Multiple Primary Carcinomata: Clinical and Genetic Management

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INTRODUCTION

We report a patient who developed seven different primary carcinomas over a 21 year period. Although patients with multiple cancers are uncommon, their recognition is important in that a satisfactory clinical outcome is feasible. Furthermore it is important in that a satisfactory clinical outcome is feasible. Furthermore it is important that an inherited condition is excluded so as to avoid overlooking the possibility of offering subsequent generations appropriate genetic counselling and screening.

CASE REPORT

A 39 year old woman presented with painless haematuria with cystoscopy demonstrating a papilliferous lesion at the right ureteric orifice. Histologically this was a well differentiated transitional cell carcinoma and she required four endoscopic resections before she remained disease free. Eight years later cervical cytology for post coital vaginal bleeding revealed invasive malignancy and she was treated by hysterectomy and bilateral salpingo-oophorectomy for a well differentiated carcinoma of the uterine body. Three years later a barium enema, performed whilst investigating an iron deficient anaemia (Hb 7.8 gm/dl) demonstrated a malignant stricture which was staged as Dukes' B. A further four years elapsed until she presented with a painless breast lump which was treated by a Patey mastectomy as frozen section histology showed invasive carcinoma. Urological symptoms recurred two years later when she presented with further haematuria and clot colic. Subsequent investigations demonstrated a large filling defect in the left renal pelvis and she underwent a nephroureterectomy. Histological examination revealed a moderately differentiated transitional cell tumour. Four years later she had a further recurrence of her rectal bleeding and a barium enema revealed metachronous cancers in the proximal descending and sigmoid colon (figure). Her previous right hemicolectomy was therefore converted to an ileo-rectal anastomosis. Both tumours were Dukes' stage B. To date (1994) she remains well without
evidence of further recurrence or metastatic disease.

DISCUSSION

By definition multiple primary cancers arise in different tissues and can be distinguished histologically. Second primary cancers are not uncommon (metachronous cancers) and each need to be treated in their own right. Such metachronous lesions need also to be distinguished from synchronous cancers, which when ‘missed’, might be inadvertently described as metachronous. In premenopausal women, for example, about 1% of second cancers are synchronous and 5% metachronous. In patients undergoing endoscopic surveillance after curative surgery for colorectal malignancy metachronous neoplasm is common with about a 4% incidence of cancer at 25 years.

This patient developed her first tumour at an early age; indeed this is one hallmark of a genetic predisposition to malignancy. Moreover at that time, and indeed to date there is no relevant family history to suggest that she has a genetic defect. However she subsequently developed numerous different cancers which is highly suggestive that she has a germline (inherited as opposed to acquired) mutation in a gene that somehow is involved in cellular control mechanisms. Such genes are broadly divided into those which lead to malignancy when they are mutated or ‘turned on’ and those which can allow malignancy to develop when they are ‘switched-off’, again by mutations or deletions. These are termed oncogenes and tumour-suppressor genes respectively.

Figure 1.  Endoscopic examination demonstrating two metachronous colorectal cancers (the more proximal is arrowed).
One of the most extensively studied tumour suppressor genes is the p53 gene which is found on chromosome 17p. Recent evidence\textsuperscript{1} has shown that germline mutations in this gene give rise to the Li - Fraumeni syndrome which is characterised by a high incidence of sarcomas and multiple types of epithelial cancers. Indeed subsequent molecular analysis of many different tumours (brain, breast, liver, colon, lung etc.) has shown that the p53 gene is probably the most widely mutated gene in human cancer.\textsuperscript{2} Furthermore point mutations in this gene appear to occur predominantly in evolutionarily conserved codons suggesting that the p53 gene has a vital role in the control of cell growth.\textsuperscript{2}

More important than the above syndrome is that of the Lynch syndrome (I & II). Indeed these may account for approximately 5% of all colorectal cancers.\textsuperscript{3} Lynch type I syndrome is often referred to as Hereditary site specific colorectal cancer syndrome and is characterised by a predominance of colorectal cancer. In the Cancer Family syndrome or the Lynch type II syndrome there are certain classical features including an increased incidence of adenocarcinomas, particularly of the colon and endometrium but also breast. Other features of the syndrome include an increased frequency of multiple cancers, an early age of onset (mean age 40 years) and an autosomal dominant pattern of inheritance. With respect to the large bowel there are a number of similarities between the two Lynch syndromes including a predominance of right sided lesions (50%) and a higher incidence of synchronous and metachronous cancers. In one series of 122 patients with the cancer family syndrome, 7 patients (6%) had multiple synchronous colorectal cancers and in 29 patients (24%) there were a total of 42 metachronous colorectal cancers.\textsuperscript{4} More importantly at ten years follow-up, the cumulative risk of a second or third colorectal cancer was 21% and 53% respectively. The diagnosis of cancer family syndrome is dependent upon taking a detailed family history and recognising the above features. It is only by this method that high-risk candidates for surveillance can be identified.\textsuperscript{5} Because of the high cancer mortality attendant to this syndrome both early detection and appropriate surgical management are essential. It has been suggested that family members in the direct genetic line should be offered prophylactic colectomy and ileo-rectal anastomosis (IRA) and that women whose families are complete undergo prophylactic hysterectomy.\textsuperscript{6} However, intensive surveillance by screening may be adequate and certainly mandatory when family members at risk have been identified. At the St Mark's Hospital family cancer clinic in London women from families with pedigrees compatible with the cancer family syndrome are offered screening for breast, uterine and ovarian cancers starting at 25 years of age.\textsuperscript{6} Such aggressive screening programmes would seem justified when the risk of dying from various cancers in these families is appreciated. Ioh et al\textsuperscript{7} estimated that the risk of colorectal cancer in affected members of such families was increased seven-fold and for ovarian, uterine and breast cancers the relative risks (observed to expected ratio) were 3.4 and 5 respectively.

Whilst we are uncertain, our patient appears to exhibit all the clinical features of the cancer family syndrome. One question is however intriguing. Why does she not have a strong or even positive family history? The reason is probably that she represents a new mutation and it is only when her offspring and descendents are adequately followed will the answer be clear. Finally the genetics of the Lynch type II syndrome has recently become clearer with Pelatma\textsuperscript{8} providing the first evidence that a gene on chromosome 2p is responsible for the syndrome which has both clinical and genetic heterogeneity.\textsuperscript{8,9} A second locus on chromosome 3p has just been described\textsuperscript{10} and it is likely that there are other loci still to be identified. In the future those individuals at risk because of an inherited predisposition to cancer might be easily identified by a simple blood test and offered either gene therapy or prophylactic surgical intervention.

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REFERENCES


