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)-κB and c-Jun N-terminal kinase (JNK) pathways (9). Inhibition of CYLD enhances activation of NF-κB 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...
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therapy with 5-aminolevulinic acid, or imiquimod 5%
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BSS lesions (7). In our patient, the treatment of
trichoepitheliomas using regular ablative CO₂ laser
causative 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 spir-
denoma 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). Find-
ing 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 repor-
ted (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 necro-
sis factor receptor-associated factor 2 and 6, and the
NF-kB essential modulator. CYLD thus regulates cell
signalling, including NF-kB 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
operations have usually been attempted for multiple
trichoepitheliomas. Erbium-doped yttrium aluminum
laser resurfacings, followed by photodynamic
therapy with 5-aminolevulinic acid, or imiquimod 5%
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