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Biological behaviour of lung carcinoids
A retrospective analysis of 71 patients

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A retrospective study of 71 patients treated for lung carcinoids during the years 1973–1992 is presented. Beside clinical and pathological data, an inquiry was performed to establish the rates of recurrence of disease and survival of the patients, Lung carcinoids represented 0.6 % of all lung carcinomas. There were 37 male and 34 female patients with age range from 14 to 78 years, and an average age 47.5 years at the time of surgery. The highest incidence of carcinoids (38 patients, 53 %) appeared in the age group 41–60 years. In three patients (4 %), associated clinical syndromes were documented: one patient had typical carcinoid syndrome, while in two others Cushing's syndrome has developed. The most common lobectomy was performed in 45 patients (63 %). Sixty-six (93 %) carcinoids were located centrally, and 5 were peripheral. Histologically, 61 carcinoids (86 %) were evaluated as typical. Two carcinoids (3 %) were composed of spindle cells, 2 had oncocytic areas, and stromal ossification was found in 4 cases (6 %). Out of 64 patients, lymphnode metastases were found in only 3 cases (5 %), and distant metastases in one patient with a recurrent tumour. Nine patients (13 %) have died: 5 (7 %) because of atypical carcinoids and 4 because of other diseases. The second primary malignancy was detected in four patients (5.6 %). Forty-six out of 47 patients (98 %) have survived 5 years, 26/28 (93 %) 10 years, and 13/18 (72 %) have survived even 15 years. The prognosis was good in patients with typical carcinoids but much worse in those with atypical carcinoids; nevertheless, even in the latter, the death occured later than in other lung carcinomas.

Key words: lung neoplasms; carcinoid tumor

Introduction

Bronchopulmonary carcinoids are well differentiated, slowly growing malignant tumours of neuroendocrine origin, rarely metastasizing to the regional lymphnodes.[1, 2] They follow a relatively indolent clinical course for long periods and are therefore amenable to surgical resection. Lung carcinoids represent about 1 % of all long tumours,[3] with usual central localisation in the bronchi. The majority of bronchial carcinoids are without evident clinical syndromes.

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Their localisation leads to nonspecific symptoms such as recurrent cough, hemophthisis and respiratory infections. The tumours are resectable with advocated conservative surgical procedures and thus even curable. Late recurrences may develop. The reported 5- to 10-year survival rates are 80–95 %. The situation is worse with atypical carcinoids. The criteria for the diagnosis of such tumours (celullar and nuclear polymorphism, mitoses, necroses) were set out clearly by Arrigoni[4] and are still used. Because of more malignant behaviour, atypical carcinoids should be treated as truly malignant tumours.[5]

The aim of our study is to evaluatie the experience with our patients in comparison with the data published. This retrospective analysis of 71 patients with carcinoid tumours was performed to establish the incidence of lung carcinoids in Slovenia and to evaluate their clinical behaviour, pathological appearance, surgical treatment and survival data.

Material and methods

The case history records of 71 patients with bronchopulmonary carcinoids surgically treated during the years 1973–1992 were analysed retrospectively. Beside clinical and pathologic data, an inquiry was performed to establish the rate of recurrences of the disease and the survival of patients. Thus, the analysed data comprised symptoms and clinical features, patient age at the time of surgery, tumour size and localization, lymphnode involvement, metastases to distant organs, treatment and survival. The histological diagnosis was based on sections routinely stained with hematoxylin and eosin, and, in recent years, with neuroendocrine markers (neurone specific enolase, chromogranin A, synaptophysin). The original histologic slides were reexamined. Four cases were studied by electron microscopy.

Results

The study group comprised 71 patients. Lung carcinoids represented 0.6 % of all lung carcinomas. There were 37 (52 %) male and 34 (48 %) female patients, in the age range from 14 to 78 years. Their mean age was 47.5 years at the time of surgery; 45.7 years for males, 49.4 years for females. The highest incidence of carcinoids – 38 patients (53 %) – appeared in the age period from 41 to 60 years (Figure 1).

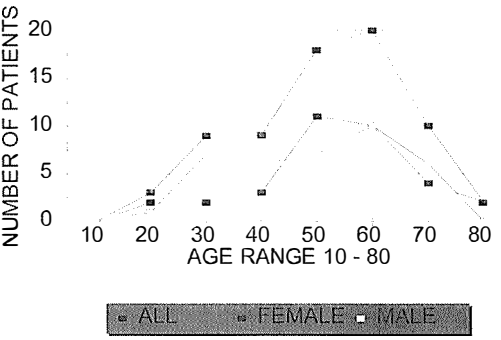

Figure 1. Lung carcinoids (N = 71). Age and sex distribution.

Twenty-nine patients suffered from recurrent or persistent respiratory tract infection, 16 from hemophthisis alone, and 9 patients from hemophthisis with other troubles. Seventeen patients were asymptomatic, their tumours were discovered by chance on chest x-ray.

In 3 patients (4 %), associated clinical syndromes were documented as follows: one patient had typical carcinoid syndrome, while in two others Cushing's syndrome due to ectopic ACTH secretin developed.

The most common lobectomy was performed in 45 (63 %), bilobectomy in 5, pulmectomy in

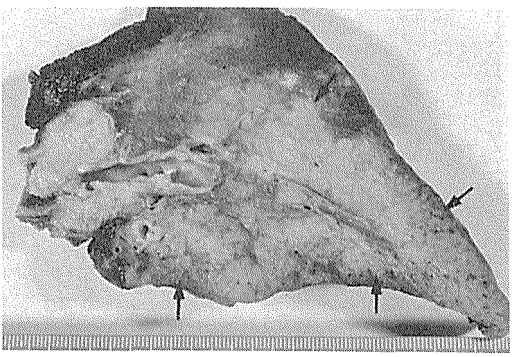

Figure 2. A central bronchial carcinoid with secondary obstructive pneumonitis (arrows).

2, segmentectomy in 8, and minor partial resections in 9 patients. Resection was contraindicated in one patient, while in another there were no exact data about surgical procedure available. Sixty-six (93%) carcinoids were located centrally, and 5 were peripheral. On gross examination, carcinoids appeared as finger-like polypoid intraluminal masses, with 6 to 55 mm in diameter. They could penetrate the bronchial wall and extend in the peribronchial lung tissue with a relatively sharp demarcation line. Endobronchial growth was also a cause of secondary obstructive pneumonitis (Figure 2).

Microscopic picture disclosed solid nests, trabecules and/or glandular structures, separated by a delicate fibrous stroma rich in capillaries. Neoplastic cells were quite uniform, with regular round nuclei. Occasionaly, some variations in cell size and shape were seen. More prominent cellular pleomorphism, together with mitotic figures and areas of tumour necroses were characteristic of atypical carcinoid. Sixty-one (86%) carcinoids were evaluated as typical and 10 (14%) as atypical variant. Ossification of the tumour stroma was found in four cases (Figure 3, 4). Two carcinoids were composed of spindle cells while two had oncocytic areas (Figure 5). In all cases examined for neurone specific enolase, immunohistochemical reaction was positive, it was not constant with chromogranine, and seldom weakly positive with synaptophysin. Electron microscopy disclosed neurosecretory dense-core bodies, characteristic for tumours of neuroendocrine origin (Figure 6).

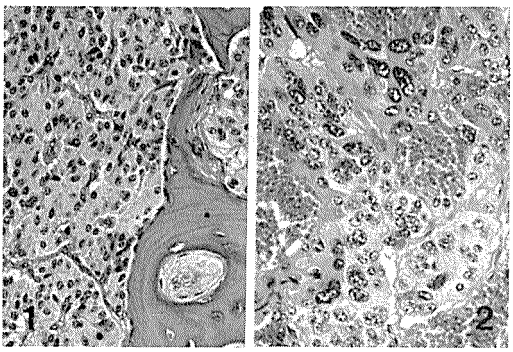

Figure 3. 1. A typical carcinoid with uniform cells and stromal ossification. 2. Prominent cellular and nuclear polymorphism with focal oncocytization in a peripheral atypical carcinoid.

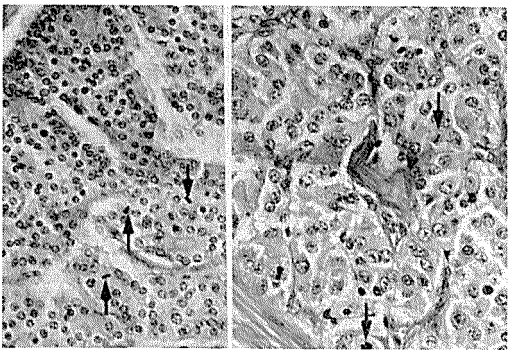

Figure 4. Obvious mitoses in two atypical carcinoids with only slight cellular and nuclear polymorphism.

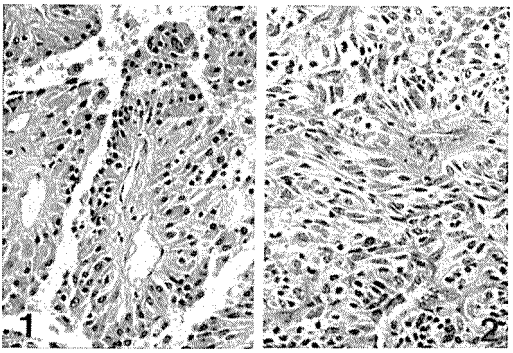

Figure 5. 1. An onocytic carcinoid with abundant cosinophilic cytoplasm of the tumour cells. 2. Peripheral spindle cell carcinoid.

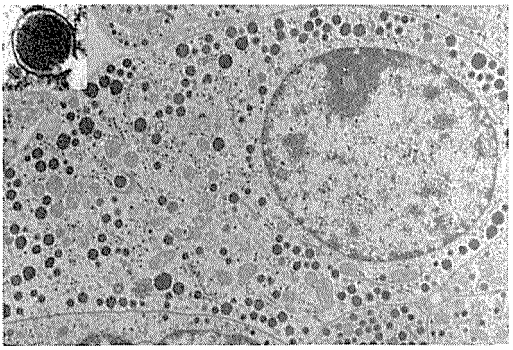

Figure 6. Electron microscopy of a carcinoid in the patient with Cushing's syndrome. Numerous dense-core neurosecretory bodies better visible in the insert.

Out of 64 patients with resected lobar, hilar or other regional lymphnodes, only 3 patients showed evidence of metastatic involvement, this was found patients with Cushing's syndrome. Metastases to distant organs were proven only in one case.

The patients were followed from 1 to 19 years after surgical resection. Carcinoid recidives were documented in 6 patients. Nine patients have died: four of them because of stomach cancer, lung cancer, leukaemia and hypertonic heart disease, respectively. Atypical carcinoid was the cause of death in another 5 patients.

In four (6%) patients with carcinoid, the second primary malignancy was found as follows: lung adenocarcinoma, lung squamous carcinoma, stomach adenocarcinoma, and leukaemia respectively. Excluding mortality from other causes, 46 (98%) out of 47 patients have survived 5 years, 26 (93%) out of 28 10 years, and 13 (72%) out of 18 even 15 years. Patients with atypical carcinoids have died 3, 7, 11, 12 and 13 years respectively after surgical resection. Three patients from our group were living in close vicinity, without any family relationship.

Discussion

Previously, bronchopulmonary carcinoids were inapropriately, classified as "bronchial adenomas" together with mucoepidermoid and adenoid cystic carcinomas. This term is still used,[6–8] but it is inadequate for bronchial carcinoid. Bronchial carcinoid and bronchial adenoma are terms reserved for two biologically and pathologically different and well defined entities.

Also, the term carcinoid could probably be reserved only for tumours secreting 5-hydroxytryptamine and developing classical carcinoid syndrome. It is known that neuroendocrine tumours are the source of various biogenic amines or polypeptides, including ectopically excreted hormones (over 30 different substances were identified up to now), which are associated with other clinical syndromes, different from the classical carcinoid syndrome. But the term "carcinoid" has been already widely known and accepted. Thus we agree with the statement that the term "carcinoid" for these "indolent carcinomas in slow motion" is already so "old, like old soldier, who died hard", that the term "carcinoid" will also survive.[9] Bronchopulmonary carcinoids are neuroendocrine tumours of the bronchopulmonary system.[10–15] They originate from the neuroendocrine Feyrter's cells, which are counterpart of Kulschitzky's cells in gastrointestinal mucosa.[16, 17] Feyrter's cells are found in the basal part of the bronchial epithelium and deeper layers of the bronchial tree (mucous glands).[18] This could explain the most often endobronchial and usual centrally located tumour growth.

The incidence of bronchial carcinoids in Slovenia is comparable with other published data.[19, 20] There is no significant difference in sex distribution. The age range and mean age in our analysis are similar to many previous reports.[19–22]

Many carcinoids remain asymptomatic for long periods of time.[23] The most common symptoms, i.e. respiratory tract infections and/or hemophthisis, are not specific for this tumour, as reported also by others.[24] Bronchopulmonary carcinoids are rarely the cause of clinical syndromes,[25–28] but they account for approximately 2% of all causes of ectopic ACTH production.[29] Both two carcinoids in our study, associated with an ectopic ACTH production and Cushing's syndrome, were classified as typical carcinoids. In both cases lymphnodes were metastatically involved, but until now, surgical treatment is believed to be curative. A carcinoid syndrome found in one patient with atypical carcinoid has developed only after the recurrence with metastases to distant organ.

Peripheral locations of carcinoids are not common, their rate ranging from 2–16%.[5, 22] Out of 5 (7%) peripheral carcinoids in our study, one was composed of spindle cells, while another was defined as an atypical carcinoid.

Most authors regard surgery as the treatment of choice, also successful in the cases of recurrence. They suggested that a pulmonary resec-

tion should be avoided unless there is histologic evidence of the tumour spread in to the lung parencyma or irreverrible inflammatory changes distally from the obstruction. Many new surgical procedures have been introduced, such as parenchyma saving bronchoplastic, procedure, bronchoscopic removal or laser techniques.[5, 22, 30, 31]

Lymphnode involvement is not common in patients with bronchopulmonary carcinoids and bears no relationship with atypical variant.[32] Only in one patient with atypical carcinoid, distant metastases were proved on autopsy. Recurrences of the disease appeared at very different intervals after surgery. Therefore, long follow up is recommended.

The long term results in this study show good survival. Only 5 patients died of carcinoid tumour, all of them with atypical carcinoid. We could also confirm that bronchopulmonary carcinoids follow a very indolent clinical course.[33–35]

The overall prognosis following tumor resection is excellent. It is better in typical carcinoids, and worse in atypical ones.

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