

Multiple Primary Intrathoracic Neoplasms:

Case Report and a Review of the Literature

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Abstract

This is a case report of a patient diagnosed with three distinct primary intrathoracic tumors (mesothelioma, carcinoid and B-cell lymphoma). The patient had previously had mycosis fungoides.

The occurrence of multiple neoplasms in a single patient, synchronous or metachronous, is not a rare phenomenon; the incidence varies from 1–11% of all neoplasms. They can be hereditary, or connected with some environmental agents or previous therapies. The incidence of multiple neoplasms increases with age. We report an extremely rare case of multiple intrathoracic neoplasms in a 71-year-old man. A left upper lobectomy was performed, followed by 6 courses of chemotherapy and irradiation of the sternum. The patient was stable two years later.

Key Words: Intrathoracic, multiple neoplasms.

Introduction

MULTIPLE PRIMARY NEOPLASMS in a single patient were reported as early as the end of the 19th century (1). The pathologic criteria of multiple neoplasms were summarized by Warren and Gates (2): tumors are considered to have arisen independently if they exhibit different histological characteristics indicative of a subtype or degree of differentiation, or if they are located in different lobes and are not accompanied by tumors of other organs (2). Molecular markers, including the pattern of DNA ploidy, chromosome 3p depletion, K-ras and p53 mutational pattern, have also been used to identify the independent origin of multiple tumors (3).

Multiple neoplasms could be defined by when they appear, as synchronous or metachronous; the latter are defined as appearing 6 months or more following the first neoplasm (4).

The etiopathogenesis of multiple neoplasms (5) includes hereditary aspects (familial occurrence with increased incidence as well as the influence of the “protective” factors) (6, 7). It also includes the influence of external factors (tobacco, combined effects of tobacco and alcohol, asbestos, nutritional factors, viruses, the loss of immunity) (8–10); the effects of previous therapies (especially with cytotoxic agents and hormones, immunosuppressants and irradiation) (11, 12); and the influence of tumor-producing hormones (secretin, gastrin, bombesin, cholecystokinin, vasoactive intestinal peptide) (13; Table 1). From a review of the recent literature it would appear that the incidence of multiple neoplasms increases with age (14).

Case Report

A 71-year-old man was admitted to the hospital with a one-month history of chest pain, dry cough, dyspnea and malaise. He was a retired clerk who had never smoked. For twenty years, he had lived in a large city, close to a major highway. Five years earlier, he had been treated for biopsy-proven mycosis fungoides with etretinate for six months, with considerable success. Chest auscultation showed diminished breath sounds in the left

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Accepted for publication December 2004.

TABLE 1
Some Etiopathogenic Factors of Multiple Primary Neoplasms in a Single Patient (5)

Causative Factor	Location and/or Type of Neoplasm
Chemical	
Tobacco	Lungs, upper respiratory tract
Tobacco + alcohol	Larynx, lungs, upper digestive tract
Asbestos	Mesothelioma, lungs
Cadmium	Prostate, kidneys, lungs
Nickel	Lungs, paranasal sinuses
Arsenic	Skin, lungs
Nutritional and/or Endocrine	Breasts, corpus uteri, ovaries, colon
Viral	Burkitt's lymphoma, non-Hodgkin's lymphoma
Immunodeficiency	Thymoma, skin cancer, non-Hodgkin's lymphoma Following the therapy for Hodgkin's disease, lymphomas and Kaposi sarcomas in AIDS

lung. Routine laboratory findings were normal, except for a sedimentation rate of 130. The chest x-rays showed hyperinflation of the parenchyma in the supradiaphragmal and retrosternal regions, a pathological process of the anterior upper mediastinum, an infiltration of the peripheral lingula 3 cm in diameter and a smaller one in the apicoposterior subsegment of the left upper lobe (Figs. 1a and 1b). Fiberbronchoscopy showed a tumor with smooth surface in the subsegmental bronchus of the left upper lung lobe. Bronchial brushing cytology (Fig. 2a) and pathohistological analysis of the tumor biopsy proved that the tumor was carcinoid. Transthoracic fine-needle aspiration of the mediastinal mass did not reveal its etiology.

The patient underwent a left upper lobectomy, and mediastinal biopsy was performed. During the operation the node in the lingula was seen to be fixed to the pericardium. Intraoperative imprint cytology of the infiltrate in the lingula and pericardium revealed a malignant tumor. The tumor was firm, grayish-white, 2.5 × 2 cm in size, composed of pleomorphic, atypical epithelial cells in tubulopapillary formations, and desmoplastic stroma (Fig. 2b). The immunohistochemistry showed neuron specific enolase (NSE) and epithelial antigen (BerEP4) negative, and epithelial membrane antigen (EMA) and cytokeratin positive tumor cells. Pathohistological diagnosis was malignant mesothelioma. A similar infiltrate was found in the upper lobe of the left lung, 0.4 × 4 cm in size. In the apicoposterior subsegmental bronchus of the left upper lobe, a sharply demarcated, smooth, soft, fleshy tumor was found, 0.8 cm in diameter, composed of uniform cells with

eosinophilic cytoplasm in acinar formations, NSE and cytokeratin positive, and EMA negative. The diagnosis was typical carcinoid. The mediastinal tumor was white, homogenous, 4 × 2 × 0.6 cm in size, composed of a mixture of small lymphocytes, plasma cells and plasmacytoid lymphocytes. Cells were CD19 and CD20 positive, and CD3 and CD5 negative, by immunohistochemistry. The diagnosis was B-cell non-Hodgkin's lymphoma-lymphoplasmacytoid type immunocytoma. In two of the synchronous tumors, immunocytoma and mesothelioma, overexpression of the p53 tumor suppressor gene product was found by immunohistochemistry.

Six months postoperatively, a painful tumor of the sternum arose. The chest computed tomography (CT) scan showed a mediastinal mass with ventral, thoracic border, which was not sharp but irregular, suggesting infiltrative growth (Fig. 1c). Fine-needle aspiration showed a mixture of small lymphocytes, plasma cells and plasmacytoid lymphocytes, which corresponds to previously described B-cell non-Hodgkin's lymphoma (Fig. 2c). The patient underwent six courses of chemotherapy (protocol CHOP - cyclophosphamide, doxorubicin, vincristine, prednisone) and irradiation of the sternum. Two years later the patient was without symptoms, conventional chest x-ray and CT scan showed only a fibrous residue, and there were no signs of local or distant spreading of any of the tumors.

Discussion

This is a case report of a patient diagnosed with three distinct primary intrathoracic tumors (mesothelioma, carcinoid and B-cell lymphoma)

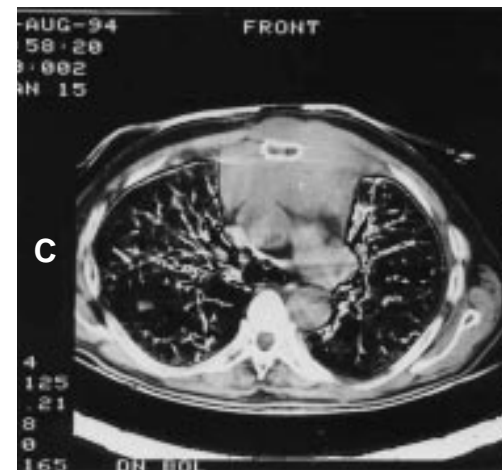


Fig. 1. Chest radiographs: (A) anteroposterior view, (B) lateral view, and (C) computerized tomography illustrating the mediastinal mass.

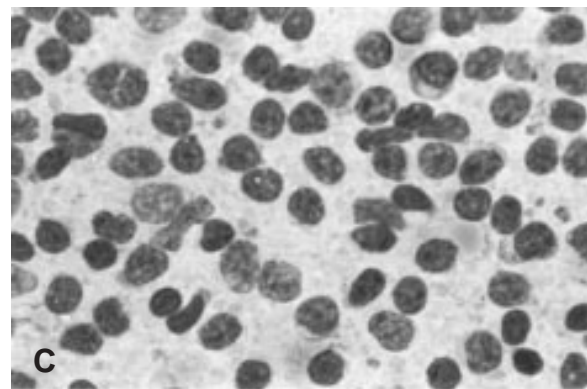
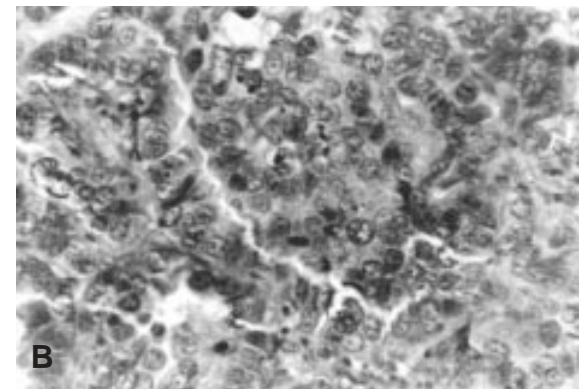
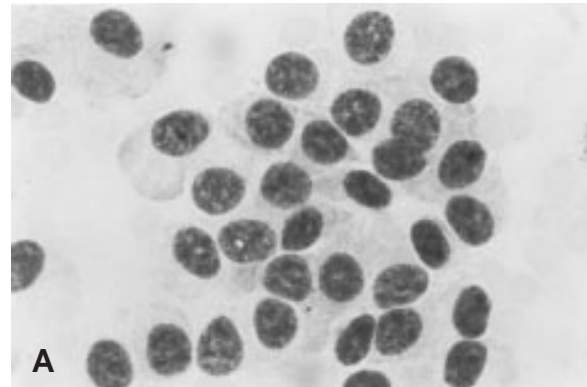


Fig. 2. Pathohistology and cytology microphotographs: (A) carcinoid imprint cytology of the tumor biopsy, (MGG, original magnification $\times 1000$), (B) biopsy specimen of the lingula and pericardium mesothelioma (H&E, original magnification $\times 400$), and (C) immunocytoma fine-needle aspiration cytology, (MGG, original magnification $\times 1000$).

MGG = May-Grünwald-Giemsa stain; H&E = hematoxylin and eosin stain.

and who had previously had mycosis fungoides. Multiple primary neoplasms in a single individual are extremely rare when more than three distinct lesions are considered (15). The incidence of multiple primary lung cancer ranges from 0.5–10% (16).

More than 10% of patients with metachronous primary lung tumors survive longer than 3 years after the diagnosis. Criteria of multiple lung neo-

TABLE 2
Reports of Multiple Primary Malignant Neoplasms

Authors	Ref	Multiple primary neoplasms	No. of patients	Year
Efremidis	22	Lymphocytic neoplasia, Mesothelioma	2	1985
Kantor	23	Cutaneous T-cell lymphoma Cancers of lung and colon NHL	35	1989
Tondini	10	Mesothelioma, NHL-B-cell	Case report	1994
Gerstle	19	Gastrointestinal carcinoid, Malignant neoplasms of gastro- intestinal or other locations	32	1995
Takabe	20	Mesothelioma, NHL-B-cell	Case report	1997
Beshay	21	Typical pulmonary carcinoids	Case report	2003

NHL-B-cell = B-cell non-Hodgkin's lymphoma

plasms, modified from Martini and Melamed, include demonstration of tumors with different histology and proof that the tumors, if histologically similar, arise from separate and distinct endobronchial foci (17). Many authors exclude cases in which there is more than one tumor of a given histological type, arguing that the second tumor cannot be distinguished from intrapulmonary metastasis (18). The patient reported in this article had three intrathoracic malignant tumors of different origins. He had carcinoid, mesothelioma, and intrathoracic B-cell lymphoma, as well as cutaneous T-cell lymphoma (i.e., mycosis fungoides).

Some reports of patients with similar multiple, primary, malignant neoplasms are listed in Table 2 (10, 19–23).

Etretinate is a monoaromatic retinoid used in the treatment of keratinizing skin disorders and cutaneous T-cell non-Hodgkin's lymphomas (24). Teratogenic potential has been described, as well as the induction of different skeletal alterations, including periosteal osteosarcoma (25). Etretnate had been administered to our patient for 6 months, five years before the diagnosis of multiple second malignancies, and we cannot exclude a possible connection between those events.

No specific hereditary syndrome could be identified from the patient's family history. A possible environmental causative agent responsible for the development of the multiple malignancies is asbestos exposure, because our patient lived near a major highway for twenty years. A strong association between asbestos exposure and incidence of mesothelioma is well known, but there are contradictory results in studies investigating the association between exposure to asbestos and incidence of non-Hodgkin's lymphoma (26).

Several studies have shown increased risk of multiple neoplasms for older patients, especially

for those treated earlier with aggressive anticancer drugs. Out of all the patients who developed multiple neoplasms, 71–94% were older than 50 years in different series (27–31). The reason for increased incidence of multiple neoplasms could be a generally older population, environmental causative agents and more effective antitumorous therapy that prolongs patients' lives and increases the risk for other primary neoplasms. Our patient, as reported, had been treated for an earlier malignancy.

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