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Muir-Torre Syndrome

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Key Words
Muir-Torre syndrome · Familial cancer · Fibrous papules

We read with interest the article 'Fibrous papule of the face with granular cells' [1]. The authors analyzed a patient with a recurrent transitional cell carcinoma of the bladder for expression of the DNA mismatch repair genes *MLH1* and *MSH2*. Unfortunately, the family history is not given in detail.

Fibrous papules of the face and neck can be found in families with different autosomal dominant tumor syndromes such as Birt-Hogg-Dubé syndrome, Cowden disease, Gardner syndrome and tuberous sclerosis [2–4].

The family history of the presented patient exhibits many different neoplasias, similar to a multisystemic cancer predisposition disorder like Cowden disease, also known as multiple hamartoma syndrome. Patients with Cowden disease have an increased potential to develop benign and malignant neoplasms in a variety of tissues. The mostly benign cutaneous tumors are indicative of internal malignancies and may precede the development of the internal manifestations by many years. Benign skin tumors are facial papules, trichilemmomas, sclerotic fibromas and fibroangiomas, for example, whereas associated malignant skin tumors are basal cell carcinoma or sebaceous carcinomas amongst others. Furthermore, malignant neoplasias could affect the internal organs like the colon, urinary bladder and stomach [4].

It would be helpful to mention the age of onset of patients as the probability for the incidence of invasive cancers arises with age. Thus, of all male individuals in the USA aged 60–69 years, 1.67% develop colorectal cancer versus 1.16% of all US females, and 0.96% develop urinary bladder cancer versus 0.26% of the female population [5]. In the population aged 70 and older there are 4.92% of the male population developing colorectal cancer versus 4.45% of females and 3.41% of males develop urinary bladder cancer versus 0.96% of females, respectively. Furthermore, colorectal cancer is the 3rd most frequent cancer in males and females, and bladder cancer is the 4th most frequent in the USA. The lifetime risk for bladder cancer in the general population is 1–3% and 4% for persons with hereditary nonpolyposis colorectal carcinoma (HNPCC; Muir-Torre syndrome is a special kind of HNPCC or Lynch syndrome), and the risk for developing colorectal cancer is dramatically enhanced in persons with HNPCC (80–82% vs. 5–6% in the general population).

Nevertheless, an appropriate tool helping in selecting families for immunohistochemical and/or molecular genetic analysis to identify MMR gene mutations are the Amsterdam criteria II and the revised Bethesda guidelines (table 1) [6, 7]. Because bladder cancer is not an HNPCC-related cancer, only the younger sister of the index patient could comply with the revised Bethesda guidelines, and their parents if they are alive. Additionally, in families where one member fulfilled at least one of the clinical

Table 1. Amsterdam criteria II and revised Bethesda guidelines

Amsterdam criteria II
There should be at least 3 relatives with CRC or with a Lynch-syndrome-associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis
– One relative should be a first-degree relative of the other 2
– At least 2 successive generations should be affected
– At least 1 tumor should be diagnosed before the age of 50 years
– FAP should be excluded in the CRC case if any
– Tumors should be verified by histopathological examination
Revised Bethesda guidelines
1 CRC diagnosed in a patient aged <50 years
2 Presence of synchronous, metachronous colorectal or other Lynch-syndrome-related tumors, regardless of age
3 CRC with MSI-H phenotype diagnosed in a patient aged <60 years
4 Patient with CRC and a first-degree relative with a Lynch-syndrome-related tumor, with one of the cancers diagnosed at an age <50 years
5 Patient with CRC with 2 or more first-degree or second-degree relatives with a Lynch-syndrome-related tumor, regardless of age

CRC = Colorectal cancer; FAP = familial adenomatous polyposis; MSI-H = high-frequency microsatellite instability. Lynch-syndrome-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract and brain tumors, sebaceous gland adenomas and keratoacanthomas, and carcinoma of the small bowel.

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selection criteria corresponding to the Amsterdam II criteria or the Bethesda guidelines, the sensitivity of the immunohistochemical analysis for *MLH1* and *MSH2* was shown to be 94% in tumors [8], whereas in sebaceous hyperplasia only 3% show microsatellite instability [9].

Concerning HNPCC and Muir-Torre syndrome, it would be even more efficient in the presented family to investigate the colon cancer of the patient's sister.

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Reply

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Thank you for your interest in our paper and for your letter. We think that the first aim of the article was to focus on a special type of fibrous papule: the granular variant which is rare. This is expressed in the title of the paper. We wanted to describe the histopathological findings and immunohistochemical characteristics of this rare tumor. We also discuss the differential diagnosis. Our patient had only 1 fibrous papule and not multiple lesions which are typically seen in Cowden's disease. The typical perifollicular fibromas with the mantle-like proliferation of the follicle are completely different from the histology of our single lesion of a fibrous papule, and this was the reason why we never thought about Birt-Hogg-Dubé syndrome. Therefore, we believe that in our case the occurrence of granular cells in a fibrous papule was an incidental finding in a patient with a family background suggesting a familial cancer syndrome which has not yet been completely classified. If in the future there are other findings in the proband or his family we will publish them.

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