

Case report

Potential histopathological pitfalls in biopsies for endometriosis, related to the use of cellulose based material in prior surgical procedures

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Abstract

Cellulose-based materials used in endometriosis surgeries, can trigger histiocytic reactions that mimic mucinous lesions. These two cases highlight diagnostic challenges due to misleading special stain positivity. Accurate biopsy interpretation requires attention to histologic features and detailed surgical history to avoid misdiagnosis.

Keywords: endometriosis, cellulose based material, mucinous lesions, granuloma

Introduction

Endometriosis is a recurring condition affecting women of reproductive age. Peritoneal biopsies are routinely employed for its diagnosis. According to a study done in 2023, up to 28% of patients may require additional surgical intervention within ten years following complete excision of endometriosis due to reappearance of symptoms(1). As a result, repeat biopsies are not uncommon in these cases; however, endometriosis may not always be detected in subsequent biopsies. Instead, post-surgical changes may be observed.

Intraoperative use of haemostatic products can induce tissue reactions that may lead to diagnostic histopathology challenges. Cellulose based materials (CBM) are among the factors contributing to such complications. Oxidized regenerated cellulose (ORC), which is a cellulose-based material (CBM), marketed under the brand Surgicel®, is a widely utilized haemostatic agent in surgical procedures. This product facilitates clot formation and effectively manages minor bleeding(2). While

generally safe and efficient, its use has been associated with complications such as foreign body reactions and granuloma formation, which can manifest months or years post-surgery. Special histochemical stains on subsequent biopsies can complicate the diagnosis, showing features that mimic mucinous lesions, characterized by intracytoplasmic positivity for mucin stains such as alcian blue, mucicarmine and and Periodic Acid-Schiff with diastase digestion(PAS-D)(3). In addition, they can be positive for fungal stains such as Grocott Methenamine Silver (GMS) and Periodic Acid-Schiff (PAS). Another CBM, Oxiplex gel, is used intraoperatively to reduce intra-abdominal adhesion formation. Comprising carboxymethylcellulose and polyethylene oxide, Oxiplex gel can induce tissue reactions similar to those seen with ORC(4).

In this report, we present two cases where the prior application of CBM during surgical procedures led to confusing results with

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special stains in peritoneal biopsies performed for the investigation of endometriosis.

Case History

Case 1

A 34-year-old woman with a history of extensive endometriosis underwent prior surgical intervention for endometrioma drainage. During the previous procedure, Surgicel® was applied as a haemostatic agent. The subsequent peritoneal biopsy showed granulomas and aggregates of foamy histiocytes. These cells demonstrated positivity for mucin stains, including Alcian blue, mucicarmine and PAS-D. Additionally, the specimen was positive for the fungal stain GMS (Figures 1 and 2). No evidence of endometriosis was identified in this biopsy.

Case 2

A 40-year-old woman presented with chronic pelvic pain. She had a history of primary subfertility and had undergone two previous laparoscopic procedures abroad, with one performed in South Africa approximately 11

years prior (records unavailable) and another in New Zealand approximately 8-9 years prior. In February 2019, a laparoscopy revealed extensive intra-abdominal adhesions. Histological assessment confirmed endometriosis, which was excised from the anterior broad ligament peritonea, pelvic sidewalls and the pouch of Douglas. Oxiplex was applied to all surgical sites. In July 2022, the patient underwent laparoscopic adhesiolysis for treatment of histologically confirmed endometriosis from the right uterosacral ligament and right pelvic sidewall. Oxiplex was used again during the procedure. A biopsy from the right anterior broad ligament peritoneum revealed only reactive changes, with no histological evidence of endometriosis. The specimen exhibited groups of histiocytic cells associated with foreign material, which were positive for mucin stains Alcian blue and mucicarmine. PAS staining was positive but not resistant to diastase digestion. GMS also demonstrated positivity.

The features of the two cases are summarised in table 1.

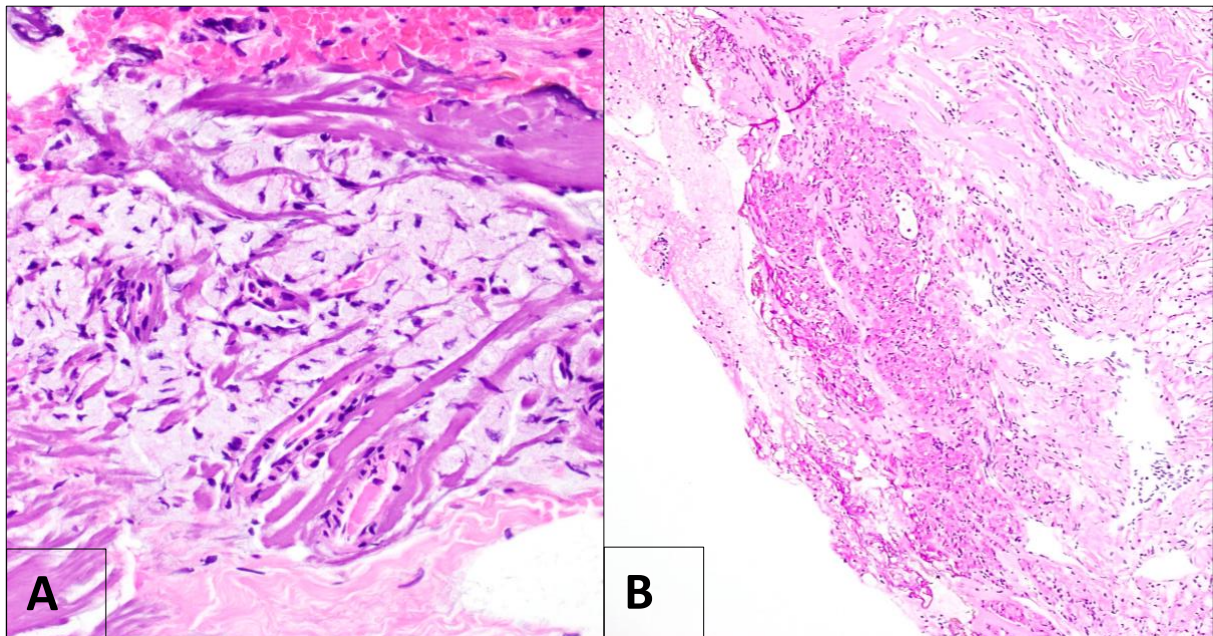


Figure 1: A - Haematoxylin and eosin-stained section of case 1 showing aggregates of large cells containing mucin-like material (x400), B - PAS-D positivity in the large mucinous-like cells (x100)

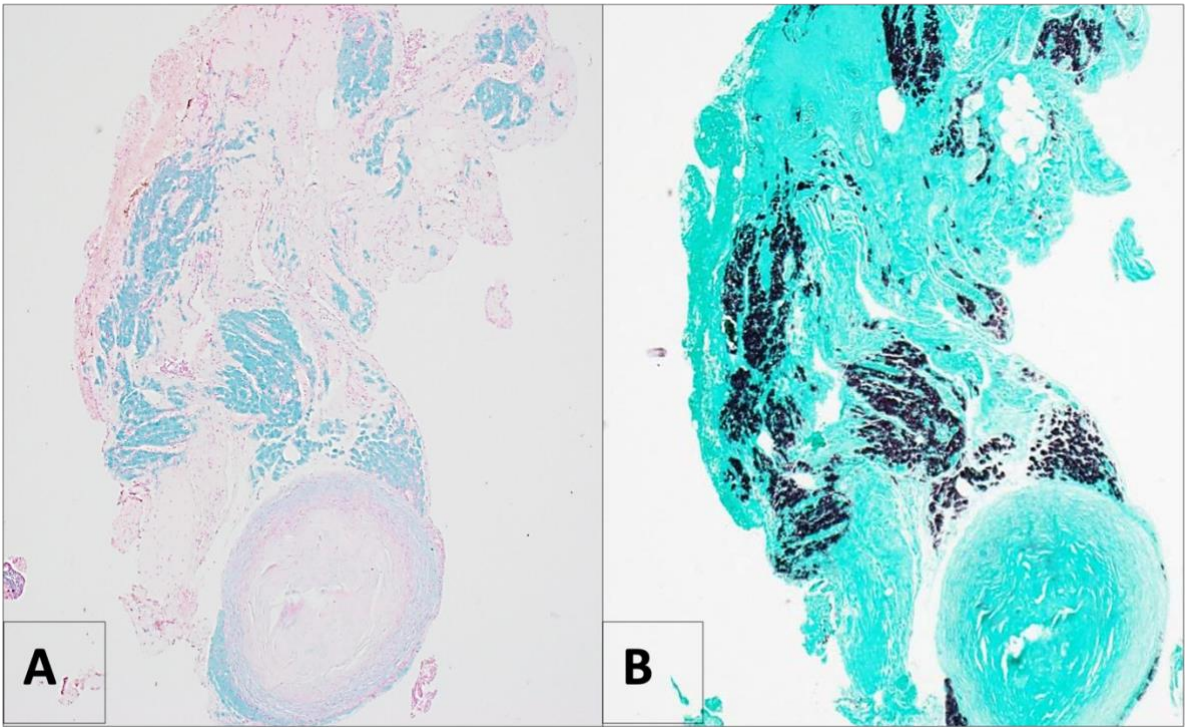


Figure 2: Figure 2: A - Alcian blue positivity in the large cells mucinous-like cells in case 1 (x40), B - GMS positivity in the large mucinous-like cells (x40)

Table 1: Summary of clinical and histological findings of the cases

		Case 1	Case 2
Age (years)		34	40
Number of previous surgeries		1	4
Type of haemostat used		Surgicel®	Oxiplex (2 previous surgeries)
Histology		Granulomas and aggregates of foamy histiocytes. No endometriosis.	Groups of histiocytes with foreign material. No endometriosis.
Special stains	Alcian blue	Positive	Positive
	Mucicarmine	Positive	Positive
	PAS	Positive (Resistant to diastase)	Positive (Not resistant to diastase)
	GMS	Positive	Positive

Discussion

These two cases involved distinct CBM types but showed similar histological features and special stain characteristics. The first case involved Surgicel®, which is an ORC derived from decomposed wood pulp, regenerated into continuous cellulose fibers(5). Its haemostatic properties involve pseudo-clot formation, increased coagulation factor concentration, and lowering of pH.

Additionally, Surgicel® exhibits in vitro bactericidal properties against many bacteria(6). Typically left in-situ post-surgery for absorption(5), its degradation timeline varies (two to six weeks), with granuloma formation reported between two to thirty-six months post-implantation(6). Surgicel's pH-lowering effect can exacerbate local inflammation(2,5). Degradation reactions include blood-material interactions,

provisional matrix formation, and acute and chronic inflammation with foreign body reactions(2,5,6). First described by Ito et al in 1989 as a granuloma to oxidized cellulose(7), Surgicel-induced granulomas have since been reported in various anatomical sites including the gastrointestinal tract, ovaries, thyroid, mediastinum, nasal cavity, liver, kidney, heart, brain and adrenal glands(2,7,8).

Patients may present with non-specific symptoms such as fever, anorexia and weight loss mimicking malignancy(5). These reactions can be mistaken for abscesses or tumour recurrence on postoperative imaging as well, leading to additional procedures(6,8). Recognition of these granulomas is important and pathologists should be familiar with this condition(2). In the two cases described here, the cells contained basophilic material resembling mucin in the haematoxylin and eosin stained sections, which were also positive for mucin stains raising the suspicion of a mucinous lesion. These histopathological changes have been previously described in other cases, as laminated fragments within phagocytic cells with a proteinaceous background(2). Gao et al. reported a histopathological appearance characterized by plump-to-flattened epithelioid cells containing basophilic material associated with multinucleated foreign body-giant cells. However, unlike in the two cases described, both the epithelioid cells and the basophilic material tested negative for mucin on PAS stain(7).

Studies have also described instances where mucin stains, such as Alcian blue and similar dyes have a high affinity to cellulose(9). Staining methods like Grocott methenamine silver (GMS), Congo red, and PAS can also highlight cellulose, due to properties similar to those of native wood(10). In the two cases reported GMS showed false positivity, similar to that previously described. In 1994 Kershnik et al. reported cases of five women treated with oxidized regenerated cellulose during abdominal surgery, that showed collections of large cells beneath the mesothelial surface with small, bland nuclei and abundant granular basophilic cytoplasm. The cells exhibited bright

red staining with mucicarmine, along with Alcian blue and PAS-D positivity. Such lesions can be mistaken for mucinous lesions and diagnosis can be particularly challenging due to strong mucicarmine and mucin stain positivity in histiocytic cytoplasm(3). In 2009 Tang et al. reported a case related to ORC in which microscopic examination of rectal serosa revealed mononuclear cells within the sub mesothelial stroma, displaying positive staining with mucicarmine and PAS-D, thereby complicating diagnosis(11). To minimize the risk of Surgicel granuloma formation, only the minimal amount required to achieve haemostasis should be used, and any excess should be promptly removed once bleeding is controlled (5). It is also important to document its application in the surgical records (2).

In the second case, histological features were attributed to Oxiplex. Intra-abdominal surgeries carry risks of peritoneal adhesions, which can lead to chronic pelvic pain, impaired fertility, and, in severe cases, intestinal obstruction with ileus. To mitigate these risks, a laparoscopically applicable absorbable gel, Oxiplex (Intercoat, Ethicon, Norderstedt, Germany), was recently introduced(4). This gel contains carboxymethylcellulose and polyethylene oxide, both known to reduce adhesion formation by potentially coating tissues and inhibiting fibrin interactions on peritoneal surfaces(4). However, this material can also cause foreign body type reactions in tissues causing later histopathological evaluation challenging. A case report highlighted initial diagnostic confusion during frozen section analysis due to excessive foreign body reaction to pools of Oxiplex gel, resembling pseudomyxoma peritonei(4). This confusion can arise, particularly in frozen sections, if the pathologist is unaware of Oxiplex gel use in the patient's history. Notably, mucin staining with PAS was negative in this case, unlike the findings in our cases.

Conclusion

Careful histological examination and clinical history are crucial for an accurate diagnosis. Pathologists must be aware of the pitfalls of misinterpreting mucin stains and recognise

mimickers of mucinous morphology. Key histological features include the histiocytic nature of lesions and the absence of cytological atypia, along with a history of prior use of CBMs at the surgical site. Special stains can be misleading, falsely staining for mucin, hence careful microscopic examination and an accurate clinical history are required for diagnosis. Distinguishing between endometriotic deposits and foreign body reactions during laparoscopy is difficult as both conditions have a similar appearance intraoperatively. When reporting these cases, additional tissue levels to identify endometriotic glands and stroma is important to confirm the presence or absence of endometriosis as they can also co-exist. Combining detailed clinical history with thorough pathological examination is essential for accurately diagnosing biopsies from patients investigated and managed for endometriosis.

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