Chapter 14

Laboratory for Patients at Risk of Multiple Primary Malignancies

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Introduction

Biomarkers are a useful laboratory diagnostic approach for the non-invasive early detection of disease and recurrent disease. An ideal tumor marker is a protein or protein fragment that can be easily detected in the patient’s blood or urine, but is not detectable in healthy people. The first of such biomarkers to be used in laboratory testing was carcinoembryonic antigen (CEA), introduced in 1965. Other biomarkers currently in use are CA 19-9 (gastrointestinal tumors), CA125 (ovarian cancer), Ca 15-3 (breast cancer). However, while the levels are very low in healthy people they become substantially elevated only when a considerable amount of cancer is present. Moreover, these markers are for the most part not specific for a single tumor. Women with breast cancer or gynecological disease may have elevated CEA and CA 125. Another cancer biomarker, and perhaps the best known one, is prostate-specific antigen (PSA), which allows for the early detection of prostate disease. The serum PSA test is used in screening programs for prostate cancer and has brought about a dramatic increase in early detection of the disease. Nonetheless, for most cancers biomarkers with high specificity and sensibility are lacking, which limits our ability to screen the majority of tumors. PSA, for example, is very sensitive but has low specificity. It remains the only tumor biomarker certified by the US Food and Drug Administration for widespread screening, which is carried out along with digital rectal examination. Technological advances in genomic and proteomics have produced candidate markers with screening potential. Most biomarkers are used in follow-up evaluation; these include CA125, which is present in a subset of ovarian cancers. CA125 is also elevated in endometriosis and some other benign conditions, CEA is a marker of colon cancer but its specificity and sensitivity are too low to recommend its use as a screening marker although is measured in follow-up examinations. In addition, CEA levels influence the surgical strategy in patients who have previously had colorectal resection or neoplasia.

In multiple primary malignancies (MPM), biomarkers have several advantages as screening too as they reveal the association of the tumors and can aid the clinician in determining the optimal therapeutic approach, either non-inva-
The newest biomarkers are based on gene arrays and proteomic technologies; others can simply be measured in the urine, including bladder tumor antigen. Thus, multiple biomarkers and/or signature protein/gene profiles can be used to identify a particular cancer. Further developments in identifying protein biomarkers together with progress in genetic and cytological markers will provide a tool of satisfactory predictive value, thus overcoming the limitations posed by low sensitivity and specificity. In the following, we describe a rational use of biomarkers in the detection and follow-up of MPM.

**Multiple Endocrine Neoplasia 1**

This hereditary syndrome is transmitted in an autosomal dominant manner and is caused by an inactivating mutation of the MEN 1 gene, which manifests as primary hyperparathyroidism, islet cell tumors, and pituitary adenomas. Patients can also present with cutaneous manifestation and other neoplastic manifestation, including carcinoids, thyroid tumors, adrenal adenomas, lipomas, pheochromocytomas, and meningiomas.

Tumoral markers provide an important test for diagnosis and follow-up (gastrin, pancreatic peptide, prolactin, IGF-1). The newest, chromogranin is a polypeptidic group that increases in the blood of patients with endocrine neoplasias, including hyperparathyroidism and tumors of pancreatic islet cells. Neuron-specific enolase (NSE) is increased in pancreatic islet cells tumor. Other biomarkers expected to aid in the diagnosis of MEN 1 are S-100, 7-B2, neurotensin, and the alpha subunit of human chorionic gonadotrophin (hCG).

**Multiple Endocrine Neoplasia 2**

This autosomal dominant disease is characterized by the presence of medullary thyroid carcinoma (MTC), primary hyperparathyroidism, and pheochromocytoma. These often clinically occult cancers are difficult to accurately diagnose and treat, although minimal elevations of plasma calcitonin (CT) can be measured by a specific immunoassay. Because MTC occurs in nearly 100% of patients with MEN IIa and MEN IIb and is usually the first abnormality expressed, diagnosis of these diseases in kindred at risk is accomplished by screening for the presence of the thyroid tumor. Measurement of the peptide pentagastrin has proved to be more potent than the standard 4-ho calcium infusion in stimulating CT secretion from MTC cells. Many authors [1] recommend that family members at risk for the development of MTC undergo annual calcium pentagastrin stimulation testing, beginning as early as age 5 and continuing until age of 40–45. The diagnosis of pheochromocytoma in MEN IIa and MEN IIb patients can be made biochemically, by measuring urinary excretion of catecholamine and catecholamine metabolites. Since Ishikawa