High-output Heart Failure Caused by a Tumor-related Arteriovenous Fistula: A Case Report and Literature Review

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Abstract:
High-output heart failure caused by a tumor-related arteriovenous fistula in adults is a rare clinical condition. We herein report a case of high-output heart failure caused by an arteriovenous fistula associated with renal cell carcinoma and a literature review of 29 published cases to date. Renal cell carcinoma seems to be the most common underlying tumor. For the diagnosis, right heart catheterization and enhanced computed tomography are considered useful. The removal of the underlying tumor and arteriovenous fistula is the best treatment for heart failure.

Key words: high-output heart failure, arteriovenous fistula, tumor, renal cell carcinoma

Introduction
High-output heart failure caused by an arteriovenous fistula associated with neoplasm in adults is rare but results in a critical condition. Its epidemiology, treatment, and clinical course, as well as the type of underlying tumor have not been fully elucidated. We herein report a case of high-output heart failure caused by an arteriovenous fistula associated with renal cell carcinoma along with a literature review.

Case Report
A 64-year-old man with lower leg edema and dyspnea on exertion visited a local doctor. His blood pressure and pulse rate were 145/79 mmHg and 93 beats per minute, respectively. Chest radiography showed cardiac enlargement with a cardiothoracic ratio (CTR) of 69%, bilateral pleural effusion, and nodule shadows in the right lung (Fig. 1A). Computed tomography (CT) incidentally revealed a right renal mass. He was referred to the urology department of our hospital. The results of a right kidney biopsy indicated clear cell renal cell carcinoma. Enhanced CT revealed a giant hyper-vascular mass arising from the inferior pole of the right kidney extending to the renal vein and inferior vena cava (IVC), as well as multiple metastases in the lungs. Taken together, these results suggested a clinical stage of T3b N0 M1 according to the TNM classification system (Fig. 2A-C).

Neo-adjuvant chemotherapy was started; however, the cardiac enlargement and lower leg edema worsened, and the patient was finally referred to a cardiologist. A systolic heart murmur was heard, but abdominal auscultation was not performed. Transthoracic echocardiography revealed mild hypokinesis with a left ventricular ejection fraction of 45%, 4-chamber dilatation, moderate mitral valve regurgitation, and severe tricuspid valve regurgitation with an estimated right ventricular pressure of 40 mmHg (Table 1). The patient was diagnosed with congestive heart failure due to unknown cause and received more intensive treatment including oral diuretics (tolvaptan 15 mg/day, furosemide 60 mg/day, and ̍

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spironolactone 25 mg/day) and an intravenous diuretic (furosemide 20 mg/day). However, dyspnea on exertion, cardiomegaly, and a high level of brain natriuretic peptide (BNP; 259 pg/mL) persisted (Fig. 1B). Right heart catheterization showed a high cardiac output of 8.68 L/min, a cardiac index of 4.72 L/min/m² (Fick), and slightly elevated pressure in each chamber (Table 1). Blood gas sampling showed high oxygen saturation at the proximal site to renal veins in the IVC (90.3%), suggesting an arteriovenous shunt in the systemic circulation. Coronary angiography revealed normal coronary arteries. Reassessment of enhanced CT images revealed enhancement of the right renal veins and IVC in the arterial phase, indicating an arteriovenous fistula (Fig. 2D). The patient was finally diagnosed with high-output heart failure.
failure due to an arteriovenous fistula associated with renal cell carcinoma.

Radical nephrectomy with a lower midline abdominal incision was performed. During the surgery, the central venous pressure was 12-16 mmHg before ligation of the renal artery, and it decreased to 7-8 mmHg immediately after the ligation. Multiple enlarged veins draining directly into the IVC were observed and then ligated and dissected, along with the renal artery. After clamping the IVC, main right renal vein was excised, and the right kidney was removed together with the extending part in the IVC. A histopathological examination confirmed clear cell renal cell carcinoma.

The postoperative course was uneventful. The cardiomegaly and lower leg edema dramatically improved, and the dose of diuretics was gradually reduced. Treatment was thus discontinued 13 days after the surgery. Postoperative right heart catheterization after the discontinuation of diuretics showed normalization of the cardiac output, pressure, and oxygen saturation in the IVC (Table 1).

At the 1-month follow-up visit, the patient was doing well. Chest radiography showed a CTR of 46%, and he had a BNP level of 28 pg/mL without diuretics (Fig. 1C). He then received postoperative adjuvant chemotherapy.

### Discussion

We herein report a case of high-output heart failure caused by an arteriovenous fistula associated with renal cell carcinoma, which can be considered a tumor-related heart disease. An arteriovenous fistula is known to cause high-output heart failure by increasing the venous return; (1) however, a tumor-related arteriovenous fistula causing heart failure is uncommon. Table 2 summarizes previously published cases of heart failure caused by a tumor-related arteriovenous fistula in the systemic circulation (2-30).

### Underlying tumors

In the majority of published cases, the tumors causing heart failure due to an arteriovenous fistula in the systemic circulation were renal cancers (22 out of 30 cases) (2-4, 6, 7, 9, 11-19, 21, 22, 24, 25, 28, 29), including mostly renal cell carcinoma. Cases of clear cell carcinoma, which is the most common type of renal cell carcinoma, frequently involve a mutated von Hippel-Lindau tumor suppressor gene.
The gene inhibits angiogenesis and cell growth (31), so most renal cell carcinoma cases show hypervascularity. Microscopically, vascular invasion and microembolism of neoplastic cells are suspected of causing vascular fragility, resulting in arteriovenous connection (29, 32). Furthermore, renal cell carcinoma commonly creates spaces that are covered in a layer of endothelium and directly communicating with both capular arteries and veins (33). These features may lead to the formation of an arteriovenous fistula. Other underlying tumor types, such as unclassified malignant mesenchymoma (5), small medullary carcinoma of the thyroid (10), hepatocellular carcinoma (20), leiomyoma (23),

Table 2. Summary of Previously Published Cases Representing Heart Failure Caused by Tumor-related Arteriovenous Fistula.

| Author (Year) | Age | Sex | CC | Cardiac murmur | Bruit of tumor | HT | Location of tumor | Type of tumor | Diagnosis of AVF | Treatment of tumor | Course of HF |
|---------------|-----|-----|----|----------------|----------------|----|--------------------|---------------|-----------------|------------------|-------------|
| Hamilton (1953)² | 29  | m   | HF | +   | +             | +       | kidney             | adenocarcinoma | bruit           | surgery          | improved     |
| Scheifley (1959)³ | 39  | f   | Both | +   | +             | +       | kidney             | hypernephroma  | bruit, AG       | surgery          | improved     |
| Abbot (1961)⁴  | 62  | f   | Tumor | +   | +             | +       | kidney             | renal cell carcinoma | bruit, AG        | surgery          | improved     |
| Crawford (1963)⁵ | 51  | m   | HF | +   | +             | +       | Ao and IVC mesenchymoma | malignant     | bruit, AG       | surgery          | improved     |
| Nicoll (1964)⁶  | 74  | f   | Both | -   | +             | +       | kidney             | hypernephroma  | bruit, AG       | surgery          | improved     |
| Thomas (1965)⁷  | 60  | m   | Tumor | +   | +             | +       | kidney             | clear cell carcinoma | bruit, AG, RHC | surgery          | improved     |
| Vetto (1966)⁸   | 73  | m   | Tumor | -   | +             | +       | scapula, pelvis    | renal cell carcinoma | bruit, AG        | surgery          | improved     |
| Norris (1971)⁹  | 39  | m   | Tumor | -   | +             | +       | bilateral kidneys | adenocarcinoma | bruit, AG, RHC | surgery, RT     | improved     |
| Damascelli (1972)¹⁰ | 33  | f   | Tumor | ND  | +             | ND      | thyroid, lymph node | small medullary carcinoma | bruit, AG        | surgery          | improved     |
| Sondag (1973)¹¹ | 67  | f   | HF | +   | -             | +       | kidney             | hypernephroma  | AG              | chemo            | ND            |
| Pickens (1973)¹² | 51  | f   | HF | +   | +             | +       | kidney             | clear cell carcinoma | RHC, bruit, AG | surgery          | improved     |
| Curtiss (1974)¹³ | 38  | f   | Tumor | +   | -             | +       | kidney             | clear cell carcinoma | AG              | surgery          | improved     |
| Rodgers (1975)¹⁴ | 63  | f   | Tumor | +   | +             | +       | kidney             | clear cell carcinoma | AG              | surgery          | improved     |
| Bass (1975)¹⁵   | 60  | m   | Tumor | -   | ND            | +       | kidney             | clear cell carcinoma | AG              | surgery          | improved     |
| Ricketts (1978)¹⁶ | 53  | f   | Tumor | +   | +             | ND      | possible hypernephroma | AG             | TAE             | improved     |
| Crawford (1979)¹⁷ | 45  | f   | HF | ND  | +             | +       | bilateral kidneys | renal cell carcinoma | AG              | surgery          | improved     |
| Thomas (1981)¹⁸  | 63  | f   | Tumor | ND  | ND            | ND      | bilateral kidneys | possible hypernephroma | AG              | surgery          | improved     |
| Nakada (1983)¹⁹  | 62  | m   | Tumor | ND  | -             | -       | kidney             | clear cell carcinoma | AG              | surgery          | improved     |
| Waki (1984)²⁰   | 59  | m   | HF | ND  | +             | ND      | kidney             | hepatocellular carcinoma | AG              | TAE             | improved     |
| Selli (1986)²¹   | 40  | f   | Tumor | ND  | +             | ND      | kidney             | renal cell carcinoma | AG              | surgery          | improved     |
| Holmes (1991)²²  | 63  | m   | HF | ND  | +             | ND      | kidney             | renal cell carcinoma | AG              | surgery          | improved     |
| Lee (1993)²³    | 44  | f   | Tumor | ND  | ND            | ND      | intrapelvis        | leiomyoma       | TEE, AG         | surgery          | improved     |
| Takahashi (1995)²⁴ | 76  | m   | Tumor | ND  | ND            | ND      | kidney             | clear cell carcinoma | AG              | surgery          | improved     |
| Piggott (2000)²⁵ | 62  | f   | HF | +   | -             | -       | kidney             | renal cell carcinoma | infert           | surgery          | improved     |
| Szucs-Farkas (2002)²⁶ | 47  | m   | Both | ND  | ND            | ND      | kidney             | malignant fibrous histiocytoma | eCT, AG         | surgery          | improved     |
| Ozaki (2003)²⁷   | 53  | f   | HF | +   | +             | -       | intrapelvis        | possible alveolar soft part sarcoma | bruit, eCT, RHC, AG | surgery          | no change   |
| Hayek (2014)²⁸   | 58  | m   | HF | ND  | +             | +       | kidney             | clear cell carcinoma | RHC, MRI, AG   | surgery          | improved     |
| Watanabe (2015)²⁹ | 64  | f   | Both | ND  | -             | +       | kidney             | clear cell carcinoma | eCT             | TAE, surgery    | improved     |
| Ando (2018)³⁰    | 78  | f   | HF | ND  | +             | ND      | iliac artery       | leiomyosarcoma   | eCT             | surgery          | ND           |
| Tobe (2020)³¹    | 64  | m   | HF | ND  | +             | ND      | kidney             | clear cell carcinoma | RHC, eCT        | surgery          | improved     |

Listed reports are written in English or Japanese. Such cases are not listed: patients’ age<18, pulmonary arteriovenous fistula, hypertension or cardiomegaly without heart failure, cardiac tumors, hematological malignancies, angiomia or angiosarcoma.

CC: chief complaint, HF: heart failure-related symptoms, Tumor: tumor-related symptoms, Both: both heart failure- and tumor-related symptoms, ND: not described, HT: hypertension, AVF: arteriovenous fistula, AG: angiography, RHC: right heart catheterization, LVG: left ventricular angioam, TEE: transesophageal echocardiography, eCT: enhanced computed tomography, MRI: magnetic resonance imaging, RT: radiation therapy, TAE: transcatheter arterial embolization.
malignant fibrous histiocytoma (26), and possible alveolar soft part sarcoma (27) and leiomyosarcoma (30), have also been reported. Arteriovenous fistulas associated with tumors might not be uncommon; the incidence of the involvement of arteriovenous fistula in renal cell carcinoma is reported to be 12%-50% (34, 35). However, it seems quite rare for congestive heart failure to develop because of this. The type or location of tumors accompanied by arteriovenous fistulas that cause heart failure might thus be limited.

**Symptoms at the first visit**

The chief complaint at the first visit was heart failure-related symptoms (2, 5, 11, 12, 14, 17, 20, 22, 25, 27, 28, 30), symptoms related to underlying tumors (4, 7-10, 13, 15, 16, 18, 19, 21, 23, 24), and both (3, 6, 26, 29) in 13, 13, and 4 previously published cases, respectively. About half of the patients presented with symptoms associated with heart failure at the first visit. Renal cancer, which is a major underlying cause, is often asymptomatic and it tends to be found incidentally. The famous triad of hematuria, flank pain, and a palpable mass is no longer a common presentation, and such a condition therefore suggests the presence of advanced stage disease (36). Therefore, heart failure-related symptoms might appear as the first symptoms. When a patient presents with high-output heart failure due to unknown cause, we may need to consider a tumor-associated arteriovenous fistula.

**The diagnosis**

- **Physical examinations**

  In most cases, an arteriovenous fistula bruit and/or a systolic heart murmur were heard (2-14, 16, 17, 20, 21, 25, 27-29). A systolic heart murmur indicates relative outflow tract obstruction caused by the high-output state. The bruit and murmur disappeared after resection of the underlying tumors and arteriovenous fistulas. Arteriovenous fistulas that cause high-output heart failure might have a large shunt flow, resulting in an audible arteriovenous fistula bruit. However, the bruit was not detected in some of the previous cases (11, 13, 19, 25), and the absence of bruit is not always indicative of the absence of an arteriovenous fistula. Systolic hypertension, which also results from an arteriovenous fistula because of an increase in cardiac output (37), was observed in most cases (2-9, 11-15, 17, 22, 24, 28, 30).

- **Right heart catheterization**

  Preoperative right heart catheterization was performed in 12 cases (5, 8, 9, 12-14, 16, 17, 23, 27, 28), and follow-up right heart catheterization was performed in 6 cases after treatment (5, 9, 13, 16, 28). The pre-treatment cardiac output was 8.14-15.2 L/min (5, 9, 13, 17, 27, 28), and an increase in the oxygen saturation level was noted in 8 cases (5, 8, 9, 12, 14, 27, 28). Interestingly, right heart catheterization revealed the presence of an arteriovenous fistula in some cases (14). The post-treatment follow-up data showed a decrease in cardiac output in all reported cases (5, 9, 13, 16, 28).

- **Imaging examinations**

  Imaging is essential to confirm the presence of an arteriovenous fistula. In the past, angiography was frequently performed, but more recently, enhanced CT has been most commonly used. Magnetic resonance imaging (MRI) and echography can be also helpful.

  To detect a tumor-related arteriovenous fistula, bruit over the site of the tumor and systolic heart murmur are helpful findings. To confirm the presence of an arteriovenous fistula, angiography was performed in the past, but enhanced CT or MRI is currently recommended. For a definitive diagnosis of arteriovenous shunt and the assessment of heart failure, right heart catheterization is helpful.

**Treatment and clinical course**

Resection of the underlying tumor was performed in most cases. After the removal of tumors and arteriovenous fistula, heart failure improved in almost all cases. In two cases, embolization of the arteriovenous fistula was performed, which resulted in the improvement of heart failure (16, 20). In one case, radiation therapy brought temporary relief of heart failure symptoms (9). When treating malignant tumor, direct therapies, including resection, embolization, or radiation, are usually considered, and these can also be used to treat heart failure. Furthermore, even if the tumor is benign and does not require invasive treatment for itself, we should consider performing such therapies in patients with heart failure that is uncontrollable by medical therapy due to severe tumor-related arteriovenous fistula.

**Conclusion**

High-output heart failure caused by a tumor-related arteriovenous fistula in adults is rare, but its incidence may not be negligible. A careful examination can lead to the correct and prompt diagnosis. Renal cancer, mainly renal cell carcinoma, seems to be the most common cause of underlying tumors. The removal of the underlying tumor and arteriovenous fistula is the best treatment for heart failure.

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