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Diagnostic Value of Bronchial Cast Sign and String of Beads Sign in Peripheral Small Cell Lung Cancer

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Abstract

Purpose: To evaluate the significance of the bronchial cast sign (BCS) and the string of beads sign (SBS) in the differential diagnosis among peripheral small cell lung cancer (pSCLC), peripheral lung adenocarcinoma (pLUA) and peripheral lung squamous cell carcinoma (pLSCC).

Methods and materials: Pathologically confirmed 78 cases of pSCLC, 69 cases of pLUA and 33 cases of pLSCC were included in this study. The positive rates of BCS, SBS, and mediastinal lymph node metastasis and mediastinal lymph nodes larger than primary lung lesions were calculated and analyzed in the groups of pSCLC, pLUA and pLSCC, respectively.

Results: In the 78 pSCLC patients, the positive rate of BCS, SBS, mediastinal lymph node metastasis and mediastinal lymph nodes larger than primary lung lesions were 23.1%, 12.8%, 80.8% and 53.8%, respectively. Mediastinal lymph nodes were all larger than primary lung lesions in the pSCLC cases with SBS. There were no BCS or SBS observed in the 69 cases of pLUA, in which 25 cases (36.2%) had mediastinal lymph node metastasis and 2 cases (2.9%) shown the mediastinal lymph nodes were larger than the original lung lesions. The positive rates of BCS, SBS, mediastinal lymph node metastasis and mediastinal lymph nodes larger than primary lung lesions were 6.1%, 2.8%, 39.4% and 16.7% of the total 33 pLSCC patients, respectively.

Conclusion: SBS and BCS in CT images reflect the biologic characters of pSCLC at a certain level and show noteworthy clinical value in differential diagnosis of pSCLC, pLUA and pLSCC. However, the two signs should be combined with other CT signs of pSCLC and mediastinal lymph node.

Keywords: Peripheral small cell lung cancer; Peripheral lung adenocarcinoma; Peripheral lung squamous cell carcinoma; Computed tomography

Introduction

Small cell lung cancer (SCLC) is one of the most common primary pulmonary neuroendocrine malignancies, accounting for around 15% of all lung cancers. It is characterized by rapid doubling time, early development of widespread metastases and an overall poor prognosis. SCLC is closely related to smoking, and the corresponding clinical symptoms are cough, expectoration, hemoptysis, chest pain, chest tightness and dyspnea. Specific symptoms may also occur, such as vena cava syndrome, hoarseness, and paraneoplastic syndrome [1].

Most SCLC are central lung cancer, but there are still 10% of peripheral SCLC (pSCLC), which is often accompanied by significantly enlarged hilar and mediastinal lymph nodes. The CT imaging characters of some pSCLC lesions are similar to benign nodules, because the rapid growth of pSCLC tumor pushes the adjacent tissue leading to smooth edges. On the other hand, the CT images of some pSCLC patients show typical signs of peripheral lung cancer, such as lobulate and spiculation. Thus, the lesion of pSCLC in CT images maybe also confused with other peripheral lung cancers, such as peripheral lung adenocarcinoma (pLUA) and peripheral lung squamous cell carcinoma (pLSCC) [2]. Comparing with pLUA and pLSCC, pSCLC metastases faster. Only SCLC with a diameter less than 30mm and no mediastinal lymph node metastasis can be potentially cured by surgical resection and subsequent chemotherapy [7]. Consequently, early differential diagnosis and treatment of pSCLC from other pathological types of lung cancer are of great significance for improving the survival rate of patients [3].

It is noticed that two CT imaging signs are observed in our routine clinical practice for peripheral lung cancer patients. One is bronchial cast sign (BCS), which refers to tumor tissue, infiltrates within the adjacent bronchus leading to finger or branching shaped bronchial lumen expansion. Another is string of beads sign (SBS), which refers to multiple nodules, arrange along the bronchial blood vessel bundle, like a string of beads, consisting of primary lung lesion, intrapulmonary lymph nodes and hilar lymph nodes. Therefore, the purpose of the present study was to evaluate the clinical potential in differentiating pSCLC from pLUA and pLSCC using BCS and SBS on CT images [4].

Materials and Method

Patients

This retrospective study was approved by the institutional ethics of our hospital, and the informed consent was provided by each patient. During 2008 January to 2022 March, 180 consecutive pathology confirmed peripheral lung cancer patients underwent chest CT scans,

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whose tumor originated from the bronchi below the lung segment, were involved in this study, consisting of 78 pSCLC (67 male and 11 female, range 32-84 years, mean age 62.8±9.3 years), 69 pLUA patients (38 male and 31 female, range 29-81 years, mean age 58.5±10.5 years) and 33 pLSCC patients (29 male and 4 female, range 43-84 years, mean age 65.3±9.8 years). The exclusion criteria were: patients with sub-solid lesions for pLUA and pLSCC, because all the employed pSCLC patients has solitary nodules or masses [5].

CT scan

All the CT scans were performed in a 64-detector row CT scanner (Brilliance, Philips) with supine position for all the patients. Breath holding was requested for all the patients during each CT scan after deep inspiration. The detailed scanning parameters were: tube voltage 120 kV, tube current automatic exposure, slice thickness 0.625-1 mm, field of view (FOV) 50×50 cm, image matrix 512×512, pitch 0.516:1, reconstructed FOV 35×35 cm. iDose recon mode and Y-Detail filter were applied for pulmonary window images, and standard recon and filter mode were used to reconstruct mediastinal window images. A cubital intravenous injection of Ultravist was administered with a volume of 80–100 mL at a rate of 3 mL/s, and followed by two CT scans, i.e. 25 s in vascular phase and 90 s in parenchyma phase. The scanned volume covered the region from the top to the base of the thorax. All images were interfaced to the picture archiving and communication system (PACS) for further evaluation [6].

Image post-processing

Pulmonary window and mediastinal window before and after the administration of contrast agent were applied for the review of lung lesions. Multiplane reconstruction technique was used to reconstruct the image along the direction of bronchus to observe the shape of SBS. In some cases, it is difficult to show the BCS in transverse plane of CT images, multi-slice reconstruction along the bronchovascular bundle was performed for a better visualization [7].

Image analysis

Two radiologists (with 15 years and 17 years of lung cancer diagnosis experience, respectively) independently reviewed the CT images on PACS in random order. The final decisions were reached by consensus if the diagnosis was inconsistent in the beginning. The mediastinal lymph node enlargement was defined as the short diameter of lymph node was longer than 10 mm. The average value of the maximum diameter and the corresponding vertical short diameter of the lesion was considered as the size of pulmonary lesions and lymph nodes [8].

Statistical analysis

The positive rates of BCS, SBS, and mediastinal lymph node metastasis and mediastinal lymph nodes larger than the primary lesions in the three lung cancer groups were calculated. The above positive rates of pSCLC were compared with those of pLUA and pLSCC, respectively. $\chi 2$ test or was employed for statistical analysis using SPSS 21.0. $p < 0.05$ was considered as statistically significant [9].

Results

In total, 18 cases of pSCLC showed BCS. For five of them, the BCS were located near the hilum with a cup-like truncation; for eleven of them, the BCS were located at the distal end of tumor; for 2 cases, the BCS were in the lateral side of the tumor. The representative images were shown in (Figure 1). In the pLSCC group, BCS was observed in 2 cases at the distal end of the tumor without bronchial truncation.

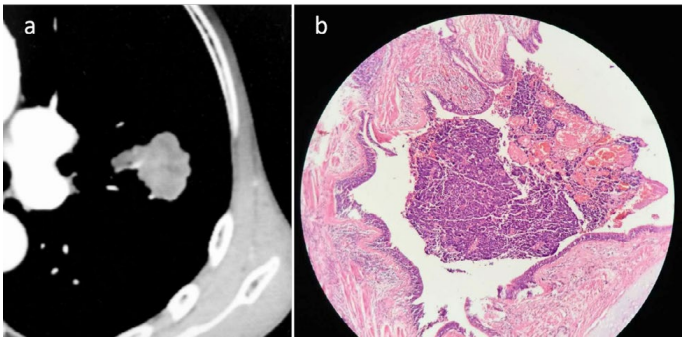

Figure 1: A 61-year-old male pSCLC patient with the lesion in inferior lobe of left lung.

(a) CT image (mediastinal window) indicates the lesion is located near hilus pulmonis and demonstrates BCS.

(b) The corresponding histopathologic specimen (x100) shows the intraluminal tumor of bronchus.

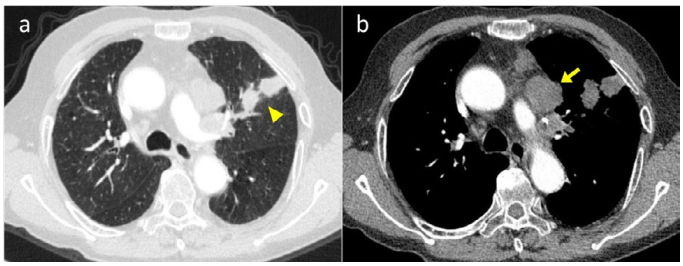

Figure 2: An 84-year-old male pSCLC patient with the lesion in superior lobe of left lung. SBS is marked in the lung window image (a, arrowhead), the diameter of mediastinal lymph node (arrow) in the mediastinal window (b) is larger than that of the primary lesion.

No BCS was observed in the pLUA group. The positive rate of BCS in three groups was summarized in Table 1, the result between pSCLC and pLSCC shown statistically difference by $\chi 2$ test. ($\chi 2=4.546$, $p=0.033$).

SBS were observed in 10 pSCLC, 1 pLSCC and 0 pLUA patients. In the10 pSCLC cases, the sizes of hilar and mediastinal lymph nodes were larger than the primary lung cancer (seen in Figure 2) (Figure 2). Furthermore, the pulmonary primary tumor and the lymph node in 8 cases showed smooth edges, 2 cases showed rough edges, and bronchovascular bundle thickening was found in 7 cases. For pLSCC, only one patient revealed SBS, and the hilar lymph nodes were significantly smaller than that of the primary lung cancer (seen in Figure 3) (Figure 3). The positive rate of SBS in three groups was calculated in (Table 1). There was a statistical difference in positive rates of SBS between pSCLC and pLUA ($p=0.002$), but there was no significant difference in positive rates of SBS between pSCLC and pLSCC ($p=0.169$).

Table 1 also showed the metastatic rate of the mediastinal lymph nodes in the three peripheral lung cancer types. The result of pSCLC is statistically different from pLUA and pLSCC (with $\chi 2=30.226$, $p=0.000$ and $\chi 2=18.3$, $p=0.000$, respectively). Finally, the rate that the size of mediastinal lymph node larger than that of the primary lung lesions in the three groups can also be found in Table 1. The result indicated that such rate of pSCLC is statistically different from those of pLUA and pLSCC (with $\chi 2 = 30.226$, $p = 0.000$ and $\chi 2 = 12.018$, $p = 0.001$, respectively) [10].

Discussion

In this study, the CT image features of three different types of

Table 1: Positive rate of BCS, SBS, and mediastinal lymph nodes metastasis and mediastinal lymph nodes larger than primary lung lesions pSCLC, peripheral small cell lung cancer; peripheral lung adenocarcinoma; pLSCC, peripheral lung squamous cell carcinoma.

	BCS (bronchial cast sign)	SBS (string of beads sign)	Mediastinal lymph nodes metastasis	Mediastinal lymph nodes larger than primary lung lesions
pSCLC (78 cases)	23.1% (18cases)	12.8% (10 cases)	80.8% (63 cases)	53.8% (42 cases)
pLUA (69 cases)	0.0% (0)	0.0% (0 case)	36.2% (25 cases)	2.9% (2 cases)
pluck (33 cases)	6.1% (2 cases)	3.0% (1 case)	39.4% (13 cases)	18.2% (6 cases)

peripheral lung cancer patients were studied, especially the diagnostic value of BCS and SBS for identifying pSCLC. The BCS can be observed in both pSCLC and pLSCC patients, which may be due to the same formation mechanism that the tumor grows in the adjacent bronchial lumen and gradually expand the bronchial lumen. By comparing the CT images and the corresponding pathology of one pSCLC and one pLSCC, respectively, we found that pSCLS tumor grew in the bronchial lumen and pLSCC originated bronchial epithelium in the bronchial lumen, which agreed the assumption above. However, the BCS was not observed in pLUA group, may be due to the histological origin of adenocarcinoma and its growth pattern along alveolar walls. Therefore, the occurrence of BCS leads to a hint of pSCLC and pLSCC. The incidence of BCS in pSCLC is higher than that of pLSCC, two factors may contribute to such observation. Firstly, pSCLC tends to spread along the bronchovascular bundle. A previous study by Siobhan indicated that, for 59 in 100 SCLC patients, the surgical specimens showed the tumor infiltrated along the airways in the examination of the tumor [9]. Secondly, pSCLC has a higher degree of malignancy with short doubling time and fast growth rate. For pSCLC, the existence of cavity structure in the connected part of tumor and bronchus decreases the tumor growth resistance, which leads to a higher occurrence of BCS comparing with pLSCC [11].

The BCS in CT images are irregular thickening of the bronchus attached to the tumor, like a "tail", and the enhancement pattern is consistent with that of the primary lesion. In the pSCLC group, 5 cases show the BCS located near the hilar side of the tumor, 1 case indicates BCS located on the hilar side of the tumor, and bronchial truncation was observed at the distal end for all the 6 patients. In the pLSCC group, the BCS of 2 cases were both located at the distal side of the tumor without bronchial truncation. Therefore, the BCS accompanied by bronchial truncation may be a hint for the diagnosis of pSCLC.

Even though BCS and spiculate protuberance are both exudate tumor tissue, they both reveal different morphology structure and need to be identified. Spiculate protuberance is pointed with convex arc-shaped edge and can be any numbers, while the BSC is finger-like with flat edge and rounder distal end. Secondly, spiculate protuberance can appear in all directions of the tumor, and the BCS only grow along with the direction of bronchial deformation.

pSCLC is highly malignant, and its early metastasis is prone to hilar and mediastinal lymph nodes along bronchovascular bundles. Abnormalities of bronchovascular bundles are common findings in pSCLC, accounting for about around 33%, which agrees the observation of this study that 39 of the 78 pSCLC showed abnormalities of bronchovascular bundles. As a result, the thickening and/or the mass of bronchovascular bundle can be seen in CT images, and tumor cells infiltrate along lymphatic vessels adjacent to bronchus can be observed in pathology. SBS, which composes of primary pulmonary lesion, intrapulmonary and hilar lymph node enlargement, were observed in 10 of all the pSCLC patients. The detachment of groups of tumor cells in an invaded lymphatic leads to the production of emboli, which become lodged in the sub capsular sinus of the regional draining lymph node. The embolized cancer cells may travel unchecked through the first draining lymph node station to the next one where they may get arrested by adhesions. If the cells survive and grow, the node can be soon replaced by the tumor, and further spread occurs to the next group of glands by way of efferent channel. The lung lymphatic fluid first flow up to peripheral lymph nodes of segmental bronchus, Then, through the hilum along the intersegment and interlobular lobes and interlobular lobes, the fluid reach to the hilum, and finally go up into the jugular angle along the ipsilateral blood vessels and trachea space. Similarly, lymphatic metastasis of pSCLC also follows the rule of sequential metastasis from the lung to the mediastinum through the hilum. Intrapulmonary lymph nodes are distributed along the bronchovascular bundle, including sub segmental lymph nodes, segmental lymph nodes, lobular lymph nodes, interlobular lymph nodes and hilar lymph nodes. Therefore, we think that one of the formation mechanisms of SBS is the gradual metastasis and formation of tumor along the bronchovascular bundle [12].

For all the three patient groups, this study also calculated the rate of the mediastinal lymph node metastasis, and the rate of mediastinal lymph nodes was larger than that of primary lung lesions. The rate of the mediastinal lymph node metastasis in the pSCLC group is higher than that of pLUA and pLSCC groups, and the mediastinal lymph node and the hilar nude of pSCLC are prone to merge together, the average diameter of which is larger than that in pLUA and pLSCC patients. The proportion of mediastinal lymph nodes larger than the primary lung lesions in pSCLC is as high as 53.8%, which is also significantly higher than that in the other two groups. The above results indicate that pSCLC is more prone to early metastasis along the lymphatic system. Skip metastasis can be observed in pSCLC as intrathoracic lymph nodes. Riqust M reported that, in the autopsy of 360 adult corpses, 20%~40% of the intrapulmonary lymphatic circulation directly entered mediastinal lymph nodes without passing the intrapulmonary lymph nodes, which may be the reason that SBS are not found some pSCLC cases. Another possible factor might be the enlarged hilar lymph nodes or the thrombosis brings high pressure or blocks the lymph vessels, leading to disruptions of the lymphatic reflux. Consequently, the lymphatic vessels are filled with cancer cells, resulting in the metastasis lymph nodes appear in connected sub-segment or segment lymph vessels, shown as SBS. Because hilar and mediastinal lymph nodes normally metastasize earlier than intrapulmonary lymph nodes, the size of the hilar and mediastinal lymph nodes are larger than that of intrapulmonary lymph nodes for the patients with SBS [13].

Two factors may contribute to the formation of SBS. Firstly, if the prime lesion is located in the middle zone of the lung, the metastatic tumor is prone to appear in sub segmental or segmental lymphatic, so that SBS cannot be formed. Secondly, high malignancy tumors develop fast, which leads to early metastasis along the lymphatic system, and nodules or masses can be observed around the primary lung lesion, hilar and lymph. The biological structure of pSCLC reflects its growth and metastasis characteristics [14]. Among all the pLUA and pLSCC patients in this study, SBS was only observed in one pLSCC patient and none in pLUA. Such finding maybe due to the malignancy and

the differentiation degrees of pLUA and pLSCC are lower than those of pSCLC. The occurrence of lymphatic metastasis is relatively late for pLUA and pLSCC comparing with pSCLC. The results of the present study reviewed that the SBS positive rate in pSCLC was significantly higher than that of pLSCC, but did not show statistical differences, which may be due to the relative small sample size. For all the 11 patients with SBS, the fact that hilar and mediastinal lymph nodes are larger than the primary lesion and intrapulmonary lymph nodes were observed in 10 of them. Therefore, pSCLC should be considered when SBS is accompanied by obviously enlarged lymph nodes in hilum and mediastinum [15].

The SBS is composed of primary pulmonary foci, enlarged intrapulmonary lymph nodes and enlarged hilar lymph nodes. Normally, SBS contains 3 beads; only 1 SBS case shows 5 beads in the current study. Smooth margin and thick bronchovascular bundles between beads are frequently observed for patients with SBS. In our study, all the SBS patients with bronchovascular bundles abnormalities (39 cases) are found to be terminal cancer patients, which agree with the statement of a previous study. We believe that, as a development process of pSLCC, the abnormal bronchial blood vessel bundle enlargement would grow into nodules or masses. Hashimoto et al reported that, for one SCLC patient, the thickened bronchial blood vessel became apparent mass after five months. Therefore, SBS is a stage in the progression of the disease and may fuse into a large lesion at a later stage [16].

There are still some limitations in this study. Firstly, the sample size of the studied lung cancers is relatively small, which may affect statistical results. Especially for pSCLC, surgery was not the main treatment, because most patients were in advanced stage, and not involved in the study group. Secondly, one specialty of our hospital is lung cancer treatment; the patient population distribution is not consistent with the published general frequency of primary pulmonary malignancies. Thus, a multi-center study of SBS and BCS in the three peripheral types of lung cancer should also be performed to involve more diagnostic experiences [17].

Conclusion

In conclusion, BCS and SBS can both reflect the biological behavior characteristics of pSCLC to a certain extent and are progression manifestations of pSCLC along the long bronchial axis. The understanding of BCS and SBS has clinical value in the identification of pSCLC, pLUA and pLSCC, but it should be combined with mediastinal lymph node and other CT features of SCLC, such as lobulation, spiculation and bronchial truncation, so that to improve the diagnostic accuracy.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the institutional ethics committee of Zhabei Central Hospital. The informed consent was provided by each patient.

Consent for publication

Not applicable

Availability of data

The datasets used and analyzed during the current study available from the corresponding author on reasonable request. The data are not publicly available due to information that could compromise the privacy of involved patients.

Competing interests

Not applicable

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Authors' contributions

HY, YXX and LZ contributed equally to this work. JL and HY designed the study; YXX, LZ, QYL, DHZ and GYY collected the patients' data and information; LC, ZBC, and DW acquired the CT images, YXX and LZ analyzed the data; HY, DHZ and GYY prepared the manuscript, JL reviewed and edited the manuscript.

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