Ceroid granulomas in the female genital system

K Ooi, C Riley, V Billson, A G Östör

Abstract
Three cases of ceroid granulomas of the female genital system are presented, involving the cervix in two and lesions in the ovaries and bowel serosa in the other. Ceroid granulomas are unusual and interesting lesions formed when suitable substrates accumulate within macrophages to such an extent that a relative lack of biological antioxidants results and auto-oxidation and conversion to ceroid is favoured. This may occur in the setting of haemorrhage and necrosis, whether from tumour necrosis or associated with endometriosis. Other sources of lipids and lipoproteins include bile, meconium and vernix caseosa.

Keywords: Lipofuscinosis, ceroid granuloma, cervix, endometriosis.

Ceroid granulomas are rare lesions which have been reported in a number of sites including the female genital system. Although in the cases presented here the granulomas were incidental findings, one of these (case 2) presented a diagnostic problem.

Case reports

CASE ONE
A 48 year old woman underwent an elective hysterectomy for persistent menorrhagia despite treatment with norethisterone. Macroscopically, the specimen consisted of a uterus 80 mm in length, measuring 40 mm between the cornua and 40 mm in the antero-posterior plane. The 25 mm cervix contained a 7 mm cyst-like lesion filled with clotted blood. Microscopic sections of cervix revealed a focus of endometriosis consisting of endometrial glandular epithelium and stroma which merged with a well circumscribed sheet of polygonal macrophages laden with a granular pigment which was predominantly golden brown but which shaded to grey in some areas. Other findings included inactive progestogen affected endometrium and superficial adenomyosis.

CASE TWO
A 50 year old woman with a long history of endometriosis underwent a hysterectomy and bilateral oophorectomy with multiple biopsies of bowel serosa. Macroscopically, the specimen consisted of an intact uterus, measuring 80 mm between the cornua, 50 mm antero-posteriorly and 100 mm in length. The right ovary contained an 80 mm "chocolate cyst", the left ovary contained a 35 mm "chocolate cyst" and a smooth haemorrhagic serosal plaque measuring 15 x 20 x 5 mm. Microscopic examination revealed extensive adenomyosis and the endometrium was in the proliferative phase. The right ovarian cyst displayed residual endometrial type stroma and glandular epithelium with sheets of pigment-laden macrophages in the surrounding tissue. The left ovarian cyst was similar but lacked endometrial tissue. The pigment was granular and predominantly of grey brown hue but some of the cells also contained a golden brown pigment resembling haemosiderin. Sections from the serosal plaque showed sheets of similar cells, again containing abundant granular pigment. These cells were originally described as "decidual type" despite the proliferative nature of the endometrium.

CASE THREE
An 84 year old woman with a past history of dementia and stroke with residual dysphagia

Figure 1. Effacement of normal cervical architecture in case 3 by xanthogranuloma (haematoxylin and eosin, original magnification x 20).
Pigment profile of ceroid granulomas

<table>
<thead>
<tr>
<th>Stain</th>
<th>Case number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Haematoxylin and eosin</td>
<td>Granular blue/grey</td>
</tr>
<tr>
<td>Sudan black</td>
<td>Black</td>
</tr>
<tr>
<td>Periodic acid-Schiff</td>
<td>Red</td>
</tr>
<tr>
<td>Schmor's</td>
<td>Dark blue</td>
</tr>
<tr>
<td>Ziehl–Neelsen Acid</td>
<td>Acid fast (red)</td>
</tr>
<tr>
<td>Perls'</td>
<td>*</td>
</tr>
<tr>
<td>S100</td>
<td>Negative</td>
</tr>
<tr>
<td>Auto fluorescence</td>
<td>Yellow-green</td>
</tr>
</tbody>
</table>

* Each case was focally positive for haemosiderin but the pigment was predominantly negative.

Discussion

In each of the cases the pigment was identified as ceroid, first described as an acid-fast brown pigment occurring in rats with experimentally induced cirrhosis of the liver. Lillie coined the term ceroid from the Greek “keros” because of its wax-like qualities. It was thought originally to be different from the lipofuscins which are breakdown products formed from lipids and lipoproteins by a cascade of reactions including auto-oxidation, peroxide formation at double bonds and polymerisation. However, ceroid is now generally considered to be an early form of lipofuscin, derived from lipids or lipoproteins which are only partly oxidised. Some authors distinguish between the two pigments, referring to lipofuscin as a naturally occurring, age-related, wear and tear pigment and reserve the term ceroid for pigment found under pathological circumstances. Likely precursor substances include unsaturated fatty acids, cholesterol, phospholipid, and glycoproteins. As the former are found in cell membranes, it has been suggested that cytotoxic processes such as haemorrhage or necrosis may result in their release. Other sources of substrate suggested include meconium and vernix. Bile also contains fatty acids and has been implicated in the formation of ceroid. Vitamin E is an important lipid soluble antioxidant and ceroid has been shown to accumulate in vitamin E deficiency states.

If sufficient quantities are present, lipofuscins may accumulate in macrophages forming ceroid granulomas. Haemosiderin, presumptively derived from degraded erythrocytes, is frequently found in association with ceroid within macrophages and was present in each of our three cases.

Similar granulomas have been reported in the female genital system within the wall of endometriotic cysts, in tubo-ovarian masses, in the placenta, the ovary, the endometrium, and the cervix.

In both cases 1 and 2 the ceroid granulomas were directly related to endometriotic deposits. Such an association has been described previously, and the cyclical changes of cell growth, haemorrhage and necrosis associated with endometriosis seem likely to provide generous amounts of suitable substrates for the formation of ceroid. This, however, does not explain why ceroid granulomas are not more commonly recognised. One possible contributing factor is that intra-cytoplasmic pigment associated with endometriosis is usually dismissed as haemosiderin by the observer. Without performing the additional stains necessary to identify ceroid. Thus, less extensive collections of ceroid representing developing or intermediate forms may be overlooked. In our cases both pigments were present but the abundance of ceroid and the sheets of macrophages prompted investigation.

Al-Nafussi et al described a case of ceroid granuloma of the cervix similar to that of our case 1 and postulated that tampon usage resulted in a chronic ulcer with embedded fibre fragments which lead to the accumulation of ceroid. As the patient had had her last men-
strual period eight years before presentation, this seems somewhat tenuous and the authors themselves suggest endometriosis as an alternative underlying factor.

A ceroid granuloma of the female peritoneum was described by White and Chan, who suggested that it represented an involutional phenomenon in a case of ectopic decidual change involving the pelvic peritoneum in a pregnant woman. They surmised that decidual cells may be engulfed by macrophages and provide the substrate for ceroid formation. Although no history of endometriosis was given, it is interesting to note that pre-existing peritoneal endometriosis may undergo decidual change during pregnancy. Ishizaki also postulated that degeneration and necrosis in trophoblastic and decidual cells in placentas may result in ceroid production. In our second case the lesions occurred in the setting of established endometriosis, and in the ovary the sheets of pigment-laden macrophages merged with an obvious deposit of endometriosis.

Case 3 did not appear to be related to endometriosis but clearly the presence of a necrotic, poorly differentiated, endometrial adenocarcinoma would provide ample substrate for ceroid production in the form of cellular debris. It is interesting that the granulomas developed in the cervix even though the tumour was located in the uterine fundus. The reason for this is unclear.

The lesions we have described bear many similarities to the necrotic pseudoxanthomatous nodules of ovary and peritoneum described by Clement et al. which they ascribed to an unusual end stage manifestation of endometriosis. The cases presented here, however, lacked the well circumscribed nodularity, central necrosis and hylalised collagen described by Clement et al. Moreover, the granulomas in our series were intimately related to, or merged with, endometriotic foci while the necrotic nodules predominantly occurred elsewhere in the peritoneum close to endometriotic foci. The presence of both ceroid and haemosiderin within sheets of macrophages, the age distribution (older women between 40 and 72 years of age in their series) and the association with endometriosis are similar, and suggest that the two lesions represent different stages in the evolution of endometriosis.

Ceroid granulomas may mimic other lesions, both macroscopically and histologically, depending on their location. In the cervix, endometrium and ovary they can be distinguished from malakoplaia by the absence of Michaelis-Gutman bodies, from decidual change by the clinical setting and by morphological and staining characteristics, and from endometriosis by the lack of glands surrounded by endometrial stroma. Endometrial stromal foam cells are present in endometrial hyperplasia or carcinoma and lack the staining profile of ceroid. Infections (including mycobacteria) should be considered and further stains including Ziehl-Neelsen performed if clinically warranted. In the peritoneum the differential diagnoses include malakoplaia, ectopic decidual reaction, infection, necrotic pseudoxanthomatous nodules and peritoneal melanosis, whether benign or associated with malignant melanoma.

Pseudoangiosarcomatous carcinoma of the genitourinary tract

M A Pitt, G Morphopoulos, S Wells, D L Bisset

Abstract

Two cases of pseudoangiosarcomatous carcinoma of the genitourinary tract, arising in the vulva in one and the bladder in the other, are presented. In case 1, an 84 year old woman, the vulvectomy specimen contained an irregular ulcerated tumour, infiltrating the left labia and extending into the clitoris. In case 2, a 59 year old woman, the excised bladder showed diffuse thickening.
Ceroid granulomas in the female genital system.

K Ooi, C Riley, V Billson and A G Ostör

doi: 10.1136/jcp.48.11.1057

Updated information and services can be found at:
http://jcp.bmj.com/content/48/11/1057

These include:

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/