

Brooke-Spiegler Syndrome Associated with Ulcerative Rectosigmoiditis

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Brooke-Spiegler syndrome (BSS, OMIM 605041) is an autosomal dominant syndrome characterized by multiple benign skin appendage tumours (1–3). The most common tumour types include trichoepitheliomas, cylindromas and spiradenomas originating from the basal cell layer of the epidermis and from hair follicles in the areas of the head and neck (3, 4). In some patients BSS may cause turban tumour (5). Familial cylindromatosis (OMIM #132700) and multiple familial trichoepithelioma (OMIM #601606) were originally described as distinct entities, but they have been shown to be allelic variations (6). In BSS, tumour growth most commonly initiates in adolescence or adulthood, but may begin earlier (3). Various surgical modalities, laser ablation and laser treatments combined with imiquimod medication or photodynamic therapy have been tried with variable results (7).

BSS results from germline mutations of the cylindromatosis tumour suppressor gene *CYLD*, which encodes a deubiquitinating enzyme (8, 9). The *CYLD* enzyme negatively regulates the nuclear factor (NF)- κ B and c-Jun N-terminal kinase (JNK) pathways (9). Inhibition of *CYLD* enhances activation of NF- κ B and contributes to carcinogenesis (10). Studies using animal models have shown that *CYLD* is involved in several processes, such as immunity and inflammation, in addition to tumourigenesis (11). Notably, *CYLD*-deficient mice are more susceptible to induced colonic inflammation, and in a colitis-associated cancer model the mice have shown an increase in the incidence of tumours (11). Genome-wide expression profiling of Crohn's disease

and ulcerative colitis have revealed down-regulation of *CYLD* gene in inflamed bowel tissue, and it has been suggested that decreased *CYLD* expression may represent an inflammation control response that is lost or impaired in inflammatory bowel disease (12).

This is the first case reporting a BSS patient with classical skin phenotype combined with inflammatory bowel disease.

CASE REPORT

A 42-year-old woman had had multiple tumours around her nose and eyebrows since her teens. At the age of 38 years she was referred to the Department of Dermatology for scalp tumours and a nodule in her chin. The result of scarring (Fig. 1a) was observed from the previous removal of trichoepitheliomas using CO₂ laser. The tumours in the scalp and chin were removed, and at histological examination the scalp tumours were shown to be cylindromas and the chin tumour was a spiradenoma. Thereafter, several cylindromas have been removed from her scalp by CO₂ laser (Fig. 1b).

To confirm the diagnosis of BSS, mutation analysis of the *CYLD* gene was performed by sequence analysis of all coding exons [4–20], exon/intron boundaries and Q-PCR analysis (laboratory of the Department of Clinical Genetics of Erasmus MC, Rotterdam, The Netherlands). A splice-site mutation, 2350+5G>A in the exon 17 of the *CYLD* gene was found. The patient is the only child of her parents and she has no confirmed evident family history of BSS. The mother and 2 half-siblings are healthy and her 2 children aged 10 and 9 years have no skin symptoms. The patient's father was not available for investigations.

At the age of 34 years the patient was diagnosed with ulcerative rectosigmoiditis of uncertain aetiology. Regular colonoscopies with biopsies have revealed inflammation and one hyperplastic

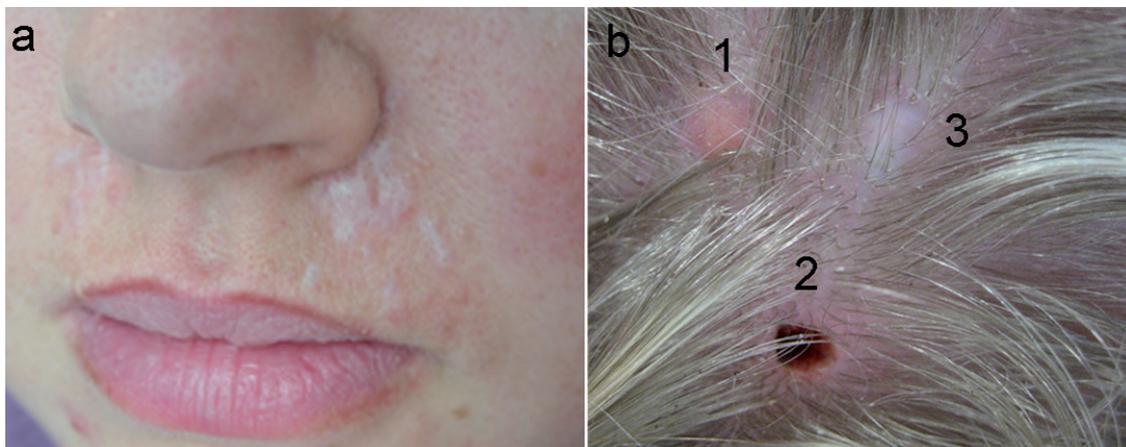


Fig. 1. Clinical presentation of tumours and results of their CO₂ laser ablation. (a) Facial scarring 8 years after the removal of trichoepitheliomas in the nasolabial folds. (b) Scalp cylindroma (1), a wound immediately after the removal of a cylindroma (2) and a scar (3) approximately 2 years after the CO₂ laser operation. On the scalp, an aesthetically acceptable result without re-growth was achieved.

polyp. Her inflammatory bowel disease has been treated with 5-aminosalicylic acid with good therapeutic response.

DISCUSSION

The clinical and histological findings of multiple facial trichoepitheliomas, scalp cylindromas and a facial spiradenoma in our patient are consistent with the diagnosis of BSS. The splice-site mutation 2350+5G>A in the exon 17 of the *CYLD* gene found in our patient has previously been described in a family with BSS syndrome (8). Finding this mutation also in our patient confirms that this splice-site mutation is pathogenic. Thus far, more than 60 mutations have been reported and majority of mutations lead to truncation of the protein, but no clear phenotype-genotype correlations have been found (4, 6, 13).

The involvement of other organs is rare in BSS. One patient with a parotid gland cylindroma has been reported (13). Our patient, however, was diagnosed to have ulcerative rectosigmoiditis at the age of 34 years. Recent research has revealed that the *CYLD* gene plays a role in inflammatory disorders. In *CYLD*-null mice an increased predisposition to inducible colitis has been observed (11). Another study investigated the genes that have the role of proteases and protease inhibitors (P/PIs) in inflammatory bowel disease in populations of European ancestry, and pointed out that *CYLD* gene is the highest ranked P/PI gene associated with inflammatory bowel diseases (14). Also, in an expression microarray study, *CYLD* was one of the most significantly down-regulated genes in the intestine of patients with inflammatory bowel disease (12). *CYLD* enzyme removes ubiquitin chains from several proteins including tumour necrosis factor receptor-associated factor 2 and 6, and the NF- κ B essential modulator. *CYLD* thus regulates cell signalling, including NF- κ B and JNK pathways (9). We suggest that the inflammatory bowel disease in our BSS patient may share the same pathophysiological background. The case presented here is the first report of BSS associated with concomitant inflammation. However, additional reports are needed to estimate whether rectosigmoiditis is a frequent extracutaneous feature of BSS.

Facial and scalp tumours form a significant disease burden to BSS patients, but surgical operations may not be feasible due to large numbers of tumours. Laser treatments have usually been attempted for multiple trichoepitheliomas. Erbium-doped yttrium aluminum garnet laser resurfacing, followed by photodynamic therapy with 5-aminolevulinic acid, or imiquimod 5% cream has been reported to achieve better clearance rates and aesthetic result than laser resurfacing alone in BSS lesions (7). In our patient, the treatment of trichoepitheliomas using regular ablative CO₂ laser caused scarring in the nasolabial area, while removal

of small cylindromas from the scalp (Fig. 1) and an eccrine spiradenoma from the chin yielded cosmetically acceptable results with no signs of re-growth during a 2-year follow-up.

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