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Membranous fat necrosis in appendices epiploicae

A clinicopathological study

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Abstract Membranous fat necrosis (MFN) is a degenerative process involving mature systemic adipose tissue. It is characterised by the presence of membranocystic foci surrounded by a lipophagic fibro-inflammatory reaction typical of fat necrosis. Membranocystic foci are cysts lined by an eosinophilic membrane with pseudopapillary infoldings having the histochemical staining profile of ceroid. Although MFN is described in an increasing number of adipose tissue sites, it has not been described as a distinct entity in appendices epiploicae (AE). Macroscopically, MFN in AE mimics nodal tuberculosis or metastatic tumour with necrosis and cystic change. Ischaemia, which can be secondary to physiological or pathologic processes, is crucial in the pathogenesis of MFN in AE. Heightened awareness of MFN as a distinct entity in AE is essential for accurate diagnosis and establishment of the pathogenesis of this enigmatic pathological process.

Introduction

Membranous fat necrosis (MFN) is a distinct but poorly recognised entity, which has been described in various systemic adipose tissue sites, including bone marrow, subcutaneous tissue, breast, and scrotum [1–3, 6–9, 12, 13, 15, 17]. It has been reported once in the appendices epiploicae (AE) as an incidental finding at laparotomy, but it remains unrecognised as a distinct entity affecting the AE [14]. We report 10 cases of MFN in AE, with an emphasis on clinicopathological recognition of the lesion. The aetiological factors responsible for, and the differential diagnosis of, MFN in AE are discussed.

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Materials and methods

A retrospective analysis of 254 slides coded as fat necrosis (FN) over a 5-year period (1 January 1990 to 31 December 1994) revealed 56 cases of MFN. These cases were retrieved from the files of the Department of Anatomical Pathology, University of Natal Medical School, South Africa. Among these 56 cases there were 9 cases of MFN in the AE. In addition, a 10th case of MFN in AE was identified prospectively at autopsy. These 10 cases form the basis of this study. Clinical details, including follow-up details, of all 10 cases were obtained from the histopathological request forms and in-patient records.

Following routine formalin fixation and paraffin-wax embedding, the biopsied tissue was sectioned at 4 μm thickness. Haematoxylin and eosin-stained sections were prepared and supplemented with PAS, PAS-diastase, long Ziehl Neelsen (ZN), and sudan black stains. In addition, unstained sections were examined under ultraviolet (UV) light.

Results

Details of the relevant clinical findings are summarised in Table 1. There were 4 men and 6 women, whose ages ranged from 25 to 70 years. In 8 cases, the AE pathology was an incidental finding seen with a variety of surgical indications that required laparotomy (Table 1). In cases 9 and 10 the diagnosis of MFN in AE was made on the basis of incidental autopsy findings. AE affected only the transverse and sigmoid colon were involved, with a predominance of the former. In cases 1, 2, 5 and 10 the AE were recognised as being the organ of pathology. Three patients had received prior radiotherapy for gastrointestinal and cervical malignancies.

The AE, which measured between 6 and 25 mm, had a fibrous capsule and foci of calcification (Fig. 1). While all were yellow in colour, 7 showed cystic degeneration and had yellowish-brown fluid inside.

Sections of the AE confirmed that they were be well circumscribed, with a prominent fibrous wall showing variable calcification. Cystic change was present in all cases. Four cases showed complete effacement of the AE architecture by a cystic structure that was lined with an eosinophilic, homogeneous membrane that was smooth or

Table 1 Clinical details (*M* Male, *F* Female, *TC* Transverse colon, *SC* Sigmoid colon, *AE* appendices epiploicae, *MFN* membranous fat necrosis, *RUL* Right upper lobe, *LN* Lymph node, *HC* Hydatid cyst)

Case	Age/sex	Site	Surgical procedure at laparotomy	Indication for surgical procedure	Diagnosis at laparotomy	Other illnesses
1	27/F	SC	Adrenalectomy (bilateral)	Cushing's syndrome, hypopituitarism	Tumour in AE	Diabetes mellitus
2	59/F	TC	Hysterectomy	Uterine leiomyomata	Tumour in AE	Chronic liver disease, hypertension
3	31/F	TC	Oophorectomy	Rupture of cystic corpus luteum	Serosal nodule: ? pathology	
4	70/M	TC	Colectomy	Amoebic stricture	Tuberculosis in LN	
5	38/M	SC	Partial colectomy	Post-traumatic disembowelment	AE - ? significance	
6	42/M	SC	Descending colostomy, gastroenterostomy	Adenocarcinoma of colon	Tumour in LN	Adenocarcinoma in stomach, rectum
7	70/F	TC	Low anterior resection	Adenocarcinoma of rectum	Tumour in LN	
8	60/F	TC	Cholecystectomy	Cholelithiasis, chronic cholecystitis	Tumour in LN	Squamous carcinoma of cervix
9	25/F	TC	Autopsy	Autopsy	TB in LN or partially calcified HC	Diabetes mellitus, rhinocerebral mucormycosis
10	52/M	TC	Autopsy	Autopsy	MFN	Lobar pneumonia RUL

crenulated in different fields and was variably thrown into multiple pseudopapillary projections, creating a scalloped contour.(Fig. 2a, b). The outer aspect of the membranocystic structure was surrounded by lamellae of fibrous connective tissue. In 2 cases, foci of the usual traumatic type of fat necrosis containing lipophages, histiocytes, few giant cells and a scattering of lymphocytes were seen entrapped in the fibrous covering (Fig. 3). Some of the histiocytes contained brown granular pigment.

Partial cystic change was present in 6 cases. In these specimens, in addition to the outer fibrous capsule, fibro-inflammatory septa were also seen bridging parts of the cyst wall and transecting lobules of mature adipose tissue within the AE. Lining the cyst lumen and the fibro-inflammatory septa were membranous structures identical to those lining the complete cysts. Foci of typical fat necrosis were also seen within the lobules of adipose tissue, fibro-inflammatory septa and within the cyst wall. The membranous structures in both sites and the intrahistiocytic granules in all 10 cases had the staining properties of ceroid, being PAS, long ZN and sudan black positive and diastase resistant (Fig. 4). Unstained sections of all cases were brilliantly autofluorescent on UV illumination (Fig. 5).

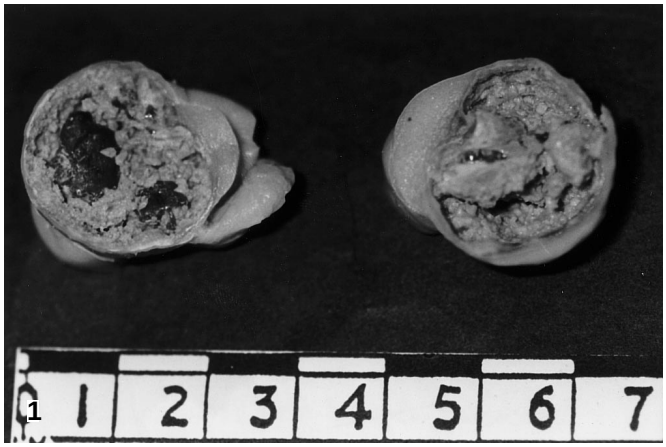
Inspection of the specimens from the 3 patients who had received prior radiotherapy also revealed the presence of prominent surrounding fibrosis, scattered plump mesenchymal cells and vascular mural fibrosis, hyalinisation and luminal narrowing. The vascular changes were confined to arterioles and small arteries.

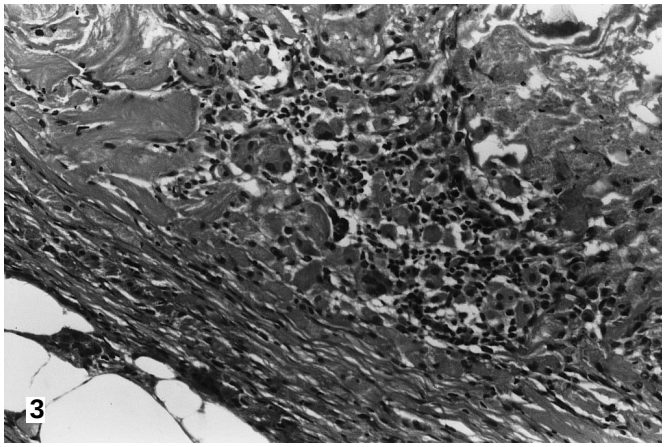
Discussion

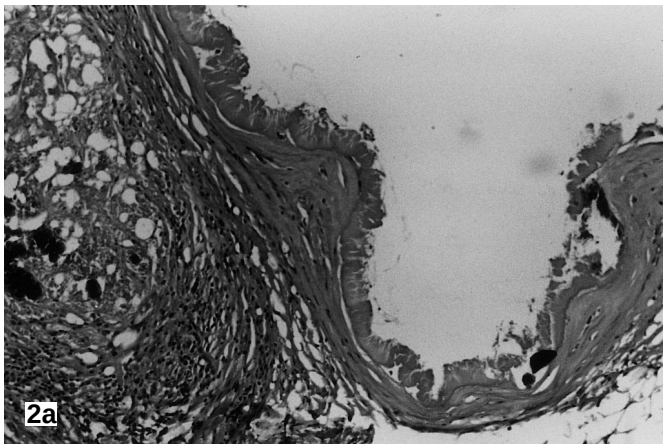
AE are pedunculated structures composed of lobulated masses of mature adipose tissue that protrude from the serosal surface of the colon. They develop in the second trimester of fetal life and are present along the colon and upper part of the rectum. They have an ovoid grapelike or oblong fingerlike configuration and are an average of 1–2 cm thick and 2–5 cm long. They are present from the caecum to the rectosigmoid junction and are commonly arranged in two separate longitudinal rows, one row situated medial to the taenia libera and the other, lateral to the taenia omentalis [11]. Occasionally they are in three rows. A total of 50–200 AE are present in the colon. They are most numerous, and also larger and longer, in the sigmoid colon and transverse colon but are not present in the rectum. The size of the AE is dependent partly on the nutritional state of the individual, being largest and most conspicuous in obese patients. The AE are supplied by one or two end-arteries derived from the vasa recta longa of the colon and they are drained by a single tortuous vein. No precise function has been attributed to AE. Postulated theories on their function include bacteriostatic, protective, absorptive and storage properties.

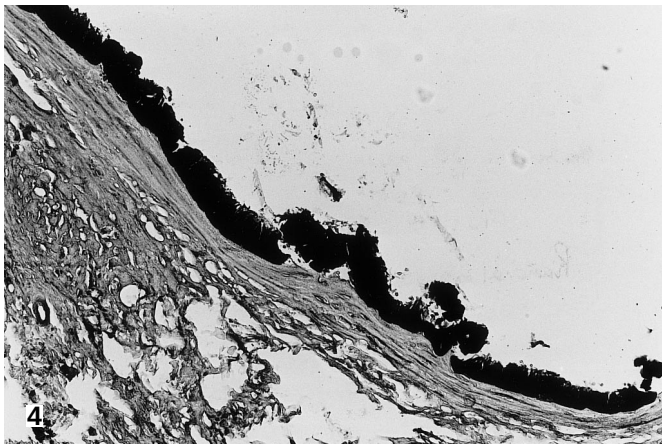
In the past century, vascular, metabolic, inflammatory and neoplastic processes in the AE have been described, mainly as clinical causes of abdominal pain. Whilst most diseases of the AE are innocuous, deaths from AE pathology have been described, mostly resulting from intestinal obstruction following adherence of bowel loops secondary to AE inflammation or from generalised peritonitis or localised abscess formation secondary to torsion and inflammation [10]. Very few histopathological or surgical pathology studies on the disease profile of AE have been reported in the pathological literature.

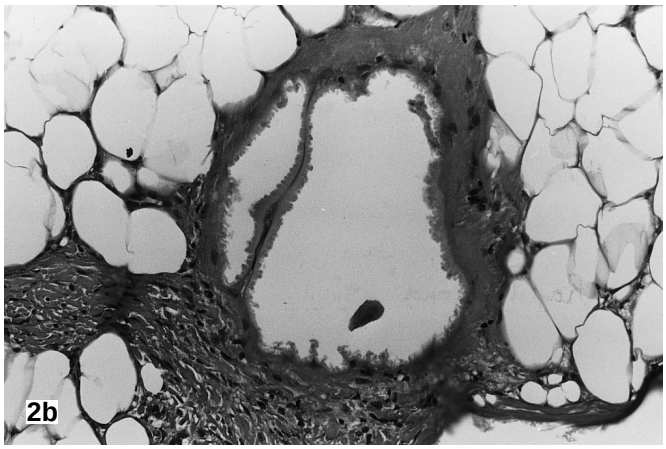
Pathologic processes unique to the AE are not rare, but the aetiological mechanisms of these diseases remain speculative. Aseptic fat necrosis has been described following torsion and infarction of the appendices epiploicae, with gradual transformation of the AE to a fibrotic or calcified mass. These calcified masses may detach from the colonic serosa and become loose intraperitoneal bodies, which have been referred to as "peritoneal mice". Calcification of AE has also been reported with severe pancreatitis, sigmoid diverticulitis and Crohn's disease [15]. None of these reports have mentioned MFN.











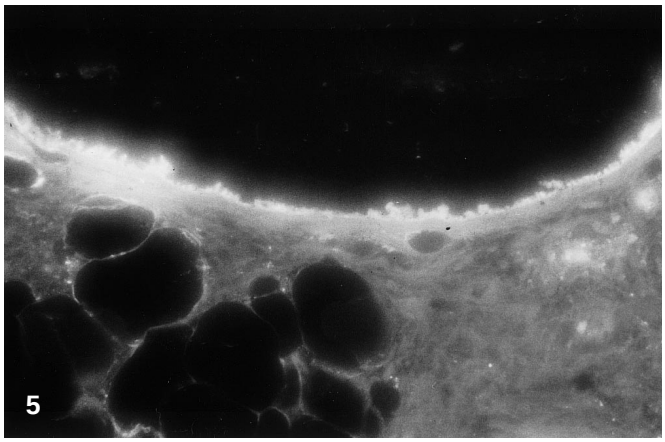


Fig. 1 Macroscopic features of membranous fat necrosis in appendices epiploicae. Architectural distortion and cystic change

Fig. 2 **a** Membranocystic focus with cyst wall lined by scalloped membrane and surrounding lamellae of dense fibrous tissue. **b** Membranous fat necrosis: cystic foci and bridging septa lined by scalloped membrane

Fig. 3 Fat necrosis in the surrounding adipose tissue. Giant cell and lipophagic reaction

Fig. 4 Sudan black positivity of membrane lining cyst

Fig. 5 Autofluorescence of membranes on UV examination of unstained sections

MFN is a curious variant of FN, characterised by the presence of membranocystic lesions surrounded by a fibro-inflammatory and lipophagic reaction. The individual membranocystic foci comprise a membranous structure with pseudo-papillary projections lining a variably-sized cyst and has the physico-chemical properties of ceroid.

MFN of the AE has been described once in the English literature [14]: in this case a freely moving intra-abdominal pseudotumour formation resembling a hard-boiled egg was discovered as an incidental finding during exploratory laparotomy for hepatocellular carcinoma of the liver in an 82-year-old patient. The pseudo-tumour

formation was the result of organisation of a twisted epiploic fringe. In this case of epiploic MFN, there was extensive fibrosis but no accompanying inflammatory reaction.

Membranocystic lesions in bone marrow adipose tissue were first described in Finnish patients in the late 1060s and early 1970s [6, 7]. The newly described entities were variously designated “cystic osteodysplasia”, “hereditary polycystic osteodystrophy” and “lipomembranous polycystic osteodysplasia”. A peculiar lipid metabolic disease, entitled “membranous lipodystrophy”, was described by Nasu et al. in 1973 [9]. The disease process encompassed abnormal systemic lipid metabolism in which bone marrow fat was transformed into undulating membrane structures with cystic change. The membranous structures were also described in the subepicardial, subcutaneous tissue, mesentery, thymus, perirenal and perinodal adipose tissue, adrenals and testes. The brain showed extensive demyelination. In 1977, Akai et al. reported 6 cases of membranous lipodystrophy with concomitant intra-osseous membranocystic lesions and neuropsychiatric disturbances [1]. It was almost a decade later that MFN of extra-osseous systemic tissue was reported [2, 3, 8, 12, 13]. The reported systemic adipose tissue sites in which MFN has been described to date include the breast, subcutis, chest wall and scrotum, in the clinical settings of diabetes mellitus, panniculitis, granulomatous inflammation and systemic lupus erythematosus [16].

Elleder’s study in 1991 on primary extracellular ceroid focused, amongst his 58 pathological specimens, on 12 cases of detached AE, the “peritoneal corpora libera”, in which changes caused by MFN were described [4]. In his brief tabulated description, the membranocystic lesions in the corpora libera were described as being undulating in type and made up of reticulated hyaline masses. In our series, in contrast to the findings of Elleder [15] and Vuong et al. [12], the AE were not free-floating in the abdominal cavity, but were still attached to the serosa. In the present study, two different pathological profiles have emerged. In 4 cases the AE were reduced to complete cystic structures, whilst in the remaining 6 cases they were partially cystic. Largely as a result of the degree of cystic change, an inverse relationship emerges between the extent of cystic change and the amount of typical fat necrosis. The reason for the different histopathological appearances is speculative, but most probably these are a function of the duration of the disease process. A continuum is postulated, with earlier lesions showing partial membranocystic transformation and concomitant typical FN and later lesions exhibiting complete membranocystic transformation and only minimal residual typical FN. The case described by Vuong et al. [12] probably represents an even later stage in the evolution of the disease process, with separation of the AE; whilst they are free-floating in the abdomen fibrosis is ongoing and replaces all the foci of typical fat necrosis. This would account for the extensive fibrosis and total lack of inflammation in this case.

The macroscopic appearance is that of a well-circumscribed, yellow mass with partial or complete cystic degeneration and with variable calcification in its fibrous capsule. The macroscopic differential diagnosis of our cases includes tumour and lymph node and nodal tuberculosis. Although both can only be definitively excluded by histopathological assessment, it is important to note that the affected AE do not have a fleshy or infiltrated consistency. It is not possible to exclude a lymph node with tumour or caseating tuberculosis on macroscopic examination. The nodulocystic appearance with calcification may simulate a partially ruptured hydatid cyst. Although the membranous structure with its crenulated appearance may be misdiagnosed by the unwary as a parasitic cuticle, there are subtle differences in the appearances of the membranous foci in MFN and the wall of a hydatid cyst. The hydatid cuticle exhibits pale eosinophilia and is laminated and wider than the membranous structures. In addition, there is an absence of scolices, germinal epithelium, brood capsule or daughter cysts.

The pathogenetic mechanisms resulting in MFN are unknown. Ischaemia and trauma have been implicated as causative factors in MFN in systemic adipose tissue sites. While trauma is an unlikely causative factor of MFN in AE, we hypothesise that ischaemia plays a pivotal role. The AE are supplied by end-arteries, and the absence of a collateral vascular system renders them susceptible to ischaemia. In addition, the AE are architecturally pedunculated, polypoid structures, with a long narrow pedicle rendering them more prone to torsion and resultant infarction. Because the appendiceal veins are longer than the corresponding arteries, it has been suggested that venous occlusion and subsequent venous infarction occurs as the veins twist around the arteries [11]. In this study, the involved AE were situated mainly in the transverse and sigmoid colon, where the AE are most numerous and larger than anywhere else. In MFN of the breast, Coyne attributed the most florid form to radiation [3]. In our series, 3 patients had received prior radiotherapy for gastrointestinal adenocarcinoma and cervical squamous carcinoma. Hence, the mechanisms it is suggested contribute to ischaemia in AE are interaction of problems associated with the anatomy of the AE in terms of their vasculature, larger size in the transverse and sigmoid colon, and pedicle length. In addition, in 3 patients the compromising effects of prior radiation cannot be ignored.

Ischaemia and hypoxia with the tissue necrosis and inflammation they cause may result in the release of enzymes and oxidation catalysts, with the possibility of enhanced lipoperoxidation and lipid unsaturation. The exact significance of these biochemical processes and their influence on cellular activity is unknown. However, cellular oxidative mechanisms have been implicated as pathogenetic mechanisms in histiocytic lipopigment accumulation. Since both the intracytoplasmic granules and the membranous structures have the staining properties of ceroid, it is highly likely that the release of intra-

cellular ceroid may initiate extracellular membrane formation.

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