CASE REPORT

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Hereditary leiomyomatosis and renal cell cancer syndrome – case report and review of the literature

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Abstract

Hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC) is an exceptionally rare autosomal dominant condition caused by a germline heterozygous mutation of the fumarate hydratase gene. It manifests as multiple piloleiomyomas, associated with numerous, early-onset uterine leiomyomas in female patients, as well as a highly increased risk of renal cell carcinoma (RCC), most often type 2 papillary RCC. HLRCC has been described in association with adrenal cortical hyperplasia, pheochromocytoma, adrenal cortical carcinoma, and other solid tumors, but the exact relationship between these disorders has not yet been clarified. We present a case of HLRCC associated with bilateral adrenal cortical hyperplasia and discuss the pathogenesis, clinical and paraclinical features of HLRCC, as well as the adequate management of these patients.

Keywords: hereditary leiomyomatosis, fumarate hydratase, leiomyoma, renal cell cancer.

Introduction

Described by Kloepfer *et al.*, in 1958 [1] and later by Reed *et al.*, in 1973 [2], hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC), also known as multiple cutaneous and uterine leiomyomatosis (MCUL) is an exceptionally rare hereditary condition. Up to this moment, it has only been reported in approximately 200 families [3]. The disorder is usually inherited in an autosomal dominant fashion with variable penetrance but can also develop *de novo* [4]. The genetic defect is represented by a germline heterozygous mutation of the MCUL 1 locus of the fumarate hydratase (*FH*) gene, located on chromosome 1q42.3–q43 [5]. The gene encodes for the FH enzyme, which converts fumarate to malate in the tricarboxylic acid (Krebs) cycle [6].

LRCC manifests as multiple piloleiomyomas, associated with numerous, early-onset uterine leiomyomas in female patients, as well as a highly increased risk of renal cell carcinoma (RCC), most often type 2 papillary RCC [7].

Germline mutations of the *FH* gene have also been detected in patients diagnosed with malignant pheochromocytomas and paragangliomas [8].

Aim

We present a case of HLRCC associated with bilateral adrenal cortical hyperplasia and discuss the pathogenesis, clinical and paraclinical features of HLRCC, as well as the adequate management of these patients.

Case presentation

A 62-year-old female patient was referred to the Department of Dermatology, Elias Emergency University Hospital, Bucharest, Romania, in January 2019 for the presence of multiple skin colored, smooth nodular lesions of different sizes, ranging from 0.3 cm to 2 cm, located on the face, trunk and limbs (Figures 1 and 2).

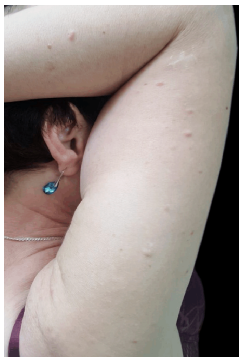

Figure 1 – ***Multiple skin colored, smooth papules and nodules, 0.3–2 cm in diameter, located on the upper limb.***

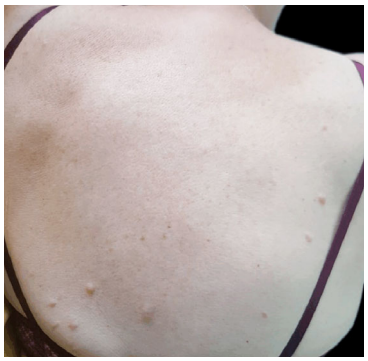

Figure 2 – ***Multiple piloleiomyomas located on the trunk.***

The skin lesions first appeared several years previously on the arms and gradually increased in number and size. The patient complained of pain in some of the lesions, both spontaneous and precipitated by touch and exposure to cold. The rest of the physical examination did not reveal pathological changes.

Her family medical history was relevant as her two sisters, her daughter and her niece had developed multiple symptomatic uterine leiomyomas in their third decade of life, necessitating repeated myomectomies and all presented similar skin lesions.

The patient had a personal history of uterine leiomyomatosis for which she had undergone multiple myomectomies before the age of 30 and eventually a total hysterectomy. She had also suffered an ureteroscopic removal of a polypoid benign tumor. She had been diagnosed with arterial hypertension, ischemic heart disease, bronchiectasis, and chronic gastritis for which she was under chronic treatment with antihypertensive, antiaggregant, and gastric antisecretory drugs. A thoracic and abdominal computed tomography (CT) scan performed 10 years previously showed, apart from bronchiectasis, a 2.4/1.4 cm hypodense nodule in the right adrenal gland and a micronodular left adrenal hyperplasia. Repeated subsequent blood tests revealed high levels of chromogranin A (a maximum level of 560 μg/L; normal levels 27–94 μg/L) and gastrin (a maximum level of 322 pg/mL; normal level <100 pg/mL). The seric levels of aldosterone, renin, basal and overnight cortisol, corticotropin, catecholamines, 5-hydroxyindoleacetic acid, serotonin were all within normal limits. A neuroendocrine tumor was suspected. Laparoscopic right adrenalectomy was performed and the histopathological (HP) diagnosis was that of micro- and macronodular hyperplasia of the *zona fasciculata* and *zona reticularis*. Extensive investigations were carried out, but a neuroendocrine tumor was not detected. A 2 cm cyst located in the right renal cortex was identified on abdominal ultrasound (US). Its cystic nature was confirmed by abdominal and pelvic CT scans and magnetic resonance imaging (MRI).

The patient was admitted to our Clinic for further investigations. Laboratory tests results were within normal limits except for the elevated seric levels of chromogranin A and gastrin. Gastritis was diagnosed on endoscopic examination. *Helicobacter pylori* infection was also found and treated. After completion of treatment for *H. pylori* infection, the gastrin level normalized (54 pg/mL). As the increased chromogranin A level could be explained by the chronic treatment with proton-pump inhibitors that our patient had followed, the administration of these drugs was ceased for approximately two weeks. After this interval, the level of chromogranin A also returned to normal (31 μg/L), confirming the clinical suspicion. The thoracic, abdominal and pelvic CT scan revealed the presence of bronchiectasis, compensatory left adrenal hyperplasia, and the 2 cm cyst of the right renal cortex.

A skin biopsy was performed and the HP examination showed the presence of a dermal tumor composed of smooth muscle fibers with yellow cytoplasm, minimal nuclear and cytoplasmic pleomorphism, perinuclear cytoplasmic vacuolization on van Gieson staining, peri- and intratumoral minimal inflammatory lymphocytic infiltrate, intertwined with collagen bundles. The overlying epidermis was atrophic, with flattened rete ridges and hyperpigmentation of the basal layer (Figures 3, A and B; Figure 4, A and B). The HP diagnosis was that of leiomyoma and it was confirmed by immunohistochemical staining that showed diffuse positivity for actin and vimentin, faint focal positivity for S100 and factor XIIIa, positivity for cluster of differentiation 34 (CD34) limited to endothelial cells and for Leu7 limited to nerve fibers, and <1% positivity for Ki67 (Figure 5, A–D).

Based on the clinical picture, the HP results and the personal and family medical history, the clinical diagnosis of HLRCC was established.

Discussions

Heterozygous *FH* mutations represent the genetic basis of HLRCC, having been documented in 76–100% of families with HLRCC [9]. Contrastingly, homozygous or compound heterozygous germline *FH* mutations inherited in an autosomal recessive fashion are responsible for neonatal progressive neurological impairment, which is usually lethal in the first few months of life [10].

The most common pathogenic variants are missense. Nonsense, frameshift, splice-site mutations, as well as partial and whole-gene deletions have also been detected in patients with HLRCC [11, 12]. However, a certain genotype does not predict the phenotype [11].

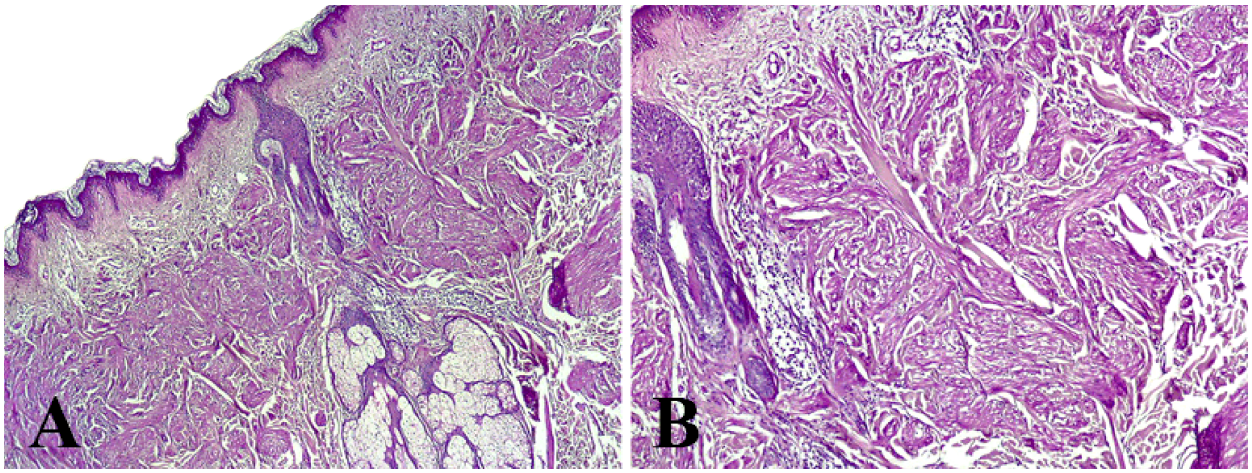

Figure 3 – ***(A and B) Dermal tumor composed of smooth muscle fibers, peri- and intratumoral minimal inflammatory lymphocytic infiltrate, intertwined with collagen bundles. The overlying epidermis is atrophic, with flattened rete ridges and hyperpigmentation of the basal layer. Hematoxylin–Eosin (HE) staining: (A) ×50; (B) ×100.***

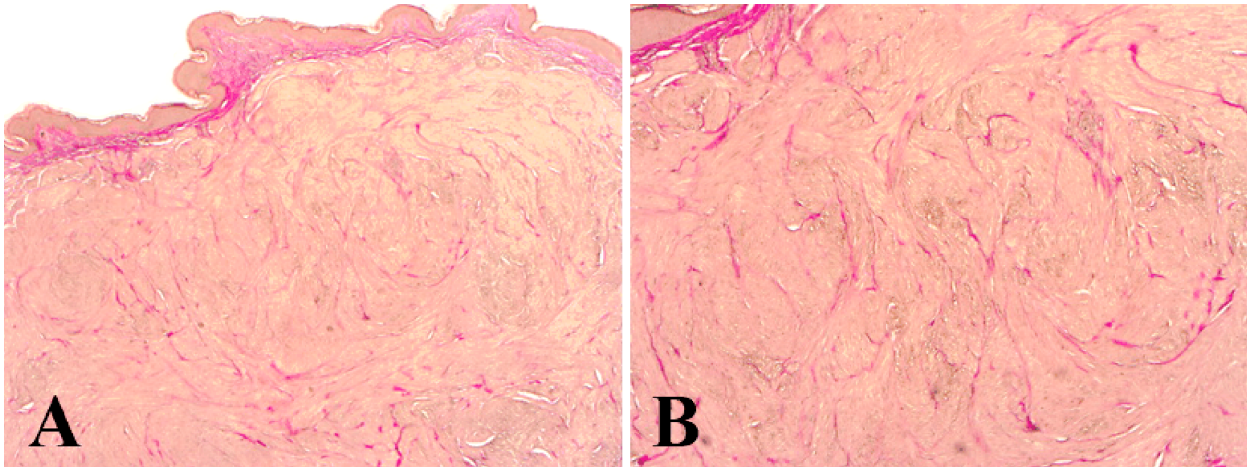

Figure 4 – ***(A and B) Dermal tumor composed of smooth muscle fibers, with yellow cytoplasm, minimal nuclear and cytoplasmic pleomorphism, perinuclear cytoplasmic vacuolization, peri- and intratumoral minimal inflammatory lymphocytic infiltrate, interlaced with collagen fibers. Van Gieson staining: (A) ×50; (B) ×100.***

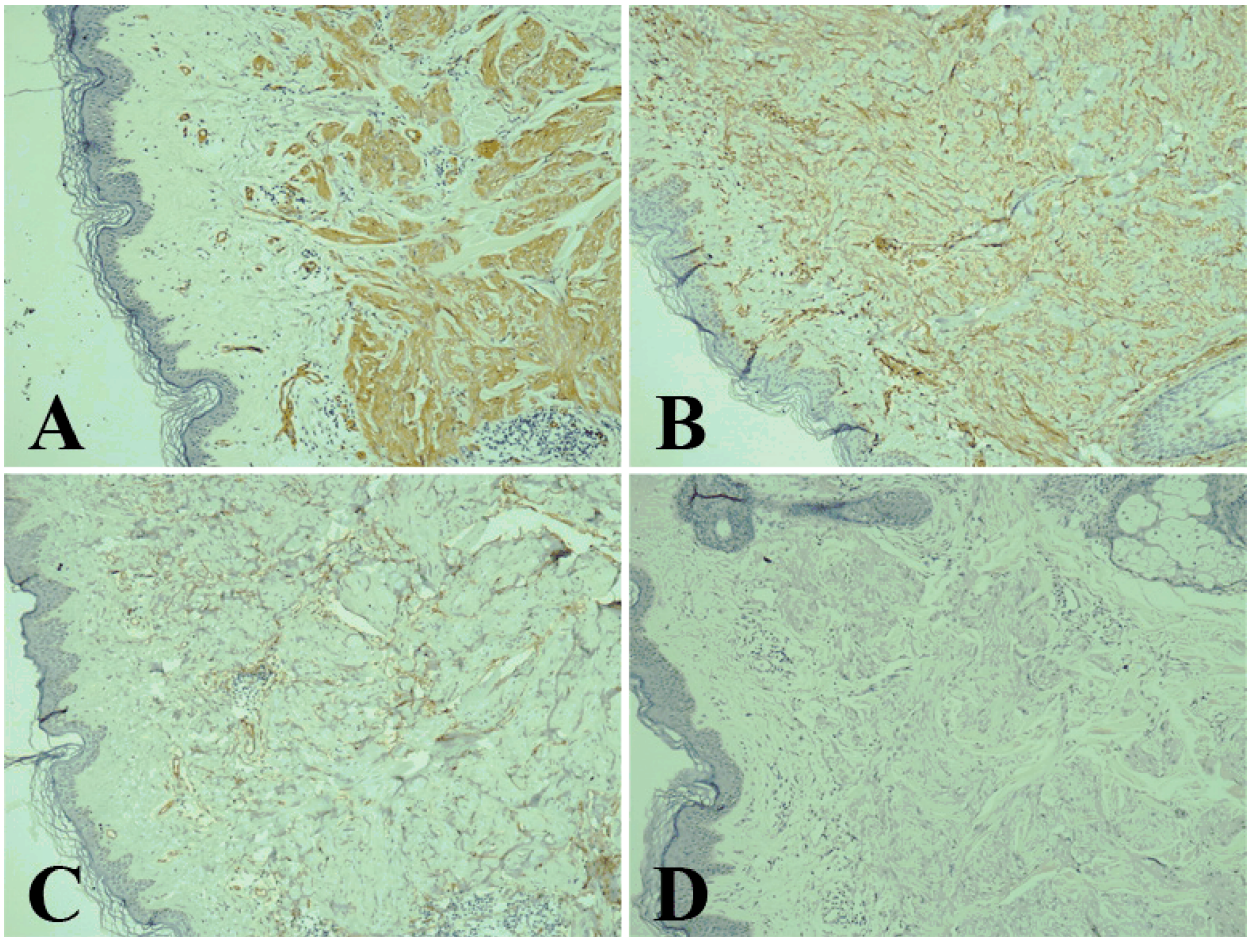

Figure 5 – ***(A–D) Immunohistochemical staining showing diffuse positivity for actin (A, ×50) and vimentin (B, ×50), positivity for CD34 limited to endothelial cells (C, ×100) and for Leu7 limited to nerve fibers (D, ×100). CD34: Cluster of differentiation 34.***

FH mutations induce carcinogenesis mainly through the activation of the hypoxia pathway. The decrease in the enzyme's function leads to the accumulation of fumarate, which competitively inhibits the degradation of hypoxia-inducible factor (HIF)-1α by prolyl hydroxylases. HIF-1 is a transcription factor that controls the response to changes in cellular oxygenation [13]. Its enzymatic lysis is reduced in case of low oxygen tension, thus promoting cell survival and growth [13]. In HLRCC, despite normal cellular oxygenation, HIF1-α level is increased, generating a state of pseudo-hypoxia that explains tumor growth [14, 15]. Additional mechanisms involved in tumorigenesis include the production of reactive oxygen species that contribute to the stabilization of HIF-1α and the potential of intracellular fumarate to mediate epigenetic effects [16].

Multiple studies have also reported an association between *FH* gene mutations and the development of sporadic tumors, therefore it has been hypothesized that it

functions as a tumor suppressor gene [5, 17]. However, this is still a controversial issue as subsequent research did not confirm the role of *FH* gene defects in sporadic tumorigenesis [18, 19].

The clinical picture of HLRCC is highly characteristic, but the severity of the disease considerably varies between families and within the same family [11, 20]. Most patients present solitary or multiple cutaneous leiomyomas. These are benign smooth muscle tumors arising most often from the arrector pili muscle (piloleiomyomas) and less frequently originating in the genital and areolar smooth muscles or the vascular smooth muscles (angioleiomyomas) [21]. They generally appear during young adulthood, the mean age of onset being 25 years [22]. On physical examination, multiple firm, smooth skin-colored or pink papules or nodules, ranging in size from 0.2 cm to 2 cm are found especially on the trunk and limbs, the face and neck being seldom involved [23]. Although they may be asymptomatic, pain or paresthesias associated with these skin lesions are common complaints [7]. Exposure to cold, trauma, even touch, as well as emotional stress can induce local pain [24]. Nevertheless, the symptoms can be present independent of such precipitating factors. Moreover, cutaneous leiomyomas may exhibit a pseudo-Darier sign [25]. The diagnosis should be confirmed by HP examination, that reveals a poorly circumscribed tumor located in the reticular dermis composed of bundles of smooth muscle fibers with eosinophilic cytoplasm and typical elongated nuclei with blunt ends, interlaced with collagen fibers [17, 24, 26, 27]. Immunohistochemistry studies show positivity for desmin and actin [28].

Malignant transformation into leiomyosarcomas has been described in HLRCC patients, but it is extremely uncommon [9, 29].

Another hallmark of the disease is uterine leiomyomatosis, which affects 70–90% of female family members [9, 26, 30]. In a study that included 108 patients diagnosed with HLRCC, 7% of women only presented uterine leiomyomas [30]. Similar to their cutaneous counterparts, uterine leiomyomas develop at young ages, the median age at diagnosis being 30 [26]. Compared to the general population, HLRCC patients develop multiple and larger uterine fibroids that cause pelvic pain, menstrual irregularities, menorrhagia, and fertility problems [31]. Due to rapid growth and severe associated symptoms, myomectomy or hysterectomy are frequently performed approximately 10 years earlier compared to the general population [26, 32–34]. Despite their benign nature, they tend to display increased cellularity, atypia, nuclear pleomorphism, and rare mitoses on HP examination [35]. Uterine leiomyosarcoma has been reported [29].

10–30% of patients develop RCC [11, 34, 36], especially type 2 papillary RCC, and less frequently tubulopapillary, or collecting-duct RCC [37]. It usually occurs during the fourth or fifth decade of life [34, 38]. As a rule, it is solitary and may be asymptomatic or manifest as hematuria and lower back pain [39]. Histopathologically, it is characterized by cells with large nuclei with eosinophilic inclusion-like nucleoli and a clear perinucleolar halo [40]. Tubulo-papillary, tubulo-solid, cystic, sarcomatoid patterns can be encountered and even a mixture of multiple patterns within the same tumor can be observed [40, 41]. Unfortunately, RCC is extremely aggressive in the majority of HLRCC patients, owing to its remarkable metastatic propensity. Metastazation to draining lymph nodes or distant sites is very frequent even with infracentimetric primary tumors. 82% of the 182 patients with HLRCC studied by Muller *et al.* already had metastatic disease at the time of diagnosis [42]. Systemic therapy has proven inefficient in this setting [43]. Therefore, it is crucial that patients diagnosed with HLRCC undergo regular and thorough renal imaging, as well as prompt surgical intervention in case renal tumors are detected. Screening for RCC should be performed by experienced physicians as benign renal cysts are also very common in patients with HLRCC (36%) [44]. This is also the case in our patient, who has not developed RCC, but presents multiple renal cysts. The problem requires further investigation as association of HLRCC with renal cysts might not be purely coincidental and the later could also represent a predisposing factor for RCC [45].

Several case reports describe associations of HLRCC with adrenal cortical hyperplasia, pheochromocytoma, and adrenal cortical carcinoma [46]. In the study conducted by Shuch *et al.*, 20 of 255 patients with HLRCC had micronodular and/or macronodular adrenal hyperplasia, justifying the assumption that these may represent additional elements of HLRCC [47]. Although initially suspected, the presence of a neuroendocrine tumor could not be demonstrated in our patient. Nevertheless, she was diagnosed with bilateral adrenal cortical hyperplasia.

Other solid tumors, such as breast cancer, bladder cancer, and testicular Leydig cell tumors have been described in association with HLRCC in isolated case reports [46].

The presence of multiple cutaneous leiomyomas confirmed by HP examination is considered a major criterion for the diagnosis of HLRCC. Minor criteria include surgery required for symptomatic uterine leiomyomata before 40 years of age, type 2 papillary RCC before 40 years of age, or a first-degree relative who meets one of the above criteria [48]. Either the major criterion or at least two minor criteria should be met in order to establish the diagnosis. Our patients met all criteria except the development of RCC. The definitive diagnosis is made once a germline *FH* mutation or reduced enzyme activity is demonstrated [37]. Genetic counseling should be offered to both patients and their families and screening for RCC should be planned. There is no consensus regarding the age the surveillance should be initiated, but many authors recommend biannual renal US and annual abdominal and pelvic MRI, starting at the age of 10 [48, 49]. Adult female family members should also undergo annual gynecological examination, as well as periodic US and pelvic MRI.

Asymptomatic cutaneous leiomyomas do not require treatment. Surgical excision is the treatment of choice for single or few painful lesions, but recurrences are frequent. Cryotherapy, electrotherapy, or laser vaporization are also efficient for isolated tumors. Drugs that inhibit the contraction of smooth muscle fibers (calcium-channel blockers, α-adrenergic receptor antagonists) and those that influence nerve activity (Gabapentin, topical analgesics) have been tried with little benefit in cases with numerous

symptomatic cutaneous leiomyomas [2, 17, 24]. Botulinum toxin type A has recently been proposed as an alternative for pain control [50].

Uterine leiomyomas require myomectomy and in severe cases, hysterectomy. Gonadotropin-releasing hormone agonists and anti-hormonal treatment can be employed prior to surgery for tumor size reduction and temporary pain relief [34].

Considering the aggressive nature of RCC in these patients, no renal solid mass, even infracentimetric tumors should be monitored, but promptly excised with wide surgical margins. Radical nephrectomy and retroperitoneal lymph node dissection are often necessary [51].

Metastatic RCC in these patients portends a very poor prognosis, as no therapy has proven efficient in halting the progression of the disease so far. Multiple agents targeting vascular endothelial growth factor receptor (Bevacizumab), epidermal growth factor receptor (Erlotinib) or both (Vandetanib) are currently studied, either as monotherapy or in combination [52]. Metformin is also investigated for its synergistic effect with the previously mentioned treatments due to its antineoplastic properties. Anti-programmed death ligand-1 (PDL-1) agents are only effective in the very rare tumors that are positive for PDL-1 [53]. Lactate dehydrogenase-A inhibitors and deoxyribonucleic acid (DNA) methyl transferase inhibitors (Guadecitabine) are also under evaluation [54].

Conclusions

We wish to underscore the value of a thorough dermatological examination that can provide useful clues for the diagnosis of severe underlying systemic diseases. In our patient, an apparently unimportant cutaneous finding lead to the diagnosis of a serious genetic syndrome, with a high risk of aggressive RCC. Although the patient and her family members had presented skin and uterine tumors suggestive of HLRCC long before the admission to our Clinic, the diagnosis was missed owing to the rarity of the condition. HLRCC must be suspected in all individuals with multiple cutaneous leiomyomas. Referral to gynecology and nephrology specialists should not be delayed and a surveillance plan should be started as early detection of RCC is the only efficient strategy to reduce morbidity and mortality in HLRCC patients. A high index of suspicion and a low threshold for surgical intervention are essential when renal tumors are detected. Genetic counseling should also be offered to the patient and his family.

Conflict of interests

The authors declare that they have no conflict of interests.

Compliance with ethical standards

We obtained the approval of the Ethics Committee of Elias Emergency University Hospital, Bucharest for the publication of this manuscript (No. 4770/24.07.2020).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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