

## CASE REPORT

# A case of myoepithelial carcinoma displaying biallelic inactivation of the tumour suppressor gene APC in a patient with familial adenomatous polyposis

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Familial adenomatous polyposis (FAP) is an autosomal dominant disorder caused by mutation of the APC gene. It is characterised by the appearance of hundreds to thousands of colorectal adenomas in adolescence and the subsequent development of colorectal cancer. Various extracolonic malignancies are associated with FAP, including desmoids and neoplasms of the stomach, duodenum, pancreas, liver, and brain. We present a family affected by FAP with an exon 14 APC mutation displaying two rare extracolonic lesions, a hepatoblastoma and a myoepithelial carcinoma. The hepatoblastoma was found in a male patient aged 2 years. The second lesion, a myoepithelial carcinoma of the right cheek, was found in a female patient aged 14 years. Inactivation of the normal APC allele was demonstrated in this lesion by loss of heterozygosity analysis, thus implicating APC in the initiation or progression of this neoplasm. This is the first reported case of this lesion in a family affected by FAP.

For individuals who inherit the colorectal cancer predisposition syndrome, familial adenomatous polyposis (FAP), prophylactic colectomy has reduced the risk of death from colorectal cancer. However, in addition to the multiple adenomas that develop within the colorectum of these patients, extracolonic tumours are frequent, and these present additional challenges for surveillance, prevention, and treatment.<sup>1</sup> The various tumours found in FAP include desmoids, upper gastrointestinal tract neoplasms, central nervous system neoplasms, osteomas, and epidermoid cysts. Hepatoblastoma, a rare embryonal tumour of infancy, has been reported in young, predominantly male patients with FAP at a frequency significantly higher than that seen in the general population.<sup>2</sup> In addition, young female patients with FAP may develop thyroid carcinomas.<sup>3</sup> Both lesions occur in the offspring of affected patients with FAP at a rate of 1%.

FAP is caused by germline mutation of the APC tumour suppressor gene. A previous report has documented the inactivation of both copies of APC within a hepatoblastoma occurring in a patient with FAP, thus implicating APC in the genesis of this extracolonic tumour.<sup>4</sup> In this report, we present a case of myoepithelial carcinoma occurring in a female patient with FAP aged 14 years. In this tumour both copies of APC were inactivated.

“Familial adenomatous polyposis is caused by germline mutation of the APC tumour suppressor gene”

### CASE REPORT AND INVESTIGATIONS

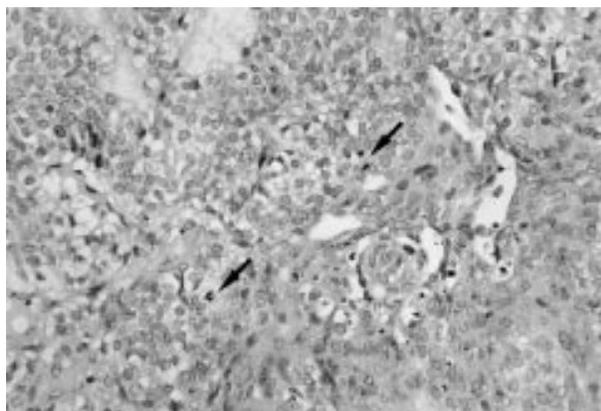
Family FP008 consists of 17 affected individuals spanning four generations with an average age of onset of polyposis of 21

years. The family phenotype is characterised by profuse polyposis, congenital hypertrophy of the retinal pigment epithelium, osteomas, and upper gastrointestinal tract neoplasms. In addition, two rare extracolonic lesions have occurred in this family, a hepatoblastoma and a myoepithelial carcinoma. The first lesion was seen in a male patient aged 2 years. This lesion was of fetal subtype with clear margins, and was removed by left hepatic lobectomy. The second extracolonic lesion, a myoepithelial carcinoma of the right cheek, was found in a female patient aged 14 years. This report implicates the APC tumour suppressor gene in the genesis of this lesion and is the first case report of such a lesion in a family with FAP.

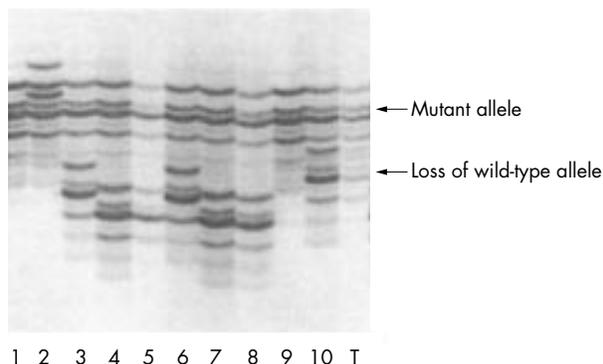
The specimen was received as a lesion of the right cheek and assumed to be an epidermoid cyst. It consisted of multiple fragments of cream and tan tissue measuring 30 × 24 × 14 mm. The largest of the fragments contained bright yellow foci. Microscopically, the tumour comprised compact nests and trabeculae separated by thin walled vessels and composed of round to oval shaped cells with eosinophilic to clear cytoplasm and indistinct cytoplasmic boundaries (fig 1). Nuclei were oval and vesicular, moderately pleomorphic, and contained the occasional small nucleolus. Apoptotic activity was conspicuous focally. Hyaline periodic acid Schiff positive material was present focally between the tumour nests. The mitotic rate was 21 mitoses/10 high power fields. No definite local invasion was seen but this was difficult to evaluate because of the extent of fragmentation. The tumour was positive for S100, smooth muscle actin, epithelial membrane antigen, and cytokeratin (CAM 5.2).

An inactivating mutation, 1751–1753 delC, in exon 14 of the APC gene, was previously detected in the germline of this family by the protein truncation assay, denaturing electrophoresis, and DNA sequencing. This mutation was found in the normal DNA of both individuals with the rare extracolonic lesions. DNA from the myoepithelioma was extracted from archival paraffin wax embedded tissue and loss of heterozygosity (LOH) analysis was performed using two polymorphic markers on chromosome 5q (D5S346 and MCC-CA), both of which are tightly linked to the APC locus. LOH in the myoepithelial tumour is shown in fig 2. A full haplotyping analysis using three APC intragenic and three tightly linked polymorphic markers had been included in the diagnostic procedures for this kindred. From the haplotyping analysis we were able to deduce that the wild-type allele had been lost from the tumour (fig 2).

**Abbreviations:** FAP, familial adenomatous polyposis; LOH, loss of heterozygosity



**Figure 1** High magnification of myoepithelial carcinoma showing clear to eosinophilic round to oval shaped cells in nests and separated by thin walled vascular channels. Two mitotic figures are present (arrows). Haematoxylin and eosin; original magnification,  $\times 400$ .



**Figure 2** Results of haplotype analysis on family F8 and loss of heterozygosity analysis on the myoepithelial tumour. DNA was amplified with primers for the microsatellite marker D5S346, which is inherited in the same linkage block as APC, and alleles were separated electrophoretically by size. Lanes 1–9 show germline DNA from clinically affected mutation carriers in family F8. Lane 10, reference normal tissue DNA; T, tumour DNA from the patient with the myoepithelial carcinoma. Note common allele in mutation carriers (top arrow). The lower arrow denotes the position of the wild-type allele in the normal tissue of the patient with myoepithelioma. A relative decrease in signal strength is seen in the corresponding position in the tumour (T), indicating loss of the normal allele in the myoepithelial carcinoma. Note that the wild-type allele varies in size in family members 2–8, and that members 1 and 9 are homozygotes.

## DISCUSSION

Malignant myoepithelioma is rare and accounts for less than 1% of all salivary gland tumours.<sup>3–6</sup> It occurs with the same frequency in both sexes. It arises from pre-existing benign lesions, such as pleomorphic adenomas and benign myoepitheliomas, but can also arise de novo. Four main histological variants of myoepithelioma are described, namely: spindle cell, plasmacytoid (hyaline), clear cell, and epithelioid. The neoplasm in our patient was classified as a myoepithelioma, clear to epithelioid cell type. Malignant myoepithelioma is distinguished from benign neoplasia on the basis of local

## Take home messages

- This is the first report of myoepithelial carcinoma occurring in a patient with familial adenomatous polyposis
- In this tumour both copies of APC were inactivated, implicating APC in the genesis of this extracolonic tumour

invasion, with cytological abnormalities serving as a guide to aggressive local behaviour, although metastases occur in up to 30% of cases.<sup>7</sup> In view of the cytological atypia, foci of tumour necrosis, and high mitotic count, our present case was regarded as malignant.<sup>6</sup> Myoepithelioma is described as having solid, myxoid, and reticular growth.<sup>8</sup> The tumour reported here was described as having a solid growth pattern. There were features of intracystic or intraluminal growth, which correlated with the surgeon's impression of a cystic tumour. The patient remains well two years after surgery.

Biallelic inactivation of APC in hepatoblastoma has been reported previously. However, the involvement of APC in myoepithelial carcinomas has not been examined. Molecular analyses of pleomorphic adenomas of the salivary glands have shown no significant involvement of sequences on chromosome 5q, with a single report of 17% LOH.<sup>9</sup> In our case, LOH was seen in the wild-type allele, thus demonstrating biallelic inactivation of APC, and implicating APC in the genesis of this lesion. The age of onset reported for myoepithelial carcinoma varies from 17 months to 81 years,<sup>5–6,10</sup> although the disease is essentially reported as one of persons over 50 years of age.<sup>8</sup> It is possible that a de novo mutation of APC may have been present in the cases reported in very young individuals. Such genetic events are common in FAP and would be unlikely to be excluded in the absence of a family history.

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## HISTORICAL PERSPECTIVES.....

### Seqenenre Taa II, the violent death of a pharaoh

A rude letter from Apophis, ruler of the Hyksos invaders, complaining about the snoring of the hippopotami in the sacred pool at Thebes<sup>1</sup> initiated the war that ultimately led to the restoration of the rule of the pharaohs in Egypt in the 16th century BC. Unfortunately, this war also led to the death of the addressee, Seqenenre Taa II, 14th pharaoh of the Theban dynasty.

Thirty four centuries later, the pharaoh's mummy has become the subject of forensic pathological interest and speculation. Found in 1881, it is in a badly damaged, disarticulated condition, but nevertheless shows remarkable details. Five different wounds to the head have been identified, including two perforating impression fractures of the frontotemporal region, severe blunt injury to the nose and right side of the face, and sharp injuries to the left cheek and below the left ear (fig 1).<sup>2</sup> Contrary to the embalming customs, the pharaoh's brain was left inside the skull, his heart was not replaced, and his limbs were not straightened into the usual position of a pharaoh's mummy, suggesting that he was hurriedly prepared for the afterlife.<sup>1</sup>

This, together with the massive head injuries, have led to the hypothesis that Seqenenre Taa II died on the battlefield, and several types of weaponry used in that period have been forwarded as possible agents of his destruction. For instance, the frontotemporal lesions may have been caused by axes, whereas the blunt injury to the nose and right face could result from the impact of a mace.<sup>1,3</sup> However, although these injuries are generally accepted as being the cause of his death, the precise chronology of their infliction remains a matter of debate.

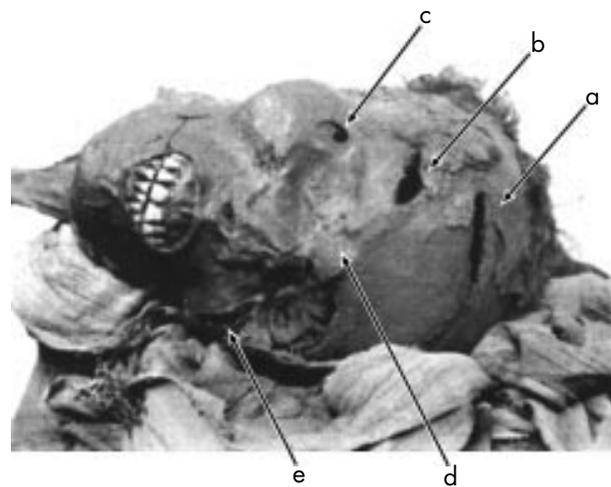
Radiological examination of the mummy showed that the fracture sides of the lower frontotemporal lesion are more radiolucent than those of the lesion above,<sup>4</sup> which might indicate active bone resorption, as seen in fracture healing.<sup>5</sup> It has therefore been hypothesised that the pharaoh initially survived the lower frontotemporal injury,<sup>4</sup> and some have gone so far as to suggest that he was finally assassinated on his sickbed, the other wounds being inflicted only then.<sup>2,6</sup>

Histological examination of the wounds might be helpful to estimate the age of the different injuries.<sup>3</sup> However, the age of Seqenenre's body and the mummification treatment it received (the exact nature of which is unknown to us, in this case) may be expected to influence the findings. Indeed, as discussed by Bockenheimer *et al*, the difference in radiolucency of the fractures could be caused by artificial bone dissolution, as a result of the use of embalming fluids.<sup>4</sup>

In our opinion, the case of Pharaoh Seqenenre Taa II demonstrates the importance of extensive and adequate clinical data. Until the discovery of an eyewitness's report, the precise circumstances of his death remain to be elucidated.

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**Figure 1** The head of Seqenenre Taa II, showing multiple injuries.<sup>2</sup> (a) A horizontal cut in the frontal bone, measuring approximately 63 mm. (b) A gaping frontotemporal wound, 31 mm long. (c) This perforation above the right jaw was caused by dislocation of the malar bones, which in its turn was caused by (d) blunt injury with fracture of the nasal bones and destruction of the right orbita. (e) An edged tool cut through the skin of the left cheek. Not visible in this picture is a sharp injury inflicted immediately below the left ear.

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