

# Urothelial Carcinoma with shadow cell, lipid cell and sebaceous (skin adnexal) differentiation: Clinicopathological and immunohistochemical study of 10 cases☆



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## ABSTRACT

We discuss the histological and immunohistochemical features of 6 cases of urothelial carcinomas of lipid cell variant and 4 cases with shadow cell differentiation, one of which showed additionally sebaceous differentiation, one of which shows additional sebaceous differentiation, from our archive cases from the last 15 years. Conventional urothelial carcinoma (UC) was seen in all lipid cell variant cases, and micropapillary carcinoma was seen in 3. The ratio of the lipid cell component was between 10% and 40% in these 6 cases. Typical histologic features of the lipid cell variant include lipoblast-like cells with a notched nuclear appearance, abundant vacuoles, an eccentric nucleus, and pagetoid spread in some areas. GATA3 and pancytokeratin AE1/AE3 immunohistochemical staining were positive in all cases. Adipophilin was positive in various degrees in 5 of the 6 lipid cell variant cases but was also positive in the case with sebaceous differentiation.  $\alpha$ -methylacyl-CoA racemase was positive in the lipid cell areas and negative or focal weakly positive in the conventional UC areas in 4 of the 6 cases. Vimentin, S-100 protein, and PAX8 were negative in the lipid cell component. Follow-up information was available for all cases with follow-up ranging from 6 to 84 months (mean, 34 months). Four patients died of the disease. One pT4 patient who had been followed up for 6 months lives with the disease, whereas another is disease free. In conclusion, the lipid cell variant is a rare UC variant that usually presents at an advanced stage, and tumor cells are histologically similar to lipoblasts, resemble sebaceous differentiation, and show positive immunohistochemical staining with adipophilin.

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## 1. Introduction

Urothelial carcinoma (UC) contains several different histologic patterns and variants because the urinary bladder develops from a variety of embryological structures, and the urothelium can be transformed into very different cells [1,2]. There is a general consensus on approximately 20 variants of UC, and most of them are included in the current World Health Organization (WHO) 2004 classification [3,4]. Although the lipid cell variant is included in the WHO 2004 classification, only 38 cases have been reported in the English medical literature [5–11]. The largest study is of 27 cases in a multicentered study, whereas another publication presents 5 cases [5,6]. Other articles are in form of single case reports [7–11].

Histologically, lipid cells usually have a lipoblast-like appearance with notched-appearing eccentric nuclei and abundant vacuoles. The vacuoles look clear and empty and are usually multiloculated. No pure

lipid cell variant has been reported so far. Lipid cell variant cases are usually seen together with high-grade UC and other UC variants. The nature of the lipid cell variant is still not clear.

Lipid cell variants are usually diagnosed with the typical histologic characteristics together with accompanying UC areas and/or variants, negative results with conventional mucin and glycogen stains, positive staining of fresh tissues with fat stain, and staining with the typical immunohistochemical markers of UC. Electron microscopy and genetic investigations have also been used for diagnosis [1,2]. Kojima et al [10] used adipophilin as an immunohistochemical marker to show fat in lipid cells in a case presentation published in 2013.

Adipophilin is a perilipin family protein associated with neutral lipid droplet synthesis. This protein is reported to be expressed in Sertoli and Leydig cells, adrenal cortex, lactating mammary epithelium, steatotic hepatocytes in alcoholic cirrhosis, and liposarcomas. Adipophilin is also commonly used to describe sebaceous tumors and sebaceous differentiation [12–14]. Sebaceous differentiation is quite rare in extracutaneous tumors, and only single cases have been reported [15–17] with no previous reports involving the urinary bladder. Sebaceous differentiation histologically consists of diffuse pagetoid spread and atypical sebocytes in various maturation stages. Lipoblast-like cells are also present in certain cases. This histologic appearance is similar to the lipid cell variant of UC.

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**Table 1**

Clinical features of the 10 cases of the UC with lipid cell variant and dermal appendage differentiation cases.

Cases	Age/sex	Clinical finding	Grade/stage	Treatment	Follow-up
Case 1	64/M	Hematuria	HG/pT2	Cystectomy	DOD (84 mo)
Case 2	73/M	Hematuria	HG/pTa	TUR and BCG therapy	AWED (40 mo)
Case 3	54/M	Hematuria	HG/pT3	Cystectomy, chemotherapy	DOD (27 mo)
Case 4	63/M	Hematuria, anemia, loss weight	HG/pT3	Cystectomy, chemotherapy	DOD (21 mo)
Case 5	60/F	Hematuria	HG/pT3	Chemotherapy	DOD (33 mo)
Case 6	71/M	Anemia, hematuria	HG/pT4	Chemotherapy	Live with disease (6 mo)
Case 7	69/M	Hematuria	HG/pTa	TUR and BCG therapy	AWED (26 mo)
Case 8	63/M	Hematuria	HG/pT2	Cystectomy, chemotherapy	Live with disease (14 mo)
Case 9	51/M	Dysuria	HG/pT1	TUR and BCG therapy	Live with disease (5 mo)
Case 10	68/M	Hematuria	HG/pT3	Cystectomy, chemotherapy	DOD (29 mo)

Abbreviations: M, male; F, female; HG, high grade; BCG, bacille Calmette-Guerin; DOD, died of disease; AWED, live without evidence of disease.

Differentiation toward hair follicles is quite rare in extracutaneous organs, akin to sebaceous differentiation. Differentiation toward hair is mostly seen as shadow cells that differentiate to the hair matrix [18,19]. Shadow cells are usually seen in pilomatrixomas (PMX), craniopharyngiomas, and odontogenic cysts, and they are one of the typical histologic characteristics of these entities. Two UC cases that are characterized by shadow cell differentiation have been reported so far [19,20]. Zamecnik et al [18] reported 13 cases with similar morphology in various nonsquamous, extracutaneous organs in their review.

Our aim was to discuss shadow cells, sebaceous differentiation, and the histologic similarities of lipid cell variants and sebaceous differentiation in UC with the help of 3 UC cases characterized with shadow cells, 1 case with concurrent differentiation toward sebaceous and shadow cells, and 6 cases of lipid cell variant of UC in this study. The aim of our considering skin appendices (shadow cell and sebaceous) differentiation and lipid cell variants in UC together was to demonstrate the presence of dermal differentiation capacity in UC and to emphasize the overlapping histologic and immunohistochemical features of sebaceous differentiation and lipid cell variants. We focused on histologic characteristics and similarities rather than on clinical findings and prognoses.

## 2. Materials and methods

We reviewed the bladder transurethral resection (TUR) specimens of our pathology department between 2000 and 2014 together with 2 consultation cases of the author. The cases containing lipid cell areas and sebaceous or hair matrix differentiation were chosen during the re-evaluation of our 4120 bladder TUR materials diagnosed as UCs, with the purpose of determining UC variants. The pathology parameters evaluated were the presence of conventional UC and its variants, presence of in situ carcinoma, percentage of UC components, grade (based on WHO 2004 classification), depth of invasion, and TNM staging. We made sure that the tumor formed at least 10% of the sample in the

lipid cell variant cases. The clinical information of the patients was obtained from the patient files.

A minimum of 6 slides from biopsy materials found to have lipid cell variants and sebaceous and shadow cell differentiation were stained with hematoxylin and eosin and reevaluated under the light microscope.

Cells and cell groups with clear-empty cytoplasm, some lipoblast-like multiple vacuoles, and with notched nuclei were sought for the lipid cell variant diagnosis. Shadow cell and shadow cell groups and the presence of squamous and transitional cells around the shadow cells were sought for differentiation toward hair matrix, whereas larger cells with a pagetoid appearance, a more bubbly cytoplasm, vacuolization, and notched nuclei were sought among the urothelial groups for sebaceous differentiation.

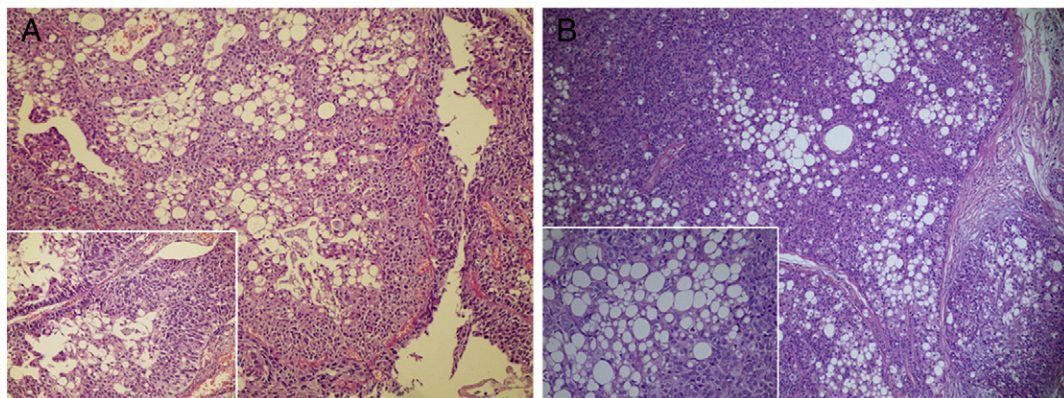
Histochemically, periodic acid–Schiff, Alcian blue, and mucicarmine staining were used for all lipid cell variant cases.

Immunohistochemical staining procedures were conducted using a Ventana Benchmark XT staining system (Ventana Medical Systems, Tucson, AZ), using antibodies for S-100 (dilution 1/50; Cell Marque Rocklin, CA), vimentin (dilution 1/50; Cell Marque), cytokeratin AE1/AE3 (dilution 1/100; Cell Marque), GATA3 (ready-to-use dilution; Cell Marque),  $\alpha$ -methylacyl-CoA racemase (AMACR) (dilution 1/100; Cell Marque), PAX8 (dilution 1/200; Biocare, Concord, CA), and adipophilin (dilution 1/200; Novus Europe, Cambridge, United Kingdom). Negative and positive controls were included for all analyses. Immunostaining was graded from – (0, negative) to +++ (1–3, positive).

## 3. Results

### 3.1. Clinical findings

The clinicopathologic features of the 10 patients are summarized in Table 1. The lipid cell variant cases (cases 1–6) consisted of 5 males and 1 female, with a mean age of 64 (54–73) years. Five of the patients had been referred to the urology clinic with hematuria and 1 with



**Fig. 1.** Cell groups with larger eosinophilic cytoplasm between typical neoplastic urothelial cells and lipid (lipoblast- and lipocyte-like) cells, mixed with typical lipid cells; similar appearance, at low magnification (insert) (A). Similar appearance in dermal sebaceous adenoma (hematoxylin and eosin) (from the author's archive) (B).

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