Multidisciplinary treatment of desmoid tumours in Gardner’s syndrome due to a large interstitial deletion of chromosome 5q

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Summary

Background and aims: Classic autosomal-dominant familial adenomatous polyposis (FAP) is clinically defined by the development of hundreds to thousands of colorectal adenomas beginning in childhood and adolescence. A variant of FAP characterized by polyposis in combination with osteomas or soft tissue tumours is called Gardner’s syndrome. FAP is caused by germline inactivation of the APC (adenomatous polyposis coli) tumour-suppressor gene located on the long arm of chromosome 5 (5q21–5q22). Cytogenetically visible deletions of chromosome 5q encompassing APC have very rarely been reported. Here, we aimed to phenotypically and genetically characterize a patient with a heterozygous 5q deletion resulting in Gardner’s syndrome.

Methods and results: A 26-year-old female patient with mild mental handicap and dysmorphic features due to a cytogenetically visible deletion on chromosome 5q (microscopically estimated region 5q14–5q23) presented at our tertiary referral centre because of mild adenomatous polyposis (<500 polyps). Twenty months after prophylactic proctocolectomy with definitive ileostomy, three rapidly growing desmoids were observed. Tumour-associated complications necessitated a multidisciplinary approach including medical treatment, surgery and radiation therapy. The characterization of the deletion by comparative genomichybridization identified a large 5q deletion expanding over a 20-Mb region (5q21.3–5q23.3) including the APC gene.

Conclusion: Chromosome deletions must be suspected in patients presenting with FAP together with mental handicap and dysmorphic features. This case also impressively shows that FAP-associated desmoids need multimodal treatment taking into account the patient’s individual symptoms, disease progression and tumour location.
Introduction

Classic autosomal-dominant familial adenomatous polyposis (FAP) is defined by the development of hundreds to thousands of colorectal adenomas in childhood and adolescence with extremely high risk for colorectal cancer. FAP is caused by germ-line inactivation of the APC (adenomatous polyposis coli) tumour-suppressor gene (NC_000005) located on the long arm of chromosome 5 (5q21–5q22). In most cases the disease is inherited as an autosomal-dominant trait with near complete penetrance, but de novo-mutations are responsible for about 25–30% of cases. In addition to common truncating mutations, gross alterations such as exon deletions or whole gene deletions have been described. However, the prevalence of these large deletions may be underestimated as they are difficult to detect by using standard sequencing methods.

Besides colorectal adenomas, many benign (e.g. duodenal and small bowel adenomas, gastric fundic gland polyps, osteomas, dental abnormalities, congenital hypertrophy of the retinal pigment epithelium, desmoid tumours, cutaneous lesions) as well as malignant extracolonic manifestations (duodenal adenocarcinoma, thyroid carcinoma, hepatoblastoma, central nervous system tumours) exist. The specific combination of colorectal adenomatous polyposis with osteomas and soft tissue tumours is called Gardner's syndrome.

Here, we present a patient suffering from Gardner's syndrome due to a large interstitial 5q deletion spanning more than 20 Mb which could be characterized in detail by a comparative genomic hybridization (CGH) array. In addition to a detailed description of the phenotype, we present the patient's complicated medical history and discuss the treatment options for FAP-related desmoids.

Methods and results

Case history with regard to FAP

A 26-year-old female patient (174 cm, 64 kg) with mild mental handicap and dysmorphic features (Figure 1A1 and A2) presented at our tertiary referral centre because of a positive faecal occult blood test. Colonoscopy uncovered polyposis with <500 colorectal polyps up to 15 mm in size throughout the entire colorectum (histologically tubular and tubulovillous adenomas with low grade and focal high grade intraepithelial neoplasia) (Figure 1B1). When FAP was suspected, oesophagogastroduodenoscopy identified numerous gastric fundic gland polyps (Figure 1B2). Moreover, several small duodenal adenomas (Spigelman stage II) were removed (Figure 1B3). Extensive work-up for extra-intestinal manifestations identified several radiopaque lower jaw lesions representing osteomas, and magnetic resonance imaging (MRI) of the abdomen identified a small adrenal tumour on the right side compatible with endocrine-inactive adrenal adenoma.

Two months after diagnosis the patient underwent total proctocolectomy with definitive ileostomy. Twenty months after proctocolectomy a large palpable abdominal mass nearby the ileostomy was detected. MRI revealed a tumour of 10 × 9 × 6 cm deriving from the left rectus sheath (Figure 2A1). Two additional tumours with identical characteristics in MRI were found in the right fossa iliaca (Figure 2A1–3) (7 cm in largest diameter) and the mesentery (left paramedian; 2.8 cm in largest diameter) (Figure 2B). As these lesions were compatible with desmoids, an anti-proliferative therapy with celecoxib (200 mg b.i.d.) and tamoxifen (40 mg t.i.d.) was initiated. Imaging 3 months later visualized significant tumour growth (largest diameter 13, 9 and 3 cm, respectively). A developing intestinal obstruction due to compression of the ileostomy between the two largest desmoids and compression of the ureter necessitated surgical treatment 4 months after the initial diagnosis. The ileostomy and 50 cm of the terminal ileum had to be resected together with the two large desmoids (proliferation rate of 5%). The smallest tumour in the mesentery was functionally unresectable. Nevertheless, the patient postoperatively suffered from short bowel syndrome with watery diarrhoea and loss of 6 kg body weight. Symptomatic therapy with loperamide and colestyramine as well as supplementation with high caloric drinks, vitamins and micronutrients led to stabilization of the nutritional status. However, 4 months after tumour debulking the remaining desmoid doubled its size (Figure 2B1).

Because of this tumour growth radiotherapy was indicated interdisciplinarily. After computerized tomography and a 3D-conformal planning procedure, the tumour region was treated applying a total dose of 45 Gy in daily single fractions of 1.8 Gy within 41 days using a box technique with 23-MV photon beams. Adjacent small bowel loops could not be spared technically, thus the dose was limited to 45 Gy. Acute side effects of radiotherapy consisted of hyperpigmentation and dry desquamation in the dorsal field, furthermore radiation enteritis with an acute decompensation of the previously compensated short bowel syndrome and acute renal failure with need for interim parenteral nutrition occurred.

Interestingly, the tumour's size progressively decreased over a 4-year period after radiotherapy (3.5 × 2 cm with only residual contrast enhancement in the
last MRI (Figure 2B2 and B3) under continuous anti-proliferative therapy. The nutritional status as well as the stool frequency stabilized over time.

Developmental aspects

The patient was born in 1979 as the second child of healthy and unrelated parents (27 and 30 years old). Her brother was born in 1970 and showed a normal development. The pregnancy was uneventful, and the patient was born by instrumentally assisted vaginal delivery. APGAR scores were recorded as 8/9/9, weight was 3170 g, and length was 50 cm. Although postnatal oedema completely disappeared over several weeks, muscular hypotonia persisted. A mild facial dysmorphism included low-set dysplastic ears, brachycephaly, relative prognathism, hypertelorism, high forehead, down-slanting palpebral fissures and drooping corners of the mouth (Figure 1A1 and A2). Additional dysmorphic features were a

Figure 1. Phenotypic characterization. (A) Photographs: Portrait of the patient at the age of 3 (A1) and 29 (A2) years. The mild facial dysmorphism includes low-set dysplastic ears, brachycephaly, relative prognathism, hypertelorism, high forehead, down-slanting palpebral fissures and drooping corners of the mouth. (B) Endoscopy: Colonoscopy identified mild colorectal polyposis (B1). Oesophagogastroduodenoscopy revealed many gastric fundic gland polyps (B2) as well as duodenal polyposis Spigelman grade II (B3).
clubfoot, congenital hip dysplasia and a crossed renal dystopia with fusion. Moreover, a statomotoric and ideomuscular retardation as well as mild mental retardation became evident. Physical development (height 174 cm) was unremarkable and there were no significant behavioural problems. The patient began to speak a few words at the age of 12 months. Some speech articulation difficulties have persisted until now. As child the patient was able to sit alone with 12 months and to run with 24 months. In conclusion, there was a slow, but steady progress in general development through intensive education. Mental development was more favourable than initially suspected so that the patient visited a special-needs school and learned to write and read. Actually she works in a sheltered workshop.

Genetics

The dysmorphic features and the developmental delay led to the suspicion of an unbalanced chromosomal aberration. After genetic counselling, conventional cytogenetic studies of the patient and her family were performed in 1981. The microscopic chromosome analysis (G-banding using trypsin and Giemsa) revealed the presence of a female karyotype (46XX) with shortening of the large dark band (5q14–5q23) in the middle portion of the long arm of one chromosome 5 (Figure 3A). The deletion could not be determined exactly with the existing methods in those days. Both parents and the healthy brother showed a normal karyotype so that a de novo interstitial 5q deletion was assumed.

When the patient presented again with colorectal polyposis several years later the deletion was re-evaluated using CGH. After DNA (deoxyribonucleic acid) extraction from peripheral blood lymphocytes, a CGH array using an Agilent 60k CGH chip on the Agilent Genomic Workbench 6.0 identified a loss of the genomic segment 5q21.3–5q23.3. The deletion minimally expands over a 20.21-Mb region spanning 64 genes (coordinates: (107111854_107206183)–(127742453_127795643); human genome freeze 18) including the APC gene.
In up to 30% of classic FAP patients, no mutation can be found using standard mutation screening methods. A large proportion (12–48%) of these patients with classical FAP but absence of dysmorphic features or mental retardation are affected from large submicroscopic APC deletions. In contrast to submicroscopic APC deletions, cytogenetically visible interstitial deletions of the middle portion of chromosome 5q are very rare. Most of these deletions are de novo alterations. So far, about 40 patients with interstitial 5q deletion syndrome have been reported, but molecular cytogenetic characterizations have only been performed in very few cases. To our knowledge, this is the third patient whose deletion has exactly been determined using a CGH array.

Based on the published reports a phenotypical differentiation into a proximal and a distal 5q deletion syndrome has been established. The proximal phenotype (5q15–5q22) is characterized by a mild mental retardation, slight dysmorphic features and further organ abnormalities such as horseshoe kidneys. Patients with distal 5q deletion (5q22–5q31) suffer from a severe developmental delay, severe mental handicap, failure to thrive and hypotonia. In addition, significant facial dysmorphism and variable organ abnormalities have been reported. However, phenotype-genotype correlations may be biased by poor characterization of the deleted segment in most of the previous reports because of the fact that the exact determination of breakpoints by conventional cytogenetic is difficult, in particular on chromosome 5q (three G-positive metaphase bands of almost equal size; 5q14, 5q21, 5q23). The patient reported here shows features of both, the proximal and the distal phenotype; consistent with this the deletion identified (5q21.3–5q23.3) encompasses the junction between the proximal and distal portion of chromosome 5q. Some other patients with deletions affecting this central region of chromosome 5q (5q21–5q23) have been reported. Similarities found in our patient as well as in at least one of the other patients are mild mental retardation and speech defect, hypotonia and psychomotor retardation. In line with our observations, facial dysmorphism was rather subtle.

So far, only 16 patients with FAP caused by large chromosome 5q deletions have been published. All but one of them had classical FAP. Moreover, 10 of 17 patients (including our patient) had extraintestinal manifestations belonging to the Gardner’s syndrome tumour spectrum. Desmoids were observed in only 4 of 17 patients. However, this frequency may be biased as some patients were not extensively worked-up.
and especially the post-colectomy follow-up period was relatively short. In conclusion, large 5q deletions encompassing APC may typically lead to the clinical picture of mild mental retardation and dysmorphism, classical but not diffuse adenomatous polyposis, and a high risk for extraintestinal manifestations, especially osteomas and soft tissue tumours.

Desmoid tumours are benign, monoclonal myofibroblastic neoplasms also called aggressive fibromatoses that grow slowly but infiltrative and thus can cause major complications by compression of tumour adjacent structures or massive bleeding.\(^1\)\(^,\)\(^8\) Although most of them arise sporadically, 10–15% of FAP patients have desmoids,\(^1\)\(^,\)\(^8\)\(^,\)\(^28\) with a predominant intra-abdominal localization most often in the small bowel mesentery.\(^8\)\(^,\)\(^28\)\(^,\)\(^29\)\(^,\)\(^30\) Significant risk factors for their development in FAP are an APC mutation 3’ of codon 1444, a positive family history and intra-abdominal surgery.\(^29\)

The treatment of desmoids is difficult as information from controlled clinical trials is lacking and tumours show a variable disease course.\(^8\) Watchful waiting with short-term follow-up may be acceptable in patients with stable and asymptomatic desmoids.\(^5\)\(^,\)\(^28\) Intra-abdominal desmoids or abdominal wall desmoids with direct contact to vital structures as seen in our case are a major therapeutic challenge and are associated with a high risk of tumour recurrence because of incomplete resection and significant morbidity.\(^8\)\(^,\)\(^28\)\(^,\)\(^30\) Thus, in FAP patients medical treatment strategies represent the first-line treatment option in most cases. The treatment regimens with non-steroidal anti-inflammatory drugs (celecoxib 200 mg b.i.d.) and anti-estrogens (tamoxifen 40 mg t.i.d.) started in our patient has recently been shown\(^31\) to result in tumour stabilization or regression in 50% of patients. Other systemic treatment options include tyrosine kinase inhibitors, such as imatinib or chemotherapy.\(^8\) In our patient, disease progression under medical therapy with an imminent ileus as life-threatening complication necessitated immediate surgery. Excessive growth of the remaining desmoid tumour after complete resection of two desmoids required further treatment.

An appropriate and effective treatment option for symptomatic desmoids is radiation therapy. A recent phase II EORTC-trial published by Keus et al.\(^32\) examining 41 patients with desmoids of the extremities and the trunk (dose 56 Gy in 28 fractions) showed a 3-year local control rate of >80%. The most frequent best local result during follow-up was stable disease in 41% followed by partial remission in 36% and complete remission in 14%. In our patient, radiation together with ongoing medical treatment led to slow but significant tumour regression over a 4-year period. Despite the low level of evidence, radiation therapy should be evaluated as reasonable therapeutic alternative in unresectable abdominal desmoids after failure of systemic treatment options although time to regression may be quite long.\(^28\)

As shown here, chromosome deletions are to be suspected in patients presenting with FAP together with mental handicap and mild dysmorphic features. This case also impressively shows that FAP-associated desmoids need multimodal treatment taking into account the patient’s individual symptoms, disease progression and tumour location.

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**References**


