



■ INSTRUCTIONAL REVIEW

The pathobiology and pathology of aseptic implant failure

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Pathological assessment of periprosthetic tissues is important, not only for diagnosis, but also for understanding the pathobiology of implant failure. The host response to wear particle deposition in periprosthetic tissues is characterised by cell and tissue injury, and a reparative and inflammatory response in which there is an innate and adaptive immune response to the material components of implant wear. Physical and chemical characteristics of implant wear influence the nature of the response in periprosthetic tissues and account for the development of particular complications that lead to implant failure, such as osteolysis which leads to aseptic loosening, and soft-tissue necrosis/inflammation, which can result in pseudotumour formation. The innate response involves phagocytosis of implant-derived wear particles by macrophages; this is determined by pattern recognition receptors and results in expression of cytokines, chemokines and growth factors promoting inflammation and osteoclastogenesis; phagocytosed particles can also be cytotoxic and cause cell and tissue necrosis. The adaptive immune response to wear debris is characterised by the presence of lymphoid cells and most likely occurs as a result of a cell-mediated hypersensitivity reaction to cell and tissue components altered by interaction with the material components of particulate wear, particularly metal ions released from cobalt-chrome wear particles.

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Introduction

An adverse response in periprosthetic bone and soft tissues to implant-derived material components of wear debris is widely recognised as a significant cause of aseptic implant failure. The material components that induce an adverse response include particulate wear and corrosion debris, organometallic complexes, metal salts/oxides and free metal ions. Certain physical and chemical characteristics of the material components influence the pathobiology of the host response in soft tissue and bone, and in this way favour the development of particular complications that lead to implant failure, such as periprosthetic osteolysis, which leads to aseptic loosening, and soft-tissue necrosis and inflammation, which can result in pseudotumour formation.

Insertion of an implant component into bone results in necrosis of bone surrounding the implant – this occurs due to trauma resulting from preparation of the implant bed, but also in cemented implants from local generation of heat that occurs when the

polymethylmethacrylate cement polymerises *in situ*.^{1–3} Following necrosis, there is formation of reparative fibrous and granulation tissue around the implant. A dense fibrous tissue pseudomembrane ultimately forms around the implant. This membrane is itself surrounded by reparative woven and lamellar bone that is remodelled along the lines of stress to which the bone is subjected. Autopsy studies have shown that well-fixed stable implants usually have little intervening fibrous tissue between the implant and surrounding cortical or cancellous bone, whereas loose implants are covered by a thick fibrous pseudomembrane which contains numerous implant-derived wear particles to which there is a foreign body macrophage and giant cell response to wear particles with a variable lymphocyte reaction.^{1,3,4} Reparative fibrous tissue may or may not be covered by a synovial lining and/or fibrinous material, and may contain bone fragments or haemosiderin. A similar cell and tissue response to implant-derived wear particles occurs in bone where there is often also evidence of

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increased bone remodelling with osteoblastic and osteoclastic activity.

It is important to recognise that, in terms of general pathology, the host response to wear particle deposition in periprosthetic tissues is fundamentally similar, whatever the nature of the implant-derived foreign material. Thus, in soft tissue and bone, regardless of whether the material is derived from a metal-on-polyethylene (MoP) or metal-on-metal (MoM) prosthesis, there will be evidence to a greater or lesser extent of cell and tissue injury and a reparative response in which there is an innate and adaptive immune response to the material components of implant wear.

Innate immune response to implant-derived wear

The host response to deposition of implant-derived wear particles in periprosthetic tissues is initially an innate non-specific foreign body response. This is mediated principally by macrophages which are specialised phagocytic cells that form part of the first-line defence against potential pathogens.^{5,6} Macrophages do not require previous exposure to a given pathogen in order to initiate a response and are specialised to sequester, remove and process foreign body material.⁷ If the implant-derived foreign body wear particles are too large to be phagocytosed by a single cell, macrophages can fuse with each other to form macrophage polykaryons or multinucleated foreign body giant cells (FBGCs) which surround or sequester the large particles. Discrete foreign body granulomas containing macrophages (+/- FBGCs) can be seen histologically in response to polymeric and metallic wear debris in periprosthetic tissues.

Phagocytosis of biomaterial wear particles depends on several factors including particle load, size, shape and chemical composition.^{8,9} The particle load (dose) in periprosthetic tissues is dependent on the average particle size and amount or volume of implant-derived wear debris. An increase in the particle load has significant effects on cells that are involved in the innate and adaptive immune response to foreign material with consequent changes in bone and soft tissue. Higher amounts of particulate debris are produced when there is component malposition, impingement, third-body wear or significant component loosening.¹⁰⁻¹² MoP articulations generally produce greater volumetric wear than MoM implants, but MoM implants generate a much larger number of particles, the metal particles being an order of magnitude smaller in size and, therefore, much more numerous.¹⁰⁻¹⁴ Ultra-high molecular weight polyethylene (UHMWP) particles can vary in size from very large (hundreds of microns) to very small (submicron) with a mean size of 660 nm. Analysis of particles generated from MoM articulations has shown that most cobalt-chrome (Co-Cr) particles are nanometre in size (mean 30 nm to 57 nm).

Wear particles that are shed from the implant components are immediately coated with host proteins derived from blood and interstitial fluid.^{7,15,16} Macrophages and other inflammatory cells react to foreign body wear particles through this protein layer which includes fibronectin, vitronectin, albumin, fibrinogen, globulins and other cell-derived proteins. These protein-associated particles tend to clump and are often presented to macrophages as a large complex. As part of the innate immune response, macrophages bind integrin receptors, Fc receptors, complement receptors and scavenger receptors. In addition, macrophages express a wide range of pattern-recognition receptors (PRRs) which monitor and react with pathogen-associated molecular patterns (PAMPs) and/or danger-associated molecular patterns (DAMPs); the latter are endogenous molecules normally found inside host cells and released when there is cell damage (e.g. due to cell toxicity). These endogenous signals (alarmins) are normally hidden from recognition by innate immune cells but, when there is cell injury, are released into the extracellular space and activate other immune cells. DAMPs include nuclear proteins, purine metabolites, uric acid and mitochondrial components. Detection of DAMPs by PRRs, such as toll-like receptors (TLRs) and inflammasomes, triggers inflammation, which is important for the clearance of dead cells and regeneration of damaged tissue.^{15,16} In the inflamed prosthetic tissues, reactive oxygen species, matrix metalloproteinases and other substances associated with the production of endogenous DAMP molecules adhere to the biomaterial surface and exacerbate the inflammatory response. Although macrophages are able to phagocytose wear particles without any opsonising proteins, particles with attached proteins, such as DAMPs, stimulate a more effective inflammatory foreign body response to wear debris.^{7,15,16}

TLRs and other PRRs on the macrophage cell surface also recognise molecular structures on microbes, such as lipopolysaccharide (LPS), beta-glycan and flagellin, which adhere to the implant surface as a subclinical bacterial biofilm.¹⁷⁻¹⁹ It has been shown that TLR4-deficient mice exhibit decreased particle-associated osteolysis and that an increase in TLR4 is present in the tissues around loose implants. TLR4 acts via myeloid differentiation primary response 88 (MyD88), resulting in the production of pro-inflammatory factors. Disruption of MyD88 signalling diminishes particle-induced production of tumour necrosis Factor α (TNF α) and other pro-inflammatory cytokines.^{17,19} Foreign body macrophages also express the macrophage receptor with collagenous structure (MARCO) which acts as a PRR.^{15,16} The expression of this scavenger receptor is strongly upregulated in macrophages by various microbial stimuli in a TLR-dependent or TLR-independent manner. MARCO binds soluble LPS and intact bacteria; its expression is induced by implant-derived wear debris and it may play an important role in

inducing the macrophage response in periprosthetic tissues.^{20,21}

Macrophages also release chemokines which are small proteins that play a central role in inflammatory cell migration and activation.²² Chemokines are up-regulated in periprosthetic tissues when there is aseptic implant failure.^{15,16} Wear particles induce expression of several macrophage chemokines including MCP-1 (or CCL2), which attracts additional macrophages to the sites of inflammation; blocking the interaction of MCP-1 with its receptor CCR2 results in inhibition of macrophage migration and a decrease in particle-induced osteolysis.^{23,24} Other cytokines, such as CCL3 (MIP-1 α), also play a role in particle-induced inflammatory cell migration.^{15,16}

Macrophages have a dynamic phenotype that changes with local microenvironment signals that broadly direct macrophages into two relatively distinct (but interchangeable) phenotypes.^{5,6,15,16} M1 or classically activated pro-inflammatory macrophages are induced by interferon γ , either alone or with LPS or TNF α . M2 alternatively activated macrophages are induced by exposure to a variety of signals including the cytokines interleukin 4 (IL-4), IL-13 and IL-10, immune complexes and certain hormones. M1 macrophages predominate where there is aseptic implant failure with osteolysis.^{15,16} The M1 phenotype is characterised by high capacity to present antigen and to produce certain pro-inflammatory chemokines (e.g. CCL2-4, CXCL8-12) and cytokines (e.g. TNF α , IL-1, IL-6, IL-12, IL-23). Alternatively activated M2 macrophages are induced following exposure to IL-4, IL-13, IL-10 or glucocorticoids. M2 polarisation is characterised by suppression of pro-inflammatory cytokines, intracellular killing and antigen presentation. Macrophages in osteoarthritic joints are predominantly M2 in type and a potential strategy to treat aseptic loosening is to promote polarisation of macrophages to the M2 phenotype.²⁵⁻²⁷

A significant adverse effect of deposition of biomaterial wear particles in periprosthetic tissues is osteolysis (bone resorption). This leads to aseptic loosening of implant components, a common cause of aseptic failure. Osteolysis has been reported in relation to all types of implant-derived wear particles. Macrophages remain viable following phagocytosis of UHMWP wear particles and are capable of further differentiation into osteoclasts, specialised cells of the mononuclear phagocyte system responsible for bone resorption.^{28,29} Macrophages that have phagocytosed wear particles are activated M1 macrophages which release numerous cytokines that promote osteoclastic bone resorption.³⁰⁻³² Macrophage colony stimulating factor (M-CSF) and Receptor Activator for NF Kappa B ligand (RANKL) are required for osteoclast formation.³³ M-CSF is produced by activated macrophages and stromal cells and RANKL is expressed by osteoblasts and fibroblast-like stromal cells in periprosthetic soft tissues.³⁴⁻³⁶ RANKL is also expressed by bone marrow stromal cells and other cells including

T lymphocytes. TNF α induces the expression of RANKL. Macrophages exposed to wear particles increase the expression of TNF α , predominantly via the NF-Kappa B pathway.^{15,16} Other cytokines that promote osteolysis include IL-1 and IL-6. The RANKL-RANK interaction activates the NF-Kappa B transcription factor that regulates numerous pro-inflammatory pathways.^{15,16,32} The expression of RANK, the receptor for RANKL, is upregulated in tissues around failed total joint arthroplasties and RANK signalling is essential for particle-induced osteoclast formation in mice. However, its disruption in knockout mice does not seem to alter particle-induced inflammation, and it is possible that other inflammatory cytokines and growth factors may play a role in inducing RANKL-independent pathways of osteoclast formation.^{33,36}

A potential consequence of phagocytosis of implant-derived wear debris is cell toxicity. This is dependent to a large extent on the nature (particle size, shape and chemical composition) of the material components of phagocytosed wear debris particles. Apoptosis of macrophages is induced by polymer and metal particles in a size and concentration-dependent manner.^{9,13,28,29} Macrophages, however, are able to tolerate UHMWP and ceramic wear particles better than metal wear particles, with significantly less apoptosis and necrosis observed in cell cultures;^{9,29,37-40} this tolerance is further demonstrated by the fact that macrophages which have phagocytosed UHMWP particles are capable of increased osteoclast differentiation compared with those which have phagocytosed Co-Cr particles.²⁸ Histologically, the response to UHMWP wear particles is dominated by a foreign body macrophage response in which many of these cells remain viable after particle phagocytosis.^{1,4,9} Co-Cr particles are also phagocytosed by macrophages as part of the innate immune response. Phagocytosed metal particles are transported to lysosomes where, in the acid microenvironment of these organelles, they are subject to corrosion, resulting in the release of chromium and cobalt ions and consequent apoptosis and cell death.^{8,9,11,41-43} This process is likely to contribute significantly to the extensive necrosis seen in MoM peri-implant tissues. The physicochemical features of nano-sized metal wear particles, which are of small size and have a large specific surface area that predicts greater biological activity (including cytotoxicity) compared with larger UHMWP particles, is likely to be significant in this regard. MoM implant-derived nanoparticles are highly reactive and high concentrations of chromium and cobalt ions are toxic to macrophages, fibroblasts and lymphocytes.^{8,9,13,41,43-47} Metal particles (and metal ion species) released from the implant are at the highest concentration in the superficial zone of the peri-implant tissue membrane, and it is in this area that necrotic and apoptotic macrophages are most commonly seen histologically in MoM peri-implant tissues.⁴⁸⁻⁵² It has been shown that the presence of Co-Cr particles in the joint is associated with synovial tissue

necrosis and surface ulceration, and that this occurs even in the absence of a loose prosthesis.⁵³

Most Co-Cr metal wear particles are round in shape, although a variable number are needle-like or elongated.^{10,14} Differences in the physicochemical characteristics of Co-Cr particles in terms of size and shape, as well as specific material composition, could explain differences in the pathological response and clinical outcome with regard to particular types of MoM implant.⁵⁴ One can imagine that the cytotoxic effect of metal ions on macrophages is likely to lead to a vicious cycle in which the release of Co-Cr implant-derived metal wear particles from an MoM implant results in macrophage recruitment and particle phagocytosis, followed by macrophage apoptosis and cell death. This would then result in a re-release of metal particles, leading to further macrophage recruitment and repetition of this process.^{51,55}

Adaptive immune response to implant-derived wear

In addition to an innate immune response, implant-derived wear particles also induce an adaptive immune response. Histologically, this is demonstrated by the presence of lymphoid cells, particularly lymphocytes, within periprosthetic tissues. A pronounced often heavy perivascular lymphocyte (and plasma cell) reaction, termed aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) is commonly seen in periprosthetic tissues in response to the deposition of Co-Cr wear particles derived from MoM articulations.^{49-51,56} This lymphoid response is thought to develop as a result of a specific adaptive, cell-mediated (type IV, delayed hypersensitivity) reaction to cell and tissue components altered by interaction with the material components of particulate metal wear debris.⁸ A cell-mediated immune response occurs when sensitised T lymphocytes recognise an antigen, together with MHC class II molecules on antigen-presenting cells (e.g. macrophages, dendritic cells). Stimulated T cells then proliferate and release lymphokines which attract and activate macrophages and other lymphoid cells. If the reaction becomes chronic, it results in a heavy macrophage infiltrate and, in some cases, immune granuloma formation. Although T lymphocytes are found in MoP peri-implant tissues, a specific cell-mediated response to UHMWP particles does not appear to play a major role in MoP implant loosening.⁵⁷⁻⁶⁰ Proteins can bind to UHMWP,⁶¹ but histologically the lymphocyte response in MoP periprosthetic tissue is not usually pronounced. In some cases, there may be small collections of lymphocytes around blood vessels, although it is possible that these are related more to metal than UHMWP particle deposition.⁶²

In regard to MoM implants, Co-Cr particles produce high levels of metal ions which can act as haptens that combine with large carrier (cell- or tissue-derived) protein molecules to become immunogenic.^{8,48,63,64} The

pathological features of a cell-mediated Type IV hypersensitivity reaction include a heavy perivascular lymphocytic infiltrate, a macrophage response and immune granuloma formation with tissue necrosis. These pathological features are characteristically seen in MoM periprosthetic tissues. A similar Type IV hypersensitivity response is seen in contact dermatitis. Contact dermatitis due to metal allergy is relatively common, occurring in 10% to 15% of the population.^{8,63,64} Metals known to induce this response include nickel, chromium and cobalt, all of which are found in implant components. As in other pathological conditions where there is a Type IV hypersensitivity response, the non-specific innate foreign body macrophage response to Co-Cr wear particles (leading to macrophage accumulation and cell and tissue necrosis) promotes and maintains the specific adaptive immune response.

Although the profound inflammatory and necrotic changes seen in MoM periprosthetic tissues are a consequence of a cytotoxic and hypersensitivity response to metal wear, clinicopathological studies have not established that there is a minimum threshold dose of Co-Cr particles that guarantees an adverse reaction in peri-implant tissues. In a recent study, it was shown that necrotic and inflammatory changes are commonly found in the periprosthetic tissues around MoM resurfacing implants, especially in patients with pseudotumours.⁵⁵ Necrosis and the extent of the macrophage infiltrate, reflecting the innate response, correlated with the amount of prosthetic wear. The extent of the perivascular lymphocyte reaction (ALVAL), reflecting the adaptive cell-mediated response also correlated with the amount of wear in most cases. However, it was noted that a small number of pseudotumours had relatively low wear and a heavy ALVAL response, and that a few had high wear with a minimal ALVAL response. Thus, it would appear that although an increase in the amount of wear from MoM components increases the frequency of an adverse reaction to metal in periprosthetic tissues, some reactions can be associated with low (or expected) wear, presumably due to variability in the adaptive immune response. The findings of most studies that have attempted to correlate serum metal ions levels in MoM arthroplasty patients with clinical and radiological outcomes are generally in keeping with this conclusion.⁶⁵⁻⁶⁷ Although serum metal ion levels are commonly measured and threshold Co and Cr ion levels for clinical concern have been proposed, it is well-recognised that profound necrotic and inflammatory changes in MoM periprosthetic tissues and implant failure can occur in patients with normal serum metal ion levels. It is possible that the measurement of metal ion levels in periprosthetic tissue correlates more strongly than serum metal ion levels with pathology in periprosthetic tissues.^{43,68,69} Some observers have correlated wear volume and ion levels with the predominance of a macrophage or lymphocyte response,¹¹ however, the extent

of the macrophage infiltrate can be underestimated in the context of necrotic and inflammatory changes in periprosthetic tissues, and is often appreciated only after immunohistochemistry.^{51,52}

MoM arthroplasties have also been strongly associated with the formation of pseudotumours.^{51,70-74} A pseudotumour is as a solid and/or cystic mass that communicates with a prosthetic hip joint. By definition, this mass is not due to neoplasia or infection. Essentially, MoM pseudotumours show features of both the innate and adaptive immune response to metal wear particles with pronounced cell and tissue necrosis, a heavy macrophage response to wear particles and, in most cases, an ALVAL infiltrate.^{51,55,70-72} It should be noted that the term 'pseudotumour' has also been used to describe the rare development of a granulomatous soft-tissue mass related to deposition of excessive UHMWP wear debris from MoP total hip arthroplasties.⁷³⁻⁷⁸ These MoP-associated pseudotumours, which have also been called 'aggressive granulomatous lesions' or 'aggressive granulomatosis', differ from the pseudotumours associated with MoM implants. The major pathological feature seen in MoP-associated aggressive granulomatosis is a very heavy macrophage response to the deposition of a very large volume of UHMWP wear particles in periprosthetic tissues.⁷⁴⁻⁷⁷ These MoP-associated lesions do not contain the significant lymphoid (ALVAL) component or the extensive necrosis typically seen in MoM pseudotumours. Carli et al⁷⁹ reviewed all case reports/series of non-MoM associated 'pseudotumours' and noted that that they were not only few in number, but also consistently showed a heavy macrophage response to abundant wear particles histologically. Only one case with an extremely high amount of metal debris due to taper corrosion had a significant lymphocytic infiltrate. This contrasts with the frequent finding of a lymphocytic infiltrate in MoM pseudotumours. Santavirta et al⁷⁷ studied the immunopathology of non-MoM pseudotumours and noted that the inflammatory infiltrate in these lesions was composed mainly of UHMWP wear particle-associated macrophages with few or no lymphocytes. This is very different from the situation with MoM pseudotumours, where there are numerous T lymphocytes.^{51,52} The persistence of this lymphoid infiltrate in periprosthetic tissues may account for poor outcomes following the revision of MoM pseudotumours.⁸⁰

Relevance of implant-related pathology

Although there are now many reports documenting an adverse local tissue response to deposition of Co-Cr particles in periprosthetic tissues related to modern third-generation MoM implants, it is worth noting that there were several studies that described a similar response in first-generation MoM implants. These studies illustrate the value of histopathology in the assessment of implant failure. It could be argued that insufficient attention was

given to the significance of the pathological findings in these studies before MoM hip implants were recently re-introduced. In 1974, Winter⁸¹ described necrosis in tissues around retrieved MoM hip arthroplasties associated with Co-Cr particle deposition in acellular collagen and in phagocytic cells. In the same year, Evans et al⁸² reported necrosis of bone and capsular tissue around MoM hip implants and suggested that these changes occurred as a result of a sensitivity reaction to Co and Cr ions derived from metal wear particles. In 1975, Jones et al⁸³ associated necrosis of bone and capsular tissues from retrieved first-generation MoM prostheses with a toxic and hypersensitivity reaction to cobalt that caused an avascular phenomenon. In 1977, Brown et al⁸⁴ examined periprosthetic tissues of 20 failed McKee-Farrar implants and found that these contained evidence of tissue necrosis in the soft tissue and bone, and that in some cases this necrosis was very extensive – all specimens showed a macrophage response to metallic debris and in some cases a lymphocytic infiltrate was noted. In 1996, Doorn et al⁸⁵ noted necrosis and extensive connective tissue degeneration (which they termed necrobiosis) in periprosthetic tissues around first- and second-generation MoM hip implants. They also noted a lymphocyte and plasma cell infiltrate in all cases. These histopathological findings of marked tissue necrosis and a heavy chronic inflammatory cell infiltrate in periprosthetic tissues were in keeping with other experimental and clinical results, which indicated that cytotoxicity and hypersensitivity can occur as a consequence of metal wear particle deposition.

In conclusion, histopathological findings in periprosthetic tissues reflect the pathobiology of the host innate and adaptive immune response to wear particle deposition. The non-specific innate foreign body response (leading to macrophage accumulation and tissue necrosis) and the adaptive immune response (characterised by the presence of numerous lymphocytes) are processes that are not mutually exclusive, but intimately related, leading to the maintenance of chronic inflammation in periprosthetic tissues. The physicochemical characteristics of implant-derived wear particles including particle size and composition, as well as particle load, play a major role in determining the nature of the host response and the specific modes of failure associated with certain types of implant. Some consistency is required in the terminology used by surgeons, radiologists and pathologists to refer to the manifestations/complications of implant failure. The term ALVAL was originally used to describe the morphological finding of a perivascular lymphoid infiltrate in periprosthetic tissues.^{49,50} It should not be used as a blanket term to describe all the pathological changes associated with MoM implant failure. Nor should it be used to refer to all the clinical manifestations of the adverse tissue reactions associated with MoM implants. The term 'pseudotumour' should also not be used in this way – its use should be restricted to mass lesions

associated with MoM implants (and not MOP implants). The acronym ARMD (adverse response to metal wear debris) has been used to describe the spectrum of clinical features and pathological changes that occur in periprosthetic tissues as a consequence of metal wear particle deposition. In histological terms, ARMD does not have a specific morphological definition and refers to features of both the innate and adaptive immune response with evidence of cytotoxicity, tissue necrosis, a macrophage response to metal particles and a heavy lymphoid infiltrate in periprosthetic tissues.

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ICMJE conflict of interest

- The author has provided expert opinion in arthroplasty-related medicolegal cases.

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