Pulmonary Tumorlet with Foci of Neuroendocrine Cell Hyperplasia in the Bronchus: A Case Report

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ABSTRACT. Herein reported is a case of pulmonary tumorlet with foci of neuroendocrine cell hyperplasia in a bronchus and bronchiole which was found in a 84-year-old man without chronic pulmonary disease. Histologically, aggregates of neuroendocrine cells were situated in peribronchial fibrotic parenchyma and had been multifocally scattered in a disparsed fashion to form a minute nodule. The lesion exceeded a little over 0.5 cm in size at greatest dimension, and was diagnosed as pulmonary tumorlet of oat cell type. In addition, minute aggregates of neuroendocrine cell hyperplasia were present in bronchial and bronchiolar epithelium and represented hyperplasia. Immunohistochemical staining for chromogranin A, synaptophysin, GRP and serotonin comfirmed that these cells were in fact neuroendocrine cells, showing a strong positivity for GRP, chromogranin A, synaptophysin and a weak positivity for serotonin. The tumor cells were negative for p53, and Ki-67 labeling indices (LI) were less than 0.5 in both lesions, indicating that these cells were not actively proliferating in the manner of a malignant neoplasm.

Our results suggest that these lesions may well be hyperplastic rather than neoplastic. The nature of the pulmonary tumorlet and its histogenesis is discussed.

Key words: pulmonary tumorlet — immunohistochemistory — carcinoid tumor — neuroendocrine cell hyperplasia

The term "pulmonary tumorlet" was coined in 1955 by Whitwell[1] who defined it as small a aggregate of neuroendocrine cell nests morphologically resembling small cell carcinoma of oat cell type. Since then many cases have been accumulated. It is now well known that this lesion is usually found in the fibrotic parenchyma adjacent to the bronchiole and is often associated with bronchiectasis and other conditions with scarring. It was generally regarded as a hyperplastic or regenerative change rather than as a neoplasm, because it is seen with hyperplastic bronchial epithelium surrounding the lesion.[2-4] There may be some difficulty in distinguishing from typical carcinoid and small cell carcinoma, and the lesion from typical carcinoid may be especially difficult when the lesion exceeds 0.5 cm in size and when thecells are scattered rather diffusely. Herein, we discribe the tumorlet in our case and discuss its histopathological significance.

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CASE REPORT

A 84-year-old man had been well untill April 11 1997, when he suddenly complained of abdominal pain and distention. He underwent transeverse colonectomy with a diagnosis of acute peritonitis due to perforated ulcer at the site of colon cancer. After the surgery, he was put on a ventilatory through tracheostomy site and could not be weaned untill two month later. when cardiac arrest suddenly occurred. Cardiopulmonary resuscitation were extensively carried out without benefit and he was pronounced dead on May 28, 1997. Autopsy was performed two hours later. Before his devise, any tumor shadows had been noted by chest X-ray of this patient.

PATHOLOGICAL FINDING

At autopsy, the main pathological finding in this patient were acute tracheitis, acute splenitis and chronic pyelonephritis. The immediate cause of death was not detected anatomically, but considered to be septic shock. The gross appearance, texture, and consistency of the lung tissue were unremarkable. Nodularity or any area of fibrosis were not glossly evident. However, histological sections revealed aggregates of small round or ovoid cells in solid nest in association with a background of mild to moderate interstitial fibrosis near small bronchi, and some within the bronchiole in a dispersed fashion. This lesion exceeded 0.5 cm in size (Fig 1), and in some areas the cells resided in the air space lined by ciliated cuboidal epithelium, as if they had filled these alveolar spaces (Fig 2). Nearby, within the epitherial layer of not only distal

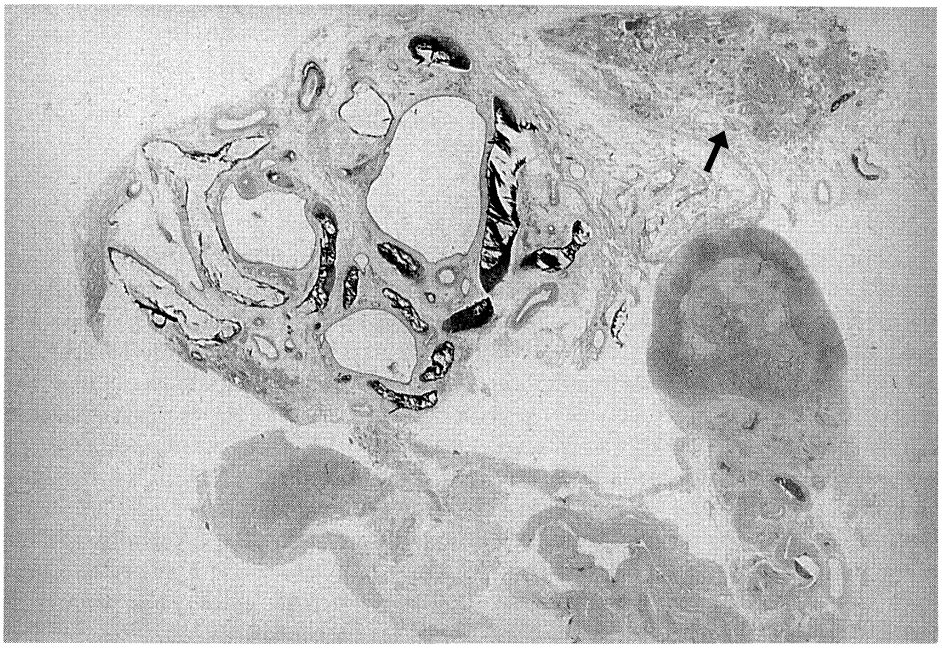


Fig 1. A tumorlet lesion
This tumorlet (arrow) consists of clusters of round cells in peribronchial and peribronchiolar fibrotic parenchyma. (H.E. ×2)

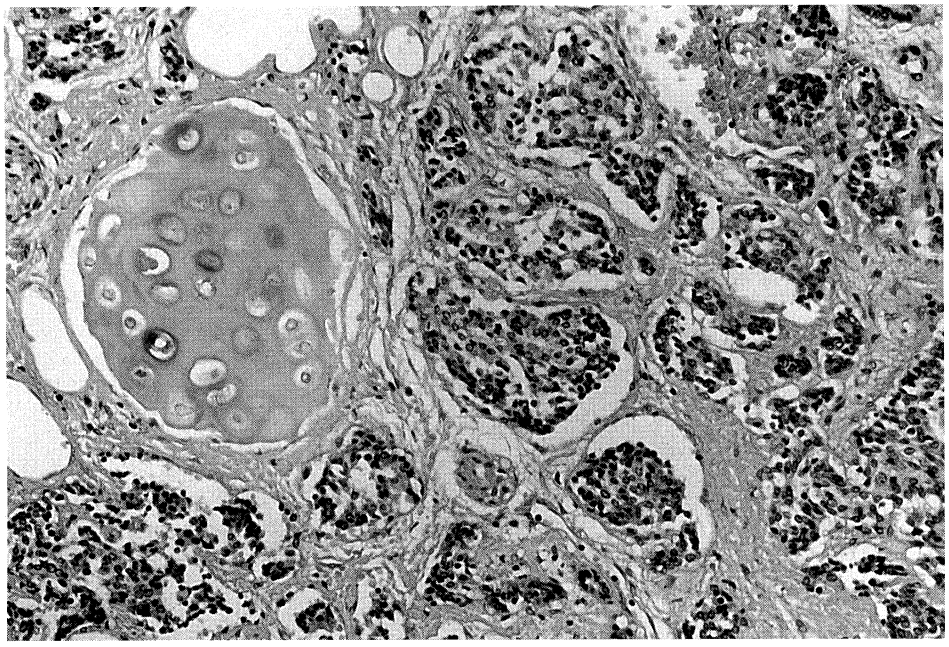


Fig 2. Neuroendocrine cells have replaced the alveolar spaces and the interstitium is fibrostic. (H.E. ×100)

airways, but also of and a bronchi and a bronchiole, small aggregates of similar cells were present. On higher magnification, these cells had oval to spindle-shape nuclei with evenly disparsed chromatins, small inconspicious nuclei, and a small amount of cytoplasm. Cytological atypism was not noted and no evidence of necrosis or mitotic figure was seen in the lesion (Fig 3).

IMMUNOHISTOCHEMICAL FINDING

Archival, formalin-fixed and paraffin-embedded lung tissue were utilized for immunohistochemical study. The tissue was fixed in 20% neutral buffered formalin for 48-72 hours, routinely processed and embedded in paraffin. Thinly cut section were immunostained with the primary monoclonal and polyclonal antibodies. Avidin biothin-peroxidase complex method with ABCkit (Elite) was used. The antibodies used in this study aree shown in Table 1. Immunohistochemical technique we used are summerized in Table 2. Dark brown colonization was regarded as immunopositive. Dark brown colonixation was regards as immunopositive. The labeling indices (%) were caluculated after counting the number of Ki-67 positive nuclei of tumor cells. Small round, ovoid and spindle cells showed strong positivity for neuroendovrine markers such as GRP, chromogranin A, synaptophysin and a small number of them were weakly positive for serotonin. They entirely negative for p53, and The Ki-67 (MIB-1) labeling index was lower than 5% in solid nests (Fig 4a,b,c,d). Similar immunohistochemical result were obtained in hyperplastic cells of intrabronchial mucosa (Fig 5).

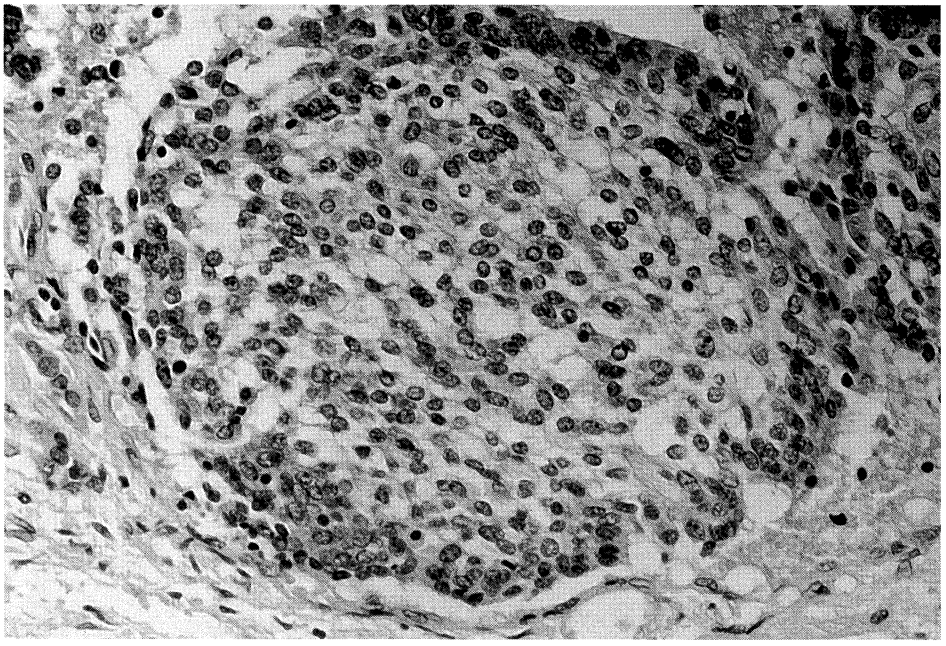


Fig 3. Neuroendocrine cells have arranged in organoid nests. These cells exhibit a moderate amount of eosinophilic cytoplasm and they are uniform in appearance except for those of the periphery. (H.E. × 100)

TABLE 1. Primary antibody used in immunohistochemistry

Antibody	clone	dilution	antigen retrival	Source
GRP	polyclonal	1:5000	MW	Dako
Chromogranin A	LK2H10	1:1200	—	B-M
Synaptophysin	polyclonal	1:500	MW	Dako
Serotonin	5HT-H209	1:20	MW	Dako
p53	MIB-1	1:200	MW	Dako
Ki-67	Do-7	1:50	MW	Immunotech

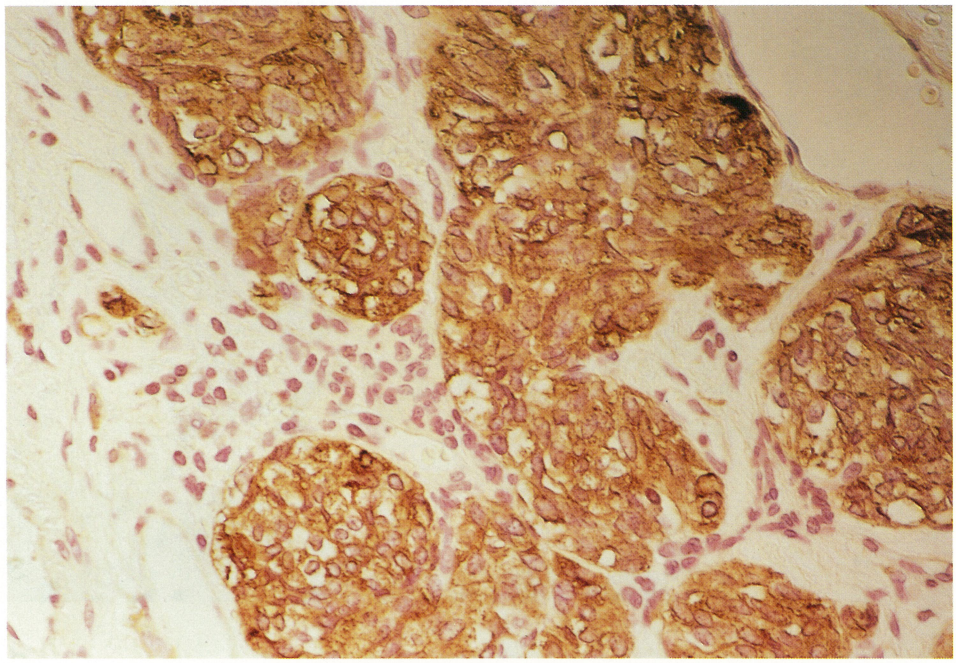
B-M : Boehringer-Mannheim

TABLE 2. Results of immunostaining

Antibody	solid nests in parenchyma
GRP	++
Chromogranin A	++
Synaptophysin	++
Serotonin	+
p53	—
Ki-67 (Labeling index)	<0.5

(—) no stain (+) positive tumor cells less than 50%
(++) positive tumor cells more than 50%

a



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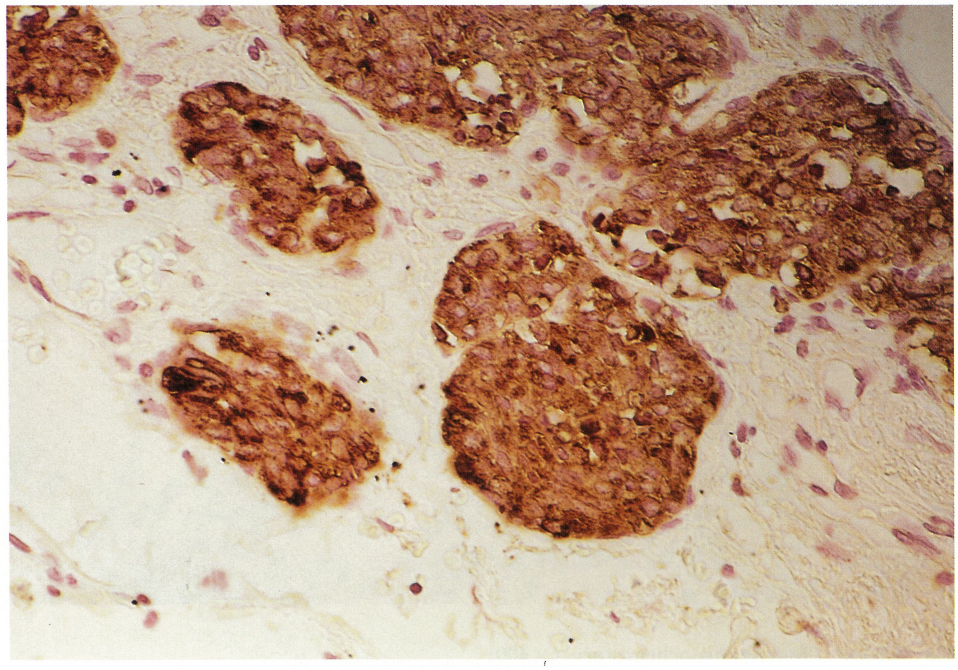

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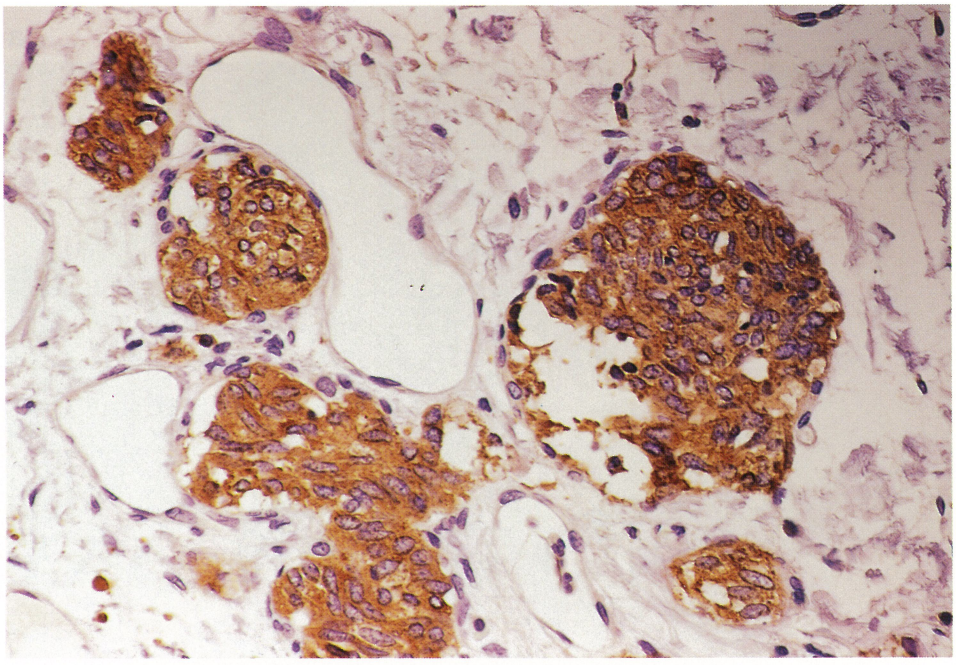

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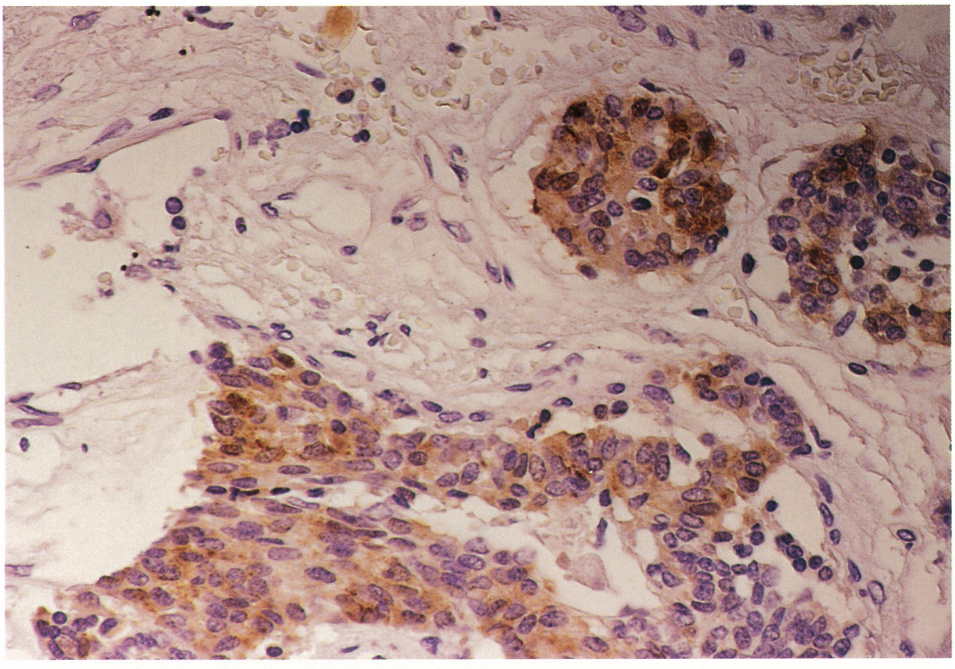

Fig 4a,b,c,d. Immunohistochemistory (×400)
a) chromogranin A b) gastrin-releasing peptide c) synaptophysin, and d) serotonin.

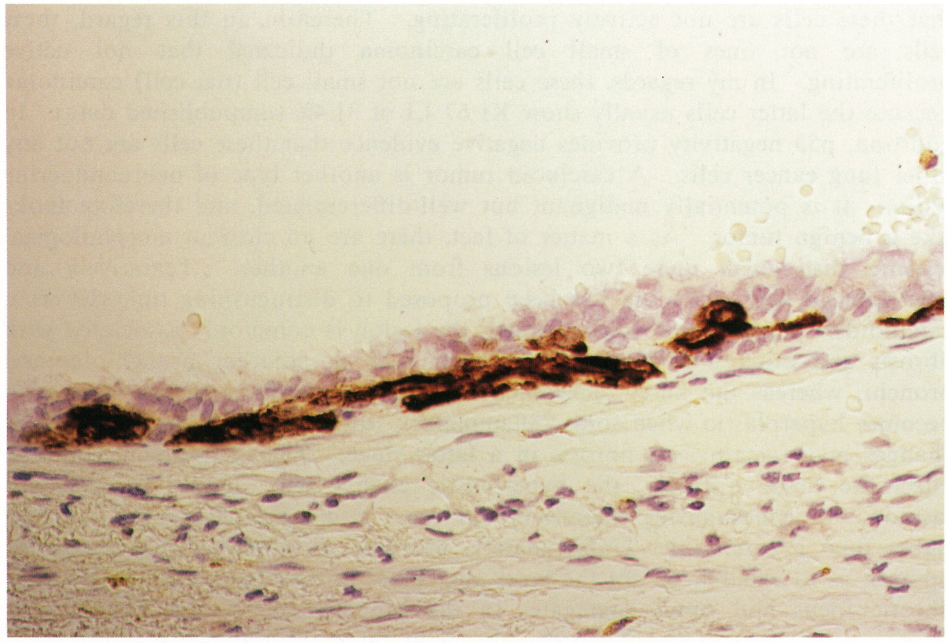

Fig 5. Immunohistochemistory for chromogranin A. Neuroendocrine cells are increased in number and situated above the basement membrane of the bronchial mucosa. (×400)

DISCUSSION

Pulmonary tumorlet are first recognized in 1955 by Whitwell,[1] minute microscopic lesion derived from bronchial or bronchiolar epithelium. In contrast to its morphological resemblance to a small cell carcinoma of oat cell type, it never developes metastasis. Therefore, Whitwell thought that it was benign and merely represented a hyperplastic lesion. It had no clinical significance. Because of its small size, he designated it as a "tumorlet" literally ,tiny tumor. The etiology and pathogenesis of such lesion has been frequently discussed by many investigator,[2-6] Now, it has become well recognized it is hyperplasic in nature, usually situated in the fibrous parenchyma near the bronchilole, and often is associated with bronchiectasis and other scarring condition. It has also been in association with hyperplastic broncial lesion, and these cells exhibit neuroendocrine markers, such as chromogranin A, GRP, serotonin and calcitonin in a variety of intensities similar to those of bronchial lesions.[2-4] However, its real nature seems to remain to be clarified by contemporary means.

The lesion in our cases was regarded as pulmonary tumorlet morphologically and immunohistochemically. Small round to oval cells in silid nests were strongly positive for chromogranin A, GRP, synaptophysin, and weakly positive for serotonin. To determine whether the tumorlet cell were proliferating as activity as malignant cells, we investigated their proliferating activity using Ki-67 immunohistochemistory. Ki-67 labeling index (LI) in our tumorlet was less than 0.5%. A similar immunohistochemical result was obtained in hyperplastic cells of intrabronchial mucosa. These results suggest

that these cells are not actively proliferating. Therefore, in this regard, these cells are not ones of small cell carcinoma indicated that not active proliferating. In my regards, these cells are not small cell (oat cell) carcinoma because the latter cells usually show Ki-67 LI of 31.4% (umpublished data). In addition, p53 negativity provides negative evidence that these cells are not any other lung cancer cells. A carcinoid tumor is another type of neuroendocrine lesion. It is potentially malignant but well-differentiated, and therefore looks like a benign tumor. As a matter of fact, there are no clearcut morphological features distinguish these two lesions from one another. Tentatively and arbitrariry, a size of 0.5 cm has been proposed to distingushing tumorlet from carcinoids.[7] In addition, in the former, the lesion is commonly associated with fibrosis and other multiple foci of similar cells in adjacent bronchioles and bronchi, whereas the latter lacks such association. This is because the leion becomes hyperplastic when some inflammatory stimuli are present. Inflamatory changes may remain as a fibrosis in a latter stage. Becuase inflammation can affect the tissue diffusely, the hyperplastic change may appear in disparsed fashion. Morphologically, therefore, our cases is compatible with a tumorlet rather than a carcinoid. Unfortunately, however, it seems to be a matter of opinion as to whether or not the large aggregates of neuroendocrine cells in the fibrotic focus and small aggregates in the bronchi are in fact hyperplastic. There is no proof of it. Theoretically, both large intrapulmonary and small bronchial lesions could be neoplastic. Or either one of them could be neoplastic and the other hyperplastic. In this situation, they might be just coincidental, or neoplasia might have developed on the hyperplasia. The definition of hyperplastic is a reversible overgrowth of monoclonal cells. When these definitions are applied to this condition and, if our lesion is in fact hyperplastic, it should show heterogeneity of neuroendocrine markers. This was another reason why we investigated the lesion immunohistochemically with several different antisera. In our case, neuroendocrine markers appeared in different amount in individual cells. However, the difference was subtle and we could not definitely tell whether they were monoclonal, polyclonal. Considering these facts and theory, however, we have concluded that the lesion we diagnosed as a tumorlet was most likely hyperplastic in nature.

In summary, we described a case of pulmonary tumorlet with foci of neuroendocrine hyperplasia in a bronchus. Immunohistochemical staning suggested heterogeneity of neuroendocrine markers in both lesions, and Ki-67 labeling indices and p53 negarivity suggested low proliferating activity of the lesions. Therefore, we concluded that the tumorlet we experienced was most likely hyperplatic in nature.,

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