Ann Thorac Surg
1998;65:252–4

Four Multiple Primary Malignant Neoplasms of the Aerodigestive Tract

Ara Keshishian, MD, Fazlul H. Sarkar, PhD, George Kucyj, MD, and Jorge O. Just-Viera, MD

Section of Thoracic and Cardiovascular Surgery and Department of Pathology, St. Joseph Mercy Hospital, Pontiac, Michigan

Multiple primary cancers of the head, neck, and upper aerodigestive tract have been documented in patients previously treated for oropharyngeal cancer. There generally is no causal relationship established between the different tumors. Two synchronous or metachronous cancers are common, three are unusual, and four are very unusual. We describe the treatment of a patient with tonsillar and synchronous esophageal and pulmonary cancers followed by a tongue cancer over a 6-year period.

(Ann Thorac Surg 1998;65:252–4)

Multiple malignancies of the aerodigestive tract noted in patients treated successfully for head and neck cancer have been identified as either metastatic or as a new second primary tumor [1]. Risk factors common to both types of cancers, such as tobacco and alcohol consumption, are etiologically suspect. We describe a patient with tonsillar cancer treated with radiation 4 years before development of synchronous esophageal and pulmonary cancers. Cancer of the left base of the tongue followed 6 years after the tonsillar cancer.

A 39-year-old black man presented in September 1990 with persistent sore throat of 2 months' duration; he was otherwise asymptomatic. He had a 25 pack-year history of smoking and drank three to four beers daily for 20 years. Initial biopsy on October 15, 1990, was negative, symptoms persisted, and a repeat biopsy on March 15, 1991, was positive for microinvasive squamous cell carcinoma of the left tonsillar trigone, T1 N0 M0, stage I. Bone scan, computed tomography, and ultrasound stud-

Accepted for publication Sep 2, 1997.

Address reprint requests to Dr Keshishian, Department of Surgery, St. Joseph Mercy Hospital, 900 Woodward Ave, Pontiac, MI 48321.

0003-4975/98/$19.00
PII S0003-4975(97)01196-X

Table 1. Tissue Analysis of the Cancer Cells

Date	Tissue	Cell Type	TNM	Stage	p53 Expression
March 1991	Tonsil	Microinvasive, squamous cell	T1 N0 M0	I	100%
July 1995 (Fig 1B)	Lung (right upper lobe)	Adenocarcinoma	T1 N0 Mx	I	0%
July 1995 (Figs 1A, 1C)	Esophagus	Polypoid, squamous cell	T1 N0 Mx	I	50%
August 1996 (Fig 1D)	Tongue (left base)	Squamous cell	T1 N0 M0	I	100%

ies were negative. A curative course of radiation therapy of 7,000 cGy was completed on July 23, 1991.

The patient presented to a different University center on June 2, 1995, with complaints of progressive dysphagia over 3 months. Computed tomography, magnetic resonance imaging of the head, neck, and chest, and esophagoscopy revealed a nodular density in the right upper lobe, and an upper one-third esophageal lesion. Initial esophageal biopsy was interpreted as proliferating squamous epithelium with high-grade dysplasia. He returned to us for further evaluation and management.

On July 31, 1995, he underwent flexible esophagoscopy, and multiple biopsies and frozen sections revealed squamous cell carcinoma, suggesting multiple synchronous primary malignancies. Right thoracotomy followed, and frozen section of the right upper lobe nodule proved adenocarcinoma of the lung. Radical right upper lobectomy, radical esophagectomy, esophagostomy, mediastinal node resection, and gastrostomy were performed. He overcame postoperative pneumonia and pleural effusion and was discharged home on tube feedings.

Having regained his preoperative weight, he underwent esophagogastric reconstruction on January 12, 1996, with cervical anastomosis, substernal gastric transplantation, resection of the left half of the manubrium and clavicular head of the first rib, jejunostomy, and pyloromyotomy. He was discharged 11 days later, and his follow-up computed tomographic scan and evaluations were all negative until August 1996, when a routine examination revealed a mass of the posterior left tongue, an invasive squamous cell carcinoma, T1 N0 M0, stage I, excised on September 23, 1996. Tissues obtained from all resected cancers were retrieved and analyzed for the p53 gene mutation. The paraffin-preserved blocks of tissue were stained using immunohistochemical method for p53 mutation (Table 1; Fig 1).

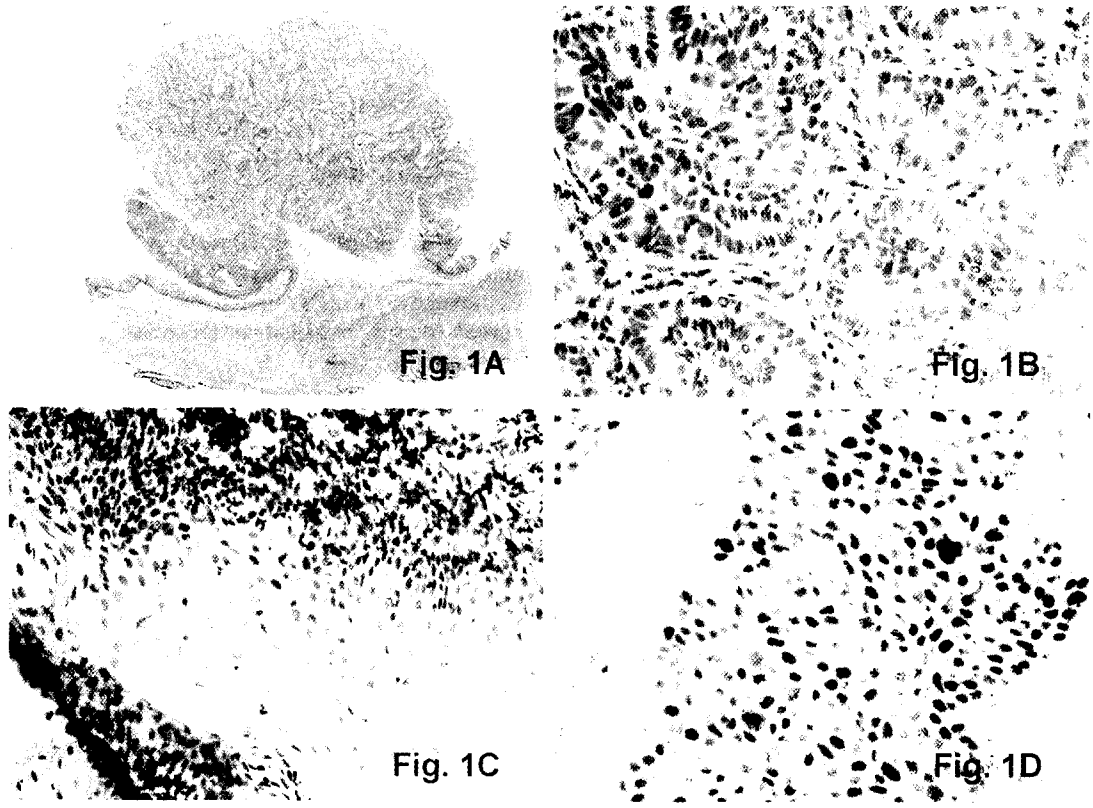

Fig 1. (A) Gross photomicrograph of esophageal mass. (Hematoxylin and eosin.) (B) Photomicrograph of right upper lobe mass: no evidence of p53 mutation noted. This would appear as brown/red staining of cytoplasm. (C) Photomicrograph of esophageal mass; 50% expression of mutated p53 evident. Note the presence of brown/red staining of the cytoplasm. (D) Photomicrograph of left base of the tongue; 100% expression of mutated p53. There is heavy brown/red staining of cytoplasm.

Comment

Multiple primary tumors have been identified in two groups: (1) those presenting in distant or unrelated tissue and (2) those with local recurrence in a "multicentric zone" [2]. Treatment of the initial head and neck cancer has not altered the recurrence of the local lesion or the appearance of a lesion at a new site [3]. The contribution of radiation treatment for one cancer to the occurrence of malignancy in the radiation field is unknown.

The p53 protein is the most common gene mutated in human cancers [4]. More than half of all neoplasms in humans are thought to have mutation of the p53 protein [5]. The protein coded by the p53 gene functions in cell cycle regulation and is involved with cell apoptosis [6]. Normal p53 (wild type) is a tumor suppresser gene. The p53 protein is a transcription factor that can modulate the expression of genes (up-regulation and down-regulation) at transcription level. There are three proposed mechanisms for p53 tumor suppressive function. It is known to act at G1-S transition of the cell cycle. If damaged DNA is detected, the cell replication is slowed to allow for repair of the damaged DNA. The p53 protein also increases the DNA repair by the proliferating cell nuclear antigen. The last proposed mechanism is the induction of apoptosis when damaged DNA is encountered by the p53 protein. It is not clear what prompts the p53 to employ one of the above-mentioned tumor suppressive mechanisms.

The significance of the data presented above is not clear. Results of immunohistochemical tests for the presence of the mutated p53 gene may also be positive in normal tissue and cancer cells that have not reacted to mutated p53 monoclonal antibodies. Thus, application of analysis of p53 in the clinical situation remains controversial and investigational at present.

The surgical goal in this patient was diagnosis and simultaneous resection of both pulmonary and esophageal masses. The radical operation was completed in two stages to reduce the potential of bronchoesophageal fistula formation because simultaneous gastroesophageal reconstruction would have localized the esophageal anastomosis quite close to the resected right upper lobe bronchus.

Because we used two stages, the interval before resection could have served for radiochemotherapy and further decreased the risk of fistula. Fortunately, the mediastinal nodes resected were negative for metastasis. Substernal gastric transfer was elected because resection of the right upper lobe precluded one-lung anesthesia to permit colon transposition through the left side of the chest. Our approach was successful and the patient did well.

In conclusion, multiple primary malignant neoplasms of the aerodigestive tract present an interesting problem in terms of common etiology. Genetic examination of these tumors, still controversial, may lead to information improving our knowledge of their causation.

Our patient had four such multiple primary neoplasms. Tonsillar carcinoma was treated with radiation. Synchronous different cell carcinomas of the lung (adenocarcinoma) and esophagus (squamous cell carcinoma) followed 4 years later. Squamous cell left lingual carcinoma developed 6 years after the initial radiation for tonsillar cancer. This last cancer may be a primary tumor, a local recurrence of the tonsillar carcinoma, or a result of the radiation therapy.

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Branch Retinal Artery Occlusion From a Retained Left Atrial Catheter 21 Years After Operation

Jonathan J. Drummond-Webb, FCS(SA), Paula M. Bokesch, MD, Makram R. Ebeid, MD, Daniel J. Murphy, MD, George E. Sarris, MD, and Roger B. B. Mee, FRACS

Center for Pediatric and Congenital Heart Diseases and Department of Cardiothoracic Anesthesia, The Cleveland Clinic Foundation, Cleveland, Ohio

A case of branch retinal artery occlusion due to an embolus from a retained left atrial catheter is presented. Removal was accomplished by reoperation. Prompt removal of any retained intracardiac catheter is recommended.

(Ann Thorac Surg 1998;65:254–5)

A previously healthy 25-year-old woman had undergone closure of a ventricular septal defect at the age of 4 years in another institution. She presented to the emergency room with sudden, complete, painless loss of vision in her left eye. She reported no other symptoms aside from an isolated episode of syncope 5 months prior. Angiographic and opthalmologic studies documented a left-sided branch retinal artery occlusion. A Holter monitor failed to document any atrial fibrillation. A transthoracic and subsequent transesophageal echocardiogram

Accepted for publication Sep 4, 1997.

Address reprint requests to Dr Drummond-Webb, Department of Pediatric and Congenital Cardiac Surgery, Area M41, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44145 (e-mail: drummoj@cesmtp.ccf.org).

0003-4975/98/$19.00
PII S0003-4975(97)01198-3