Case Report

Malignant pheochromocytoma with lung metastasis after right adrenalectomy for pheochromocytoma eleven years ago

Won Suk Choi[1], Jong Yoon Park[1], Mee Sook Roh[2], Pil Jo Choi[1]

[1]Department of Thoracic and Cardiovascular Surgery, [2]Department of Pathology, Dong-A University College of Medicine, Busan 602-715, South Korea
Correspondence to: Pil Jo Choi, MD, PhD. Department of Thoracic and Cardiovascular Surgery, Dong-A University College of Medicine, 26, Daesingongwon-ro, Seo-gu, Busan 602-715, South Korea. Email: pjchoi@dau.ac.kr.

Abstract: A 30-year-old woman had multiple masses on right adrenalectomy site, posterior mediastinum, and left lung on computed tomography (CT) and positron emission tomography. She had a right adrenalectomy for pheochromocytoma eleven years ago. She received proper alpha and beta blocker and completed surgical resection. Pheochromocytoma was confirmed by histopathology. Here we report the case of metastatic malignant pheochromocytoma with very poor prognosis.

Keywords: Adrenalectomy; metastasis; neoplasm; pheochromocytoma; recurrence

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Introduction

Pheochromocytoma is a catecholamine-secreting tumor presenting with high blood pressure. When there is no chromaffin tissue in previously noted tumor existence area, it is diagnosed as malignant pheochromocytoma (1). Although malignancy rate of these tumors are approximately 10% (1), their overall 5-year survival rate is less than 60% (2). Malignant pheochromocytoma usually has poor prognosis. However, accurate diagnosis and proper surgical resection might yield good clinical outcome.

Case report

A 30-year-old woman with palpitation was found with retroperitoneal tumor on her regular checkup. Eleven years ago, she had systolic blood pressure up to 280 mmHg. Thus, she went through contrast-enhanced abdominal-pelvic computed tomography (CT) which revealed right adrenal pheochromocytoma. She underwent right adrenalectomy to remove the tumor. After the surgery, she ceased her regular follow up because she felt that her symptoms had subsided. At her recent admission for her checkup, she only had intermittent palpitation with normal blood pressure. Considering the patient was a young female and she had previous adrenalectomy operation, an endocrinology professional recommended her genetic tests for multiple endocrine neoplasia type 2 (MEN 2), Von Hippel-Lindau disease, neurofibromatosis, and familial paraganglioma. However, she and her family members refused to have tests because they didn't have a history of associated symptoms. In addition, the cost was too expensive. In preoperative CT, there were four nodules at less than 1 cm in the left lung (one in upper lobe, three in lower lobe), a 4.6 cm high attenuated mass in the right retrocrural area at diaphragm level, and a 2.8 cm high enhanced mass at the previous right adrenalectomy site (*Figure 1*). Laboratory findings were: plasma metanephrine at 0.03 mg/day, plasma normetanephrine at 20.92 mg/day, serum epinephrine at 315.83 pg/mL, and serum norepinephrine at 1,501.61 pg/mL (*Table 1*). Even if her biochemistry findings did not suffice the diagnostic criteria for pheochromocytoma or paraganglioma, she was highly suspected of pheochromocytoma based on imaging studies (*Figure 2*). To rule out recurrent pheochromocytoma at the previous right adrenalectomy site, we performed surgical resection with the general surgery team. Preoperative CT-guided wire hooking was performed on the smallest nodule in segment 6 of the left lung. During the operation, alpha blocker was pre-medicated to control blood pressure for 6 weeks. In right lateral decubitus position, video-

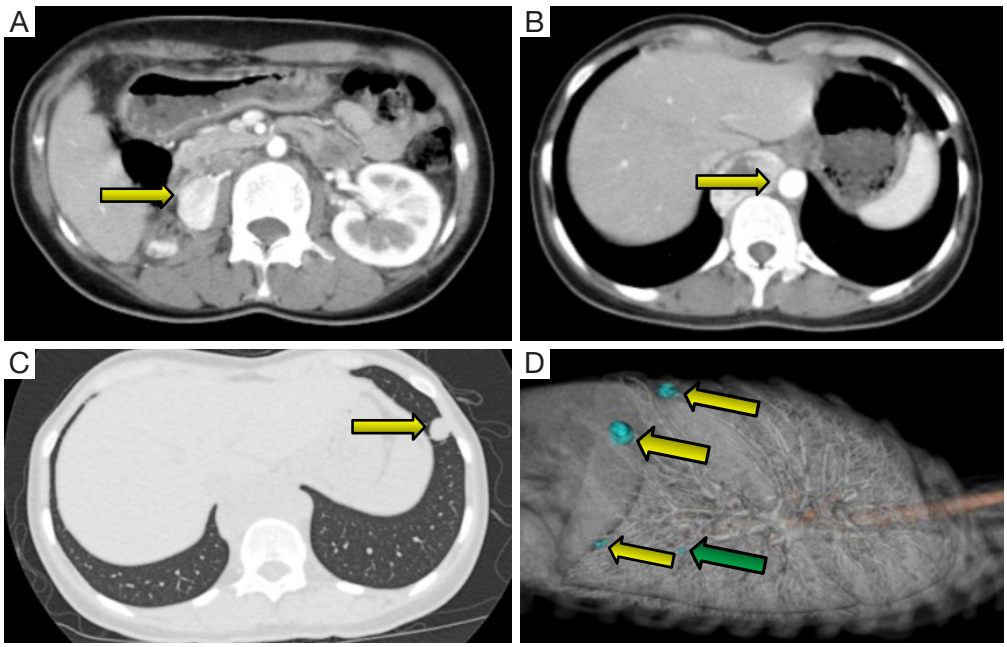

Figure 1 Preoperative chest and abdominal contrast enhanced CT findings after the first right adrenalectomy (yellow arrow indicating mass lesion). (A) Right adrenalectomy site mass; (B) right posterior mediastinal (retrocrural) mass; (C) left upper lobe pulmonary nodule; (D) left four pulmonary nodules in 3D CT (the nodule indicated by green arrow was identified as no tumor). 3D CT, 3 dimension computed tomography.

Table 1 Biochemical laboratory findings comparing before with after redo operation

Variables	Pre (pg/mL)	Post (pg/mL)	Normal range (pg/mL)
Metanephrine (plasma)	0.03 mg/day	0.03 mg/day	12-60
Normetanephrine (plasma)	20.92 mg/day	1.71 mg/day	18-111
Epinephrine	315.83	17.42	<120
Norepinephrine	1,501.61	218.89	<410

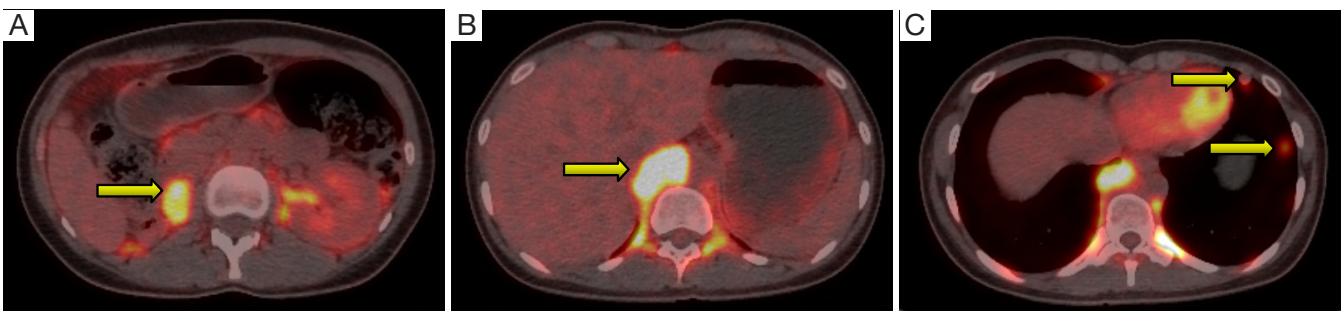

Figure 2 Preoperative chest and abdominal positron emission tomography findings after first right adrenalectomy (yellow arrow indicating the mass lesion). (A) Right adrenalectomy site mass (mSUV: 10.84); (B) right posterior mediastinal (retrocrural) mass (mSUV: 17.55); (C) two nodules in left upper lobe pulmonary nodules (mSUV: 5.65 & 5.64). CT, computed tomography; mSUV, maximum standardized uptake value.

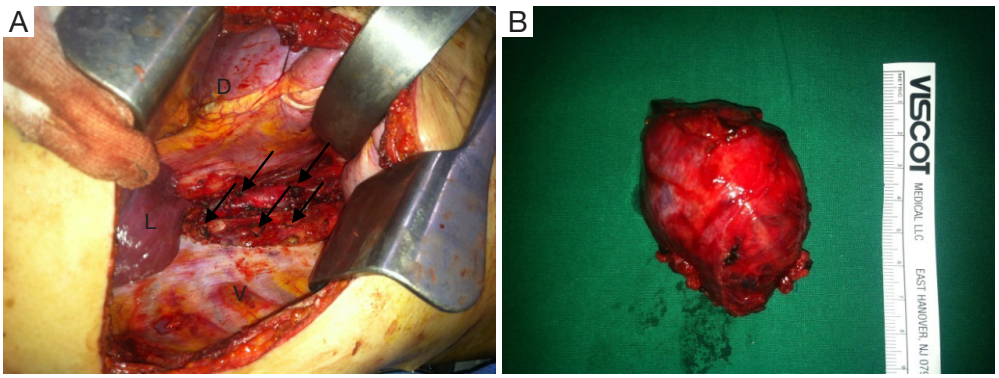

Figure 3 Operative findings. (A) Rich feeding vessels to mediastinal mass in right retrocrural area at T10-L1 level; (B) resected 6.5 cm × 4.5 cm mediastinal mass with characteristic of hypervascularity. D, diaphragm; L, lung; V, vertebra; black arrow, feeding vessels to mediastinal mass.

assisted thoracoscopic multiple wedge resection of left lung was done by our surgical staff. After we changed the position of the patient to supine, right thoracotomy along the 9th intercostal space was done. Retrocrural mass resection was followed. The hypervascular pulsating mass at T10-L1 level was 6.5 cm × 4.5 cm in size (*Figure 3*). In the same field, the general surgery team opened retroperitoneum to perform complete resection at the adrenalectomy site. The retroperitoneal mass was 3 cm × 2.5 cm in size and well-capsulated. The entire surgical procedure was finished without difficulties. Histopathological diagnoses of all specimens were pheochromocytoma (*Figure 4*). After the surgery, plasma normetanephrine and serum epinephrine were normalized (*Table 1*). Postoperative PET image showed that the uptake amount and size of previous noted hypermetabolic nodular lesions were decreased. However, such lesions had not been disappeared. Moreover, we noticed residual hypermetabolic lymph nodes at aortocaval and retrocaval area. We assumed that these lesions were residual masses and metastases. Changes of preoperative and postoperative maximum standardized uptake value (mSUV) in the adrenalectomy site, retrocrural, and largest two lung nodules were from 10.84 to 13.92, 17.55 to 0, and 5.65, 5.64 to 0, respectively (*Figure 5*). In postoperative ^{123}iodine-metaiodobenzylguanidine (^{123}I-MIBG) imaging, increased uptake of residual pheochromocytoma in right adrenalectomy site, retroperitoneal lymph nodes, and residual mass were observed (*Figure 6*). After one ^{131}I-MIBG treatment at 200 mCi, further treatment was stopped due to pregnancy and delivery. Any sign of severe high blood pressure or symptom of paroxysmal palpitation was not present during the close monitoring period.

Discussion

Most pheochromocytomas are originated from chromaffin cells of the adrenal medulla. Approximately 10% of them are extra-adrenal paragangliomas containing chromaffin cells (3). It is difficult to diagnose malignant pheochromocytoma with histopathologic studies (4). Other methods of identifying malignancy from benign pheochromocytomas include pheochromocytoma of adrenal gland scaled score (PASS), Ki-67 index, HSP 90 (heat-shock protein 90), and activator of transcription 3 (STAT 3). However, their efficacy is still controversial (5-7).

Regardless of recurrence, malignant pheochromocytomas is defined as an occurrence of distant metastasis where chromaffin tissue is absent, not by local invasion (8). Typical sites of metastasis are bone, lung, liver, and lymph node (2,9). Malignancy rate of primary adrenal pheochromocytoma and sympathetic paraganglioma are 25% and 60%, respectively (10). Several literatures reported independent risk factors of malignancy, including the presence of succinated dehydrogenase subunit B (SDHB) mutation, multifocal and extra-adrenal location, size of the primary tumor (5 cm or larger), heavy tumor (250 g or greater), younger age, early onset postoperative hypertension, increased levels of plasma methoxytyramine, and higher plasma or urine metadrenalins (9-15). In our case, risk factors of malignant pheochromocytoma are were: young age (30 years old), paraganglioma larger than 5 cm, and extra adrenal gland location.

Although there is no clear symptom or laboratory finding for pheochromocytoma or paraganglioma, if such disease is suspected based on imaging studies, we can conclude malignancies base on previous operative history and risk

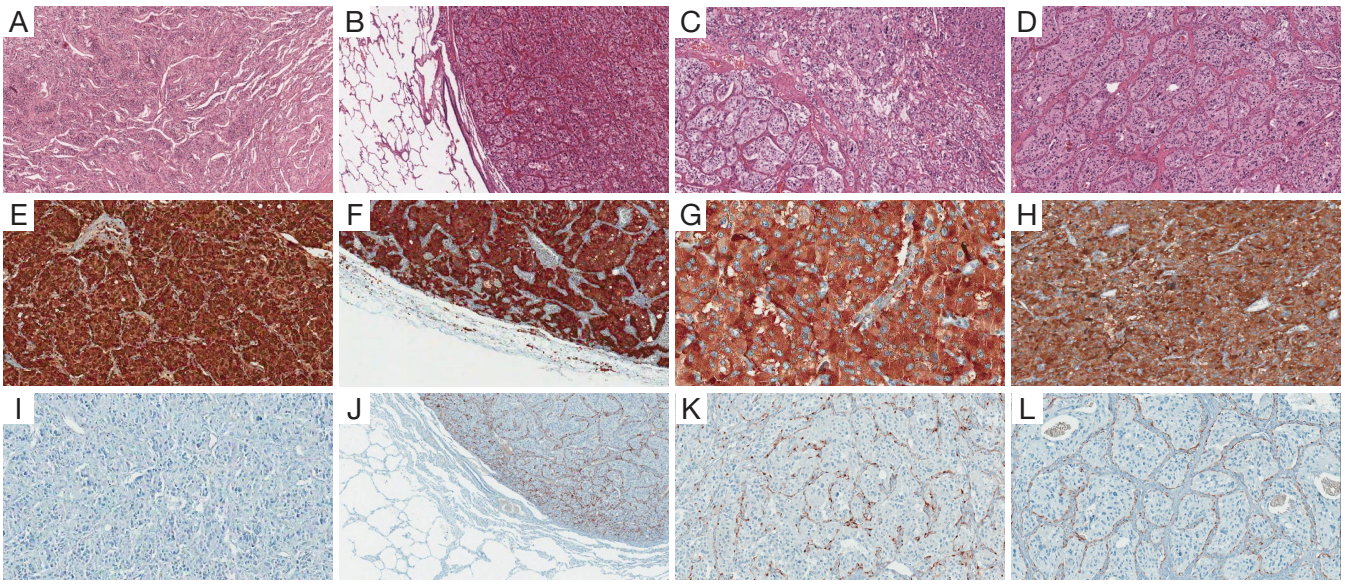

Figure 4 Resected tumors showing well-defined cell nests called 'Zellballen' as characteristic of pheochromocytoma (A-D, hematoxylin and eosin stainging). Tumor cells showing diffuse strong positive immunoreactivity with synaptophysin (E-H). All sustentacular cells around the 'Zellballen' showed strong immunoreactivity with S-100 protein (I-L). (A,E,I) Right adrenal mass in 2002 (×40); (B,FJ) left lung nodule in 2014 (×40); (C,G,K) right mediastinal mass in 2014 (×100); (D,H,L) right adrenalectomy site mass in 2014 (×100).

factors because metastatic pheochromocytoma has very poor prognosis.

In our case, the mass at the previous right adrenalectomy site was considered as a recurrence of remnant tumor cell or spillage during manipulation of first right adrenalectomy. Moreover, posterior mediastinal mass in the retrocrural area at T10-L1 level could be a primary paraganglioma from nerve sheath because pheochromocytoma is a hypervascular solid mass. However, we cannot preclude the possibility of disseminated seeding through retroperitoneum from remnant tumor during previous operative manipulation.

Brennam *et al.* (16) reported that failure to find extra lesions at primary exploration will develop metachronous primary tumor in remnant adrenal or extra-adrenal chromaffin tumor due to disruption and implantation during previous operation. They also suggested that such failure in finding extra lesions might cause metastatic disease after surgical resection. In the case reported here, the origin of lung metastasis was unclear based on histopathological findings. It might be a hematogenous spread from either remnant retroperitoneal tumor or posterior mediastinal tumor. As mentioned above, paraganglioma has more frequent metastasis risk than pheochromocytoma. Therefore, the lung nodules in our patient might be metastases from paraganglioma.

Based on postoperative PET and MIBG studies, residual masses might be seeded from manipulation during previous operation. We thought that all four nodules in the lung and retrocrural mass were totally resected. However, since residual mass of adrenalectomy site in PET and MIBG was seen, suggesting incomplete radical resection. Moreover, unchanged mass of retrocaval and aortocaval area in PET suggested incomplete exploration. Characteristics of pheochromocytoma in the sympathetic chain and other area associated with chromaffin tissue will make complete resection difficult. We conclude that close observation of these residual tumors by MIBG study is crucial.

Due to the hormonal effect of catecholamine of pheochromocytoma during multiple site resections, we studied the patient's unstable hemodynamic status. Fortunately, alpha blocker and beta blocker premedication more than six weeks made patient stable. After being diagnosed of malignant pheochromocytoma, some patients survived more than 20 years (17). However, prognosis of malignancy is generally poor, with less than 60% on 5-year survival rate (2). However, the survival rate of benign pheochromocytoma is 90% on 5-year survival rate (18). Classic symptoms of pheochromocytoma include headache, diaphoresis, and flushing (appear in 40% of all patients with pheochromocytoma). The rest do not show any

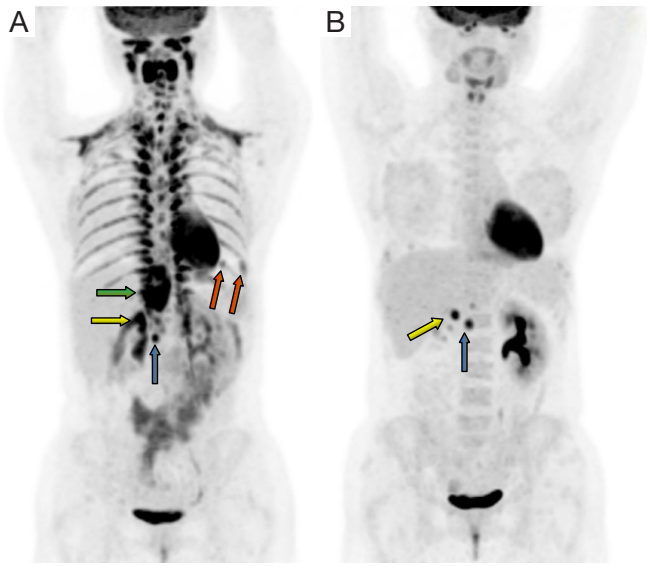

Figure 5 PET image comparing pre-redo operation to post-redo operation. (A) Preoperative PET. The hypermetabolic mass (mSUV 10.84) at first right adrenalectomy site was indicated by yellow arrow. There is hypermetabolic nodular lesion in the retrocaval area (indicated by blue arrow). The largest hypermetabolic mass (mSUV 17.55) of retrocrural (mediastinal) area was indicated by green arrow. Two hypermetabolic nodules (mSUV 5.64, 5.65) in left lung were indicated by red arrow; (B) postoperative PET. The hypermetabolic nodular lesion (mSUV 13.92) at the site of redo mass excision of adrenalectomy site was indicated by yellow arrow. The hypermetabolic lymphadenopathy in the retrocaval area was indicated by blue arrow. PET, positron emission tomography; mSUV, maximum standardized uptake value.

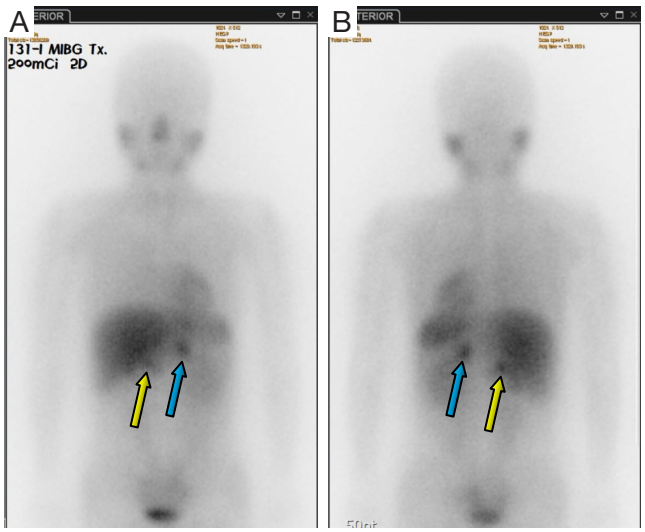

Figure 6 Images showing ^{131}I-MIBG (200mCi) after redo operation. Well uptake of residual pheochromocytoma at the right adrenalectomy site was shown by yellow arrow. Physiologic uptake in the left adrenal gland was shown by blue arrow. (A) Anterior view; (B) posterior view. ^{131}I-MIBG, ^{131}iodine-metaiodobenzyl guanidine.

specific symptoms (19). For that reason, the diagnosis of phemochoromycytoma is difficult. In addition, patients have poor prognosis. When risk factors of malignant as mentioned above are presented when the first episode starts, more careful follow up is needed. Noshiro *et al.* (20) have reported recurrence in more than 10 years after primary adrenalectomy for pheochromocytoma which is similar to our case. It was recommended that the follow up period should be at least 10 years from 1st operation or 1st diagnosis of pheochromocytoma.

Conclusions

When silent pheochromocytoma with biochemical inactivity is identified, we have to consider surgical resection instead of therapeutic modalities if risk factors of metastatic malignant pheochromocytoma are presented with suspicious radiologic findings. Surgery will lead to better outcome. Although we thought that we completed radical excision of all masses, there might be possibilities of recurrence or metachronous development along the chromaffin tissues. Therefore, we should follow up at least 10 years by MIBG study.

Here we report a patient who underwent right adrenalectomy eleven years ago developed multiple metastases at the previous right adrenalectomy site as well as retrocrural and lung lesions. In this case, we completely excised metastatic masses and closed observe patient on MIBG can without side effects.

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