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Samuel E, Halpern
Hani Abdel-Nabi
J. Lee Murray
Department of Radiology
University of California
San Diego, California
Veterans Administration Medical Center
Buffalo, New York
M.D. Anderson Cancer Center
University of Texas
Houston, Texas

Nonantigen-Specific Tissue Localization of Monoclonal Antibodies

TO THE EDITOR: With great interest we read the recent editorial by A. J. Fischman in The Journal of Nuclear Medicine (1). In his contribution, Fischman stresses the importance of considering nonantigen-specific tissue localization when specific antibody targeting is evaluated. While conducting radioimmunoimaging studies of patients with ovarian carcinoma, we recently encountered a case which may provide complementary information, supporting his editorial message.

We studied 31 patients suspected to have primary or recurrent ovarian carcinoma by using indium-111-labeled-OV-TL 3 F(ab')2. OV-TL 3, a murine monoclonal antibody (MoAb), recognizes a cell-surface antigenic determinant (OA3) present on more than 90% of human ovarian carcinomas of various histologic types (2). Twenty-two out of the 31 patients underwent surgery within 5–7 days following intravenous administration of 140 MBq 111In-OV-TL 3 F(ab')2. In these 22 patients, imaging results were compared with histopathologically confirmed findings at operation (3). In only 1 out of 22 patients was a false-positive result obtained at immunoscintigraphy. The tumor-to-background ratio using a region of interest technique with measurement in lesion and contralateral site was 1.3 throughout the 96-hr study period. In this patient, a large colon carcinoma was removed at operation. Extensive immunohistochemical analysis, using standard indirect immunoperoxidase techniques, indicated that this carcinoma was negative for the OV-TL 3 associated antigenic determinant OA3.

This result clearly demonstrates that in this case localized 111In uptake was the result of one or more nonspecific mechanisms. Enhanced vascular permeability in tumor tissue, as suggested to explain accumulation of 111In-labeled human polyclonal nonspecific IgG in inflammatory processes in rats, is one possible mechanism (4). Secondly, trapping of 111In in tumors similar to that in the reticuloendothelial system could provide an additional explanation. These and other nonspecific mechanisms probably play a role in cases where the presence of specific antigens is clearly demonstrated.

We agree with Fischman that demonstration of the specific antigen in a tumor does not necessarily mean that positive immunoscintigraphy is primarily due to antigen-antibody interaction. Further studies on the mechanism of nonspecific localization of MoAbs in tumors and other lesions are needed to clarify the impact of the hybridoma technology on daily clinical nuclear medicine.

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Leon Massuger
Roland Claessens
Peter Kenemans
Ton Hanseelaar
Frans Corstens
University Hospital Nijmegen
Nijmegen, The Netherlands

Nonspecific Uptake in Radioimmunoscintigraphy

TO THE EDITOR: We found the article of Kairemo et al. (1) and the editorial by Fischman (2) very interesting in understanding aspecific uptake in radioimmunoscintigraphy (RIS). Since 1984, we demonstrated the possible effect of pathophysiologic conditions, such as changes in permeability or "biologic barriers," on the in vivo distribution of radiolabeled monoclonal antibodies (MoAbs) (3,4). In fact, in one of our melanoma patients, analyzed two days after the complete removal of the neoplastic lesion, a slight activity was demonstrated at the level of the surgical area (3). In this case, a F(ab')2, labeled with technetium-99m, reacting against a high molecular weight melanoma-associated antigen was utilized (Tecnemab, Sorin, Saluggia).

Similar results were obtained in other fields of our experience, mainly related to the evaluation of colon and ovarian cancer (5–7). For example, an intense uptake of MoAb B72.3 labeled with iodine-131 (131I) was observed at the level of surgical scar in a patient with ovarian cancer, disease free at the moment of the study, 20 days after second-look surgery. The increased activity was apparent in scans performed at different times, between 24 and 72 hr after i.v. injection of 111MBq of 131I-B72.3 (Sorin, Saluggia). No significant amount of free iodine was present. Serum levels of CA 125 were increased at the moment of the study (184 U/ml). At present, this patient is disease-free and shows normal levels of CA 125.

Possibility of nonspecific uptake has been also found in brain lesions, in the absence of neoplastic localization, because of brain-blood barrier rupture. In these cases, as demonstrated
by Blasberg et al. in animals (8), specific and nonspecific uptake (the latter mainly related to pathophysiologic parameters such as permeability, blood volume, etc.) can be clearly differentiated by a quantitative analysis or by evaluating kinetics of specific and nonspecific radiolabeled antibodies.

This approach would not be practical for clinical use in humans. In this respect, in order to avoid mistakes, the knowledge of the "pathophysiologic state" of a patient (i.e., the knowledge of the presence of conditions that could create nonspecific uptake) is mandatory. In this way it could be possible to minimize false-positive results, particularly in the differential diagnosis of recurrences, that is, in the main clinical utilization of RIS. Furthermore, an opposite conclusion could be derived from the article of Kairemo et al. False-negative results at RIS could be explained not only in terms of lack of expression of the specific antigen but also because of pathophysiologic conditions (blood-brain barrier, basal membranes, low blood flow, etc.) that do not permit the access of the radiolabeled antibody to its target. In this sense, RIS can anticipate the efficacy of a therapeutic strategy utilizing antibodies by demonstrating the in vivo tumor/nontumor ratio. Tumorcidal effect cannot be obtained if the uptake is not present at the level of one or more neoplastic lesions. In conclusion, RIS could be proposed as a necessary preliminary step to all immunologic therapeutic approaches in oncology using MoAbs, also without radionuclides.

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Luigi Mansi
Secondo Lastoria

Marco Salvatore
Istituto Nazionale Tumori
Cattedra di Medicina Nucleare
II Facoltà di Medicina
Napoli, Italy

Nicola Panza
Ospedale A. Cardarelli
Napoli, Italy

Quo Vadis Radioimmune Imaging?

TO THE EDITOR: The editorial by Fischman, Khaw, and Strauss (1) in the November 1989 issue of The Journal of Nuclear Medicine represents a substantial effort to provide insights into the explosively developing area of radioimmune imaging. There is much to be learned from this editorial, and it is understandable that certain topics were over simplified and others provoked some difference of opinion. In recognition of the need for diversity at this stage of development of radioimmune imaging, we would like to provide the following perspectives: Our major purpose is to provide additional information that has become available relative to the efficacy of radioimmune imaging for cancer since the original editorial was in preparation, and which has dramatically altered circumstances to the point where we, and others, are now convinced that radioimmune imaging (and treatment) will soon play a major role in the management of patients with cancer. Before considering this topic let us address a few concepts developed in the original editorial.

The in vivo situation is very different from the in vitro situation so that the association formulae provided in the editorial are not necessarily relevant to the in vivo situation. Indeed, Weinstein (2) has shown that a high avidity constant may actually decrease permeation and tumor uptake of the antibody.

It is unlikely that the quantity of antigen will be a limiting factor for most radioimmune imaging wherein the amount of administered antibody is not large (3–5). The quantity of antigen on the target could be a factor when large amounts of unconjugated antibody are used for direct treatment of cancer. While the amounts of antibody ordinarily used for radioimmune imaging are unlikely to saturate the target antigen, this possibility should always be considered. However, for many antibodies, the amount of administered antibody has to be increased to saturate nonspecific antibody receptor sites, circulating antigen and cross-reacting tissue antigen in order to optimize the results of imaging (6–12). We do not believe that indiscriminate increases in the amount of administered antibody beyond this level improve localization (13).

Several studies reported recently have substantially increased our knowledge of the human anti-mouse antibody (HAMA) response (14–18). These data indicate, as one would expect, that the Fc region of the antibody is the more likely site for reaction with a HAMA, but it is not correct to suggest that Fab fragments do not elicit any immune response. The Fab region, whether administered as part of the intact antibody or as the fragment, has been shown to elicit a HAMA response (19). It is less likely to do so than the intact antibody and radioimmune imaging with small amounts of Fab fragments of murine monoclonal antibodies which has been performed repeatedly without eliciting a HAMA response (20,21).