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ATYPICAL CARCINOID TUMORS OF LUNG: CLINICOPATHOLOGIC STUDY OF SIX CASES

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ABSTRACT

This retrospective study of 6 cases of atypical carcinoid tumor was carried out to highlight their clinicopathological features and behavior. All patients were over 40 years of age and were treated by surgical excision of the tumor. Four tumors were central and 2 were peripherally located in the lung. Grossly, the tumors were large with spotted areas of necrosis. Microscopically, all tumors had a typical carcinoid pattern with spotted areas of necrosis and mitotic activity in the range of 2 to 5 per 10 high-power fields. On immunohistochemistry, the tumors were positive for neuron-specific enolase and cytokeratin. Follow-up ranging from 1 to 5 years was available in 4 patients; 2 are currently alive, 1 with local recurrence and distant metastasis one year postoperatively, the other with no disease after 5 years. Two patients died; one had a local recurrence at 2 years and the other had liver metastasis at 3 years.

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INTRODUCTION

The classification of pulmonary neuroendocrine tumors of the lung has evolved substantially over the past two decades. Previously, only two major categories of pulmonary neuroendocrine tumors were recognized; the relatively benign typical carcinoid and the highly aggressive small-cell carcinoma. However, some tumors cannot be satisfactorily placed in these polar groups because they show focal necrosis and some mitotic activity, unlike the typical carcinoid, while still retaining the overall carcinoid pattern. The behavior of these tumors is intermediate to that of the typical carcinoid and small-cell carcinoma. In 1972, Arrigoni and colleagues[1] coined the term atypical carcinoids to describe such tumors. Essentially, atypical carcinoids can be distinguished within the spectrum of neuroendocrine tumors by the following histologic criteria: increased mitotic activity in the presence of a recognizable carcinoid pattern; pleomorphism and irregularity of nuclei with prominent nucleoli, hyperchromatism, and an abnormal nucleocytoplasmic ratio; areas of increased cellularity with disorganization of architecture; and areas of necrosis.

The clinicopathological features of 6 atypical carcinoid tumors recorded at a cancer hospital over a 10-year period are described with the aim of highlighting this little known and underdiagnosed entity.

PATIENTS AND METHODS

During analysis of all lung tumors accessioned from 1985 to 1995, 6 cases were found to fulfill the criteria for atypical carcinoids on histology. Five were primarily

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examined from cases treated surgically in this hospital; representative material was available for review in the 6th case. Intraoperative frozen-section diagnosis of carcinoid tumor was made in the first 5 cases prior to receiving the fresh surgical specimens. Sections were fixed in 10% formalin, embedded in paraffin wax, stained with hematoxylin and eosin, and studied by light microscopy. Immunohistochemical staining included a panel of antibodies to cytokeratin (Dakopatt, Carpinteria, CA, USA; dilution, 1:100), neuron-specific enolase (Dakopatt; dilution, 1:50), synaptophysin (Dakopatt; dilution, 1:100), chromogranin (Dakopatt; dilution, 1:100), and S-100 protein (Dakopatt; dilution, 1:300), using the avidin-biotin-peroxidase complex and the peroxidase-antiperoxidase technique with 3,3'-diaminobenzidine as the chromogen. Samples of typical carcinoids were used as controls for immunohistochemistry. Clinical and operative details were obtained from the patients' records.

RESULTS

All 6 patients with atypical carcinoids were over 40 years of age (range, 40 to 60 years; mean, 49.8 years) and there was an equal number of men and women. Clinical history and details of treatment are listed in Table 1. Four tumors were central and 2 were peripherally located in the lung; they ranged in size from $3 \times 3 \times 2$ cm to $7 \times 6 \times 5$ cm. Grossly, they were firm, yellowish white, and homogenous with spotted areas of necrosis and hemorrhage (Figure 1). No nodes were dissected from the lung specimens and none of the tumors involved the pleura.

Microscopically, each tumor revealed a readily identifiable carcinoid growth pattern that comprised a variety of architectural types. Three tumors had a lobular and trabecular pattern, 2 showed a mixture of lobular and insular patterns, and 1 was predominantly lobular. Prominent palisading at the periphery of the tumor nests was seen in 3 specimens. A striking feature visible in all tumors was the presence of spotted areas of necrosis in the center of the lobules (Figure 2), despite the overall carcinoid-like growth pattern. A focal micro-acinar pattern was also seen (Figure 3). The individual tumor cells were three times the size of a normal lymphocyte and contained a moderate amount of eosinophilic cytoplasm. The nuclei were round with fine stippled salt-and-pepper-like chromatin. Nuclear pleomorphism and prominent nucleoli were seen in 3 tumors (Figure 4). Mitotic figures were infrequent. However, 3 tumors had 2 mitotic figures per 10 high-power fields (HPF), whereas the other 3 had 5 mitoses per 10 HPF.

Immunohistochemistry revealed a focal weak positivity for cytokeratin and strong positivity for neuron-specific enolase in all 6 tumors. On the other hand, S-100 protein, chromogranin, and synaptophysin were uniformly negative in all tumors. The samples of typical carcinoid used as controls showed strong positivity for cytokeratin, neuron-specific enolase, chromogranin, and synaptophysin.

Table 1. **Clinical Details of 6 Patients with Atypical Carcinoid Tumors**

Age (years)	Sex	Symptom	Duration of Illness (months)	Radiological Findings	Location	Treatment	Follow-Up (months)
60	F	Cough, dyspnea	5	$7 \times 6 \times 5$ cm heterogenous opacity	Right upper lobe	Right upper lobectomy	Local recurrence at 1 year, metastasis in year 2
40	M	Cough, chest pain	3	$3 \times 3 \times 2$ cm opacity	Left lower lobe	Left lower lobectomy	Lost to follow-up
50	M	Cough, purulent expectoration	2	$6 \times 6 \times 5$ cm heterogenous opacity	Right upper + middle lobes	Right pneumonectomy	Died of recurrence at 2 years
43	F	Cough, chest pain	6	5-cm lesion close to pleura	Right lower lobe	Right pneumonectomy	Lost to follow-up
57	M	Cough	12	$6 \times 5 \times 3$ cm homogenous mass	Left lower lobe	Left lower lobectomy	Free of disease at 5 years
49	F	Cough, chest pain, hemoptysis	4	$4 \times 4 \times 3$ cm opacity	Left upper lobe	Left pneumonectomy	Died of metastasis at 3 years

Follow-up of 1 to 5 years was available in 4 cases (2 patients were lost to follow-up). Two of these 4 patients died of the disease; one developed a local recurrence 2 years postoperatively and the other developed liver metastasis 3 years after surgery. Both patients received adjuvant therapy comprising chemotherapy as well as radiotherapy after developing recurrence and metastasis. However, they did not respond. The other 2 patients are currently alive; one had a local recurrence in the first postoperative year, which was treated with radiotherapy. She was free of disease for 1 year but was found to have metastatic deposits in the perineum at a recent follow-up. The other patient received local radiotherapy and is free of disease after 5 years.

DISCUSSION

Atypical carcinoids are uncommon tumors and together with the typical carcinoids constitute less than 5% of all lung tumors.[2] In this 10-year period (1985 to 1995), 40 cases of typical carcinoids were recorded but there were only 6 cases of atypical carcinoids. The largest series of atypical carcinoids, comprising 33 cases, was reported by Valli and colleagues[3] in 1994. Smaller series comprising 23, 17, and 6 cases have been published.[1,4,5] It is most likely that the 41 cases reported under the term bronchopulmonary Kulchitzky-cell carcinoma type II by Paladugu and colleagues[2] in 1985 were also atypical carcinoids.

The 6 patients with atypical carcinoids in this study had a mean age of 49.8 years, whereas in the previous series, the mean ages were 55, 51, 58, and 33.2 years.[1,3–5] The age range for typical carcinoids is 23 to 70 years.[5] The average size of the atypical carcinoids was $5 \times 5.5 \times 3.5$ cm, whereas the average size of typical carcinoids recorded in this hospital was 2.5 cm in diameter. Grossly, the large-cell neuroendocrine carcinomas average 3.2 cm in diameter, whereas the small-cell carcinomas are frequently large, destructive, and surgically unresectable lesions when first seen.[5]

Microscopically, the atypical carcinoids maintained the carcinoid growth pattern yet revealed mitosis and spotty necrosis. Mitotic activity was 2 to 10 per 10 HPF in the

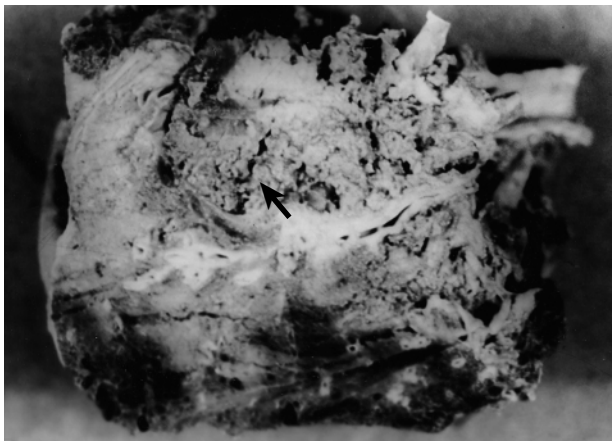

Figure 1. Pneumonectomy specimen showing a large central tumor with areas of necrosis (arrow).

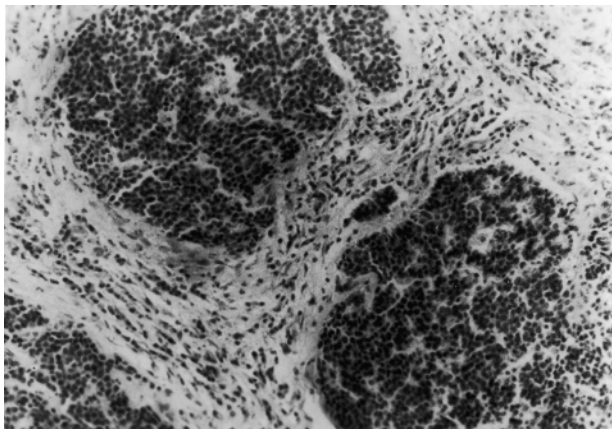

Figure 3. Atypical carcinoid of the lung showing a nesting pattern. A micro-acinar pattern is also noted (hematoxylin and eosin stain, original magnification ×100).

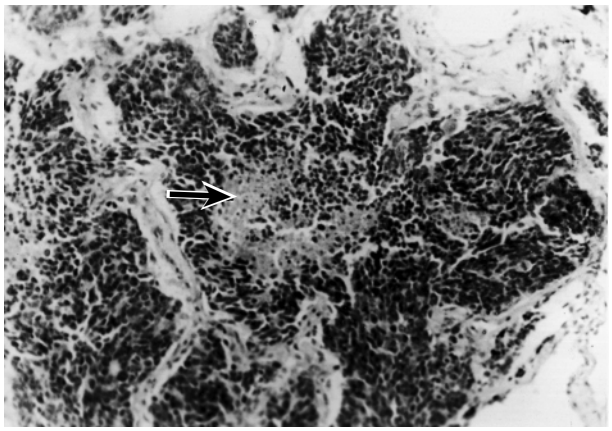

Figure 2. Atypical carcinoid of the lung showing a prominent nesting pattern, spotted areas of necrosis, and focal peripheral palisading (arrow). (Hematoxylin and eosin stain, original magnification ×100.)

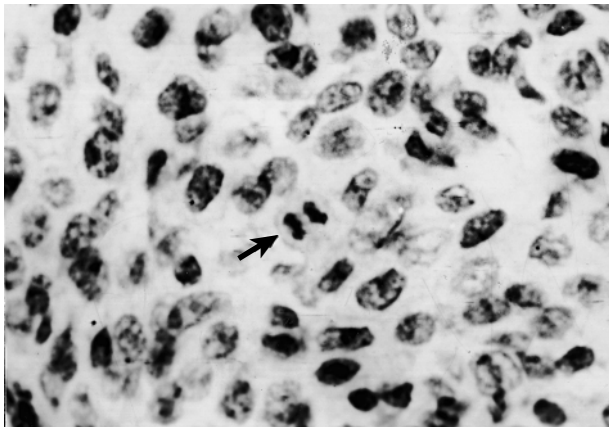

Figure 4. Tumor cells showing round nuclei with moderate pleomorphism, fine stippled chromatin, and infrequent mitotic activity (arrow). (Hematoxylin and eosin stain, original magnification ×200.)

6 atypical carcinoids. Necrosis has not been described in typical carcinoids and the mitotic activity is sporadic (0 to 1 per 10 HPF).[5] In contrast to both typical and atypical carcinoids, the small-cell carcinomas and large-cell neuroendocrine carcinomas have large areas of infarct-like necrosis. The cells of small-cell carcinoma are less than three times the size of a small lymphocyte, with finely granular chromatin, no nucleoli, and a mitotic rate higher than 10 per 10 HPF (range, 28 to 124 per HPF). Nuclear moulding and hematoxylin staining of DNA encrustation of the vessel walls (Azzopardi effect) are frequently seen. The tumor cells of large-cell neuroendocrine carcinoma are larger with a low nuclear-cytoplasmic ratio, vesicular or fine nuclear chromatin with frequent nucleoli, and a high mitotic activity of 11 to 70 per HPF.[6] Thus, the atypical carcinoids occupy an intermediate morphological position in the spectrum of bronchopulmonary neuroendocrine tumors.

The immunohistochemical results in our study revealed weak positivity for cytokeratin and strong positivity for neuron-specific enolase, whereas S-100, chromogranin, and synaptophysin were uniformly negative. In contrast, the typical carcinoids that served as controls showed strong positivity for cytokeratin, neuron-specific enolase, chromogranin, and synaptophysin. Neuron-specific enolase can often stain nonspecifically and chromogranin and synaptophysin are superior antibodies for assessing the neuroendocrine origin of any tumor. However, these markers sometimes do not stain atypical carcinoids well, as noted in this study. Travis and colleagues[5] also found a slightly lower overall percentage, distribution, and intensity of immunohistochemical staining for neuroendocrine and hormonal markers in atypical carcinoids compared to typical carcinoids. They attributed this to a lower degree of differentiation of atypical carcinoids than typical carcinoids.

In the present study, 2 of the 4 patients in whom follow-up was available, died within 3 years. The 3rd patient had a local recurrence in the first year and metastasis in the second year, whereas the last patient was without recurrence after 5 years. The atypical carcinoids have a larger tumor size, a higher rate of lymph node metastasis (76%), and disease-free survival rates of 69% and 25% at 5 and 10 years, respectively.[7] The mortality rate for atypical carcinoids reported in most series is approximately 30% and the mean survival of patients who die of atypical carcinoids is less than 2 years.[7] Hence, a more radical approach in the form of lobectomy or pneumonectomy is justified. The typical carcinoids are generally small tumors with a lower rate of lymph node metastasis (4% to 6%) and disease-free survival rates of 100% and 87% at 5 and 10 years, respectively.[7]

Small-cell carcinoma of the lung is the most frequent neuroendocrine tumor and accounts for approximately 25% of lung tumors.[8] It is highly aggressive and usually located centrally. Clinically, it is characterized by rapid growth and early metastatic dissemination. The small-cell carcinomas are highly chemosensitive with a response rate greater than 80% in both limited and extensive disease, yet the 5-year survival rate is only 4%.[9] Before the advent of systemic therapy, local surgical or radiation therapy alone resulted in a very poor median survival ranging from 8 to 17 weeks.[9] The median survival with combination chemotherapy is 14 to 16 months for patients with limited disease and 8 to 11 months for those with extensive disease.[10]

The distinction of atypical carcinoids from other neuroendocrine tumors should be based on morphological parameters that include the amount and pattern of necrosis, cell size and amount of cytoplasm, nuclear chromatin, nucleoli, and most importantly, the mitotic rate. Immunohistochemistry can be used as a supplementary tool to morphology. Apart from the other neuroendocrine tumors, atypical carcinoids may also be confused with Askin-Rosai tumor (primitive neuroectodermal tumor of the chest wall) and with a monophasic synovial sarcoma. Both of these tumors lack the carcinoid pattern and often have their dominant components in the chest wall or pleura with a smaller contiguous pulmonary component, unlike the atypical carcinoid that is largely an intraparenchymal tumor. In addition, immunoreactivity for Mic-2 in primitive neuroectodermal tumor and lack of immunoreactivity for neural markers in synovial sarcoma are additional differentiating features.

The atypical carcinoid is underdiagnosed and often unrecognized. The distinguishing features described in this report are important in view of the therapeutic and prognostic implications.

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