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*Original articles*

# Non-Hodgkin's lymphoma after successful therapy of small cell lung carcinoma

**Raymond B. Weiss[1,3] and Michael A. Klein[2]**

[1] Section of Medical Oncology, Walter Reed Army Medical Center Washington, DC 20307, USA
[2] Department of Pathology, Walter Reed Army Medical Center, Washington DC 20307, USA
[3] Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA

***Summary.*** *A patient is presented who developed a diffuse mixed lymphoma after successful treatment of small cell undifferentiated carcinoma of the lung. The patient was treated with cytotoxic chemotherapy and irradiation for the lung cancer, and had no recurrence during 6 years with no treatment. He then developed stage IV lymphoma. The relationship between these two cancers and the occurrence of treatment-induced second malignancies in small cell carcinoma are discussed.*

## Introduction

The appearance of second malignancies after successful treatment of an initial malignancy is now a well-recognized phenomenon [7, 8, 10]. Patients with Hodgkin's disease treated with either chemotherapy alone or chemotherapy plus irradiation have an increased risk for subsequently developing acute leukemia [2]. Some patients with Hodgkin's disease have developed non-Hodgkin's lymphoma as a second cancer [1, 3]. Small cell carcinoma of the lung is curable in a minority of patients, particularly in those who have limited disease [12]. Recently, cases of acute leukemia developing in patients successfully treated for small cell carcinoma have been reported [4–6, 9, 11]. In analogous fashion to patients with treated Hodgkin's disease, we have observed a patient who has been cured of small cell carcinoma and has developed non-Hodgkin's lymphoma as a second cancer.

## Case report

A 66-year-old white man presented at Walter Reed Army Medical Center in February 1975 with a left hilar mass on chest roentgenogram. Bronchoscopy was performed and a diagnosis of small cell undifferentiated carcinoma was made histologically. He was appropriately staged and found to have no disease outside the left hemithorax. He was entered on a Cancer and Leukemia Group B (CALGB) protocol (#7283) and received cyclophosphamide 2,000 mg/m$^2$, methotrexate 250 mg/m$^2$ with citrovorum factor rescue, and vincristine 1.5 mg/m$^2$ administered at 3-week intervals. After two courses of chemotherapy he received 3,280 rad in 10 fractions to the primary tumor and mediastinum. He completed six courses of intensive chemotherapy in December 1975 and had achieved a complete remission.

For the next 14 months (until February 1977) he received the same chemotherapy but at lower doses of cyclophosphamide and methotrexate.

*Offprint requests to:* R. B. Weiss

The patient remained well except for symptoms and signs of hypothyroidism and hypogonadism, which were appropriately treated. In early 1983 he developed frequent nocturia and a urologic investigation was initiated. A large retroperitoneal mass was found, which was obstructing the right ureter and had caused renal atrophy. Exploratory surgery and nephrectomy were accomplished. The histologic diagnosis of the mass was diffuse mixed lymphoma.

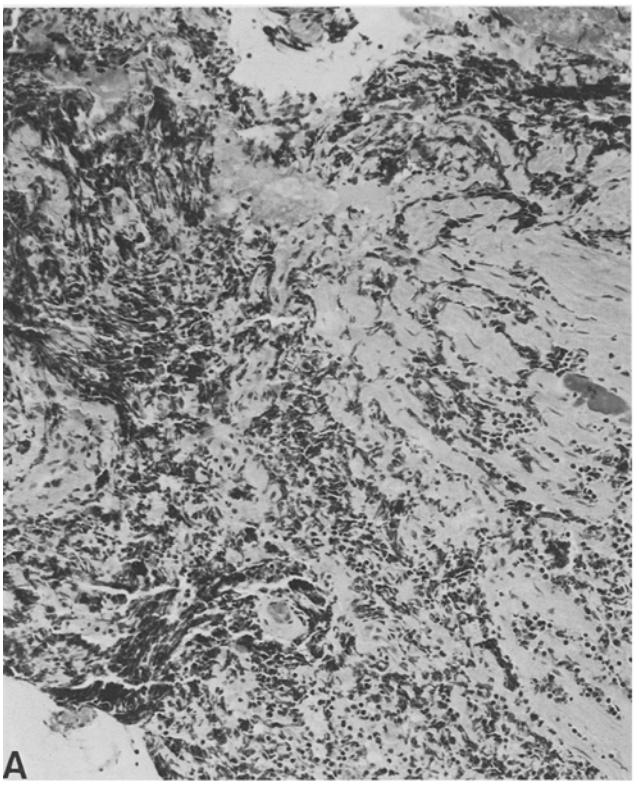
After the new cancer was diagnosed appropriate staging procedures were performed. The only other indication of lymphoma besides enlarged retroperitoneal nodes was a positive bone marrow. He was thus in stage IV, and chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone was started. The patient has completed eight courses of this combination regimen and is in complete remission. No further therapy is planned at present.

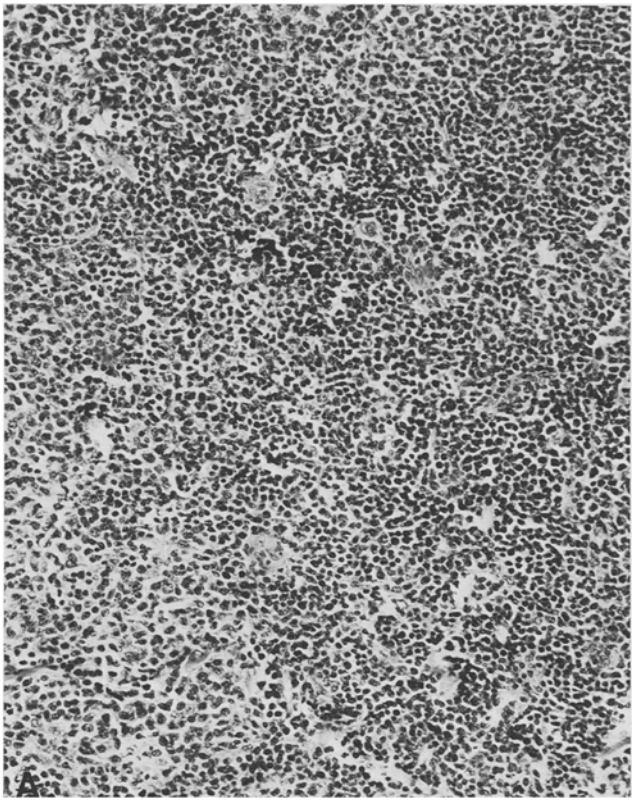
Both specimens diagnostic of the two separate cancers were reviewed by multiple pathologists. The endobronchial lesion was described as "cheesy" by the bronchoscopist. Microscopically the lesion showed an infiltrate demonstrating a pronounced crush artifact effect accompanied by a desmoplastic reaction (Figs. 1A and B). Viable cells contained hyperchromatic angulated nuclei with adjacent cells often showing nuclear molding, which contributed to a distinct impression of cellular cohesiveness. The slides were also reviewed by the reference pathologist for the CALGB protocol, and a diagnosis of small cell carcinoma (polygonal/fusiform type) was confirmed.

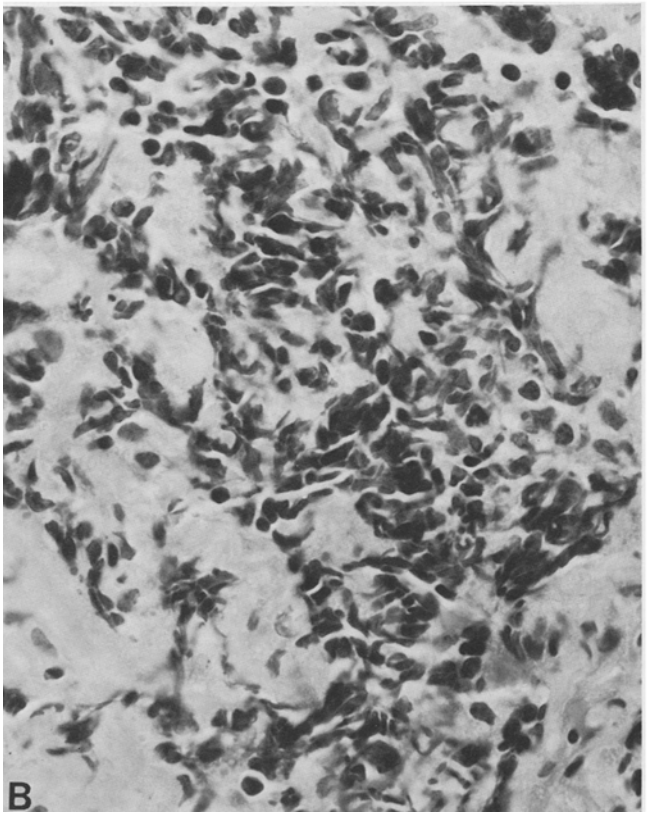
The microscopic features of the retroperitoneal lesion were characterized by a diffuse infiltrate of small and large lymphoid cells engulfing and invading the wall of the ureter (Figs. 2A and 2B). Nuclear clefts were easily identified, and many of the larger cells had open, vesicular nuclei with amphophilic nucleoli. This tumor differed most from the bronchial lesion by the absence of a cohesive growth pattern. In addition, nuclear molding, crush artifact, and desmoplasia were not prominent features of this tumor.

## Discussion

Patients who are cured of one cancer can develop a second cancer. Until the past decade, few patients with small cell lung carcinoma were actually cured of their disease, and their survival was usually not long enough for a second cancer to appear. With the use of intensive chemotherapy with or without irradiation, 10%–20% of the patients who have limited stage tumors are free of disease for over 24 months.



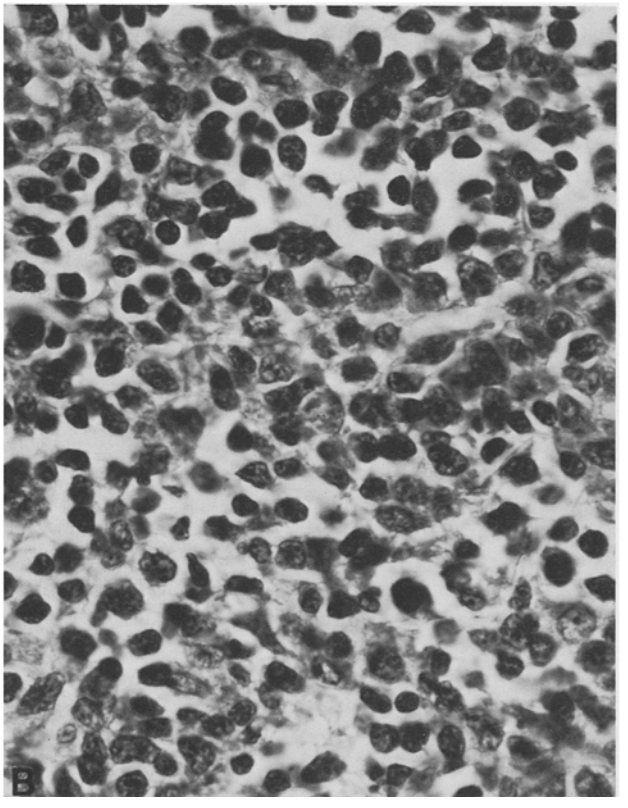




**Fig. 1A, B.** Bronchial biopsy showing small cell undifferentiated carcinoma: **A** Prominent nuclear streaming in absence of stromal crush effect; H & E, × 160. **B** angulated, hyperchromatic nuclei infiltrating in cordlike fashion. Adjacent cells occasionally show nuclear molding. H & E, × 630

**Fig. 2A, B.** Retropertioneal mass, non-Hodgkin's lymphoma: **A** Diffuse infiltrate of variably-sized lymphoid cells in a noncohesive pattern; H & E, × 160. **B** small and large lymphoid cells showing varying degrees of nuclear atypia. H & E, × 630

This appreciable number of long-term survivors has led to the recognition of instances of acute leukemia developing in some patients. We add to the list of possible second cancers in these patients by reporting a patient in whom non-Hodgkin's lymphoma has appeared.

Alkylating agents and radiation are carcinogenic. There are numerous instances where acute leukemia has appeared in patients with cancer who have been treated with one or both of these modalities, [7, 8, 10]. It appears clear that the treatment contributed to the onset of the leukemia in these patients. The patients with small cell cancer who have developed acute leukemia [4–6, 9, 11] probably also did so as a result of the therapy.

Our patient developed a non-Hodgkin's lymphoma. This is not a cancer that ordinarily has an etiology obviously related to chemotherapy and/or irradiation. Thus, the fact that lymphoma appeared in a patient who previously had small cell carcinoma may be entirely coincidental. However, some patients with Hodgkin's disease who have received extensive treatment have been reported to develop either acute leukemia or non-Hodgkin's lymphoma [1–3]. In such cases the patient had usually received both combination chemotherapy and large-field irradiation. Our patient had intensive therapy with cyclophosphamide and had irradiation to a hilar and mediastinal portal. The appearance of the second cancer thus could be due to this treatment.

This patient was entered on a CALGB treatment protocol. Of 257 evaluable patients entered on this study from 1972 to 1975, there are five still alive, one of them being this patient.

We report the first instance of a long-term survivor from small cell carcinoma developing non-Hodgkin's lymphoma as a second cancer. Other instances of such second cancers may be recognized, besides acute leukemia. Any patient who has a possible second malignancy should be carefully studied to be certain it is not a recurrence of the first one. Although the therapy may have been carcinogenic, one should not be deterred from applying the intensive treatment for small cell carcinoma that has resulted in meaningfully prolonged survival.

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