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CASE REPORT

Hereditary leiomyomatosis and acute lymphoblastic leukemia: A link through fumarate dyshydratase mutation?

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ABSTRACT

Background: : Hereditary leiomyomatosis (HL) is an autosomal dominant condition due to a variety of fumarate hydratase (FH) mutations in which individuals tend to develop cutaneous leiomyomas, multiple uterine leiomyomas and are at risk for developing aggressive papillary renal cell carcinoma.

Case presentation: : A 26-year-old man with a past history of acute lymphoblastic leukemia (T-ALL) presented with numerous painful light brown papules and nodules spread all over his body except for the head, appearing since infancy. Similar lesions were present in his mother's family. A cutaneous biopsy revealed a cutaneous leiomyoma. His mother died from metastatic uterine neoplasia and his sister suffered from leiomyoma of the uterus. No renal cancer was reported in his family. A heterozygous pathogenic variant was detected in the FH gene.

Conclusion: : To our knowledge, this is the first case possibly linking HL and T-ALL through FH deficiency.

KEYWORDS

Hereditary leiomyomatosis; T-cell acute lymphoblastic leukemia; T-All; fumarate hydratase; mutation

Introduction

Hereditary leiomyomatosis (HL) (Orpha number 523, Reed's syndrome), is an autosomal dominant condition due to mutations in fumarate hydratase (FH), a tumor suppressor gene, localized on chromosome 1q [1,2]. More than 30 different germline mutations have been described including missenses, frameshifts, nonsenses, deletions/insertions, splice site and complete deletion [3,4]. Sporadic cases are rare [5,6]. Inactivation of the FH enzyme involves a malfunction of the tricarboxylic acid (TCA) (Krebs) cycle which manifests clinically with multiple cutaneous leiomyomas (CLM), uterine leiomyomas as well as an aggressive form of papillary type II renal cell cancer [2,7].

Acute lymphoblastic leukemia of the T-lineage (T-ALL) is a rare malignant hematological disease of T-cells lineage representing up to 25% of acute lymphoblastic leukemia (ALL) and affecting 1.7 per 100,000 persons with a poorer prognosis in adults [8,9]. Integrated genomic analysis disclosed at least 100 driver genes in the T-cell lineage. The diversity of the driver gene, including for example NRAS/FLT3, JAK3/STAT5B or PTPN2, suggests a variety of signaling pathways playing a different role in maturational stage [9]. Up until recently, none of these genes has been linked to FH. The precise etiology of T-ALL is still unknown but there seems no evidence of a hereditary origin [10].

Case report

For one year a 26-year-old man with T-ALL, diagnosed 18 months previously, was treated according to the GRAALL 2014 protocol [11] and was currently under maintenance therapy with 6-mercaptopurine and methotrexate. Other medication consisted of acyclovir, sulfamethoxazole and trimethoprim. In his medical history cigarette smoking and occasional use of cannabis was noted. Physical examination revealed numerous diffuse painful light brown papules and nodules on the trunk and the limbs (Figure 1a,b). These lesions appeared around the age of 10 and progressively increased in number. The patient complained about bursts of pain, especially under cold and on pressure. During T-ALL related treatment no skin changes were observed. No other cutaneous particularities were evidenced. Histology revealed a benign proliferation of smooth muscle cells, consistent with leiomyoma (Figure 1c). Immunohistochemistry evidenced signals for desmin and actin (Figure 1d,e).

His mother and sister presented similar cutaneous lesions. The patient mentioned that his mother died some years ago from metastatic uterine neoplasia. In addition, his sister also presents painful uterine leiomyomas. No cases of renal cancer were reported in the family. A heterozygous pathogenic variant was detected in the FH gene

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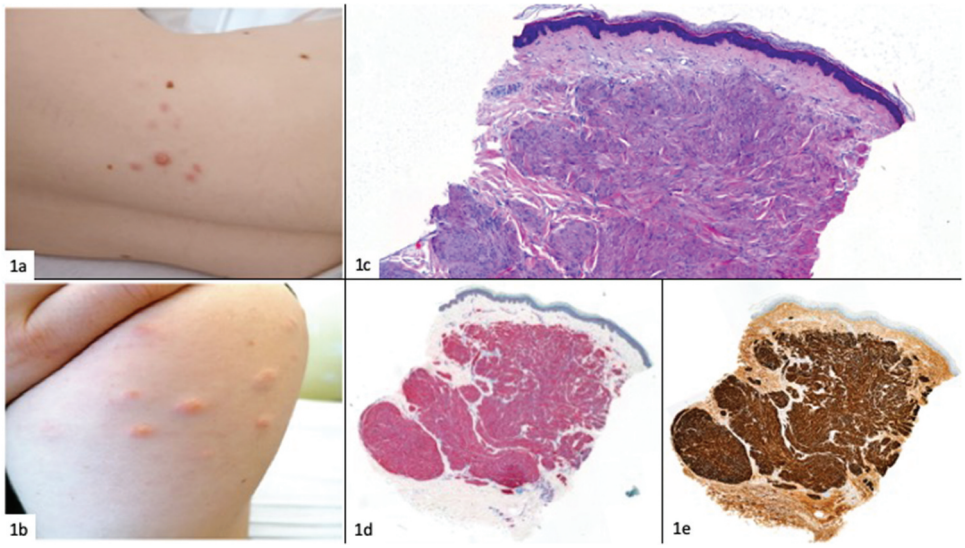

Figure 1. Numerous small cutaneous leiomyomas on the trunk (a) left hip (b), histology of leiomyomatosis (H/E) (c), desmin immunostaining (d) and actin immunostaining (e).

(NM_000143.3) by DNA sequence analysis, a splice variant likely to disrupt the consensus splice donor site of exon 6, c.904_904 + 1insCTGT p.

Discussion

HL patients tend to develop multiple CLMs, multiple uterine leiomyomas and an aggressive form of papillary renal cell cancer [1,2,7,12–14]. HL is described in approximately 200 families worldwide but the incidence is probably underestimated [6,15]. The overall penetrance approaches 90% to 100% with benign and malignant forms [15–17]. Uterine leiomyomas are present in up to 77% of women [16]. The cumulative lifetime renal cancer risk reaches 15 to 20 % whereas 75% of affected individuals tend to develop CLMs [16,17].

The cutaneous manifestations consist of firm reddish or brownish skin papules or nodules appearing usually around the age of 25 years but sometimes may appear in younger patients [6,12,14,18]. The CLMs are commonly localized on the extensor surfaces, the trunk, the face and the neck [19]. CLMs may cause shocking bursts of pain [6,12,14], that are often the first manifestation of the disease [14]. Pain may occur spontaneously or induced by cold, stress, touch, trauma, pressure or emotions [20,21]. Paresthesia may also be observed. Transformation into cutaneous leiomyosarcoma is rare [14,22,23].

The major and minor diagnostic criteria for HL were recently published (Table 1). The final diagnosis relies on the identification of the FH mutation [24].

CLMs can be treated by cosmetic camouflage, surgery, CO2 laser ablation, cryotherapy or electrodessication [7,17] according to their number, the pain the patient experiences and the impact on his quality of life scores [24]. The identification of triggering factors can be helpful. First-line medical treatments include alpha-blockers, phenoxybenzamine (20–60 mg/day) or doxazosin (1 mg/day), calcium channel inhibitors like nifedipine (10 mg 3–4x/day), nitroglycerine (0.8–1.6 mg/day) and antidepressants (duloxetine 60 mg/day). Gabapentin (300 mg 1–3 x/day) or pregabalin (300 mg 2x/day) are the next in line options, either as mono or combination therapy. Lidocaine or capsaicin, botulinum toxin and intralesional triamcinolone acetonide are adjuvant options [7,17,24].

Table 1. Diagnostic criteria for HL.

Major criteria	Minor criteria
Multiple cutaneous leiomyomata with at least one biopsy proven/ histologically confirmed	- Solitary cutaneous leiomyomata and family history for HL
	- Early onset renal tumors of type 2 papillary histology
	-Multiple early onset (<40 years) symptomatic uterine fibroids

Definitive diagnosis: positive germline FH-mutation test

The uterine leiomyomas can be relieved using traditional pain killers. Ulipristal acetate, a progesterone receptor modulator, was efficient but reports of liver injury requiring liver transplant lead to a recent suspension [25]. Gonadotrophin liberating hormone agonists such as levonorgestrel represent a good alternative. Surgery consist of a myoectomy or hysterectomy [17]. Uterine artery embolism and electrosurgery can also be performed [6,12,17].

Total nephrectomy is recommended for patients with a renal mass due to the high aggressiveness of renal cancers associated with Reed's syndrome [22,24,26,27]. The prognosis primarily relies on the early detection of HL-associated renal cancers in order to treat them as soon as possible [28].

Following diagnosis, the management should include annual screening for renal cell carcinomas using contrast-enhanced magnetic resonance imaging (IRM) starting in infancy [17,24,28]. Ultrasound could assist MRI in the screening program although some discrepancy exists among authors [28]. Annual ultrasonic gynecological examinations starting at the age of 20 as well as a skin examination to evaluate a rare but potential transformation into leiomyosarcomas are recommended [7,17,24]. Education of the patient in the detection of rapid growth of skin lesions is a cost-effective diagnostic method. Follow-up is important because of the significant morbidity related to pain from CLMs and uterine leiomyomas and increased mortality [17]. However, therapeutic guidelines may vary according to the phenotypic variation ranging from minor skin lesions to fatal cancer [17,29]. A genetic testing should be performed in family members of confirmed FH mutation carriers to detect the mutation and include them in surveillance programs [24,28].

Reed's syndrome is caused by a mutation of the FH (1q42.1) gene coding for the FH enzyme that metabolizes fumarate during the nucleotides cycle and the synthesis of arginine in the cytoplasm [30–32]. FH represents a key enzyme in energy production through the TCA and plays a role in DNA repair and tumor suppression [33]. When this enzyme is mutated, there is an increased level of fumarate pro-oncogenic signals that can directly contribute to malignant transformation and tumorigenesis. The germline heterozygous loss-of-function mutations of FH predispose to CLMs, to uterine leiomyomas and to papillary type II renal cell carcinomas [19,26] whereas the sporadic loss of FH has been reported in many tumors such as sporadic clear cell carcinomas [34] adrenocortical carcinoma [35], Ewing's sarcoma [36], neuroblastomas [35,36], glioma, ependymoma, osteosarcoma, pheochromocytomas, paragangliomas [37], colorectal cancer [38], breast, bladder, and testicular cancers [39,40]. This array of non-hematopoietic cancers contrasts with the lack of any reports of hematopoietic malignancies.

The eventual involvement of non-functional FH in T-ALL, a malignant disease in which lymphocytic B-lineage or T-lineage cells proliferate abnormally, is not clear at all. One hypothesis stipulates that FH deficiency results in cellular fumarate accumulation leading to a decreased mitochondrial respiration and to increased histone H3 trimethylation in hematopoietic stem cells (HSC), subsequently promoting a gene expression that facilitates hematopoietic defects [41]. In addition, mitochondrial FH seems to be essential for HSC self-renewal through an intact TCA cycle and a maximal mitochondrial respiration. In sum, FH deficiency seems necessary for leukemia-initiating cells development but appears to have no impact on the maintenance of leukemia-initiating cells. The lack of mitochondrial FH impacts the lymphoid line rather than the myeloid one [41].

Considering these data, it seems plausible that in this patient the FH mutation could represent a link between his Reed's syndrome and the T-ALL.

Conclusion

To our knowledge, this patient is the first case possibly linking HL and T-ALL, through non-functional FH leading to a dysfunctional TCA cycle and an abnormal mitochondrial respiration.

Further studies are required to determine the exact role of non-functional FH in T-ALL. Whether a systematic screening for malignant hemopathies is relevant for patients with HL in addition to dermatological, gynecological and nephrological surveillance programs remains to be determined.

Disclosure statement

No potential conflict of interest was reported by the authors.

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