

Case Report

Chromophobe renal cell carcinoma with liposarcomatous dedifferentiation - report of a unique case

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Abstract: Sarcomatous transformation of chromophobe renal cell carcinoma (CRCC) is a well recognized phenomenon. Of the published cases with sarcomatous transformation of CRCC, none have shown liposarcomatous differentiation. Out of a cohort of 250 cases of CRCC, 19 (7.6%) showed sarcomatous differentiation. In one case (female, age 46 years), the sarcomatous component of the tumor displayed histological features of a pleomorphic liposarcoma. Light microscopic examination revealed a biphasic pattern with a chromophobe renal cell carcinoma (CRCC) and a high-grade sarcomatous component containing large pleomorphic lipoblasts. In several areas both components were intermingled. The conventional CRCC component showed classic histological features with calcifications, medium-sized polygonal cells arranged in solid-alveolar structures with raisinoid nuclei, pale-eosinophilic flocculent cytoplasm with perinuclear haloes. In addition, a microcystic-adenomatous component had luminal spaces filled with erythrocytes. The CRCC was positive with Hale's colloidal iron-stain whereas the sarcomatous component was negative. The CRCC component was diffusely positive for cytokeratin 7, parvalbumin and racemase but negative for cytokeratin 20, vimentin, CD10, carboanhydrase IX and S100-protein. The pleomorphic liposarcomatous component displayed immunoreactivity for CD10, vimentin, racemase and focally for carboanhydrase IX. The proliferative activity (Mib-1/Ki-67) was 5% in the CRCC and 30% in the pleomorphic liposarcomatous component. No immunoreactivity for MDM2 or CDK4 was detected. This is the first reported case of a sarcomatoid CRCC where the sarcomatous component displayed features of a pleomorphic liposarcoma. The patient died from widespread metastatic disease 12 months after nephrectomy.

Keywords: Chromophobe renal cell carcinoma, liposarcoma, sarcomatous transformation, sarcomatoid

Introduction

Chromophobe renal cell carcinoma (CRCC) was first described by Thoenes et al in 1985 [1]. In addition to the conventional and granular cell types, a pigmented-microcystic variant is on record [2, 3]. CRCC in its pure forms typically display low-grade nuclear features and have a relatively favourable prognosis. Sarcomatous transformation/dedifferentiation of CRCC and/or distant metastasis do occur [4-6]. Among previously published cases of CRCC with sarcomatous transformation [7-23], we are not aware of any case of CRCC with sarcomatous dedifferentiation showing liposarcomatous features. In this paper we present one such case.

Materials and methods

The routine and consultation files of the authors contain 250 cases of CRCC of which 19 (7.6%) show sarcomatous dedifferentiation. These cases were reviewed and in one case, a 46 year old female, the sarcomatous component displayed areas with a pleomorphic, high-grade liposarcomatous morphology. The patient came to medical attention after a one year history of hematuria and flank-pain. A right renal tumor was diagnosed and a nephrectomy was performed. The immediate postoperative course was uneventful. However, 12 months after the operation the patient died from generalized metastatic disease. No autopsy was carried out.

On gross section there was a 15 cm large renal tumor. The tissue was fixed in 4% formaldehyde and embedded in paraffin and cut in 5µm thick sections and stained with Hematoxylin and Eosin and Hale's colloidal iron.

An immunohistochemical study using the following commercial primary antibodies was performed according to the manufacturers' instruction: Cytokeratin 7 (Novocastra, Newcastle), cytokeratin 20 (DAKO, Glostrup), Cam5.2 (Becton Dickinson, Erembogeden), CD10 (Novocastra, Newcastle), Vimentin (Neomarkers, Westinghouse), parvalbumin (Sigma, Steinheim), carboanhydrase IX (R& D Systems, Minneapolis, MN), Mib-1 (DAKO, Glostrup), S100-protein (Novocastra, Newcastle), p504S/racemase (Ann Arbor, MI), MDM2 (Millipore, Temecula, CA) and CDK4 (Santa Cruz, Santa Cruz, CA). Appropriate positive controls were applied.

Results

Routine histology

Light microscopic examination revealed a tumor with a biphasic pattern, with on the one hand chromophobe CRCC with conventional and focally a component of the adenomatous-microcystic pattern, and on the other hand a high-grade sarcomatous component consisting of large neoplastic cells with strikingly pleomorphic nuclei and abundant micro- and macrovacuolated cytoplasm. The different components were focally intermingled (**Figure 1**). The conventional CRCC component showed in addition to areas with calcification, medium-sized polygonal cells arranged in solid-alveolar structures with raisinoid nuclei, pale-eosinophilic flocculent cytoplasm with frequently occurring perinuclear haloes. In areas displaying the microcystic-adenomatous pattern luminal spaces were frequently filled with erythrocytes in various stage of lysis (**Figure 2**). In addition to bizarre giant cell forms, cells in the high-grade sarcomatous areas showed focally characteristics of pleomorphic lipoblasts with cytoplasmic vacuoles indenting on the nuclear contour (**Figure 3**). Areas with necrosis and numerous mitotic figures including atypical forms were easily identified in the sarcomatous areas. No other lines of heterologous differentiation were identified. The CRCC was positive with Hale's colloidal iron-stain whereas the sarcoma-

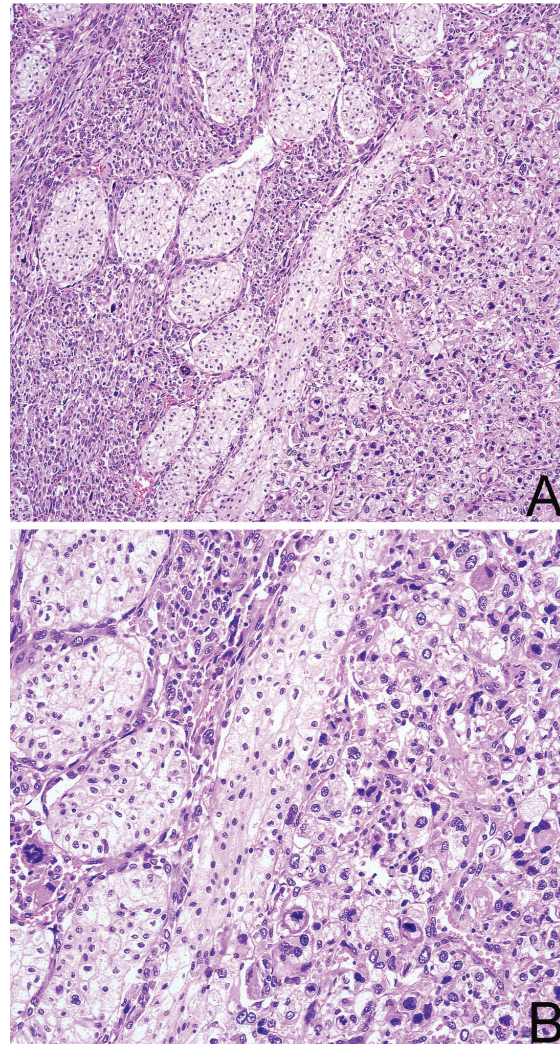


Figure 1. A & B: Hematoxylin and Eosin stained sections showing the chromophobe carcinomatous and high-grade sarcomatous components intermingled.

tous component was negative.

Immunohistochemistry

The results of the immunohistochemical study are summarized in **Table 1**.

The CRCC component was diffusely positive for cytokeratin 7, parvalbumin and racemase but negative for cytokeratin 20, vimentin, CD10, carboanhydrase IX and S100-protein. The pleomorphic liposarcomatous component displayed immunoreactivity for CD10, vimentin, and focally for carboanhydrase IX and racemase. The prolifer-

Table 1. Results of the immunohistochemical study

Antigen/antibody	CH RCC	High-grade liposarcoma
Cytokeratin 7	+	-
Cytokeratin 20	-	-
Cam 5.2	-	-
CD10	-	+
Vimentin	-	+
Parvalbumin	+	-
Carboanhydrase IX	-	focal +
Ki-67	5%	30%
S100-protein	-	-
p504S/racemase	+	focal +
MDM2	-	-
CDK4	-	-

Cam 5.2 targets CK,8,18; syn. p504S/racemase – AMACR; MDM2, murine double minute 2; CDK4, cyclin dependent kinase 4.

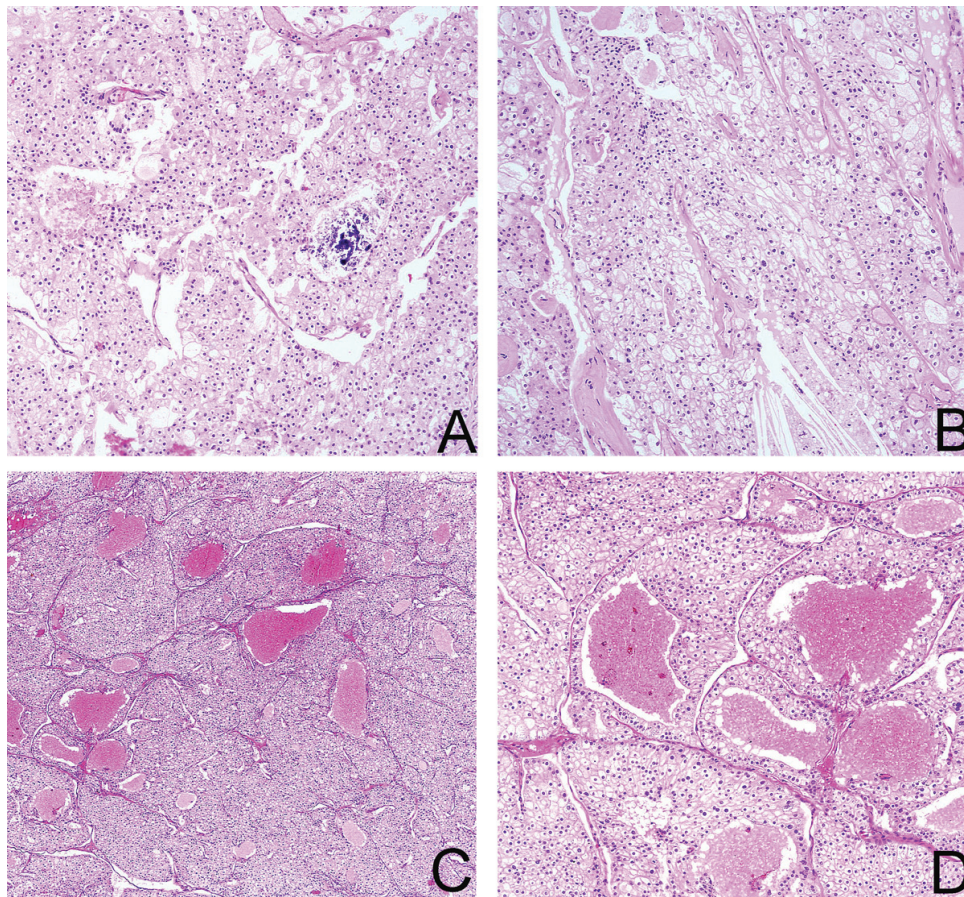


Figure 2. Hematoxylin and Eosin stained sections of the conventional chromophobe carcinoma showing areas with calcification (A) and medium-sized polygonal cells arranged in solid-alveolar structures with raisinoid nuclei, pale-eosinophilic flocculent cytoplasm with frequently occurring perinuclear haloes (B). In areas displaying the microcystic-adenomatous pattern, luminal spaces were frequently filled with erythrocytes in various stage of lysis (C,D).

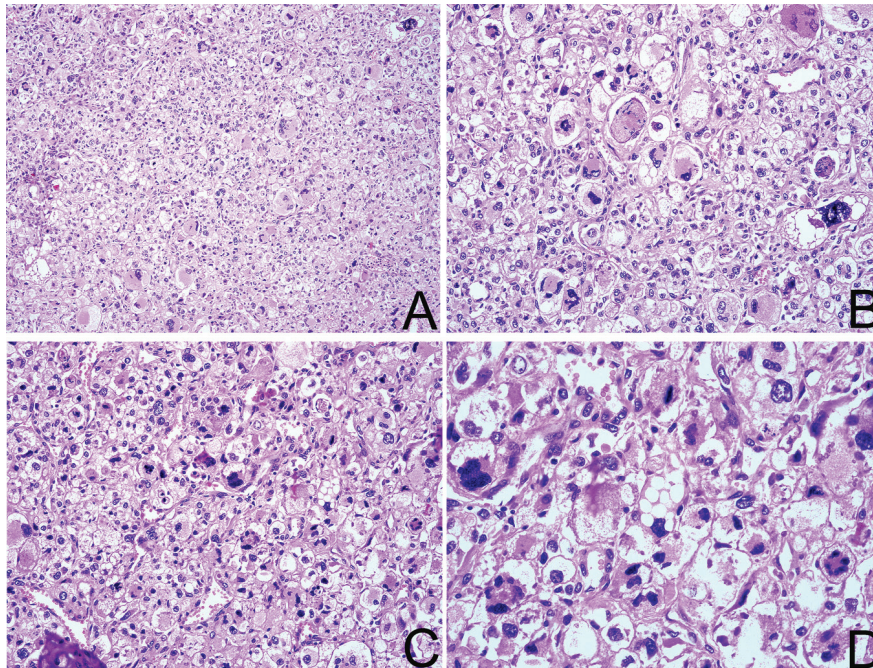


Figure 3. In addition to bizarre giant cell forms, cells in the high-grade sarcomatous areas showed multivacuolated pleomorphic lipoblasts with cytoplasmic vacuoles (A, B, C) and focally indenting on the nuclear contour (D).

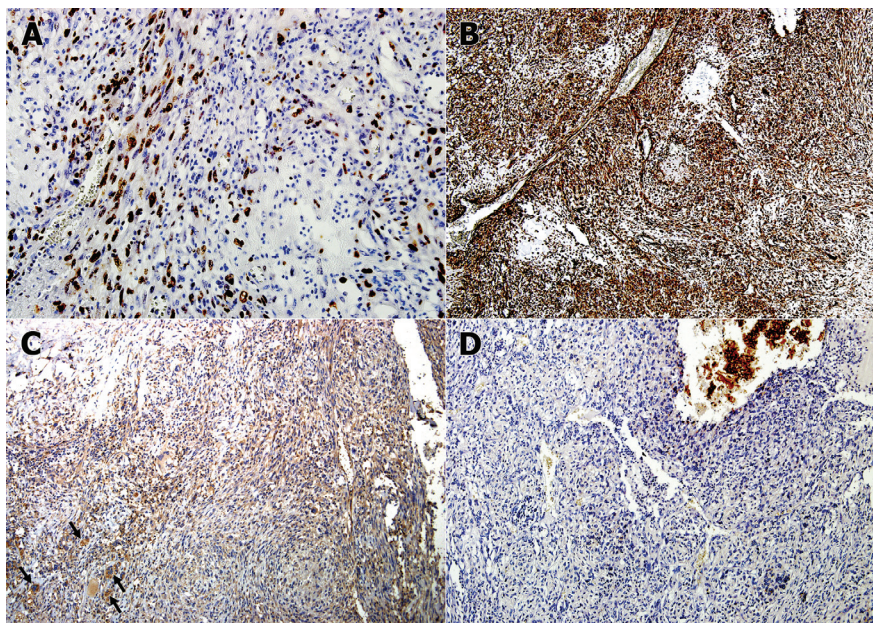


Figure 4. Photomicrographs from the immunohistochemical study of the sarcomatous component showing (A) high proliferative activity (original magnification x200), (B) diffuse positivity for vimentin (original magnification x40), (C) focal cytoplasmic positivity for racemase (arrows, original magnification x100) and (D) no immunoreactivity for parvalbumin (original magnification x100).

erative activity (mib-1/Ki-67) was 5% in the CRCC and 30% in the sarcomatous component, respectively (**Figure 4**). No immunoreactivity for MDM2 or CDK4 was detected in either the CRCC- or the sarcomatous component.

Discussion

Dedifferentiation with sarcomatous transformation is a well known phenomenon in all kinds of

RCC and is in fact a quite common occurrence in CRCC with frequencies up to 9% reported in the literature [4]. Sarcomatous transformation is associated with a significantly poorer prognosis [21] and in CRCC with and without sarcomatous dedifferentiation the 2 year survival has been reported to be 95% and 28%, respectively. [5]. The CRCC in our case showed in addition to classic histologic features also a component of the microcystic and adenomatous growth pat-

tern first described by Michal et al in 1998 [2]. Our case showed the highly characteristic histomorphological features and classic immunohistochemical profile of CRCC.

No sarcomatous dedifferentiation has ever been published in a CRCC with such (microcystic-adenomatous) growth pattern. The sarcomatous areas in RCC may in addition to a non-specific spindle cell morphology show more specialized lines of differentiation. In a series of 101 sarcomatoid RCCs, areas with fibrosarcomatous, malignant fibrous histiocytoma-like pattern or rhabdomyosarcomatous differentiation was seen in 54%, 43% and 2%, respectively. CRCC with heterologous dedifferentiation has been recorded in only a few cases. The cases presented by Itoh et al and recently by Quiroga-Garza et al displayed both chondrosarcomatous and osteosarcomatous differentiation [15, 23]. In addition to these lines of differentiation, the case presented by Hes et al contained rhabdomyosarcomatous elements [18]. As expected, the pleomorphic liposarcomatous component in the tumor presented herein displayed no immunoreactivity for cytokeratins or parvalbumin. The negative reaction for S100-protein is not surprising since only 50% of pleomorphic liposarcomas show positive reaction for this marker. The positive immunoreactivity for racemase in both the CRCC and liposarcomatous component is not surprising as this enzyme do not have any specificity for a particular tumor type. We found no well differentiated liposarcomatous component in the tumor but the pleomorphic features of the spindle cell component led us to investigate the tumor for increased expression of MDM2 and CDK4. Dedifferentiated (and well differentiated) liposarcomas manifest a highly specific genetic change characterized by amplified sequences of the 12q13-15 chromosomal region containing the *MDM2*- and *CDK4*-genes which are overexpressed and these proteins can be demonstrated with immunohistochemistry [24]. Data on chromosomal changes in pleomorphic liposarcomas are scarce but in a study using comparative genomic hybridization by Rieker et al, no gains of the 12q13-15 chromosomal region were found in any of the studied pleomorphic liposarcomas [25]. Furthermore, in a study by Italiano et al, two cases of spindle liposarcomas were studied and these lacked 12q amplification and displayed monosomy of chromosome 7 [26]. The recently described sclerosing poorly differenti-

ated liposarcoma by Suster and Morrison showed high level amplification of MDM2 in 4 out of seven cases [27]. However, the sclerosing poorly differentiated liposarcoma display different histological features than the sarcomatous component in our case.

Sarcomatous dedifferentiation in RCC in general and CRCC in particular is an enigmatic event from a genetic point of view. The liposarcomatous component in the case presented herein has features of a pleomorphic liposarcoma. This type of sarcoma is characterized by gains of genetic material, notably involving 5p13-15, 1p21, 1q21-22 and 7q22 [25] whereas CRCC is characterized by loss of multiple chromosomes, notably chromosome 1, 2, 6, 10 and 17. Interestingly, it has recently been suggested that the hypodiploid neoplastic cells in CRCC may undergo polyploidization thereby serving as the underlying genetic change, i.e. gain of chromosomal material, and in conjunction with genetic instability, "setting the stage" for sarcomatous dedifferentiation in these tumors [21, 28].

From a diagnostic point of view when faced with a core biopsy showing liposarcomatous tissue from the kidney one first has to exclude a liposarcoma of the renal capsule or retroperitoneum and a renal metastasis from a primary soft tissue liposarcoma. This cannot be done purely on histological ground but needs clinicopathologic and radiological correlation. Primary renal liposarcomas are extremely rare tumors with only a few documented examples in the English literature and is a diagnosis of exclusion. A liposarcoma arising in angiomyolipoma, an extremely rare event, [29] should also be considered. However, again this could be impossible to solve by morphology alone (sampling). The occurrence of two separate malignant tumors, i.e. collision tumor could theoretically be contemplated but the radiological and gross features in addition to the intimate mixture of the neoplastic tissue types in a sarcomatoid carcinoma (as seen in our case) should resolve this. The rare variant of lipoid urothelial carcinoma should easily be excluded by its different histomorphology and immunohistochemical profile [30]. A pseudosarcomatous fibroblastic/myofibroblastic proliferation in perinephric adjacent to renal cell carcinoma as recently described by Tanas et al [31] with reactive changes in the adipose component could also come into the differential diagnosis.

In summary, we present a unique case of a chromophobe renal cell carcinoma with a component of the microcystic –adenomatous pattern showing pleomorphic liposarcomatous differentiation. In keeping with the highly malignant nature of sarcomatoid renal cell carcinomas, the patient died one year after the nephrectomy with widespread metastatic disease.

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References

- [1] Thoenes W, Storkel S and Rumpelt HJ. Human chromophobe cell renal carcinoma. *Virchows Arch B Cell Pathol Incl Mol Pathol* 1985; 48: 207-217.
- [2] Michal M, Hes O, Svec A and Ludvikova M. Pigmented microcystic chromophobe cell carcinoma: a unique variant of renal cell carcinoma. *Ann Diagn Pathol* 1998; 2: 149-153.
- [3] Hes O, Vanecek T, Perez-Montiel DM, Alvarado Cabrero I, Hora M, Suster S, Lamovec J, Curik R, Mandys V and Michal M. Chromophobe renal cell carcinoma with microcystic and adenomatous arrangement and pigmentation—a diagnostic pitfall. Morphological, immunohistochemical, ultrastructural and molecular genetic report of 20 cases. *Virchows Arch* 2005; 446: 383-393.
- [4] de Peralta-Venturina M, Moch H, Amin M, Tamboli P, Hailemariam S, Mihatsch M, Javidan J, Stricker H, Ro JY and Amin MB. Sarcomatoid differentiation in renal cell carcinoma: a study of 101 cases. *Am J Surg Pathol* 2001; 25: 275-284.
- [5] Cheville JC, Lohse CM, Zincke H, Weaver AL, Leibovich BC, Frank I and Blute ML. Sarcomatoid renal cell carcinoma: an examination of underlying histologic subtype and an analysis of associations with patient outcome. *Am J Surg Pathol* 2004; 28: 435-441.
- [6] Onishi T, Oishi Y, Yanada S, Abe K, Hasegawa T and Maeda S. Prognostic implications of histological features in patients with chromophobe cell renal carcinoma. *BJU Int* 2002; 90: 529-532.
- [7] Nagashima Y, Okudela K, Osawa A, Nakamura N, Kawasaki C, Moriyama M, Nakamura N, Nakatani Y, Kitamura H and Aoki I. Chromophobe renal cell carcinoma with sarcomatoid change. A case report. *Pathol Res Pract* 2000; 196: 647-651; discussion 652.
- [8] Mai KT, Veinot JP and Collins JP. Sarcomatous transformation of chromophobe cell renal carcinoma. *Histopathology* 1999; 34: 557-559.
- [9] Kuroda N, Hayashi Y and Itoh H. A case of chromophobe renal cell carcinoma with sarcomatoid foci and a small daughter lesion. *Pathol Int* 1998; 48: 812-817.
- [10] Hirokawa M, Shimizu M, Sakurai T, Terayama K and Manabe T. Sarcomatoid renal cell carcinoma with chromophobe cell foci. Report of a case. *Apmis* 1998; 106: 993-996.
- [11] Tardio JC. Chromophobe cell renal carcinomas with sarcomatoid areas. *Histopathology* 2000; 36: 184-185.
- [12] Gomez-Roman JJ, Mayorga-Fernandez M, Fernandez-Fernandez F and Val-Bernal JF. Sarcomatoid chromophobe cell renal carcinoma: immunohistochemical and lectin study in one case. *Gen Diagn Pathol* 1997; 143: 63-69.
- [13] Cserni G, Kovacs BR, Tarjan M, Sapi Z, Domjan Z and Szabo Z. Sarcomatoid renal cell carcinoma with foci of chromophobe carcinoma. *Pathol Oncol Res* 2002; 8: 142-144.
- [14] Shimomura T, Ikemoto I, Yamada H, Hayashi N, Ito H and Oishi Y. Sarcomatoid renal cell carcinoma with a chromophobe component producing beta-human chorionic gonadotropin. *Int J Urol* 2005; 12: 835-837.
- [15] Itoh T, Chikai K, Ota S, Nakagawa T, Takiyama A, Mouri G, Shinohara N, Yamashita T, Suzuki S, Koyanagi T and Nagashima K. Chromophobe renal cell carcinoma with osteosarcoma-like differentiation. *Am J Surg Pathol* 2002; 26: 1358-1362.
- [16] Redondo Martinez E, Rey Lopez A, Rivero Vera JC, Lopez-Tomasetti JB, Sanchez Lobo MV and Camacho Galan R. [Renal carcinoma of sarcomatoid chromophobe cells]. *Arch Esp Urol* 2000; 53: 700-707.
- [17] Abrahams NA, Ayala AG and Czerniak B. Chromophobe renal cell carcinoma with sarcomatoid transformation. *Ann Diagn Pathol* 2003; 7: 296-299.
- [18] Hes O, Michal M, Kinkor Z, Tomes P, Zuchova M and Napravnik I. [Sarcomatous chromophobe cell renal carcinoma. 2 case reports]. *Cesk Patol* 1999; 35: 15-19.
- [19] Parada D, Pena K and Moreira O. Sarcomatoid chromophobe renal cell carcinoma. A case report and review of the literature. *Arch Esp Urol* 2006; 59: 209-214.
- [20] Martignoni G, Pea M, Brunelli M, Chilosi M, Zamo A, Bertaso M, Cossu-Rocca P, Eble JN, Mikuz G, Puppa G, Badoual C, Ficarra V, Novella G and Bonetti F. CD10 is expressed in a subset of chromophobe renal cell carcinomas. *Mod Pathol* 2004; 17: 1455-1463.
- [21] Akhtar M, Tulbah A, Kardar AH and Ali MA. Sarcomatoid renal cell carcinoma: the chromophobe connection. *Am J Surg Pathol* 1997; 21: 1188-

- 1195.
- [22] Gira F, Barbieri A, Fellegara G, Zompatori M and Corradi D. Dedifferentiated Chromophobe Renal Cell Carcinoma With Massive Osteosarcoma-Like Divergent Differentiation: A Singular Entity in the Spectrum of Retroperitoneal Calcifying Tumors. *Int J Surg Pathol* 2008;
- [23] Quiroga-Garza G, Khurana H, Shen S, Ayala AG and Ro JY. Sarcomatoid chromophobe renal cell carcinoma with heterologous sarcomatoid elements. A case report and review of the literature. *Arch Pathol Lab Med* 2009; 133: 1857-1860.
- [24] Binh MB, Sastre-Garau X, Guillou L, de Pinieux G, Terrier P, Lagace R, Aurias A, Hostein I and Coindre JM. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. *Am J Surg Pathol* 2005; 29: 1340-1347.
- [25] Rieker RJ, Joos S, Bartsch C, Willeke F, Schwarzbach M, Otano-Joos M, Ohl S, Hogel J, Lehnert T, Lichter P, Otto HF and Mechttersheimer G. Distinct chromosomal imbalances in pleomorphic and in high-grade dedifferentiated liposarcomas. *Int J Cancer* 2002; 99: 68-73.
- [26] Italiano A, Chambonniere ML, Attias R, Chibon F, Coindre JM and Pedeutour F. Monosomy 7 and absence of 12q amplification in two cases of spindle cell liposarcomas. *Cancer Genet Cytogenet* 2008; 184: 99-104.
- [27] Suster S and Morrison C. Sclerosing poorly differentiated liposarcoma: clinicopathological, immunohistochemical and molecular analysis of a distinct morphological subtype of lipomatous tumour of soft tissue. *Histopathology* 2008; 52: 283-293.
- [28] Brunelli M, Gobbo S, Cossu-Rocca P, Cheng L, Hes O, Delahunt B, Pea M, Bonetti F, Mina MM, Ficarra V, Chilosì M, Eble JN, Menestrina F and Martignoni G. Chromosomal gains in the sarcomatoid transformation of chromophobe renal cell carcinoma. *Mod Pathol* 2007; 20: 303-309.
- [29] Chandrasoma S, Daneshmand S, Wilson S and Skinner EC. Renal angiomyolipoma with liposarcomatous transformation: a case report and review of the literature. *Urol Oncol* 2004; 22: 425-427.
- [30] Leroy X, Gonzalez S, Zini L and Aubert S. Lipoid-cell variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of five cases. *Am J Surg Pathol* 2007; 31: 770-773.
- [31] Tanas MR, Sthapanachai C, Nonaka D, Melamed J, Oliveira AM, Erickson-Johnson MR and Rubin BP. Pseudosarcomatous fibroblastic/myofibroblastic proliferation in perinephric adipose tissue adjacent to renal cell carcinoma: a lesion mimicking well-differentiated liposarcoma. *Mod Pathol* 2009; 22: 1196-1200.