

Multifocal squamous cell carcinoma of the oesophagus following radiotherapy for bilateral breast carcinoma

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Abstract

A 60 year old woman who presented with dysphagia and weight loss was found to have multiple foci of dysplasia and in situ and invasive squamous cell carcinoma scattered along the whole length of the oesophagus, with intervening areas of normal mucosa. The patient had a history of two breast carcinomas 19 and one year previously for which she had repeated radiotherapy. Several members of the patient's close family had histories of malignant disease. All oesophageal lesions and the more recent breast cancer showed positive immunostaining for p53 protein. p53 mutations, some involving different exons, were also detected in these lesions. No p53 immunostaining or mutations were detected in the normal oesophageal mucosa. The findings suggest an independent origin of the multiple dysplastic and neoplastic foci, which might have developed in a background of a field change, possibly related to the previous radiotherapy. The strong family history of malignant diseases raises the possibility that, in addition, genetic factors might have played a role in the development of the oesophageal disease.

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A recent American population based, retrospective, cohort study has shown an increased risk of developing oesophageal carcinoma in women with breast cancer who received radiotherapy and were followed up for 10 or more years.¹ The risk for squamous cell carcinoma was 5.42 and that for adenocarcinoma was 4.22. No increased risk was seen in patients with breast carcinoma who did not have radiotherapy. In another recent study from France, four patients (three females and one male) developed squamous cell carcinoma of the oesophagus seven to nine years after receiving radiotherapy for breast cancer.² None of the cancers in these two studies was reported as being multifocal. Here, we report a case of multifocal squamous cell carcinoma of the oesophagus in a patient who had bilateral breast carcinomas 19 and one year previously, which were treated on both occasions with postoperative radiotherapy.

Case report

A 60 year old British woman presented with a two and a half month history of progressively worsening dysphagia and weight loss. Barium swallow showed oesophageal narrowing with mucosal irregularity at the level of C7/T1. Subsequent oesophagoscopy and biopsy confirmed a diagnosis of oesophageal carcinoma. The patient was a non-smoker and had no history of alcohol intake.

Past history included an anaplastic carcinoma of the left breast 19 years before (1979), which was treated with simple mastectomy and axillary clearance. A year later, the patient presented with an axillary recurrence, for which she was given radiotherapy to the left chest wall, axilla, and internal mammary chain: 5000 rads were given in five fractions, plus an extra 750 rads in three fractions to the axilla. The patient also received chemotherapy in the form of 5FU, cyclophosphamide, and methotrexate, eight cycles intravenously, then four cycles orally. The treatment was stopped at that stage because the patient could not tolerate the side effects. Two years later (1982), the patient developed two basal cell carcinomas on the forehead and chin, which were also treated with radiotherapy, and for which no more data are available. Fifteen years later (1997), the patient developed an invasive carcinoma of the right breast. This was treated with wide local excision, after wire localisation, and axillary clearance. The breast tumour was a grade 3 invasive ductal carcinoma, 8 mm in diameter, associated with high grade ductal carcinoma in situ. The tumour was oestrogen and progesterone receptor negative, and p53 positive, as assessed immunohistochemically. No lymphovascular invasion was present, and all the lymph nodes dissected from the axilla were free of tumour. Postoperative radiotherapy was then given to the right breast in the form of 50 Gy in 25 fractions over six weeks, including a breast boost of 10 Gy in five fractions over four weeks.

Several members of the patient's family had histories of malignant disease. Her mother died from colonic cancer at the age of 72, a maternal aunt died from leukaemia at the age of 32, a brother died aged 42 with multiple intra-abdominal and liver metastases with no identified primary, and a sister died aged 52 with ovarian cancer after having colonic cancer diagnosed nine years earlier. The patient also had a niece diagnosed with breast cancer at the age of 37 for which she had surgery, radiotherapy, and chemotherapy. Now aged 40, she

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shows no evidence of recurrence. No genetic studies have been done.

Bone scan and thoraco-abdominal computed tomography showed no evidence of extra-oesophageal extension of the tumour or distant metastases. A trans-hiatal oesophagectomy was thus carried out.

The specimen received at the histopathology laboratory consisted of a piece of oesophagus 9.5 cm in length, with a 3 mm grossly irregular area seen in the mucosa, 3 cm away from one of the resection margins. This area was sampled for microscopic examination, and several random sections were taken from the rest of the specimen.

Microscopically, sections from the grossly abnormal area showed a poorly differentiated squamous cell carcinoma infiltrating the mucosa and superficial part of the submucosa. All the random sections, in addition to further sections taken later, showed small scattered foci of variable degrees of dysplasia, some amounting to squamous cell carcinoma in situ, as well as two further foci of superficially invasive squamous cell carcinoma, the larger measuring 4 mm in maximum dimension. However, both resection margins were free of dysplasia and malignancy. No viral inclusions were seen in the normal or abnormal mucosa.

Four months later, the patient developed a local recurrence and died shortly afterwards.

Immunoperoxidase stains for p53 using the monoclonal antibody DO-7 (Novocastra, Newcastle, UK) showed strong nuclear positive staining of all the malignant and dysplastic epithelium (fig 1).

Several tumour foci, in addition to areas of epithelium of normal appearance, were microdissected from dewaxed paraffin wax embedded sections using a 22 gauge needle. Tissue was digested in a proteinase K containing buffer and DNA was extracted. p53 genomic sequences spanning exons 5, 6, 7, and 8/9 were amplified using the polymerase chain reaction (PCR). By means of additional 5' T7 promoter sequences on the primers, RNA was transcribed from the p53 PCR products, hybridised to RNA similarly synthesised from wild-type DNA, and subjected to RNase digestion. Mutations were indicated by the detection of RNase cleavage products observed on agarose gel electrophoresis. This procedure was performed using the Mismatch Detect system from Ambion Inc (Austin, Texas, USA), according to the manufacturer's instructions.

The most recently occurring breast carcinoma showed p53 mutations in the fragments containing exons 7 and 8/9. No tissue was available from the first breast carcinoma for analysis. One of the original oesophageal invasive squamous cell carcinomas showed mutations involving exons 5 and 8/9, whereas two other invasive foci showed mutations in the exon 8/9 fragment. No mutations were seen in four different sections of normal oesophageal mucosa taken from areas distant to cancer foci. The recurrent oesophageal carcinoma showed mutations in fragments including exons 7 and 8/9. Not enough DNA could be obtained for analysis from the small foci of dysplasia.



Figure 1 Positive p53 immunostaining of a focus of primary invasive squamous cell carcinoma (thick arrow), as well as scattered small foci of dysplasia (thin arrows). Note intervening p53 negative, non-stained, normal mucosa. Immunoperoxidase stain; original magnification, $\times 16$.

Discussion

This case is unusual in two respects: the multifocality of the disease and the presence of a strong family history of malignancy. Multifocal superficial oesophageal carcinoma seems to be relatively more commonly encountered in Japan,³ although a few cases have been reported from France⁴ and the USA.⁵ In this respect, it is interesting to note that multifocal accumulation of p53 protein has been reported recently in the oesophagus in carcinomas from Chinese patients.⁶ To the best of our knowledge, multifocal superficial oesophageal carcinoma and accumulation of p53 protein have not been reported previously in association with postoperative radiotherapy for breast carcinoma.

We have also confirmed the presence of p53 gene mutations in the breast carcinoma available for examination, in addition to three primary oesophageal cancers and the recurrent tumour. However, although a mutation in exon 8/9 was common to all the invasive lesions, an exon 5 mutation was present in one of the primary invasive foci, and an exon 7 mutation was found in the recurrence. These differences suggest an independent origin for some of these lesions. The microscopically uninvolved mucosa in between the lesions was p53 immunohistologically negative (fig 1), and no p53 mutations were detected in four sections of normal oesophageal mucosa. This makes a p53 germline mutation unlikely.

The findings raise the possibility of a field change that may be, at least in part, related to

the previous irradiation, but which was associated with the development of scattered independent foci of dysplasia and neoplasia separated by normal mucosa. The strong family history of malignant diseases in close relatives of this patient suggests the presence of other (in this case genetic) confounding factor(s), which might have been contributory to the development of the disease.

1 Ahsan H, Neugut AI. Radiation therapy for breast cancer and increased risk of esophageal carcinoma. *Ann Intern Med* 1998;128:114-17.

2 Perrier G, Teniere P, Graoc Y, *et al.* Squamous cell carcinoma of the thoracic esophagus following radiation therapy for breast cancer. *Hepatogastroenterology* 1998;45:2197-201.

3 Kuwano H, Morita M, Matsuda H, *et al.* Histopathologic findings of minute foci of squamous cell carcinoma in the human esophagus. *Cancer* 1991;68:2617-20.

4 Bogomoletz WV, Molas G, Gayet B, *et al.* Superficial squamous cell carcinoma of the esophagus. A report of 76 cases and review of the literature. *Am J Surg Pathol* 1989;13:535-46.

5 Schmidt LW, Dean PJ, Wilson RT. Superficially invasive squamous cell carcinoma of the esophagus. A study of seven cases in Memphis, Tennessee. *Gastroenterology* 1986;91:1456-61.

6 Tian D, Feng Z, Hanley NM, *et al.* Multifocal accumulation of p53 protein in esophageal carcinoma: evidence for field cancerization. *Int J Cancer* 1998;78:568-75.

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