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Detection of *BCL-2* RNA in Low Grade Tumours of the Urinary Bladder

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THE MAINTENANCE of homeostasis in normal tissues can be considered a balance between cell proliferation and cell death; thus any condition that alters these parameters may contribute to tumour development. While most oncogenes are believed to influence the cellular proliferation rate or differentiation, *BCL-2* overexpression suppresses the active cell death process referred to as apoptosis [1].

BCL-2 proto-oncogene, originally described at the breakpoint site of the chromosomal translocation t(14;18) in a follicular lymphoma [2], is now known to be involved in a variety of haemopoietic [3] and solid tumours [4, 5], where its presence is often associated with chemotherapy resistance [6]. Despite its association with some forms of human cancer, a number of normal tissues examined by immunohistochemistry have been shown to lack *BCL-2*; these include lung, liver, heart, cervix, ovary, testis, kidney and bladder [7].

Bladder cancer is the fifth common cancer in men in the Western society, being responsible for 5% of all cancer deaths. The 5 year survival rate is highly dependent on the pathological stage, and ranges from 10% for patients with pT4 tumours to 70% for those with pT2. In recent years, molecular studies have concentrated on the identification of 'initiating' factors and markers for disease progression, with a view to early diagnosis and follow-up of patients with low grade disease [8].

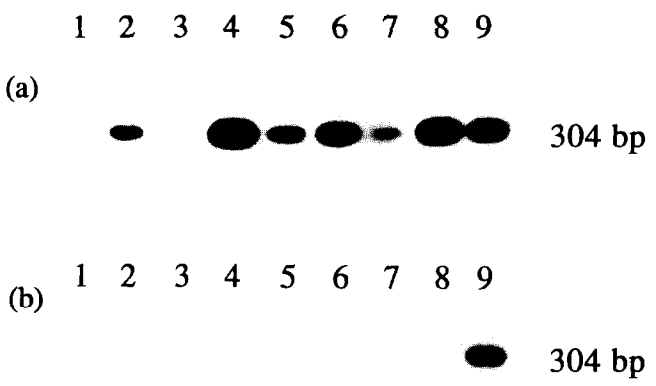

Figure 1. Autoradiography of RT-PCR products blotted and hybridised with a ^{32}P oligonucleotide probe specific for *BCL-2*. (a) Lane 1: negative control for *BCL-2* expression (HeLa cell line); lanes 2–8: urinary bladder tumour tissue; lane 9: positive control for *BCL-2* expression (CaSki cell line). (b) Lanes 1 and 9: the same as in (a); lanes 2–8: adjacent normal tissues corresponding to samples 2–8 shown in (a).

In order to better investigate the role of *BCL-2* in the very early stage of the disease, we analysed by RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction) 30 low grade tumours from the urinary bladder (Ta, Tis, T1 and T2) and normal adjacent bladder tissue. While we found the expression of *BCL-2* at the RNA level in 19/30 (63%) of the tumour samples, no expression was detected in any normal tissue (Figure 1). To our knowledge, this is the first report of *BCL-2* expression in urinary bladder tumours.

BCL-2 is known to block programmed cell death, giving the cells that overexpress the protein a survival advantage over normal cells. Thus, the expression of *BCL-2* in low grade bladder tumours and its absence in adjacent normal tissue may suggest its possible implication in the initiation of the multistep process of bladder carcinogenesis. Alternatively, the finding that not all the low grade lesions examined expressed *BCL-2* at the RNA level suggests a possible role of this gene in the more rapid evolution, observed in some types of bladder cancer, toward metastatic growth and invasion.

In conclusion, *BCL-2*-expressing tumours may have different clinical behaviour in comparison with those that do not, as previously described for prostate tumours and other neoplasms, where the overexpression of this gene has been often correlated to chemotherapy resistance, poor prognosis, and decreased survival of the patients. This would be of some importance in the screening of low grade bladder cancer and in the follow-up of the post-TUR (transurethral resection) patients.

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Malignant Teratoma Undifferentiated (MTU) Metastasising Solely as Differentiated Teratoma: Implications for the Aetiology of Residual Differentiated Disease Following Successful Chemotherapy

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FOLLOWING SUCCESSFUL chemotherapy for metastatic teratoma, up to 15% of patients demonstrate residual disease which should then be surgically excised. Differentiated teratoma is found in approximately 40–45% of these patients [1]. We report the first case of undifferentiated teratoma metastasising solely as differentiated teratoma in a patient who had received no treatment following orchidectomy, and discuss the implications for the aetiology of residual differentiated disease.

A 40-year-old patient underwent a right inguinal orchidectomy. Histology revealed undifferentiated tumour with yolk sac elements classified as malignant teratoma undifferentiated (MTU). Postoperatively, staging diagnosed stage I disease and he was placed on a surveillance programme with no chemotherapy.

Eighteen months into surveillance, an abdominal computed tomography (CT) scan demonstrated enlarged para aortic nodes, 2 cm in diameter, anterior to the left psoas at the level of the renal hilum. These had not been present on the postoperative staging scan. Chest CT scan and serum markers were normal. The nodes were radiologically unchanged 2 months later and so were excised for definitive diagnosis.

Histology of the nodes demonstrated multilocular structures surrounded by muscle, lined by intestinal epithelium with goblet cells and argentaffin cells, and ciliated epithelium. The features were consistent with deposits of mature teratoma showing enhanced differentiation, with no evidence of malignancy or atypia.

The patient was unwilling to accept further surveillance. As he had demonstrated metastatic disease (although differentiated) and a complete para aortic node dissection had not been performed, he received three cycles of bleomycin, etoposide and cisplatinum chemotherapy. He remains well and disease-free 3.5 years later.

Mature teratoma has been reported up to 7 years following complete remission, induced by chemotherapy and surgery [2, 3], and may subsequently undergo malignant transformation [4]. A number of hypotheses have been proposed to explain the finding of metastatic differentiated teratoma.

Therapy-induced differentiation

This is also reported in other tumours, including neuroblastoma, ovarian teratomas and cystadenocarcinomas. *In vitro* exposure of germ cell lines to agents, including retinoic acid, methotrexate and interferon-β, may induce differentiation, and in some instances the exact route of differentation is dependent on either concentration of the agent or growth characteristics of the cell line. However, recent animal and clinical evidence does not support this *in vivo* [5].

Spontaneous differentiation

Pugh and Cameron [6] described patients with differentiated testicular teratoma subsequently developing metastatic disease. This may represent either sampling failure of the primary tumour, or spontaneous differentiation of the primary lesion.

Metastasis of mature teratoma

Anecdotal reports of mature teratoma in both primary tumour and metastases appear. Synchronous spontaneous differentiation may have occurred or the primary may have contained atypical elements, with metastatic potential [7]. Smithers [8] described differentiated metastases in patients, but details of prior treatment are not clear. Snyder [9] reported a pulmonary deposit of mature teratoma from a patient with MTU and metastatic testicular trophoblastic (MTT), although other metastases had been irradiated or resected.

Overgrowth of chemo- or radio-insensitive mature teratoma

Here, differentiated elements are thought to be resistant to chemotherapy and radiotherapy and may even increase in size during systemic therapy, the so called "growing teratoma" syndrome [10]. This is supported by animal data demonstrating that therapy destroys metastatic malignant clones, leaving residual mature elements which have co-metastasised.

This case confirms that purely differentiated teratoma can metastasise from tumour within the testis. Mature elements in residual disease, resected following chemotherapy, may thus represent chemoresistant metastasised differentiated clones, and need not be due to any differentiating effect of chemotherapy. Metastatic differentiated disease should always be considered in either spontaneous regression or unexplained progression of metastatic disease.

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