

Syncytial giant cell component. Review of 55 renal cell carcinomas

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Summary. Different types of multinucleated giant cells (MGC) have been documented in tumors with osteoclast-like appearance, with trophoblastic differentiation or as tumoral malignant giant cells. A new variety of MGC has been described in renal cell carcinoma. In order to study the frequency, nature and significance of this cellular type, we have reviewed our files.

To assess the presence, nature and significance of these MGC in renal cell carcinomas and associated histologic subtype.

To review all malignant renal tumors diagnosed in the last 5 years in our hospital and to carry out a morphologic and immunohistochemical study in renal cell carcinomas with syncytial type MGC.

55 renal cell carcinomas were reviewed. Clear cell (conventional) renal cell carcinoma was the most common type encountered (40 cases); two of these cases showed syncytial type MGC and low grade malignancy. Microscopically the MGC contained from 5 to 40 nuclei. Immunohistochemically, mononucleated and multinucleated cells were positive for cytokeratin CAM 5.2, cytokeratin AE1/AE3 and weakly positive for vimentin. Histiocytic, muscular, neural markers, beta-HCG and alpha-fetoprotein were negative.

The presence of syncytial type MGC in renal cell carcinomas is an exceptional event. Among 55 renal cell carcinomas we found two cases, both of which were of clear cell subtype and low grade malignancy. The MGC proved positive for epithelial markers and probably are the result of mononucleated tumoral cell fusion. We are unaware of the impact of this MGC in the outcome of patients; such cells appear in low grade carcinomas and do not seem to be of dismal prognosis.

Key words: Multinucleated cells, Syncytial component, Renal carcinoma

Introduction

The presence of multinucleated giant cells (MGC) is well-documented in different types of neoplasms in many localizations. These giant cells have been observed in different situations, such as bizarre cells in pleomorphic tumors, with osteoclast-like appearance, and in tumors with trophoblastic differentiation.

Pleomorphic tumors with MGC frequently correspond with sarcomatoid phenotype and high grade malignancy; this situation has been reported in thyroid gland (Walter, 1980), liver (Sola-Pérez, 1995), salivary glands (Moore and Bocklage, 1998; Takeda, 1999), ovary (Young and Scully, 1983), breast (Douglas-Jones and Barr, 1989; Pruneri et al., 2002), uterus (Jones et al., 1991; Prayson et al., 1997), lung (Jackson et al., 1984; Barbas et al., 1997), kidney (Staelens, 1997), testicles (Albores-Saavedra, 1996) and central nervous system (Kawano et al., 1995; Katoh et al., 1995; Klein et al., 1998; Sabel et al., 2001).

MGC similar to osteoclasts of monocytic-histiocytic origin are seen in a variety of neoplasms from many organs, including stomach (Baschinsky et al., 1999), gallbladder (Trias et al., 1990; Grosso and González, 1992), pancreas (Nojima et al., 1993; Mullick and Mody, 1996; Deckard-Janatpour et al., 1998) and soft tissues (Rodríguez-Peralto et al., 2001), as well as in many organs, as mentioned above (Veliath et al., 1975; Hood et al., 1990; De Rosa et al., 1991; Gaffey et al., 1991; Bleiweiss et al., 1992; El-Naggar et al., 1993; Guiter and DeLellis, 1996; Donath et al., 1997; Gaumann et al., 2001; Iacocca and Maia, 2001).

In other tumors, MGC display trophoblastic differentiation and immunohistochemically express beta-HCG positivity; this situation has been described in testis (Mostofi, 1973; Requena et al., 1991), pulmonary giant cell carcinoma (Attanoos et al., 1998), adenocarcinoma of the colon (Metz et al., 1985), ovarian germ cell tumors (Kaplan and Hawley, 1981; Nakakuma et al., 1983; Sekiya et al., 1987; Morimura et al., 1998) as well as jejunum (Harada et al., 1991), stomach (Ramponi et al., 1986) and mediastinum (Moran and Suster, 1997a; Moran et al., 1997b). Recently a variant

of MGC has been described in renal cell carcinomas (RCC), so-called "syncytial" type (Lloreta et al., 2002). In order to study the frequency and nature of this peculiar type of MGC in renal tumors we have reviewed all radical nephrectomies for RCC in the last five years in our hospital.

Materials and methods

Surgical specimens from 55 renal carcinomas were reviewed. Surgical specimens were fixed for more than 24 hours in 4% buffered formalin solution. Representative tumoral and non-tumoral kidney samples were embedded in paraffin. For histopathology 5 μ m-thick sections were stained with hematoxylin and eosin.

The histopathology review of all renal carcinomas allowed us to categorize with the Störkel classification, adopted by both European and American authorities, based on a combination of histological and genetic features (Störkel et al., 1997), and to identify the presence of syncytial type MGC. In these cases tumoral sections were also stained using the periodic acid-Schiff base (PAS) method with and without diastase digestion. We performed immunohistochemical studies using a standard avidin-biotin immunoperoxidase method and diaminobenzidine as chromogen. The antibody panel used comprised: cytokeratin (CK) CAM 5.2, CK AE1/AE3, CK7 (clone OV-TL12/30), CK8 (clone 35BH11), CK20 (clone KG 20.8), vimentin (clone V9), alpha-actin (clone 1A4), desmin (clone D33), S-100 protein, HMB-45, beta-HCG, alpha-fetoprotein,

lysozyme, CD68 (clone KP1), MAC 387, CD45 (clone 2B11+PD7/26) and MIB-1. Except for the CAM 5.2 antibody from Menarini (Florence, Italy) and MAC 387 antibody from Novocastra Laboratories Ltd (Newcastle-upon-Tyne, England), the rest of the antibodies used were from Dako Corporation (Glostrup, Denmark).

The grading scheme used was that of Fuhrman et al. in this system the neoplasm is classified by the highest grade of any of its component cells (Fuhrman et al., 1982).

Results

Fifty-five cases were obtained from nephrectomies for RCC performed between 1997-2002. The Störkel classification yielded the following results: 40 cases (72.7%) clear cell (conventional) RCC; 8 cases (14.5%) chromophobe RCC; 6 cases (10.9%) papillary RCC and 1 case (1.8%) collecting duct RCC. Clear cell carcinoma accounted for the majority of cases in this series (72.7%). The distribution of different RCC subgroups was similar to series published by other authors.

Among 40 cases of clear cell RCC only two were identified as syncytial type MGC; in both tumors the staging was low-grade malignancy; nuclear grade II in the Fuhrman classification.

Gross findings of the surgical specimens showed in the first case a tumor of 7x5.5 cm (Fig. 1) and 4.5x4 cm in the second case; both had a cortical location and were yellowish with hemorrhagic areas and soft consistency.

Microscopical findings in both tumors revealed a



Fig. 1. Macroscopic appearance in the cortex of a yellowish and well-circumscribed mass.

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malignant neoplastic proliferation characterized by round to polygonal cells with slightly irregular nuclei, nucleoli were visible at high magnification but not readily seen and clear cytoplasm.

The architectural pattern was predominantly of the alveolar or acinar variety, delimited by a network of thin and delicate vascular structures. The other cell population was composed of syncytial type MGC that

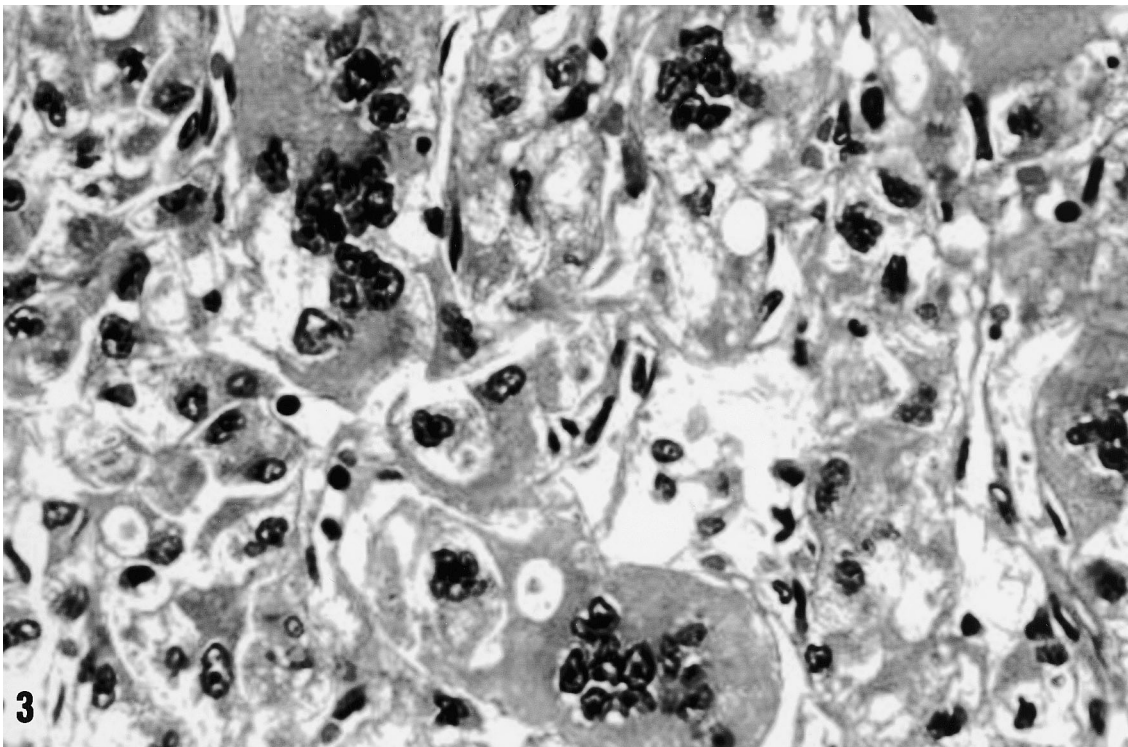
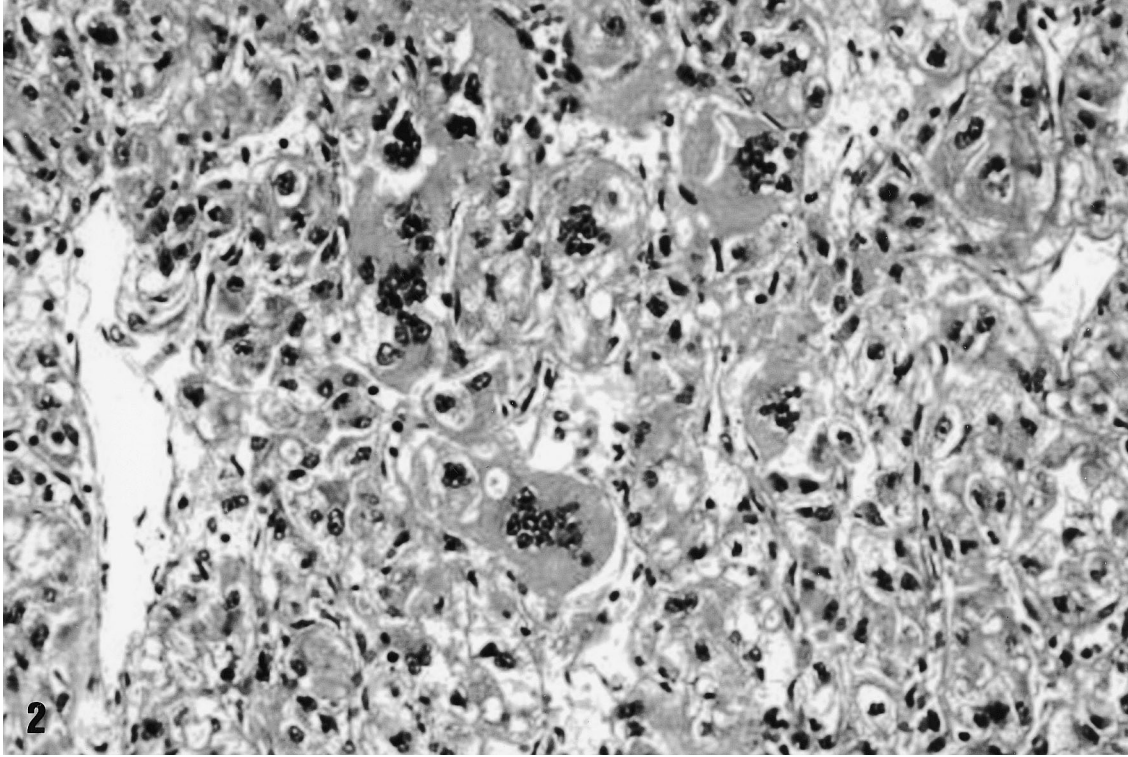


Fig. 2. Conventional (clear cell) renal cell carcinoma with multinucleated giant cells intermingled with mononuclear tumor cells x 100

Fig. 3. Conventional (clear cell) renal cell carcinoma. Multinucleated giant cells in detail. x 400

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was intermingled with mononuclear tumor cells (Fig. 2). A perihemorrhagic arrangement was also observed.

The MGC had abundant eosinophilic and finely granular cytoplasm, containing from 5 to 40 large nuclei,

with slightly irregular contours, in central localization, with three-dimensional image, coarse chromatin, prominent and single nucleoli and without molding (Fig. 3). The nuclei in both populations (conventional clear

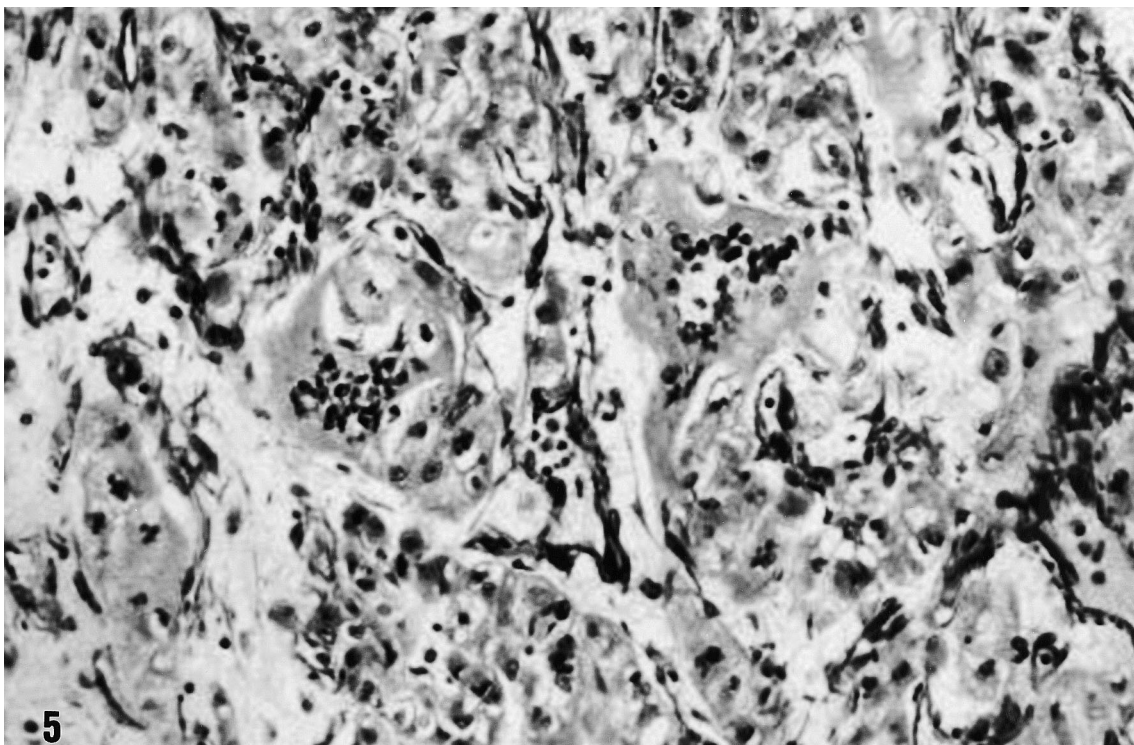
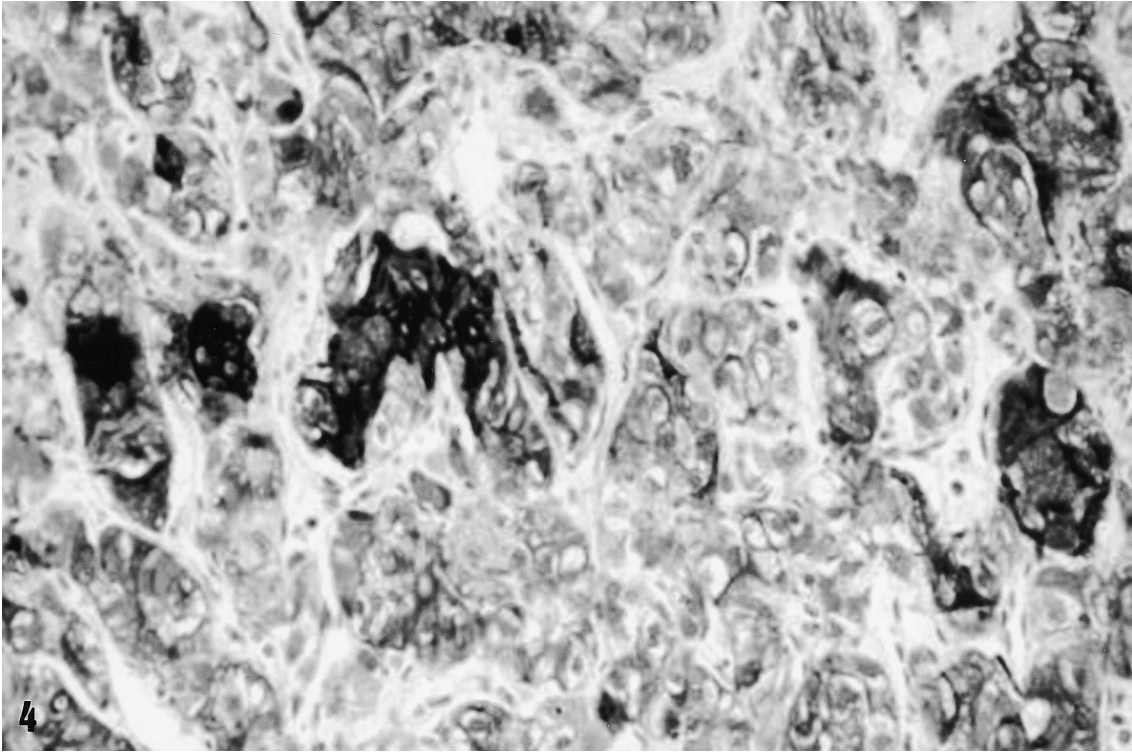


Fig. 4. Positive cytokeratin cytoplasm staining CAM 5.2 in both populations (immunoperoxidase x 200).

Fig. 5. Weakly positive vimentin cytoplasm staining in both populations (immunoperoxidase x 200).

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cells and syncytial component) had identical histologic features. In non-tumoral parenchyma we observed renal arteriolosclerosis.

All tumor cells were positive with PAS stain and extracted by diastase digestion. Immunohistochemically both cellular types were strongly positive, with cytoplasmic staining pattern for CK CAM 5.2 (Fig. 4), CK AE1/AE3 and weakly positive for vimentin (Fig. 5). The antibodies to CK7, CK8, CK20, desmin, alpha-actin, S-100 protein, HMB-45, beta-HCG, alpha-fetoprotein, lysozyme, CD45, CD68 and MAC 387 proved consistently negative in all cells. Only occasional and isolated mononuclear tumor cells showed focal nuclear staining for MIB-1 (<5%).

Discussion

The distribution of different RCC subgroups in our files was similar to series published by other authors (Amin et al., 2002; Moch et al., 2002; Renshaw, 2002).

Pleomorphic (Staelens et al., 1997), osteoclast-like (El-Naggar et al., 1993) and recently, syncytial type MGC (Lloreta et al., 2002) have been described in RCC. The presence of syncytial type MGC is a rare event; to date only one case has been published as a single case report.

In our study of 55 cases of RCC we observed two cases with syncytial type MGC. In these two renal cell carcinomas, the MGC were found in low grade tumors, all clear cell subtypes with slight pleomorphism and without sarcomatoid changes. Moreover, in our two tumors there was concordance between low grade malignancy and the immunoeexpression in tumor cells with MIB-1 displaying a low proliferative index (<5%).

In our study an epithelial origin was established because cytokeratins were positive. The negative results with MAC 387, CD45, lysozyme and CD68 ruled out a monocytic-histiocytic origin; with alpha-fetoprotein and beta-HCG we also ruled out a trophoblastic differentiation; non immunoeexpression of HMB-45 also excluded an epithelioid angiomyolipoma as origin (Cibas et al., 2001).

We believe that MGC is the result of mononuclear tumor cell fusion, since they displayed the same morphologic characteristics and identical immunophenotype.

We agree with Lloreta et al. (2002) that the term "syncytial type" for these MGC would be more appropriate in such cases. The prognostic importance of these MGC is difficult to assess due to their rarity and the absence of series in the literature. These giant cells do not appear to be associated with an adverse effect on the prognosis of renal cell carcinoma, but the role that these syncytial type MGC play in determining prognosis needs to be further investigated.

In the case from Lloreta et al. (2002) the patient was alive and free of disease 6 years after surgical excision. In the two cases of our study, patients with follow-up of 4 years and 3 months respectively are currently alive and free of residual disease. In our opinion is very difficult to

conclude on behavior with this short follow-up.

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