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Glucagon-like Peptide 1–Receptor Scans to Localize Occult Insulinomas

TO THE EDITOR: The precise localization of some insulinomas (islet-cell adenomas that secrete insulin) with the use of conventional imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), endosonography,¹ and indium-111 (¹¹¹In)–labeled pentetreotide scintigraphy (OctreoScan),² is a challenging clinical problem. In vitro studies have demonstrated that receptors for glucagon-like peptide 1

(GLP-1) are highly overexpressed in almost all insulinomas.^{3,4} Therefore, GLP-1-like radioligands retaining high binding affinity to GLP-1 receptors have been developed. One such radioligand, [Lys⁴⁰(Ahx-DTPA-¹¹¹In)NH₂]exendin-4, successfully targeted insulinomas in the Rip1-Tag2 mouse.⁵ We evaluated the diagnostic value of GLP-1–receptor scintigraphy in two patients with insulinomas that either were not localized (Patient 1) or were

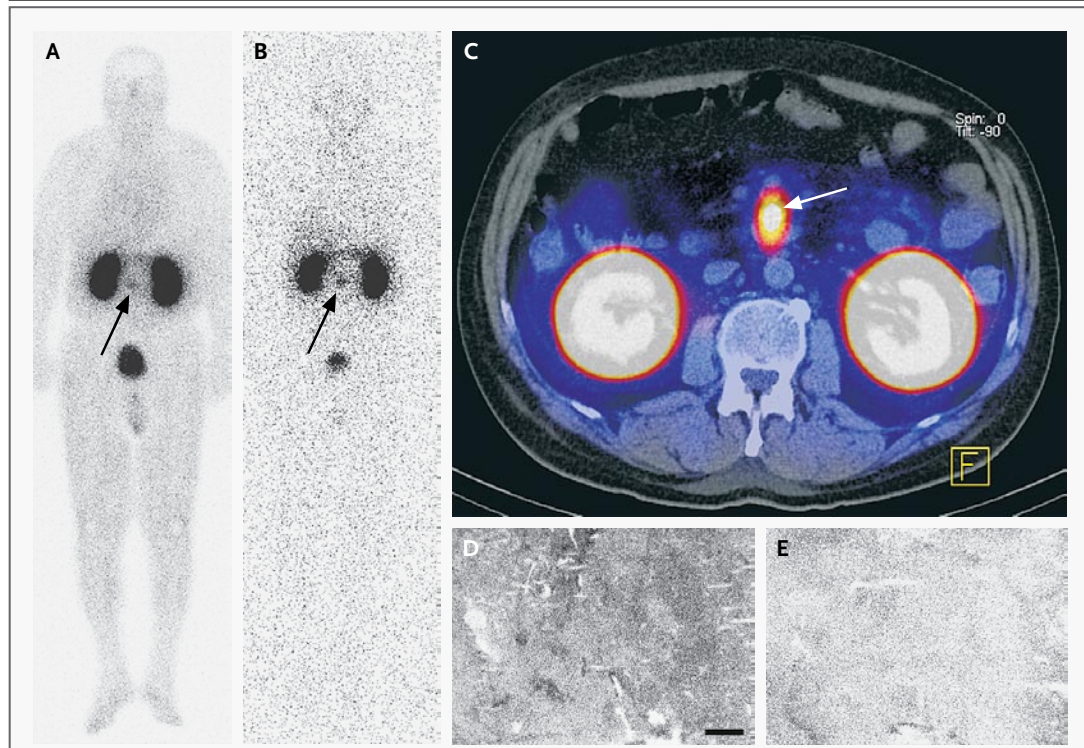


Figure 1. GLP-1–Receptor Imaging of an Insulinoma in Patient 1.

In Patient 1, a 64-year-old man with symptomatic neuroglycopenia and biochemically confirmed endogenous hyperinsulinism, whole-body planar scans show an insulinoma (arrow) with a tumor-to-background ratio of 5.8 at 4 hours after injection of a radioligand (Panel A) and of 13.4 at 4 days after injection (Panel B). Because of urinary excretion of the radioligand, the kidney and bladder labeling are less prominent on day 4 than at 4 hours, so late scans (2 to 4 days after injection) are recommended. Transaxial single-photon-emission CT (SPECT) that was performed 4 days after the injection of a radioligand shows uptake in a small nodule between the duodenum and the superior mesenteric artery (Panel C, arrow). A glucagon-like peptide 1 (GLP-1)–receptor autoradiograph shows total binding of iodine-125–labeled GLP-1(7-36) amide in tumor tissue (Panel D); an autoradiograph with nonspecific binding is shown for comparison (Panel E). The bar represents 1 mm.

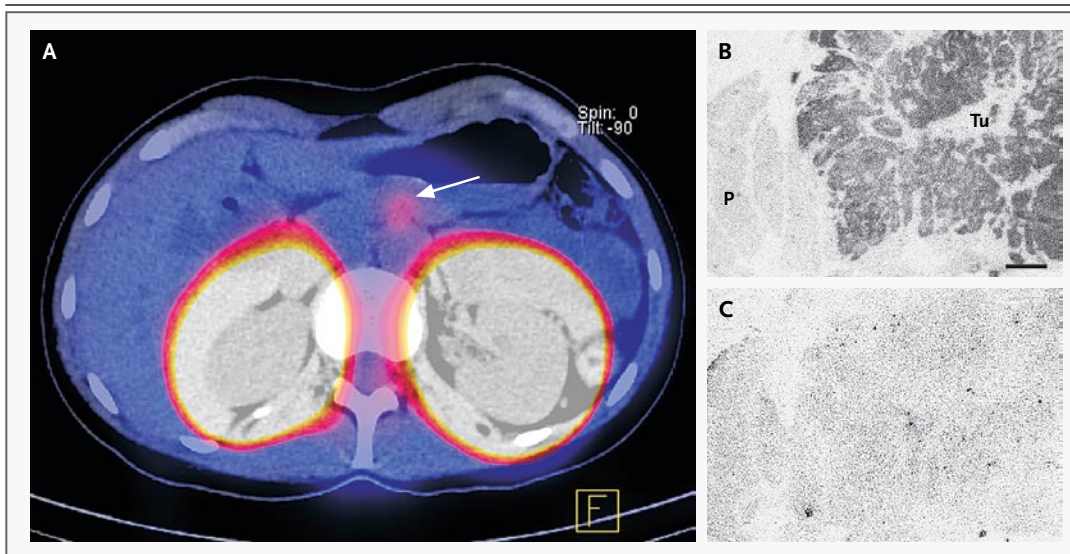


Figure 2. GLP-1–Receptor Imaging of an Insulinoma in Patient 2.

In Patient 2, a 31-year-old woman with biochemically confirmed endogenous hyperinsulinism who presented with a 2-week history of fainting, endosonography showed a suspicious lesion in the transition zone between the pancreatic body and tail. Transaxial single-photon-emission CT (SPECT) that was performed 23 hours after the injection of a radioligand reveals an insulinoma (Panel A, arrow). A glucagon-like peptide 1 (GLP-1)–receptor autoradiograph shows total binding of iodine-125–labeled GLP-1(7-36) amide in the tumor (Tu) but not in the pancreas (P) (Panel B); an autoradiograph with nonspecific binding is shown for comparison (Panel C). The bar represents 1 mm.

unsatisfactorily localized (Patient 2) with the use of conventional imaging methods.

The radioligand was labeled with ^{111}In and was administered intravenously (90 MBq) during a 5-minute period.⁴ Whole-body planar imaging and single-photon-emission CT (SPECT) imaging of the abdomen were performed at various times. The results provided proof of concept that a GLP-1–receptor scan can identify barely detectable insulinomas that express GLP-1 receptor. Histologic analysis of surgically removed tissues that corresponded to the tumor “hot spots” identified in both patients confirmed that the lesions were insulinomas containing GLP-1 receptors in high density.

In Patient 1, a 64-year-old man with neuroglycopenia and endogenous hyperinsulinism, the tumor could not be localized with any of the conventional preoperative imaging methods (including CT, endoscopic ultrasonography, octreoscan scintigraphy, and selective arterial calcium stimulation and hepatic venous sampling), whereas GLP-1–receptor scintigraphy precisely identified the lesion, which was confirmed on removal as an ectopic insulinoma (Fig. 1 and the Supplementary Appendix, available with the full text of this letter at www.nejm.org). In Patient 2, a 31-year-old woman with endogenous hyperinsulinism, the tu-

mor location on the GLP-1–receptor scan (Fig. 2) was found to overlap with that of a suspicious lesion seen on endosonography. All other imaging methods had been unsuccessful. In both patients, the GLP-1–receptor scan enabled the surgeon to localize and resect the tumor. Not only were the SPECT images decisive, but the large accumulation of radioactivity in these small tumors also permitted in situ localization with a probe during surgery.

These findings indicate that GLP-1–receptor scanning may offer a new diagnostic approach that permits the successful localization of small insulinomas. Since virtually all insulinomas express GLP-1 receptors,³ we speculate that the rate of success of such diagnostic scintigraphy would be high.

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Anti–Glomerular Basement Membrane Disease after Alemtuzumab

TO THE EDITOR: Alemtuzumab (Campath-1H) is a humanized anti-CD52 monoclonal antibody, the administration of which causes profound B- and T-lymphocyte depletion. It is licensed for use in the treatment of chronic lymphocytic leukemia, and it is increasingly used in the treatment of autoimmune diseases (particularly multiple sclerosis) and as an induction agent in renal transplantation. Although alemtuzumab is a potent immunosuppressant, several groups have described the paradoxical occurrence of autoimmune disease after

its use, including thyroid disease and cytopenias. We describe two patients in whom anti–glomerular basement membrane disease developed after treatment with alemtuzumab.

Patient 1 was a 40-year-old white woman with relapsing–remitting multiple sclerosis who received a total dose of 100 mg of alemtuzumab. Nine months after treatment, she received the diagnosis of acute renal failure secondary to anti–glomerular basement membrane disease (Table 1). Patient 2 was a 43-year-old white man with a re-

Table 1. Characteristics of the Patients.*

Variable	Patient 1	Patient 2
Age (yr)	40	43
Sex	Female	Male
Indication for alemtuzumab	Multiple sclerosis	ANCA-associated vasculitis (without renal involvement)
Duration of disease before alemtuzumab therapy (mo)	12	18
Previous immunosuppressive drugs	Methylprednisolone	Prednisolone, azathioprine, cyclophosphamide
Total dose of alemtuzumab (mg)	100	788
Time to development of anti-GBM disease (mo)	9	10
Renal-biopsy findings	Crescentic glomerulonephritis (95% crescents), linear deposition of IgG	Crescentic glomerulonephritis with fibrinoid necrosis (60% crescents), strong linear IgG staining
Results of autoantibody screening at onset of anti-GBM disease	Anti-GBM–positive, ANCA-negative, antinuclear antibody–negative	Anti-GBM–positive, ANCA-negative, antinuclear antibody–negative
C3 and C4 complement	Normal	Normal
Lymphocyte count at presentation (cells/mm ³)		
CD4 (normal range, 300–1400)	190	110
CD8 (normal range, 200–900)	190	80
CD19 (normal range, 100–500)	100	100

* ANCA denotes antineutrophil cytoplasmic antibody, and GBM glomerular basement membrane.