Human Pathology (2007) **38**, 793–796

ELSEVIER

Human PATHOLOGY

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Case study

Conventional renal cancer in a patient with *fumarate hydratase* mutation☆

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Received 18 April 2006; revised 13 September 2006; accepted 17 October 2006

Keywords:
HLRCC;
Bilateral renal cell cancer;
Clear cell;
fumarate hydratase;
FH

Summary Hereditary leiomyomatosis and renal cell cancer (HLRCC) is a tumor predisposition syndrome caused by mutations in the *fumarate hydratase* (*FH*) gene. HLRCC is characterized by uterine and cutaneous leiomyomas, renal cell cancer, and uterine leiomyosarcoma. Typically, renal cell cancers in HLRCC are unilateral and display a papillary type 2 or ductal histology. We describe here a 23-year-old patient carrying a novel *FH* mutation (N330S) with a bilateral renal cell cancer. Carcinoma of the right kidney showed papillary structure, but the left tumor was diagnosed as a conventional (clear cell) renal carcinoma, a type not previously described in HLRCC. The clear cell renal carcinoma also displayed loss of the normal *FH* allele and the FH immunostaining. Our finding extends the number of cases in which HLRCC can be suspected, and the FH immunohistochemistry may serve as a useful tool to screen for HLRCC in young individuals with clear cell renal carcinoma.

1. Introduction

The recently identified tumor predisposition syndrome hereditary leiomyomatosis and renal cell cancer (HLRCC) is characterized by a high penetrance occurrence of cutaneous and uterine leiomyomas. Renal cell cancer (RCC) and uterine leiomyosarcoma (ULMS) are detected in a subset of the families [1,2]. HLRCC is caused by heterozygous mutations in the *fumarate hydratase* (*FH*, *fumarase*) gene, which encodes one of the tricarbocylic acid cycle's enzymes. Altogether, 47 different *FH* mutations have been identified so far [1,3-10]. Because biallelic inactivation of the gene is observed in most benign and malignant HLRCC tumors, *FH* is suggested to function as a tumor suppressor [1-3,10,11].

At present, 117 families with HLRCC have been reported throughout the world, mainly in Europe and North America [1,3-11]. The prevalence of RCC seems to differ between and within the affected families because only about a fifth of the families (21%, 25/117) display RCC. These families are from the UK (1 patient in 1 family), Poland (1 patient in 1 family), Finland (12 patients in 5 families), and North America

☆ The study was supported by grant numbers 213183 and 214268 from the Academy of Finland, Helsinki, Finland; and the Center of Excellence in Translational Genome-Scale Biology, the Research and Science Foundation of Farmos, Espoo, Finland; and the Paulo Foundation, Helsinki, Finland.
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doi:10.1016/j.humpath.2006.10.011

Table 1 Immunohistochemical stainings of renal tumors

Antigen	Case right RCC	Case left RCC	FAM-1[a] M19	FAM-1[a] M17	FAM-1[a] M13
FH	+	−	−/+	−	−
vimentin	+	+	+	+	+
EMA	+	+	−	+	+
S-100	+	+	+	+	−
CD10	+	−/+	−	−	−
CK8	+	+	−	−	−
CK7	−	−	−	−	−
AE1/AE3	−	+	+	+	+

Symbols: +, positive staining; −, negative staining; −/+, light staining.
[a] FAM-1 is a Finnish HLRCC family previously published by Launonen et al [1].

(33 patients in 18 families) [1,3,4,7-9,12]. Although the prevalence of the malignant tumors (RCC, ULMS) varies between and within the families with HLRCC, no clear correlation between the type or site of the *FH* mutation and the phenotype has been found. Identical mutations can be seen in the families with and without RCC. Therefore, existence of other genetic factors modifying the risk for RCC (and ULMS) has been widely discussed [2,7,13,14]. In addition, the lower prevalence of RCC in HLRCC compared with other hereditary RCC syndromes such as von Hippel-Lindau (VHL) disease and hereditary papillary renal cancer support the hypothesis [7].

HLRCC-associated RCCs are usually solitary, unilateral, and aggressive. The typical histological features are a papillary type 2 structure, a high Fuhrman grade (from 3 to 4), tall cells with an abundant cytoplasm, and large nuclei with prominent eosinophilic owl-eye-like nucleoli [1,3]. Originally, the specific histology of RCCs led to the identification of the syndrome. The 47 HLRCC-associated RCC cases reported to date have included also 4 collecting duct carcinomas and 1 oncocytic tumor [4,7,9], but the most common type of RCC, a conventional (clear cell) carcinoma (CRCC), has to our knowledge not yet been reported in the context of HLRCC. The histology of the RCCs has played a key role in the diagnosis of HLRCC. In individuals with CRCC, HLRCC is typically not suspected because that tumor type has not been associated with *FH* germline mutations.

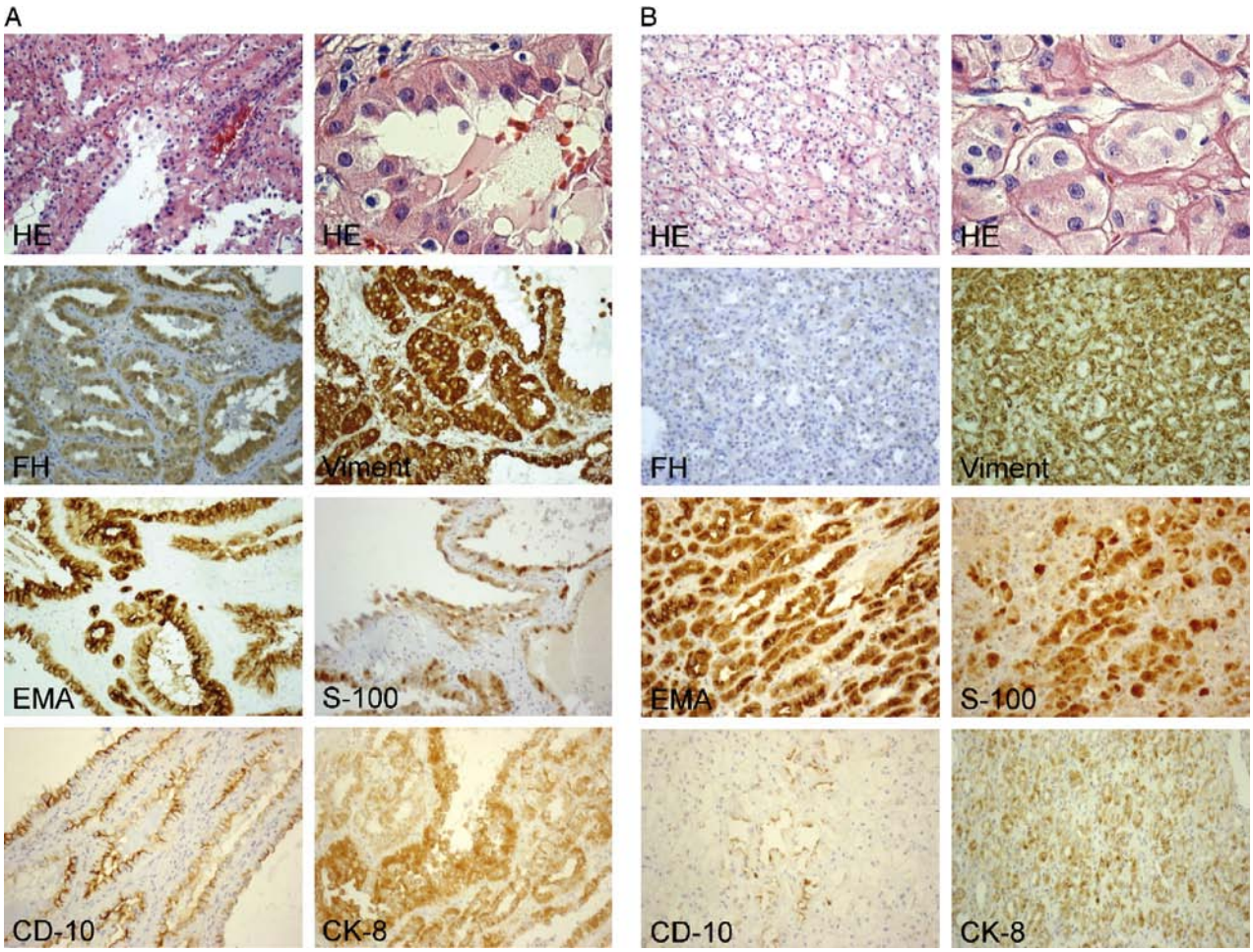

Fig. 1 Hematoxylin-eosin and positive immunohistochemical stainings of the 2 renal cancers. A, Right-side tumor. B, Left-side tumor. Original magnification of the photos is ×100, and the HE staining is, in addition, shown with ×400 magnification. HE indicates hematoxylin-eosin; Viment, vimentin; EMA, epithelial membrane antigen; CK-8, cytokeratin 8.