Short reports

Ceroid granulomas in the female genital system

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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.

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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. Histological 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 progesterone 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 × 20 × 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

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Figure 1 Effacement of normal cervical architecture in case 3 by xanthogranuloma (haematoxylin and eosin, original magnification × 20).

Pigment profile of ceroid granulomas

Stain	Case number		
	1	2	3
Haematoxylin and eosin	Granular blue/grey	Granular blue/grey	Granular brown/grey
Sudan black	Black	Black	Black
Periodic acid-Schiff	Red	Red	Red
Schmorl's	Dark blue	Dark blue	Blue-green
Ziehl-Neelsen	Acid fast (red)	Acid fast	Acid fast
Perls'	*	*	*
S100	Negative	Negative	Negative
Auto fluorescence	Yellow-green	Yellow-green	Yellow-green

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

Figure 2 Staining characteristics of ceroid showing positivity for (A) periodic acid-Schiff reagent, (B) Perls' stain, (C) Ziehl-Neelsen, and (D) Schmorl's reagent (original magnification x 400).

and hemiparesis was referred from her nursing home with a history of postmenopausal bleeding. An examination was performed under anaesthetic and a diagnosis of pyometra was made and a growth of *Escherichia coli* subsequently obtained. A total abdominal hysterectomy was performed. The hysterectomy specimen comprised the body of the uterus and part of the cervix and measured 18 mm in length. On sectioning, a fungating, papillary tumour was found, filling the fundus and most of the body of the uterus. Below this, the lining of the cavity had a fine nodular cobblestone-like appearance. Microscopic examination confirmed the presence of a poorly differentiated endometrioid adenocarcinoma with minimal invasion of the myometrium. In addition, the normal cervicovaginal architecture had been replaced by a xanthogranulomatous reaction extending through the entire wall composed of plump histiocytes laden with granular yellow-brown pigment (fig 1). In some areas there was associated pseudoepitheliomatous hyperplasia of the overlying epithelium alternating with foci of superficial ulceration and an underlying mixed inflammatory infiltrate.

Histochemical and immunohistochemical stains to define the granular pigment further are summarised in the table and illustrated in fig 2.

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.¹ 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.² 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.³ Likely precursor substances include unsaturated fatty acids, cholesterol, phospholipid, and glycoproteins. As the former are found in cell membranes, it has been suggested that cyto-destructive processes such as haemorrhage or necrosis may result in their release. Other sources of substrate suggested include meconium and vernix.⁴ Bile also contains fatty acids and has been implicated in the formation of ceroid.³ Vitamin E is an important lipid soluble antioxidant and ceroid has been shown to accumulate in vitamin E deficiency states.⁴ If sufficient quantities are present, lipofuscins may accumulate in macrophages forming ceroid granulomas.⁵ Haemosiderin, presumably 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.⁵⁻⁷

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.⁸ 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*⁵ 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,⁹ 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. Ishizaki⁴ 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*,¹⁰ which they ascribed to an unusual end stage manifestation of endometriosis. The cases presented here, however, lacked the well circumscribed nodularity, central necrosis and hyalinised 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 malakoplakia by the absence of Michaelis-Guttman 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 malakoplakia, ectopic decidual reaction, infection, necrotic pseudoxanthomatous nodules and peritoneal melanosis, whether benign or associated with malignant melanoma.

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Pseudoangiosarcomatous carcinoma of the genitourinary tract

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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 thick-