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Analysis of Bcl-2 and p53 protein expression in non-Hodgkin’s lymphoma

The growth of the lymphoid cells is regulated by a delicate balance between molecules controlling cell survival and cell death. The Bcl-2 gene product is an anti-apoptotic molecule that modulates the mitochondrial release of cytochrome c, and the interaction of Apoptosis activating factors with caspase 9 and Bax (Bcl-2 associated X protein). p53 is a tumor suppressor gene that maintains genomic stability either by inducing cell cycle arrest or apoptosis. Although some studies examined p53 and bcl-2 protein expression in non-Hodgkin’s lymphoma (NHL), side-by-side analysis of these proteins in the different grades of NHL is still lacking [1–3].

To address this issue, formalin-fixed, paraffin-embedded tissue specimens representing 47 cases of NHL were obtained from the Departments of Pathology, Assuit University Hospitals. Immunohistochemical evaluation was carried out using immunoperoxidase staining methods and mouse monoclonal antibodies (clones 124, IgG1, kappa, and DO1 for Bcl-2 and p53, respectively; DAKO Corporation, Denmark). Additional sections, running in parallel but with omission of the primary antibodies, served as the negative controls. The positive controls consisted of lymph nodes with reactive hyperplasia (for bcl-2) and squamous cell carcinoma (for p53). The percentages of positive cells (PP%) of p53 (nuclear staining) and bcl-2 (cytoplasmic staining) protein expression, apoptotic (AI) and mitotic (MI) indices were evaluated [4].

Figure 1. Gradual upregulation of p53 (square), and downregulation of Bcl-2 protein expression (diamond) with the transition from low to intermediate to high grade non-Hodgkin’s lymphoma. Also both apoptotic (triangle) and mitotic (cross) indices showed upregulation with these transitions.

Our results revealed gradual down-regulation of bcl-2 staining values with the transition from low to intermediate- to high-grade NHL (87.7 ± 4.9 > 72.60 ± 3.4 > 66.1 ± 3.3, P = 0.041). This down-regulation may be due to (i) up-regulation of bcl-2 antagonists, i.e. p53 protein, (ii) another prosurvival molecule rather than Bcl-2 protein takes over its role and (iii) epigenetic mechanisms such as Bcl-2 promoter hypermethylation [5]. Alternatively, the p53 staining values showed gradual up-regulation with the transition from low to intermediate- to high-grade NHL (6.50 ± 3.4 < 12.8 ± 4.8 < 18.5 ± 5.1, P = 0.023). This up-regulation may be due to the presence of p53 gene mutations that stabilize the mutant p53 protein, and increase its half-life leading to its accumulation in the cells [3]. The negative correlation between bcl-2 and p53 protein expression in NHL (r = −0.221, P = 0.165) suggests that the former is negatively regulated by the latter (Figure 1).

The increase in the AI and MI with the transition from low (2.60 ± 0.4 and 2.0 ± 0.3) → intermediate (5.2 ± 0.5 and 5.1 ± 0.5) → high (7.1 ± 0.6 and 6.9 ± 0.4) grade NHL is in agreement with previous studies [1–3] (Figure 1). The increased MI may be due to inactivation of p53 gene → loss of its inhibitory effects on its downstream effector genes → promotion of cell cycle progression and cellular proliferation. Alternatively, the increased AI may be due to (i) down-regulation of bcl-2 and (ii) induction of p53 independent apoptosis due to activation of another oncogene such as c-Myc that takes over the role of inactivated p53 in apoptosis [1].

In summary, our study proposes that altered bcl-2 and p53 protein expression is involved in lymphomagenesis.

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CDX-2 should be included in the work-up of patients with lung metastases from unknown primary

Two Cdx homeobox genes have been identified so far in humans [1, 2]. CDX-2 is the product of the Cdx-2 homeobox gene and is expressed in normal colonic epithelia and most colorectal adenocarcinomas. Lung and pleural neoplastic lesions require the distinction between primary and metastatic malignancy when occurring alone. Colorectal carcinoma (CRC) must be included in the differential diagnosis as it is one of the most frequent neoplasms giving rise to metastases to the lung. We describe two clinical cases in which CDX-2 was of primary importance to define the colonic origin.

A 63-year-old man with a symptomatic right pleural effusion underwent thoracic computed tomography (CT) scan that described an ipsilateral pleural thickening, without adenopathies and lung lesions. Several cytological examinations of the sputum were negative. Total-body FDG PET scan showed right basal pleural uptake alone. Thoracoscopy revealed multiple small nodular localizations in the right pleura and lung. The pleural expository histologic examination indicated a mesothelioma, whereas the definitive one reported an adenocarcinoma. TTF-1 expression was negative and CK20 positive. CDX-2 positivity prompted us to carry out a colonoscopy which showed a right colon neoplasia, histologically typified as adenocarcinoma. FOLFIRI regimen was proposed.

An asymptomatic 54-year-old man with a neoplastic lesion in the lower lobe of the left lung, casually detected with a routine chest X-ray, underwent a total-body CT scan that did not show any other signs of neoplasia. Fine-needle aspiration biopsy of the lesion was positive for adenocarcinoma. Since the pathologist could not be sure about the lung origin on the basis of morphologic examination alone, the patient underwent gastroscopy and colonoscopy, which showed an ulcer in the antrum and an infiltrating lesion in the right colon, respectively. Histologically both lesions were adenocarcinomas. Though the origin of the lung lesion was not definable with certainty, the patient firstly underwent lung lobectomy and then subtotal gastrectomy and concurrent right hemicolectomy. Histology was (i) lung metastasis of digestive tract adenocarcinoma, CDX-2 positive and TTF-1 negative, pN0, (ii) gastric adenocarcinoma of intestinal type, G2 pT1 pN0, and (iii) colic adenocarcinoma, G2 pT3 pN0, respectively. Colon-oriented chemotherapy was proposed.

Histologic features are often inadequate to distinguish between primary and metastatic lung malignancies. Some immunohistochemistry patterns could be useful. At present, only thyroid transcription factor-1 (TTF-1) for lung origin, and cytokeratin 7 and 20 (CK7/CK20) co-expression pattern for colonic origin are available. Nevertheless, TTF-1 is expressed in most but not all lung adenocarcinomas, its sensitivity being reported to be low in some subgroups of pulmonary mucinous adenocarcinomas and in mucinous bronchioloalveolar carcinomas [3]. Moreover, although characteristic for colorectal origin, the CK7−/CK20+ profile is not 100% specific [4], whereas CDX-2 is highly specific. It has been reported to identify all cases of colorectal metastases to the lung, without any false-negatives or false-positives [5]. Therefore, it is a reliable, specific and sensitive immunohistochemical marker of the neoplastic intestinal epithelium, and it can be easily applied to routine histological and cytological material. Our experience prompted us to recommend that CDX-2 should be included in the work-up of lung and/or pleural neoplastic lesions of undefined origin, as it could guide the therapeutic plan.

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