Mediastinal and retroperitoneal fibrosis as a manifestation of breast cancer metastasis

A case report and literature review

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Abstract

**Rationale:** Mediastinal and retroperitoneal fibrosis as a manifestation of metastasis from malignancies is rare disease and particularly, cases of mediastinal fibrosis have been rarely reported.

**Patient concerns:** A 60-year-old woman presented with dyspnea and bilateral flank pain. The patient had no previous history of malignancy.

**Diagnoses:** A contrast-enhanced chest computed tomography scan revealed a left breast mass and infiltrative soft tissue masses in the mediastinum and retroperitoneum, which showed high fluorodeoxyglucose uptake on positron emission tomography scan. The left breast mass was proven as a malignancy on biopsy and surgical excisional biopsy of the mediastinal mass revealed metastasis from the breast cancer on histopathologic examination.

**Interventions:** Our patient was treated with palliative hormone therapy for the primary breast cancer and metastasis with mediastinal and retroperitoneal fibrosis.

**Outcomes:** Follow-up imaging studies showed improvement of the primary breast cancer and also metastasis.

**Lessons:** We report this rare case to emphasize that mediastinal and retroperitoneal fibrosis can be a presentation of metastasis from various primary malignancies. We expect that appropriate diagnosis and treatment for metastatic mediastinal and retroperitoneal fibrosis can have a beneficial effect on disease course and prognosis of the patient.

**Abbreviations:** CT = computed tomography, ER = estrogen receptor, FDG = fluorodeoxyglucose, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, IVP = intravenous pyelography, PET-CT = positron emission tomography-computed tomography, RGP = retrograde pyelography, US = ultrasonography.

**Keywords:** breast cancer, mediastinal fibrosis, metastasis, retroperitoneal fibrosis

1. Introduction

Mediastinal and retroperitoneal fibrosis is an uncommon condition characterized by proliferation of fibrous tissue in the mediastinum and retroperitoneal space.\(^{[1]}\) Most causes of mediastinal and retroperitoneal fibrosis are benign conditions including infection, autoimmune diseases, systemic fibro-inflammatory disorders, and treatment-related condition such as radiation therapy and drugs.\(^{[2]}\)

Malignant and metastatic retroperitoneal fibrosis is relatively well-known entity with case reports.\(^{[3,4]}\) Malignancies associated with retroperitoneal fibrosis are lymphoma, gastric cancer, breast cancer, lung cancer, carcinoid, and so on.\(^{[5]}\) On the other hand, malignant mediastinal fibrosis (fibrosing mediastinitis) is a rare disease entity and case reports are very limited.\(^{[6,5]}\)

We report a case of pathologically proven concurrent mediastinal and retroperitoneal fibrosis as a metastasis from breast cancer.

2. A case report

A 60-year-old woman presented with dyspnea and pain in both flank areas, which started 3 weeks ago. She had no specific medical history. Initial laboratory tests including complete blood count showed mild elevation of erythrocyte sedimentation rate level of 40mm/h (normal range, 0–30mm/h). There was no leukocytosis or neutrophilia. On the chemistry panel, C-reactive protein was within normal range. No other significant finding was revealed on routine laboratory examinations.

Initial chest radiography showed bilateral pleural effusions and increased cardiothoracic ratio with suspicion of pericardial
effusion. A contrast-enhanced chest computed tomography (CT) scan was performed (Fig. 1), which revealed diffuse infiltrative mass with soft tissue attenuation in anterior and middle mediastinum (Fig. 1A and B). There are moderate amount of pericardial effusion with mild pericardial thickening (black asterisk in C) and bilateral pleural effusions. An enhancing mass is noted in left breast (open arrow in C) and there are multiple enlarged left axillary lymph nodes (black arrow in A). There is seen a metastatic soft tissue mass on left pectoralis muscle (white arrow in B). Diffuse infiltrative soft tissue lesions are also noted in retroperitoneum (white asterisk in D), which are associated with encasement of abdominal aorta and bilateral hydronephrosis (D). CT = computed tomography.

Differential diagnoses for the diffuse infiltrative mediastinal and retroperitoneal disease on chest CT scan included neoplasms (metastasis and lymphoma), diffuse infiltrative non-neoplastic diseases (tuberculosis, autoimmune diseases, drug, and radiation) and also idiopathic cause. Imaging findings of malignant mediastinal and retroperitoneal fibrosis are not specific and not so different from those of benign condition. Therefore, further evaluation was necessary to exclude malignancy.

On 18F-fluorodeoxyglucose (FDG) positron emission tomography-CT (PET-CT) scan (Fig. 2), increased metabolic activity was revealed in the diffuse infiltrative soft tissue lesions of the mediastinum and retroperitoneum (SUVmax = 4.0). But, these findings were not sufficient for differentiation between malignancy including metastasis and benign systemic inflammatory diseases such as IgG4-related disease and tuberculosis.

Ultrasonography (US)-guided biopsy was done for the left breast mass, which was reported as an invasive mammary carcinoma on pathologic review, but the subtype of breast cancer was not diagnosed. Systemic evaluation and diagnosis of metastasis in patients with primary malignancy is critical for cancer staging and treatment planning. And then we decided to undergo histopathologic confirmation for the mediastinal and retroperitoneal disease in our patient. The patient underwent a video-assisted thoracoscopic surgery (Fig. 3). The mediastinal fat was very firm on intraoperative findings probably due to fibrosis, which can be seen in either benign or malignant mediastinal fibrosis. Excisional biopsies for the parts of mediastinal fat and pericardium were performed.

Histopathologic review of the surgical specimen showed diffuse infiltrations of atypical cells with stromal fibrosis for the mediastinal lesion and metastatic adenocarcinoma from breast cancer was finally diagnosed (Fig. 4). The specimen revealed strong positive for estrogen receptor (ER) and also positive for cytokeratin 7 (CK7) on the immunohistochemical stain. And the results of immunohistochemical stains with E-cadherin and P120 catenin suggested invasive lobular carcinoma (ILC).
The patient started palliative treatment with letrozole, which is an aromatase inhibitor for ER positive breast cancer. About 6 months later, follow-up chest CT scan and PET-CT scan were performed for evaluation of treatment response. The follow-up chest CT scan (Fig. 5) revealed slightly decreased size and enhancement of the left breast cancer and also improvement of metastasis with malignant mediastinal and retroperitoneal fibrosis. Resolution of bilateral pleural and pericardial effusions was noted and also improvement of hydronephrosis was seen. On follow-up PET-CT scan, decreased metabolic activity was noted in the left breast cancer and also in diffuse metastasis with mediastinal and retroperitoneal fibrosis (Fig. 6).

3. Discussion

Mediastinal fibrosis, also known as fibrosing mediastinitis or sclerosing mediastinitis, is first described in 1995 by Goenka et al.\textsuperscript{[5]} It is generally considered as a rare benign condition associated with proliferation of dense fibrous tissue. It produces symptoms by gradual compression and obstruction of vital structures.
Figure 4. Histopathologic findings of surgical biopsy specimen in a 60-year-old woman. There are seen diffuse infiltrations of atypical cells with stromal fibrosis in the mediastinum (asterisks in A: ×100, H&E). The tumor cells are scattered in the background stroma and show irregular hyperchromatic nuclei (arrows in B: ×400, H&E). On immunohistochemical stains, strong estrogen receptor positivity (C: ×200) and cytokeratin 7 positivity (D: ×200) were revealed in the tumor cells. H&E = hematoxylin and eosin.

Figure 5. Comparison of initial and follow-up chest CT scans in a 60-year-old woman after treatment. Follow-up chest CT scan was performed in our patient after treatment with letrozole for 6 months. In comparison of initial (A–C) and follow-up (D–F) axial contrast-enhanced chest CT scans, decreased extent of metastatic mediastinal fibrosis (white asterisks in A and D) is well seen. The primary left breast cancer also shows slightly decreased size and enhancement (arrows in B and E) and there is seen resolution of bilateral pleural and pericardial effusions (black asterisks in B). Metastatic retroperitoneal fibrosis shows decreased extent (white asterisks in C and F) with improvement of bilateral hydronephrosis (F). CT = computed tomography.
mediastinal structures in affected patients. Mediastinal fibrosis usually presents nonspecific symptoms including cough, dyspnea, hemoptysis, chest pain, and recurrent respiratory infection.[7] Many conditions including infectious and noninfectious causes can be related to mediastinal and retroperitoneal fibrosis. Until now, histoplasmosis, tuberculosis, autoimmune disease, radiation therapy, drug therapy with methysergide maleate, and also other idiopathic fibroinflammatory disorders such as sclerosing cholangitis have been reported as the etiology.[7] Mediastinal fibrosis also can be associated with a malignancy. Some of the malignances have a tendency producing fibrosis and causing desmoplastic reaction. These malignances include sclerosing non-Hodgkin lymphoma, nodular sclerosis variant of Hodgkin disease, malignant mesothelioma, thymic carcinoma, and low-grade sarcoma.[7] Retroperitoneal fibrosis is a less unusual manifestation of malignancy rather than mediastinal fibrosis, but has similar clinical, pathologic and radiologic features to those of mediastinal fibrosis. Malignancies account for 8% to 11% of all cases of retroperitoneal fibrosis.[2,8] Like mediastinal fibrosis, malignant retroperitoneal fibrosis can occur with primary retroperitoneal tumors such as lymphoma and sarcomas or desmoplastic response of metastatic malignancies such as breast, stomach, prostate, lung, kidney, colon, and carcinoid tumors.[2] Clinical presentations of retroperitoneal fibrosis, regardless of its etiology, are nonspecific in common with mediastinal fibrosis and symptoms include abdominal or flank pain and weight loss. Laboratory tests are also not helpful for diagnosis and evaluation of retroperitoneal fibrosis.

Mediastinal and retroperitoneal fibrosis can be seen as a poorly defined soft tissue mass, which is plentiful of infiltrative fibrous tissue with obliteration of adipose tissue on pathologic examination.[7] The radiologic findings well correlate with these characteristics and imaging studies play important role in the diagnosis and further evaluation of the disease. Radiologic findings of mediastinal fibrosis include mediastinal widening, mediastinal or hilar mass, airway narrowing, and septal thickening.[7] In case of retroperitoneal fibrosis, conventional radiography can shows a central soft-tissue mass and loss of the normal psoas shadow in late stages.[8] Intravenous pyelography (IVP) and retrograde pyelography (RGP) can be used to check the presence of associated urinary obstruction. Abdominal US can reveal hypechoic or isoechoic irregular contoured retroperitoneal mass.[8] But, these imaging studies mentioned above are inaccurate and nonspecific.[8] CT is a better imaging modality for diagnosis of mediastinal and retroperitoneal fibrosis. On CT scans, infiltrative mass of soft tissue attenuation with obliteration of fat planes and encasement with or without obstruction of adjacent structures is a typical manifestation.[7] According to the prior studies, there are two (focal and diffuse) patterns of mediastinal fibrosis on CT scans.[7,9] The focal pattern manifests as a localized soft tissue attenuation mass and calcification is usually seen in the mass. This pattern is associated with histoplasmosis infection.[7,9] The diffuse pattern manifests as a diffusely infiltrating and noncalcified mass. A PET-CT scan can show disease activity with abnormal FDG uptake and provides better detection of active lesions with high sensitivity.[8] Therefore, PET-CT scan is helpful in initial diagnosis, assessment, and also determining proper sites for biopsy. It also provides quantitative information about treatment response on follow-up.[8] Mediastinal and retroperitoneal fibrosis secondary to malignancy has a poor prognosis, then differentiation of benign and
malignant fibrosis is important. However, the distinction between benign and malignant fibrosis may be difficult. The standard clinical and radiologic features and even gross macroscopic appearances may not distinguish the malignant from benign disease.\[1\] It was reported that most patients who have metastatic mediastinal and retroperitoneal fibrosis have been diagnosed with primary cancer recently or treated for malignancy in the past. A previous history of malignancy can be helpful but not diagnostic for metastatic mediastinal and retroperitoneal fibrosis. On the other hand, like the patient of our case, some of the patients have no specific medical history and signs or symptoms related to metastatic mediastinal and retroperitoneal fibrosis can be an initial presentation. Although CT can be helpful in evaluation the disease extent, it cannot distinguish a malignant from benign process in the absence of obvious features of metastasis. Even though CT- or US-guided percutaneous biopsy is feasible, this technique may not reliably obtain a sufficient specimen for confident differential diagnosis. The dense desmoplastic response with stromal fibrosis may prevent identification of scattered nests of tumor cells. Then, requirement for surgical exploration with multiple deep biopsies was well remarked in previous reports.\[1,4\]

Malignant retroperitoneal fibrosis associated with breast cancer has been previously reported in several cases.\[2–4\] Most of patients of the reported cases had previous medical history of breast cancer. However, some of the reported patients presented with no history of previous malignancy similar to our patient.\[3\]

Obstructive uropathy is a typical feature of retroperitoneal fibrosis and bilateral flank pain is the most common clinical symptom.\[2–4\] Our patient revealed typical clinical presentation with bilateral flank pain and hydropneumorhesis. Imaging studies such as IVP or RGP reveals hydropneumorhesis and CT shows diffuse infiltrative enhancing soft tissue mass with encasement of the retroperitoneal structures, and which are typical imaging features of retroperitoneal fibrosis.

Intrathoracic metastasis from breast cancer is relatively common, which can involve the lungs, pleura, mediastinum, airways, and also heart including pericardium.\[10\] Mediastinal involvement of breast cancer usually presents as metastatic lymphadenopathy and a manifestation as mediastinal fibrosis is extremely rare. Cases of mediastinal and retroperitoneal fibrosis as a manifestation of recurrent breast cancer were reported by John et al.\[4\] In this case report, a 70-year-old woman presented with dysphagia and she had a history of a left modified radical mastectomy 80 months before the clinical presentation. A chest CT revealed a posterior mediastinal mass with compression and infiltration of the thoracic esophagus, which was seen as metastatic mammary ductal cancer cells with firm fibroadipose tissue covering the esophagus on histopathologic examination. A few cases of mediastinal metastasis with fibrosis also have been reported in patients with breast cancer presenting with dysphagia due to esophageal obstruction.\[5\]

Common histopathologic types of breast cancers include invasive ductal carcinoma (IDC) and ILC. IDC accounts for almost 90% of breast cancers.\[11\] Two histologic types of breast cancer can show different patterns of metastasis.\[11\] IDC often shows metastasis to the lung, liver, bone, and brain. On the other hand, ILC tends to spread to the gastrointestinal tract, genitourinary tract, peritoneum, and retroperitoneum.\[11\]

The patient in our case report is also diagnosed as metastatic ILC on immunohistochemical stain of the surgical specimen obtained from the mediastinum and pericardium.

Treatment of the secondary mediastinal and retroperitoneal fibrosis is based on the underlying causes. Metastatic mediastinal and retroperitoneal fibrosis should be treated with systemic chemotherapy and hormone therapy for the primary malignancy. Surgical approach can be performed to confirm diagnosis and also can be therapeutic to relieve compression or obstruction of the vital mediastinal or retroperitoneal structures and associated symptoms. Nonsurgical interventions such as balloon dilation, and intravascular graft or endobronchial stent also can be helpful.\[6\] Acute renal failure secondary to urinary obstructions requires prompt intervention such as percutaneous nephrostomy or double J catheter insertion.\[7\] Prognostic effects of treatment including surgical or nonsurgical interventional procedures and chemotherapy for metastatic mediastinal and retroperitoneal fibrosis have not been well reported yet because of rarity of the cases. However, some of the reported cases\[2,4\] and also our case revealed relatively favorable prognosis. So we expect appropriate treatments for the metastatic mediastinal and retroperitoneal fibrosis can have a beneficial effect on improvement of disease course and prognosis of the patient. Therefore, we should bear in mind that mediastinal and retroperitoneal fibrosis can be a manifestation of metastasis and can come up with the diagnosis when evaluation of the patients with primary malignancies. Imaging studies including chest radiography, contrast-enhanced chest CT scan, and PET-CT scan are important for the diagnosis, assessment of the disease extent and associated findings, guiding interventional procedures, and monitoring after proper management.

Author contributions

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