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Case Report

Yttrium-90 Selective Internal Radiation Therapy Plus Cryoablation for Recurrent Adrenocortical Carcinoma With Liver Metastases

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Abstract

Advanced adrenocortical carcinoma (ACC) has a poor prognosis and is often resistant to the conventional regimens of mitotane administration and systemic chemotherapy. In addition to surgery, local therapeutic measures can be valuable. Here, we present the case of a 33-year-old woman who developed left retroperitoneal local recurrent ACC with hepatic and pulmonary metastases 1 year after radical adrenalectomy. The tumors progressed under chemotherapy and mitotane treatments. She was treated with yttrium-90 selective internal radiation therapy (^{90}Y SIRT) for hepatic metastases and cryoablation of the local recurrent tumor, after which significant tumor shrinkage was observed. She then received radiofrequency ablation for the residual hepatic metastases and radiotherapy to the residual local recurrent tumor. Complete remission was achieved and maintained at least until the data cutoff day (15.8 months after the last treatment). This is the first published report of cryoablation in a patient with ACC and the third report of ^{90}Y SIRT use for hepatic metastasis of ACC. Cryoablation and ^{90}Y SIRT are local treatment choices for ACC that are worthy of further study.

Key Words: advanced adrenocortical carcinoma, yttrium-90 selective internal radiation therapy, cryoablation

Abbreviations: ACC, adrenocortical carcinoma; ACTH, adrenocorticotropic hormone; CT, computed tomography; CRC LM, metastatic colorectal cancer in the liver; DHEAS, dehydroepiandrosterone sulfate; EDP-M, etoposide, doxorubicin, and cisplatin plus mitotane; ^{90}Y SIRT, yttrium-90 selective internal radiation therapy.

Primary adrenocortical carcinoma (ACC) is extremely rare. The annual incidence is 0.7 to 2 per million population [1]. About 80% of ACC cases are functional. Glucocorticoids are the most commonly secreted hormones [2]. The prognosis of ACC is poor, with a 5-year survival rate of less than 20% [2]. Complete surgical resection offers the only chance of cure. However, 75% of the patients initially present with metastatic spread [3]. A combination of mitotane administration and chemotherapy comprising etoposide, doxorubicin, and cisplatin (EDP-M) is recommended as the first-line treatment for advanced ACC, but the response rate is as low as 23.2% [4, 5]. Local therapeutic measures such as radiofrequency ablation and chemoembolization are, therefore, of value and suggested for metastatic ACC [6]. Yttrium-90 (^{90}Y) selective internal radiation therapy (^{90}Y SIRT) is a novel therapy that includes angiography-guided injections of ^{90}Y-containing microspheres into the feeding arteries to irradiate tumors [7]. It has been approved for the treatment of hepatocellular carcinoma and metastatic colorectal cancer in the liver (CRC LM). Only 2 cases of ACC with hepatic metastasis treated with ^{90}Y SIRT have been reported in the literature [8, 9]. Cryoablation therapy is a 2-phase process involving freezing and then thawing a tumor, resulting in cell rupture. There have been reports of using it to treat CRC LM, pheochromocytoma,

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and metastatic cancers in the adrenal glands [6, 10, 11] but no reports for treating ACC. Here, we present a case of ACC with pulmonary and hepatic metastases that showed complete remittance after multimodality treatment, including ^{90}Y SIRT and cryoablation. To our knowledge, this is the first published report of cryoablation therapy and the third report of ^{90}Y SIRT for ACC.

Case Presentation

Informed consent was obtained from the patient.

A 33-year-old woman presented with secondary amenorrhea for 3 months, which was accompanied by a buffalo hump and acne over the face and trunk. Her only relevant medical history was of mitral valve prolapse. A workup series revealed the following: increased daily excretion of urinary-free cortisol (224.7 μg/24 hours, normal range 4.3-176 μg/24 hours); suppressed serum adrenocorticotropic hormone (ACTH) level (ACTH < 5 pg/mL, cortisol 21 μg/dL); nonsuppressible serum cortisol level (14.4 μg/dL) in a low-dose dexamethasone suppression test; elevated serum testosterone (2.77 ng/mL, normal range 0.14-0.53 ng/mL), and dehydroepiandrosterone sulfate (DHEAS) levels (399.6 μmol/L, normal range: 2.6-13.9 μmol/L); and a left adrenal tumor measuring 5.1 cm in diameter on computed tomography (CT) (Fig. 1).

A cortisol-secreting adrenal tumor was suspected; therefore, a left-sided robotic adrenalectomy was performed. The pathology showed an adrenocortical tumor with a high nuclear grade, <5 mitoses per 50 high-power fields, atypical mitotic figures, diffuse architecture, multiple foci of tumor necrosis, venous invasion, sinusoidal invasion, and capsular invasion; these findings supported ACC diagnosis according to the Weiss criteria. Immunohistochemical staining was positive for inhibin α, and Ki-67 expression was 2%. The surgical margins were free of cancer. No malignancy-related uptake was found on postoperative whole-body ^{18}F-fluorodeoxyglucose positron emission tomography. This ACC was classified as T2N0M0, Stage II, with a low/moderate risk of recurrence [5]. Serum cortisol (0.82 μg/dL), testosterone (<0.2 ng/mL), and aldosterone (<7.6 ng/dL) levels were decreased to lower than the normal limit, and DHEAS level (5.5 μmol/L) was normal. The patient was prescribed glucocorticoid and fludrocortisone supplements.

There was no evidence of residual cancer or recurrence in the biochemistry survey and whole-body CT scans conducted at 7 weeks or 23 weeks postoperatively. However, a CT scan 9 months postoperatively showed multiple tumors in the bilateral hepatic lobes and lungs (Fig. 2A-C). A positron emission tomography scan showed abnormal ^{18}F-fluorodeoxyglucose uptake in the bilateral lungs, liver, and left abdominal paraaortic area. A liver biopsy was performed, and the pathology revealed metastatic ACC. Mitotane was prescribed. The patient's maximal tolerable dose was 500 mg twice daily; higher doses induced severe nausea and vomiting. Systemic chemotherapy was initiated with a regimen of paclitaxel, cisplatin, and 5-fluorouracil. Cisplatin was replaced with carboplatin after the second cycle of chemotherapy because of concern about ototoxicity. Four cycles of chemotherapy were performed over approximately 3 months. However, the metastatic hepatic

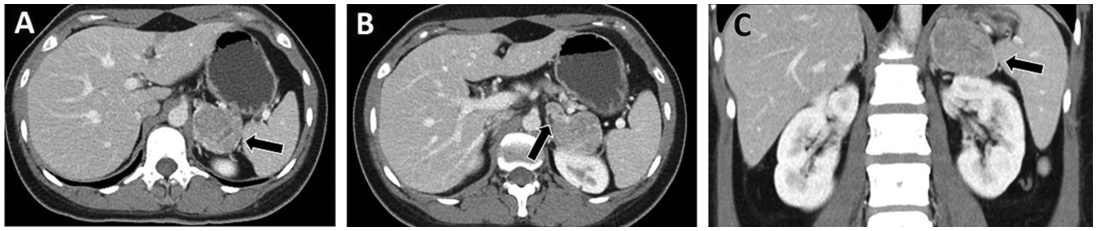

Figure 1. The initial computed tomography scan revealed a 5.1-cm heterogeneous enhanced left adrenal tumor. (A) Axial view; (B) irregular shape of tumor with a protruding part behind the pancreas; and (C) coronal view.

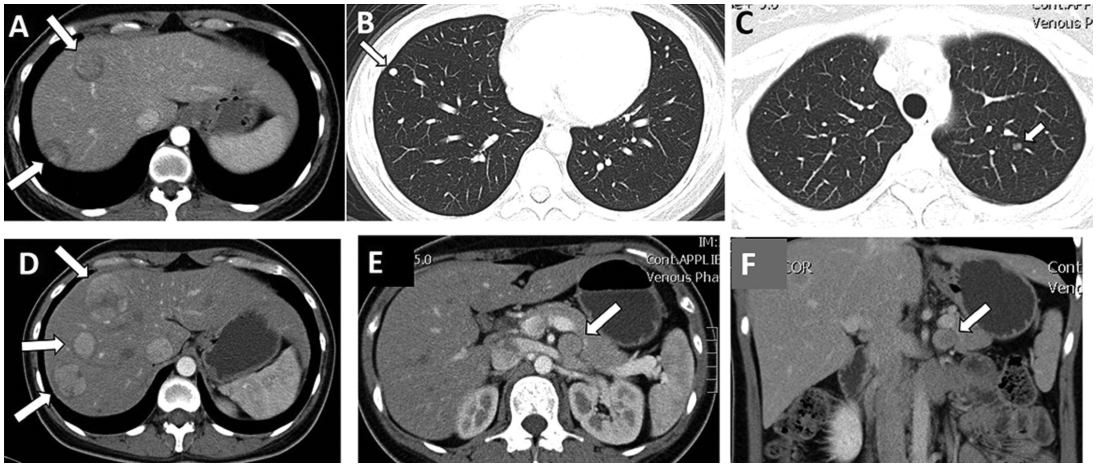

Figure 2. A computed tomography (CT) scan 9 months after the operation showed multiple newly identified metastases in the liver (A) and lungs (B,C). A CT scan after 4 months of systemic chemotherapy and mitotane treatment revealed progression of the liver metastases (D) and a recurrent retroperitoneal adrenocortical carcinoma (E,F).

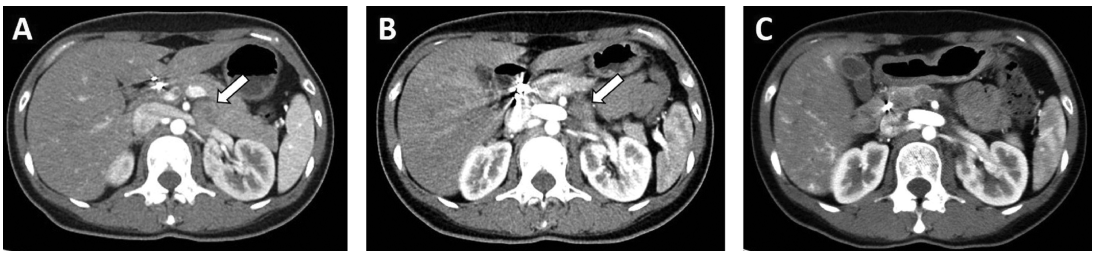

Figure 3. Follow-up computed tomography scans 2 months before (A), 4.1 months after (B), and 9.8 months after (C) cryoablation revealed complete resolution (C) of the left retroperitoneal recurrent adrenocortical carcinoma.

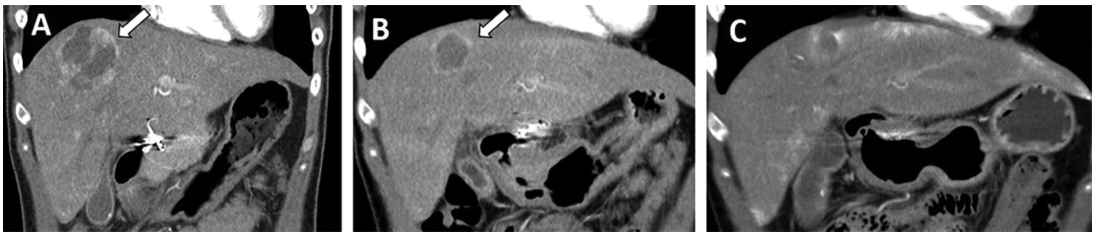

Figure 4. Follow-up computed tomography (CT) scans 1.1 months (A) and 7.3 months (B) after yttrium-90 selective internal radiation therapy revealed reduced size of liver metastases. A CT scan showed complete remission of the hepatic metastases 1.1 months after radiofrequency ablation (C).

tumors continued to grow, and a recurrent left retroperitoneal tumor measuring 2.5 cm in diameter appeared on a CT scan 13 months postoperatively (Fig. 2C-2E). Some of the pulmonary nodules were enlarged and some had shrunk.

The patient was then prepared for ^{90}Y SIRT. Angiography revealed multiple hypervascular tumors in both hepatic lobes, supplied by the right and left hepatic arteries. For arterial redistribution, transarterial embolization was performed with microcoil embolization of the gastroduodenal and right gastric arteries. A subsequent perfusion study with ^{99m}Tc-macroaggregated albumin administrated to the proper hepatic artery demonstrated that the tracer activity ratio of tumor to nontumor parts was 4.11, indicating the potential benefit of radioembolization. Four days later (14.6 months postoperatively), ^{90}Y SIRT was performed, delivering 0.3 GBq of Y^{90} microspheres to the left hepatic lobe and 0.7 GBq to the right. The estimated absorption dose was 108.24 Gy to the left hepatic metastasis and 122.54 Gy to the right. One month later, CT scans showed stable hepatic metastasis with necrosis, stable pulmonary metastases, and an enlarging left adrenal tumor measuring 3 cm in diameter.

Cryoablation therapy was then planned for recurrent left retroperitoneal ACC. Angiography was performed to evaluate the vascular distribution. The results showed 2 left renal arteries. The left renal vein was compressed and suspiciously invaded by the ACC, resulting in venous stenosis. Two J-curve catheters were inserted to localize and protect both left renal arteries. Left renal vein stenosis was treated and protected with a wall stent. Thereafter, CT-guided cryoablation was performed on the ACC with 2 Endocare V-Probe cryoprobes and 2 freeze–thaw cycles. Both cryoprobes had a setting of 4 cm and 80% power to prevent injury to the adjacent bowel and pancreas. A follow-up CT 1 month later (15.7 months postoperatively) showed that the left retroperitoneal ACC and metastatic hepatic tumors had reduced in size, and the pulmonary nodules were almost completely resolved.

Radiotherapy with a total dose of 30 Gy to the left retroperitoneal ACC was performed 2.2 months after cryotherapy. The pulmonary and retroperitoneal tumors were invisible on CT scans performed at 7.3 months and 9.8 months after cryotherapy (Fig. 3). There were now only 3 hepatic tumors, each less than 2 cm in diameter (Fig. 4). Radiofrequency ablation of the residual hepatic tumors was performed. One month later, a whole-body CT scan showed no recurrence and no metastasis. The patient underwent a regular biochemistry survey and CT scan. She continued taking low-dose mitotane (500 mg once daily) and a cortisone acetate supplement (12.5 mg twice daily). She had been disease-free for 15.8 months at the data cutoff date, which was 43.5 months after the initial adrenalectomy and 34.2 months after cancer recurrence.

Discussion

According to a 2013 report from the University of Texas MD Anderson Cancer Center, the overall median survival time for patients with ACC is 3.21 years. The median survival times for patients in Stages I, II, III, and IV were 24.1, 6.08, 3.47, and 0.89 years, respectively [12]. Our patient had ACC recurrence with multiple metastases 9.3 months after her initial adrenalectomy. It is a Stage IV disease with poor prognosis. She survived for another 34.2 months and stayed disease-free for at least 15.8 months after a series of treatments, including mitotane administration, chemotherapy, ^{90}Y SIRT, cryotherapy, radiotherapy, and radiofrequency ablation. To our knowledge, this is the first published report on using cryotherapy for ACC and the third on using ^{90}Y SIRT for hepatic metastasis of ACC. Our experience treating this patient demonstrated the effectiveness of combining cryotherapy with ^{90}Y SIRT for ACC.

According to the clinical practice guidelines for ACC from the European Society of Endocrinology, adjuvant therapy is not routinely recommended for patients at low or moderate risk of recurrence [5]. Therefore, our patient did not receive mitotane and radiotherapy after her initial adrenalectomy.

Mitotane was applied as soon as ACC recurred with metastases. The suggested dose of mitotane is 3.0 to 4.0 g/day, with adjustments according to blood concentrations and tolerability [5]. However, our patient could not tolerate a mitotane dosage higher than 1 g/day, and we doubted the therapeutic effectiveness of mitotane. Moreover, the hepatic tumors enlarged, and the adrenal tumor recurred under mitotane and chemotherapy. Therefore, we hypothesized that other treatments play important roles in the remission of ACC.

For hepatobiliary cancers, ^{90}Y SIRT is well studied and is considered a viable option for arterially directed local therapy in the National Comprehensive Cancer Network guidelines [13]. For CRC LM, ^{90}Y SIRT offers an improved median overall survival of 7.9 to 12.6 months in chemotherapy-refractory cases [14] and can significantly increase resectability for previously unresectable cases [15]. Complications with ^{90}Y SIRT are rare and include radioembolization-induced liver disease, hepatic failure, and gastrointestinal ulceration [6]. As for the hepatic metastases in our patient, ^{90}Y SIRT was applied for palliative purposes. A CT scan showed a good response with tumor necrosis initially; the tumor then shrank in the following 2 months and 6.5 months. For the intention of curative treatment, radiofrequency ablation was performed when the hepatic tumors reduced to fewer than 3, each less than 3 cm in diameter, and complete remission was achieved. The literature contains 2 reports of using ^{90}Y SIRT to treat hepatic metastases of ACC, with both combing that treatment with EDP-M [8, 9]. In 1 case, the tumor shrank significantly [9]; in the other, complete remission was achieved [8]. Further studies are needed to evaluate the overall effectiveness of ^{90}Y SIRT in hepatic metastases of ACC.

Cryoablation uses the Joule–Thompson effect in a 2-phase process of freezing followed by thawing to cause cell rupture. A major benefit of cryotherapy is the visibility of an ice treatment zone on CT [10]. Cryotherapy to hepatic lesions of CRC LM yields a 5-year survival rate of 44%, which is higher than the 36% with resection [16]. Complications are predominantly related to bleeding, the risk of which correlates with the size of the tumor [6]. Welch et al used cryotherapy to treat adrenal metastasis of renal cell carcinoma, melanoma, hepatocellular carcinoma, lung cancer, urothelial carcinoma, and penile squamous cell carcinoma [10]. In their study, local control was achieved in 92% of the patients. The patients also experienced a significant increase in systemic blood pressure. Hypertensive crisis developed in 41.7% of the patients during the final thaw phase of cryoablation. Therefore, pretreatment with α-blockers is suggested. Another study showed a technical success rate of 90.3% in patients with adrenal metastases [17]. Zhang et al studied cryoablation for pheochromocytoma in 8 patients, all of whom received partial ablation and achieved biochemical remission [11]. Five patients (62.5%) experienced a hypertensive crisis during the procedure, and 1 experienced hypovolemic shock after cryoablation. Our patient is the first reported case of cryoablation for ACC. The procedure was performed smoothly. She had no history of hypertension or bleeding during the treatment course. The tumor shrank after cryoablation. Thus, cryoablation was an efficacious choice for local treatment of ACC.

After mitotane administration and chemotherapy, our patient's pulmonary metastasis did not show significant regression until 1 month after cryotherapy to the retroperitoneal ACC, after which CT scans showed near resolution of the pulmonary lesions. Four months later, the pulmonary nodules had completely disappeared. Early reports have demonstrated the abscopal effect of cryotherapy: spontaneous remission of metastatic lesions after treatment of the primary site [18]. This might be due to a systemic immune response to the antigen released from local necrotic cells. A mouse model has provided evidence of enhanced T cell responses after cryoablation [19]. Among all ablation techniques resulting in an in situ release of tumor antigens, cryoablation is superior to other techniques, probably due to its ability to preserve native antigen structure during cold damage [20]. Preliminary data have demonstrated a good synergy between cryoablation and immunotherapy [20]. The abscopal effect might be why our patient's pulmonary metastases regressed after cryotherapy. However, since pulmonary metastases were diagnosed based on imaging characteristics and clinical correlation without pathologic proof, another explanation for the regression of pulmonary lesions could have been the resolution of previous pulmonary infections. However, this was not the case with our patient because she had no symptoms or signs associated with pulmonary infections and received no antibiotic treatment.

Conclusion

Our case highlights the importance of considering multidisciplinary approaches and the role of local therapeutic measures for advanced ACC. To our knowledge, this is the first published report of a patient receiving cryoablation for ACC, and the third report of receiving ^{90}Y SIRT for hepatic metastases of ACC. The response was considerable, indicating that the combined use of cryoablation and ^{90}Y SIRT should be considered for local treatment of ACC and is worthy of further study.

Funding

None.

Conflict of Interest

There is no conflict of interest.

Data Availability

All datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding authors on reasonable request.

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