23. Functional Histopathology

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Cancers of unknown primary site (CUPS) present major diagnostic and therapeutic problems. The incidence of metastatic malignant diseases of undetermined origin ranges between 0.5 and 7.0%, depending upon the scope and duration of the diagnostic investigation [1]. CUPS account for as many as 10–15% of the referred patients with solid tumors in major cancer centers [2]. Despite extensive clinical investigation, the primary cancer site in a substantial number of these patients is unlikely to be found; in approximately 15–30% of patients, a primary cancer site is not identified even at autopsy [3, 4].

Conventional histochemistry (i.e. special stains for tissue or cellular constituents based on dye binding or enzymatic reactions) has been used for many years and is of great value in identifying microorganisms, in studying the pathogenesis of certain disease processes and in the classification of some tumors. However, the chemical reactions involved do not generally distinguish among

the many different compounds within a class of substances, and they are of limited value in tumor classification.

The recent introduction of immunocyto-chemical methods has provided a much more powerful tool for the identification of tissue and cellular constituents, and uses the high specificity and sensitivity of antibodies as probes for such tissue antigens. With this technique it has become apparent that certain cell constituents can now be readily detected and reflect cell type, differentiation or functional status among other properties.

It is becoming increasingly evident that differentiation antigens and tumor-associated antigens, as well as protein products encoded by oncogenes, play some role in the development of human cancer [5]. Because they reflect the origin and function of the tumor, monoclonal antibodies to these antigens are potentially of value to the pathologist to characterize and subclassify undifferentiated neoplasms and tumors with similar morphology but of different origin or clinical behavior. While it is possible that a single highly specific antibody will

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recognize a particular tumor, most cancers probably will require a battery of several antibodies for their identification and sub-classification.

The value of immunocytochemistry in the histopathologic diagnosis of malignant tumors has been recently evaluated by different groups in a series of anaplastic and un-differentiated cancers, including cases of CUPS. Correlation between the initial histologic opinion and immunohistologic diagnosis resulted in the reclassification of these neoplasms as follows: 22% carcinoma cases, 67% lymphoma cases, and 11 % unclassified tumor lesions [6]. In another report, dealing with immunohistologic analysis of large cell undifferentiated tumors, the diagnoses were altered in 60% of the cases [7]. Furthermore, review of clinical details has shown that clinical management in several instances was influenced by establishing the correct diagnosis [8, 9].

There are several approaches to the care of patients with CUPS. One is to utilize chemotherapeutic regimens with agents active against the most likely primary cancer site, as well as those sites most responsive to chemotherapy. Adenocarcinomas are the commonest neoplasms identified, ranging between 24 and 48% of all cases [1]. Of those patients with CUPS in whom a primary cancer site is ultimately determined, cancer of the pancreas, lung and colon predominate. A smaller percentage have gastric cancer; less than 3 % have more responsive tumors such as breast and ovarian cancers [1]. Malignant melanomas and sarcomas represent 5–7% of the total number of CUPS with microscopically confirmed diagnoses [1, 10]. Thus, although chemotherapy is a theoretically attractive concept, the cancers most likely to present as CUPS are also those tumors

highly refractory to conventional antineoplastic agents.

Nonetheless, the role of the pathologist in providing a better and more accurate classification of neoplasms is an important one for the future. To such increased accuracy of diagnosis must be added the observation that, today, pathologists can identify a wide variety of functional and differentiation parameters such as receptors for growth factors and hormones. These observations, in time, should also assist in the better planning of appropriate therapeutic regimens.

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