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Orijinal Makale

Giant Cell Carcinoma of the Lung: Management of Surgical Treatment

Akciğerin dev hücreli tümörü: cerrahi tedavi yönetimi

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ABSTRACT

Objectives: Pulmonary giant cell carcinoma (PGCC) is a histological type of nonsmall cell lung cancer and classified as one of the five subtypes of sarcomatoid carcinoma of the lung. Pure PGCC is very rare.

Material and Method: We represent our experience in the management of 7 patients (6 males and 1 female, with a range of 44-63 yr) with PGCC. The most representing symptoms were cough and hemoptysis. Upper lobectomy (n=7) and additionally mediastinal lymphadenectomy were performed in all patients.

Results: Definitive histological examination confirmed the diagnosis of PGCC in all cases. Even though there was no perioperative mortality, postoperative complications developed in a case were hemorrhage in the early perioperative period and bronchus fistula after two months from the operation. The mean survival of the patients was estimated as 28.8 months (38 days - 116 months).

Conclusion: The main treatment for PGCC is the complete surgical resection. Complete surgical resection was found to be usefull as a treatment of choice of PGCC in the early stage and contributed to survival.

Keywords: chemotherapy, giant cell carcinoma, radiotherapy, surgery, World Health Organization

ÖZ

Amaç: Pulmoner dev hücreli karsinom (PDHK) küçük hücreli dışı akciğer kanserinin bir histolojik tipidir ve akciğer sarkomatoid karsinomunun beş subtipinden biri olarak sınıflandırılır. Pür PDHK çok nadirdir.

Gereç ve Yöntem: Kliniğimizde PDHK nedeni ile tedavi gören 7 hastayla ilgili tecrübelerimizi sunduk (6 erkek ve 1 kadın, yaş aralığı 46-63 yıl). En sık görülen semptomlar öksürük ve hemoptizi idi. Üst lobektomi (n=7) ve ek olarak mediastinal lenfadenektomi bütün hastalara uygulandı.

Bulgular: Kesin histolojik inceleme ile tüm hastalarda PDHK tanısı doğrulandı. Herhangi bir perioperatif mortalite görülmemesine rağmen bir olguda ameliyat sonrası komplikasyon gelişti; erken perioperatif dönemde hemoraji ve operasyondan iki ay sonra bronşiyal fistül gelişti. Hastaların ortalama sağkalımı 28,8 ay (38 gün-116 ay) olarak bulundu.

Sonuç: PDHK için asıl tedavi komplet cerrahi rezeksiyondur. Komplet cerrahi rezeksiyonun erken evre PDHK için yararlı bir tedavi tercihi olduğu ve sağkalıma katkı sağladığı bulunmuştur.

Anahtar kelimeler: kemoterapi, dev hücreli karsinom, radyoterapi, cerrahi, Dünya Sağlık Örgütü

INTRODUCTION

Giant cell carcinoma of the lung is a rare histological type of non-small cell carcinoma (NSCLC), which consists of huge pleomorphic and multinucleated giant cells. This type of tumor was first described by Nash and Stout in 1958 that presented difficult challenges for surgical pathologists [1]. It accounts for 0.1%–0.4% of all lung cancers, and presents as a large peripheral mass, and most frequently is found in the upper lobes [2,3]. The tumor may occur in patients predominantly in fifth and sixth decades, with a male predominance (approximately 5:1). The main treatment is complete surgical resection of the tumor with negative tumor margins, and chemotherapy and/or radiotherapy are the other options for these tumors. Long-term follow up is mandatory because of these tumors have frequent recurrence after resection. In this study, the results of 7 patients whom underwent surgery with a diagnosis of PGCC were evaluated.

MATERIAL AND METHOD

Between January 2007 and 2014, 2000 patients underwent surgery due to lung malignancies in department of chest surgery in Ataturk Chest Diseases and Chest Surgery Education and Research Hospital. Patients with diagnosis of PGCC on their postoperative pathologies were retrospectively reviewed. The preoperative assessments included chest roentgenography, computed tomography (CT) of the chest, abdominal and cranial tomography, and positron emission tomography (PET/CT). Spirometry tests were routinely carried out in all of the patients, and preoperative fiberoptic bronchoscopy (FOB) was also performed. Thoracotomy was done on these patients based on the localization of the tumor. We performed an anatomic complete resection while preserving most of the functioning lung tissue. During the operation, undiagnosed tumors were confirmed by frozen section (FS) examinations. For centrally located lesions, FS examination of the cut edges was performed routinely, with the hope of finding a tumor-free margin. All resected specimens, including the primary tumor and resected hilar and mediastinal lymph nodes were examined to determine both the tumor histology and the extent of lymph node metastases. All of the tissues were sent for routine histopathological examination and immunohistochemical stains after the surgery. Immunohistochemical studied cases were stained with panel including pankeratin and EMA. Mucine was investigated with mucine carmine stain. All the specimens were reviewed by experienced pathologist from our institution's department of pathology, according to the revised histological classification standards of lung cancer for the diagnosis and classification of PGCC established by the 2015 fourth edition of the WHO classification of Tumours. The following parameters were investigated from the medical records: gender, age, primary symptoms, smoking histories, bronchoscopic findings, tumor localizations, postoperative stages, adjuvant therapy situations, surgical methods, and survival status respectively. During the follow-up period, these data were prospectively recorded in the database, and then all patients were contacted either in person or by telephone. We performed routine follow-ups of patients 4 times per year, checking symptoms and chest roentgenography. We also performed chest CT at least one time per year. If abnormal findings were observed, we used PET/CT to evaluate the

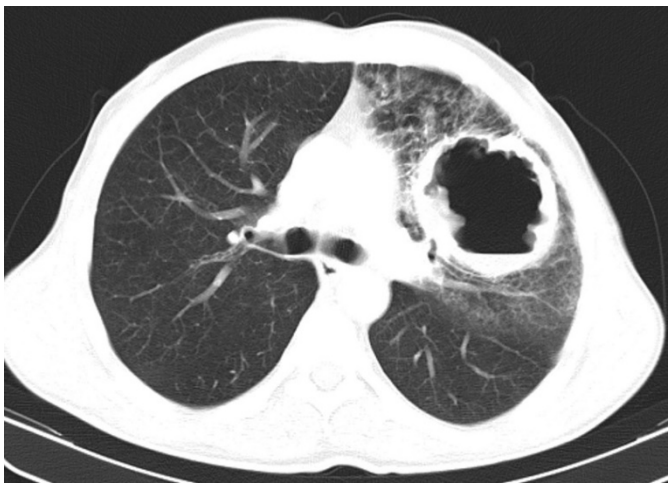

Figure 1. Computerized tomographic scan of the thorax

hilar-mediastinal and extrathoracic lymph nodes, the lung field, and the abdomen.

RESULTS

The study includes seven patients, one female and six males. The mean age was 52.5 (range; 44-63 years). The most common presenting symptoms were cough (42.8%) and hemoptysis (42.8%). All male patients were smokers while female patient was not. All the patients underwent routine laboratory studies and electrocardiography, there were no abnormalities. Pulmonary function testings applied to all patients and forced expiratory volume in 1 second (FEV1) value was found more than 2 liters in all of them. In the CT findings one of the patients had centrally located masses while 6 of them were peripheral (**Figure 1**). PET-CT has been performed in five of seven patients. The masses of 6 patients were located in the right upper lobe and were in varying sizes between 3-11 cm. One patient had 12 cm mass on the left upper lobe. One patient had SUV uptake on a hilar lymph node and there were no mediastinal lymphadenopathy findings in other patients' radiological investigations. There was no sign of distant metastasis in all patients. No endobronchial lesions were observed in all patients. Cytologic examination of bronchial lavages showed no malignancy. The surgical approaches we used presented in **Table 1**. One patient underwent left upper lobectomy and the remaining patients underwent right upper lobectomy. There was an invasion to chest wall in one patient so we performed chest wall resection and reconstruction. All the patients who underwent curative surgical resection were subjected to systematic mediastinal lymph node sampling and five stations were sampled averagely. In one patient intrathoracic hemorrhage developed after seven days from

Table 1. Characteristics of Giant Cell Carcinoma Patients, Tumor Size, Location, Cause of Death and Survival Period

Patient No:	Sex & Age	Location & size & surgery	Chemotherapy	Survival	Cause of death	immunohistochemical features
1	M/51	Right upper lobe 11 cm Upper lobectomy and chest wall resection Stage 3A(T4N0M0)	-	6 months; dead	Respiratory Failure caused by Acinetobacter pneumonia	EMA (+), Pankeratin (-), Vimentin(-)
2	M/44	Right upper lobe 3 cm Upper lobectomy Stage 1A3(T1cN0M0)	+	116 months; alive		EMA (+), Pankeratin (-), Vimentin(-)
3	M/63	Right upper lobe 5.5 cm Upper lobectomy Stage 3A (T3N1M0)	+	7 months; dead	Died with no evidence of disease	Musin (-), EMA (-), b-HCG (-), AFP (-), P63 (-), TTF-1 (-), CEA (-), CK5/6 (-), CD30 (-), CK7 (-), calretinin (-), actin (-)
4	F/46	Right upper lobe 10 cm Upper lobectomy Stage 3A (T4N0M0)	-	3 months; dead	Miyocardial infarction	CK7 (+), pankeratin (+) HCG (-), CEA (-), CD45 (-), musin (-)
5	M/63	Right upper lobe 4 cm Upper lobectomy Stage 1B(T2aN0M0)	+	12 months; dead	Distant metastasis	EMA (+), CEA (+), Vimentin focal (+), musin (-), pankeratin (-), P63 (-), CK5/6 (-), TTF-1 (-)
6	M/53	Left upper lobe 12 cm Upper lobectomy Stage 3A(T4N0M0)	+ (one cycle)	38 days; dead	Complication after first cycle of chemotherapy	Pankeratin (+), EMA (+), Keratin (+), CEA (+), Actin (-), CD31 (-), TTF-1 (-), Napsin A (-), P63 (-), Surfactant A (-), musin (-)
7	M/48	Right upper lobe 3.5 cm Upper lobectomy Stage 1B(T2aN0M0)	+	53 months: alive		CEA (+), CK7 (+), Pankeratin focal (+), CK20 (-), TTF-1 (-), P63 (-), musin (-)

Table 2. Summary of Giant Cell Carcinoma in the Literature Examined

	Number of Cases	Age (Mean)	Gender Male/Female	Treatment	Survey (Mean)
Nash and Stout (1958)	5	51	4/1	(3) supportive (1) lobectomy & XRay (1) XRay	After the onset of symptoms: 15.4 weeks
Flanagan and Roeckel(1964)	4	54.2	4/0	(1) XRay (1) XRay & 5fluorouracil (1) Cobalt60	After the onset of symptoms: 15.25 weeks
Kallenberg and Jaque(1979)	14	71.3	10/4		After the onset of symptoms: 5.42 months
Hellstrom and Fisher(1963)	17	52.0			After the onset of symptoms: 4.6 months
Kennedy (1969)	3	57.6	3/0	(1) lobectomy + wedge resection & RT (2) lobectomy	After the operation: 50.6 months
Ginsberg and Buzaid (1992)	16	58.3	11/5	(7) lobectomy (2) bilobectomy (2) pneumonectomy (9) RT (7) KT	24.5 months 5 cases alive 20, 34, 51, 116, 70 months
Our series (2016)	7	52.5	6/1	(2) lobectomy (4) lobectomy + chemotherapy (1) lobectomy + chest wall resection	(7) After the operation: 35.5 Months 2 cases alive 53,116 months

the operation and we performed re-thoracotomy to control hemorrhage. There were no obvious reason for hemorrhage but we found multiple microhemorragic focus that located in the posterior thoracic wall. We identified bronchus fistula at the same patient after two months from the operation. One patient developed empyema after surgery. The other patients were discharged without any complications within a normal range of time. Tumor cells of all cases consisted of giant tumor cells with abundant eosinophilic cytoplasm and large, irregular multilobated nuclei. Giant tumor cells were positive with pankeratin or EMA. Postoperative staging revealed 4 patients had stage IIIA (57.1%), two patients had stage IB (28.5%), and one patient had stage IA (14.2%). One patients had lymph node metastasis, with regional lymph node involvement. Three patients completed the chemotherapy program. One of the patients with stage IA has completed chemotherapy protocol and is still alive without recurrence 116 months after surgery. The second patient with stage IB is also still alive 53 months after surgery. The third one with stage IB has completed chemotherapy protocol and died in postoperative 12nd month due to distant metastasis. The patient with bronchus fistula died in the postoperative 6th month due to respiratory failure caused by acinetobacter pneumonia. The patient who had N1, had 4 cycles of chemotherapy and died in the postoperative 7th month. The patient with empyema has never had chemotherapy and died in the postoperative 3rd month due to myocardial infarction. The last patient had only 1 cycle of chemotherapy and died in postoperative 38th day due to complications of the chemotherapy. The mean survival of the patients was estimated as 28.8 months (38 days - 116 months).

DISCUSSION

Sarcomatoid carcinoma is a general term that classified in five categories in the 2015 WHO classification of lung cancers: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma [4,5]. These tumors are rare accounting for less than 1% of all lung cancers and no major changes in the terminology or diagnostic criteria since the 2004 Classification [4-6]. Pure PGCC is very rare, with a reported incidence of 0.1%–0.4% of all lung cancers [2,3]. In 1958 Nash and Stout reported a series of 5 cases of tumors were extremely anaplastic and were composed dominantly of pleomorphic multinucleated giant cells, which suggested the appropriate descriptive for these lesions name as “giant cell carcinoma” [1]. In our department between January 2007 and 2014, 2000 patients underwent surgery due to lung malignancies. Seven of these patients (0.35%) had diagnosis of PGCC. The details of the our series are given in **Table 1**, PGCC is usually diagnosed at necropsy and specimens removed of primary tumor; the published accounts are summarized in **Table 2**. In 1964 Flanagan et al reported four cases of giant cell carcinoma among the 3,403 autopsies performed [7]. In 1963, Hellstrom and Fisher’s review of the histological features of 478 primary pulmonary carcinomas collected at autopsy disclosed 17 cases of PGCC [8]. In 1992 the study of Ginsberg et al, pathologic specimens of 16 patients with giant cell carcinoma were reviewed [9]. Pulmonary giant cell carcinomas are diagnosed by

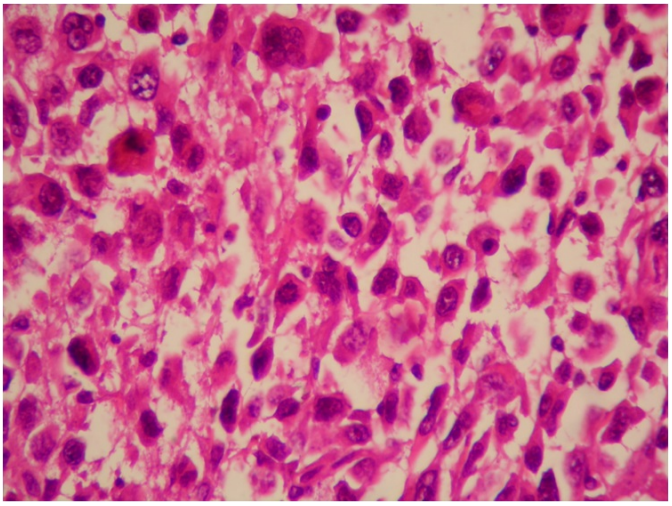

Figure 2. Giant cell features (HEx400)

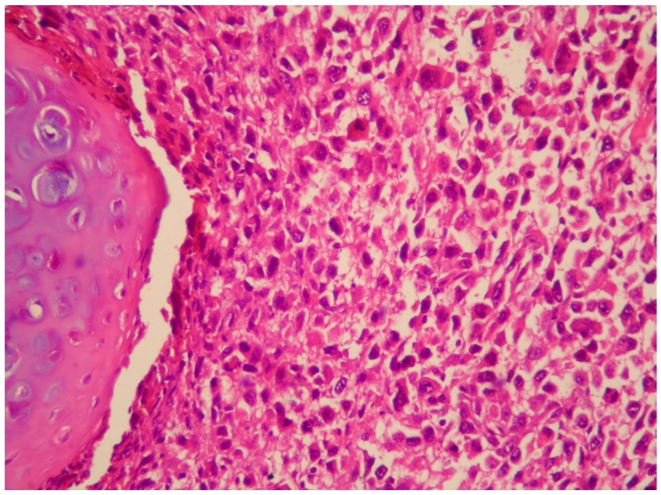

Figure 3. Tumour cell was positive for pancytokeratin (pancytokeratinX400)

morphology, immunohistochemistry may highlight epithelial differantiation. Our cases were positive for EMA and pankeratin. Different immunohistochemical panel were used each case, but EMA and pankeratin were included all panel. It is not associated with a unique epidemiology beyond the established risk factors for lung cancer, except that there appears to be a male predominance (approximately 5:1). They occur primarily in the sixth and seventh decades. It particularly affects males over 50-60 years of age and with a smoking history [8]. Fishback et al. [3] also reported that their patients had a diagnostic age of 62 years; while Ginsberg et al. [9] determined that theirs had a diagnostic age of 59 years. Also they reported the male-to-female ratio as 2.2 to 1. Depue et al.[10] had a ratio of 7.4:1. In our study diagnostic age was 52.5 years and the male to female ratio was 6:1. Although a very few reports associated asbestosis with PGCC, the primary factor in many patients is smoking, with most PGCC patients being heavy smokers. Depue and Ballard found reports of 119 cases of pulmonary giant cell carcinoma with smoking histories of the patients. Only eight of these cases were female [10]. In our study all male patients were smokers while female one was not. One patient had history of exposure to asbestosis and one had exposure to biomass. Most PGCC patients have nonspecific symptoms. Some studies have reported that patients with a centrally located tumor present with a cough, hemoptysis, progressive dyspnea, fever, and recurrent pneumonia, whereas those with peripheral tumors have pain as the main symptom due to the early pleural and chest wall invasion [11]. In our series, 3 patients had cough, 3 patients had hemoptysis, and 1 patient had joint pain. PGCC to be located peripherally makes diagnosis via cytology or small tissue biopsies difficult [12]. Furthermore, due to sampling issues and histological heterogeneity, the diagnosis of virtually all sarcomatoid carcinomas requires a surgical specimen [13]. While the pathological findings of 7 patients in our study could not been obtained via preoperative diagnostic methods, all of these patients in our series were diagnosed with PGCC after surgery (**Figures 2** and **3**). Although the definitions of "central" and "peripheral" can vary between studies, PGCC are consistently diagnosed much more frequently in the lung periphery. In a review of literature reported by Kallenberg, about 70% of PGCC located in lung periphery [14]. Most of our cases were peripherally located, the rate of peripheral location was 85.7% and c/p (central/peripheral) was 1/6. A significant predilection for genesis of PGCC in the upper lobes has also been postulated [8]. As in numerous earlier series, we note a predilection for the right upper lobes [15]. All of our PGCC patients who underwent surgery had disease in their upper lobes. However, it does appear of interest that, contrary to the impression gained from the perusal of isolated reports of this type of tumor, at least one third of the cases in this series were 4.0 cm or smaller in diameter [7]. In our series the sizes of the masses were in varying between 3-12 cm (**Table 1**). Only one patient (25%) had lymph node involvement, being N1 (bronchial) in one. Complete surgical resection of the tumor with negative tumor margins constitutes the desired treatment approach. Sarcomatoid carcinoma is associated with poor prognosis and high rate of resistance to chemotherapy. There is still limited information on systemic treatment options. Although chemotherapy and/or radiotherapy are the other options for these tumors. One patient underwent left upper lobectomy and the remaining patients underwent right upper lobectomy. There was an invasion to chest wall in one patient so we performed thoracic chest wall resection and reconstruction. None of the patients required reoperation due to local recurrence or pulmonary metastasis. Four patients completed the

chemotherapy program. One patient did not accept chemotherapy after operation. One patient had empyema after surgery so could not receive chemotherapy postoperatively. PGCC have a poor prognosis due to high aggressiveness compared to other pulmonary cancers. Nash and Stout mentioned the courses of patients with PGCC were characterized by extensive local and distant tumor spread, particularly to extrathoracic organs such as the kidneys, adrenal glands, liver, gastrointestinal tract and mesentery, and extremely short survival (5 days to 7 months) [1]. Ginsberg et al found the median overall survival for the entire group was 14 months [10]. Mean survival time was less in patients with stage 3A (4.25 months) compared to with stage 1B (32 months) and stage 1A (116 months). In our series, the mean survival was 28.8 months (38 days - 116 months) and expected one year and five-year survival rates were 42.8% and 16.6%, respectively. When we compare our patients' with early stage overall mean survival with the literature, our results are encouraging.

CONCLUSION

The optimal approach to PGCC is surgical resection of the tumor, the diameter, stage, and lymph node involvement of the tumor are among factors that determine the prognosis. Complete surgical resection is the treatment of choice for early and local advanced stage PGCC. Surgery is the most effective treatment modality in early stage PGCC and contributing to survival.

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