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Original Article / Özgün Makale

Carcinoid tumors of the lung and coexistence of malign epithelial tumors

Akciğerin karsinoid tümörleri ve malign epitelyal tümör birlikteliği

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Background: In this article, we describe five cases of carcinoid tumors of the lung presenting with epithelial tumors who were surgically treated and discuss our experiences on diagnostic and pathologic examinations in the light of literature.

Methods: Five cases (4 females, 1 male; mean age 61.8 years; range 50 to 72 years) of carcinoid tumors presenting epithelial tumors of the lung were enrolled in the study. Coughing was the predominant symptom in all cases. Intraoperative lymph node dissection or lobe-specific lymph node dissection were performed in all cases. The mean duration of follow-up was 30 months (range, 14 to 72 months).

Results: Anatomic resections were performed in all cases. In four cases with carcinoid tumors, three carcinomas were found incidentally including one of them detected during bronchoscopy. The fifth case had an adenocarcinoma in whom the carcinoid tumor was detected incidentally during bronchoscopy. The case with an adenocarcinoma was also found to have a second carcinoma during follow-up. All carcinoid tumors were typical pathologically with a size ranging between 4 and 12 mm and stages of non-small cell lung cancer were T_1aN_0 in two cases and T_2aN_0 in three cases. At present, all cases are alive and symptom-free with a follow-up 14 to 72 months (mean 30 months).

Conclusion: Carcinoid tumors of the lung are low-grade malignancies and may present with a synchronous tumor, which could be either another carcinoid tumor or a carcinoma. Both combinations are quite rare and may complicate surgery sometimes. A thorough bronchoscopic examination and pathologic examination, either preoperatively or postoperatively, is essential in thoracic surgery.

Keywords: Carcinoid tumor; epithelial tumor; pulmonary neoplasm; satellite tumor.

Amaç: Bu çalışmada epitelyal tümörün eşlik ettiği akciğer karsinoid tümörlü ve cerrahi olarak tedavi edilen beş olgu tanımlandı ve tanısal ve patolojik incelemelere ilişkin deneyimlerimiz literatür eşliğinde tartışıldı.

Çalışma planı: Akciğer epitelyal tümörünün eşlik ettiği karsinoid tümörlü beş olgu (4 erkek, 1 kadın; ort. yaş 61.8 yıl; dağılım 50-72 yıl) çalışmaya alındı. Öksürük tüm olgularda en belirgin semptom idi. Tüm olgulara ameliyat sırasında lenf nodu diseksiyonu veya lob spesifik lenf nodu diseksiyonu yapıldı. Ortalama takip süresi 30 ay (dağılım 14-72 ay) idi.

Bulgular: Tüm olgulara anatomik rezeksiyon yapıldı. Karsinoid tümörlü dört olguda, üç karsinom tesadüfen bulundu; bunların biri bronkoskopi sırasında tespit edildi. Beşinci olguda adenokarsinom vardı ve karsinoid tümör bronkoskopi sırasında tesadüfen saptandı. Adenokarsinomlu olguda takip sırasında ikinci bir karsinom bulundu. Karsinoid tümörlerin tümü 4 ila 12 mm arasında değişen boyutlarda patolojik olarak tipik idi ve küçük hücreli dışı akciğer kanseri evresi iki olguda T_1aN_0 ve üç olguda T_2aN_0 idi. Şu anda tüm olgular sağ olup, 14 ila 72 aylık (ortalama 30 ay) takipte semptomsuzdur.

Sonuç: Akciğerin karsinoid tümörleri düşük dereceli maligniteler olup, eş zamanlı başka bir karsinoid tümör veya karsinom ile birliktelik gösterebilir. Her iki birliktelik de oldukça nadirdir ve kimi zaman ameliyatı zorlaştırabilir. Ameliyat öncesinde veya sonrasında kapsamlı bir bronkoskopik ve patolojik inceleme göğüs cerrahisinde önemlidir.

Anahtar sözcükler: Karsinoid tümör; epitelyal tümör; pulmoner neoplazm; uydu tümör.

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Carcinoid tumors of the lung make up between 1 and 2% of all pulmonary neoplasms.[1,2] They have neuroendocrine differentiation and a slow growth pattern but have a favorable prognosis. The well-known characteristics of carcinoid tumors are their right-sided predominance, primarily central location, and rare endocrine manifestations. A carcinoid tumor may develop synchronously with an epithelial tumor anywhere within the lung just as synchronous double primary epithelial cancers do.[3] In this article, we review five surgically treated cases and share our thoughts regarding the diagnostic and pathological examinations.

PATIENTS AND METHODS

Between January 2001 and January 2012, we operated on 130 carcinoid tumors, and five if these cases (4 females, 1 male; mean age 61.8 years; range 50 to 72 years) with coexisting carcinoid and epithelial tumors of the lung were enrolled in this study. The five epithelial tumors were among 945 cases that were operated for pulmonary neoplasms within the same period. Coughing was the predominant symptom in the cases, but hemoptysis was also seen in two of the patients. Chest computed tomography (CT), routine blood examinations, and pulmonary functional tests were performed on all of the patients.

Positron emission tomography (PET) was not performed on any patient when a histological diagnosis had been established, nor was a mediastinoscopy necessary because there was no pathological assessment of mediastinal lymph nodes. The macroscopic appearance was compatible with carcinoid tumors, but no pathological symptoms related to these tumors were found elsewhere (Table 1). The histopathological examinations were performed according to the 2004 World Health Organization (WHO) classification of lung tumors, and immunohistochmical staining was carried out for all of the cases.

Either a fiberoptic or a rigid bronchoscopy was performed on each of the patients to identify the location of the tumor, identify the operability, and obtain a tissue diagnosis. Rigid bronchoscopy was preferred when the tumor was located centrally and had a tendency to bleed. In all five cases, the tumors were visible on bronchoscopy, and pathological specimens were obtained. In the end, all of the tumors were identified as typical carcinoid tumors.

In two of the patients, there was an incidental preoperative diagnosis of non-small-cell lung carcinoma (NSCLC), with one case being detected via bronchoscopy and the other by CT. In addition, three other cases of this type of cancer were diagnosed during the pathological examinations of the surgical specimen.

RESULTS

All of the patients underwent an anatomic resection, and a sleeve resection was performed when necessary

Table 1. Carcinoid tumors, age, gender, site, pathology and operations

Patients no	Gender/age	Date of operation	Operation	Pathology	Size	NSCLC stage	Remarks	Follow-up
1	64/F	Apr 2007	LLL Adenocarcinoma	Typical carcinoid 4 mm same lobe	3x1x1 cm	$T_2aN_0M_0$	Incidentally found at frozen section	Alive at 72 months
2	50/F	March 2010 Oct 2011	LLL Sleeve RML	Typical carcinoid Typical carcinoid + adenocarcinoma	1.5x1.5 cm 4.5x3 cm + 8 mm same lobe	$T_1aN_0M_0$	Biateral carcinoid tumors Adenocarcinoma is incidentally found on the pathological examination at the middle lobe	Alive at 19 months
3	72/F	Jun 2011	RML	Typical carcinoid Epidermoid carcinoma	2x1.5x1.5 cm 8 mm	$T_1aN_0M_0$	Incidentally found on the pathological examination on the same lob	Alive at 22 months
4	65/F	May 2011	Resection of left lingulectomy	Typical carcinoid	8 mm	$T_2aN_0M_0$	Incidentally found via brochoscopy	Alive at 14 months
		Feb 2012	RLL	Adenocarcinoma	1.2x1x1 cm			
5	58/M	May 2011	LUL	Adenocarcinoma Typical carcinoid (satellite)	3.5x3.5 cm 7 mm	$T_2aN_0M_0$	Carcinoid was seen on CT as a satellite lesion	Alive at 24 months and
		Feb 2012	Right upper lobe	Epidermoid carcinoma	2.5x2.5 cm	$T_1bN_2M_0$	Multiple mediastinal N2 disease CT4 RT	15 months

NSCLC: Non-small cell lung cancer; LLL: Left lower lobectomy; RML: Right middle lobectomy; LUL: Left upper lobectomy; CT: Computed tomography; RT: Right thoracotomy.

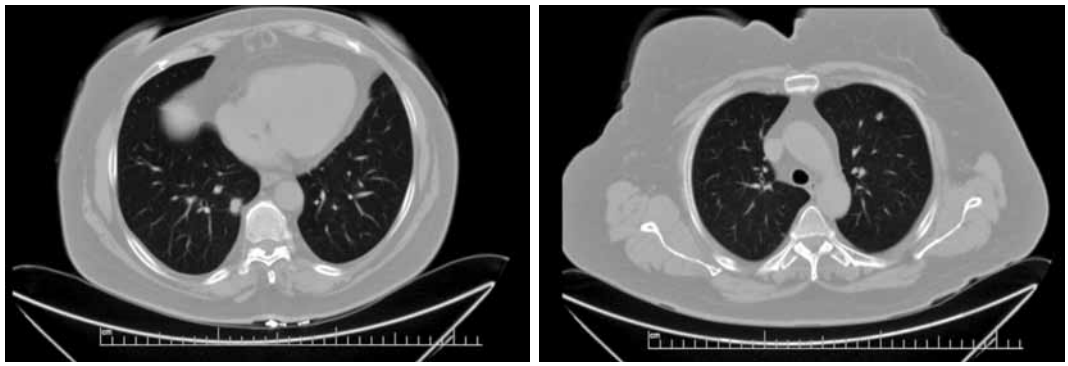

Figure 1. Right lower lobe carcinoma was incidentally found on a bronchoscopy; an adenocarcinoma as seen on chest computed tomography. The carcinoid tumor was located at the lingula.

in order to preserve lung tissue. Frozen-section examinations of the surgical margins were also performed to determine whether they remained tumor-free since this had been the preoperative diagnosis. Furthermore, intraaoperative or lobe-specific lymph node dissection was performed in all of the cases. The mean follow-up duration was 30 months (range 14-72).

The fourth case featured the synchronous presentation of two tumors, with right lower lobe carcinoma and a coexistent tumor at the lingula, which were identified incidentally via the bronchoscopy (Figure 1). The fifth case presented with a satellite tumor, and a third tumor (epidermoid carcinoma) was detected at the ninth postoperative month during a follow-up appointment. Palliation (chemotherapy) was the treatment of choice for this patient because of excessive mediastinal lymphatic involvement.

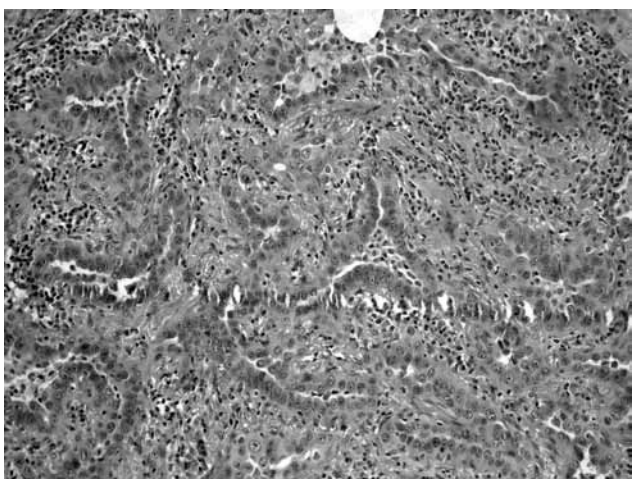

Figure 2. Typical carcinoid tumor in an organoid structure (H-E x 200).

The surgical margins were tumor-free in all of the cases. Despite the incidental discovery of tumors in three of the patients with diameters ranging between 4 and 12 mm, these were accepted as being stage $T_2aN_0M_0$ because of their location at the lobar orifice. The patient demographics, tumor characteristics, diagnostic remarks, and treatment are shown in Table 1.

No complications developed postoperatively, and all of the patients were discharged between the postoperative fourth and ninth days (mean 6.3 days). Pathologically, all of the carcinoid tumors were typical (Figure 2).

All of the cases were followed-up at six-month intervals with chest CT, and no additional adjuvant therapy was necessary, except for the fifth case. For that patient, the third tumor was inoperable at presentation, so palliative treatment consisting of chemoradiotherapy was initiated.

DISCUSSION

It is common in these days to encounter patients with two or more cancers occurring either synchronously or metacronously.[4] Surgical resection of synchronous multiple lung cancer is a challenge in thoracic surgery and requires special expertise, meticulous preoperative examinations, parenchyma-preserving surgery, and specific pathological studies.

A problem arises with the presence of a second mass lesion when it is not carcinoid in nature. The second lesion could be located anywhere in the lung, and it can be found within the same lobe or in another lobe. In addition, it can also be detected incidentally following a bronchoscopic examination or be discovered on a pathological examination. Therefore, the possibility of a second lesion should be considered in order to have better preoperative planning and a more accurate

evaluation of whether an operation is necessary. If the second lesion is a malignant epithelial tumor, surgical treatment is almost always required.

A synchronous tumor may or may not be within the same lobe. Another possibility when considering the location of the second primary tumor is there can be a mixture of two tumors or one tumor that contains two components. Both Nagamatsu et al.[5] and Sano et al.[6] described this occurrence and named it "cancer in cancer" and "a mixture of two tumors", respectively. The clinical features of synchronous tumors remain unknown because they are very rare,[6] and we believe that meticulous pathological examinations are needed to reveal the presence of this mixture. In our study, two of the carcinoid tumors were primary lesions that were synchronous and separate from other carcinomas. No composite or mixture formations were detected in our five patients.

In cases that involve multiple carcinoid tumors, palliative therapy might be helpful for detecting the possible involvement of other organs while a careful bronchoscopic examination is essential for detecting the airway tract. Spaggiari et al.[7] found that PET is less effective for low-grade malignancies and determined that it may be useless for detecting carcinoid tumors. They also reported 73% and 93% PET positivity for typical and atypical carcinoid tumors, respectively. In patients with synchronous carcinoid and epithelial tumors, PET might be beneficial because it can show whether tumors with a higher standard uptake value (SUV) are cancerous.

Open discussion continues regarding the physiopathological features of multiple primary cancers. On one hand, the mechanism of tobacco-related carcinogenesis has been proposed,[8,9] and the frequency of the combination of NSCLC with head and neck.[10] or urinary tract.[11] malignancies supports this theory. However, Pagès et al.[12] made strong clinical arguments that minimized the role of tobacco-related carcinogenesis and proposed that individual susceptibility might play a role.[12] Hence, it is quite possible that the carcinogenesis of multiple primary cancers of the lungs could be induced by the use of tobacco, individual susceptibility, or a combination of both.

The synergy of carcinoid and non-carcinoid tumors is between 18 and 40.7%, with the second most common tumor being adenocarcinoma.[13-15] Additionally, synchronous tumors occur at a rate of 53% in the gastrointestinal system and 7% in the lungs. Most of these cases were incidentally identified or discovered via autopsy.

The pathogenesis of this synergy causes phenotypic changes in the target cell by several agents, such as long-term growth factors.[16] Wang et al.[17] determined that the many carcinogens in cigarettes cause multiple lung tumors by the independent development of p53 and K-ras mutations.[17] However, because this condition is so rare, it is not possible to pathologically determine whether or not it leads to a typical cancer combination. Generally, patients who have had previous malignancies are followed up regularly, so their second and third tumors are diagnosed at earlier stages.

Even though carcinoid tumors which coexist with other types of cancer are not very common, they are still usually diagnosed incidentally at an earlier stage at either the bronchoscopic or pathological examination.

We performed 130 operations that involved carcinoid tumors between the years of 2001 and 2012, and in five cases (3.8%), we found a second primary epithelial tumor. This ratio was higher than expected and indicates that older patients with low-grade carcinoid tumors may have a greater likelihood of developing pulmonary carcinomas than epithelial tumors.

Conclusion

Carcinoid tumors are low-grade malignancies and may appear in conjunction with a synchronous tumor, which could be either another carcinoid tumor or a carcinoma. As in other double primary synchronous tumors, combined carcinoid tumors of the lung or coexistent epithelial tumors need special attention during all phases of treatment. Careful bronchoscopic and meticulous pathological examinations, either perioperatively or postoperatively, are essential in thoracic surgery. Frozen-section studies are also important, even in low-grade tumors, and we should bear in mind that they could possibly be used to identify unexpected findings which might be missed during a bronchoscopy.

As seen in cases 2 and 5, more than two tumors may develop in one patient; therefore, further studies are needed to clarify the etiopathogenesis of multiple tumor combinations.

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REFERENCES

1. Wurtz A, Benhamed L, Conti M, Bouchindhomme B, Porte H. Results of systematic nodal dissection in typical and atypical carcinoid tumors of the lung. J Thorac Oncol 2009;4:388-94.
2. Thomas CF Jr, Tazelaar HD, Jett JR. Typical and atypical pulmonary carcinoids: outcome in patients presenting with regional lymph node involvement. Chest 2001;119:1143-50.
3. Kocaturk CI, Gunluoglu MZ, Cansever L, Demir A, Cinar U, Dincer SI, et al. Survival and prognostic factors in surgically resected synchronous multiple primary lung cancers. Eur J Cardiothorac Surg 2011;39:160-6.
4. Travis LB. The epidemiology of second primary cancers. Cancer Epidemiol Biomarkers Prev 2006;15:2020-6.
5. Nagamatsu Y, Iwasaki Y, Omura H, Kumazoe H, Hyashida R, Shirouzu K. A case of resected synchronous multiple primary lung cancer comprising adenocarcinoma and carcinoid (cancer-in-cancer). Gen Thorac Cardiovasc Surg 2012;60:518-21.
6. Sano A, Takeuchi E, Hebisawa A, Nakajima Y. Combined typical carcinoid and acinic cell tumor of the lung. Interact Cardiovasc Thorac Surg 2011;12:311-2.
7. Spaggiari L, Veronesi G, Gasparri R, Pelosi G. Synchronous bilateral lung carcinoid tumors: a rare entity? Eur J Cardiothorac Surg 2003;24:334.
8. Liu YY, Chen YM, Yen SH, Tsai CM, Perng RP. Multiple primary malignancies involving lung cancer-clinical characteristics and prognosis. Lung Cancer 2002;35:189-94.
9. Wynder EL, Mushinski MH, Spivak JC. Tobacco and alcohol consumption in relation to the development of multiple primary cancers. Cancer 1977;40:1872-8.
10. Priante AV, Castilho EC, Kowalski LP. Second primary tumors in patients with head and neck cancer. Curr Oncol Rep 2011;13:132-7.
11. Duchateau CS, Stokkel MP. Second primary tumors involving non-small cell lung cancer: prevalence and its influence on survival. Chest 2005;127:1152-8.
12. Pagès PB, Mordant P, Grand B, Badia A, Foucault C, Dujon A, et al. History of multiple previous malignancies should not be a contraindication to the surgical resection of lung cancer. Ann Thorac Surg 2013;95:1000-5.
13. Marshall JB, Bodnarchuk G. Carcinoid tumors of the gut. Our experience over three decades and review of the literature. J Clin Gastroenterol 1993;16:123-9.
14. Saha S, Hoda S, Godfrey R, Sutherland C, Raybon K. Carcinoid tumors of the gastrointestinal tract: a 44-year experience. South Med J 1989;82:1501-5.
15. Berge T, Linell F. Carcinoid tumours. Frequency in a defined population during a 12-year period. Acta Pathol Microbiol Scand A 1976;84:322-30.
16. Oberg K. Expression of growth factors and their receptors in neuroendocrine gut and pancreatic tumors, and prognostic factors for survival. Ann N Y Acad Sci 1994;733:46-55.
17. Wang X, Christiani DC, Mark EJ, Nelson H, Wiencke JK, Gunn L, et al. Carcinogen exposure, p53 alteration, and K-ras mutation in synchronous multiple primary lung carcinoma. Cancer 1999;85:1734-9.