and mitotic (MI) indices were evaluated [4]. bcl-2 (cytoplasmic staining) protein expression, apoptotic (AI) tags of positive cells (PP%) of p53 (nuclear staining) and bcl-2) and squamous cell carcinoma (for p53). The percen-
trals consisted of lymph nodes with reactive hyperplasia (for antibodies, served as the negative controls. The positive con-
trasts, running in parallel but with omission of the primary
body (clones 124, IgG1, kappa, and DO1 for Bcl-2 and p53,
noperoxidase staining methods and mouse monoclonal anti-
mmunohistochemical evaluation was carried out using immu-
the Departments of Pathology, Assuit University Hospitals.
To address this issue, formalin-fixed, paraffin-embedded tissue
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-regu-
lation with the transition from low to intermediate to high-
grade NHL (6.50 ± 3.1 < 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 nega-
tive correlation between bcl-2 and p53 protein expression in
NHL (r = −0.221, P = 0.165) suggests that the former is nega-
tively 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-regu-
lation 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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References
treated for Hodgkin’s disease: a report from the German Hodgkin
2. Hamajima N, Hirose K, Tajima K et al. Alcohol, tobacco and breast
cancer—collaborative reanalysis of individual data from 53 epidemi-
ological studies, including 58,515 women with breast cancer and
95,067 women without the disease. Br J Cancer 2002; 86:
1234–1245.
tobacco related cancers. In De Vita VT Jr, Hellman S, Rosenberg SA
(eds): Cancer: Principles and Practice of Oncology, 6th edition. Phila-
140: 603–613.
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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 suppres-
sor 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 immu-
noperoxidase staining methods and mouse monoclonal anti-
bodies (clones 124, IgG1, kappa, and DO1 for Bcl-2 and p53,
respectively; DAKO Corporation, Denmark). Additional sec-
tions, running in parallel but with omission of the primary
antibodies, served as the negative controls. The positive con-
trols consisted of lymph nodes with reactive hyperplasia (for
bcl-2) and squamous cell carcinoma (for p53). The percen-
tages of positive cells (PP%) of p53 (nuclear staining) and
bcl-2 (cytoplasmic staining) protein expression, apoptotic (AI)
and mitotic (MI) indices were evaluated [4].

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References
1. Du M, Singh N, Huseinein A, Isaacson PG et al. Positive correla-
tion between apoptotic and proliferative indices in gastrointestinal
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 extemporaneous 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 typed as adenocarcinoma. FOLFIRO 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 bronchioalveolar 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.

References


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