Regression of Advanced Refractory Ovarian Cancer Treated with Iodine-131-Labeled Anti-CEA Monoclonal Antibody

Malik Juweid, Robert M. Sharkey, Abass Alavi, Lawrence C. Swayne, Thomas Herskovic, Debra Hanley, Arnold D. Rubin, Michael Pereira and David M. Goldenberg

Garden State Cancer Center, Center for Molecular Medicine and Immunology, Belleville, New Jersey; St. Joseph's Hospital and Medical Center, Paterson, New Jersey; and Division of Nuclear Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

Advanced chemotherapy-resistant ovarian cancer has a poor prognosis, thus requiring new therapeutic modalities. A complete clinical remission, using two cycles of ^{131}I-labeled murine MN-14 anti-CEA monoclonal antibody (MAb), given intravenously, is reported in a patient with advanced ovarian cancer refractory to paclitaxel (Taxol) therapy. The patient first received radioimmunotherapy with ~74 mCi ^{131}I-MN-14 IgG, followed 4 mo later by a similar dose of radiolabeled MAb. A partial remission was seen by CT 1 mo after the first radioimmunotherapy, and a further objective response was documented after the second radioimmunotherapy. CT scans performed 6 and 11 mo after the second radioimmunotherapy showed stable and minimal residual changes. However, a whole-body PET scan with [^{18}F]fluorodeoxyglucose (FDG-PET) was negative in these regions. The CA-125 also decreased to only 13 U/ml, compared to the baseline value of 7700 U/ml. Based on CT, FDG-PET, serum CA-125 and physical exam, the patient was in complete clinical remission for 8 mo when the CA-125 levels rose. CT also showed a new suspicious lesion, presumably a peritoneal implant. No toxicity was seen after the first injection, and only Grade 1 thrombocytopenia and Grade 2 leukopenia developed after the second injection, both reversing within 6 wk. This is a report of a complete clinical remission with radiolabeled anti-CEA antibodies in a patient with chemotherapy-refractive metastatic ovarian cancer.

Key Words: ovarian cancer; iodine-131-labeled anti-CEA monoclonal antibody; radioimmunotherapy

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In 1995, ovarian cancer will account for an estimated 14,500 or 6% of all cancer deaths in American women (*1*). Unfortunately, in most patients, the disease is diagnosed at an advanced stage and has spread beyond the ovary to involve the pelvis or peritoneal cavity (*2*). Despite the availability of several effective chemotherapeutic agents for the treatment of ovarian cancer, survival is still poor, with a 5-yr survival rate of only 40% (*1*). Ovarian cancer is known to produce carcinoembryonic antigen (CEA), and the plasma CEA level is frequently elevated in patients with advanced stage and amount of tumor (*2,3*). Moreover, Goldenberg and associates have reported a high CEA content, ranging from 115 to 17,800 ng/g in malignant ovarian tumors, even when the plasma CEA level was normal (*4*). These findings are consistent with reports of other investigators that tumors manufacturing CEA do not necessarily secrete it into the circulation (*5*).

As part of an ongoing Phase I radioimmunotherapy trial in ovarian cancer with ^{131}I-labeled MN-14 anti-CEA monoclonal antibody (MAb), we report a case in which a complete clinical response, based on CT, FDG-PET and serum CA-125, was achieved after two MAb cycles given intravenously.

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For correspondence or reprints contact: David M. Goldenberg, ScD, MD, Garden State Cancer Center, 520 Belleville Ave., Belleville, NJ 07109-0023.

CASE REPORT

A 71-yr-old woman was referred to our clinic with metastatic, chemotherapy-refractive ovarian cancer. The patient first presented with a pelvic mass in February 1993 and underwent total abdominal hysterectomy, bilateral oophorectomy and omentectomy. Histopathology revealed a high-grade, mixed, clear-cell endometrioid ovarian cancer. At the time of surgery, the ovarian mass was adherent to the bowel. However, the omentectomy did not reveal any evidence of tumor and the disease was considered to be Stage II. After surgery, she received four cycles of adjuvant chemotherapy with carboplatin and cytoxan, in addition to decadron, from March 1993 to May 1993. However, in March 1994, the patient presented with pain in the pelvis, and a CT revealed recurrent ovarian cancer with diffuse seeding on the surface of the liver and the mesentery and fluid collection in the pelvic cul-de-sac. The patient then received intravenous salvage chemotherapy with Taxol from April 1, 1994, until May 17, 1994. The disease did not respond to chemotherapy, and there was clinical evidence of disease progression. The serum CA-125 level was 2137 U/ml, and a CT scan performed on June 7, 1994, demonstrated marked progression of disease with multiple peritoneal implants and advanced ascites. However, the patient's plasma CEA was normal (<2.5 ng/ml). Due to her chemotherapy-refractive disease the patient was then considered for radioimmunotherapy with radiolabeled MAbs and was referred to our center for initial antibody targeting studies and subsequent therapy. The baseline CT study, performed on July 25, 1994, continued to demonstrate extensive peritoneal carcinomatosis with involvement of the surface of the liver.

On July 26, 1994, the patient first received an 8-mCi (0.7 mg) infusion of CDR-grafted (humanized) ^{131}I-MN-14 IgG intravenously (*6*), and 1 wk later, the patient received another diagnostic 8-mCi infusion of murine MN-14 IgG (0.6 mg) intravenously. Both studies demonstrated intense uptake in the abdominal cavity consistent with peritoneal carcinomatosis. On August 9, 1994, the patient received 73.8 mCi (5.3 mg) therapeutic intravenous doses of murine ^{131}I-MN-14 IgG on an inpatient basis. This dose was based on a level of 40 mCi/m^2 that was allowed at the time by our protocol. Even though the patient had a low human antimouse antibody (HAMA) titer of 168 ng/ml at the time of the therapy study, the post-therapy scans showed intense uptake in the peritoneal cavity, similar to that seen after the diagnostic infusion (Fig. 1). Two weeks post-therapy, the patient's HAMA titer reached a maximum of 390 ng/ml. However, the HAMA titer gradually declined over the next 6 wk and was within normal limits (<74 ng/ml) 2 mo later.

One month after the treatment, a CT scan of the abdomen and

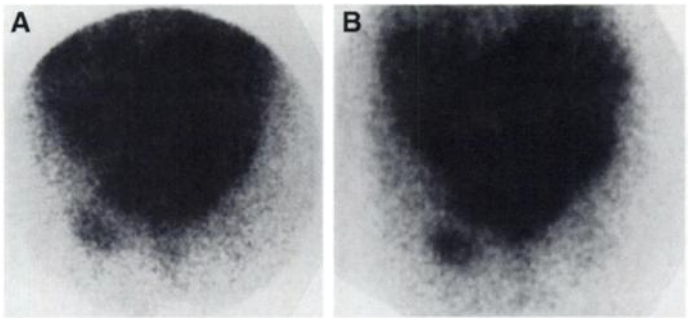

FIGURE 1. Anterior abdomen and pelvis planar images 168 hr after diagnostic infusion of 8 mCi (A) and therapeutic infusion of ~74 mCi (B) of murine ^{131}I-MN-14 IgG. Both images demonstrate targeting of abdominal and pelvic peritoneal carcinomatosis and accompanying ascites.

pelvis showed a marked improvement (>50% reduction) in the extent of peritoneal implants and the associated ascites. In addition, there was a marked regression of capsular liver metastases and metastases in the porta hepatis. Three months after therapy, a new CT scan showed a complete regression of the capsular liver metastases (Fig. 2A) and further reduction in peritoneal implants, with only isolated pockets of ascites and cystic collections left (Fig. 2B). The serum CA-125 decreased from 7700 U/ml 1 wk after therapy (baseline value) to 4340 U/ml 1 mo thereafter and to only 60 U/ml 3 mo later (normal range, 0–35 U/ml) (Fig. 3). The CA-125 values were measured using an assay that is resistant to HAMA. No hematologic or nonhematologic toxicity was seen after the first radioimmunotherapy. Even though the patient had a partial remission both by CT and biochemical markers for 4 mo, residual disease was still seen by CT in association with an elevated serum CA-125 titer (60 U/ml). Therefore, the patient was given another intravenous ^{131}I-MN-14 IgG dose.

On December 6, 1994, or 4 mo after the first radioimmunotherapy, the patient was given 74.4 mCi (5.3 mg) of murine ^{131}I-MN-14 IgG intravenously. The post-therapy scan showed considerably less uptake in the peritoneum; however, there was still evidence of residual disease by the antibody scan. Subsequent CT scans performed over the next 6 mo after the second treatment showed progressive reduction of tumor. A CT scan performed 6 mo after the second radioimmunotherapy showed only minimal residual changes. However, a whole-body PET scan with [^{18}F]FDG-PET performed at that time showed no evidence of disease in these regions, or elsewhere in the body (Fig. 4), probably suggesting that the CT findings represent fibrosis. Another CT scan performed 11 mo after the second radioimmunotherapy did not show any change in the putative residual fibrosis. Furthermore, the serum CA-125 was now only 13 U/ml. Thus, based on CT, PET and serum CA-125, the patient was considered in complete clinical remission. She remained in remission for 8 mo, when the CA-125 levels rose again and CT showed a new suspicious lesion, presumably a peritoneal implant. The patient developed a Grade 2 leukopenia (WBC 2900) 6 wk after the second radioimmunotherapy but recovered completely within 6 wk without intervention. A Grade 1 thrombocytopenia developed at 4 wk after radioimmunotherapy but recovered rapidly within 1 wk. Two weeks after the second radioimmunotherapy, HAMA again developed, and the HAMA level remained elevated at 5474 ng/ml at 13 mo after the second radioimmunotherapy.

Due to the diffuse nature of disease in this patient, the associated ascites and the limited spatial resolution of the gamma camera, we were unable to calculate the radiation dose to focal tumor sites. However, since the patient developed a low level of HAMA after the first therapeutic infusion, further studies were performed to examine the possibility of an anti-idiotypic response in this patient. For this purpose, samples of the patient's plasma taken before each injection and at various times thereafter were analyzed by size-exclusion high-performance liquid chromatography (HPLC) to determine if there was any reactivity with radiolabeled humanized MN-14. The humanized MN-14 carries the idiotypic murine region of the antibody, and therefore complexation of the antibody with the patient's plasma is indicative of an anti-idiotypic response (*6*). However, complexation of the labeled humanized MN-14 can occur with CEA as well as with an anti-idiotypic antibody. When the plasma is heat-extracted (90°C for 15 min), only CEA will remain in the plasma while other proteins, including the antiantibodies, will be denatured and precipitated (*7,8*). Complexation of humanized MN-14 in a heat-extracted plasma is then only related to CEA. Thus, the percentage of complexation in a heat-extracted serum is subtracted from the nonheat-extracted sample, to determine if an anti-idiotypic response can be implicated. According to our preliminary data, if a residual percentage is >10%, it is highly suggestive of an anti-idiotypic response (*6*). Our findings indicated no difference between the heat-extracted and nonheat-extracted sample 1 mo after the treatment with murine MN-14. Furthermore, 2 mo after the first radioimmunotherapy, there was evidence of a relatively minor anti-idiotypic response (only 16% residual complexation). Two months later, at the time of the second radioimmunotherapy, there was no significant anti-idiotypic response

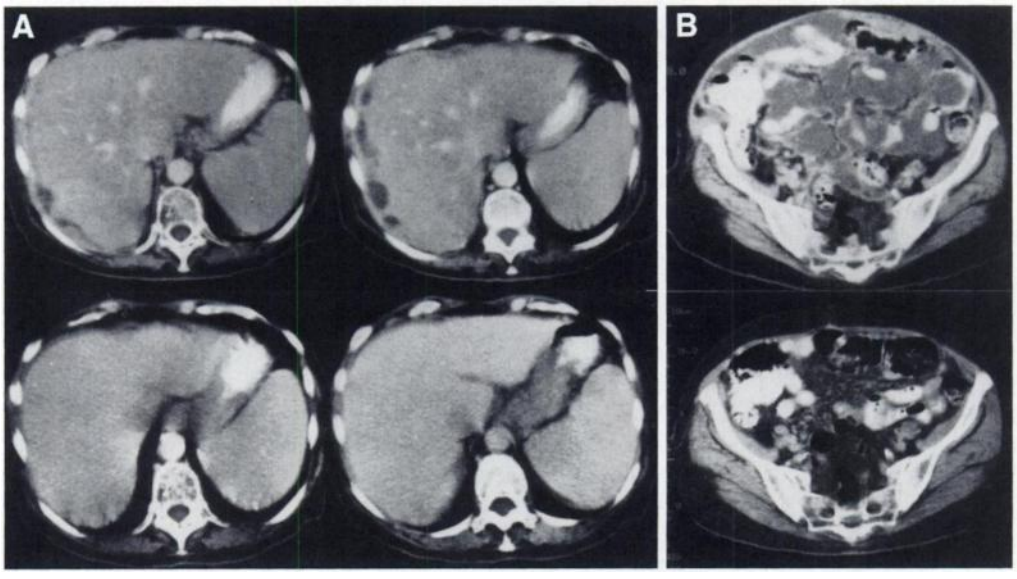

FIGURE 2. CT scan of the abdomen 2 wk before the first radioimmunotherapy with radiolabeled MN-14 (top) and 3.5 mo post-therapy (bottom) shows complete regression of capsular liver metastases (A). CT scan of the pelvis 2 wk before the first radioimmunotherapy with radiolabeled MN-14 (top) and 3.5 mo post-therapy (bottom) shows complete regression of peritoneal implants previously apparent as "pancaking" and resolution of ascites (B).

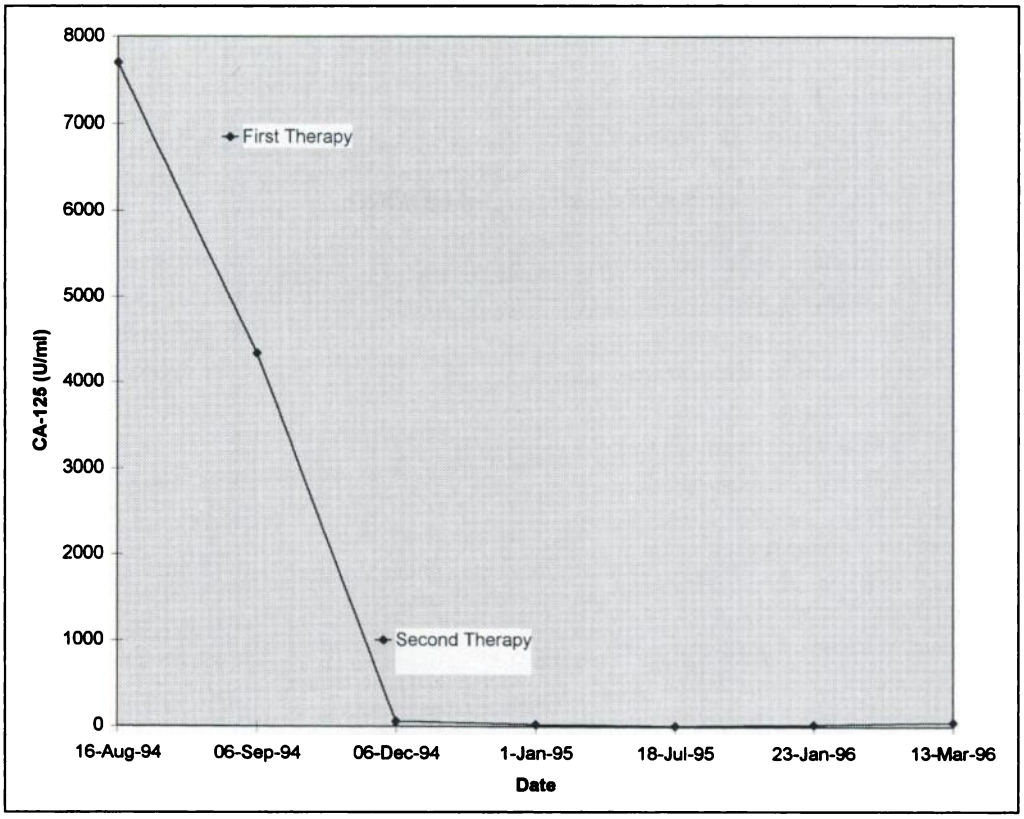

FIGURE 3. Graphical depiction of serum CA-125 changes with time after the first and second radioimmunotherapy. Normal CA-125 level is < 0–35 U/ml. The values were obtained using a HAMA-resistant CA-125 assay.

(6.5% residual complexation). However, 2 wk after the second treatment, an anti-idiotypic antibody was clearly detectable (11.9% residual complexation), reaching a maximum 2 mo after therapy. This response was still persistent 17 mo thereafter, when the last assay was performed.

DISCUSSION

The impressive response in this patient presented in this case report is interesting for several reasons. First, the response was seen in a patient with advanced ovarian cancer refractory to chemotherapy; antitumor responses were seen despite a large tumor burden and with relatively low doses of radioactivity (<75 mCi of ^{131}I). Second, the treatment could be repeated in this patient after a 4-mo interval despite the development of HAMA, and an additional response was achieved. Finally, no toxicity was seen after the first radioimmunotherapy, and only a Grade 1 thrombocytopenia and Grade 2 leukopenia developed after the second radioimmunotherapy, with both reversing within only 6 wk.

An important issue is whether this rather dramatic response is attributed to nonspecific radiation, tumor-targeted radiation and/or immunological mechanisms which could trigger host effector functions directed against the tumor cells (*9,10*). Even though some of the diffuse tumor uptake seen in this patient may be due to nonspecific MAb accumulation, resulting in nonspecific radiation of the ascites fluid in the peritoneal cavity, our dosimetric calculation indicated that the putative nonspecific radiation dose delivered to the ascites fluid or peritoneal space was only 400 cGy, a dose unlikely to result in this dramatic response. Thus, it is much more likely that specific targeted radiation to the diffuse small implants played a more significant therapeutic role. Due to the diffuse nature of disease in this patient, the associated ascites and the limited spatial resolution of the gamma camera, it was impossible to calculate the radiation dose to these focal tumor sites. However, it is important to note the possibility that radiation doses much higher than the average dose of 400 cGy may have been delivered to individual small peritoneal implants or clusters of tumor cells in the malignant ascites.

The other possibility is that the antitumor effects may be related to the induction of an anti-idiotypic antibody (i.e., Ab-2 antibody), which could then elicit an active humoral immunity through the formation of Ab-3 antibody (i.e., anti-anti-idiotypic antibody) (*9*). In this patient, there was no evidence of an Ab-2 antibody until two months after the first radioimmunotherapy, and since the antitumor response was already apparent one month after the first radioimmunotherapy, it is unlikely that the initial response was caused solely by Ab-3 antibody. However, we cannot exclude that cellular immunity developed in response to the murine immunoglobulin infusions and contributed to these antitumor effects, particularly since the patient developed HAMA at the time of the therapy study. Indeed, Kosmas et al. (*10*) have reported that ovarian cancer patients receiving murine monoclonal antibody therapy develop T-cells that proliferate in vitro in response to these antibodies as antigens. Also, Bast et al. (*11*) have reported that the activation of cellular immunity through Corynebacterium parvum i.p. administration leads to responses in patients with minimal i.p. disease documented on second look laparotomy or laparoscopy. Support of the role of immunological mechanisms is also based on the observation of extended survival of patients with advanced ovarian cancer who have developed anti-idiotypic HAMA responses after immunoscintigraphy with ^{99m}Tc-labeled anti-CA-125 antibodies, compared with their historically expected poor survival (*12*), or compared with patients who remained HAMA-negative after the antibody infusions (*13*). It is therefore conceivable that the synergistic effects of radiation and immunological activity are responsible for this marked antitumor response.

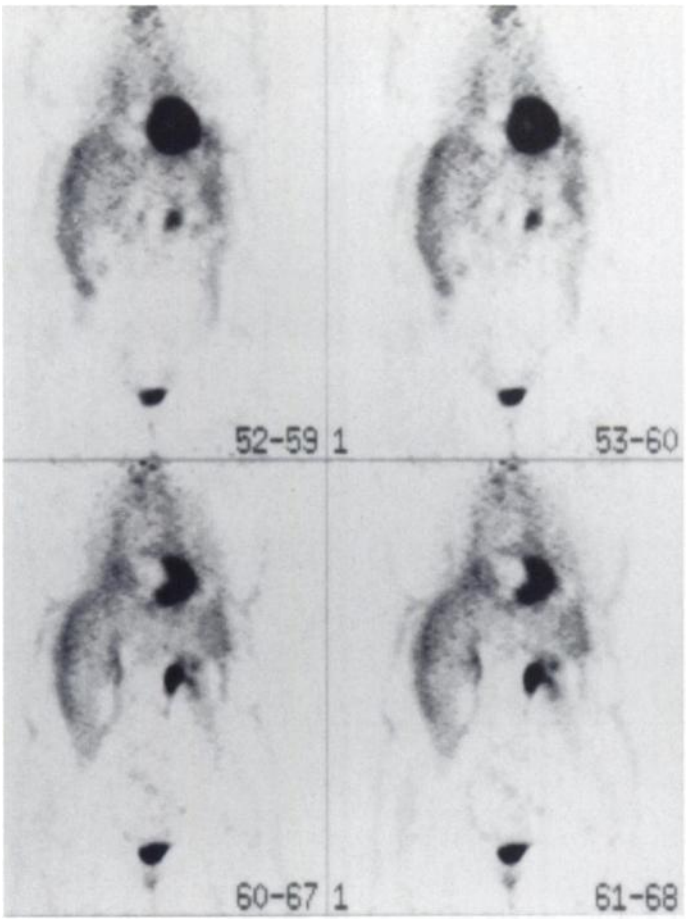

FIGURE 4. Coronal images of a whole-body PET scan with [^{18}F]FDG-PET shows no evidence of disease 11 mo after the initial therapy with radiolabeled anti-CEA antibodies. The images proceed from left to right, starting from the anterior to the posterior part of the body.

CONCLUSION

This case demonstrates the prospect of achieving excellent targeting and antitumor responses in ovarian cancer with intravenously administered antibodies directed against carcinoembryonic antigen. Therefore, further studies are in progress to confirm this finding and to elucidate the mechanisms involved in tumor response.

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REFERENCES

1. Wingo PA, Tong T, Bolden S. Cancer statistics. *CA Cancer J Clin* 1995;45:8–30.
2. Young RC, Perez CA, Hoskin WJ. Cancer of the ovary. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Principles and practice of oncology*. Philadelphia, PA: JB Lippincott; 1989:1226–1263.
3. Di Saia PJ, Morrow CP, Haverback BJ, et al. Carcinoembryonic antigen in cancer of the female reproductive system. Serial plasma values correlated with disease state. *Cancer* 1977;39:2365–2370.
4. Van Nagell JR, Kim E, Casper S, et al. Radioimmunodetection of primary and metastatic ovarian cancer using radiolabeled antibodies to carcinoembryonic antigen. *Cancer Res* 1990;40:502–506.
5. Martin MW, Halpern SE. Carcinoembryonic antigen production, secretion and kinetics in BALB/c mice and a nude mouse-human tumor model. *Cancer Res* 1984;44:5475–5481.
6. Sharkey RM, Juweid M, Shevitz J, et al. Evaluation of a CDR-grafted (humanized) anti-carcinoembryonic antigen (CEA) monoclonal antibody in preclinical and clinical studies. *Cancer Res* 1995;55:5935s–5945s.
7. Primus FJ, Kelley EA, Hansen HJ, et al. "Sandwich"-type immunoassay for carcinoembryonic antigen in patients receiving murine monoclonal antibodies for diagnosis and therapy. *Clin Chem* 1988;34:261–264.
8. Hansen HJ, La Fontaine G, Newman ES, et al. Solving the problem of antibody interference in commercial "sandwich"-type immunoassays of carcinoembryonic antigen. *Clin Chem* 1989;35:146–151.
9. Courtenay-Luck NS, Epenetos AA, Sivolapenko GB, et al. Development of anti-idiotypic antibodies against tumor antigens and autoantigens in ovarian cancer patients treated intraperitoneally with mouse monoclonal antibodies. *Lancet* 1988;ii:894–897.
10. Kosmas C, Epenetos AA, Courtenay-Luck NS. Patients receiving murine monoclonal antibody therapy develop T cells that proliferate in vitro in response to these antibodies as antigens. *Br J Cancer* 1991;64:494–500.
11. Bast RC, Berek JS, Obrist R, et al. Intraperitoneal immunotherapy of human ovarian carcinoma with corynebacterium parvum. *Cancer Res* 1983;43:1365–1401.
12. Baum RP, Niesen A, Herte IA, et al. Activating anti-idiotypic human antimouse antibodies for immunotherapy of ovarian carcinoma. *Cancer* 1994;73(suppl):1121–1125.
13. Wagner U, Oehr P, Reinberg J. Immunotherapy of advanced ovarian carcinomas by activation of the idiotypic network. *Biotechnol Ther* 1992;3:81–89.

Graves' Disease Triggered by Autoinfarction of an Autonomously Functioning Thyroid Adenoma

Elizabeth Gallegos, Donald A. Meier and Michael Garcia

Department of Nuclear Medicine, William Beaumont Hospital, Royal Oak; Department of Nuclear Medicine, William Beaumont Hospital, Troy, Michigan

A patient whose nontoxic autonomously functioning thyroid adenoma had been stable for at least 3 yr developed enlargement of the nodule and hyperthyroidism. It was assumed the hyperthyroidism was caused by evolving toxicity in the autonomous adenoma, but imaging showed the nodule had undergone infarction and the hyperthyroidism was secondary to Graves' disease. This case demonstrates the necessity of thyroid imaging in patients with nontoxic autonomously functioning thyroid adenomas when there is a change in nodule size or thyroid function which requires treatment.

Key Words: autoinfarction; autonomously functioning thyroid adenoma; Graves' disease

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For correspondence or reprints contact: Donald A. Meier, MD, Dept. of Nuclear Medicine, William Beaumont Hospital, 44201 Dequindre, Troy, MI 48098-1198.

Hyperthyroidism can be caused by autoimmune Graves' disease (GD) or be secondary to increased function in nodules