Adverse reactions to metal debris: histopathological features of periprosthetic soft tissue reactions seen in association with failed metal on metal hip arthroplasties

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ABSTRACT

Aim To describe the histopathology of localised adverse reactions to metal debris (ARMD) seen in association with failed metal on metal (MoM) hip arthroplasties. The nature of aseptic lymphocytic vasculitis associated lesion (ALVAL) is investigated.

Methods Periprosthetic soft tissues biopsied at time of revision from failed MoM hip arthroplasties from January 2007 to March 2011 were analysed. The inflammatory cell response was categorised into perivascular lymphocytic cuffing (ALVAL), lymphoid aggregate formation with or without germinal centres, metallosis characterised by sheets of macrophages with intracytoplasmic metallic debris and well-defined granulomas.

Results 123 patient samples were analysed, 36 males (29.2%) and 87 females (70.8%). Three cases showing complete tissue necrosis were excluded. Patients were reviewed between 3.27 to 69.6 months postarthroplasty, with an average of 30.92 months. 103 cases (85.8%) showed ALVAL, 18 cases also showed well-defined granulomas. Of the 103 cases with ALVAL, 60 cases also showed a diffuse chronic lymphocytic synovitis, and 40 cases showed lymphoid aggregates with germinal centres. 17 cases (14.2%) showed pure metallosis. Small vessels showing ALVAL expressed peripheral node addressin.

Conclusions ARMD is a spectrum of changes comprising of pure metallosis, ALVAL and granulomatous inflammation. ALVAL, a distinctive inflammatory response seen in ARMD, is a precursor of lymphoid neogenesis. Lymphoid neogenesis documented in a variety of chronic inflammatory conditions most probably contributes to tissue necrosis and prosthetic failure seen in MoM hip arthroplasties. The role of vascular changes in contributing to necrosis is unclear at this stage.

INTRODUCTION

Metal on metal total hip arthroplasties were used in the 1960s and 1970s. Modern hip resurfacing became a popular procedure in the late 1990s.[1–4] It was introduced in younger patients as only the degenerate cartilage was removed along with very little bone, bone stock was preserved and hip replacement could be used in the future, in the event of failure.[1–4] Over the years, metal hip articulations gained popularity and were preferred over polyethylene devices, in cases where osteolysis and aseptic loosening of the prosthesis were a concern. A variety of resurfacing devices are present in the market, which consist of ceramic or metal together or on their own.[1–4] Metal on metal (where the acetabular cup and femoral head are resurfaced with metal) is a popular option and the National Institute for Health and Clinical Excellence guidelines (UK) for its use were published in 2002.[5] The metal used is usually an alloy of cobalt and chromium. When the triad of patient characteristics, type of device and surgical technique are optimised, the chances of failure of the device are minimised.[1] On implanting metal on metal devices, there is a usual run in period of approximately 6–12 months when blood concentrations of cobalt/chromium rise due to wear, and reach a steady state thereafter.[1] There is a simultaneous rise in local tissue levels of metal ions. Failure of metal on metal hip devices is usually associated with raised tissue levels and blood levels of metal ions. The Medicines and Healthcare products Regulatory Agency, UK, has issued a warning for all metal on metal hip implants. This involves monitoring of blood metal ion levels and looking for symptoms of pain and large hip joint effusions.[6]

Willert *et al* introduced the concept of aseptic lymphocytic vasculitis associated lesion (ALVAL) in 2005.[7] A lymphocyte dominated immunological response within the periprosthetic tissues from metal on metal hip articulations obtained at the time of revision was described. The inflammatory response comprised a diffuse and perivascular chronic lymphocytic infiltrate with development of high endothelial venules (HEVs). Davies *et al* further detailed this unusual perivascular lymphocytic inflammation within the synovium.[8] It was considered to be unusual because the usual response seen in polyethylene devices consisting of a macrophagic response with engulfed polyethylene debris leading to osteolysis was not seen. A semiquantitative analysis of the chronic inflammation was performed in various hip prostheses including metal on metal and metal on polyethylene. The perivascular lymphocytic cuffing was typically seen within the deeper subsynovium in metal on metal articulations. Both studies noted surface necrosis and metal debris, but did not clearly state the significance of the perivascular lmphocytic cuffing with regard to vascular damage. Subsequently, there have been articles describing the adverse reactions clinically

as pseudotumours, which are cystic/solid masses developing in relation to failed metal prostheses.[9–12] These studies noted the presence of ALVAL or perivascular lymphocytic cuffing, but did not elaborate any further on whether there was lymphocyte mediated vascular damage, that is, fibrinoid necrosis, onion skinning, hyalinisation and/or vascular occlusion. Evans *et al* in 1974 noted vascular obliterative changes in the form of fibrous intimal proliferation and fibrinoid necrosis in the periprosthetic tissues and concluded the vascular changes caused tissue and bone necrosis. Similar vascular changes were also seen by Brown *et al*, Jones *et al* and Winter *et al*.[13–16] However, Brown *et al* could not conclude that the vascular wall changes seen led to the necrosis as such changes were commonly seen in the synovium affected by a chronic disease process.

Lymphoid neogenesis, also known as formation of tertiary lymphoid organs, has been described in various chronic inflammatory conditions including *Helicobacter*-induced active chronic gastritis, autoimmune diseases, neoplasia and graft rejection.[17 18] The reorganisation of a chronic inflammatory cell response into lymphoid aggregates and follicles with germinal centres has been the subject of great interest. This is a dynamic process in which lymphocytic infiltrate evolves into lymphoid aggregates with germinal centres.[19] Development of HEVs and dendritic cell networks play an important role in lymphoid neogenesis.[18] In the face of a sustained immune response to a persistent antigen, the local tissue chronic inflammatory cell response is organised into tertiary lymphoid organs with ectopic germinal centres, capable of locally generating B cells and T cells. Anatomically, tertiary lymphoid organs are similar to secondary lymphoid organs also known as lymph nodes.[20–22] Lymphoid neogenesis while optimising the local immune response causes considerable tissue destruction and loss of function.[18] There has been a vast amount of interest in its pathophysiology in the hope that it could be a potential target for treatment of chronic inflammatory conditions. Within the synovium, lymphoid neogenesis has been documented in inflammatory arthropathies but more significantly in rheumatoid arthritis (RA).[19 23 24]

In this article, we will describe the histopathology seen in association with metal on metal hip arthroplasties including ALVAL, lymphoid neogenesis, granulomatous inflammation and metallosis. The pathology has been described by a generic all encompassing term, adverse reactions to metal debris (ARMD). The histopathology is briefly compared with other common inflammatory arthropathies.

MATERIALS AND METHODS

Patients

As a routine procedure, all patients considered for revision of metal prostheses undergo a preoperative protocol, according to the Medicines and Healthcare products Regulatory Agency, UK, guidance. This includes the measurement of Harris hip scores, updated pelvic radiographs, blood metal ion testing, ultrasound scan or aspiration of the hip joint effusion. During revision surgery, intraoperative macroscopic appearances were meticulously recorded by the senior surgeon, and tissue samples from periprosthetic soft tissue were sent to histopathology for analysis. Tissue samples were provided from between two and four sites surrounding the metal on metal implant. There was no attempt made to distinguish if the tissue was sent from the hip capsule, acetabulum or bursa. No femoral or bony tissue was included in this study. Up to 10 paraffin blocks/cassettes were processed per site, to avoid sampling error due to necrosis and to ensure the viable tissue was well represented. Tissue samples were sent to microbiology to rule out sepsis. All explants underwent wear analysis using the coordinate measuring machine at an independent centre. In this study, we have included all the samples received from January 2007 to March 2011.

Histology

Routine H&E stained slides were examined by a histopathologist independently of the clinical findings. Up to six tissue levels were examined where a chronic lymphocytic infiltrate was noted within and around large blood vessels (a larger vessel is defined as any vessel larger than an arteriole or venule). T lymphocyte markers used were CD4, CD8 and CD43 (SP35, SP57, L60 Ventana, Roche. Prediluted), and B lymphocyte markers used were CD 20 (L26 Ventana, Roche. Prediluted). HEVs were stained with MECA-79, also known as peripheral node addressin (PNAd) (Novus Biologicals, Littleton USA Dilution, 10 μg/ml).

The surface tissue necrosis was typed according to Davies *et al*.[8] Type 1 surfaces showed intact synovial surface epithelium. In Type 2 surfaces there was a loss of the synoviocyte layer without fibrin deposition. Type 3 surfaces were associated with fibrin deposition, and in Type 4 surfaces, there was extensive necrosis with loss of architecture. The extent of Type 4 surface necrosis was used to grade the overall tissue necrosis within a given sample. In Grade 4 necrosis, more than 75% of the tissue sample showed Type 4 necrosis. In Grade 3 necrosis, between 25% and 75% showed Type 4 necrosis. Necrosis was considered to be Grade 2 when either less than 25% of the tissue showed Type 4 necrosis or the tissue showed Type 3 surface. Grade 1 necrosis consisted of Type 2 surface.

The inflammatory response

On H&E stained sections, the chronic lymphocytic infiltrate present was categorised into: (a) diffuse synovitis, (b) lymphoid aggregate synovitis and (c) germinal centre containing synovitis.

Diffuse synovitis was defined as a chronic lymphocytic infiltrate not organised into follicles or aggregates. Lymphoid aggregates were defined as perivascular collections of lymphocytes. The blood vessels in the centre of the aggregates were similar to HEVs seen within lymph nodes. Lymphoid aggregates contained two or more such vessels. Lymphocytic cuff thickness was measured using a graticule (eyepiece micrometre disc 21 mm Nikon Eclipse 80i). The radial thickness was measured from a centre within a cuff along the longest axis of the cuff. An average of approximately 10 cuffs was taken. Lymphocytic cuff thickness was graded 1–4. Grade 1 cuffs were <0.25 mm, Grade 2 were from 0.25 to 0.5 mm, Grade 3 were from 0.5 to 0.75 mm and Grade 4 were >0.75 mm. Lymphoid aggregates with germinal centres consisting of immature lymphoblasts, with or without plasma cells, were classified as germinal centre containing synovitis. T cell and B cell lymphocytic markers showed organisation into T cell and B cell areas. The presence of lymphoid aggregates within skeletal muscle if present was noted.

Vascular changes within blood vessels surrounded by the lymphoid infiltrate

Vascular changes such as hyalinisation and onion skinning due to pericyte proliferation were noted. Hyalinisation extending

into the surrounding extracellular tissues was stained with Periodic acid Schiff (PAS) and Congo red.

Other features

Granulomatous inflammation whether organised into well-defined granulomas or sheets of histiocytes containing metallic debris was noted. The thickness of the sheets of histiocytes present was measured with the graticule. Grade 1 was <1 mm thick, Grade 2 between 1 and 2 mm and Grade 3 >2 mm. Metal particle load within the macrophages was assessed by the method used to assess tissue iron overload in liver biopsies[25 26] (table 1).

Energy dispersive x-ray spectrometry (EDX) was used to confirm the presence of metal particles and the components on deparaffinised tissue. The microscope used was environmental scanning electron microscope field emission gun (FEI XL30 ESEM-FEG). The samples were coated with carbon in order to make them electrically conducting. High vacuum was used to look at the samples for both imaging and analysis.

RESULTS

There were 123 patient samples in total; three of these showed complete tissue necrosis with no viable tissue for assessment and were excluded from the study. There were 36 males and 87 females, with an age range from 32 to 82 years. There were 87 (70.7%) patients who were under the age of 65 years. Indications for the arthroplasty were primary, secondary osteoarthritis and congenital hip dysplasia. None of these patients had RA. The patients were reviewed from between 3.27 and 69.6 months with an average of 30.92 months. Intraoperatively, there was variable amount of fluid collection within the periprosthetic tissue with foci of metallic tingeing. Necrotic tissue was often cheesy in appearance. Grossly, the non-necrotic tissue showed areas of metallic tingeing. The tissue was thickened, fibrotic and partly necrotic. With large fluid collections, the tissue had the appearance of a thinned out cyst wall. Rarely, there were preserved synovial villi. None of the cases showed features of sepsis on histology and microbiology. EDX was used on two cases, which confirmed the presence of cobalt and chromium. The type of metal on metal implants used is shown in table 2.

Typically, all cases showed varying grades of surface necrosis with complete loss of surface synoviocytes and architecture (figure 1A–H). The pathology seen is summarised in tables 3 and 4. The surface synovium was not intact in any of our cases, and there was no synoviocyte hyperplasia or villous hyperplasia. Multinucleated synoviocytes were not seen. Ghost outlines of necrotic synovial villi could be seen. Beneath the necrosis, aggregates and sheets of histiocytes containing fine black metallic debris were present. Often the histiocytes were arranged in aggregates adjacent to small blood vessels. The histiocytes had slate grey discolouration. In two cases, the histiocytes had a xanthomatous appearance. The metal particles were either needle shaped (figure 2A) or dot-like (figure 2B). Foreign body giant cells with larger metal debris were interspersed. In 17 cases, there was a pure metallosis type reaction without lymphocytic infiltration (figure 2C). Well defined naked sarcoid-like granulomas were seen in 18 cases (figure 2D) in addition to the chronic lymphocytic infiltrate. The majority of the granulomas consisted of pallisading epithelioid histiocytes, and multinucleated giant cells when present were of Touton type. Occasionally, necrotic bony fragments or calcific debris could be seen beneath the areas of necrosis. The deeper tissues showed the characteristic perivascular lymphocytic cuffing (103 cases) (figure 3A) with or without germinal centres. Germinal centres were seen in 40 cases. The germinal centres had a paler centre with immunoblasts with occasional plasma cells (figure 3B). In places with florid lymphoid aggregate formation with germinal centres, the inflammatory response bears a resemblance to small lymph nodes but without a capsule or peripheral sinuses. Russel bodies were not seen. Plasma cells in small numbers were seen in 45 cases with ALVAL. T and B lymphocytic markers showed organisation into distinct central B cell areas with surrounding T cell areas (figure 3C,D). A background of diffuse chronic lymphocytic inflammation was seen in 60 cases. This lymphocytic infiltrate consisted predominantly of admixture of CD4 and CD8 T lymphocytes with interspersed B lymphocytes, and plasma cells. Plasma cell infiltrate is usually mild in comparison with the lymphocytic infiltrate. Eosinophils and neutrophil polymorphs were seen in only one case in our study. Overall, the inflammatory cell response can be patchily distributed and can be of varying intensity in different sections. HEVs were seen centrally within the lymphocytic aggregates. HEVs showed plump cuboidal endothelium, and lymphocytes could be seen transiting from the lumen (figure 4A,B). The vessels were PNAd positive (figure 4C,D), while those vessels not surrounded by the infiltrate were PNAd negative. Structural changes in the vessel walls could be seen in the form of hyalinisation, onion skinning and luminal obliteration (figure 5A–D) in 47 cases. The material was PAS positive and Congo red negative. Fibrinoid necrosis of the vessel wall was not seen. Leucocytoclasis was not seen, but in one case nuclear dust was noted (figure 6C). Eosinophils and neutrophil polymorphs were seen in small numbers in a predominantly lymphocytic infiltrate in this case (figure 6A,B,D). In five cases, vessels larger than the calibre of arterioles or venules showed lymphocytic infiltrate in the walls. In one case, the lymphocytes were identified to be CD8 T lymphocytes. The infiltrate was segmental and cut out in further levels (figure 7A–D).

Table 1 Assessment of metal particle load within the macrophages

Grade	Ease of observation and magnification (eyepiece×objective lens)
0	Granules absent or barely discernable ×400
1+	Barely discernable ×250, easily confirmed ×400
2+	Discrete granules resolved ×100
3+	Discrete granules resolved ×25
4+	Masses visible ×10, naked eye

Table 2 Distribution of the type of metal implants

Implant type	Resurfacing, n=69	Stemmed, n=54
36 MOM	0	31
Adept	1	0
ASR	59	0
ASR XL	0	21
BHR	8	0
BHR Hybrid	1	0
Conserve	1	0

DISCUSSION

The spectrum of changes seen in ARMD is distinctive. The conglomerate of surface necrosis, with macrophagic response containing fine metallic debris, sometimes forming granulomas, along with an evolving ALVAL /perivascular lymphocytic

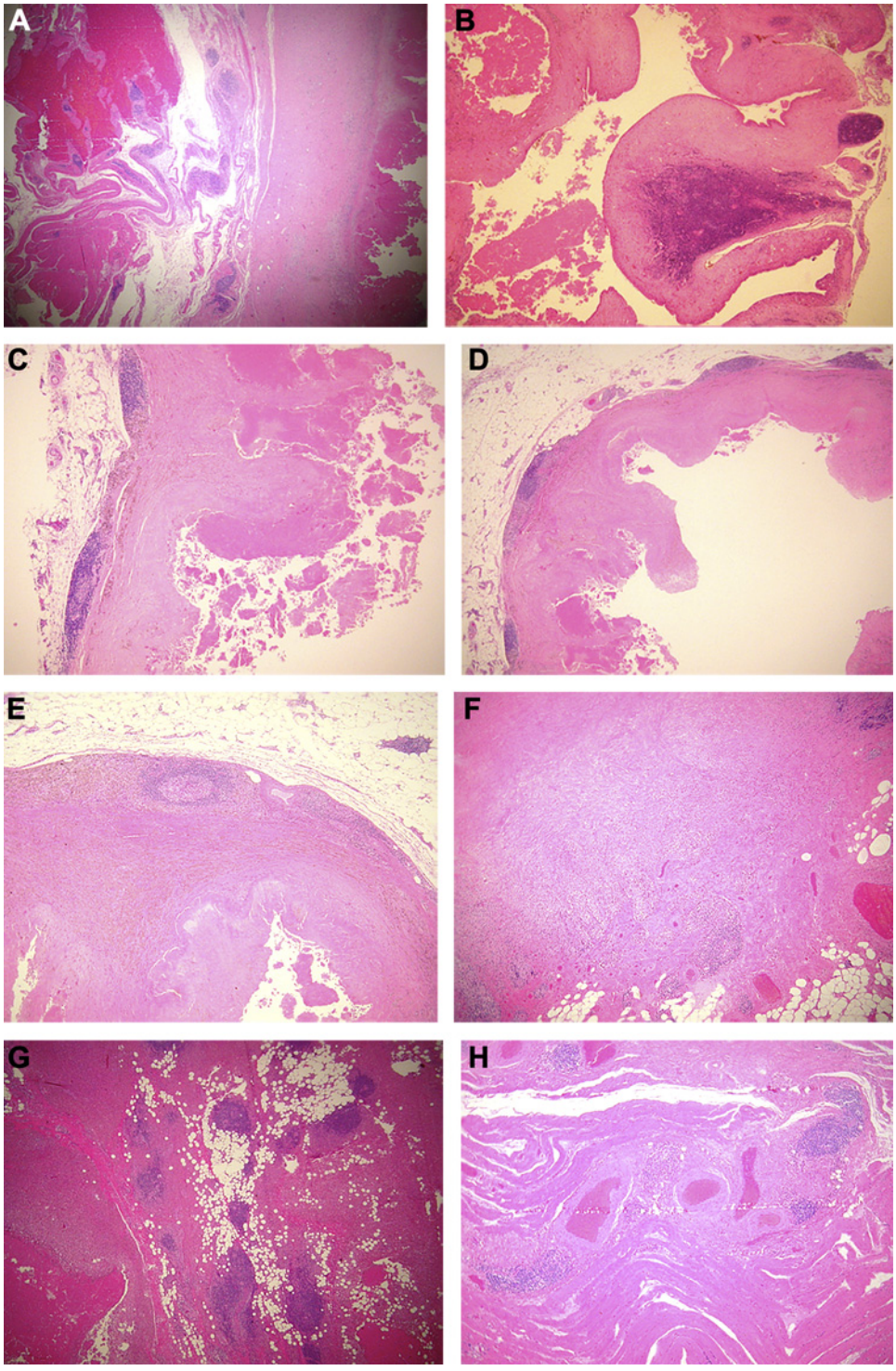

Figure 1 (A–D, E–H) These photomicrographs (magnification ×100) show surface necrosis, beneath which are seen sheets and aggregates of histiocytes containing metallic debris. Aseptic lymphocytic vasculitis associated lesion response is seen in the deeper tissues, for example, adipose tissue (G) and skeletal muscle (H).

infiltrate with or without germinal centres combined with a history of metal on metal implants is diagnostic of ARMD. The surface necrosis is variable and extensive. When there is minimal necrosis and the ALVAL response is not well developed, and because the synovium shows a limited repertoire of chronic inflammatory response, the tissue response in ARMD may be difficult to distinguish from other more common chronic inflammatory arthropathies. Lymphoid aggregate synovitis with or without germinal centres is seen in chronic inflammatory arthritides including osteoarthritis, psoriatic arthritis and more commonly in RA. The majority of rheumatoid synovia show a diffuse chronic synovitis-like picture. A third of the rheumatoid patients show follicular synovitis with or without germinal centre formation.[24] There is no associated surface necrosis, and synovial villous hyperplasia with synoviocyte proliferation is typically seen.[27] Synovial multinucleated giant cells are seen on the surface, with the underlying tissue showing variable chronic inflammation. Plasma cells with Russel bodies are commonly seen. The inflammation in psoriatic arthritis does not vary significantly from RA, and the synovial inflammation seen in osteoarthritis is of a milder degree and intensity as compared with RA.[28] What distinguishes ARMD seen in metal on metal tissues from others is the feature of extensive but variable surface necrosis. The inflammation is less often diffuse and is

Table 3 Spectrum of changes in ARMD seen in this study

	Stemmed hip arthroplasty (54)	Resurfacing hip arthroplasty (69)	Total (123)
Gender			
Male	16	20	36
Female	38	49	87
Necrosis			
Grade 1	02	07	9 (7.3%)
Grade 2	19	21	40 (32.5%)
Grade 3	06	15	21 (17.1%)
Grade 4	27	26	53 (43.1%)
Histiocytes sheets			
<1 mm	23	12	35 (29.2%)
1–2 mm	15	24	39 (32.5%)
>2 mm	10	27	37 (30.8%)
Absent	04	05	09 (7.5%)
Granuloma			
Absent	37	65	102 (85%)
Present	15	03	18 (15%)
Particle load			
0+	10	07	17 (14.2%)
1+	11	18	29 (24.2%)
2+	22	25	47 (39.2%)
3+	05	14	19 (15.8%)
4+	04	04	8 (6.6%)
Diffuse synovitis			
Absent	23	37	60 (50%)
Present	29	31	60 (50%)
Plasma cells			
Absent	33	42	75 (62.5%)
Present	19	26	45 (37.5%)
Lymphoid aggregates			
Absent	07	10	17 (14.2%)
Present	45	58	103 (85.8%)
Germinal centre			
Absent	32	48	80 (66.7%)
Present	20	20	40 (33.3%)
Lymphocyte cuff thickness			
<0.25 mm	25	34	59 (49.2%)
0.25–0.5 mm	14	13	27 (22.5%)
0.5–0.75 mm	03	05	8 (6.7%)
>0.75 mm	03	06	9 (7.5%)
Absent	07	10	17 (14.1%)
ALVAL in skeletal muscle			
Absent	46	58	104 (86.7%)
Present	06	10	16 (13.3%)
Vascular wall changes			
Absent	33	40	73 (60.8%)
Present	20	27	47 (39.2%)

ALVAL, aseptic lymphocytic vasculitis associated lesion; ARMD, adverse reactions to metal debris.

more commonly organised into either lymphoid aggregates with or without germinal centres. Russel bodies are not seen, and there are no multinucleated synoviocytes. None of our cases were known to have RA; the most common indication for the arthroplasty was osteoarthritis. A time zero biopsy would have been ideal to compare and quantify the inflammatory changes seen pre-arthroplasty and at the time of revision surgery. This was not done in this study, as failure of the implants was not anticipated. How much would a time zero biopsy have contributed to the understanding is not known, as the intensity of the inflammation is variable. It does however beg the question if such biopsies, and how many, are necessary when new devices are implanted.

Table 4 Distribution of cases with vascular wall changes

Vascular wall changes	47/120 (39.2%)
Necrosis	
Grade 1	0/9
Grade 2	13/40 (32.5%)
Grade 3	09/21 (42.8%)
Grade 4	25/53 (47.1%)
Histiocytes sheets	
<1 mm	19/35 (54.2%)
1–2 mm	17/39 (43.5%)
>2 mm	11/37 (29.7%)
Granuloma	
Absent	34/102 (33.3%)
Present	13/18 (72.2%)
Particle load	
0+	09/17 (52.9%)
1+	11/29 (37.9%)
2+	18/47 (38.2%)
3+	07/19 (36.8%)
4+	02/08 (25%)
Plasma cells	
Absent	23/75 (30.6%)
Present	24/45 (53.3%)
Germinal centre	
Absent	20/80 (25%)
Present	27/40 (67.5%)
Lymphocyte cuff thickness	
<0.25 mm	19/59 (32.2%)
0.25–0.5 mm	15/27 (55.5%)
0.5–0.75 mm	06/8 (75%)
>0.75 mm	07/9 (77.7%)
ALVAL in skeletal muscle	
Absent	37/104 (35.5%)
Present	10/16 (62.5%)

ALVAL, aseptic lymphocytic vasculitis associated lesion.

Lymphoid neogenesis is a dynamic process in which perivascular lymphocytic cuffs expand and evolve into lymphoid aggregates with germinal centres. During this process, there is significant tissue remodelling of the inflamed tissues. Blood vessels acquire the morphological and immune-phenotype of HEVs as seen in lymph nodes. HEVs are efficient in homing and recruiting lymphocytes by expression of relevant ligands like PNAd.[19] Follicular dendritic cell network and a fibroblastic reticular framework are the essential ingredients for lymphoid neogenesis.[18] It has been shown that synovial blood vessels readily acquire the phenotype of HEVs in RA.[29] In all 103 cases of this case series, the synovial vessels surrounded by the lymphocytes histomorphologically showed tall and plump endothelial cells, similar to HEVs in lymph nodes. This was noted in all the papers describing ALVAL.[7–12] In our study, PNAd positivity was seen in those vessels surrounded by lymphocytes, whereas those vessels without the lymphocytic cuffing failed to express PNAd. Recently, the morphology of HEVs has been described in detail.[30] The endothelial cells are tall and plump, on Electron Microscopy (EM) have increased mitochondria, free ribosomes and well-developed Golgi apparatus, suggesting an increased metabolic activity. HEVs are surrounded by multiple layers of pericyte-like cells called fibroblastic reticular cells (FRCs). A narrow space between the endothelial basal lamina and the FRC allows the lymphocytes to move easily into the extravascular space. The FRCs also produce and lay down extracellular matrix components including fibronectin, collagen

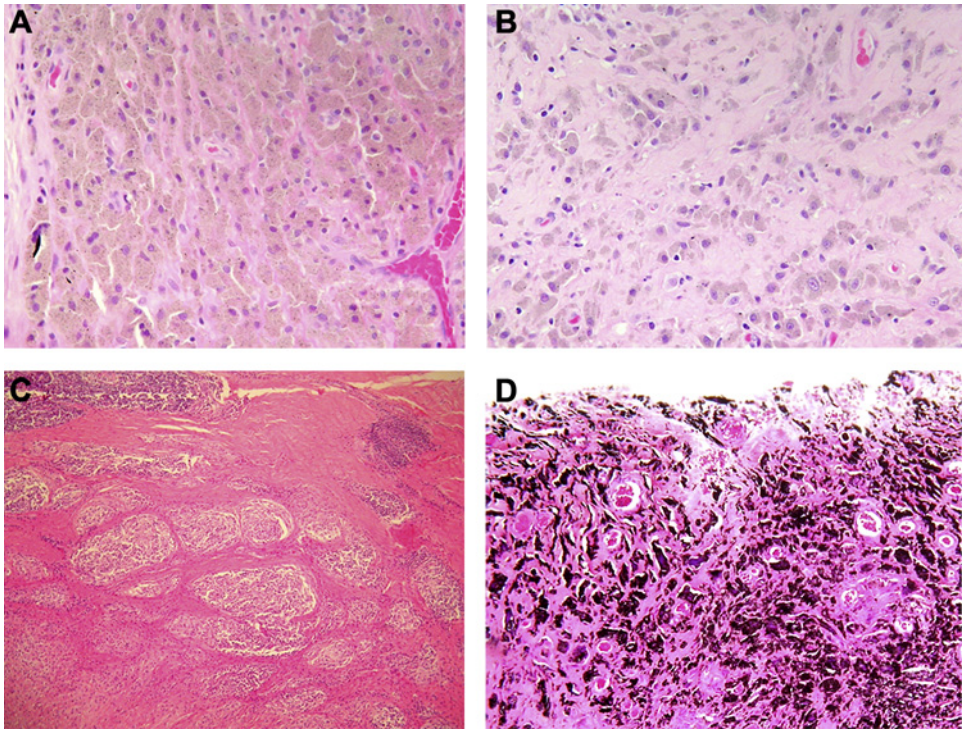

Figure 2 (A–C) These photomicrographs (magnification ×200) show metallic debris within the histiocytes. The debris is either needle shaped as seen in A or fine dot-like as in B. Larger deposits of metallic debris are seen without lymphocytic response in C. (D) This photomicrograph (magnification ×200) shows well-defined granulomas. Lymphoid aggregates can also be seen.

IV and laminins forming the thick basal lamina of HEVs. Histologically, HEVs show cuboidal plump endothelium, thick basal lamina and sheath of pericytes. The hyalinisation and onion skinning seen in the smaller vessels in 47/103 cases showing ALVAL can be explained as part of the process of development of HEVs. The transformation to HEVs appears to be progressive, with early development of high endothelial morphology, followed by laying down of thick basal lamina.

When ALVAL was first described, a T lymphocyte cell mediated immunologic response was proposed, but the authors did not elaborate on whether the perivascular lymphocytic response was causing actual vascular damage,[7 8] although vascular occlusion and fibrinoid necrosis were noted in earlier studies with metal on metal implants.[13–16] Evans *et al* noted vascular obliterative changes in periprosthetic tissue around the areas of necrosis and concluded that necrosis was a direct consequence of the vascular changes.[13] Brown *et al* argued that vascular obliterative changes were commonly seen in the synovium of chronic diseases, and these changes were unlikely to have led to the necrosis.[14]

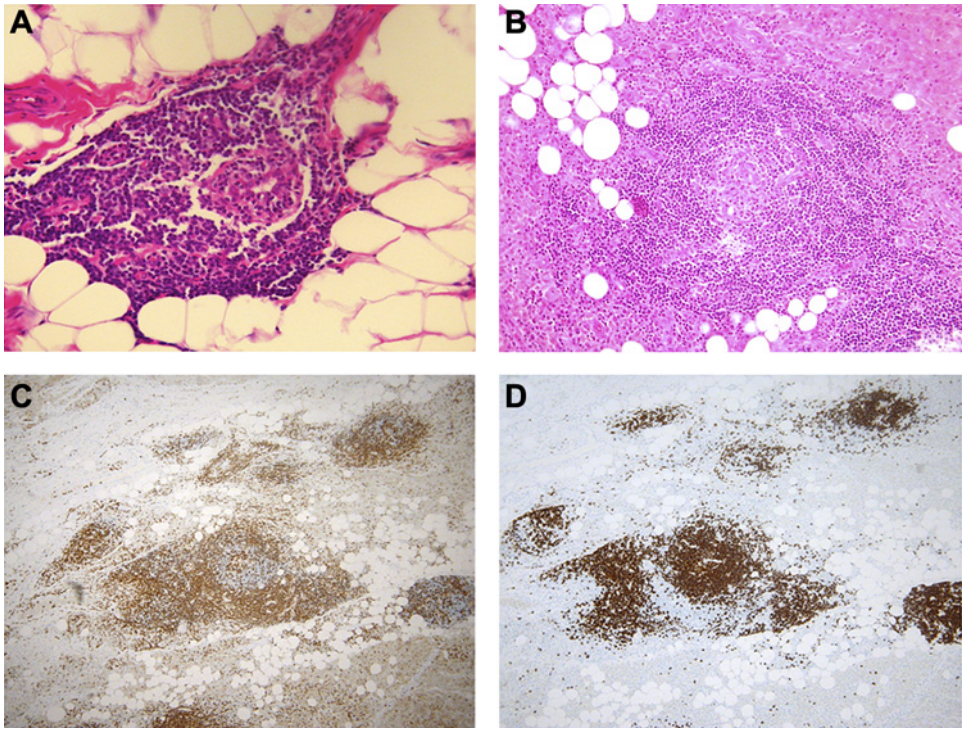

Figure 3 (A) This photomicrograph (magnification ×200) shows a typical lymphoid aggregate centred on a blood vessel. The vessel shows lymphocytes within its wall and high endothelial venule morphology. There is no hyalinisation of the wall. (B–D) These photomicrographs (magnification ×200) show germinal centre formation. Immunohistochemistry showing organisation into central B cell areas (D) with surrounding T cell areas (C) is seen.

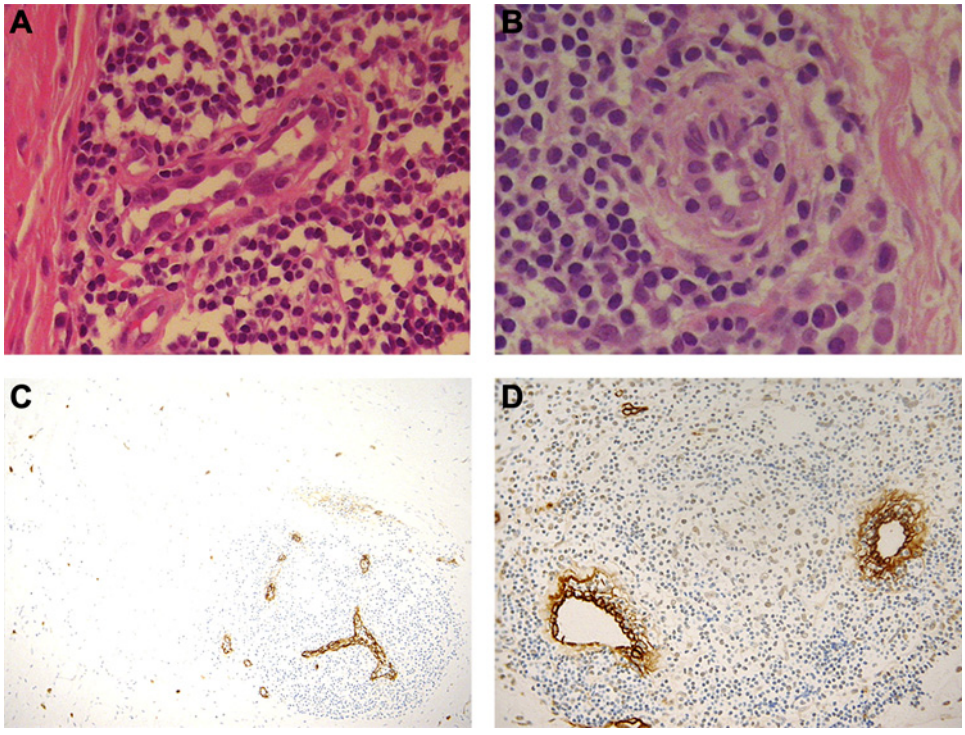

Figure 4 (A–D) These photomicrographs (magnification ×200) show development of high endothelial venules with plump cuboidal endothelium. Lymphocytes can be seen transiting from the lumen into the wall. Concentric lymphocytic cuffing can be appreciated in B. Occasional plasma cells are also seen. (C, D) High endothelium highlighted by peripheral node addressin (PNAd) immunostain (MECA 79). In C, negative expression of PNAd in vessels not surrounded by the lymphocytic infiltrate is seen.

When the term vasculitis is used, one expects to see structural damage to the involved blood vessels with associated functional changes. This is easily seen histologically in immunologic leucocytoclastic vasculitides. However, cutaneous lymphocytic vasculitis is identified by the characteristic perivascular lymphocytic cuffing and changes within the vessel wall are more subtle. Structural and functional changes within the vessel walls are less readily identifiable, and hence there is uncertainty with regard to lymphocytic vasculitis being a true vasculitis. Are the lymphocytes just in transit through the vessel wall or do they cause actual damage? This is an argument that is often discussed in various dermatopathology review articles, giving a range of definitions that define lymphocytic vasculitis. When lymphocytes are seen in the muscular walls of the vessels it is de facto evidence of vasculitis. Diapedesis or transit of lymphocytes does not occur in arteries or veins.[31–34]

In five cases, we have seen lymphocytes within larger vessel walls in the deeper tissues. The lymphocytic inflammation present was segmental, and did cut out in further tissue levels. In one case, we were able to identify this population to be CD8

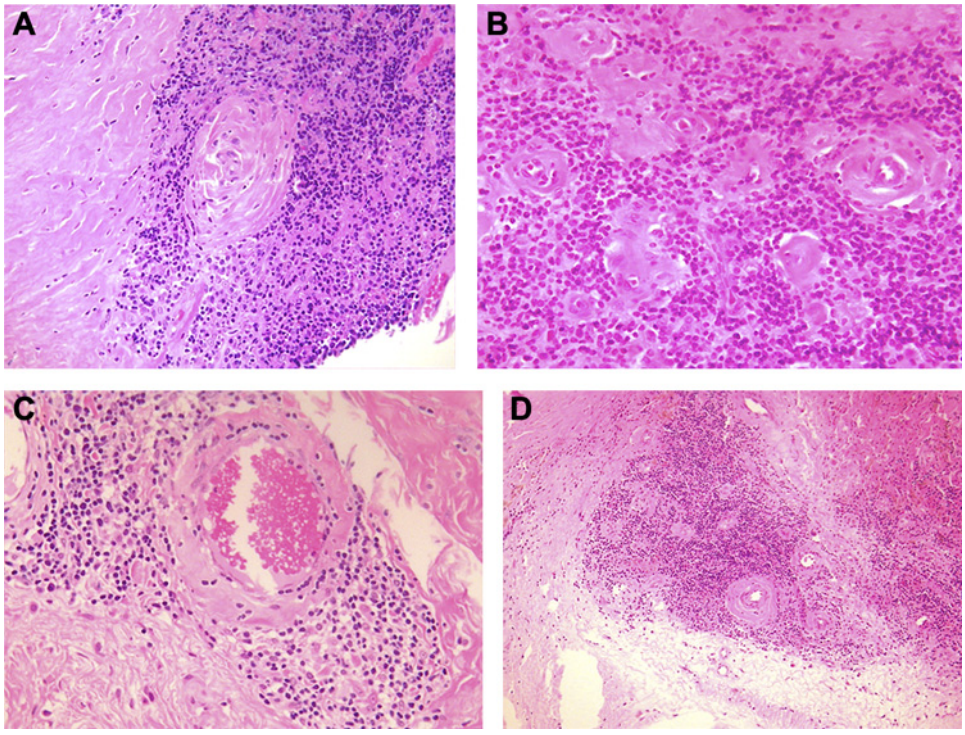

Figure 5 (A–D) These photomicrographs (magnification ×200) show hyalinisation of the vessels surrounded by the lymphocytic inflammation. Note the laminated hyalinisation particularly prominent in (A).

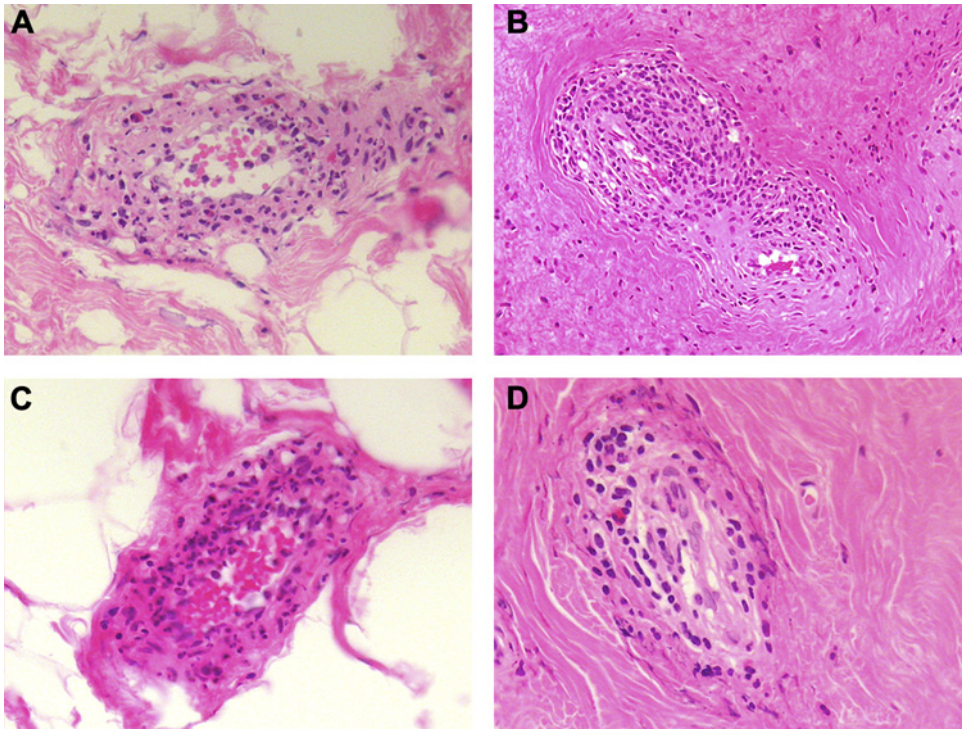

Figure 6 (A–D) These photomicrographs (magnification ×200) show lymphocytic infiltrate in vessels larger than arterioles or venules. There is no fibrinoid necrosis, but nuclear dust can be seen in (C). The infiltrate is predominantly lymphocytic with a few eosinophils seen in A and D. Note the lack of perivascular lymphocytic cuffing, indicating this may be the earliest stage in the immune response.

positive T cells. Evidence of vascular wall destruction was seen in one case, and a further case showed nuclear dust (figure 6A,B,D). In 47 cases, we have seen vascular wall changes in the form of hyalinisation, onion skinning and occlusion in the smaller vessels. These changes could be seen due to one of two reasons: a direct consequence of lymphocyte mediated damage or as a result of transformation to HEVs. In our opinion, the sensitised lymphocytes play a pivotal role in causing necrosis. The vascular hyalinisation could be a reactive response secondary to 'innocent bystander' damage caused by the transiting sensitised lymphocytes, the main target of the lymphocytes being the metal debris. This could further contribute to ischaemic pain and necrosis. The vascular changes may not be the only reason for the necrosis, as is evident from our study. All 47 cases with small vessel wall changes showed variable amounts of necrosis. Twenty-five of these showed Grade 4 necrosis. However, the remaining 28/53 cases that showed Grade 4 necrosis did not show any vascular wall changes. Our study, like the earlier studies,[13–16] does not demonstrate a clear association between the small vessel wall changes and the extent of necrosis. The role

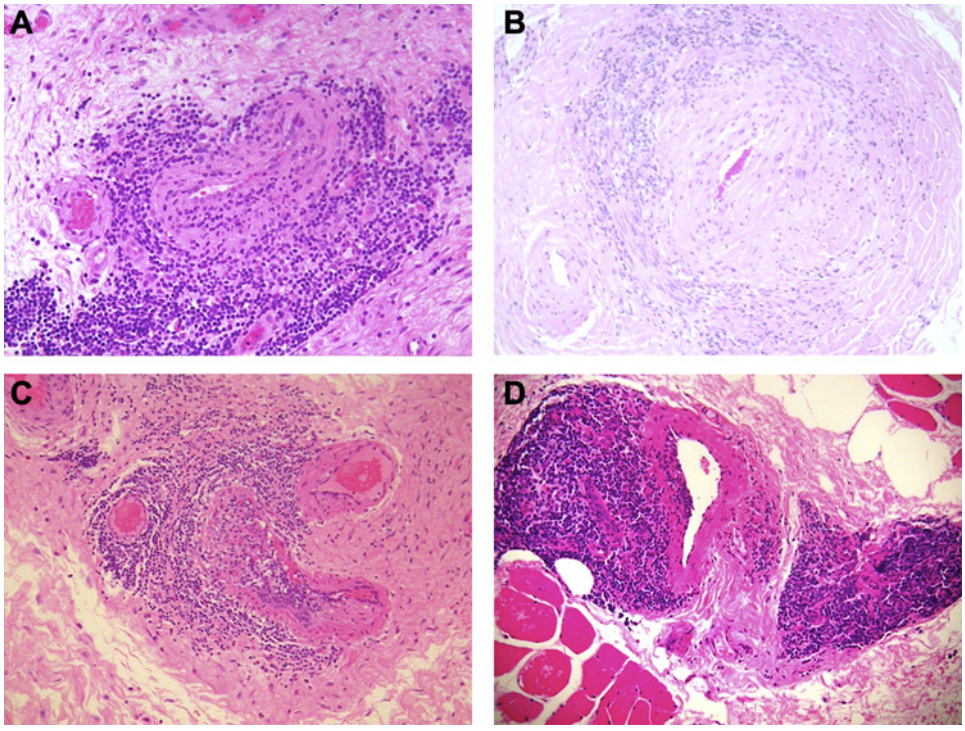

Figure 7 (A–D) These photomicrographs (magnification ×200) show evolving lymphocytic cuffing around larger blood vessels. Again note lack of fibrinoid necrosis of the vessel walls, although luminal obliteration with destruction of the vessel wall can be seen in C. In B, the lymphocytes present in the wall expressed CD8 T lymphocyte markers.

of large vessel involvement is not completely understood at this stage.

Local tissue destruction and loss of function are the hallmark of chronic inflammation.[35 36] The term metallosis is used to describe the condition where macrophages containing cytoplasmic metal debris predominate without an ALVAL type chronic lymphocytic response.[37 38] Interestingly, none of these 13 cases with pure metallosis without ALVAL showed well-defined granulomas. The presence of cobalt and chromium was confirmed by EDX. Deparaffinised tissue was used, as unstained tissue sections were unsuitable. The metal debris seen was similar in all cases, and the high cost of EDX precluded us from using it for all our cases. Distinct sarcoid-like naked granulomas were seen 18 cases, indicating that cell mediated immunity (Type IV hypersensitivity) is seen in response to the metal debris. These granulomas were seen in addition to the perivascular ALVAL response. The granulomas were more commonly seen with total hip stemmed implants, where the only difference is the presence of titanium within the femoral stems as opposed to the resurfacing implants that contain cobalt chromium alloy. The presence of granulomatous inflammation in extensive necrosis can be mistaken for other necrotising granulomatous inflammation, in particular mycobacterial infection. A negative ZN stain and the history of metal implants would help make a diagnosis of ARMD. Mahendra *et al* observed a predominant macrophagic and T cell response in 45/52 cases and proposed a cytotoxic and cell-mediated response to cobalt and chromium particles.[12] The presence of granulomas in our study is indicative of Type IV delayed type hypersensitivity response. Host factors may determine why some cases show a purely metallosis type response.

The necrosis seen in ARMD can be caused by the inflammatory mediators generated by macrophages, lymphoid neogenesis and the granulomas present. The joint fluid collection seen in association could be due to defective lymphatic drainage. Defective lymphatic drainage has been proposed to be a trigger for lymphoid neogenesis.[39] Fluid collection could initiate and perpetuate a cyclical response leading to further pressure necrosis.

The findings described by us are only the beginning of an understanding of the pathogenesis of ARMD seen in metal on metal prostheses. The study has a few shortcomings. The data have not been standardised with regard to age, sex, duration and type of metal on metal implant. We have not been able to explain why some cases showed a pure metallosis type reaction without the development of ALVAL. Patient or host characteristics have an important role to play in determining the nature of the immune response. Earlier revisions (screening cases rather than symptomatic cases) will throw further light on this.

In summary, periprosthetic tissues from metal on metal arthroplasties show necrosis with associated chronic lymphocytic immune response. This response consists of lymphoid neogenesis which is a dynamic process, beginning as perivascular lymphocytic aggregates (ALVAL) leading to lymphoid follicles with germinal centres. These are responsible for perpetuating the immune response to the metal debris, most probably leading to tissue necrosis. Vascular hyalinisation seen within vessels surrounded by the immune response is either secondary to lymphocyte mediated vasculitic damage or could be due to transformation to HEVs. It remains to be seen if these changes contribute further to ischaemic pain or necrosis. Macrophages are an important component of this inflammatory response and in a small number of cases can be the only cell type without any lymphocytic infiltration.

Take-home messages

- Adverse reactions to metal debris consist of a spectrum of changes ranging from a pure metallosis type reaction to aseptic lymphocytic vasculitis associated lesion (ALVAL) and granulomatous inflammation.
- ALVAL is a distinctive response seen in failed metal on metal hip arthroplasties and can be distinguished from chronic inflammatory arthropathies by the presence of extensive surface tissue necrosis and loss of architecture, and metallic debris within macrophages.
- ALVAL begins as perivascular lymphocytic cuffing evolving into lymphoid aggregates with or without germinal centres.
- There does not appear to be a clear association between small vessel wall changes and the extent of necrosis. A small number of cases also showed lymphocytes within larger vessels. It is unclear at this stage if these changes contribute to the degree of necrosis.
- The inflammatory cell response contributes to tissue destruction, but further work needs to be done in elucidating the pathogenesis of necrosis.

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