EDITORIAL

Somatostatin Receptor-Based Imaging in Malignant Lymphomas

Somatostatin receptor-based imaging for Hodgkin's and non-Hodgkin's lymphomas can be viewed either as yet another moderately effective staging tool in an already crowded diagnostic arsenal or as a potential tool to probe the complex biological realm where immunobiology and neuroendocrinology meet.

Somatostatin is a 14 amino acid neuropeptide widely distributed throughout the brain and body. In the brain, somatostatin serves as a neurotransmitter/neuromodulator involved in cognitive function and locomotor activity (*1*). In peripheral tissue, its effects are generally suppressive of target-cell function as evidenced by inhibition of growth hormone, gastrin, insulin or glucagon release from pituitary, gastric or islet cells, respectively. The effects of somatostatin are mediated by a distinct family of G-protein coupled cell surface receptors, through which ligand binding results in inhibition of adenylyl cyclase (*2*). Five structurally related glycoproteins currently compose this family, and this multiplicity is thought to be important in achieving the diversity of biological effects associated with somatostatin. The plasma half-life of the native somatostatin peptide is 2–3 min, imposing the cumbersome requirement of administration by continuous infusion for any clinical application. However, the development of octreotide, an 8 amino acid somatostatin analog with a half-life 2–3 hr made it possible to examine the role of a somatostatin receptor agonist in the management of neuroendocrine tumors (pituitary adenoma, islet cell tumors, carcinoid, medullary thyroid carcinoma, pheochromocytoma, paraganglioma and small-cell lung cancer) which almost uniformly express high levels of this receptor. The results have been striking in carcinoid and islet cell tumors where administration of octreotide results in profound improvement in diarrhea, bronchospasm, dizziness and symptoms of hypoglycemia (*3*). Understanding the importance of somatostatin in regulating secretion in a variety of endocrine tissues has led to substantial progress in the diagnosis and management of tumors derived from these tissues.

By comparison, our knowledge of the role of somatostatin in normal and malignant lymphoid growth and development is far less advanced. Fully understanding this role will be far more difficult than was the case with neuroendocrine cells. The reason for this lies in the unique nature of B- and T-cell development. For most cells in the body the purpose of cell division and differentiation is the production of a new cell, exactly like every other cell of given tissue type. By contrast, the production of new B and T lymphocytes occurs to insure the maximum genetic and phenotypic diversity among the fully differentiated cells. To accomplish this, B lymphocytes, the cells of origin for over 85% of lymphomas, undergo a complex differentiation process such that at multiple discrete points in development, these cells undergo clonal expansion under the influence of a variety of growth stimulating or inhibiting factors. Each of these stages of clonal expansion can give rise to a unique form of lymphoma with specific genetic, phenotypic and clinical features. This accounts in part for the complexity of this group of diseases. Since most lymphomas arise from the antigen dependent stage of B-cell differentiation occurring in lymph node germinal centers, somatostatin receptor expression in this location might be involved in some aspect of the disease process. Reubi et al. (*4*) used ^{125}I-tyr-octreotide as an autoradiographic probe for somatostatin receptor expression, to examine histologic sections of lymphoid tissue obtained from tonsils, ileal Peyer's patches, appendix and colonic lymphoid follicles. Somatostatin receptor expression was readily detectable and largely confined to the germinal centers (sites of B-cell proliferation). Greater intensity of expression was noted in regions rich in centrocytes compared to the region of centroblasts. Mature non-proliferative lymphocytes in the coronal region surrounding the germinal center had no somatostatin receptor expression. Similar expression was noted in germinal centers of hyperplastic lymph nodes and in granulomatous lymphadenitis (*5*). These data, together with in vitro studies demonstrating an inhibitory effect of somatostatin on mitogen-stimulated lymphocyte proliferation and antibody production (*6*), are part of an evolving body of evidence indicating a potentially important role for somatostatin as a regulator of lymphoid development. If this is indeed the case, then somatostatin agonists may be of use in the clinical management of benign or malignant lymphoid disorders. As such, the capability to detect somatostatin receptor expression in lymphoid tumors in situ would greatly facilitate the study of somatostatin based therapeutic approaches to these diseases.

In this issue of the *Journal*, Lipp et al. (*7*) report on their study of ^{111}In-DTPA-d-Phe-1-octreotide scintigraphy for somatostatin receptor-based imaging of malignant lymphomas. Eleven patients with Hodgkin's disease (HD) and 23 patients with non-Hodgkin's lymphomas (NHL) were studied. Although the number of patients evaluated was small, the rates of

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scintigraphic detection in HD (7/10 patients), low-grade NHL (7/12 patients) and high-grade (according to Kiel classification) NHL (6/10 patients) are sufficient to encourage further indepth study of this novel diagnostic modality. The importance of this and other reports (*8,9*) is the demonstration that somatostatin receptor expression can be easily detected in situ in patients with a wide range of malignant lymphomas. From this foundation, a more precise determination of the utility of this imaging modality will require the study of larger groups of patients with specific histologic subtypes of lymphoma both pre- and post-treatment. With this information comes an understanding of how this imaging modality is best used in the diagnostic evaluation of these diseases or as an adjunct to therapeutic development. The usefulness of ^{67}Ga scanning in the evaluation and management of HD and NHL is firmly established (*10*). Such imaging can provide prognostic information and a means of assessing viability of residual radiographic abnormalities remaining after treatment. Octreotide scanning should be similarly assessed by studying groups of patients with specific types of lymphomas throughout the course of their disease. A clear drawback to ^{67}Ga scanning is the 48-hr delay between injection and imaging. If optimal imaging with octreotide can be obtained at 4 hr as these investigators report, then this would represent one immediate advantage of this agent over ^{67}Ga.

If octreotide scintigraphy ultimately finds a role in the routine diagnostic evaluation of lymphomas, it is not likely to be for defining anatomic features but rather for defining a biological feature of these diseases. It appears that the value of octreotide imaging lies not in where it has brought us but rather in where it may lead.

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