Metal-on-Metal Bearings and Hypersensitivity in Patients with Artificial Hip Joints

A Clinical and Histomorphological Study

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Background: Some patients who have a total hip replacement with a second-generation metal-on-metal articulation have persistent or early recurrence of preoperative symptoms. Characteristic histological changes in the periprosthetic tissues suggested the development of an immunological response. Therefore, in order to determine the relevance of these symptoms, we performed a study of the clinical data and periprosthetic tissues associated with endoprostheses with a metal-on metal articulation that had been retrieved at revision.

Methods: Periprosthetic tissues as well as the clinical data on the patients were obtained from the first nineteen consecutive revisions performed at the treating hospitals. At the time of the revision, fourteen patients had the metal-on-metal articulation exchanged for either an alumina-ceramic or a metal-on-polyethylene articulation. Five patients received another second-generation metal-on-metal total joint replacement. Five-micrometer sections were prepared from the tissue samples, were stained with routine and immunohistochemical methods, and were examined histologically. Histological specimens from three groups of patients, two of which were treated with non-metal-on-metal implants, served as controls.

Results: The majority of patients had persistence of their preoperative pain or early recurrence of the pain after the original total hip replacement, and often a pronounced hip joint effusion had developed after the original replacement. Radiographic follow-up showed the development of radiolucent lines in five hips and of osteolysis in another seven hips. At the revision surgery, both the cup and the stem were found to be well fixed in nine patients. The characteristic histological features were diffuse and perivascular infiltrates of T and B lymphocytes and plasma cells, high endothelial venules, massive fibrin exudation, accumulation of macrophages with droplike inclusions, and infiltrates of eosinophilic granulocytes and necrosis. Only a few metal particles were detected. Immunohistochemical analysis demonstrated that the cellular reaction was still active. The patients who received another second-generation metal-on-metal articulation at the time of the revision had no decrease in symptoms. In the control group of tissues obtained at revisions of endoprostheses without cobalt, chromium, or nickel articulations, there were no similar signs of immune reactions.

Conclusions: These histological findings support the possibility of a lymphocyte-dominated immunological response. Although the prevalence of this reaction is low, the persistence or early reappearance of symptoms, including a marked joint effusion and the development of osteolysis, after primary implantation may suggest the possibility of such a reaction.

Classic metal-on-metal prostheses made of cobalt-chromium-molybdenum alloys (McKee-Farrar, Huggler, and Müller types), which were used in the 1960s and 1970s, showed an extremely low rate of wear of the articulating surfaces, even ten to twenty years after implantation[1-3], and only a mild foreign-body reaction to the metal debris[3-5]. A second generation of cobalt-chromium-molybdenum-alloy metal-on-metal bearings for hip endoprostheses were manufactured with improved materials and methods[1,6,7] and were implanted by Weber[8] starting in 1988.

Histological evaluation of the changes in the periprosthetic tissues of a few patients who had revision of a hip replace-

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TABLE I Grading of Periprosthetic Particle Storage and Tissue Reactions

–	None	No or only isolated phagocytized particles without major macrophage reaction
+	Few	A few particles phagocytized in some spots and/or accumulated perivascularly (in the lymphatics)
++	Many	Evident accumulation of particles phagocytized in macrophages (also perivascular in the lymphatics)
+++	Abundant	Tissue loaded with particles, including foreign-body granulomas
++++	Excessive	Tissue overstuffed with particles; foreign-body granulomas dominating the structures everywhere

ment with a second-generation metal-on-metal articulation suggested a cell-mediated type-IV hypersensitivity reaction (delayed-type hypersensitivity[9-12]). The changes were characterized by vasculitis with perivascular and intramural lymphocytic infiltration of the postcapillary venules, swelling of the vascular endothelium (high endothelial venules), recurrent localized bleeding, and necrosis. In addition, fibrin exudate and the accumulation of macrophages with droplike inclusions were frequent findings[13]. In order to determine the relevance of those findings, we reviewed a larger series of unselected patients who had had a revision of a hip replacement with a second-generation metal-on-metal articulation.

Materials and Methods

This investigation was based on tissue obtained from the first consecutive twenty-four revisions of second-generation metal-on-metal total hip articulations performed in a group of hospitals. Five patients had a clinically and bacteriologically proven infection and were excluded. In fifteen of the remaining nineteen patients, infection was ruled out by negative preoperative or intraoperative cultures, and none of the nineteen patients had neutrophilic granulocytes in histological specimens obtained at surgery.

Sixteen of the nineteen revised joint replacements had a Metasul articulation (Centerpulse, Winterthur, Switzerland). Two articulations were distributed by Synthes-Stratec, Oberdorf, Switzerland, and one, by Plus Endoprothetik, Rotkreuz, Switzerland.

The tissue samples from seventeen patients were obtained from the joint capsule, with additional material taken from the acetabular implant-bone interface in two of them, from the femoral implant-bone interface in two, and from a bursa in one. In two cases, only material from the acetabulum was available. The formalin-fixed tissues were decalcified if necessary, and 5 to 10-µm microtome sections were stained with the hematoxylin and eosin, Giemsa, van Gieson, Prussian blue, and periodic acid-Schiff methods. The sections were examined histologically under normal light and with polarization (BX 50; Olympus, Hamburg, Germany).

The amount of metal particles in the tissue was estimated according to a modified rating system[3] (Table I). The visible metal particles were characterized by their high density, black color, and bizarre shape. Their sharp edges light up in polarized light. Lymphocytic infiltration was assessed by counting the individual cells of a diffuse infiltration and the number of perivascular agglomerations per field of view (Table II).

Immunohistochemical analysis was performed to characterize macrophages and lymphocytes[14-23] (Table III). Hematoxylin was used as a counterstain. Sections of lymph nodes from patients with tuberculosis and from pharyngeal tonsils with follicular, lymphatic hyperplasia were stained in the same manner to serve as positive controls. Specimens from seven patients were overfixed with formalin, and they could not be further analyzed immunohistochemically.

The patients included ten men and nine women. Their mean age at the time of the revision was sixty years (range, forty to seventy-six years). The indication for the primary total hip replacement was degenerative osteoarthritis in eighteen patients and pseudarthrosis after a femoral neck fracture in one. The primary metal-on-metal prosthesis had been cemented in two hips, had been implanted with hybrid fixation (a cemented stem) in one hip, and had been implanted without any cement in sixteen hips. Two of the cemented stems (Cases 2 and 3) were made of iron-based alloy S30, and one (Case 1) was made of Ti-6Al-7Nb alloy. All noncemented stems were made of Ti-6Al-based alloys, and the metal back of the noncemented cups was pure titanium. Most of the cups had a polyethylene insert enclosing the articulating metal surface.

Evaluation of questionnaires and additional inquiries provided a complete set of clinical data as summarized in the Appendix.

Three groups of patients who had undergone revision of a total hip replacement served as controls. Existing histological sections from those patients were examined with light microscopy. No additional material was available, and no further immunohistochemical analyses were done. Control group I in-

TABLE II Grading of Lymphocytic Infiltration per Field of View

Grading		Amount per Field of View	
Symbol	Description	Cells of Diffuse Infiltration*	Perivascular Infiltrates†
–	None	≤10	0
+	Few	11-30	1-2
++	Many	31-50	3-6
+++	Abundant	51-100	7-10
++++	Excessive	>100	>10

*Magnification ×40. †Magnification ×4.

TABLE III Immunohistochemical Staining Methods Used to Characterize the Cellular Reactions

Immunohistochemical Marker	Detection of:	References	Obtained from:
Monoclonal antibody, Ki-M1P against CD68	Macrophages, all populations	16	Dept. of Pathology, University of Kiel, Germany
Monoclonal antibody 25F9	"Old" macrophages: inactive, storing foreign material	17-19	Dianova, Hamburg, Germany
Monoclonal antibodies against S100A8 (MRP8, clone 8-5C2) and S100A9 (MRP14, clone S32.2)	"Young" macrophages: active, recently invaded	18	Dianova, Hamburg, Germany
Monoclonal antibody L26 against CD20	B lymphocytes	20	Dako, Hamburg, Germany
Monoclonal antibody against CD 3	T lymphocytes	21	Dako, Hamburg, Germany
Monoclonal antibody MiB1 against Ki-67	T lymphocytes expressing proliferation-associated antigen	22	Dako, Hamburg, Germany

cluded eighteen noncemented endoprostheses free of cobalt, chromium, molybdenum, and nickel. The prostheses consisted of a titanium-alloy stem (Zweymüller; AlloPro, Baar, Switzerland), an Al_2O_3 ball head (Biolox; CeramTec, Plochingen, Germany), and an ultra-high molecular weight polyethylene screw cup (Endler; AlloPro). The revisions were performed three to sixteen years (average, 10.9 years) after implantation, and they were due to aseptic loosening of the cups[24]. Tissue samples from three revisions, performed thirty-six, thirty-eight, and seventy months after the primary implantation, were also available for immunohistochemical analysis. Control group II included eleven all-cemented Müller-Charnley prostheses consisting of a curved monobloc cobalt-chromium-molybdenum femoral component and a polyethylene cup (Protek, Münsterlingen, Switzerland). These curved stems had loosened aseptically in the cement mantle after two to sixteen years (average, 9.6 years). A high degree of polish by metal abrasion was noted on the surfaces of the loosened stems[24]. Control group III comprised fifteen cemented, classic metal-on-metal joint replacements (McKee-Farrar). Those devices were revised ten months to 23.5 years (average, 8.5 years) after implantation. The histopathological investigation of the fifteen cases has been previously reported[3], and these were reinspected.

Results

The majority of the patients had had either persisting or recurrent pain in the hip and thigh, especially with weight-bearing, early after the primary implantation of the metal-on-metal articulation. Some also had symptoms at rest. Other symptoms included a limp (four patients), squeaking sounds during joint movement (three), and multiple dislocations (two).

Radiographic follow-up of seventeen patients (two patients had no radiographic follow-up) revealed the development of radiolucent lines in the proximal part of the femur in five patients, and two of those patients also had radiolucent lines in the acetabulum. Two patients had osteolysis in the proximal part of the femur only, and five had osteolysis in the femur and acetabulum. Only five patients had no major radiographic changes around the implants.

Revision of the metal-on-metal joint replacement became necessary at an average of thirty-three months (range, ten to eighty-one months) after the primary implantation. The indications for revision were increasing pain and the occurrence of osteolysis.

During the revision surgery, the anchorage of the devices was tested for stability. In nine hips, both the cup and the stem were still fixed; in four of them, however, osteolysis was found, primarily in the proximal part of the femur. In two patients, the cup was fixed but the stem was loose; in two patients, the stem was fixed but the cup was loose; and in five patients, both components were completely loose. No information on the fixation of the components was available for the remaining patient. An extensive joint effusion was noted in eight patients, and it was often combined with bursa formation. In five of the eight patients, both the stem and the cup were still fixed.

The stem was exchanged in ten hips. The acetabular shell and liner were left in place in one patient, both the shell and the liner were replaced in eight patients, and only the liner was exchanged in another eight patients. No information on the stem or acetabular shell was available for two patients. In twelve patients, an alumina ceramic-on-polyethylene bearing was used to replace the metal-on-metal articulation. In two patients, a metal-on-cross-linked polyethylene combination was inserted. Another cobalt-chromium-molybdenum metal-on-metal articulation was implanted in the remaining five patients.

In fourteen hips, the revision implants were again fixed without cement. The type of fixation was changed in three hips: two uncemented stems were replaced with a cemented stem (hybrid fixation) and one cemented cup was replaced with an uncemented one (hybrid fixation). In two hips, the stem and the acetabular shell were left unchanged in situ; one of those prostheses was completely cemented, and the other had hybrid fixation (cemented stem and uncemented cup).

At the time of follow-up, one to seven years after revision, the fourteen patients who had had an exchange of the primary metal-on-metal articulation with an alumina-on-polyethylene or a metal-on-cross-linked polyethylene articulation reported total relief of pain. However, hip and thigh pain persisted in the five patients who had received a second metal-on-metal articulation. Two of those five patients became free of symptoms after repeat revision four months and five years after the first revision.

TABLE IV Time of Function, Amount of Metal Particles, and Lymphocytic Infiltration

Case	Time of Function of Prosthesis *(mo)*	Grade of Amount of Metal Particles*	Grade of Lymphocytic Infiltration†	
			Diffuse	Perivascular
1	17	++	++	+++
2	33	+	+	++
3	55	++	+	+
4	41	+	++	++
5	50	+	+	++
6	32	++++	++	++++
7	36	+++	++	++
8	33	+++	++	++
9	39	+	++	+
10	11	+	++	++
11	38	+	++	+++
12	52	+	++	+++
13	39	+	++	++++
14	10	+	++	++
15	81	+++	+	++++
16	10	+	++	++++
17	10	+	+	++
18	25	+	+++	++++
19	16	+	+++	+++

*The grading system is described in Table I. †The grading system is described in Table II.

Histological examination of the periprosthetic tissue from all of the nineteen patients who had had a revision of a metal-on-metal implant showed only a mild foreign-body reaction to wear particles from the implants. However, varying numbers of mononuclear and multinuclear macrophages were found, mainly next to the vessels, in all cases. A few giant cells were also present in six cases.

Metal particles, visible on light microscopy, were mainly stored in macrophages. They were very small, measuring from 0.5 to 5 μm in diameter. The amount of metal particles was rated as "many" (++) or "abundant" (+++) in five cases and as "excessive" (++++) in one. The specimens from the other thirteen hips had only a "few" (+) metal particles (Table IV). These findings represent a relatively mild foreign-body reaction. Polyethylene particles were found in the tissues around one cemented and three uncemented endoprostheses. Fragments of polymethylmethacrylate were present in one case, and zirconia contrast medium was found in the tissue around two of the three cemented implants.

A distinct lymphocytic infiltration, sometimes accompanied by plasma cells, was observed in the specimens (Table IV and Fig. 1). In the inner layer of the neocapsule, the lymphocytes were diffusely distributed (Fig. 1, *A*) and were rated as few (+) in five hips, as many (++) in twelve, and as abundant (+++) in two. In the intermediate vascular layer, the infiltrates mostly surrounded postcapillary venules and were also interspersed within the walls of these venules (Fig. 1, *B*). High endothelial venules were identified in seven of the nineteen cases (Fig. 1, *C*). The rating of the perivascular lymphocytic infiltrates revealed few (+) aggregates in only two hips, many (++) in eight, abundant (+++) in four, and excessive (++++) in five. Eosinophilic granulocytes of varying density were present in the tissue from eight patients. Sometimes mast cells were also observed.

A characteristic finding of small droplike inclusions in the cytoplasm of the macrophages was noted in the tissue from thirteen hips (Fig. 2). Their size ranged from the detection limit of 0.5 μm to 15 μm. The inclusions stained light yellow or greenish with hematoxylin and eosin (Fig. 2, *A*), deep blue with Giemsa stain, and pale blue with Prussian-blue stain (Fig. 2, *B*), and they were positive on periodic acid-Schiff staining (Fig. 2, *C*). In contrast, the inclusions were negative for the CD68 marker (Fig. 2, *D*). The material was not birefringent and appeared to be amorphous. On the basis of the morphological characteristics, this material did not resemble wear debris from any of the implant materials used.

The tissues often showed an extensive fibrin exudation and areas of necrosis. In fourteen of the nineteen cases, marked fibrin exudates covered the surface of the neocapsule, while a cellular lining was lacking. The fibrin was organized by

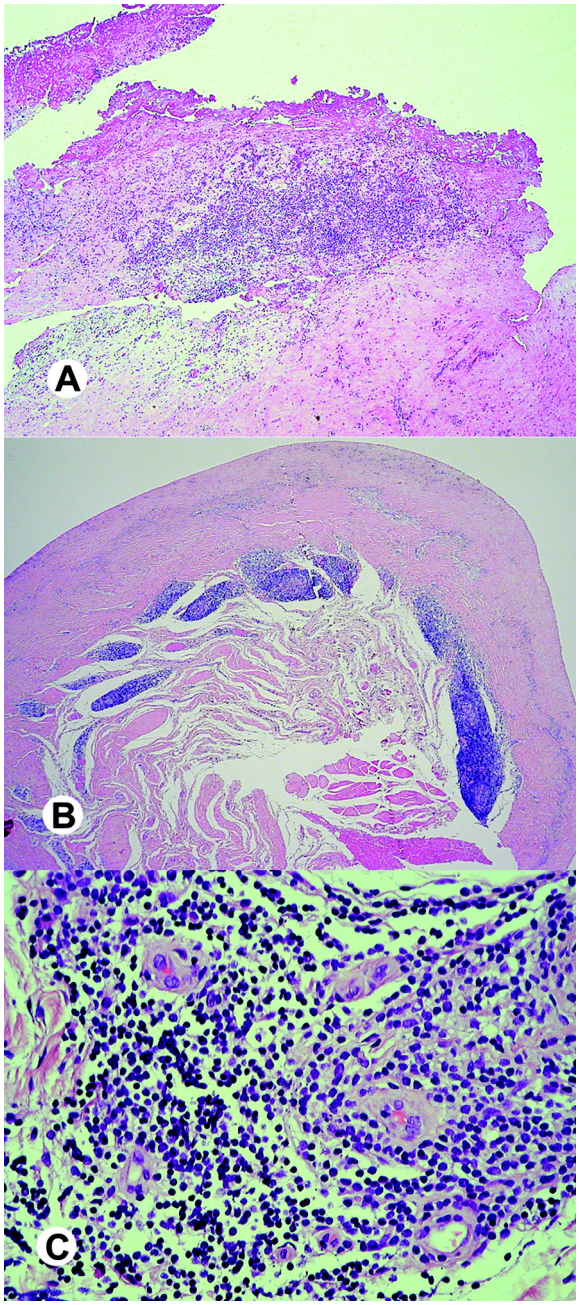

Fig. 1

Histological sections showing lymphocytic infiltrates in the capsular tissue and fibrin exudation (paraffin technique, transmitted light, hematoxylin and eosin). *A,* Case 18. Inner capsular layer with infiltrates of diffusely distributed lymphocytes and fibrin exudates at the surface (original magnification ×4). *B,* Case 11. Perivascularly agglomerated lymphocytic infiltrates with secondary reaction centers, in the intermediate vascular layer of a joint capsule (original magnification ×20). *C,* Case 18. High endothelial venules with narrow lumina and dense infiltrates of mononuclear cells in the capsular tissue around the metal-on-metal articulation (original magnification ×40).

ingrowing cells and vessels from the underlying tissues, which resulted in thickening of the capsule. Large necrotic areas were found in eleven cases. There were also signs of recent or older bleeding, with the latter characterized by hemosiderin.

Immunohistochemical analysis revealed numerous CD68-positive mononuclear and multinuclear cells. The subtypes of the CD68-positive macrophages, mature (25F9-positive) as well as recently invaded (MRP8/MRP14-positive) macrophages, were regularly present in the tissues. The drop-shaped inclusions in the cytoplasm were enveloped by a CD68-positive edge (Fig. 3, *A*).

The lymphocytic infiltrates, either diffusely distributed or perivascularly aggregated, consisted of CD20-positive B lymphocytes (Fig. 3, *B*) and CD3-positive T lymphocytes, which outnumbered the B lymphocytes (Fig. 3, *C*). Sometimes, lymph follicles with B lymphocytes were found, and they were often surrounded by CD3-positive T lymphocytes. The monoclonal antibody Mib-1 showed that >5% to 10% of the lymphocytes expressed the antigen Ki-67, which is associated with proliferation (Fig. 3, *D*).

Periprosthetic tissues of control group I contained large amounts of polyethylene wear particles[4]. The foreign-body reaction with extensive phagocytic granulomas, large numbers of giant cells, and areas of necrosis was much stronger than that in the tissue surrounding the metal-on-metal implants. Slight fibrin exudation was noted in four control cases. A single perivascular lymphocytic infiltrate (+) could be detected in only one case. High endothelial venules were absent (−). Immunohistochemical analysis, performed in three cases, demonstrated CD68-positive macrophages containing large amounts of polyethylene particles. In contrast to the tissues from the hips with the second-generation metal-on-metal articulation, old macrophages (25F9-positive) were predominant; only some had recently invaded (MRP8 and MRP14-positive). Very few lymphocytes could be differentiated as single cells with the use of L26 or CD3, and there was a lack of signs of activation.

The polished surface of the cemented curved cobalt-chromium-alloy stems (control group II) had released a large amount of metal debris into the surrounding tissues, but particles of bone cement, contrast medium, and polyethylene exceeded the number of metal wear particles. The foreign-body reaction was dominated by macrophages and foreign-body giant cells containing the polymer debris[24]. A small number of lymphocytes was present in four of the eleven cases. There were few (+) diffuse lymphocytic infiltrates in three cases and many (++) in one case. Few (+) perivascular infiltrates were present in three cases.

In the tissues around the classic metal-on-metal implants (control group III), the foreign-body reaction to a low number of metal particles was found to be mild and the histological appearance of the tissues again was dominated by a reaction to bone cement debris[3]. Some lymphocytic infiltrates were observed in ten of the fifteen cases. There was a diffuse distribution of a few (+) lymphocytes in five cases, many (++) lymphocytes in one, and an excessive number (++++) in an-

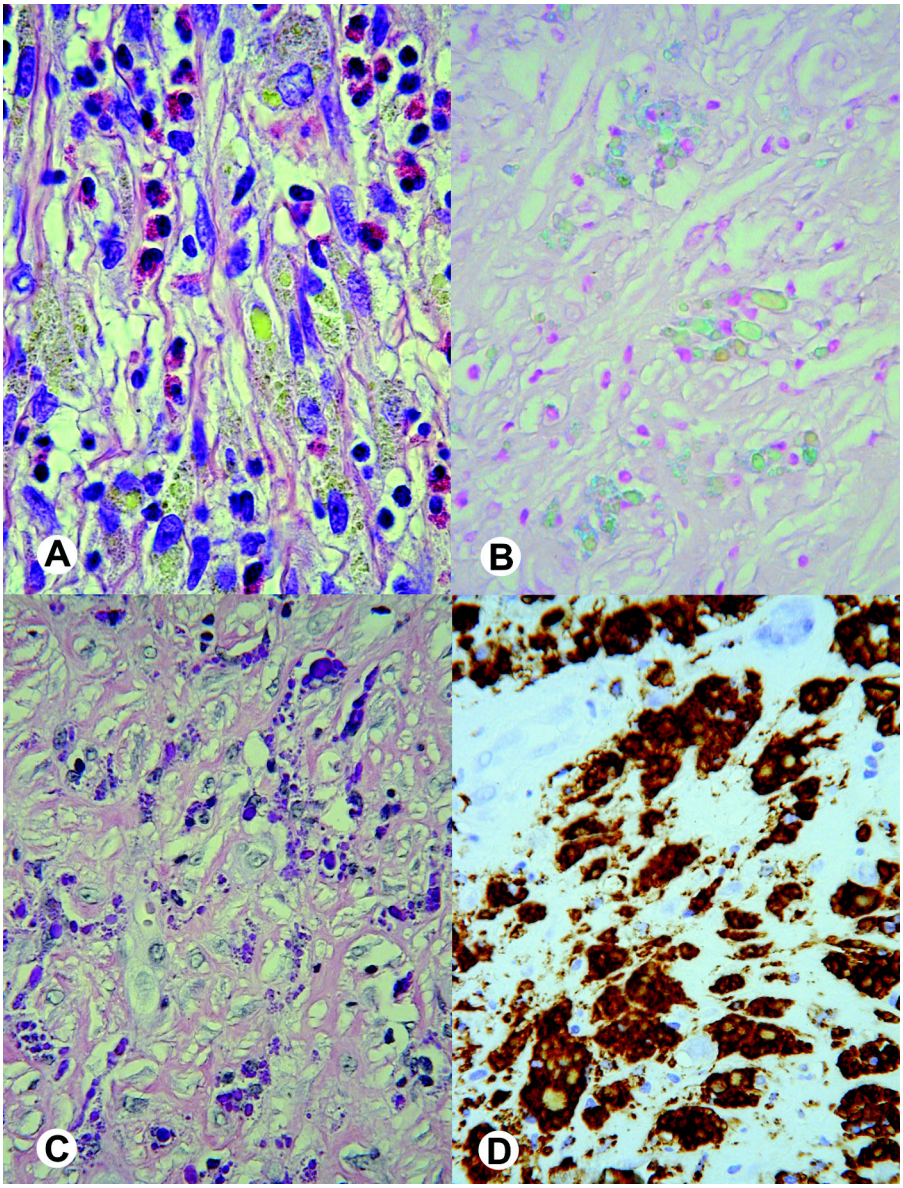

Fig. 2

Histological sections showing macrophages containing drop-shaped inclusions and fine-grained material in the capsular tissue (paraffin technique, transmitted light, routine and immunohistochemical staining, original magnification ×40). *A,* Case 19. While the drop-shaped material has taken on a greenish coloring, the fine-granulated material adds to the grayish appearance of the cytoplasm of the macrophages. The tissue also contains a number of eosinophilic granulocytes (hematoxylin and eosin). *B,* Case 12. Most of the drop-shaped inclusions are negative for iron, at least in their centers; some of the fine granulated material, however, has stained positive for iron (Prussian blue). *C,* Case 12. Many of the drop-shaped inclusions are positive on periodic acid-Schiff staining. *D,* Case 19. The cytoplasm of the CD68-positive macrophages turned brown while the inclusions remained unstained.

other. Perivascular infiltrates were found in the tissues from five hips, two of which had a few (+) aggregates, two of which had many (++) aggregates, and one of which had abundant (+++) aggregates. Eosinophils were present in four cases. Thus, in the tissues surrounding the classic metal-on-metal bearings, signs of a hypersensitivity reaction were less frequent and of minor intensity compared with those around the second-generation metal-on-metal articulations.

Discussion

Pain, osteolysis, and joint effusion typically are not present after a successful total hip arthroplasty. If pain with weight-bearing or at rest or radiolucent lines or osteolysis develop over the long term in a patient with an artificial hip joint, these findings are considered to be nonspecific. However, our study indicated that, when these problems persist or reappear soon after a hip replacement with a metal-on-metal articulation and infection has been excluded, an immunological response should be suspected. This diagnosis is strongly supported by the development of rapidly increasing osteolysis and radiolucent lines and the occurrence of a joint effusion.

None of the five patients in this study in whom the revision was done with a second metal-on-metal articulation had relief of symptoms. Symptoms were relieved only following revision without an all-metal articulation. This finding suggests that an immunological response persisted after the first revision and that the patients had been sensitized to the components of the all-metal articulation.

The histological examination of the periprosthetic tissue retrieved at the revision surgery revealed an immunological response. The characteristic phenomena consisted of diffuse and perivascularly oriented infiltration of lymphocytes ac-

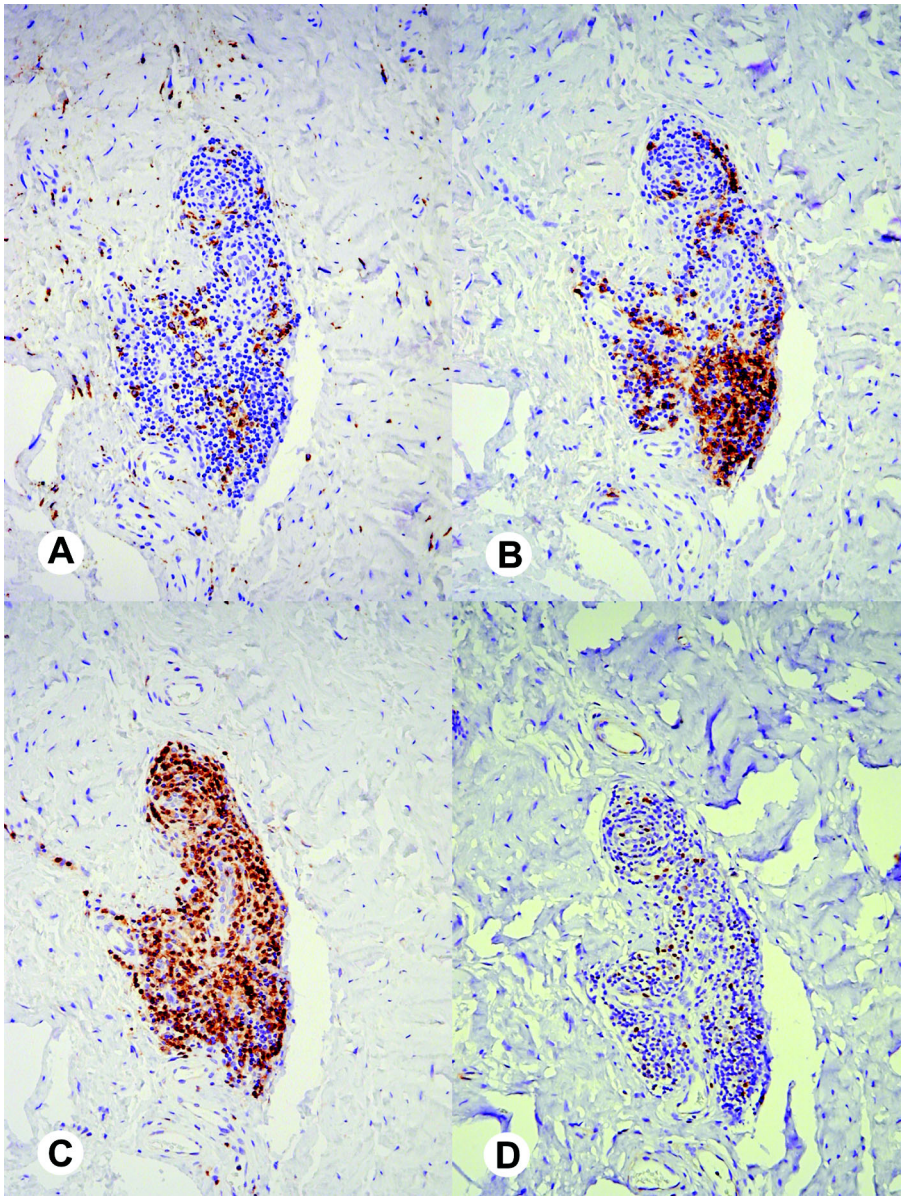

Fig. 3

Case 11. Histological sections from the same block showing perivascularly agglomerated infiltrates of macrophages and lymphocytes in the capsular tissue (paraffin technique, immunohistochemical staining [red-brown coloring] counterstained with hematoxylin, transmitted light, original magnification ×20; routine hematoxylin and eosin staining is shown in Fig 1, *C*). *A,* CD68-positive macrophages. *B,* CD20-positive B lymphocytes. *C,* CD3-positive T lymphocytes. The T lymphocytes outnumber the other types of mononuclear cells. *D,* Activated T lymphocytes express the proliferation-associated antigen Ki-67.

companied by plasma cells and sometimes eosinophilic granulocytes, high endothelial venules, localized bleeding, fibrin exudation, necrosis, and macrophages with drop-like inclusions. The presence of infection should be considered if more than a very few neutrophilic granulocytes are present[25].

Findings such as B lymphocytes, plasma cells, and massive fibrin exudation are not characteristic of a type-IV delayed-type hypersensitivity reaction[9,26-29]. Nevertheless, they support the hypothesis of a relationship between wear of the all-metal cobalt-chromium articulation and the diagnosis of a hypersensitivity reaction, which can be described as an aseptic lymphocyte-dominated vasculitis-associated lesion or as a lymphocyte-dominated immunological answer (LYDIA).

The majority of the tissue that was examined contained only small amounts of histologically visible metal wear particles. Correspondingly, the foreign-body reaction to the metal was relatively mild; sometimes there were large numbers of phagocytosing macrophages, but there was no substantial granuloma formation.

Immunohistochemical analysis demonstrated that macrophages that had already phagocytized foreign material were almost all positive for 25F9 but negative for MRP8 and MRP14. The relatively high content of freshly recruited MRP8 and MRP14-positive macrophages suggests chronic inflammation with a continuous recruitment of inflammatory macrophages from the peripheral blood, as can be observed in diseases with cell-mediated immune reactions[23]. Fibrin exudation can also be considered to be part of this type of inflammatory reaction.

Also, the diffuse, perivascular, and intramural lymphocytic aggregates, composed of CD3-positive T lymphocytes (5% to 10% of which express the proliferation-associated anti-

gen Ki-67) and of CD20-positive B lymphocytes, suggest a cell-mediated immune response, in the course of which proliferation of sensitized T lymphocytes could be induced after a second contact with the antigen. It is possible that the expression and secretion of pro-inflammatory cytokines by those reactivated T lymphocytes contribute to the establishment of a secondary endotheliosis (high endothelial venules) as well as to the recruitment and activation of monocytes and/or macrophages from the peripheral blood. These cells then might produce proteases and induce the degradation of matrix, followed by the disintegration of the tissue[30,31], and contribute to the development of radiolucent lines and osteolysis despite the absence of generalized granuloma formation due to excessive particle release. We speculated that the low but continuous release of metal ions from the metal-on-metal articulations and their biochemical reactions with the surrounding tissues, which start immediately after implantation, accelerate or at least facilitate sensitization and the consequent immunological response.

The appearance of abundant drop-shaped inclusions in the macrophages is an unusual finding in periprosthetic tissues and their nature is not yet clear. The shape, size, and hematoxylin and eosin, Giemsa, and periodic acid-Schiff staining of these inclusions did not suggest the phagocytosis of particles from the implants but more likely indicated the phagocytosis of organic material. Jacobs et al. described an amorphous chromium orthophosphate hydrate-rich material found both on the devices and in the periprosthetic tissues as a corrosion product resulting from implant modularity of the head and neck junctions[32]. We found that, in contrast to the drop-shaped inclusions, these precipitates were so large that they were incorporated in foreign-body giant cells and could be recognized on unstained tissue sections by the appearance of their crystallinity.

In order to find out whether the development of hypersensitivity might be related to the amount of cobalt and chromium released from the articulating surfaces, we compared the amount of metal particles seen histologically in the tissues with the intensity of the lymphocytic infiltrate and found that the amount of metal wear abraded from the joint was not consistent with that found in the tissue. In other words, a connection between the immunological response and the amount of metal contained in the tissue could not be established.

In the control groups, the morphological features of the tissues around the total hip endoprostheses with components made of cobalt-chromium-molybdenum alloy were clearly different from those around the prostheses without any chromium or cobalt. In the latter, there were neither lymphocytic infiltrations nor changes of the vessels that would indicate a cell-mediated hypersensitivity. While almost all of the periprosthetic tissues from patients with components made of cobalt-chromium-molybdenum alloy contained metal particles, lymphocytic infiltrates were found in only one-third of the cases with abrasion marks on a cemented cobalt-chromium-molybdenum stem and in one-half of the cases with a classic metal-on-metal joint. Moreover, the number of cells within the infiltrates was markedly lower in those two groups than it was in the group with a second-generation metal-on-metal bearing.

Our findings suggest that lymphocytic infiltration may also occur in the tissues around other cobalt-chromium-molybdenum-containing implants, as was demonstrated by Jasty et al.[33]. Therefore, the reaction seen with these second-generation metal-on-metal articulations is not a new phenomenon. However, at present, we cannot explain the different intensity of the reaction.

The prevalence of hypersensitivity reactions in patients with an all-metal joint replacement appears to be low. However, we believe that, despite its low probability, patients should be informed about the risk of becoming sensitive to a metal-on-metal articulation. Early intervention may halt the progression of osteolysis and avoid loosening of the implants. Furthermore, when failure of an implant with a metal-on-metal articulation is associated with a possible hypersensitivity reaction, early exchange of the prosthesis with an implant that has another combination of material for the bearing surfaces is mandatory.

Appendix

eA A table presenting the clinical data on all nineteen patients is available with the electronic versions of this article, on our web site at jbjs.org (go to the article citation and click on "Supplementary Material") and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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