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A CASE OF THE COSTAL METASTASIS OF BRONCHIOLAR CARCINOMA WITH UNUSUAL RADIOLOGIC FINDINGS

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The rate of frequency of tumor metastasis depends to some extent on the degree of differentiation. It is also known that skeletal metastasis of the cancer tends to be of the osteolytic type. Furthermore, bronchiolar carcinoma is regarded as a well-differentiated lung cancer and may generally remain localized with metastasis limited to the regional lymph nodes.

In the present paper a case of bronchiolar carcinoma involving metastasis to the sixth right rib in which the tumor was first strongly osteolytic and later turned to osteoplastic is presented to provide a histological background for metastasis to the bone.

Clinical Course of Case

The patient was a 60 year old housewife. Radiologic examinations of the chest for back pain were conducted in August, 1964. A moderate of peribronchial markings over the left middle pulmonary field was noted. The right lung showed no abnormality, but the sixth right rib revealed a focal periosteal thickening such as seen in an osseous union after fracture (Fig. 1).

She complained of productive cough in September 1964. On that occasion, scattered nodular shadows were noted in the left middle pulmonary field. Despite of the repeated negative smears and cultures of sputa for tuberculous bacilli, a diagnosis of lung tuberculosis was made and antituberculous chemotherapy of streptomycin, para-aminosalicylic acid and isoniazid was given.

The patient continued to complain of an intense back pain and a close to complete disappearance of the sixth rib was noted in the chest x-ray film in February 1965 (Fig. 2). A bone biopsy carried out in June 1965 revealed metastatic adenocarcinoma. Thereafter, she was treated with endoxan, an anticancerous agent.

The sixth rib bone which was noted to have disappeared, became visible again showing the appearance of a large bone around September 1964 (Fig. 3). She died of pneumonia on January 26, 1966.

Autopsy Findings

Bronchiolar carcinoma of both lungs accompanied by bronchopneumonia and cancer metastasis to the sixth right rib were found. No metastases to other organs were detected. No tuberculous lesions in the lung or the bone were observed.

Sixth right rib bone:

The sixth right rib bone was enlarged with a diameter of three to five centimeter. The surface of the bone was smooth and covered with periostium and connective tissue. Only a small portion of the bone retained its hardness, and a large portion of the rib was easily changed in shape by manual pressure.

Histologically, the periosteal tissue was fibrous and expansive without any findings of destruction or invasion of tumor tissue. The osseous cortex of the rib was almost lacking and replacement by cancer tissue was seen (Fig. 5).

The metastatic cancer tissues accompanied by a large amount of cancer stroma appeared as a pattern of micro-alveolar adeno-carcinoma. However, a larger part of the tumor tissue was accompanied by a small amount of cancer stroma and a pattern of papillary adenocarcinoma with numerous mamillary processes was apparent (Fig. 6). This histological pattern is quite similar to that of the central portion of the pulmonary massive lesion. No osseous trabeculae were observed in the areas of microalveolar adenocarcinoma, but the areas of papillary adenocarcinoma contained a moderate number of atrophic osseous trabeculae (Fig. 6). These trabeculae were faintly eosinophilic and were surrounded by flat cells which were considered as atrophic osteoblastic cells. Osteocytes in the trabeculae were also strongly atrophic and disappeared at many points. Some of the trabeculae were surrounded by cancer stroma and some were directly surrounded by single layer of cancer cells (Fig. 6).

The central portions of the rib consisted of edematous granulation tissue in which were contained a small portion of amorphous necrotic areas (Fig. 5). The granulation tissues also contained a small number of capillaries with an infiltration of histocytes and lymphocytes. In the granulation tissue necrotic osseous fragments were scattered. These were faintly eosinophilic without any osteocyte or osteoblast. The finding of osteoclastic absorption was not observed in the vicinity (Fig. 10).

The most conspicuous findings in granulation tissue were the presence

of a large number of cholesterol clefts in clusters and numerous hemosiderin bearing macrophages (Fig. 10). Most of the cholesterol crystals were surrounded by foreign body giant cells (Fig. 10).

No histological finding which may be considered as tuberculous lesion of lesions indicative of necrotic cancer tissue were observed in these areas.

Fibrous connective tissues accompanied by a moderate number of the small sized and markedly dilated blood vessels were seen developing in the boundary between the cancer tissue and the centrally located edematous granulation tissue.

Areas of intetrabecular spaces of bone marrow which showed neither tumor tissue nor granulation tissue, in which foamy cells and cholesterol clefts appeared in abundance and in which hematopoietic cells disappeared were noted (Fig. 11 and 12). In some osseous trabeculae, a part of them were compressed and fragmented by cholestrol crystals. An increase of foreign body giant cells and foamy cells arround these trabeculae was also seen (Fig. 11 and 12).

Newly formed osseous tissues were found mainly in the region between the periostium and tumor tissue, and in the region of fibrous connective tissue. Osteoid tissues were found in the subperiosteal areas and in the surroundings of the pre-existing trabeculae of the above mentioned regions (Fig. 7 and 9).

Lung:

A greyish white walnut sized massive lesion was seen in the left upper lobe. A large number of nodules from pin-point to miliary size were

scattered throughout both lungs. The peripheral portions of massive lesions were histologically similar to the appearance of scattered nodules. But the central portion of the massive lesion presented a pattern of adeno-papillary carcinoma with a moderate amount of cancer stroma and numerous mamillary processes. This histological pattern is quite similar to that of the metastatic tumor tissues in bone.

The lesions of small nodules scattered throughout both lungs showed a histological appearance of typical bronchiolar carcinoma as seen in the presence of a neoplastic epithelium lining the alveolar walls judging from presence of a network of capillaries and a framework of elastic fibers (Fig. 13). The alveolar walls were lined with a single layer of cuboidal cells with faintly eosinophilic cytoplasm and basally situated nuclei (Fig. 13 and 14). No cilia or mucinous droplets were observed in the cytoplasm.

The adhesiveness between neoplastic epithelium and alveolar wall is loose and is separated at many points. Some alveoles contained single cancer cells or clusters of cancer cells, apparently exfoliated into their cavities (Fig. 16). Some contain one layer of neoplastic epithelium lying free within the alveolar space (Fig. 14 and 15). The neoplastic cells on the alveolar wall were usually uniform, but the exfoliated tumor cells within the alveolar space present a slight cellular pleomorphism (Fig. 16).

Discussion

Routes of Metastasis to the Bone

The metastasis of lung cancer to the bone in the present case is suspected to be via the vascular routes, rather than by direct invasion to

the adjacent bone or via lymph channels. This may be said because of the lack of adhesion between the lung and the thoracic wall, and the lack of destruction of the periostium.

Originally, the part played by the lymphatic system as a route of metastasis to the bone is questionalbe, because of the absence of lymph channels in the bone marrow (1). Further, radiologic and histologic examination showed the absence of cancer tissue in thoracic vertebra, thus metastasis by way of the vertebral vein system (2) may be considered as unimportant. The metastasis to the bone may have commenced by the destruction of pulmonary vessels by lung cancer which subsequently led the cancer cells to the arterial side of the circulation. On the other hand, the fact that the tumor metastasis was limited to right sixth rib bone is quite unusual. This may be related in part to the low grade of biological malignancy of bronchiolar carcinoma. As a rule, a bronchiolar carcinoma is considered as a well-differentiated and relatively slow growing tumor, which may remain localized within the thoracic cavity with distant metastasis seen rarely (3, 4).

Osteolytic vs. Osteoplastic Metastases in Bone

In the present case the entire rib bone disappeared six months after the notice of radiologic alteration such as a focal periosteal thickening. Subsequently seven months the bone became visible again as a markedly large bone. At first the metastasis of lung cancer to the bone was of a strongly osteolytic type and later it changed to a osteoplastic type.

Essentially the metastasis to the bone from a cancer is of the osteolytic type (5). The cases showing osteoplastic cancer metastases may be explained as follows; new bone is mainly formed as a result of internal fracture and

collapse induced by proliferation of the tumor, and not in response to the chemical effect of the cancer cells (5). Accordingly osteoplastic and osteolytic areas must be found intermingled (1).

In the present case, the osseous cortex of the entire rib bone was almost destroyed and a replace of cancer was seen. The disappearance of the osseous cortex may have been caused by the growth pressure from the proliferating tumor tissue. The areas of the tumor revealed papillary adenocarcinoma with a small amount of the cancer stroma containing atrophic trabeculae, but the areas of the micro-alveolar adenocarcinoma with a large amount of stroma did not contain any osseous trabeculae. This may be attributed to the fact that mechanical forces against the trabeculae in the former areas was much less than that of the latter areas.

There is no evidence indicating that the osteoclast plays a part in the resorption of the osseous tissue in any area of the bone.

The central portion of the bone was occupied by edematous granulation tissue and amorphous necrotic masses. Neither cancer tissues nor necrotic areas considered to be derived from the tumor tissue were observed in the central portion. The necrotic osseous fragments of the trabeculae located in the central portion were not adjacent to the center tissue. Therefore, the osteolysis of the trabeculae located in the central portion of the rib is not responsible for the direct mecahnical effect of the tumor tissue.

It is possible that the vascular supply to the tissues located in the central portion may have been severely interrupted as a result of the occupation of the tumor tissues at the superficial layer along the entire rib bone. It seems that severe disturbances of blood circulation to the

central portion were present. This may be said by the presence of numerous hemosiderin bearing macrophages in the granulation tissue.

The necrosis of the osseous trabeculae and the hematopoietic tissue located in the central portion may be responsible for the prolonged ishemic conditions. Subsequently, revasculization to the necrotic areas may have occured in some instances and the areas of central necrosis became organized into edematous granulation tissue.

Various reasons for the occurrence of revasculization to the ishemic necrotic areas were considered in the present case.

The most outstanding reason is the alteration of the growth rate of tumor tissue in the bone. A decrease of the growth rate in tumor tissue results in a decrease of the mechanical forces against periostium, osseous trabeculae and blood vessels. As a result, the blood supply and the organization of the necrotic areas may occur.

The development of the fibrous connective tissue in the boundary between the cancer and the edematous granulation tissue represents the earliest and extensive occurrance of the process of organization.

In the present case, osteogenesis was found only in the immediate vicinity of the periostium and in the fibrous connective tissues between the cancer and edematous granulation tissue.

The extent of the intermixture of osteolytic and osteoplastic foci was slight in the present case. Therefore, the osteoplastic changes in the case were interpreted as not being the result of a reaction of internal fracture, but was caused by the occurrance of an organization produced by the decrease in tumor growth. Osteogenesis may have begun in the

periostium and the trabeculae may have remained in certain areas owing to the decrease of mechanical pressure against them. The decrease of mechanical pressure affecting the periostium and the trabeculae may have periostium and the trabeculae may have been produced by the decrease of tumor proliferation.

It is highly possible that the reduction in tumor growth rate of the metastatic bronchiolar carcinoma are produced by the following conditions; (1) the effect of the anticancerous agent of endoxan, (2) the limitation of he periosteal expansion and (3) the reduction in blood flow in the tumor tissue.

Cholesterol crystals and foamy cells

Many cholesterol crystals and foamy cells appeared in the edematous and necrotic granulation tissue located in the central portion of the bone. Judging from the fact the bone disappeared entirely for a relatively short period, and from the fact that the central granulation tissue contained many cholesterol crystals and amorphous necrotic areas, it may be said that the changes of bone might not only have been produced by metastasis of the tumor but also by the presence of tuberculo us osteomyelitis. However, the fact remains that histologically no lesious indicative of the characteristics of tuberculosis were found in the eight cross sections of the rib examined.

The numerous cholesterol crystals and foamy cells may have come from ishemic necrosis of pre-existing hematopoietic and fat tissue in the bone marrow.

Conclusion

A case of costal metastasis of bronchiolar carcinoma was presented. The metastasis to the bone was osteolytic which was later altered to an osteoplastic type. The mechanisms of the osteolytic and osteoplastic skeletal metastases were discussed.

It was suggested that the persistence of the periosteal tissue and the alteration of the growth rate of tumor may play a major part in the osteoplastic change of the demonstrated case.

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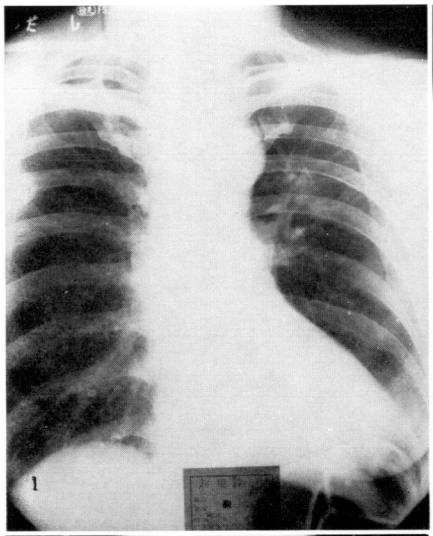
Explanation of Figures

Fig. 1 In August 1964, this chest roentogenogram was taken showing a moderate increase of the peribronchial markings in the left middle pulmonary field and a focal periosteal thickening of the sixth right rib bone.

Fig. 2 After half a year from Fig. 1, a complete disappearance of the right sixth rib was noted.

Fig. 3 After half a year from Fig. 2, the rib became visible again as a large bone.

Fig. 4 The right sixth rib, viewed from behind, is large sized, 3 to 5 cm in diameter. The surface of this bone is smooth and covered with periostium.



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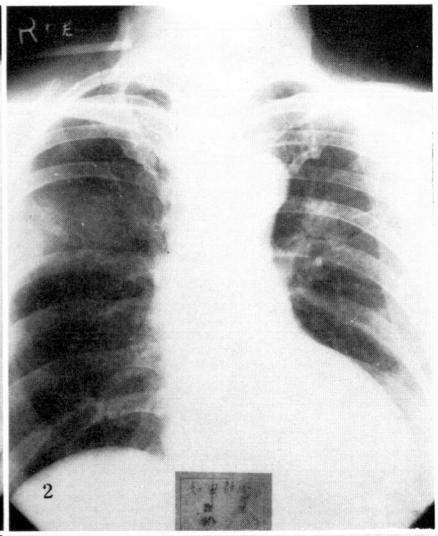

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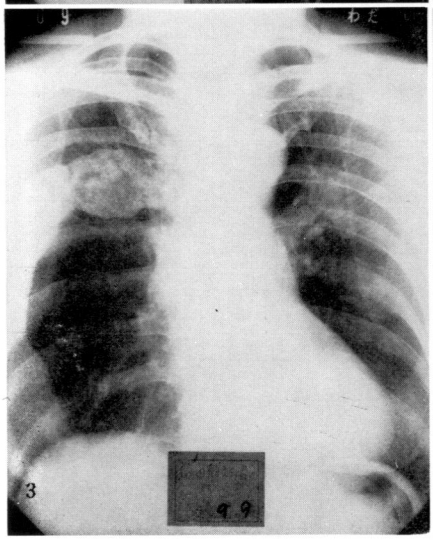

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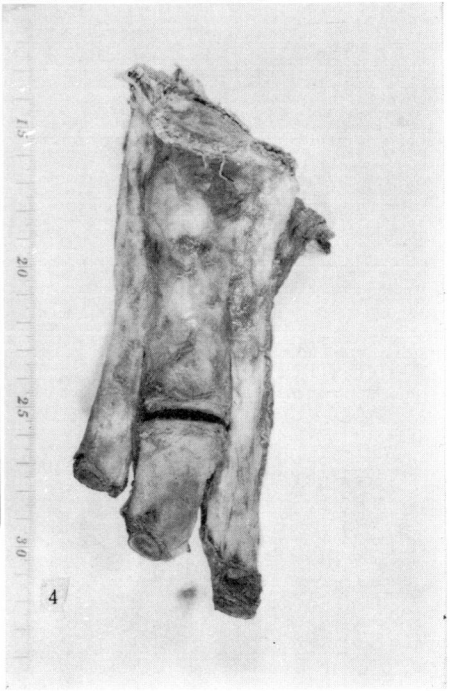

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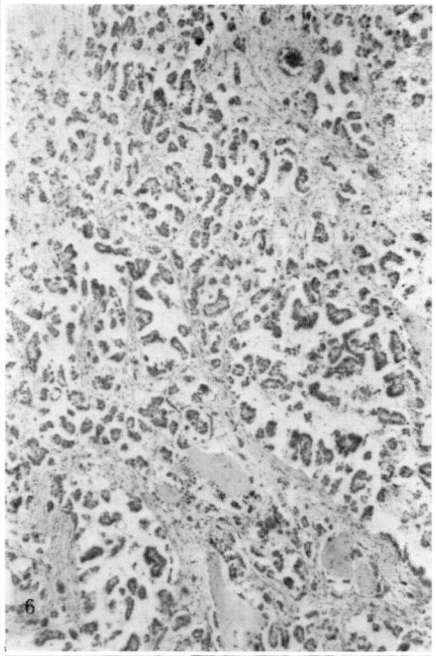

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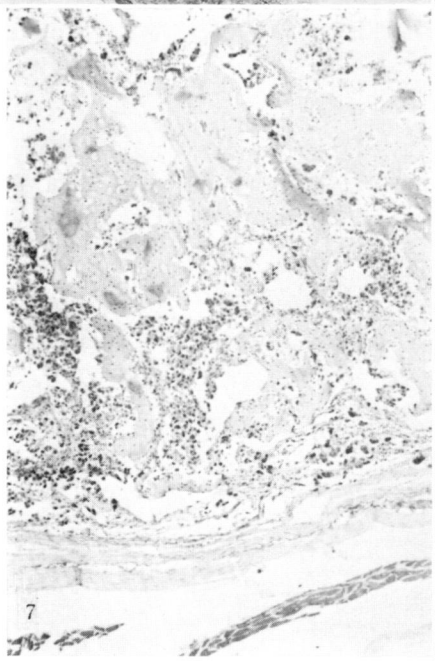

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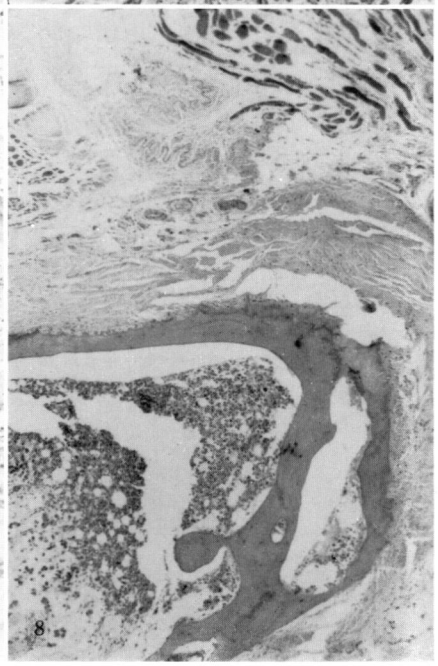

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Fig. 5 A cross section of the rib bone covered with smooth periostium. A cortical portion of the bone is occupied with the tumor tissue (dark zone). A central portion of the bone consists of edematous granulation tissue and amorphous necrotic areas (light zone). New bone formation is seen in the subperiosteal regions and in the regions between the dark and light zone. H-E stain. x 5.

Fig. 6 Metastatic cancer tissues in bone marrow show a pattern of papillary adenocarcinoma with numerous micropapillary projections. Stromas of cancer are seen contained in the necrotic osseous trabeculae. H-E stain. x 100.

Fig. 7 Osteoid tissues surrounding the pre-existing trabeculae is abundantly observed in the vicinity of the periostium. The cancer cells are seen scattered in the intertrabecular spaces. H-E stain. x 100.

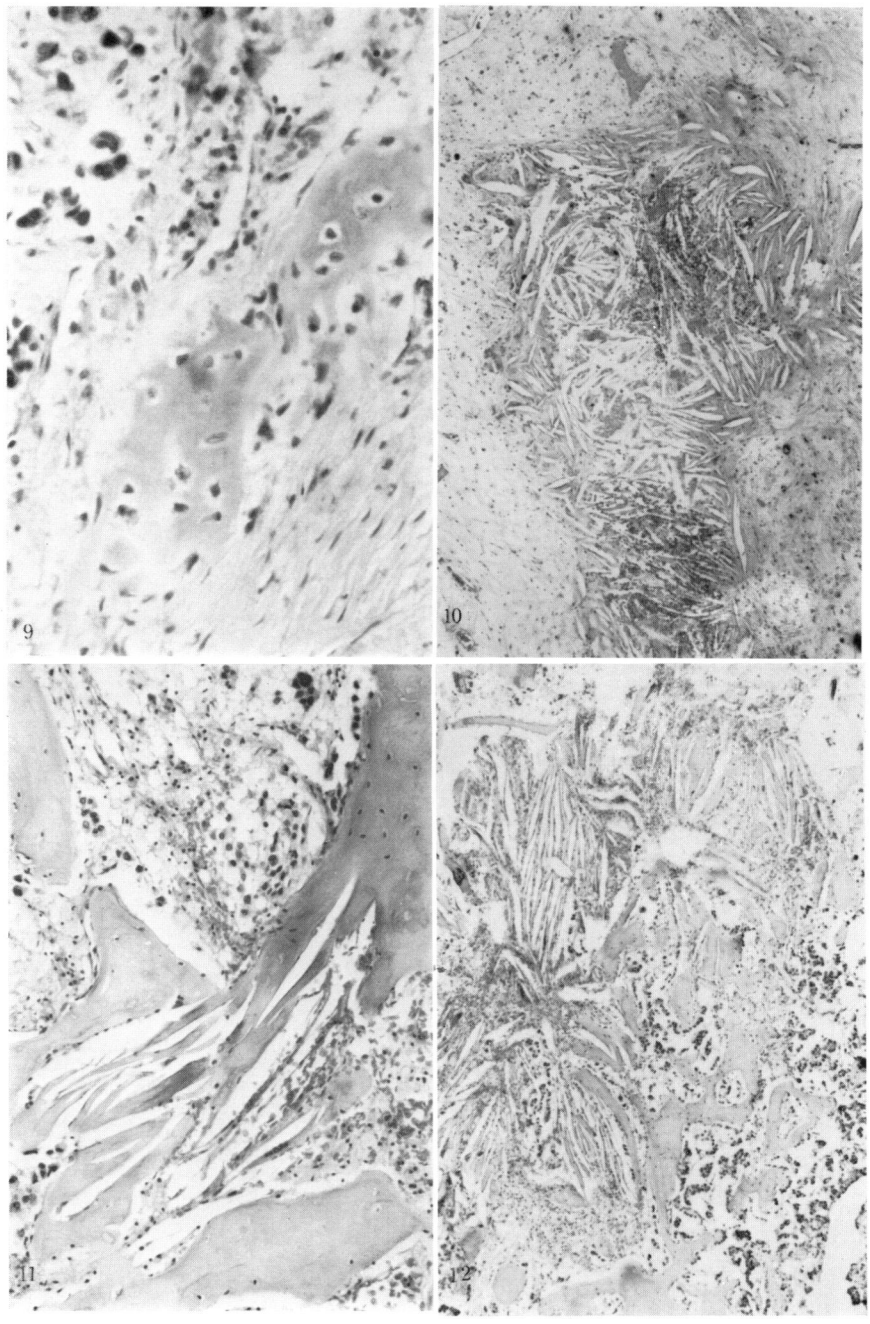
Fig. 8 The cortex of the bone partly remains. Hematopoietic tissues also remain in the bone marrow spaces. H-E stain. x 60.

Fig. 9 Subperiosteally located newly formed bone tissue. Bone marrow spaces contain dilated blood vessels and exfoliated cancer cells. In the lower right the periosteal tissue is seen. H-E stain. x 400.

Fig. 10 In the central edematous granulation tissue, cholesterol clefts in clusters are seen surrounded by foreign body giant cells. Fragments of trabeculae are seen scattered in granulation tissue. H-E stain. x 100.

Fig. 11 Osseous trabeculae are fragmented by chlesterol crystals. The intertrabecular spaces are occupied by foamy cells and cholesterol clefts, and hematopoietic tissues have disappeared. A small number of cancer cells are seen scattered in these spaces. H-E stain. x 300.

Fig. 12 The destruction of trabeculae by the cholesterol crystals. Some of the atrophic trabeculae are surrounded by a single layer of cancer cells. H-E stain. x 100.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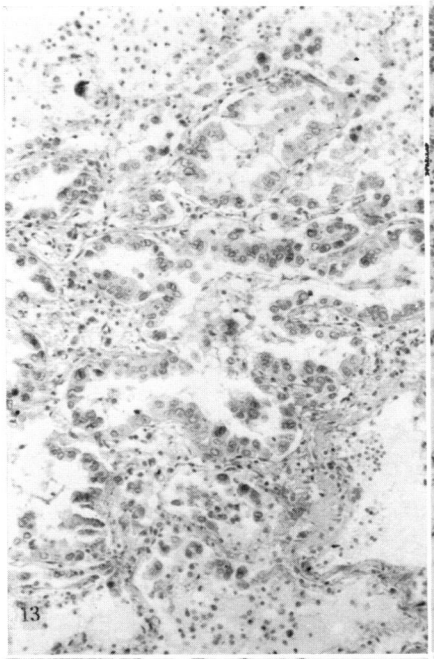

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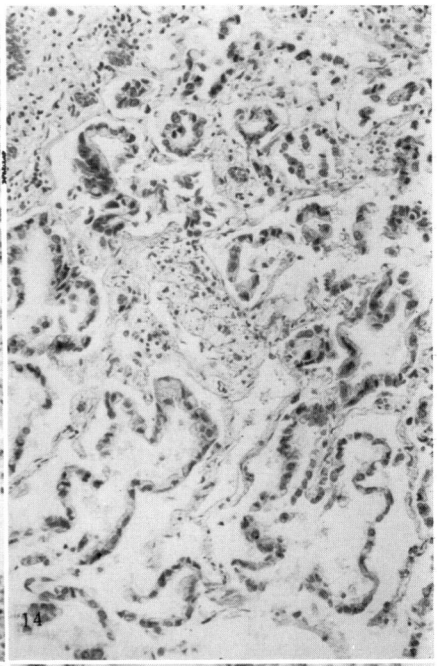

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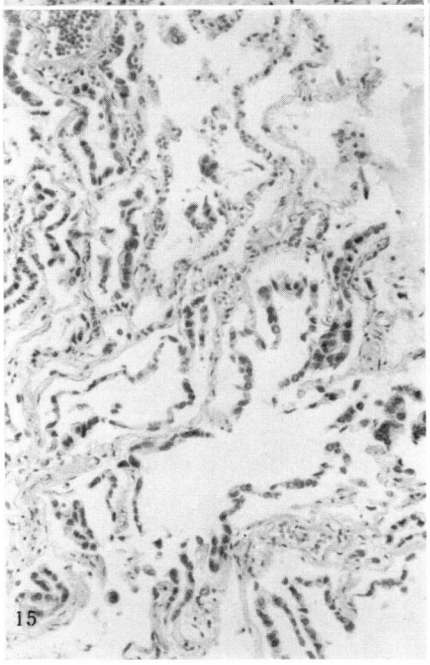

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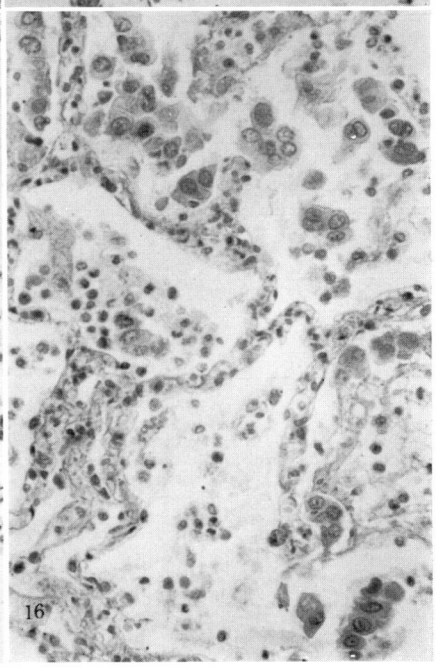

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Fig. 13 Bronchiolar carcinoma in the lung. The stromas of tumor are continuous to the neighboring alveolar walls. H-E stain. x 400.

Fig. 14 The alveolar walls are lined by a single layer of neoplastic cuboidal cells with a faintly eosinophilic cytoplasm and basally situated nuclei. H-E stain. x 200.

Fig. 15 A loose connection is seen between the alveolar walls and the neoplastic epithelium. A single layer of neoplastic epithelium is seen lying free within the alveolar space. H-E stain. x 200.

Fig. 16 Exfoliated cancer cells within the alveolar space present a slight cellular pleomorphism. H-E stain. x 400.