The Relevance of Somatostatin Receptor Expression in Malignant Lymphomas

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Somatostatin (SRIF) receptor (sst) expression on lymphoid cells may be related to activation or proliferation of these cells. We investigated the effectiveness of sst scintigraphy in the staging of malignant lymphomas compared with conventional methods. One hundred twenty-six patients with newly diagnosed, histologically proven malignant lymphoma (54 with Hodgkin's disease [HD] and 72 with non-Hodgkin's lymphoma [NHL]) received ^{111}In-labeled DTPA-octreotide (>200 MBq ^{111}In) and were assessed by planar total-body scintigraphy and single-photon emission computed tomography (SPECT) images of the upper abdomen. The sst scintigraphy was positive in 98% of HD patients. Compared with conventional methods, additional lymphomas were detected in 37%, while lesions escaped detection in 7% (all located in the abdomen); 10 HD patients were downgraded and one was upgraded. The sst scintigraphy was positive in 85% of NHL patients, but positivity did not correlate with the degree of malignancy. Additional lesions were detected in 21% of NHL patients, with false-negatives in 7% and upgrading in 13 NHL patients. The results indicate that sst scintigraphy is sensitive in patients with HD and NHL and may reveal sites of active disease undetected by conventional methods, making it a useful diagnostic tool for malignant lymphomas. Further studies should define its value in clinical management.

SOMATOSTATIN (SRIF) receptors (ssts) are expressed on normal and also activated monocytes, lymphocytes, lymphocytic leukemia cells, and lymphoid cell lines. Normal granulocytes and red blood cells do not possess ssts. Normal lymphocytes have ssts of low affinity, whereas activated lymphocytes and leukaemia cells carry ssts of high affinity. This suggests that sst expression is related to activation or proliferation of these cells.[1]

Reubi et al investigated several normal human lymphatic tissues, using in vitro set autoradiography with an iodinated SRIF octapeptide analog, [^{125}I-Tyr^3]-octreotide.[2] The presence of high-affinity ssts was demonstrated in all four human gut-associated lymphatic tissues investigated (palatine tonsils, ileal Peyer patches, vermiform appendix, and colonic solitary lymphatic follicles). The ssts were preferentially located in the germinal centers. The human thymus, spleen, and reactive lymph nodes were found to express ssts as well. These receptors were also of high affinity.[3]

Reubi et al also evaluated the sst status of malignant lymphomas that had been surgically removed from 31 patients.[4] Of 11 low-grade malignancy B-cell non-Hodgkin lymphomas (NHL), 10 were sst-positive, with a high receptor density restricted to neoplastic follicles. All of the eight intermediate-grade lymphomas were sst-positive. Of the B-cell lymphomas of high-grade malignancy, seven of 10 were sst-positive, often with a high density of receptors. In most high-grade NHL, a homogeneous distribution of ssts reflected the diffuse histopathology of these tumors. One T-cell NHL and one Hodgkin's disease (HD) lymphoma were also positive.

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sst SCINTIGRAPHY IN MALIGNANT LYMPHOMAS

The ^{111}In-labeled SRIF analog DTPA-octreotide (OctreoScan®; Mallinckrodt Medical BV, Petten, The Netherlands) has been used for the visualization of sst-positive tumors. Similarly, the presence of ssts on malignant lymphomas allows for in vivo imaging of these tumors. In a pilot study, the lymphoma tissue of 10 patients with different types of malignant lymphoma showed binding of the radiolabeled SRIF analog in vivo.[5] Exact staging is of utmost importance in assessing the prognosis of patients with malignant lymphomas, and in selecting the treatment of choice.

STAGING STUDY

We performed a prospective study comparing sst scintigraphy with conventional methods of staging, in patients with newly diagnosed, histologically proven, malignant lymphoma.[6,7] Conventional methods of staging included physical examination, chest radiography, computed tomography (CT) scans of the chest, abdomen, and pelvis, bone marrow biopsy, and, occasionally, lymphangiography. The dose of ^{111}In administered was more than 200 MBq. Planar total-body scintigraphy was performed at 24 hours and, if necessary, 48 hours postinjection, and in all patients, 24-hour single-photon emission computed tomography (SPECT) images of the upper abdomen were made. A total of 126 consecutive patients were investigated, consisting of 54 patients with HD and 72 with NHL.

Results in Patients With HD

The sst scintigraphy was positive in 53 of 54 patients (98%) with HD (Fig 1). In 20 patients (37%), additional, previously unsuspected lesions suggestive of lymphoma were detected using sst scintigraphy. Most new lesions were found above the diaphragm. In seven patients, new lesions were detected below the diaphragm.

In four patients (7%), sst scintigraphy failed to demonstrate selected sites of disease. All lesions that escaped detection were located in the abdomen. As a result, sst scintigraphy findings altered the clinical stage in 11 pa-

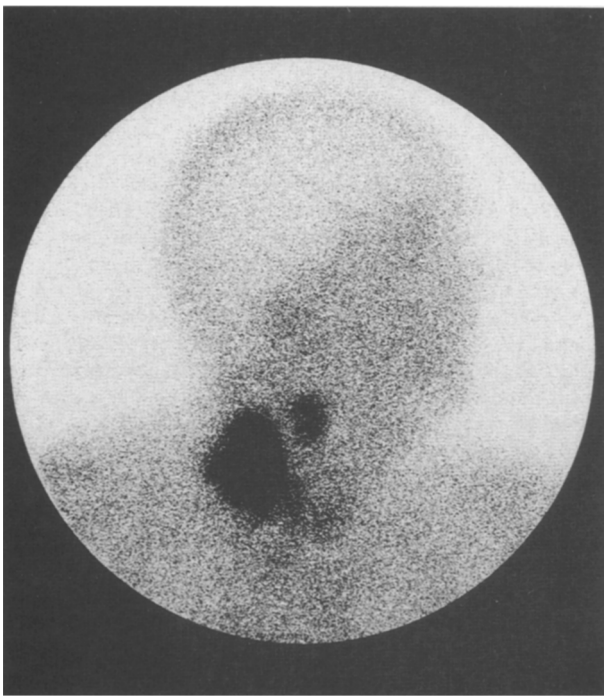

Fig 1. Right lateral image of the neck scanned at 24 hours in a patient with HD, nodular sclerosis subtype. The sst scintigraphy reveals positive right cervical and supraclavicular lymph nodes. Normal accumulation of radioactivity is seen in the thyroid.

tients; in 10 patients, this resulted in upgrading of the disease and, in one patient, a downgraded stage.

Results in Patients With NHL

The histological subtypes among the patients with NHL represented 29 cases of intermediate-grade malignancy, 24 of low-grade malignancy, 17 of high-grade malignancy, and two of unclassified type. Positive scans were obtained in 61 of 72 patients (85%) and a complete negative scan in 11 patients (15%). The positivity for NHL did not correlate with the degree of malignancy. In 15 patients (21%), sst scintigraphy disclosed activity suggestive of lymphoma, which had not been revealed following physical and radiological examination. False-negative findings using sst scintigraphy were seen in five patients (7%). As a result of scintigraphy, the clinical stage would have been upgraded in 13 patients and falsely underestimated in three.

CONCLUSIONS

The interim analysis of this ongoing study shows that sst scintigraphy has a high degree of positivity in patients with HD and NHL. It may disclose sites of active disease not revealed by conventional staging methods in approximately 30% of the patients.

These results appear superior to those reported by other groups.[8,9] This difference might be explained by several factors. First, we included in the study only newly diagnosed, previously untreated patients with histologically proven malignant lymphoma. Second, we administered a high dose of ^{111}In (always >200 MBq), which may enhance the sensitivity of detection. Finally, we used a triple-head camera with 30 seconds of detection per cycle, so that we could collect more counts in SPECT and obtained 15-minute planar spot images with a single- or dual-head camera.

Modest activity of SRIF as a single agent has been demonstrated by Witzig et al[10] in low-grade NHL and cutaneous T-cell lymphoma. Using sst scintigraphy, sst expression can be easily detected in situ in the majority of patients with malignant lymphomas. It is tempting to postulate that patients who have tumors that are positive on sst scintigraphy will be most likely to respond to therapy with SRIF or to radiotherapy with a radiolabeled SRIF analog.

In conclusion, sst scintigraphy provides a useful method of diagnostic evaluation of patients with malignant lymphomas. Additional prospective studies, both pretreatment and posttreatment, will be needed to fully define its value and place in the management of patients with malignant lymphoma.

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