

**Case study**

Azzopardi phenomenon in cystic pseudotumours associated with retrieved metal-on-metal arthroplasty^{☆,☆☆}



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Summary The Azzopardi phenomenon represents a morphologically well defined lesion characterised by a deposition of basophilic material in the vessel walls associated with several malignant tumours. We report on 4 cases (3 men and 1 woman) showing the Azzopardi effect in retrieved metal-on-metal arthroplasty unrelated to malignancy. All cases were revised for groin pain and radiological findings of so-called pseudotumours. The Azzopardi phenomenon was seen in cases with cystic pseudotumours characterised by superficial necrobiosis, proliferative desquamative synovitis, finding of metal and corrosion wear particles and cellular infiltration by macrophages. The lesions, which were recognized as bluish substance in the hematoxylin and eosin staining, demonstrated a positive Feulgen reaction. We report on the Azzopardi phenomenon in non-neoplastic cystic pseudotumours from retrieved metal-on-metal arthroplasties. Although clinical relevance of this finding remains unclear, further research is necessary to investigate the possible relationship of this lesion with deliberation of metal ions from metal and corrosion wear particles and their role in a broad spectrum of adverse reactions to metal debris.

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1. Introduction

The Azzopardi phenomenon is a well-known morphological feature associated with several malignancies such as small cell carcinoma [1], Burkitt lymphoma [2], Merkel cell

carcinoma [3] and medulloblastoma [4]. It is characterised by a deposition of basophilic material in the vessel walls and fibers of the extracellular matrix adjacent to the large areas of tumour necrosis. Azzopardi performed histochemical analyses of this finding using von Kossa's and alizarin red staining methods and demonstrated a positive Feulgen reaction, suggesting that the basophilic substance was DNA. Azzopardi concluded that this phenomenon of DNA in the vessel wall is presumably the result of deliberation of nucleic acids in large amounts from degenerating neoplastic cells [1].

Necroses of bone [5,6] and soft tissues [7] are common microscopic findings in periprosthetic tissues obtained

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during revision surgery of failed retrieved metal-on-metal (MoM) prostheses. Furthermore, proliferative changes of the synovium [8] and cellular lymphocyte and macrophage infiltrations [7] within the periprosthetic soft tissues were reported to be characteristic morphological changes linked with revisions of so-called pseudotumours [9,10] and groin pain after implantation of MoM prosthesis.

Here, we describe four cases of retrieved MoM hip resurfacing without neoplastic disease revised for groin pain and radiological findings of periprosthetic pseudotumours.

2. Case reports

Our patients included 3 men (aged 61, 66, and 72 years old) and one 71-year-old woman who developed progressive groin pain after the implantation of the hip resurfacing arthroplasty (Table). Radiological examination revealed a so-called cystic pseudotumor consistent with fluid-filled periprosthetic bursa extending into the soft tissue in all cases. Loosening of the prosthesis was radiologically not suspected. The prostheses were revised to total hip arthroplasty from 49 to 139 months after the index surgery. The tissues were fixed in buffered formalin immediately after the resection and sent to our laboratory. Following a 24-hour fixation procedure, periprosthetic soft tissues were lamellated and completely embedded in paraffin wax. The sections were stained with hematoxylin and eosin stain, and histochemical staining methods (Feulgen reaction, von Kossa, alizarin red) were performed.

3. Histopathological analysis

The gross analysis showed a synovial membrane with a superficial 2-mm-thick zone of grey-metallic coloured tissue divided from the deeper fibrous joint capsule by a thin linear ferruginous rim of tissue (Fig. 1A). Microscopically (Fig. 1B), there was a band-like superficial necrosis containing numerous macrophages apparent under low-power magnification. At the border of the deeper viable fibrous tissue of the joint capsule, focal dark blue colouration of blood vessel walls (Fig. 1C) and fibres of the extracellular matrix (Fig. 1D) surrounded by cellular infiltrate of macrophages with ingested metal wear and corrosion particles and scattered hemosiderophages was seen.

Histochemical staining methods demonstrated a positive (Fig. 2) Feulgen reaction of the blue material, which was negative for von Kossa's and alizarin red stainings. The tissues did not contain bony particles on gross examination and were thus not decalcified before processing. There was no evidence of excessive lymphocyte infiltration in the areas of Azzopardi phenomenon. The remaining 3 cases showed analogous macroscopic and microscopic findings.

4. Discussion

Although the Azzopardi phenomenon [1] represents a specific morphological pattern which can be seen in several malignant tumours, this feature has not yet been reported in non-neoplastic conditions. We observed characteristic bluish substance in pathologically changed periprosthetic membranes in four cases of adverse reactions to metal debris that clinically presented with progressive groin pain and were radiographically characterised as so-called pseudotumours [9,10]. The periprosthetic pseudotumours can be either cystic or solid and are considered to be caused by idiopathic adverse reaction to metal wear particles. Although some authors have suggested a pathogenic role of local hypersensitivity reaction of periprosthetic tissues to metal material deliberated from the prostheses by corrosion or abrasion, this issue has not yet been sufficiently proven. To date, there is no evidence of a carcinogenic effect of the metal wear particles, and the so-called pseudotumours are defined as non-neoplastic lesions associated with inflammatory reactions to metal wear particles.

In all 4 presented cases, the finding of the characteristic bluish substance was typically focal, comprising about 5% to 20% of the length of the border of superficial geographic necrosis of the synovial membrane. In order to explore its staining characteristics, we performed several histochemical analyses and demonstrated a positive Feulgen reaction; however, further research using modern analytical methods would be needed to shed more light on this interesting phenomenon. Interestingly, in our case study cohort, the Azzopardi effect was always observed in the areas of excessive infiltration by macrophages with few metal and corrosion particles and hemosiderophages. Although the presence of the corrosion particles suggests a longstanding presence of metal wear within the periprosthetic tissues, it

Table Characteristics of the case study patients

	Sex/age	In situ time (months) / site	Type of pseudotumor	Extent of the Azzopardi effect lesion	Metal wear particles	Corrosion particles
Case 1	♀/71yo	96/left hip	Cystic	5%	Present	Present
Case 2	♂/66yo	83/right hip	Cystic	20%	Present	Present
Case 3	♂/61yo	49/left hip	Cystic	15%	Present	Present
Case 4	♂/72yo	139/left hip	Cystic	10%	Present	Present

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