical staining around a granuloma adjacent to an area of necrosis of the pseudotumour with monoclonal antibody NCL-L-CD4-368 showing the presence of numerous CD4+ T lymphocytes

arthroplasty, would suggest that a type IV immune response plays a role in their pathogenesis.

A type IV response develops when primed memory T cells, recognise an antigen (often intracellular) which is presented by appropriate HLA-DR-expressing cells such as macrophages; the T cells are then stimulated to undergo blastic transformation, resulting in the release of lymphokines which attract and activate macrophages that may aggregate together to form granulomas [14]. In all the pseudotumours in our series, there were granuloma-like collections of macrophages in areas of coagulative necrosis and well-formed granulomas in the surrounding viable tissue. This pseudotuberculoid macrophage and giant cell reaction and the presence of numerous HLA-DR+/CD14+/CD68+ macrophages in both the viable and necrotic areas of the pseudotumours are consistent with a type IV response. Also typical of a type IV reaction is the fact that all the pseudotumours in our series developed after a second resurfacing arthroplasty, i.e. following previous exposure to MoM implant components. It is upon second exposure to the antigen that the series of events triggered by antigen-sensitised T cells leads to the tissue destruction and inflammation characteristic of a type IV response; it is also in keeping with this response that the pseudotumours were bilateral, developing around both MoM implants.

In addition to lymphocytes and macrophages, scattered plasma cells and eosinophil polymorphs were noted in the pseudotumours. These inflammatory cells have been noted in periprosthetic tissues around failed MoM arthroplasties in previous studies which concluded that this inflammatory infiltrate, particularly the ALVAL component, is associated with a hypersensitivity response to cobalt–chrome particles [5, 9, 10]. Metal wear particle deposition in periprosthetic tissues was not extensive in these studies or in the pseudotumours in our cases; this is not surprising as, although MoM articulations generate huge numbers of cobalt–chromium wear particles, these particles are submicron in size and not visible by light microscopy unless they form tiny aggregates. It has been shown that phagocytosis of these cobalt–chrome particles can induce cytotoxicity and chromosomal damage [10]. Necrosis was a prominent feature of all the pseudotumours in our study. Both necrosis and what some observers have termed “necrobiosis” (on the basis that the connective tissue changes resemble those seen in necrobiosis lipoidica diabeticorum) have previously been noted in periprosthetic tissues around first- and second-generation MoM bearings [6]. It is thus possible that a cytotoxic effect on macrophages which had phagocytosed metal particles may have contributed to the extensive necrosis seen in these pseudotumours.

Skin tests for metal allergy and lymphocyte transformation tests have provided indirect evidence that hypersensitivity to metal alloys may play a role in MoM implant loosening [2, 9, 12]. Morphological and immunophenotypic features of a necrotising granulomatous response, similar to that seen in the MoM-associated pseudotumours, can be seen in the hypersensitivity response to contact metal allergens in cheap jewellery containing nickel and chromate [1, 4]; MoM implants contain only very small amounts of nickel but it should be noted that 13% of patients presenting with contact dermatitis to nickel are sensitised to both nickel and chromium [16, 17]. In this regard, it may be of significance that all of the patients in our series were female and that a recently reported benign psoas mass which formed around a unilateral MoM implant also occurred in a female patient [3]; histologically, this lesion showed tissue necrosis and a heavy lymphocytic infiltrate (but no evidence of a granulomatous response).

The pseudotumours noted in the present series of cases are distinct from those previously reported as granulomatous pseudotumours associated with metal–polymer arthroplasties [7, 8, 15]. These lesions, which are also called aggressive granulomatous lesions or aggressive granulomatosis, have been reported to develop in association with both cemented and cementless hip arthroplasties. They may occur in patients with well-fixed prostheses and may present as soft tissue masses adjacent to the prosthesis. In most cases, these lesions are associated with extensive osteolysis. Histologically, these lesions are distinct from the necrotic granulomatous pseudotumours described in this paper in that they contain a heavy macrophage and giant cell response to particulate debris, particularly ultra-high molecular weight polyethylene particles. Granulomatosis has been reported in both males and females, unlike necrotic granulomatosis pseudotumours, which appear to arise almost exclusively in females [13]. Inflammation in aggressive granulomatosis lesions and in periprosthetic tissues around metal–polymer implants does not contain a prominent lymphocytic infiltrate; scattered T lymphocytes have been noted but these do not express interleukin-2 or transferrin receptors, indicating that these cells are resting T lymphocytes [15]. Extensive tissue necrosis is not generally associated with aggressive granulomatous pseudotumours which are thought to form on the basis of a pronounced foreign body macrophage response to deposited wear particles rather than a hypersensitivity immune response.

The similar chronological history of previous exposure to MoM implant components preceding development of all the pseudotumours in our series, taken with the morphological findings of a granulomatous response and a lymphocytic infiltrate, predominantly T cell in nature, would argue in favour of a cell-mediated immune response playing a role in the formation of these lesions. Clinically, these patients presented with a mass that resembled a neoplasm and caused some diagnostic difficulty. The initial biopsy in some of our cases showed only extensive necrosis which was difficult to

distinguish morphologically with certainty from a necrotic tumour; even in those cases where a pseudotuberculoid granulomatous response could be identified, it was difficult to distinguish this reaction from that seen in other necrotic granulomatous conditions, such as mycobacterial or fungal infections, or Wegener's granulomatosis. Clinicians should be aware that necrotic granulomatous pseudotumours can develop around a MoM resurfacing hip arthroplasty and that these lesions can be bilateral in patients with two MoM implants.

Acknowledgement The authors thank Chris Lowe for typing the manuscript.

Conflict of interest statement We declare that we have no conflict of interest.

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