CASE REPORT

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Diagnostic Challenges in Fumarate Hydratase-Deficient Leiomyomas: Report of Two Cases

Fumarat Hidrataz-Defektif Leiomyomlarda Tanısal Zorluklar: İki Olgunun Sunumu

Gülhan Özüm[1], Eren Altun[2]

[1]*University of Health Sciences Türkiye, İstanbul Bağcılar Training and Research Hospital, Clinic of Gynecology, İstanbul, Türkiye*

[2]*University of Health Sciences Türkiye, İstanbul Bağcılar Training and Research Hospital, Clinic of Pathology, İstanbul, Türkiye*

ABSTRACT

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal dominant syndrome caused by germline mutations in the fumarate hydratase (FH) gene, which encodes the FH enzyme. Most women with HLRCC develop uterine leiomyomas, typically during the second and third decades of life. Patients may also present with cutaneous leiomyomas, which generally manifest in the fourth decade of life. Pathological features—such as staghorn vasculature, alveolar-pattern edema, eosinophilic cytoplasmic inclusions, ovoid nuclei, bizarre, dispersed nuclei, and large eosinophilic nucleoli with perinucleolar halos—are suggestive but not definitive. Immunohistochemically, FH staining has high specificity, whereas 2-succinocysteine (2SC) staining demonstrates both high sensitivity and specificity. Although molecular testing is the diagnostic gold standard, it is not widely available. We present two patients diagnosed with FH-deficient leiomyoma (FH-dUL). The first is a 52-year-old woman who previously underwent nephrectomy for renal cell carcinoma. A subsequent positron emission tomography scan revealed high fluorine-18 fluorodeoxyglucose uptake in a uterine myoma, prompting hysterectomy. The second case involves a 34-year-old woman who underwent myomectomy due to a rapidly enlarging uterine myoma. Histopathological evaluation in both cases confirmed FH-dUL. FH-deficient uterine leiomyomas present diagnostic challenges due to overlapping morphological and immunohistochemical (IHC) findings. FH loss does not always indicate HLRCC, underscoring the need for careful evaluation. Although FH and 2SC IHC analyses are useful screening tools, molecular testing remains the gold standard for definitive diagnosis, requiring multidisciplinary assessment for optimal patient management and follow-up.

Keywords: Fumarate hydratase-deficient leiomyoma, 2-succinocysteine, fumarate hydratase, immunohistochemical analysis

ÖZ

Kalıtsal leiomyomatozis ve renal hücreli karsinom (HLRCC), fumarat hidrataz (FH) genindeki germline mutasyonlardan kaynaklanan otozomal dominant kalıtılan bir sendromdur ve bu gen FH enzimini kodlar. HLRCC'li kadınların çoğunda, genellikle ikinci ve üçüncü dekatta uterin leiomyomlar gelişir. Hastalar ayrıca kutanöz leiomyomlarla da başvurabilir ve yaklaşık %15'inde genellikle dördüncü dekatta agresif bir renal hücreli karsinom gelişir. Patolojik özellikler—staghorn benzeri damar yapıları, alveoler patern ödemi, eozinofilik sitoplazmik inklüzyonlar, ovoid nükleuslar, dağınık bizar nükleuslar ve perinükleer halo ile çevrili büyük eozinofilik nükleoller—önerici olup kesin tanı için yeterli değildir. İmmünohistokimyasal olarak, FH ve 2-süksinosistein (2SC) boyamaları FH-defektif tümörlerin tanımlanmasında yaygın olarak kullanılmaktadır; FH yüksek spesifiteye sahipken, 2SC hem yüksek sensitivite hem de yüksek spesifite gösterir. Moleküler testler tanısal altın standart olmasına rağmen, yaygın olarak erişilebilir değildir. FH-defektif leiomyoma tanısı alan iki hasta sunulmaktadır. İlk olgu, daha önce RCC nedeniyle nefrektomi geçirmiş 52 yaşındaki bir kadındır. Takipte yapılan pozitron emisyon tomografisi taramasında uterin myomda yüksek flor-18 florodeoksiglukoz tutulumu saptanmış ve buna bağlı olarak histerektomi uygulanmıştır. İkinci olgu, hızlı büyüyen uterin bir myom nedeniyle myomektomi yapılan 34 yaşındaki bir kadındır. Her iki hastanın histopatolojik değerlendirmesi FH-defektif leiomyoma olarak doğrulanmıştır. FH-defektif uterin leiomyomlar, morfolojik ve immünohistokimyasal bulguların örtüşmesi nedeniyle tanısal zorluklar oluşturur. FH

Address for Correspondence: Gülhan Özüm, University of Health Sciences Türkiye, İstanbul Bağcılar Training and Research Hospital, Clinic of Gynecology, İstanbul, Türkiye

E-mail: gulhanozum86@gmail.com **ORCID ID:** orcid.org/0009-0006-7741-3681

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ÖZ

kaybı her zaman HLRCC anlamına gelmez; bu durum dikkatli değerlendirme gerektirir. FH ve 2SC immünohistokimyasal analizler yararlı tarama araçları olsa da kesin tanı için moleküler test altın standarttır ve optimal hasta yönetimi ile takibi için multidisipliner yaklaşım gereklidir.

Anahtar Kelimeler: Fumarat hidrataz-defektif leiomyom, 2-süksinosistein, fumarat hidrataz, immünohistokimyasal analiz

Introduction

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal dominant syndrome caused by germline mutations in the fumarate *hydratase* (FH) gene (1,2). Women with HLRCC develop multiple symptomatic uterine leiomyomas and cutaneous leiomyomas at a young age and are at risk for aggressive renal tumors that can metastasize even when small (1). FH-deficient leiomyomas (FH-dUL) exhibit variable morphological features that are not specific in isolation (2). Although FH loss and 2-succinocysteine (2SC) positivity provide diagnostic clues, molecular analysis is required for a definitive diagnosis; however, this method is not readily available in all centers (3). This case report aims to emphasize the diagnostic challenges in morphological and immunohistochemical (IHC) analysis of rare FH-dUL, to demonstrate that FH negativity is not always associated with HLRCC, and to discuss the diagnostic approach through two different clinical examples in light of the literature.

Case Report

Case 1

The patient, who underwent nephrectomy for renal cell carcinoma (RCC), was referred to the gynecology clinic two months after nephrectomy due to intense ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake in the uterus on positron emission tomography (PET) imaging. The 52-year-old patient, in menopause for three years, had no history of disease other than RCC. Her children had no history of disease or cancer. Her mother had endometrial cancer, one sister had breast cancer, the other sister had stomach cancer, and her nephew had cervical cancer. Gynecological examination revealed a 3-cm degenerated myoma. Due to intense FDG uptake on PET (standardized uptake value maximum: 31.5), laparoscopic hysterectomy and bilateral salpingo-oophorectomy were performed. Gastroscopy and colonoscopy were performed simultaneously, and adjuvant chemotherapy was planned. Macroscopic examination revealed multiple intramural myomas. Histopathology showed focal alveolar edema, staghorn- or hemangiopericytoma-like vessels, spindle or epithelioid cells with ovoid nuclei, and prominent eosinophilic nucleoli surrounded by perinuclear halos; focal multinucleated and bizarre cells were also observed (Figure 1). In IHC, CD34 was positive in vascular structures, CD117 in mast cells, and desmin in neoplastic cells; FH was negative. CD10 was negative; caldesmon and ER were positive, Ki67 was 2–3%. Based on morphological and IHC findings, the case was diagnosed as FH-dUL. The patient was discharged without complications and received genetic counseling due to high-risk for HLRCC. Genetic analysis revealed only a somatic FH defect. The patient has been under regular medical oncology follow-up for two years, including three-monthly magnetic resonance imaging/computed tomography imaging and routine biochemical surveillance, as well as annual PET imaging. No pathological findings have been detected to date, and no systemic oncological treatment has been required. Written informed consent was obtained from the patient for publication of this case report.

Case 2

A 34-year-old patient with one normal delivery and a body mass index of 39.6 presented for myoma follow-up. Her past and family history were otherwise unremarkable except for a 12-cm myoma detected during an examination two years earlier. The patient had no personal or family history of cancer. Examination revealed a giant myoma measuring 14 × 20 cm with indistinct borders from the uterus. Due to rapid growth and the patient being of reproductive age, myomectomy was performed. Macroscopic examination showed a hard myoma measuring 20 × 14 cm with a hemorrhagic nodular cut surface. Histopathology revealed focal spindle or epithelioid cells with ovoid nuclei and prominent eosinophilic nucleoli surrounded by perinuclear halos. IHC showed FH (–), CD10 (–), and Ki67 3–5%. The pathology report diagnosed FH-dUL (Figure 2). Following the pathological diagnosis, renal screening with ultrasonography was performed one month after surgery, revealing no renal pathology. Genetic analysis was not considered necessary due to the absence of a personal or family history of cancer and the lack of pathological findings on renal screening. The patient was followed for one year post-myomectomy without any complications. She had a desire for fertility and is currently maintaining a healthy pregnancy in the third trimester. Written informed consent was obtained from the patient for publication of this case report.

Discussion

This study presents two FH-negative cases: an elderly woman with RCC and FH-negative myoma, and a young woman with a giant FH-negative myoma. The *FH* gene is located on chromosome 1q42.3-43 and encodes a common mitochondrial enzyme (1). HLRCC syndrome arises from germline mutations in the *FH* gene, placing carriers at risk for renal carcinoma and cutaneous and uterine leiomyomas (4). Somatic mutations in the *FH* gene may also occur and have been reported in cutaneous and uterine smooth muscle tumors (5). While sporadic FH mutations are predominant in FH-dUL, FH-deficient renal carcinomas are generally associated with germline FH mutations (1). Consequently, fumarate and succinate accumulation in tumor cells promotes oncogenic effects by stabilizing hypoxia-inducible proteins and causing their overexpression (4). In our RCC patient with FH-dUL and a family history of cancer, genetic counseling was recommended, and a somatic FH mutation was detected.

FH-dULs are typically large and numerous, with non-specific symptoms, and usually require early surgery (1). While sporadic leiomyomas are diagnosed in the fourth decade, FH-dUL patients are diagnosed in the second decade and undergo surgery in the third decade. Women with HLRCC have an 8–9-fold higher risk of developing uterine leiomyomas compared to the general population (5). FH-dULs are known for a high recurrence rate of 35.2–52.8% after myomectomy (6). Cutaneous leiomyomas are the most specific and sensitive clinical marker of HLRCC. When genetic testing is unavailable, dermatologic examination for cutaneous leiomyomas can help identify high-risk HLRCC women (7). HLRCC-associated renal carcinomas are clinically aggressive regardless of tumor type and often present at an advanced stage, causing significant morbidity and mortality (8). The lifetime incidence of RCC in HLRCC patients is 15–20% (4). Renal tumors may occur at an early

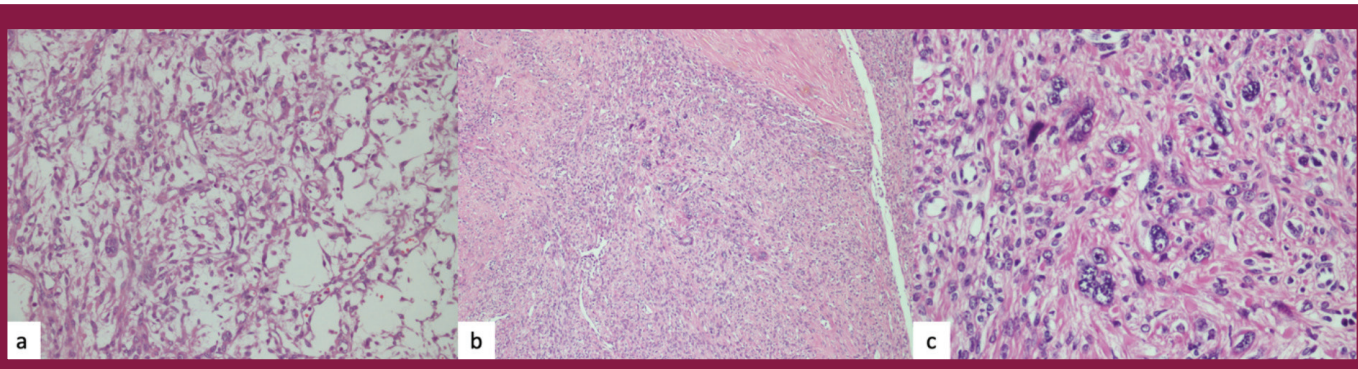

Figure 1. On microscopic examination, focal alveolar edema (H&E, 200x) (a), spindle or epithelioid cells with oval nuclei and prominent eosinophilic nucleoli surrounded by perinucleolar halos were observed in the cases examined (H&E, 100x) (b). Focal multinucleated and bizarrely nucleated cells were observed (H&E, 400x; c).
H&E, hematoxylin and eosin.

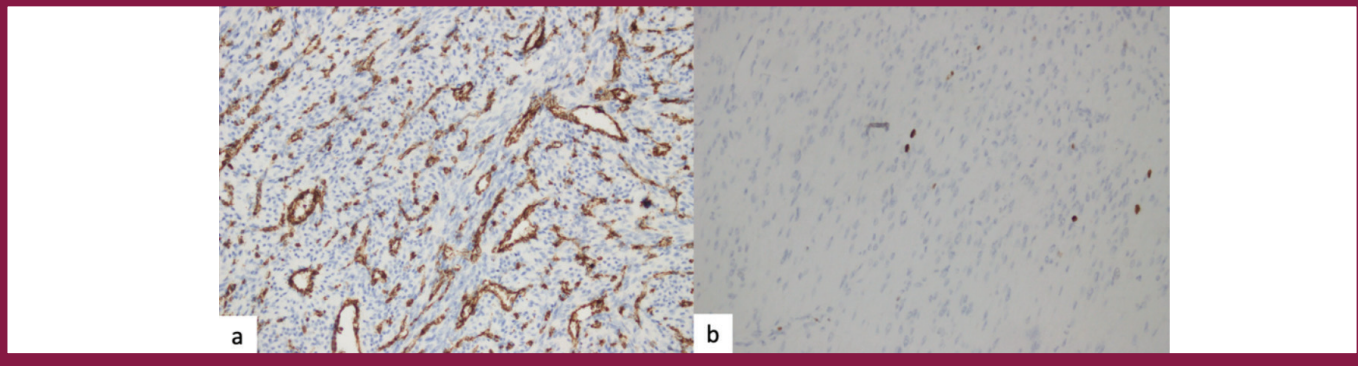

Figure 2. On immunohistochemical examination, atypical cells do not show reactivity for FH, whereas FH reactivity is present in the vascular structures (FH, 200x) (a). In the Ki67 index evaluation, very low reactivity was observed (Ki67, 200x) (b).
FH, fumarate hydratase.

age (10–44 years), although the average age at diagnosis is in the fourth decade (2,9,10). Poor prognosis and syndrome-related mortality are associated with high-grade RCCs, which frequently present with advanced metastatic disease at diagnosis (8), and metastasis can occur even at small sizes (1). HLRCC-associated renal tumors typically exhibit type 2 papillary architecture but can also be cystic, tubulopapillary, tubular, or solid, and may be bilateral or multifocal (8,9).

Characteristic morphologic features of FH deficiency include staghorn-like vessels, focal alveolar stromal edema, ovoid nuclei arranged in chains, eosinophilic cytoplasmic inclusions, and perinuclear haloed eosinophilic macronuclei (2). A "schwannoma-like" growth pattern with nuclear palisading has also been described. Among these findings, staghorn vasculature is the strongest morphologic indicator for FH-dUL. Additional features, such as alveolar edema and nuclear chain formation, may not be evident in every tumor. However, due to variable FH-dUL morphology, definitive diagnosis based solely on histology is challenging (1). IHC, FH loss, and 2SC positivity serve as widely used screening methods for tumors associated with FH deletion; FH shows high specificity, while 2SC shows both high sensitivity and specificity (1,3). FH IHC is not fully sensitive for FH deficiency, as missense mutations in the *FH* gene may produce a non-functional protein detectable by IHC. The 2SC stain appears sensitive and specific for FH deficiency, but its clinical use is limited due to unavailability (2). Molecular genetic testing remains the gold standard for confirming HLRCC syndrome, but limited access in many centers represents a significant diagnostic constraint (3). However, 2SC immunohistochemistry could not be performed in our cases because this staining is not routinely available in our institution.

These two cases provide important contributions to the literature. First, they illustrate that FH-dUL can occur in both elderly and young women, and FH negativity does not always indicate HLRCC, emphasizing the importance of thorough clinical evaluation. Second, our cases demonstrate that characteristic morphologic and IHC features can support diagnosis even in the absence of genetic testing, providing practical guidance for centers with limited molecular resources. Finally, the long-term clinical follow-up and reproductive outcomes of our second case highlight that conservative management and fertility preservation are feasible in selected FH-dUL patients, information that is currently scarce in the literature.

Conclusion

This case report highlights the diagnostic challenges of the rare FH-dUL in terms of morphology and IHC. Demonstrating that FH negativity is not always associated with HLRCC emphasizes the need for careful clinical and genetic evaluation in diagnostic approaches. While IHC, showing FH loss and 2SC positivity, serves as a useful screening tool for FH-dUL diagnosis, molecular genetic testing remains the gold standard for definitive diagnosis. Therefore, multidisciplinary assessment and genetic counseling, when indicated, are important for patients suspected of FH-dUL.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Ö., E.A., Concept: G.Ö., Design: G.Ö., E.A., Data Collection or Processing: G.Ö., Analysis or Interpretation: G.Ö., E.A., Literature Search: G.Ö., Writing: G.Ö., E.A.

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