Radiocolloid Lymphoscintigraphy in Neoplastic Disease

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Abstract

The transport and intralymphatic deposition of interstitially injected radiocolloid of suitable physical properties are mediated through physiological processes and provide the means for obtaining scintigraphic images of drainage lymph nodes relevant to the injection site. In a large series of patients with breast carcinoma, high correlation has been shown between the internal mammary lymphoscintigram and clinicopathological stage of disease and prognosis. Since radiocolloid transport to, transit through, and deposition within the lymph node are effected through cellular elements concerned with immunological mechanisms, it is proposed that the radiocolloid lymphoscintigram be viewed not only as a technique for documenting morphologically established neoplasms in regional lymph nodes but also as a modality for the recognition of functional changes which may influence the development of such neoplasms.

Introduction

In view of the role played by lymphatics in constituting a natural pathway for the dissemination of tumor emboli and the propagation of a neoplasm remote from its origin, an accurate assessment of lymphatic drainage sites from a primary tumor is mandatory and implicit within the UICC (30) tumor-node-metastasis classification of tumors. Upon this appraisal rests the prediction of prognosis and a management decision appropriate to the stage of disease. Also considered, but poorly understood, is the function of regional lymph nodes in initiating immunological recognition, in retarding tumor growth locally, or in sustaining generalized tumor immunity.

Diagnostic modalities for providing an accurate assessment of all lymphatics are limited. Palpation of superficial sites has proven inadequate in determining the status of lymph nodes, and criteria considered indicative of the presence or absence of tumor involvement have been misleading (31).

The lymphogram utilizes contrast medium passively introduced into lymphatic vessels to display normal or disrupted lymph node architecture. The necessity of cannulating lymphatics limits applicability to lymph node groups which drain a suitable peripheral site with accessible lymphatic vessels.

Since tissue density differentials between normal and abnormal lymphatics or abnormal lymphatics and surrounding structures are not great enough to accentuate the distinction, the use of computer-assisted tomography in this regard has been confined to distinguishing enlargement and distortion rather than intrinsic abnormality (23).

The principle underlying the radiocolloid lymphoscintigram consists of physiological transport of a radiocolloid of suitable properties from an appropriate interstitial injection site to the drainage lymph nodes, where the radiocolloid is lodged and a scintillation camera image providing functional, as well as anatomic and morphological data, is obtained (27). Because lymphatic cannulation is not required, the technique is versatile and is applicable to many more anatomic sites than is the lymphogram.

To date, interstitial lymphoscintigraphy has been most widely used to study the internal mammary lymphatics in patients with breast carcinoma with the objective of improving current staging criteria (1, 7, 8, 9). The technique has also provided precise lymph node localization for accurate parasternal radiation (4, 6). More recently, interstitial radiocolloid lymphoscintigraphy has been utilized for visualizing pelvic lymphatics (10).

Materials and Methods

Of the many agents used in radionuclide lymphoscintigraphy, \textsuperscript{99m}Tc ASC\textsuperscript{2} (Union Carbide Corp., Tuxedo, N.Y., and Byk-Mallinckrodt CIL B.V., Petten, The Netherlands) has the most suitable properties (small uniform particle size of 4 to 12 nm) for interstitial lymphoscintigraphy (13). The use of a preformed radiocolloid is recommended in view of the unpredictable behavior of in vivo colloids when injected interstitially (12, 19).

Experiments with rabbits have demonstrated that the primary transport mechanism following the interstitial injection of radiocolloid is phagocytosis by tissue macrophages, although lymphatic transport of free particles is also likely (26). In our own laboratory, studies with rabbits have shown that radioactivity in lymph nodes reaches a plateau at 2 to 3 hr (Chart 1), and images or studies delayed beyond 6 hr do not contribute further diagnostic or kinetic information.

Saturation of lymph node sinusoids and reticuloendothelial cells may occur with successive injections, showing progressively diminishing uptake of radiocolloid (Chart 2). Clearance of colloid from the lymph node requires 5 to 7 days, which must be remembered if a study is to be repeated.

The radiocolloid internal mammary lymphoscintigram is carried out following the alternating subcostal injection of 500 \textmu Ci of \textsuperscript{99m}Tc ASC into the posterior rectus sheath. In patients with breast carcinoma, the side corresponding to the site of primary disease is injected initially in order to demonstrate any evidence of lymphatic cross-drainage which may put the opposite parasternal lymphatics at risk. The initial image is obtained at 3 hr, the contralateral subcostal injection is carried out, and the final image is obtained at 6 hr (B). A lateral lymphoscintigram is also carried out to determine the depth of parasternal nodes (Chart 3A).

A scintillation camera interface with a remote PDP 11/40 computer uses a program for edge detection to provide full-scale isocontours of the lymphoscintigram to localize individual lymph nodes and to determine the percentage of injected radioactivity in each node (4) (Chart 3B).

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\textsuperscript{1} Presented at the UICC Workshop on Radioimmunodetection of Cancer, July 19 to 21, 1979, Lexington, Ky.

\textsuperscript{2} The abbreviation used is: \textsuperscript{99m}Tc ASC, \textsuperscript{99m}Tc-antimony sulfide colloid.
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With studies to date on reproducibility of the technique, anatomic validity as well as variability in normal lymphatics and drainage pathways have been documented, and criteria for interpretation of the lymphoscintigram have been developed and defined (1, 7, 8) (Chart 4). Radiocolloid localization within any lymph node group depends upon patency of lymphatic pathways, the effective transport to, transit through, and deposition within a sequence of lymphatics. Pathological or physiological processes which interfere with or modify any one of these mechanisms may be recognized in a deviation from the normal image displayed on the lymphoscintigram (Chart 5).

Results

Between November 1972 and October 1979, 5901 internal mammary lymphoscintigrams were carried out on 4669 patients with malignant disease referred to The Princess Margaret Hospital. Variability in the position of the parasternal lymphatics and disparity between internal mammary nodes and standardized parasternal radiation fields have been demonstrated in many instances (7).

Correlation of the lymphoscintigram with histological findings (22), clinicopathological stage of disease, axillary histology (8), prognosis in patients with breast carcinoma (9), and the place of internal mammary lymphoscintigraphy in the management of malignant ascites (3) has been reported.

There is progressive rise in the incidence of abnormal lymphoscintigrams with advancing stages of disease in breast carcinoma (Table 1). The identification of parasternal metastases with lymphoscintigram, in addition to histologically verified axillary involvement, indicates a poor prognosis, corroborated by data obtained from surgical studies (8, 9, 21) (Table 2). The technique has been useful in the follow-up of patients for evaluating the extent of disease, as well as response to treatment (11).

Discussion

Mechanical factors which impair the flow of radiocolloid from the injection site (hereditary lymphedema) (17), or preclude the
Chart 3. In A, 3 hr following the left subcostal injection of $^{99m}$Tc ASC in a patient with left breast carcinoma, parasternal lymphatics, upper left parasternal, substernal, right upper parasternal, and right supraclavicular nodes are visualized. Three hr following the subsequent right subcostal injection, proximal right parasternal nodes are visualized. Lateral scintigrams with markers on the sternal notch and sternomanubrial junction are also obtained. Asymmetry between the right and left parasternal lymphatics is within normal limits. Substernal communication between these lymphatics would have been obscured had bilateral subcostal injections been carried out simultaneously in the first instance. B, computerized isocontours of the lymphoscintigram indicating the percentage of injected radioactivity in individual nodes. The full-scale size of the isocontours facilitates radiation treatment planning. XP, xiphoid process, SN, sternal notch.

deposition within and transit through the node, due to neoplastic proliferation and disruption of lymphatic pathways and lymph nodal structure, have been well documented (28, 29). Manifestations of distal obstruction to lymphatic flow with retrograde tissue permeation of radiocolloid (8) have been variously described as a "flare" (18) or "blush" (11) proximal to the site of the obstruction. Also recognized is the transient reversible impairment of radiocolloid deposition within the internal mammary nodes of patients with breast carcinoma in the immediate postoperative period, due to probable blockage of lymphatic sinusoids by surgical "debris" (8).

Less well understood are the potential immunological implications of alterations in radiocolloid transport and deposition. Any colloid, although nontoxic and nonallergenic, by nature of its foreign particulate character is a phagocytic stimulant and a challenge to the host defense mechanisms for its appropriate disposal. The manner in which radiocolloids are handled by lymphatics, which are major components of the immunological organ complex, may reflect an enhanced or depressed host immune status.

Davidson and Hobbs (5) in 1974 described lymphatic microcirculatory spaces which appear in lymph nodes during an immune response. In comparison with normal lymph glands, those regional to an injected antigen, keyhole limpet hemocyanin, when infused with Microfil and examined using stereomicroscopy and radiography, demonstrated increased filling with alteration of lymphatic spaces and saccule formation adjacent to follicles both in the cortex and medulla. They concluded that such multiplication and enlargement of lymphatic spaces with diversion of flow throughout the entire sinusoidal system is an integral part of the immune reaction, serving the purpose of distributing antigen-containing lymph more uniformly throughout the node, maintaining contact with receptors of adjacent cells.

Histologically, the lymphoreticular response occurring in nodes regional to a neoplasm is recognized in sinus macrophage proliferation, proliferation of cells in germinal centers, and migration of cells from postcapillary venules (14). These 2 observations constitute the visually apparent sequelae of an immunological event and may be components of the same phenomenon. It is feasible that variations in radiocolloid distribution and uptake in individual nodes or node groups may reflect changes accompanying a lymphoreticular response to antigenic stimuli and development of the lymphatic microcirculation earlier described.

The lymphoscintigram which demonstrates relatively in-
increased radiocolloid uptake (Chart 6) may therefore be interpreted as indicating a local lymphoreticular response to tumor antigen, the sinus histocytosis recognized in regional lymph nodes, which may have prognostic significance (15). Such a response may be part of a sequence of events starting with the initial immunohistological reaction to the presence of a neoplastic process in the region, concluding either with tumor rejection or tumor proliferation, and replacement of the lymph node with decreasing lymphatic radiocolloid uptake.

With histological examination of parasternal nodes removed in 106 patients with breast carcinoma who had undergone preoperative internal mammary lymphoscintigraphy with $^{198}$Au colloid, Matsuo (22) demonstrated a high correlation between lymphoscintigraphy and pathological results. In one instance, a minimal tumor deposit was demonstrated in a node which had shown increased radiocolloid uptake on lymphoscintigram. The postulated mechanism was probable obstruction to radiocolloid outflow from the node due to tumor emboli. Alternatively, one could view this phenomenon as representing reticuloendothelial hyperplasia in response to antigenic stimulus from the primary neoplasm.

Boak and Agwunobi (2) report studies in inbred C3H mice bearing a syngeneic mammary carcinoma challenge, as well as control animals bearing irradiated tumor, irradiated syngeneic spleen cells, and Dulbecco’s solution in the right hind foot that were given injections of $^{99m}$Tc ASC in both hind feet 5 weeks later. The mice were sacrificed 15 to 90 min after injection, when right and left popliteal nodes were removed, weighed, and counted; results were expressed as cpm/mg. They show inhibition of radiocolloid uptake in the right popliteal or primary node draining the tumor-bearing area relative to the left, but not in the sacral or secondary node, concluding that
depressed radiocolloid uptake by regional nodes draining a tumor is due to a local inhibition of phagocytic activity of regional lymph node macrophages. Their data show significantly depressed radiocolloid uptake in the primary drainage node in control animals as well, and their conclusion regarding inhibition of macrophage phagocytic function may not be unique to a tumor-bearing site but does represent a nonspecific process. Scintigraphic studies carried out by the same authors in rabbits bearing VX2 carcinoma in the right forefoot showed depressed uptake by right axillary nodes of 99mTc ASC injected into both forefoot pads 5 weeks later. Since these animals showed reportedly obvious tumor in the axillary nodes by 10 weeks, it is likely that the depressed radiocolloid uptake documented by scintigraphy at 5 weeks was due to lymphatic tumor invasion, rather than inhibition of macrophage phagocytic activity.

Although there is much evidence associating depressed macrophage function and neoplasia (20), the unequivocal elucidation of the mechanisms involved using interstitially injected radiocolloid remains to be documented.

The possibility that the behavior of different radiopharmaceuticals may distinguish lymph nodes with or without neoplastic infiltration is suggested by Osborne et al. (24). In studies comparing 99mTc ASC and 99mTc-stannous phytate in rats bearing histologically confirmed lymph node metastases from the transplantable Rd/3 tumor, there is a greater difference between normal and abnormal nodes in the uptake of 99mTc-stannous phytate than in that of 99mTc ASC. Our data (12) and those of Kaplan et al. (19) suggest that 99mTc-stannous phytate, an in vivo colloid, may be a less efficacious lymphoscintigraphic agent than 99mTc ASC, and the results reported reflect inadequate lymphatic distribution rather than suppressed lymph node uptake specific to neoplasms.

The same authors report the use of interstitially introduced
radionuclide-labeled liposomes for lymph node visualization (25), postulating that, apart from imaging lymph nodes and detecting tumors, there may also be the possibility that such phospholipid vesicles may act as carriers for therapeutic agents.

Goldenberg et al. (16) have reported a technique for tumor detection and localization by external photoscanning using radiolabeled antibodies to carcinoembryonic antigen administered i.v. The feasibility of raising antibodies to tumor markers, which may subsequently be radiolabeled, would confer remarkable specificity upon current detection methods, provided such agents retain their unique immunological properties. Affinity for such labeled antibodies administered i.v. or interstially may not correspond in all instances to sites of histologically verifiable neoplasm but may precede these developments by a variable interval depending on other operational factors and may identify regions of host response to tumor antigen and possibly even circumstances unfavorable for neoplastic proliferation.

**Conclusion**

It is inevitable that diagnostic modalities must not only be directed at confirming the presence of morphologically recognizable neoplasm, but they must also anticipate detecting conditions within the host which may precede, predispose to, or preclude the establishment of a neoplasm in a particular biological environment.

Since components of the immune system, including tissue macrophages and the sinus histiocytes within the lymph node, play an essential role in the transport, lymphatic distribution, and retention of radiocolloid, variations in these parameters have the potential of reflecting alterations in the immunological expression of the host organism.

With the availability of different approaches, it is apparent that many facets of the host-tumor interaction may yet be evaluated, and all data must be viewed carefully to ensure that further dimensions to this diagnostic process are not overlooked.
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References

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