CT features of bronchiolo-alveolar carcinoma

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Bronchioloalveolar carcinoma (BAC) is a histologically distinct form of pulmonary adenocarcinoma, accounting for 1 to 9% of all pulmonary neoplasms. Its radiological appearance includes nodular, pneumonic and diffuse patterns. The aim of the study is to report the different radiographic patterns of this neoplasm with particular emphasis on CT findings and those signs that may help in identifying the lesion as BAC. We analysed retrospectively the CT scans of 19 patients (7 women and 12 men) with histologically proven BAC to identify the signs, which could lead to improved diagnostic criteria. These signs are represented by ground-glass opacity in 79% (n=15) and alveolar consolidation 53% (n=10), with a plurilobular, segmentary or lobar distribution. The lesions were bilateral in 47.4% (n=9) cases and abnormal mediastinal lymph nodes were found in 42% (n=8) cases. Air bronchiologram was seen in 40% (n=6) of the diffuse forms and in 60% (n=3) of nodular cases. Our experience shows that CT is a useful tool in the diagnostic workup of BAC, which has a long and slow evolution and is underestimated at plain chest radiograph in its early stages. Moreover CT can help to distinguish this condition from other lung diseases characterized by diffuse air-space consolidation, whose clinical history is useless in making an accurate diagnosis. [Turk J Cancer 2000;30(4):155-166]

Key words: Lung, neoplasms, CT, bronchioloalveolar carcinoma

Histologically bronchioloalveolar carcinoma (BAC) is an adenocarcinoma with purely bronchioloalveolar growth, without stromal, vascular or pleural invasion (1). It constitutes 1-9% of all pulmonary tumors and shows a tendency to increase in frequency in the last years (2). One of its main features is the specific type of growth of the tumor cells along the terminal bronchioles and alveoli, using the supporting structures of the pulmonary parenchyma as its own
stroma, the so-called lepidic growth. This type of growth is the reason for the unexpected way of growing and spreading, and explains the polymorphism in BAC's presentation. Depending on the type of presentation one can differentiate three major types: nodular, pneumonic, and diffuse.

The aim of the study is to report the different radiographic patterns of bronchiolo-alveolar carcinoma with particular emphasis on CT findings and those signs that may help in identifying the lesion as BAC.

**Patients and Methods**

We have analysed the CT findings of 19 patients (7 female and 12 male) with an average age of 54.7 years, all of whom had a histologically proven BAC of the lung. Cases were accepted as BAC only if there was no evidence of another primary adenocarcinoma and if light microscopy revealed abundant cellular growth along apparently intact alveolar walls (lepidic tumor growth). The morphological diagnosis was based on operative material in 10 patients, on transbronchial biopsy in seven and on transthoracic needle aspiration in two.

Twelve of the CT examinations were performed on a Somatom AR T, Siemens, Erlangen in suspended deep inspiration, from the apexes to the lung bases. The scans were at 7 mm intervals and 5 mm collimation, with standard image reconstruction. Several additional 2 mm scans targeted on the most demonstrable pathology were obtained in each patient (2s scanning times, 350 mAs, 120 kV, reconstructed with a high spatial resolution algorithm). In the remaining 7 patients we analyzed CT scans performed in other hospitals. In all patients, the images were reviewed at lung windows for lung parenchyma (level -700 HU, width - 1200 HU) and mediastinal windows for the soft tissue structures (level - 35 HU, width - 250 HU) separately. In 15 cases there was contrast media enhancing predominantly in patients with nodular or segmental form of the disease.

The CT scans of the patients were analyzed according to several different criteria: a) Extent of the lesions: The radiographic findings were divided into three main groups: nodular, pneumonic/segmental or lobar and diffuse. Nodular pattern was accepted when there was a focal lesion with a diameter between 5 to 40 mm, well demarcated from the neighbouring parenchyma. The lesions were defined as pneumonic when the distribution was limited into a segment or lobe without breaking/trespassing the limits of the interlobar pleura. The diffuse form was diagnosed, when more than 2/3 of the lung parenchyma was affected unilaterally or bilaterally, irrespective of the interlobar pleura. Disseminated form was diagnosed also when metastatic nodules have been found in the uni- or contralateral lung. b) Characteristics of the lesions: The presence of ground-glass opacities, acinar nodules, consolidating acinar changes, peribronchial or perivascular lesions were also separately recorded. Assessing the internal characteristics of the lesions, the presence of internal homogeneity or inhomogeneity, air broncho- or bronchiologram, air alveologram and pseudocavitation were noted. c) Additional changes: In addition, other different findings were identified: pleural effusion, enlarged mediastinal or hilar lymph nodes, or signs of a paraneoplastic syndrome.
Results

Of 19 patients included in the study, seven had diffuse form of the disease, five were with nodular and the remaining seven were with segmental and lobar consolidation (or the so called pneumonic form). Of the 19 patients only two (10%) had a history of bronchorrhea, and both presented with the diffuse form of the disease. Two of the patients presented with a paraneoplastic syndrome as leading symptoms. Patients with the nodular form were asymptomatic, with the X-ray lesions being diagnosed by chance in all five. All patients were operated on, four of whom had a preoperative diagnosis of BAC, and one had squamous cell carcinoma. Of the patients with segmental spread, five were deemed to be operable, and the correct preoperative diagnosis was BAC in only three of them. The remaining two patients had been misdiagnosed as adenocarcinoma.

<table>
<thead>
<tr>
<th>Form of presentation</th>
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<tr>
<td>Diffuse form</td>
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<td>Segmental form</td>
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<td>Lobular form</td>
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<td>Nodular form</td>
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The frequency and distribution of the CT signs in the whole group is given in table 2.

<table>
<thead>
<tr>
<th>CT signs</th>
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<tr>
<td>Ground glass appearance</td>
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<tr>
<td>Acinar nodules</td>
<td>10/19</td>
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<tr>
<td>Acinar consolidation</td>
<td>10/19</td>
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<tr>
<td>Air bronchogram</td>
<td>15/19</td>
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<tr>
<td>Air alveologram</td>
<td>11/19</td>
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<tr>
<td>Pseudocavitation</td>
<td>8/19</td>
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<tr>
<td>Perivascular thickening</td>
<td>7/19</td>
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<tr>
<td>Pleural effusion</td>
<td>6/19</td>
</tr>
<tr>
<td>Enlarged lymph nodes</td>
<td>8/19</td>
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We described five patients (26%) with nodular changes. All of them exhibited focal changes, which had a peripheral distribution, predominantly subpleurally, with dimensions between 8 and 22 mm. In three of them, we noted ground-glass opacities, and in one demonstrable emphysema of the centrilobular type. Three patients showed lobulated well-defined nodules, while the other two had typical spiculated circumferences, forming a so called “corona radiata”.

![CT scan image](image)

**Fig 1.** CT scan through left upper lobe shows a 4-cm nodular bronchiolo-alveolar carcinoma with heterogeneous attenuation and well visible pleural "tail" sign.

In two of the cases with nodular opacities an air bronchogram, in another two an air alveologram, and in three pseudocavitation was noted. The remaining two cases had homogenous structure, with a density close to that of the chest wall muscles. In three of the cases, there was perifocal ground-glass opacity – the so-called “halo sign”. None of the patients with nodular form of the disease had enlarged mediastinal or hilar lymph nodes, or pleural effusion.

Seven patients with segmental or lobar form of the disease typically presented with an acinar consolidation (n=4), with or without neighbouring acinar nodules. The opacities were well demarcated from the interlobar pleura and the lung parenchyma outside of the borders of the lobe was absolutely intact. In five of our patients a ground-glass appearance was noted in several zones. All patients with the segmental or lobar form had a air bronchogram sign, five had an air alveologram sign and four presented with pseudocavitation. In a single patient, there was a total engagement of the left lower lobe, with an almost homogenous low-density structure and a prominent angiographic sign. Two of the patients had mediastinal and hilar adenopathy and two had bilateral pleural effusions.
Fig 2. CT scan demonstrates a small nodule with spiculated margins surrounded by a large halo of ground-glass attenuation (halo-sign)

Fig 3. CT scan shows bronchioloalveolar carcinoma surrounded by a large halo of ground-glass attenuation. Subpleuraly another small satellite nodule can be seen, infiltrating a secondary pulmonary lobule
Fig 4. The CT scan through lingula demonstrates a pneumonic-like zone of consolidation with heterogeneous attenuation. Small radiolucencies can be seen near the air-bronchograms.

Fig 5. The CT shows a pneumonic-like lesion with well demarcated mucoid bronchogram and angiographic sign.
Fig 6. CT scan obtained with high-resolution technique shows areas of ground-glass attenuation and consolidation in both lungs. Lymphatic spread superimposed a pattern of interstitial abnormalities.

Fig 7. CT scans shows large areas of parenchymal consolidation with marked air-bronchogram sign surrounded by a large halo of ground-glass attenuation represented lepidic tumor growth. Intratumoral bronchioles, multiple pseudocavitations and fine acinar nodules can be seen.
The number of patients with the diffuse form of the disease were seven, and all had acinar nodules, some confluent to a degree of consolidation (n=6). In six of the patients there was an air bronchogram, in four an air alveologram and in all seven ground-glass opacities of differing extent.

Enlarged hilar and mediastinal lymph nodes were found in six of the patients with diffuse BAC, pleural effusions in four, and peribronchial as well as perivascular opacities in five. Four of the cases had micronodular opacities, similar to haematogenic spread of the process.

Discussion

BAC is a subtype of the pulmonary adenocarcinoma with a relatively good prognosis, showing a specific type of local growth, using the alveolar wall as stroma (3). The tumor spreads along the alveolar walls and septa, without significantly disturbing the structure of the lung parenchyma, with a so-called lepidic growth. According to the WHO International Histological Classification of tumors (1) there are three cell types of BAC: mucinous (Goblet cell type), non-mucinous (Clara cell) and mixed mucinous and non-mucinous cell type. The first, accounting for about a quarter of cases, consists of high columnar, mucin-producing cells showing little nuclear atypia. These tumors have a marked propensity to spread via the airways so that one or more lobes are diffusely affected. Accumulation of large amounts of mucus in the pulmonary parenchyma results in a pneumonia-like picture. The second group of BAC, which constitutes the majority of cases, exhibits cuboidal or low columnar tumor cells, with a higher degree of nuclear atypia, and producing little or no mucin. Rarely, numerous psammoma bodies are present. This type also disseminates via the airways although to a lesser degree than its mucin-producing counterpart. The third, more recently recognized subgroup is characterized by the presence of a central area of sclerosis. Multi-focality appears to be especially common in these tumors (4).

The three histological types have a uniform growth along the alveolar walls, without stromal invasion. BAC can present as a single nodule or engage a whole lobe similar to a lobar pneumonia. The latter morphological variant frequently resembles secondary adenocarcinoma (metastatic extrathoracic adenocarcinoma).

The clinical presentation is predominantly non-specific, and the nodular form of the disease is often discovered by chance on X-ray performed for other reasons. Bronchorrhea is a rare symptom, which is typical of the diffuse form of the disease. In rare cases, the clinic is dominated by the paraneoplastic symptoms, as was the case in two of our patients.

The conventional X-ray findings from patients with BAC, closely correspond to the pathological substrate, which define three types of presentation: nodular, segmental or lobar consolidation and the disseminated or diffuse form. Rarely atypical forms as atelectasis or focal zones of ground-glass opacities are present (5,6). The prognosis of patients with BAC is closely related to the X-ray differentiation of the disease form, and not the histological subtype. Patients with solitary nodules have a good prognosis, and those with diffuse disease have the poorest prognosis (7,8).
Documented findings in the literature show that the frequency of the nodular form is reported to be the highest, ranging between 30 to 43%. Hill et al. (9) analysing the results of 136 patients describes 59 (43%) with the nodular form of BAC. In most cases, as in our study, the zones are localized peripherally and subpleurally, with fine streaks towards the pleura. The spicular halo towards the surrounding parenchyma, can be explained with the lepidic growth, and the desmoplastic reaction (10). A sign characteristic of BAC is the air bronchogram and air alveologram (11,12). Pathologically these signs are due to unrestricted bronchiolar lumens and alveoli, contrasting to the BAC nodule. Gaeta et al. (13) describe the so-called serpentine lucencies, which result from free intranodular bronchioles and air containing cystic glandular spaces. The reactive fibrosis, which develops along the route of the slowly enlarging tumor, leads to a further thickening and architectural disorganisation of the bronchiolar walls, with the formation of dilated lucent zones and paracicatricial emphysema, which is termed as pseudocavitation (11).

In their work Gaeta et al. (13) stress on the so called "halo sign" in the nodular form of BAC. They see the analogy with the description of the similar sign in the nodular form of aspergillosis, and explain it with the lepidic growth of the tumor next to the nodule (11). In the group we analysed, this sign was noted in only three cases, which is about 2/3 of the patients with nodular disease.

None of the signs described is typical of BAC, but according to Kuhlman et al. (14) BAC could be diagnosed with a sensitivity of 75% and a specificity of 41% by means of computer tomography. Having analysed the CT signs in 11 patients with nodular form BAC, Ho et al. (15) report the most frequent combination to be that of a parenchymal nodule with speculated circumference, the bronchographic sign, pleural spicula and pseudocavitation. In their work with four patients with histologically proven BAC, Jang et al. (6) report focal changes of the ground-glass types, the only sign of the early non-mucin producing BAC. In our five cases of nodular form BAC, we found an association of three of the signs in two cases and two of the signs in three cases. Our group is too small to make any relevant conclusions on these results.

The localized form of the disease with the acinar consolidation with a segmental or lobar extent, can be described in 20-25% of the cases with BAC. Data from the literature gives a lower percentage of this form of the disease. Initially described by Messer in 1903 this type of BAC consists of approximately 30% of the cases (9,10). The usual images of acinar consolidation are these engaging a segment or a whole lobe. The tendency towards localized growth is characteristic in these cases too, as the pathological foci are limited to a single segment or lobe, not transversing the interlobular pleura (16). When performing comparisons with CT and pathology specimens, Kushihashi et al. (17) conclude that these types of opacities are due to a partial reduction of the intraalveolar airspaces, as well as hyperplasia of the cuboidal alveolar cells and alveolar septal thickening.

On contrast-enhanced CT scans, the consolidated lung is usually of lower attenuation than muscles because of the relative low density of mucin or other fluid materials filling the alveolar spaces (18,19).

The parenchymal consolidation may be segmental or may involve an entire lobe or lung and may mimic diffuse pneumonia in the stage of gray hepatization.
In other cases, volume loss may be seen as a consequence of the desmoplastic reaction and it might be difficult to discern it from an atelectasis. In the latter case BAC causes bulging of the interlobar fissures, due to the increased volume of the involved segment or lobe. Apart from the purely dislocational changes, there is also a difference in the density of the consolidated parenchyma. The low attenuation of consolidated lung in the combination with the lepidic growth of BAC accounts for the visualisation of normally branching pulmonary vessels within areas of consolidation on contrast-enhanced CT scans (20). In atelectasis, one cannot demonstrate the angiographic, or the air bronchograms signs. The first has been reported in patients with lymphoma, acute pneumonia and pulmonary infarction (20,21), so that its presence should be considered suggestive but not specific for BAC.

The diffuse form of BAC can be seen in approximately 1/3 of the patients, and these have a worse prognosis than those with localized disease. The most frequently described forms are those with a multiple and different in shape and size consolidations of the lung parenchyma, acinar nodules – some confluent, with the characteristic air bronchogram and bronchiologram (22). While the neighbouring spread can be explained by the lepidic growth and rarely engages extralobar structures, lymphogenic and haematogenic spread can lead to the superposition of the image of interstitial engagement. Rarely, one can see peribronchial and perivasal spread, closely resembling lymphangitis carcinomatosa, as well as multiple metastatic nodules in the midst of ground-glass opacities.

It has not been resolved yet, whether BAC is a primarily solitary nodule, which can develop through lobular form towards the disseminated form, or whether the three types are separate, independent expressions of the disease (23). Most of the authors support the second theory, and consider that the multicentric form is a result of the dissemination of the process by lymphatic and haematogenic spread. In their study on 136 patients, Hill et al. (9) disclose that most of the patients with nodular and segmental forms of BAC, who were not operated on in a two year period, developed disseminated disease. They summarize that most probably the three forms represent different stages of one biological process.

The differential diagnosis of the separate forms of the disease can be done with different entities. Some of the CT signs of the nodular form can be seen in benign diseases of the lung (24). The homogenous structure and the lobulated circumference in solitary nodules can lead to differentiation with tuberculoma. Ground-glass opacities can be seen in eosinophilic pneumonia, parasitic infections, lymphoma or alveolar hemorrhage. The air bronchiologram in a nodular or confluent opacity can be seen in lymphoma, focal organising pneumonia and pulmonary infarction (25,26). Atypical presentation of the segmental or lobular form of BAC cannot rule out diagnoses like pneumonia, infiltrative tuberculosis, and BOOP. In the latter two diagnoses, one can often discern the tree in bud sign, as a result of the bronchogenic and bronchiologenic spread of the process – always lacking in BAC. The diffuse form has to be differentiated from metastatic processes from another primary focus, and the X-ray and pathological image might be identical.
In conclusion, our study shows that the CT method of investigation has its place in the diagnostic work up of BAC, especially in the early forms of the disease, when the clinical presentation is atypical and the conventional X-ray is inadequate. The combination of signs set out in this article, allows the differentiation of BAC from other disease entities, which lead to an alveolar type consolidation in the lung parenchyma.

References