Cardiac metastasis from primary anaplastic thyroid carcinoma: report of three cases and a review of the literature

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Abstract
Background: Clinically evident cardiac metastases from malignant neoplasms are uncommon. The frequency of thyroid metastasis to the heart is very low. To our knowledge, over the last 20 years only a few cases have been reported in the entire literature. Metastatic cardiac involvement occurs most often during the terminal stage.
Patients: We present three cases of anaplastic thyroid cancer with metastatic involvement of the heart.
Results: Two of the patients died from cardiac problems. The absence of early symptoms makes the clinical diagnosis of metastatic carcinoma difficult.
Conclusions: Anaplastic thyroid cancer is an aggressive cancer with a dismal prognosis. It should be borne in mind as a source of cardiac metastasis and a cause of cardiac death.

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Introduction
Clinically evident cardiac metastases from malignant neoplasms are uncommon, although they are more frequent than primary cardiac tumors (Loffler & Grille 1990, McAllister 1991, Lam et al. 1993, Pavithran et al. 1997). The most commonly involved primary tumors are carcinoma of the lung, carcinoma of the breast, lymphoma, and malignant melanoma (Abraham et al. 1990, Klatt & Heitz 1990). Metastatic cardiac involvement occurs most often during the terminal stage of the malignant disease, associated with wide spread of the tumor, and it is generally diagnosed at autopsy. The frequency of thyroid metastasis to the heart is very low – 0% and 2%, in two recent large autopsy series (Abraham et al. 1990, Klatt & Heitz 1990). The thyroid tumors themselves, in most cases, have a favorable outcome. However, in contrast to differentiated thyroid cancer (papillary and follicular), anaplastic thyroid cancer (ATC) is considered one of the most aggressive neoplasms encountered in humans (Giuffrida & Gharib 2000). To our knowledge, over the last 20 years, only four cases of cardiac metastasis from thyroid cancer have been reported in the English (Carcangiu et al. 1985, Murabe et al. 1992, Kim et al. 2000), five in the Japanese (Kurasawa et al. 1981, Inoue et al. 1984, Hara et al. 1986, Yamamori et al. 1986, Murata et al. 1991), and two in the French (Larsimont et al. 1998) literature. Here, we present three cases of ATC with metastatic involvement of the heart. Two of the patients died from cardiac problems.

Case reports
Case 1. A 69-year-old woman was operated on at the Mayo Clinic for Hashimoto’s thyroiditis in February 1981. Two years later, she was re-admitted because of a large, rapidly increasing mass in the right side of the neck. She underwent a near-total right lobectomy. The histologic report described an undifferentiated, spindle cell ATC, grade 4, measuring 6 cm × 4 cm × 2.5 cm, with extensive extrathyroid spread. After surgery, the patient received external radiotherapy to the bed of the thyroid gland and the superior mediastinum, with delivery of 150 cGy twice daily over 19 days (total dose 4350 cGy). Fifteen days after the end of the radiotherapy, one course of chemotherapy was given, consisting of cisplatin (60 mg/m²), doxorubicin (40 mg/m²), and mitomycin (8 mg/m²). The patient died after a radically deteriorating course. The immediate cause of death was acute left-sided heart failure due to massive involvement of the myocardium by metastatic malignancy.
At autopsy, there was no evidence of residual tumor at the thyroid bed. The heart was invaded by numerous metastatic nodules, some of which were as much as 2 cm in diameter. The single largest nodule was in the left ventricle and involved about 60% of the left ventricular wall thickness. Other nodules were present over the aortas and the right ventricle. The nodules were found inside venues, and they also directly invaded the myocardium. Two-thirds of the thickness of the myocardium was invaded by the malignancy, beginning on the pericardial surface and extending toward the endocardium. Metastases to the lungs (innumerable nodules from several millimeters up to 1 cm in diameter), liver (numerous nodules), adrenal glands, kidneys, and gastrointestinal tract were also found.

Case 2. A 73-year-old man was seen at the Mayo Clinic because of a large, hard, and rapidly increasing mass in the neck, and underwent surgery for debulking of the mass. The histopathologic report described an ATC, grade 4, measuring 8.3 cm × 6 cm × 5 cm, invading muscle, vessels, and extrathyroidial tissue.

Four months later, because of recurrent disease in the neck, the patient was started on external radiotherapy to the bed of the thyroid gland and the superior mediastinum, with delivery of 180 cGy per day over 23 days (total dose 4140 Gy). After the radiotherapy, one course of chemotherapy was given, consisting of cyclophosphamide (600 mg/m²), doxorubicin (40 mg/m²) and vincristine (2 mg). One month later the patient died suddenly, presumably because of cardiac arrhythmia with subsequent acute myocardial ischemia.

Autopsy revealed a residual neoplasm (2.5 cm × 2.5 cm × 1.5 cm) in the thyroid bed, with obstruction of the left internal jugular vein by neoplasm and thrombus. In the heart, a large part of the right ventricle and cardiac chamber was replaced by tumor, with many tumor thrombi within myocardial vessels. Metastases to the lungs (multiple nodes), pleura, liver (four nodules), pancreas, and cecum were also found.

Case 3. An 85-year-old man was admitted to the emergency room at the Mayo Clinic with a rapidly expanding neck mass of 1 month’s duration. Tracheostomy was performed with biopsy of the left neck mass. The histopathologic report described a large-cell ATC. The diagnosis of ATC was confirmed after immunostaining for keratin and epithelial membrane antigen proved positive and immunostaining for S-100 protein and thyroglobulin was negative. Seventeen days later, the patient’s condition deteriorated and he died of an arrhythmia with cardiac arrest, without having had any further treatment for the tumor.

Autopsy revealed that a large part of the thyroid gland was replaced by an ATC, giant cell variant, grade 4; invasion of adjacent structures was noted. In the heart, a large part of the pericardium, endocardium, and myocardium was replaced by the tumor. Metastases were present in the lungs (bilateral miliary pulmonary carcinomatosis), adrenal glands, liver, pancreas, gastrointestinal tract, esophagus, and colon. Lymph node metastases (cervical, mediastinal, thoracic, and abdominal) were found as well.

Discussion

The extreme aggressiveness of ATC is well known, the prognosis being extremely poor, with a mean survival of 6 months (Franssila 1975). In the present report, three examples of primary ATC were associated with widespread metastases, including cardiac involvement, with death apparently caused by the metastases. Cancer arising from any organ is capable of metastasizing to the heart. The forms of malignant disease that most frequently metastasize to the heart are malignant melanoma, carcinoma of the lung, lymphoma, and carcinoma of the breast (Abraham et al. 1990, McAllister 1991, Batchelor et al. 1997). The reported incidence of cardiac metastasis from thyroid carcinoma varies from 0% to 2% among autopsy series (Prichard 1951, Cohen et al. 1955, Malaret & Aliaga 1968, Abraham et al. 1990, Klatt & Heitz 1990). Myocardial metastases, which are rarely diagnosed ante mortem, often represent the terminal stage of a malignant disease and are associated with generally widespread metastasis. Over the last 20 years, only 10 cases of cardiac metastasis from thyroid tumors have been described in the total literature (Kurasawa et al. 1981, Inoue et al. 1984, Carcangiu et al. 1985, Haras et al. 1986, Yamamori et al. 1986, Murata et al. 1991, Murabe et al. 1992, Larsimont et al. 1998).

A number of theories have been advanced to explain the route of involvement of the heart by metastatic carcinoma. One is embolic tumor seeding by hematogenous spread or by invasion through the thoracic duct into the right side of the heart (Lemus et al. 1998). Another is direct invasion through the lymphatics of the heart (Kountz 1993). Cardiac metastasis is also thought to occur by contiguous spread to the heart from local malignancies (Charles et al. 1977, Batchelor et al. 1997). The most common sites for metastatic disease in the heart are the pericardium and the epicardium (Loffler & Grille 1990). Less frequent sites include the endocardium, myocardium, and cardiac chambers. The right side of the heart is more commonly involved than the left (Labib et al. 1992). The less frequent involvement of the myocardium could be explained by the relatively low myocardial blood flow (approximately 240 ml/min) compared with that in other organs such as bone (600 ml/min) or brain (750 ml/min) (Nelson & Rose 1993, Batchelor et al. 1997). Local factors are also important in determining the patterns of metastatic spread (Charles et al. 1977, Loffler & Grille 1990).

In the cases reported here, the sites of metastasis to the heart were predominantly the left ventricle (case 1), cardiac chamber (case 2), and myocardium (case 3). These findings
confirm that ATC metastasizes to the heart in sites not usually involved by metastasis from other tumors. Differential patterns of metastasis may also be related to the interaction between the target organ and cancer cells, and it is possible that the particular aggressiveness of ATC cells permits metastasis even to parts of the heart where the blood flow is relatively low.

The clinical diagnosis of metastatic carcinoma to the heart is difficult because there are no early symptoms (Labib et al. 1992). Dyspnea and symptoms of pericarditis may be noted. Other forms of presentation are cardiac arrhythmias and sudden death (Dickens et al. 1992), as observed in cases 2 and 3. A non-invasive workup (echocardiography) is often useful in searching for evidence of metastasis (Prichard 1951, Cohen et al. 1955, Malaret & Aliaga 1968, Franssila 1975, Charles et al. 1977, Labib et al. 1992, Kountz 1993, Nelson & Rose 1993, Batchelor et al. 1997, Larsimont et al. 1998, Lemus et al. 1998). Cardiac metastasis from all types of cancer has a poor prognosis, and in most cases survival is limited to a few weeks or months.

In conclusion, ATC, an aggressive cancer with a dismal prognosis, should be borne in mind as a source of cardiac metastasis and a cause of cardiac death.

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