DERMATOLOGY PRACTICAL & CONCEPTUAL
www.derm101.com

Cutaneous and uterine leiomyomatosis and ovarian cystadenoma associated with deficiency of fumarate hydratase

Cornelia Hüller, M.D.[1], Norbert Grunow, M.D.[2], Torsten Nadler, M.D.[3], Michael Bär, M.D.[1*]

[1]Department of Dermatology, Görlitz Municipal Hospital, Görlitz, Germany
[2]Department of Pathology, Görlitz Municipal Hospital, Görlitz, Germany
[3]Department of Gynecology, Görlitz Municipal Hospital, Görlitz, Germany

Key words: uterine leiomyomatosis, ovarian cystadenoma, fumerate hydratase

Citation: Hüller C, Grunow N, Nadler T, Bär M. Cutaneous and uterine leiomyomatosis and ovarian cystadenoma associated with deficiency of fumerate hydratase. Dermatol Pract Concept 2011;1(1):7. http://dx.doi.org/10.5826/dpc.0101a07.

Editor: Harald Kittler, M.D.

Received: March 29, 2011; **Accepted:** June 1, 2011; **Published:** October 31, 2011

Funding: None.

Competing interests: The authors have no conflicts of interest to disclose.

All authors have contributed significantly to this publication.

Corresponding author: Michael Bär, M.D., Department of Dermatology, Görlitz Municipal Hospital, Girbigsdorfer Straße 1–3, 02828 Görlitz, Germany, Tel. ++49.3581.371490, Fax. ++49.3581.371499. Email baer.michael@klinikum-goerlitz.de.

ABSTRACT We report on an exceedingly rare case of cutaneous and uterine leiomyomatosis in a 58-year-old Caucasian woman associated with ovarian cystadenoma and complete deletion of the fumarate hydratase gene. All patients and their family members with verified mutation have to be regularly screened for associated neoplasms, in particular papillary renal cell carcinoma (HLRCC, hereditary leiomyomatosis and renal cell cancer).

Case report

We report on a 58-year-old Caucasian woman that was hospitalized owing to a monstrous ovarian tumor on the right side with a three-month history of sudden abdominal growth and subsequent dyspnea. Sonography and CT scan rendered an additional myomatous uterus with requirement of a bilateral hysterosalpingectomy. The last consultation with a gynecologist had been about eight years prior. The complete staging was without evidence of further neoplasms and the patient was otherwise healthy. The patient had eight deliveries and one abortion. She finally was referred to a dermatologist because of multiple agminated dense erythematous nodules restricted to the skin of the left shank and the right flank with a few aberrant lesions at the dorsal trunk only (Figure 1). The patient reported occasionally associated painful sensations but did not request further treatment. The nodules obviously had rapidly appeared in the context of alvine tuberculosis at the age of 13. However, a relapse of the previous mycobacteriosis was excluded upon punctuation of the ovarian tumor.

Histopathologically, there was evidence of a severe fibroleiomyomatosis of the uterus with an associated dexter ovarian cystadenoma (diameter 25 cm) (Figure 2). A biopsy of the

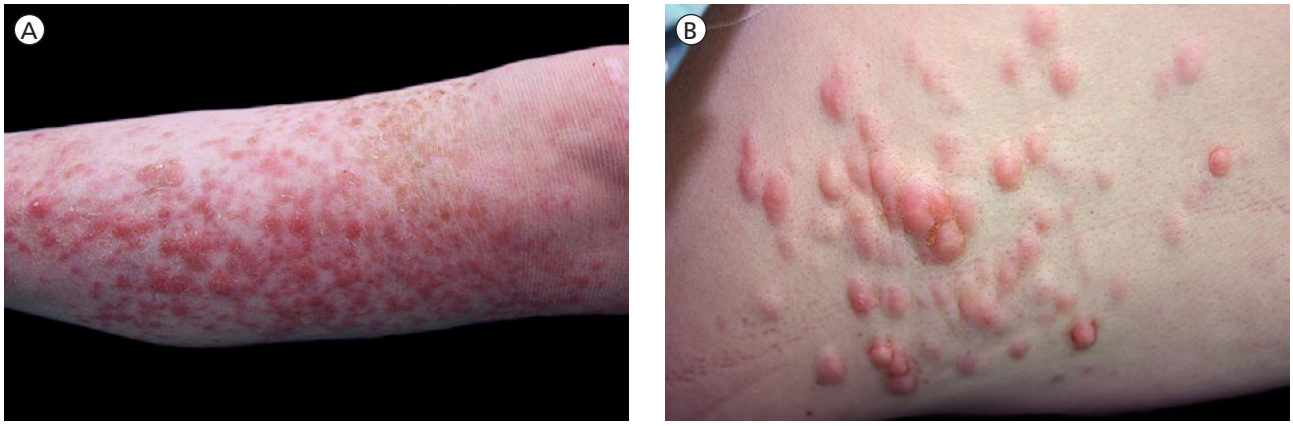

Figure 1. Agminated, in part, plaque-like confluent dense erythematous papules restricted to the skin of the left shank (A) and the right flank (B), with few aberrant lesions at the dorsal trunk only. There is no obvious relation to Blaschko's lines or dermatomes.

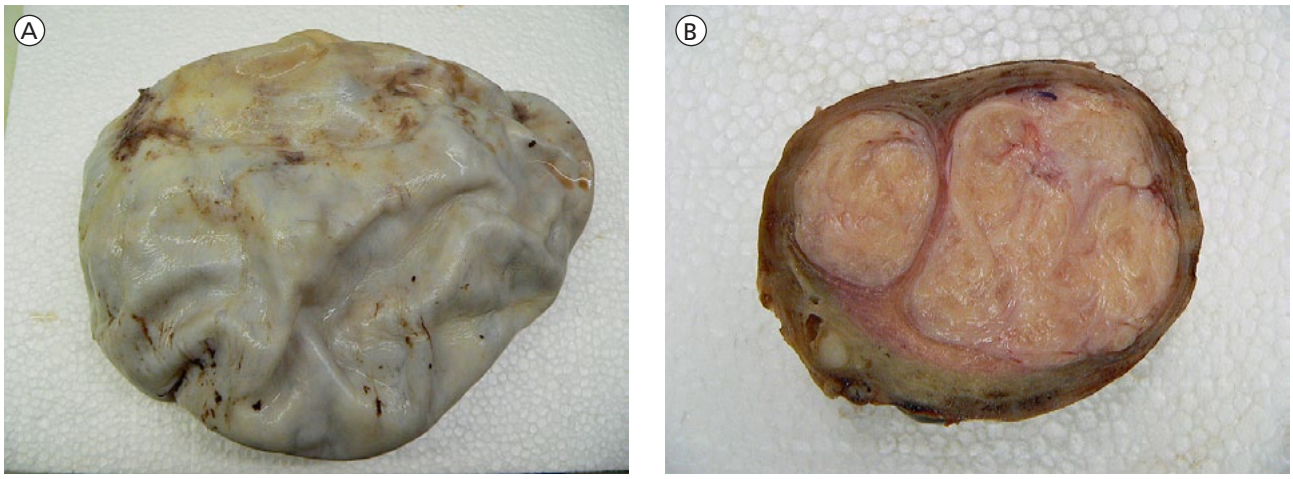

Figure 2. An ovarian cystadenoma measuring 25 cm fixed by a standard formaldehyde solution (A); section across the uterine corpus revealing several intramural leiomyomas with obstruction of the uterine cavum (B).

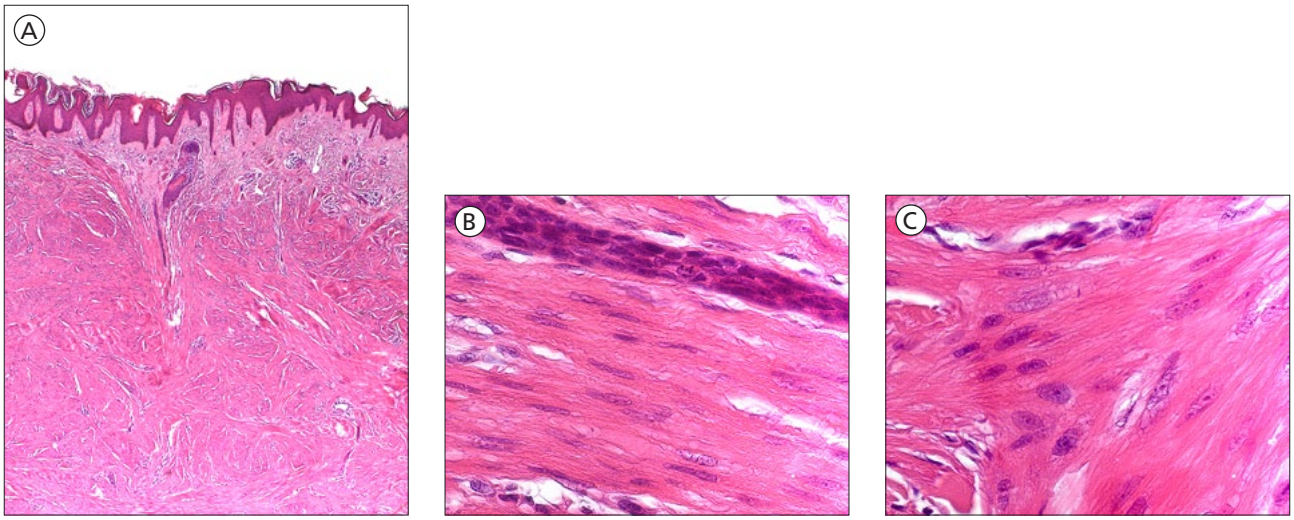

Figure 3. Piloleiomyoma consisting of a plaque-like confluent fascicular spindle cell proliferation obviously originating in the muscle of hair erection (A, HE 40x). Nuclei were cigar-shaped and in part exhibited vesicular pseudoinclusions (B, HE 400x). There was no mitotic activity. However, some plump cells were seen and interpreted as a clue to ancient changes (C, HE 400x).

cutaneous lesions on the right flank revealed pilar leiomyomas consisting of a plaque-like confluent fascicular spindle cell proliferation obviously originating in the muscles of hair erection. Nuclei were cigar-shaped and in part exhibited vesicular pseudoinclusions. There was no mitotic activity. However, some plump cells were seen and interpreted as a clue to ancient changes (Figure 3). Smooth muscular differentiation was confirmed immunohistochemically by coexpression of actin, desmin and smooth muscle actin. The proliferation index as detected by nuclear Ki67 expression was less than 1%. Blood samples with addition of EDTA were analyzed molecularpathologically and a complete deletion of the fumarate hydratase gene was detected.

Commentary

In contrast to the frequent uterine leiomyomas, cutaneous leiomyomas are rare and benign, but occasionally painful tumors originating in the smooth muscles of the pilar apparatus, the vessels or the genital skin. In patients suffering from multiple cutaneous leiomyomas a germline mutation of the fumarate hydratase with incomplete penetrance may be frequently found. In females, this mutation may be frequently associated with uterine leiomyomatosis. Our patient was not aware of a similar disease in other family members, however, had not been in contact with any of them for years; thus, a reliable statement about a given episodic versus familiar disease can not be given.

Fumarate hydratase is a constituent of the citric acid cycle and usually catalyzes the hydratation of fumarate to L-malate. However, the corresponding gene might be of additional impact as a tumor suppressor gene.

Leiomyomatosis cutis et uteri was first described in 1954 by Blum and Jean [1]. However, the eponymical denomination as Reed's syndrome was based on a corresponding case report published in 1973 [2]. The cutaneous lesions usually appear during adolescence, predominantly affecting the trunk and extremities in an agminated pattern [3]. A subset of patients is at relevant risk of early development of associated aggressive papillary renal cell cancer, a constellation then termed hereditary leiomyomatosis and renal cell cancer, HLRCC. Further tumors associated with deficiency of the fumarate hydratase are cutaneous or uterine leiomyosarcomas, carcinomas of the bladder or prostate gland, breast cancer, gastrointestinal stroma tumors, but also benign tumors like adrenal adenomas, renal cysts or rarely, like in our patient, ovarian cystadenomas [4]. All patients and their family members with verified mutation have to be regularly screened for associated neoplasms, in particular, papillary renal cell carcinoma. Females with cutaneous lesions only should be regularly screened for uterine disease, too, in order not to miss a relevant syndromal context. Thus, eventually associated malignomas might be detected at an early stage with rather curative treatment options.

Among the reported, although experimental, treatment options of the cutaneous leiomyomas are excision or ablation by laser, but also analgetic approaches using Botox, nifedipine, nitroglycerine, phenoxybenzamine, gabapentin, doxazosin or local anaesthetics [5].

References

1. Blum P, Jean L. Leiomyome eruptif de Besnier. Bull Soc F Dermatol Syph 1954;61(4):349-50.
2. Reed WB, Walker R, Horowitz R. Cutaneous leiomyomata with uterine leiomyomata. Acta Derm Venereol 1973; 53(5):409-16.
3. Alam NA, Barclay E, Rowan AJ, et al. Clinical features of multiple cutaneous and uterine leiomyomatosis: an underdiagnosed tumor syndrome. Arch Dermatol 2005;141(2):199-206.
4. Ylisaukko-oja SK, Cybulski C, Lehtonen C, et al. Germline fumarate hydratase mutations in patients with ovarian mucinous cystadenoma. Eur J Hum Gen 2006;14(7):880-3.
5. Kim G. Multiple cutaneous and uterine leiomyomatosis (Reed's syndrome). Dermatol Online J 2005;11(4):21.