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Histological characterization of periprosthetic tissue responses for metal-on-metal hip replacement

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Abstract

The histology of periprosthetic tissue from metal-on-metal (MOM) hip devices has been characterized by a variety of methods. The purpose of this study was to compare and evaluate the suitability of two previously developed aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL) scoring systems for periprosthetic hip tissue responses retrieved from MOM THR systems revised for loosening. Two ALVAL scoring systems (Campbell and Oxford) were used to perform histological analysis of soft tissues from seventeen failed MOM THRs. The predominant reactions for this patient cohort were macrophage infiltration and necrosis, with less than half of the patients (41%) showing a significant lymphocytic response or a high ALVAL reaction (6%). Other morphological changes which varied among patients included hemosiderin accumulation, cartilage formation and heterotopic ossification. Both scoring systems correlated with macrophage and lymphocyte responses and with each other, however given the diversity and variability of the current responses the Oxford-ALVAL system was more suitable for scoring tissues from MOM THR patients revised for loosening. It is important that standardized methods to score MOM tissue responses be used consistently so multiple study results can be compared to one another and a consensus can be generated.

Keywords

ALVAL; metal-on-metal; necrosis; histology; inflammation; total hip replacement; implant loosening

I. Introduction

Histological analysis of periprosthetic tissue reactions, including necrosis, lymphocyte infiltration, histiocytosis, and intracytoplasmic metallic debris has been previously reported in MOM resurfacing and THR devices.¹⁻¹⁰ Tissue reactions referred to as pseudotumors have also been observed in patients who have received MOM bearings.^{6, 11-17} Pseudotumor tissues frequently show a type IV hypersensitivity reaction to metal ions, identified histologically by an aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL).^{7, 9, 11} Thus, a complex range of inflammatory reactions, including a response to metal wear debris may occur independently of one another in the periprosthetic tissues of retrieved metal-on-metal (MOM) total hip replacements.

Although histology is frequently used to characterize tissues from retrieved MOM bearings, the assessment techniques are not always well defined.^{8, 18} Two defined methodologies for histological analysis have emerged in the literature. In a 2010 study, Campbell et al. developed the Campbell-ALVAL scoring system for pseudotumor tissue analysis. This system assesses synovial lining thickening and integrity, tissue organization, and the combined innate and adaptive inflammatory cell infiltrations.¹¹ The Campbell-ALVAL scoring system has been applied to a range of retrieved tissues from MOM total hip and resurfacing bearings, including those revised with and without pseudotumors.^{1, 2} More recently, Grammatopoulos et al. (2013) developed the Oxford-ALVAL scoring system¹, which unlike the Campbell-ALVAL scoring system strictly assesses the amount of perivascular lymphocytic aggregates. This system was developed to separately identify inflammatory reactions due to cytotoxicity involving a foreign-body macrophage response and a hypersensitivity (ALVAL) reaction involving an adaptive immune response in periprosthetic tissues from failed MOM hip tissues revised for both pseudotumor formation and other MOM tissue adverse local tissue reactions (ALTRs). The authors reference the scoring system developed by Willert et al. (2005)⁵, this system evaluated immune cell infiltrates using a magnification of 400× and therefore developed scores with higher numbers per field of view.

Standardized methods to score tissue responses need to be used consistently so multiple study results can be compared and a consensus of the results can be generated. Consequently, the purpose of this study was to compare previously developed ALVAL scoring systems for periprosthetic hip tissue responses around retrieved MOM bearings. We hypothesized the Campbell-ALVAL scoring system results would correlate with the Oxford-ALVAL scores. Specifically, we evaluated the suitability of these scoring systems for modern, second generation MOM THA systems used in the United States.

II. Methods

A. Tissue Collection and Patient Clinical Information

Hip tissue specimens from regions adjacent to implanted MOM THRs were obtained from 17 THR patients prior to the removal of the femoral head at the time of revision surgery. All surgeries and tissue specimen retrievals were performed at two surgical centers in collaboration with an urban biomedical engineering department. Tissues were de-identified

and collected in accordance with an IRB-approved protocol. We excluded one sample because of a previous revision surgery. Thus, all the tissues in this study were obtained from primary total joint replacements.

The patients in our series were revised for acetabular loosening (16/17) or femoral loosening (1/17) (Table 1). The radiographs and operative notes were reviewed in all cases. None of the patients were revised due to ALTR. One patient with acetabular loosening was also diagnosed with osteolysis. The implants were provided by two manufacturers (Table 1). Ten of the 17 patients were male. The average age of patients understudy at implantation was 63 (range: 31-85), and the mean duration of implant survival was 2.7 years (range: 0.8-7.0 years). Tissue specimens were retrieved from the following regions for analysis: pseudocapsule/synovium (16/17), fovea (2/17), retroacetabulum (6/17), intermedullary femur (1/17) and proximal femur (1/17).

B. Tissue Preparation and Histological Stains

Tissues collected from revision surgeries were fixed in 10% formalin fixative and decalcified as needed based on microCT analysis (μ CT 80, Scanco Medical, Brüttisellen, Switzerland). After photodocumentation, at least one, but routinely two to three 4-mm punches from each tissue, considering variations in color, texture, and size of specimen, were embedded in paraffin blocks for 6- μ m serial sectioning and staining with Alcian blue (Electron Microscopy Sciences, #26026-13, Hatfield, PA, USA), hematoxylin, and eosin (H&E) (ThermoFisher Scientific, #23-245-697, #23-245-827, Waltham, MA, USA). Entire tissue sections were imaged (typically 16 fields) under transmitted light microscopy at 100 $\times$ (10 $\times$ objective) using a Motic BA300POL microscope (Motic, Richmond, British Columbia, Canada), equipped with a stepper-motor controlled stage and ProgRes SpeedXT core 5 (Jenoptik, Jena, Germany) microscope camera.

The presence of inflammatory cells was confirmed using a buffered Wright-Giemsa stain (Electron Microscopy Sciences, #26149-01, Hatfield, PA, USA), and each slide was viewed at 400 $\times$. Slides were pretreated with 0.02 M sodium acetate buffer at pH 4.4 and transferred into a Wright-Giemsa working solution (4 mL of stain diluted with 200 mL of 0.02 M sodium acetate buffer at pH 4.4) for 2 hours. Slides were washed in 0.02 M acetate buffer at pH 4.4, twice differentiated in 100% ethanol, and cleared in xylene. Finally, Prussian blue staining method was used to detect hemosiderin in additional serial sections. Slides were stained in a 1:1 mixture of 2% potassium ferrocyanide (Electron Microscopy Sciences, #26170-Series, Hatfield, PA, USA) and 2% hydrochloric acid for 1 hour. After washing in distilled water, slides were counterstained in Safranin O (Electron Microscopy Sciences, #26170-03, Hatfield, PA, USA), washed with 1% acetic acid, differentiated twice in both 95% and absolute ethanol, and cleared in xylene.

C. Histological Response Scores

Tissues were scored using two ALVAL scoring systems described by Campbell et al. (Campbell-ALVAL),¹¹ and Grammatopoulos et al. (Oxford-ALVAL).¹ The Campbell-ALVAL score is determined using three subscores: synovial lining integrity, inflammatory infiltration, and tissue organization (Table 2). The sum of the three criteria generates the

final Campbell-ALVAL score, which are ranked as low (a score of 4 or less), moderate (a score of 5 through 8), and high (a score of 9 or 10) with 10 being the highest. The Oxford scoring system examines each histologic marker individually, as summarized in Table 2. The Oxford-ALVAL score was defined by the presence of perivascular lymphocytic infiltrate and degree of lymphocyte cuffing of blood vessels. The tissues were scored by 2 independent observers, and the results were within 90%.

Separate from either scoring system, the deposition of hemosiderin was semi-quantitatively scored as 0 (absent), 1+ (<10% of tissue area), 2+ (10-50% of tissue area), and 3+ (>50% of tissue area). In addition, the presence of bone and cartilage were determined using alcian blue with H&E.

D. Statistical Analysis

The images for each patient tissue were scored and the scores for multiple tissue punches from each region were combined to generate a median score. The Spearman correlation coefficient (ρ) was used to evaluate correlation between histological features and ALVAL scores (Campbell and Oxford). Significance was set at $p < 0.05$. Statistical analysis was performed with the SPSS statistical program (version 20.0; SPSS, Chicago, Illinois).

III. Results

A. Histological Findings

Representative images are shown for pseudosynovial membrane surfaces (Fig. 1), inflammatory infiltrates within the membrane (Fig. 2), and localized macrophage, lymphocyte, plasma cell and ALVAL inflammatory responses (Fig. 3). The histological findings for the individual patients are presented in Table 3, and the histological response percentages are presented in Table 4.

In general, the majority of tissues showed signs of inflammatory-mediated degeneration or necrosis, which was observed in areas of the tissue from 13 of the seventeen patients (scores range from 0-3+). The majority of patient tissues had either a 2+ ($n = 6$) or 3+ ($n = 5$) score for necrosis. The overall inflammatory infiltrate was primarily a mix of macrophages, lymphocytes, and plasma cells. Macrophage infiltration was observed in 15 of the patients' tissues with scores of 1+ ($n = 5$), 2+ ($n = 8$) or 3+ ($n = 2$), and two patients (Patient #7 and Patient #16) exhibited no macrophage infiltration (scores range from 0-3+). Tissues from these two patients had 3+ and 2+ scores for necrosis, respectively. The overall lymphocyte response was much less; the 10 patients showing a response had scores of 1+ ($n = 3$), 2+ ($n = 5$), or 3+ ($n = 2$), and tissues from the other seven patients exhibited no lymphocytic infiltrate (scores range from 0-3+). The ratio of lymphocytes to plasma cells was approximately 5:1.

Based on the Campbell-ALVAL scoring criteria, 41% of patients had low scores of 1 ($n = 1$), 2 ($n = 1$), 3 ($n = 3$), and 4 ($n = 2$), 24% of patients had moderate scores of 5 ($n = 2$), 6 ($n = 3$), 7 ($n = 3$), and 8 ($n = 2$), 6% of patients had a high score of 10 ($n = 1$). In contrast, the Oxford-ALVAL scoring system indicated that 47% of patients ($n = 8$) did not have significant perivascular lymphocytic cuffing of the blood vessels (score of 0), 24% exhibited

very little evidence of ALVAL (score of 1, $n = 4$), 24% exhibited 5-10-cell thick perivascular lesions ($n = 4$), and 6% exhibited perivascular lesion greater than 10 cells in thickness ($n = 1$).

Other histological features separately scored were hemosiderin (Table 3; Fig. 4) detected in 59% of the patients, with scores of 1+ ($n = 7$) or 2+ ($n = 3$). One patient tissue (Patient #7) retrieved from around the femoral head, contained cartilage associated with completely necrotic tissue (3+) and was excluded from the study. Two other patient tissues taken from the retroacetabular region (Patient #2 and Patient #5) contained both cartilage and bone. The surrounding tissue for both patients received the same scores for necrosis (2+) and macrophage infiltration (2+). Another patients' tissues that were from the retroacetabulum and intermedullary femur (Patient #17) contained primarily bone, bone marrow, and red blood cells and were excluded. The remaining tissues from the same patient had a macrophage infiltration score of 2+ and a necrosis score of 3+.

Three patients' tissues contained large metal debris. Two patient tissues (Patient #4, Patient #13) contained visible metal wear in both fibrous and inflamed tissue regions. The patients received the same Oxford-ALVAL scores (0), necrosis (1+), macrophage infiltration (1+) and hemosiderin (1+). One had a higher synovial lining score (2+ vs 0) and Campbell-ALVAL score (3+ vs 2+), and lymphocytes were observed in this patients' tissues (1+ vs 0). A third patient with visible wear debris (Patient #17) had the following scores: Oxford-ALVAL (0), necrosis (2+), macrophage infiltration (2+) and hemosiderin (2+), synovial lining (2+), Campbell-ALVAL (6+) and lymphocytes (1+).

Correlations observed between histological features are presented in Table 5. Increased macrophage infiltration correlated with higher Campbell ALVAL ($\rho = 0.67$, $p = 0.003$) and Oxford-ALVAL scores ($\rho = 0.54$, $p = 0.024$). Additionally, increased lymphocytic infiltration correlated with a higher Campbell-ALVAL score ($\rho = 0.75$, $p < 0.0001$) and similarly with a higher Oxford-ALVAL ($\rho = 0.85$, $p < 0.0001$) score. Finally, the Campbell-ALVAL and Oxford-ALVAL scores showed a strong correlation ($\rho = 0.74$, $p = 0.0007$). Correlations were not observed for necrosis or hemosiderin.

The correlations of histological features with patient clinical information are presented in Table 6. Positive correlations were observed for increased hemosiderin and both increased implantation time ($\rho = 0.62$, $p = 0.008$) and UCLA Score Onset ($\rho = 0.56$, $p = 0.019$). The UCLA Score Onset is an activity score that is taken 3 months prior to revision surgery, and the UCLA Score DOS is taken after primary joint replacement recovery.

IV. Discussion

In support of our hypothesis, we found a strong correlation between the Campbell-ALVAL and Oxford-ALVAL scores. Both scoring systems also correlated with the infiltration of lymphocytes and macrophages, the predominant inflammatory cell type found in the current MOM THR tissues. These scoring system were both developed to score pseudotumor responses or tissues with significant ALVAL reactions; however the Oxford scoring system was designed to separately score tissue responses. This feature made it more suitable for tissues with a nonspecific foreign-body macrophage response and those with varying

amounts of adaptive immune responses (lymphocyte infiltration and ALVAL responses). This is important since we plan to evaluate tissues from MOM implants revised for a variety of reasons, such as osteolysis, loosening, fracture and malalignment.

The scope of the study was constrained by several limitations. The study included the implants from two manufacturers in the United States, based on the types of implants revised by surgeons participating in our multicenter retrieval program. Thus, the initial limitation is the small sample size. Another limitation is that all the tissue was retrieved at revision surgery due to loosening and does not necessarily reflect the responses of tissue in patients who have not yet been revised, or patients who have been revised for reasons other than loosening. Clearly the histological methods we employed can be generalized to autopsy or a broader array of retrieval specimens.

The majority of the patients' (13 out of 17) tissues had some regions within the tissue that were necrotic, presumably due to a prior inflammatory response to metal wear debris that progressed to tissue degeneration¹⁹⁻²¹ and ultimately heterotopic ossification (3 of 17).²² The presence of necrosis in pseudotumor tissues and tissues from patients revised for other ALTRs has been a consistent finding.^{1-3, 6, 9}

The dominant local tissue response was inflammation (15 of 17); however only 10 patients had lymphocyte infiltration, of which 9 received an Oxford-ALVAL score, but only 5 had a score higher than a 1+. The inconsistency in lymphocytic infiltration in these non-pseudotumor tissues emphasizes that only some patients develop a metal hypersensitivity response each varying in severity. In contrast, 15 of the 17 patients' tissues had macrophage infiltration, 10 of which were higher than a 1+, indicating this was the predominant inflammatory response. It is therefore important to include multiple criteria to look for adverse tissue response correlations, as the responses vary and early inflammation can progress to localized regions of necrosis.

Hemosiderin due to vascular hemorrhage and macrophage ingestion of red blood cells is frequently observed in patients with MOM implant corrosion²³ and implant wear⁵, but little is known concerning its significance. A prior study suggested that the presence of hemosiderin may be associated with early implant loosening (< 6 yr) of THRs, but this was never validated.²⁴ We found a significant correlation for the presence of increased hemosiderin, which was present in small amounts (<10% of tissue area) but was a frequent observation (59% of the patients), and implantation time ($\rho = 0.57$, $p = 0.018$). However, most of our implants were revised early (median 2.5 yr), with the longest implantation time of 7 yr. It is still unclear whether hemosiderin has a significant impact on tissue function or why it is so frequently observed in these tissues. The presence of hemosiderin made it more difficult to determine the amount of intracellular wear debris (size limitation at 100 $\times$ is 0.5 μ m), especially since most of the metal wear debris is generally 0.5 μ m in early revisions.²⁵ Large metal wear debris was only detected in three patients' tissues, which were implanted for 2.09, 1.85 and 7.01 yr.

V. Conclusion

The predominant local tissue responses for this patient cohort were macrophage infiltration and necrosis. Less than half of the patients' tissues (41%) contained lymphocytes, but only 6% had a significant ALVAL reaction. In general, the responses varied considerably between patients, and differed within patients depending on the anatomical site the tissue was taken from around the implant. Thus, for this and future studies the Oxford scoring system provides a flexible, direct and valid method for scoring tissues from MOM THRs revised for loosening, fracture and malalignment.

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Figure 1.

Representative images of pseudosynovial membrane surfaces (black arrows; Alcian blue, hematoxylin and eosin, 200×). **(A)** Intact synovial lining (score 0), **(B)** disrupted synovial lining (score 1), **(C)** fibrin deposition (blue arrows) at the synovial surface (score 2), and **(D)** fibrin deposition and disruption (blue arrows; score 3).

Figure 2. Transmitted light micrographs illustrating inflammatory infiltration near the synovial lining

(**A and C**) Alcian blue, hematoxylin, and eosin stained tissues and (**B and D**) Wright-Giemsa stain (100×). A and B show inflammation predominantly confined to layer 3 (Campbell-ALVAL 7; Oxford-ALVAL 2), and C and D show regions with inflammatory infiltration throughout layers 2 and 3 (Campbell-ALVAL 8; Oxford-AVLAL 3).

Figure 3.

Transmitted light micrographs illustrating observed inflammation (Wright-Giemsa stain). **(A)** Mixed inflammation, predominantly macrophages (black arrows) with yellow-brown hemosiderin deposits (Campbell inflammation 1; Macrophages 2; Lymphocytes 1, Campbell-ALVAL 4, Oxford-ALVAL 1). **(B)** Mixed inflammation at a higher magnification showing the infiltration of macrophages (black arrow), lymphocytes (green arrows) and plasma cells (red arrows) (1000×, Campbell inflammation 2, Macrophages 2, Lymphocytes 2, Campbell-ALVAL 6, Oxford-ALVAL 1). **(C)** Severe inflammation with ALVAL (black box, 200×, inset 1000×; (Campbell inflammation 4; Macrophages 2; Lymphocytes 3, Campbell-ALVAL 10; Oxford ALVAL 3).

Figure 4. Transmitted light micrographs showing the presence of hemosiderin (A) Alcian blue, hematoxylin, and eosin, (B) Prussian blue, and (C) Wright-Giemsa stain. The Prussian blue stain denotes the presence of hemosiderin. No active inflammation was observed in this tissue.

Table 1

Summary of patient clinical information.

Patient ID #*	Gender	Age at Implantation(y)	Implantation Time(y)	BMI (kg/m ²)	UCLA DOS Score	UCLA Onset Score	Implant Manufacturer [†]	Reason for Revision
1	M	67	0.8	25.8	9	4	Z	Acetabular loosening
2	M	55	1.76	25.8	6	2	Z	Acetabular loosening
3	F	69	1.67	28.1	2	2	B	Acetabular loosening
4	M	73	2.09	23.1	8	4	Z	Acetabular loosening
5	F	62	2.97	29.3	7	2	Z	Acetabular loosening
6	F	58	2.65	42.9	6	2	Z	Acetabular loosening
7	M	59	2.17	26.4	8	6	Z	Acetabular loosening
8	M	66	2.88	28.1	3	3	Z	Acetabular loosening
9	F	75	3.45	23.4	6	3	Z	Acetabular loosening
10	F	85	2.49	29.4	6	3	Z	Acetabular loosening
11	F	61	2.54	22.3	6	3	Z	Acetabular loosening
12	M	63	2.82	27.9	8	3	Z	Acetabular loosening
13	M	59	1.85	33.9	8	5	Z	Acetabular loosening
14	M	72	3.01	25.8	8	8	Z	Acetabular loosening
15	F	61	2.44	22.7	4	2	Z	Acetabular loosening
16	M	31	3.43	30.0	4	2	Z	Acetabular loosening
17	M	67	7.01	32.2	7	3	B	Femoral loosening

[†]Zimmer Inc., Warsaw, IN, USA (Z) and Biomet, Warsaw, IN, USA (B).

Table 2

Campbell and Oxford scoring criteria.

Oxford Criteria				
Score	Necrosis	Inflammation (Macrophages & Lymphocytes)		Oxford-ALVAL
	Tissue %	# of Cells	Tissue % Area	Lymphocytic Cuffing, Cell Thickness
0+	0	0	0	0
1+	Scattered or Isolated	1-9	<10	<5 cells
2+	<25	10-50	10-50	5-10 cells
3+	>25	>50	>50	> 10 cells
Campbell-ALVAL Score Criteria *				
Score	Synovial Lining	Inflammation		Tissue Organization
	Description	Description	Tissue % Area	Description
0+	Intact	Minimal	0 %	Normal
1+	Focal loss, fibrin attachment may occur	Macrophages > Few Lymphocytes	<50 %	Small areas of synovial hyperplasia, focal necrosis
2+	Moderate to marked loss, fibrin attachment	Mixed Macrophages and Lymphocytes (small aggregates)	<50 %	Distinct acellular zones, thick fibrous layer
3+	Complete Loss, Abundant Fibrin, Necrotic Lining	Mixed Macrophages and Lymphocytes (large aggregates)	>50 %	Distal Perivascular Lymphocytic aggregates, thick acellular zones
4+		Lymphocytes, perivascular aggregates	>50 %	

* Campbell-ALVAL score is the sum of three Criteria (maximum of 10).

Table 3

Summary of histological findings.

Patient ID #*	Synovial Lining (Campbell)	Inflammatory Infiltrate (Campbell)	Tissue Organization (Campbell)	Campbell-ALVAL	Oxford-ALVAL	Necrosis	Macrophages	Lymphocytes	Hemosiderin
1	3	2	3	7	2	3	2	2	0
2	1	3	2	6	1	2	2	2	0
3	0	2	2	1	1	3	1	2	0
4	2	0	1	3	0	0	1	0	1
5	1	1	2	4	0	2	2	0	0
6	3	4	3	10	2	3	3	3	0
7	3	0	3	5	0	3	0	0	1
8	2	2	3	5	0	3	1	1	1
9	3	3	2	7	2	2	2	2	2
10	3	2	2	6	1	1	3	1	0
11	2	4	2	8	3	0	2	3	1
12	1	2	1	4	1	0	1	0	1
13	0	0	2	2	0	0	1	0	1
14	0	1	2	3	0	2	2	0	2
15	2	2	2	7	2	1	2	2	0
16	2	0	2	3	0	2	0	0	1
17	2	2	2	6	0	2	2	1	2
Median	2	2	2	5	1	2	2	1	1
Interquartile Range	2	2	0.5	4	2	3	1	2	1

Table 4

High, Moderate and Low Responder percentages

Score	Frequency	Percent	Score	Frequency	Percent
Necrosis					
Lymphocyte					
0 to 1	6	35%	0 to 1	10	59%
2 to 3	11	65%	2 to 3	7	41%
Macrophage					
Hemosiderin					
0 to 1	7	41%	0 to 1	14	82%
2 to 3	10	59%	2 to 3	3	18%
Campbell-ALVAL					
Oxford-ALVAL					
0 to 4	7	41%	0	8	47%
5 to 8	9	53%	1	4	24%
9 to 10	1	6%	2	4	24%
			3	1	6%

Table 5

Histological feature correlations.

	Macrophage	Lymphocyte	Hemosiderin	Campbell-ALVAL	Oxford-ALVAL
Necrosis	-0.01 (0.97)	0.25 (0.33)	-0.21 (0.42)	0.12 (0.65)	-0.03 (0.90)
Macrophage		0.58 (0.015)	-0.31 (0.22)	0.67 (0.003)	0.54 (0.024)
Lymphocyte			-0.38 (0.14)	0.75 (<0.0001)	0.85 (<0.0001)
Hemosiderin				-0.19 (0.47)	-0.38 (0.14)
Campbell-ALVAL					0.74 (0.0007)

The values are given as the Spearman rho coefficient, with the p value in parentheses. Significant correlations are in bold.

Table 6
Correlations between Histological Features and Patient Clinical Information

	Age at Implantation	Implantation Time	UCLA Score DOS	UCLA Score Onset
Necrosis	-0.08 (0.76)	-0.04 (0.88)	-0.22 (0.40)	-0.15 (0.57)
Macrophage	0.24 (0.35)	0.11 (0.68)	-0.04 (0.88)	-0.22 (0.40)
Lymphocyte	-0.03 (0.90)	-0.21 (0.42)	-0.46 (0.06)	-0.43(0.09)
Hemosiderin	0.23 (0.38)	0.62 (0.008)	0.25 (0.33)	0.56 (0.019)
Campbell-ALVAL	-0.09 (0.74)	0.09 (0.73)	-0.10 (0.69)	-0.20 (0.45)
Oxford-ALVAL	0.02 (0.93)	-0.24 (0.35)	-0.22 (0.39)	-0.31 (0.22)

The values are given as the Spearman rho coefficient, with the p value in parentheses. Significant correlations are in bold.