Venous Gangrene in a Patient with Adenocarcinoma of the Lung

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Cancer-related thromboembolism is a severe but not uncommon paraneoplastic syndrome in mucinous cancer patients. However, cancer-induced venous gangrene is extremely rare and has never been reported in the English literature. Here, we present a case of lung cancer complicated with venous gangrene of the left foot. An elevated serum anticardiolipin level was detected during hospitalization, but the patient’s clinical condition stabilized after heparinization. We suggest that in cancer patients, an elevated serum anticardiolipin antibody level might be a warning sign of an impending thrombotic event and that low-molecular-weight heparin is a sensible choice in treating this kind of cancer-related thromboembolism.

Key words: lung cancer – venous gangrene – anticardiolipin antibodies

INTRODUCTION

Thromboembolic event is a common paraneoplastic syndrome in cancer patients, especially in mucin-producing tumors (1). However, venous gangrene is an extremely rare condition and is often accompanied by a grave prognosis. Serum anticardiolipin antibodies may play an important role in the pathogenesis of cancer-related coagulopathy (2). Here we present a case of adenocarcinoma of the lung complicated with venous gangrene of the left foot, demonstrated by venous ultrasound with negative findings in angiographic examination. The clinical course, pathogenesis of cancer-related venous gangrene and therapy are discussed.

CASE REPORT

A 51-year-old woman was brought to the emergency unit of our hospital in December 1998, with the complaints of dry cough, shortness of breath and a progressively enlarging left chest wall mass. Chest X-ray (Fig. 1) and CT scan examination revealed the existence of bilateral pleural effusion and a left pulmonary mass lesion obliterating the bronchial tree, with several small nodular lesions in both lung fields. After insertion of a chest tube on the left side, she was admitted under the impression of lung cancer. The left chest wall mass was excised for pathological study and the result turned out to be adenocarcinoma in nature. Later image studies disclosed multiple metastatic lesions in the liver, right adrenal gland and bones.

She was discharged in February 1999, when her disease was brought to a stable condition after treatment with two cycles of intravenous gemcitabine plus carboplatin. However, purplish discoloration over the second, third, fourth and fifth toes of her left foot developed soon after she refused further chemotherapy and led to her being admitted once again in March 1999.

Dry gangrene of the left foot was diagnosed (Fig. 2) and bilateral lower limb pitting edema, more severe on the left side, was also noted. Patency of the bilateral common iliac, internal iliac, external iliac, femoral, anterior tibial, tibioperoneal, peroneal and posterior tibial arteries proved by angiographic examination ruled out arterial occlusion as the cause of gangrene.

However, a disseminated intravascular coagulation profile did reveal the existence of a hypercoagulative state, with prothrombin time 15.3 s (control 12.5 s), partial thromboplastin time 41.4 s (control 34.1 s), D-dimer three plus in a qualitative test and a fibrin degradation product 320 µg/ml (normal <10 µg/ml). Thrombosis over the left femoral and popliteal veins detected by Doppler ultrasound examination finally led to a diagnosis of venous gangrene. The gangrene did not become exacerbated after proper heparinization, but the patient died of sepsis 2 weeks later despite broad-spectrum antibiotic treatment.

When the gangrene appeared, elevated titers of both IgM and IgG anticardiolipin antibodies were detected in her serum by ELISA (QUANTA Lite ACA IgM and IgG, INOVA Diagnostics, San Diego, CA). IgM antibody 67 MPL unit/ml (control <12.5 MPL unit/ml), IgG antibody 27 GPL unit/ml (control <15 GPL unit/ml).

DISCUSSION

Hypercoagulability, a notorious paraneoplastic syndrome in malignant disease, is frequently seen in mucinous cancer, such
as pulmonary, gastrointestinal or pancreatic malignancies (1). The clinical manifestations of cancer-related thrombosis include spontaneous recurrent migratory venous thrombosis, arterial thrombosis, microangiopathy, non-bacterial thrombotic endocarditis and acute or chronic disseminated intravascular coagulation. In lung cancer patients, a thromboembolic phenomenon is thought to be a sign of poor prognosis, with an average survival time of less than 6 months from the thrombotic events to death (3).

There are several possibilities for the pathogenesis of cancer-associated venous thromboembolism. Decreased levels of antithrombin III and acquired deficiencies in the protein C/protein S natural anticoagulant pathway have previously been reported in cancer patients (4). Membrane-bound tissue factors on cancer cells also seem to be able to stimulate factor VII to initiate the extrinsic blood coagulation pathway (5).

Recently, there have been growing numbers of reports in the medical literature about the association between antiphospholipid antibodies and malignancy-related coagulopathy. Antiphospholipid antibodies are chiefly composed of the lupus anticoagulants and anticardiolipin antibodies. Generally, antiphospholipid syndrome is commonly found in a wide range of situations such as long-term administration of diverse drugs, monoclonal gammopathy of uncertain significance, advanced hepatic or renal dysfunction, polymyalgia rheumatica/temporal arteritis, myeloproliferative disorders, lymphomas and solid tumors (6). However, malignancies are the major concern in the elderly because a higher incidence of occult malignancy has been noted in the elderly compared with young patients with antiphospholipid syndrome (6). The increased serum level of anticardiolipin antibodies appears to be an important contributory factor in the development of paraneoplastic thrombosis in cancer patients. These antibodies predispose to thrombosis either by interacting with phospholipids on the platelet and vascular endothelium or by inhibiting protein C activation and prostacyclin formation in the endothelial cells (2).

In 1995, Zuckerman et al. (2) reported that anticardiolipin-positive cancer patients had a significantly higher rate of thromboembolic events than anticardiolipin-negative patients (28% versus 14%), based on the results of their study, which is the largest series to date on the relationship between anticardiolipin and malignancy. They also suggested that patients with high IgM antibody titers (>60 MPL units/ml) are more prone to thromboembolic events than those with lower titers.

Probably owing to its rarity, only sporadic reports of cancer-induced venous gangrene have been published (7,8). To the best of our knowledge, no cases of paraneoplastic venous gangrene associated with anticardiolipin antibodies, such as the one we present here, have been reported before in the English literature. Based on our experience here and a review of the literature, we suggest that for patients with malignant diseases, examination of serum anticardiolipin antibodies may be helpful in providing a warning sign of potential thromboembolic events.

As for treating cancer-associated thromboembolism, low-molecular-weight heparin may be the most sensible choice (9,10). There is a trend towards lower mortality with low-molecular-weight heparin, compared with standard heparin (11). The reduction in mortality may be due to the inhibitory effect that low-molecular-weight heparin can exert on tumor growth.
References