A Case of Bronchogenic Cancer of Oat Cell Type Associated with Hypertrophy and Adenomatous Hyperplasia of the Adrenal Cortex

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Since Thorne[14] reported two cases of Cushing's syndrome with bronchogenic carcinoma of oat cell type, many cases of adrenal hyperfunction associated with various types of carcinoma have been published[2, 3, 6, 7], On the other hand, Parker and Sommers[11] called attention to the fact that adrenal cortical hyperplasia not accompanied by clinical manifestation of hypercorticism is found in higher frequency in cancers than in noncancer controls.

In this paper the author describes an autopsy case of oat cell carcinoma accompanied with diffuse hypertrophy and adenomatous hyperplasia of the adrenal cortex but not with clinical evidence of Cushing's or adrenogenital syndrome.

REPORT OF A CASE

A 64-year-old woman was seen at Medical Clinic of Yamaguchi Medical School several months prior to admission complaining paroxysmal coughs with occasional bloody sputum, dyspnea, and chest pain. A tentative diagnosis of pulmonary tuberculosis was considered and antibiotic therapy was instituted immediately. However, her physical condition was rapidly aggravated. She was admitted on Apr. 11, 1962, because pulmonary cancer was suspected.

The chest X-ray film showed enlargement of mediastinal shadow and streaky densities in the left upper lung field. Physical examination revealed accumulation of bloody fluid in the left pleural cavity and enlargement of the right supraclavicular and pre-sternal lymph nodes. Major laboratory findings were 1) remarkable decrease in serum albumin (2.6 g/dl) and A/G ratio of 0.77, 2) slight hyperglycemia (120 mg/dl), and 3) marked diminution of serum cholinesterase activity (0.40 ΔpH). Hematologic studies indicated 1) moderate leukocytosis (13,100 cells/mm^3) with neutrophilia (82.5%), 2) eosinopenia, and 3) rubricyte count (4.62×10^6/mm^3) and hemoglobin content (13.0 g/dl) within normal range. Surgical biopsy of the enlarged lymph nodes revealed presence of undifferentiated carcinoma composed of spindle-shaped cells with hyperchromatic nucleus. She died 3 days after admission, so that endocrinologic examination could not be performed.

AUTOPSY EXAMINATION

The autopsy material was that of an emaciated female, 38 kg in weight and 157 cm in statue. The major changes were in the lung, mediastinal lymph nodes, adrenal cortex, and thyroid.

Lung: The left lung was deformed due to shrinkage of thickened visceral pleura. Particularly marked was the thickening over lateral aspect of the upper lobe where it measured about 0.7 cm in thickness. This thickening was due to presence of medullary tissue yellowish white in color. Pleural adhesion was marked over the surface of the lung, except for small areas near the pericardial sac and the diaphragm. In these spaces there was accumulation of bloody fluid about 100 ml in amount. The lung tissue was anthracotic and felt tougher than normally.

On section, it was disclosed that there was a small tumor with irregular outline about 2 cm in diameter near the hilum of the left upper lobe. It showed radial extension along the vessels towards the pleura. The tumor was elastic firm and yellowish white.

The right lung also was anthracotic. There were emphysematous bullae at the apex and fibrous pleural adhesion over the surface of lower lobe. Otherwise, the right lung was unremarkable.

Mediastinal lymph nodes: In the mediastinum there was a fist-sized mass of conglomerated lymph nodes. It enclosed the aortic arch and was continuous to the hilum of the left lung. In between the anthracotic areas there were medullary lesions yellowish white in color. The mass was firmly attached to the sternum. There was no tissue which suggested thymus.

Adrenal: The left adrenal was enlarged, $5 \times 2.6 \times 1$ cm in size and about 7 g in weight: the weight was measured after formalin fixation. The enlargement was due to increased thickness of a part of the cortex. The hypertrophic area was nodular but not circumscribed sharply from the surrounding tissue. It was lightly yellow and there was no hemorrhage (Fig. 1).

The right adrenal was slightly thickened due to diffuse hypertrophy of the cortex.

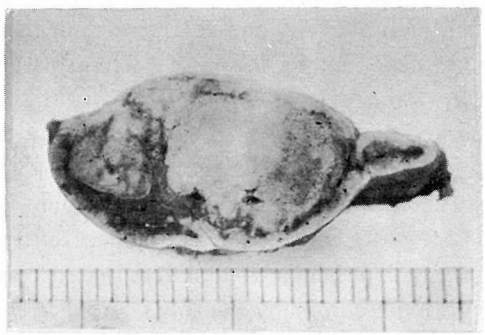

Fig. 1. Cut surface of the left adrenal. Note nodular enlargement of the cortex.

It measured $3 \times 3 \times 0.7$ cm and weight about 4 gm.

Thyroid: The thyroid was normal in size and grossly unremarkable.

Other macroscopic changes were 1) small metastatic lesions in the cardiac sac, pancreas, and lymph node of the omentum, 2) focal pneumonia and small abscesses in the left lower lobe, 3) cholelithiasis, and 4) atrophy of the spleen and pancreas. Intracranial structure could not be autopsied.

MICROSCOPIC EXAMINATION

Lung: The tumor of the left lung was composed of small darkly staining cells which were loosely arranged in alveoli. They were mostly spindle-shaped cells and their cytoplasm was scanty and ill defined: the nuclei were hyperchromatic and round, oval or spindle in shape (Fig. 2). Such cells were grouped into small masses in which they were disposed in bundles, in parallel rows, or in whorls. Interlacing connective tissue was scarce, but where present, the spindle cells tended to be arranged perpendicular to the length of the fibers.

In some other areas there was a mixture of oat cells and small round cells somewhat resembling lymphocytes. Necrosis of neoplastic cells was marked.

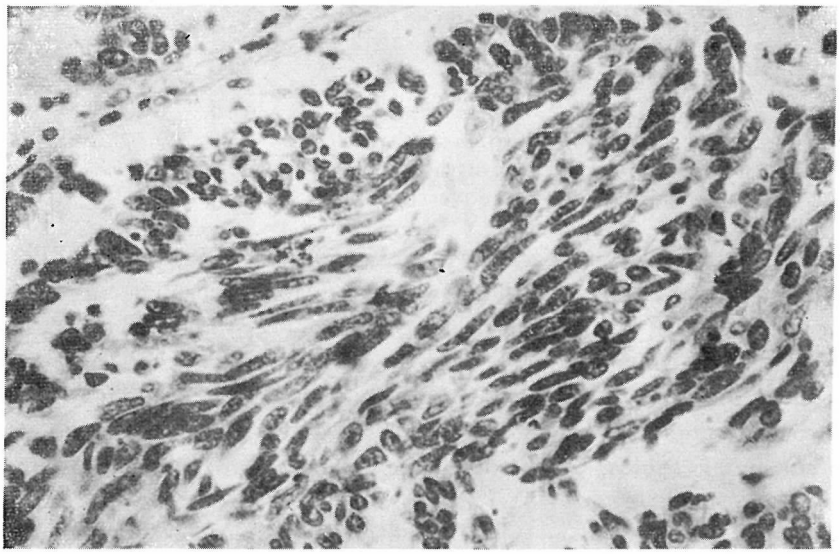

Fig. 2. Oat cell carcinoma of the left lung
(H. E. stain, $\times 200$)
Spindle-shaped cells running in bundles. This picture may suggest sarcomatous character, but the cells were arranged in alveoli and there was no reticulum fibers between the individual cells.

Adrenal: The adrenal cortex was thickened by hypertrophy and hyperplasia of the zona fasciculata and partly of zona reticularis. The cells in these zones were

enlarged and had abundant clear cytoplasm. Staining with Sudan III demonstrated that it was due to accumulation of large amount of lipid. The cytoplasm was slightly eosinophilic and appeared reticular. The nuclei were generally small and hyperchromatic. Such cells formed tubular structure having distinct lumen (Fig. 3), although in some areas they were arranged in cords as in normal cortex.

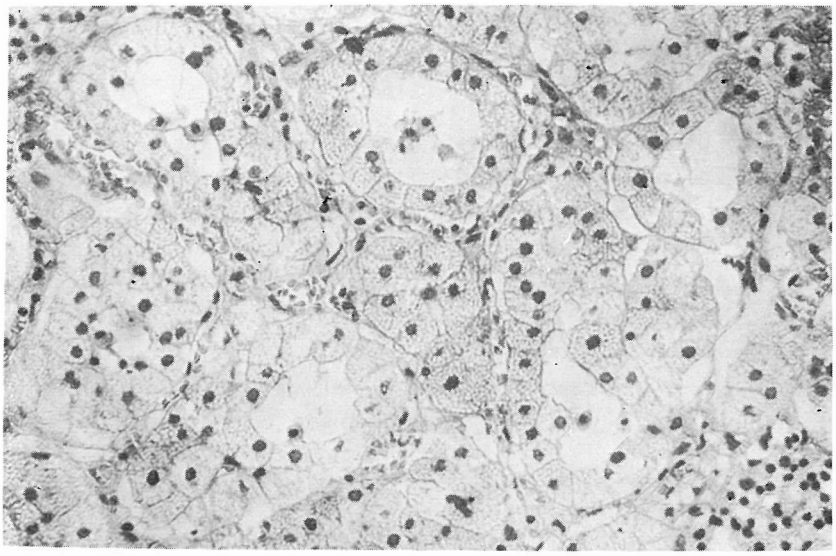

Fig. 3. Zona fasciculata of the left adrenal
(H. E. stain, ×200)
The cells are large and the cytoplasm is clear due to accumulation of large amount of lipid. Note tubular arrangement of the cells.

Histological feature of both adrenal was essentially the same except for difference in the degree of the changes. In the left adrenal there was adenomatous hyperplasia of about $2 \times 1 \times 1$ cm in size, in addition to diffuse hypertrophy of zona fasciculata, while in the right adrenal the hypertrophy was less marked and there was no nodular enlargement. The nodule of the left adrenal was not well circumscribed but merged imperceptibly to the surrounding hypertrophic area. There were neither pleomorphism nor mitotic figures. The zona glomerulosa was narrowed and in some areas absent.

Thyroid: Follicles were generally atrophic. The epithelium was flattened. The colloid was thin and pale staining. There was a small nodule which was encapsulated with thin connective tissue. The nodule was composed of thyroid follicles, the lining epithelium was hypertrophic, columnar or cuboidal in shape. The follicles varied greatly in size: larger follicles were macroscopically visible and smaller ones consisted of solid cell nests.

The other endocrine glands were unremarkable histologically. The pituitary gland

could not be obtained.

DISCUSSION

Characteristic features in the present case were 1) coexistence of oat cell carcinoma of the lung and adrenocortical hypertrophy and adenomatous hyperplasia, 2) asymmetrical enlargement of the adrenal: the left adrenal gland in which there were metastatic lesions of microscopic size being about twice as heavy as the right, 3) abundance of lipid in the cells of zona fasciculata and zona reticularis, 4) tubular arrangement of the cells in these zones, 5) absence of clinical manifestation of Cushing's or adrenogenital syndrome, and 6) coincidental occurrence of small follicular adenoma in the thyroid.

The left adrenal of this patient weighed over the average (4.80 ± 0.47g) of normal Japanese of the age.[1] The tubular structure made up from fasciculata cells has been described in cases of adrenocortical adenoma.[9] However, the present case seems interesting in that such change was observed not only in the hyperplastic area but also in most part of zona fasciculata of both adrenals. Absence of clinical manifestation of Cushing's or adrenogenital syndrome does not exclude adrenocortical hyperfunction of short duration. Clinical data, e.g. slight hyperglycemia, eosinopenia, and normal rubricyte count and normal hemoglobin content in cachectic patient suggest latent hyperactivity of the adrenal cortex, although urinary excretion of adrenal steroids was not examined. Bagshawe[3] collected 8 cases from literature in which metastatic carcinoma in the adrenal glands is accompanied by adrenocortical hyperplasia and hyperfunction but physical changes of Cushing's syndrome are absent or very slight and he ascribed it to rapid progression of the illness to fatal termination.

Among tumors hitherto described in association with Cushing's syndrome, most frequent was the association of undifferentiated bronchogenic carcinoma of oat cell or small cell type[2,6,8]. Preponderance of particular types of carcinoma points to causal relationship rather than coincidental occurrence of Cushing's syndrome and the neoplasm. Various hypotheses have been proposed to account for the causal relationship. The idea that the neoplasm produces corticotropic substance has gained positive support in the finding of Marks and his associates[10] that the injection of homogenized oat cell carcinoma maintained adrenal weight of hypophysectomized animals. According to Tepperman and others,[13] adrenal enlargement occurs in various conditions in which protein breakdown is increased, e.g. hyperthyroidism, inanition, burns, infections, etc. They conceived that degradation product of protein can be a stimulus for adrenal hypertrophy and hyperfunction.

In the reported cases of oat cell carcinoma accompanied by clinical manifestation of Cushing's syndrome, the adrenal cortex is thickened by the hypertrophy and hyperplasia of the zona fasciculata and partly of the zona reticularis, and the cells

in these zones have abundant eosinophilic cytoplasm as seen in hyperactive adrenal cortex.[4, 5, 8, 10] Therefore, it seems likely that present case differs significantly from those mentioned above. On the other hand, histological features of the adrenals of this patient have much in common with those cases studied by Parker and Sommers [11] which showed no clinical evidence of hypercorticism. Although the elucidation of causal relationship is beyond the scope of this case report, the speculation of Marks and his associates[10] is attractive in this connection which postulates that certain neoplasm, oat cell carcinoma in particular, may be capable of secreting more than one type of corticotropin and some of them have effect only upon adrenal cortical cell size and not upon the actual secretion of adrenal steroid.

Abnormalities of various endocrine glands other than the adrenal have been noted in frequent association with cancers of non-endocrine organs[7, 12] although the pathogenesis is still obscure.

SUMMARY

An autopsy case of oat cell carcinoma of the left lung associated with hypertrophy and adenomatous hyperplasia of the adrenal glands was reported. The cells of zona fasciculata and partly of zona reticularis were enlarged with the accumulation of lipid. There was also a small follicular adenoma in the thyroid.

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