Two Cases of Gastric Carcinoma with Autosomal Dominant Polycystic Kidney Disease in the Same Family

Aynı Ailede Otozomal Dominant Polikistik Böbrek Hastalığı ile Birlikte İki Mide Kanseri Olgusu

Ali Osman KAYA,[a]
İbrahim AKDAĞ,[b]
Esra Zeynep COŞKUNOĞLU,[c]
Mehmet TÜRKELİ,[b]
Arif YILMAZ[b]

Clinics of
[a]Medical Oncology,
[b]Internal Medicine,
[c]Pathology,
Rize Training and Research Hospital,
Rize

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Yazışma Adresi/*Correspondence:*
Ali Osman KAYA
Rize Training and Research Hospital,
Clinic of Medical Oncology,
Rize,
TÜRKİYE/TURKEY
aosmankaya@gmail.com

ABSTRACT Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common hereditary renal disorders. The association of gastric carcinoma with ADPKD has not completely been elucidated. We describe two cases with gastric adenocarcinoma (44 and 48-year-old brothers) with a history of ADPKD. The elder brother was on maintenance hemodialysis for the last 3 years due to chronic renal failure secondary to ADPKD. In addition, a third member of the family (younger brother) had been diagnosed with intestinal metaplasia in the stomach. To the best of our knowledge, so far, the development of gastric cancer in such cases has been reported in only one family with a history of ADPKD. The coexistence of gastric cancer in patients with ADPKD is very rare and it worsens the prognosis.

Key Words: Polycystic kidney, autosomal dominant; stomach neoplasms

ÖZET Otozomal dominant polikistik böbrek hastalığı (ODPKH) en sık görülen kalıtsal böbrek hastalıklarından biridir. Mide kanserinin ODPKH ile ilişkisi tam olarak açıklanmamıştır. Aynı zamanda ODPKH öyküsü olan iki mide kanseri olgusu (44 ve 48 yaşında iki erkek kardeş) sunuyoruz. Büyük kardeş son 3 yıldır ODPKH'a bağlı kronik böbrek yetmezliği nedeniyle hemodiyaliz tedavisi alıyordu. Ayrıca, ailenin üçüncü bir üyesine (küçük kardeş) midede intestinal metaplazi tanısı koyulmuştu. Bildiğimiz kadarıyla, bugüne kadar böyle hastalarda mide kanseri gelişimi ODPKH öyküsü olan bir ailede bildirilmişti. ODPKH olan hastalarda mide kanserinin birlikte bulunuşu çok nadirdir ve prognozu kötüleştirir.

Anahtar Kelimeler: Polikistik böbrek, otozomal baskın; mide tümörleri

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Autosomal dominant polycystic kidney disease (ADPKD) is a well-known inherited cystic renal disease.[1] ADPKD has an annual incidence rate of 1.38/100 000 individuals.[2] It is characterized by cyst development and growth leading to renal insufficiency in both kidneys.[1,3] There are two forms of the disease that are linked with mutations on chromosomes 16 (PKD1) and 4 (PKD2), respectively.[4] In general, patients with the PKD1 mutation have more severe renal insult and reach end-stage renal disease about 10-15 years earlier than patients with the PKD2 mutation.[5]

The most commonly reported malignancy in this in patients with ADPKD is renal cell carcinoma[6-9]. On the other hand, the presence of gas-

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tric cancer in a family with ADPKD was reported only as a case presentation so far in the English literature.[10] Herein, we report two cases of gastric adenocarcinoma with a history of ADPKD in the same family.

CASE REPORTS

CASE 1

A 44-year-old man with the history of ADPKD was admitted to our hospital with epigastric pain, nausea, weight loss, abdominal distension and fatigue in December 2008. On physical examination, both kidneys were enlarged and tender. Laboratory examination revealed anemia and elevated erythrocyte sedimentation rate. His other two brothers had polycystic kidney disease and were on hemodialysis. Nevertheless, two years before, his eldest brother had died because of advanced gastric cancer while he was undertaking hemodialysis therapy. His younger brother had intestinal metaplasia in stomach and he was still alive.

The detailed family pedigree was investigated for ADPKD. Their father had been treated for a long time due to gastric ulcer. However, he had died because of heart attack 12 years previously. Their mother had received maintenance hemodialysis due to chronic renal failure secondary to polycyctic kidney disease for 2 years. However, she died 7 years previously due to renal failure. There was no polycyctic kidney disease in the children of patients.

Upper gastrointestinal endoscopy was performed. It revealed an ulcerovegetative mass located at the lesser curvature of the stomach. The histologic examination revealed a poorly differentiated adenocarcinoma with two components. Approximately 50% of the tumor was composed of singly infiltrating signet-cell like cells with large, pleomorphic, hyperchromatic nuclei and a vacuolated cytoplasm (Figure 1A). The second component which also made up of about 50% of the tumor was mucinous adenocarcinoma. Mucinous adenocarcinoma component consisted predominantly of extracellular mucin lakes containing freely floating single tumor cells (Figure 1B). The intracytoplasmic and extracytoplasmic mucin was stained positive with d-PAS (Figure 1C) and mucicarmine (Figure 1D).

Thorax computer tomography (CT) was normal. Whole abdominal CT scan revealed multiple cysts within both kidneys (the greatest one measuring 14.6x6.5 cm in diameter) (Figure 2). The patient was referred to surgery and he underwent total gastrectomy with perigastric lymphadenectomy and omentectomy in January 2009. The histological examination of specimen confirmed the initial diagnosis. After surgery, he received adjuvant chemotherapy with a combination of fluorouracil and folinic asid (FU-FA) and concomitant radiotherapy (45 Gy in 25 daily fractions, over 5 weeks). Approximately 6 months later, after completion of the adjuvant therapy, the disease relapsed with local recurrence and liver metastases. Palliative chemotherapy was not administered due to poor performance status of the patient. The patient died while under the best supportive care in November 2009.

CASE 2

A 48-year-old man on maintenance hemodialysis for the last 3 years because of chronic renal failure secondary to ADPKD was admitted to our hospital with upper gastrointestinal bleeding in June 2008. Endoscopic examination revealed an ulcerovegetative mass at the lesser curvature of the stomach. The endoscopic biopsy specimen of the 48-year-old brother also revealed poorly differentiated adenocarcinoma. Tumor was composed of signet ring-like tumor cells infiltrating the mucosa. The presence of intracytoplasmic mucin was confirmed by positive staining with d-PAS and alcian yellow-toluidine blue stains (Figure 3). Thorax CT was normal. Whole abdominal CT scan revealed wall thickening at the lesser curvature of stomach, metastatic solid masses in right lobe of liver and multiple cysts of various sizes (up to 6 cm in diameter) in both kidneys. The patient underwent palliative subtotal gastrectomy due to uncontrollable hemorrhage. While he was on maintenance hemodialysis, he died due to progression of disease in March 2008.

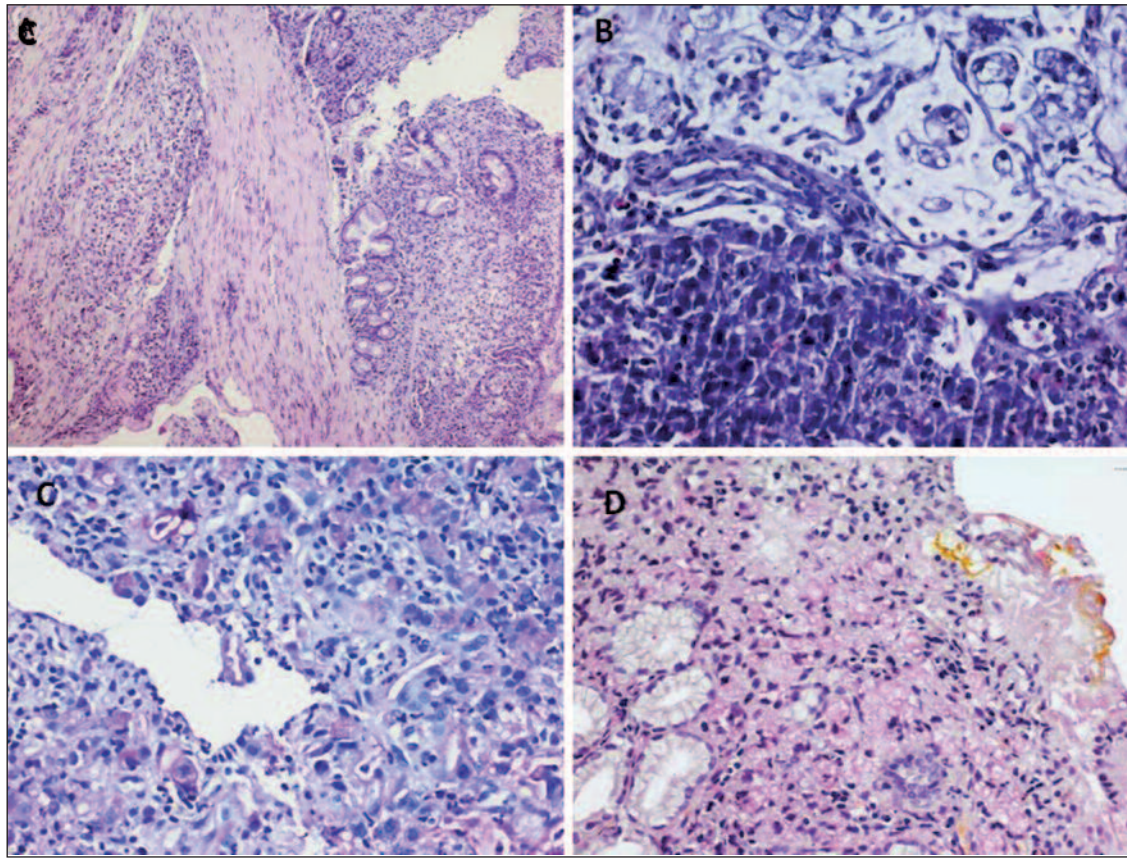

FIGURE 1: Signet ring cell carcinoma component; overview showing numerous signet ring-like tumor cells infiltrating the lamina propria (HE stain, x10) **(A)**. Mucinous adenocarcinoma component; single tumor cells (arrows) -with hyperchromatic nuclei and large, vacuolated cytoplasm- floating freely in mucin lakes (HE stain, x40) **(B)**. Sparsely dispersed signet ring like tumor cells containing PAS positive-diastase resistant intracytoplasmic mucin* (d-PAS stain, x40) **(C)**. Mucin containing signet ring cells expanding the lamina propria (Mucicarmine stain, x40) **(D)**.
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

DISCUSSION

We report two brothers with adenocarcinoma of stomach with signet ring cell component and ADPK. To the best of our knowledge, the gastric carcinoma complicating ADPKD has been only reported once as a case presentation so far.[10] Moreover, renal cell carcinoma has been reported most commonly in these patients.[6-9] However, other types of neoplasms such as lung adenocarcinoma, cholangiocarcinoma, central nervous system lymphoma and urothelial kidney carcinoma have been less frequently described in patients with ADPKD.[11-14]

It has not been clearly understood why gastric carcinoma develops in patients with ADPKD. In cases with ADPKD, the incidences of mutations in the PKD-1 gene on chromosome 16 and in the PKD-2 gene on chromosome 4 have been reported as 85% and 15%, respectively.[15] The patients with PKD-1 gene mutations have a more severe course

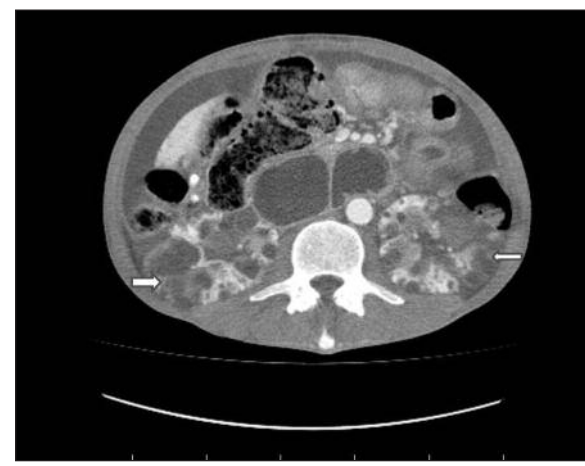

FIGURE 2: Whole abdominal CT scan revealed multiple cysts in both kidneys (the greatest one 14.6x6.5 cm in diameter).

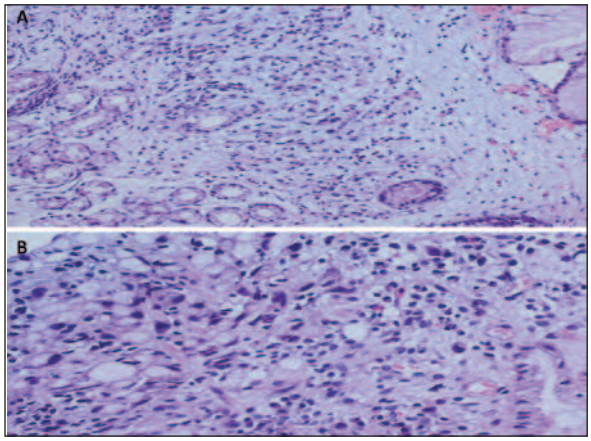

FIGURE 3: Signet ring-like tumor cells in the lamina propria (HE stain, x20) (Figure 1A). A closer view of tumor cells exhibiting large, hyperchromatic nuclei and a vacuolated cytoplasm (HE stain, x40) (Figure 1B).
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than patients with PKD-2 gene mutation. In patients with PKD-2 gene mutation, end-stage renal disease (ESRD) occurs at an average age of 54 years, which is roughly ten years earlier than the patients with PKD-2 gene mutation.[15] Our reported cases were 44 and 48 years old. They have died due to progression of disease. We were no able to determine gene mutations in these cases.

Gastric cancer is the fourth most common cancer worldwide with 930,000 cases diagnosed in 2002.[16] It is a disease with a high mortality rate (approximately 800,000 per year) making it the second most common cause of cancer mortality worldwide after lung cancer.[17] Gastric cancers are overwhelmingly adenocarcinomas (95%). Histologically, there are two major types of gastric adenocarcinoma (Lauren classification): intestinal type and diffuse type.[18]

The diffuse type of gastric cancer is associated with germline mutations in the type 1 E-cadherin (epithelial) gene (CDH1) which predisposes to the autosomal dominantly inherited hereditary diffuse gastric cancer (HDGC) syndrome.[19-21] CDH1 mutations have been identified in approximately 40-50% of well defined HDGC families.[19-21] The average onset age of diffuse gastric cancer in HDGC families is approximately 38 years, but it can range between 16 and 82 years.[22] Our cases were 44 and 48 years old, respectively. Additionally, both patients had ADPKD histories and have died because of advanced stage gastric cancer. We performed endoscopic biopsy in the third brother. The pathologic examination of specimen revealed an intestinal metaplasia in his stomach. Because of history of gastric cancer in the family, he was offered the option of prophylactic total gastrectomy. He underwent surgery and is stil alive.

In conclusion, types of renal and extra-renal cancers may rarely develop in patients with ADPKD. The development of familial gastric cancer in such cases has been reported in only one family so far in English literature.[10] The comorbidity of cancer in patients with ADPKD worsens the prognosis.

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