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Case report

Granular cell tumour of the appendix in a patient irradiated for a rectal carcinoma

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Summary. We report on a 47-year-old man with a granular cell tumour of the appendix, discovered incidentally during surgery for a rectal adenocarcinoma that had been irradiated preoperatively. A detailed immunocytochemical analysis revealed positivity for S-100 and neuron-specific enolase (NSE). Electron microscopically, the cytoplasm of the tumour cells contained numerous pleomorphic lysosomes. In the appendix tissue adjacent to the tumour a neuroma and the histological features of radiation injury were present. Our findings suggest that this granular cell tumour may have originated from a pre-existing appendix neuroma which underwent granular degeneration, possibly as a result of radiation.

Key words: Granular cell tumour – Appendiceal neuroma – Appendix – Radiation injury

Introduction

Despite their early recognition (Muller 1836), granular cell tumours were classified until recently amongst "tumours and tumourlike lesions of uncertain histogenesis" (Enzinger and Weiss 1983), "benign growths" (Stout and Lattes 1980), or "miscellaneous soft tissue tumours" (Hajdu 1979). They are currently considered to be of neural (Enzinger and Weiss 1988) or primitive mesenchymal (Miettinen et al. 1984; Sobel et al. 1973) origin. Most cases have been identified in the dermis or subcutis; very few have been reported in the appendix (Fried et al. 1984; Johnston and Helwig 1981; Sarma et al. 1984).

This report describes a granular cell tumour of the appendix in a patient with a rectal carcinoma that was irradiated preoperatively. On the basis of the histological, immunocytochemical and ultrastructural findings the tumour's origin from a pre-existing and irradiated appendix neuroma is discussed.

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Case report

A 47-year-old male was referred to our hospital for the treatment of an advanced rectal adenocarcinoma with lymph node metastases. The patient was submitted to 4 weeks of radiotherapy (total dose: 40 Gy) and treated with vinblastin (2 × 5 mg per week). This treatment was stopped 2 days before an abdominoperineal resection was performed. During surgery a concurrent appendiceal tumour was discovered. A frozen section of this lesion revealed a granular cell tumour.

After 6 months, multiple hepatic metastases of the rectal adenocarcinoma developed and the patient died 1 year after surgery. An autopsy was not performed.

Materials and methods

The surgical specimen was fixed in Bouin's and paraffin sections were stained with haematoxylin and eosin (H & E), periodic acid-Schiff (PAS), PAS after diastase digestion, and with PA silver methenamine (PASM) (Jones 1957). Sections were also examined for the presence of neuron specific enolase (NSE), serotonin and S-100 using the peroxidase- antiperoxidase method (Sternberger et al. 1970) and commercially available antisera. Serotonin antiserum was a gift from Dr. A.A.J. Verhofstad, Nijmegen, The Netherlands. Known positive and negative tissue controls were included.

Specimens for electron microscopy were fixed in glutaraldehyde (4.5% in 0.1 M cacodylate, pH 7.3), postfixed in osmium tetroxide and embedded in epoxy-resin (Spurr 1969). Ultrathin sections were stained with uranyl acetate and lead citrate and examined in a Zeiss EM9S electron microscope.

Results

The appendix measured 9 cm in length. Its distal portion contained an ill defined, intramural tumour protruding into the lumen. The tumour was white to yellow, moderately soft and measured 4 × 2.5 cm.

Microscopically, tumour infiltrated mucosa, submucosa, muscularis propria and serosa. It was composed of nests and fascicles of polygonal cells (Fig. 1A). Their cytoplasm contained numerous granules, mostly small and occasionally coarse, irregular or vacuolated. The nuclei were moderately pleomorphic. No mitoses were

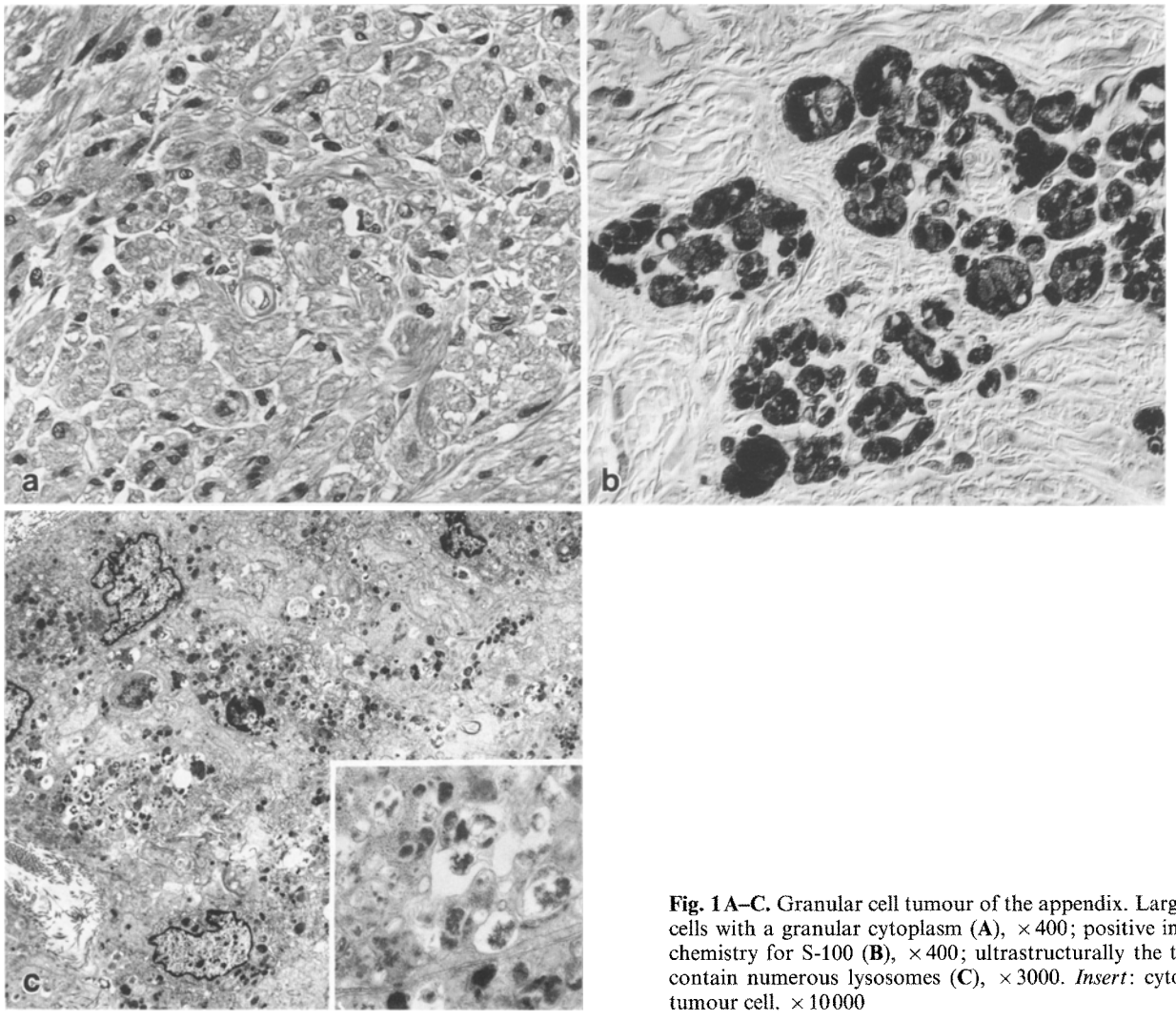

Fig. 1 A–C. Granular cell tumour of the appendix. Large polygonal cells with a granular cytoplasm (**A**), ×400; positive immunocytochemistry for S-100 (**B**), ×400; ultrastructurally the tumour cells contain numerous lysosomes (**C**), ×3000. *Insert*: cytoplasm of a tumour cell. ×10000

noticed. The tumour was infiltrated by polymorphonuclear leucocytes, plasma cells, histiocytes and mast cells. There was a focal desmoplastic reaction. With PAS the fine granules stained faintly, the coarse granules more strongly; staining was not affected by prior diastase digestion. PASM stained very few fine granules, but most vacuolated coarse granules.

In the proximal one-third of the appendix, the wall was thickened. Most epithelial cells were flattened or cuboidal and showed a moderate nuclear pleomorphism; a few crypt abcesses were present. The mucosa contained plasma cells and eosinophils, but lymphoid follicles were rare. The muscularis mucosa was hypertrophic. The submucosa showed considerable oedema and contained scattered inflammatory cells. The blood vessels were telangiectatic with a fibrotic or hyalinized wall. Collections of smooth muscle cells were present. The muscle fibres in the muscularis mucosae and submucosa were vacuolated. The tunica muscularis was hypertrophic and the outer muscle coat and the serosa partly sclerotic.

Electron microscopy revealed the classical features of a granular cell tumour (Fig. 1C). The cytoplasm of the cells contained numerous pleomorphic lysosomes. No cell junctions were found between the cells. They contained fine filaments that lacked any condensation. No pinocytotic activity was noticed.

Immunocytochemical staining using antisera against S-100 (Fig. 1B) and NSE showed staining of the cytoplasm of the tumour cells. S-100 antiserum also stained Schwann cells and satellite cells in the tumour-free tissue, but failed to stain ganglion cells; the latter were positive for NSE. The perivascular plexus of the medium-sized arteries showed an accentuated NSE and S-100 staining. Serotonin was not detected in the tumour cells, but serotonin cells were present in the crypt epithelium of the overlying appendiceal mucosa and, to variable amounts, in the lamina propria. Their number was increased focally.

Discussion

Granular cell tumours have seldom been described in the appendix (Fried et al. 1984; Johnston and Helwig 1981; Sarma et al. 1984). All cases reported have been considerably smaller than the present tumour (4 cm in diameter). In the study of McSwain et al. (1980), who

described 96 cases from sites other than the appendix, only 9% exceeded 3 cm in diameter. Lack et al. (1980) examined 118 granular cell tumours, with the largest being 3.5 cm in diameter, whereas the largest in the series of 74 tumours reported by Johnston and Helwig (1981) measured 4 cm and was located in the stomach.

Histologically, the present tumour compared well with the granular cell tumours reported in the literature (Bedetti et al. 1983; McSwain et al. 1980; Miettinen et al. 1984; Sobel et al. 1973). Its cytoplasmic granules stained positively with PAS and PAS after diastase digestion, with a particularly intense reaction in the coarse granules, a typical feature of granular cell tumours (Sobel and Churg 1964).

While granular cell tumours are rarely found in the appendix, microscopic collections of granular cells are encountered more frequently in this organ. They have been found in as many as 5% of autopsy appendices (Churg and Work 1959; Hausman 1963; Sobel and Churg 1964) and in 2% of appendices removed for "chronic appendicitis" (Pour et al. 1973). The cells forming the granular cell lesions appear to be of smooth muscle origin (Sobel et al. 1971). The PASM reaction can differentiate the reactive granular cells in granular lesions from those in granular cell tumours (Sobel and Churg 1964). In the lesions, both the fine and the coarse granules are blackened by this reaction, while in the tumour only coarse granules are silver positive. In our case, most fine granules remained silver negative, supporting the diagnosis of "tumour". Furthermore, the ultrastructural features corresponded to those previously described for granular cell tumours and differ from those described for granular cell lesions (Sobel et al. 1971).

In accordance with previous reports (Armin et al. 1983; Bedetti et al. 1983; Lloyd and Warner 1984; Mukai 1983; Nakazato et al. 1982; Rode et al. 1982), tumour cells were strongly positive for S-100 and NSE. The tumour described here thus showed the "classical" immunostaining pattern of a granular cell tumour.

The origin and cause of granular cell tumours are still controversial. In our case, the histology of the appendix proximal to the tumour was suggestive of radiation injury (Berthrong and Fajardo 1981) which was also seen in rectum adjacent to the adenocarcinoma. This suggests that the appendix was included in the radiation field for the rectal carcinoma (presumably due to an abnormal location). Radiation may thus be considered as a possible cause for the development of this granular cell tumour. In an extensive review of radiation injury of the digestive tract, Berthong and Fajardo (1981) mentioned that the oral cavity may present histological changes in the muscle cells which resemble those observed in granular cell tumours. Anniko et al. (1981) have shown that cultured neurinoma cells become rounded or oval and acquire pleomorphic electron-dense inclusion bodies when irradiated. These can aggregate and merge. However, we found only one report on a granular cell tumour that originated after irradiation (Domen et al. 1979): the tumour was located in the oesophagus, measured 4 mm in diameter and was detected 9 months after irradiation.

That our case is solely the consequence of irradiation seems unlikely. First, the last radiation was given only 2 days before resection of the tumour. Second, radiation is used so extensively in modern medicine that granular cell tumours should occur more frequently, if this alone were their cause. We rather suspect that a pre-existing lesion in the appendix of our patient gave rise to a granular cell tumour. Non-neoplastic neuromas are frequently encountered in this region – Michalany and Galindo (1973) found them in 15% of surgically removed appendices. These lesions are intra-appendicular growths of neurofibrils and Schwann cells, and were first described by Masson (1930) as neuromuscular hypertrophy. Appendiceal neuromas stain with both S-100 and NSE, and present in their vicinity an abundant S-100-positive plexus in the medium-sized vessels of submucosa and serosa, as well as a focal increase of serotonin-containing cells (Stanley et al. 1986). These two features were also noted in our case.

Schwann cells are very slender cells, and have a diameter that is less than one-fifth of that of a granular cell. If this granular cell tumour originated from a neuroma the diameters of the original tumour would have been 0.4 cm × 0.8 cm. This size is consistent with the size of appendiceal neuromas.

On the basis of these findings and considerations, we assume that the present tumour was originally a neuroma of the appendix, which due to irradiation degenerated and acquired a granular cell pattern. This case further supports the hypothesis that granular cell tumours, despite their characteristic histology, do not form a homogeneous tumour group (Rosai 1989). They are probably of heterogeneous origin, resulting from different degenerative processes that can occur in various neoplastic and non-neoplastic lesions (Bedetti et al. 1983; Fisher and Wechsler 1962; Pour et al. 1973).

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