CASE REPORT

REVISED Case Report: Multifocal biphasic squamoid alveolar renal cell carcinoma [version 2; referees: 3 approved]

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Abstract

A multifocal biphasic squamoid alveolar renal cell carcinoma in a 68-year-old man is reported. Four different peripheral tumor nodules were identified on gross examination. A fifth central tumor corresponded to a conventional clear cell renal cell carcinoma. Biphasic squamoid alveolar renal cell carcinoma is a rare tumor that has been very recently characterized as a distinct histotype within the spectrum of papillary renal cell carcinoma. Immunostaining with cyclin D1 seems to be specific of this tumor subtype. This is the first reported case with multifocal presentation.

Open Peer Review

Referee Status: ✓ ✓ ✓

	Invited Referees 1	2	3
REVISED version 2 published 24 May 2016	✓ report		✓
version 1 published 08 Apr 2016	? report	✓ report	✓ report

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REVISED **Amendments from Version 1**

The new version takes into consideration all the reviewers's comments and clarify a misunderstanding in the text. On one hand, figures have been modified, as requested, to highlight the squamoid cell nests and to give a more detailed approach to the immunohistochemical profile of the tumor. On the other, the distinct distribution of the cyclin D1 along the tumor has been detailed. In fact, cyclin D1 immunostaining was restricted specifically to the squamoid cells, a point that was not clear in the former version. Finally, some references supporting that cyclin D1 can also be detected in other renal neoplasms have been included in the reference list.

See referee reports

Introduction

The so-called biphasic squamoid alveolar renal cell carcinoma (BSARCC) was described for the first time in 2012 by Petersson *et al.*[1] and has been very recently revisited and fully characterized by Hes *et al.*[2]. Histological, immunohistochemical, comparative genomic hybridization and fluorescence *in situ* hybridization analyses have revealed that BSARCC is a renal neoplasm closely related to papillary renal cell carcinoma (PRCC)[2].

The present paper describes a new BSARCC with multifocal presentation that was associated with a conventional clear cell renal cell carcinoma (CCRCC). To note, multifocality has not been reported in BSARCC so far.

Case report

A 68-year-old man presented with transient hematuria. CT scan revealed multiple tumors on his right kidney, four of them being located at the periphery (Figure 1). Radical nephrectomy was performed. Post-surgery period did not show any clinical complication. The patient is asymptomatic and free of disease at the last contact, 6 months after diagnosis.

On gross examination up to five tumors and several small intrarenal micronodules were discovered (Figure 1). Four tumors were subcapsular and showed a whitish homogeneous cut surface, measuring between 1 and 3 cm in diameter. The fifth tumor was centrally located, presented mixed solid and cystic areas with a yellowish cut surface and measured 4.5 cm in diameter.

Histologically, the yellowish central tumor was a conventional organ-confined CCRCC grade 1 (ISUP 2013)[3] (Figure 2). On low-power view, all the whitish peripheral tumors and the micronodules displayed a similar histology consisting in areas reminiscent to glomerular-like structures (Figure 2 and Figure 3) alternating with others typical of type 1 PRCC. On high magnification, these structures were composed of a single row of small cells with scant cytoplasm displaying an alveolar disposition. The alveoli were filled with cell groups with large cytoplasm and squamoid appearance (Figure 3). True squamous cell differentiation, however, was not observed. Mitosis and necrosis were not seen.

By immunohistochemistry (Figure 4), the tumor was positive with CK7, vimentin, PAX-8, racemase, RCC marker, AE1/AE3, 34βE12, carbonic anhydrase IX, CD10, and cyclin D1 (SP4-R clone, Ventana, USA). Immunostaining pattern was distinct depending on the cell type. For instance, cyclin D1 and 34βE12 immunostained selectively the squamoid cells whilst RCC marker and carbonic anhydrase IX did it only in small alveoli-forming cells. The rest of the antibodies immunostained both cell types. The tumor was negative with p63 and CK20.

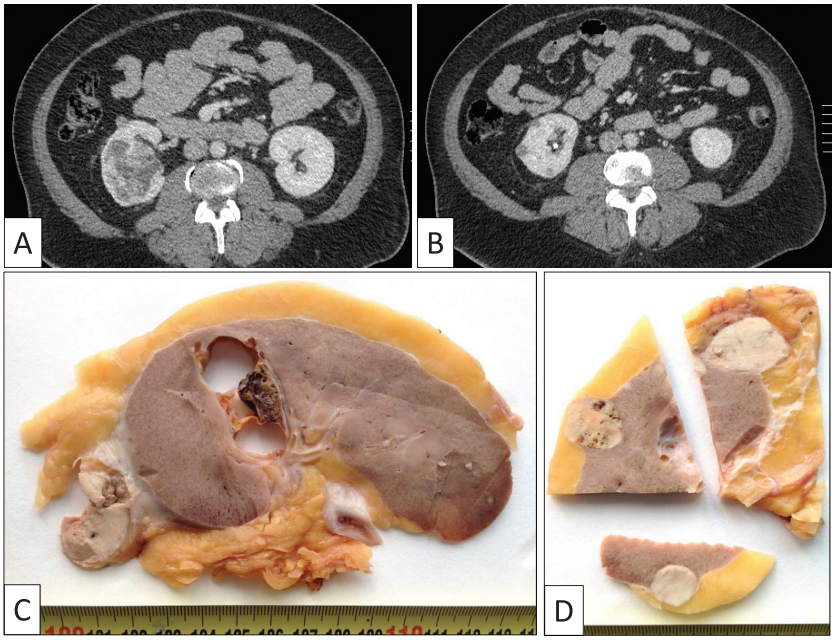

Figure 1. CT scans show multiple tumors in the right kidney (**A** and **B**). Gross examination displays a yellowish central tumor with solid-cystic areas corresponding to a clear cell renal cell carcinoma (**C**) and four peripheral whitish tumors and several intrarenal micronodules corresponding to biphasic squamoid alveolar renal cell carcinomas (**C** and **D**).

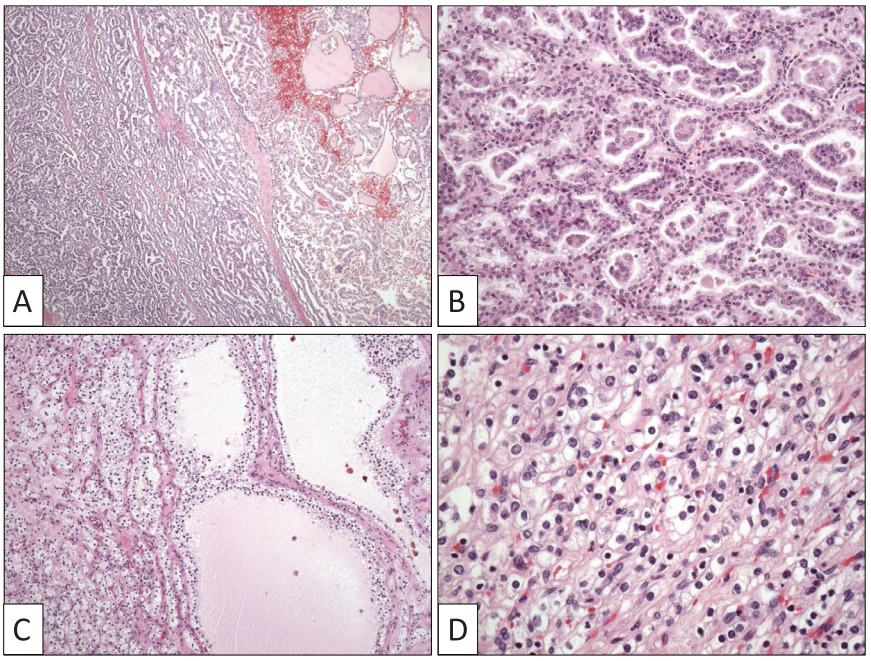

Figure 2. Panoramic view of both tumors, Biphasic squamoid alveolar renal cell carcinoma (BSARCC) (**A** and **B**) and conventional renal cell carcinoma (CCRCC) (**C** and **D**). BSARCC displayed some areas of type1 papillary renal cell carcinoma (**A**, right side) and presented the typical alveolar structures filled with large cells (**A**, left side and **B**). CCRCC showed solid and cystic areas composed of nests low-grade cells with clear cytoplasm (**C** and **D**).

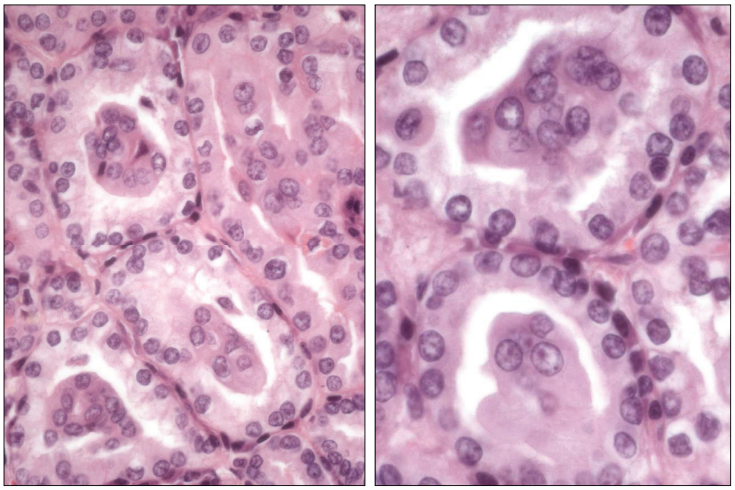

Figure 3. Microscopic detail of the alveolar structures containing small groups and single large squamoid cells (**A** and **B**).

Discussion

BSARCC is a recently recognized variant of renal carcinoma[1,2]. Its pathological diagnosis can be suggested on hematoxylin-eosin slides and is based on the recognition of two different cell types arranged in a distinct architecture. Small groups of large cells with abundant cytoplasm and squamoid appearance are surrounded by small cells with scant cytoplasm forming alveolar-like structures. This distinct growth pattern can be more or less evident in different tumor areas and, same as happens in the case here presented, can be combined with areas of conventional PRCC[2]. The combination of BSARCC and PRCC histologies in almost half of the previously published cases favors the inclusion of this tumor within the broad

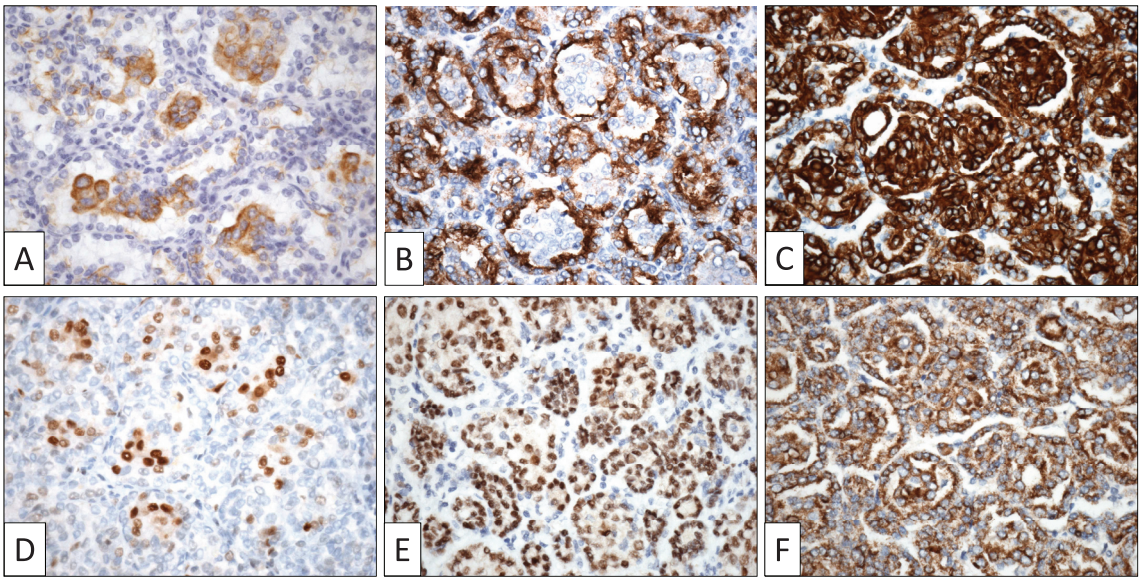

Figure 4. Immunohistochemical study with 34βE12 (**A**), RCC marker (**B**), CK7 (**C**), cyclin D1 (**D**), PAX-8 (**E**) and AMACR (**F**). Noteworthy, 34βE12 and cyclin D1 selectively immunostain the central squamoid cell groups and, conversely, RCC marker does it only in peripheral alveolar cells. CK7, PAX-8 and AMACR immunostain both cell types**.**

spectrum of PRCC[2]. No association of BSARCC with CCRCC, as in the case here presented, has been reported so far.

Morphological diagnostic features of BSARCC can be supported by immunohistochemistry and, if necessary, by genetics. All BSARCC reported to date are positive with cytokeratin 7, epithelial membrane antigen, vimentin and cyclin D1. To note, cyclin D1 shows a selective immunostaining restricted to the central squamoid cell groups. This distinct cyclin D1 distribution seems to be specific of this tumor and may be of help in its recognition. This marker, however, can also immunostain other renal cell neoplasms, as recently reported[4–6]. Molecular-genetic data show gains of chromosomes 7 and 17, thus linking BSARCC to PRCC.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images and/or other details that could potentially reveal the patient's identity.

Competing interests

No competing interests were disclosed.

Grant information

The author declared that no grants were involved in supporting this work.

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PubMed Abstract | Publisher Full Text
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PubMed Abstract | Publisher Full Text
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PubMed Abstract | Publisher Full Text

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Current Referee Status: ✓ ✓ ✓

Version 2

Referee Report 03 June 2016

doi:10.5256/f1000research.9388.r14154

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The author has sufficiently addressed our concerns.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 25 May 2016

doi:10.5256/f1000research.9388.r13949

Claudio Doglioni
Anatomy and Histopathology Department, IRCCS (Scientific Institute of Hospitalization and Care), San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Version 1

Referee Report 28 April 2016

doi:10.5256/f1000research.9099.r13306

Claudio Doglioni
Anatomy and Histopathology Department, IRCCS (Scientific Institute of Hospitalization and Care), San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

The Author describes an unusual multifocal presentation of Biphasic squanoid alveolar renal carcinoma associated with a conventional Clear Cell Carcinoma. BSARCC is a recently described rare entity with a peculiar squamoid differentiation characterized by cyclin D1 immunoreactivity; Cyclin D1 per se is not limited to this type of renal tumor, but its pattern of reactivity seems specific for BSARCC. I suggest, considering some, although limited, similarity to squamoid morules in other epithelial tumors (colon, endometrium) to perform also immunostaining for beta-catenin.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 28 April 2016

doi:10.5256/f1000research.9099.r13402

Jose Luis Rodriguez-Peralto
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The authors report for the first time a multifocal variant of the recently described squamoid alveolar renal cell carcinoma, a distinct microscopic tumor in the spectrum of papillary renal cell carcinoma.. This is the first reported case on this location. The paper is original, elegant and well written, and the quality of figures nicely reflect the morphologic, and immunohistochemical aspects of this infrequent neoplasm. The references are acceptable and recent. Thus, I consider this paper acceptable in the current version, but some changes may improve the content of the manuscript:

- Since Cyclin D1 has also been reported in other variant of renal cell carcinoma, I recommend to the author to delete in the discussion the sentence Cyclin D1 immunohistochemistry is specific of this tumor. Moreover, I also included a sentence emphasizing that although Cyclin D1 is characteristic of BSARCC, it may be rarely observed in other variants of RCC.

- I considered that there are many immunohistochemical pictures of Cyclin D1, I would change figure C by a new H&E of the conventional clear cell renal cell carcinoma

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 20 April 2016

doi:10.5256/f1000research.9099.r13307

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The study describes a multifocal biphasic squamoid alveolar renal cell carcinoma in association of clear cell renal cell carcinoma. The Author claims that staining for cyclin D1 is specific for this entity; however,

labelling for cyclin D1 has been reported in clear cell renal cell carcinoma, papillary renal cell carcinoma, chromophobe renal cell carcinoma and oncocytoma (1, 2) and more recently in clear cell papillary renal cell carcinoma (3) and SDH-deficient renal cell carcinoma (4). Since the immunoreactivity might depend of the clone used, the Author should supply information regarding the antibody to cyclin D1. It would be also interesting to know whether cyclin D1 is positive in the clear cell renal cell carcinoma. Finally, pictures of clear cell renal carcinoma and more detailed pictures demonstrating the squamoid features of biphasic squamoid alveolar renal cell carcinoma should be added.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.