Brief Note
Intranuclear Filamentous Inclusion in Lung Cancer

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Intranuclear filamentous inclusions are bundles of closely packed filaments present in the nuclei of a variety of cells. Because these filaments are usually tightly packed and assume a rodlet structure, and because they occasionally showed to have exhibited a parallel arrangement in the lattice, they have also been referred to as intranuclear rodlets or lattice inclusions in the nucleus. Since Mann's report in 1984,[1] such inclusions have been mostly limited to the cells of nervous system, but later they have also been reported in other types of cells and organs. There are several forms of intranuclear inclusions and some are known to appear in lung tissue cells. Many cases[2-4] of bronchiolo-alveolar carcinoma, for example, have been reported to contain intranuclear tubular inclusions. However, to the best of our knowledge, there have been no reports on the presence of intranuclear filamentous inclusions in the lung in either physiological or pathological states. While studying lung cancer cases electron microscopically, we found filamentous inclusions in the nucleus of adenocarcinoma cells. Herein, we describe our findings and discuss their significance.

Cancer cells were aspirated from the tumor mass in the left lower lobe removed from a 59-year-old man. Cell pellets were fixed in 2.5% glutaraldehyde buffered with phosphate (pH 7.4) for three hours, postfixed in phosphate-buffered 1% osmium tetroxide for one hour, dehydrated with graded alcohol and embedded in an epon mixture. Ultrathin sections were stained with uranyl acetate and lead citrate, and examined under a Hitachi H-500 electron microscope. Separately processed paraffin sections histologically showed typical features of a well-differentiated adenocarcinoma growing at the periphery in lepidic fashion. Although retrospective scrutiny for the intranuclear filamentous inclusions light microscopically was unsuccessful, electron microscopic examination disclosed that one of approximately 50 cells present on an ultrathin section had an intranuclear filamentous inclusion. On the longitudinal plane, slightly curved filaments, each 10-14 nm diameter, were observed to be running in parallel with each other, and they formed a bundle or rodlet 6 μm in length and 0.5 μm in diameter (Figs. 1-3). This inclusion was not membrane-bound, but was distant from the karyomembrane without any connection, and was located in the central portion of the nucleus. No clear-cut associations were noted between the filaments and chromatin particles nor were any virus-particle-like or crystalloid structures present within the nucleus. The cells bordering the acinar lumen were to each other by junctional complexes. Cells were fringed with microvilli along the luminal border and secretory granules were found abluminally in the cytoplasm.

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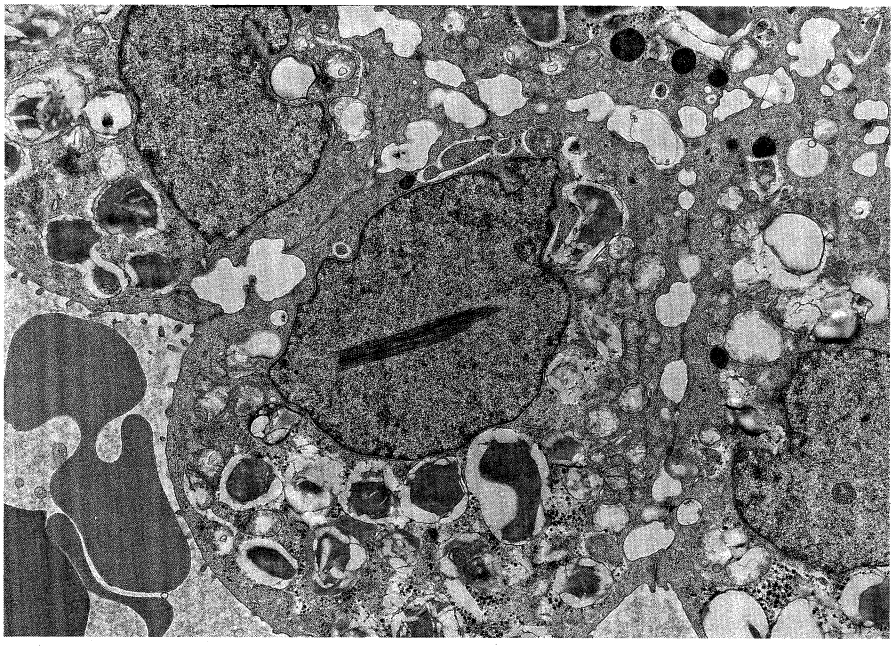

Fig. 1. An electron micrograph of tumor cells, showing a typical filamentous inclusion in the nucleus. Tumor cells are adherent each other with junctional complexes (desmosomes). A few microvilli are seen on the surface and mucinous granules are seen within the cytoplasm (×4500).

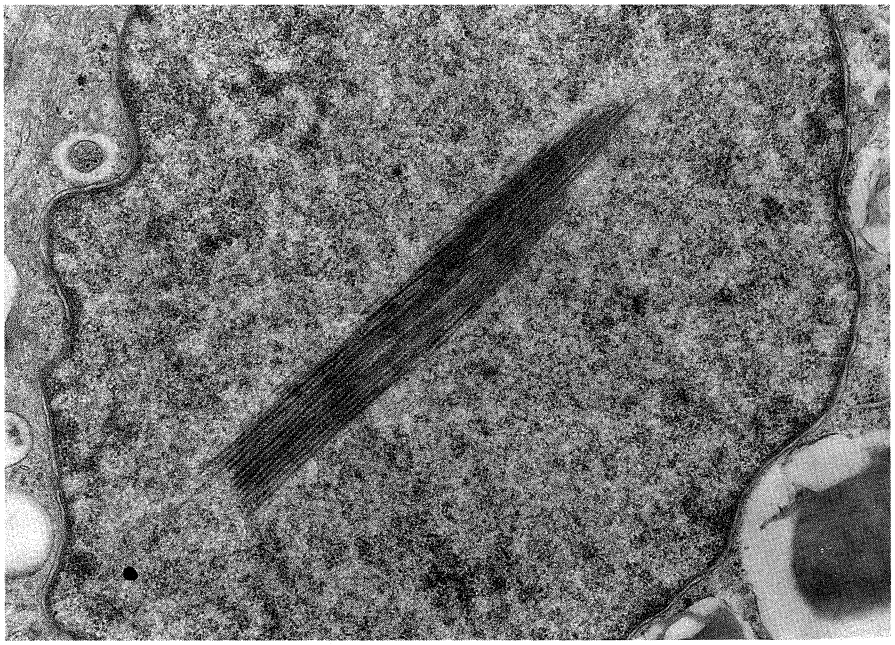

Fig. 2. An inclusion in the nucleus. It is composed of fine filaments, 10–14 nm in diameter, running in parallel with each other and forming a bundle (×1400).

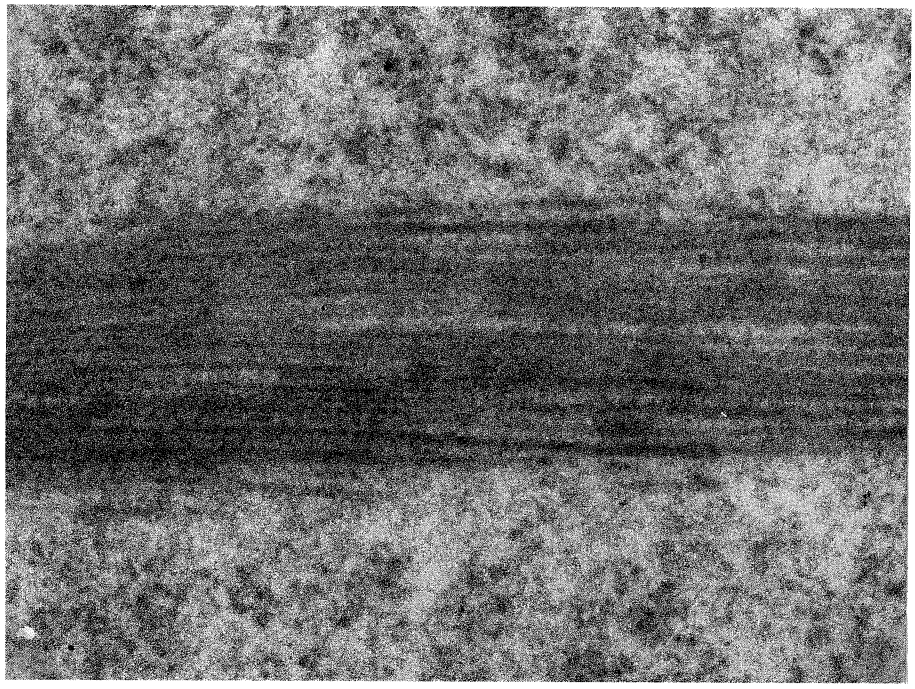

Fig. 3. Intranuclear inclusion body. It does not show any crystalline substructure (×46,000).

Non-viral inclusion are much more frequently recognized in the nuclei of tumors than in normal cells, and are best appreciated by an electron microscope. Most nuclear inclusions contain cytoplasmic structures and, therefore, they are, in fact, pseudoinclusions surrounded by membrane. True inclusions, like the one in this case, are quite rare, and the included materials lie freely in the karyoplasm. There are three theories regarding the development of true inclusions: first, that they are derived from a dissolution of invaginated nuclear membrane surrounding a pseudoinclusion; second, that the materials could be accidentally included in the nucleus during mitosis, and third, that they might be synthesized within the nucleus.

Intranuclear filamentous inclusions have been seen in a variety of cells and organs in normal and pathological conditions; namely, in cerebral cortex neurons in Reye's syndrome,[5] in parietal cortical neurons in Altzheimer's disease and hydrocephalus,[6] in normal and leukemic lymphocytes[7-8] (including Sézary cells)[9] and the plasma cells in multiple myeloma,[10-11] in giant cells in Paget's disease of the bone,[12] in infantile haemangiopericytoma,[13] in lung tissue from a case of influenza viral pneumonia,[14] in an intrathyroid tumor associated with hyperparathyroidism,[15] in pleural mesothelioma cells in an infant with a cardiac anomaly,[16] in actinomycin D-treated oocytes,[17] in various muscular disorders,[18] in human endothelial cells after administration of medroxyprogesterone acetate,[19] in B-cells of a human insulinoma,[20] in malignant gliomas[21], and in Langerhans-type histiocytes infiltrating the pituitary gland.[22]

Bronchioloalveolar carcinomas of the lung may contain intranuclear

tubular inclusions.[2] They are thought to arise from the inner nuclear membrane. Their morphology, however, is different from that of our inclusions, and we are not aware of any previous report of such inclusions in lung cancer.

The significance and possible function of these filamentous inclusions or rodlets are not known. A correlation may exist between their appearance and the physiological activity of the cells. Seite *et al.*,[23] and Clattenburg *et al.*[24] demonstrated an increase in their number after electrical stimulation and treatment with cyclic AMP, and their disappearance from hypothalamic cells after coitus. On the other hand, intranuclear bundles of filaments have also developed after actinomycin-D treatment and exposure to dimethyl sulphoxide. According to these authors, they are caused by metabolic disturbances of the cells. They also showed that these filaments are, in fact, actin filaments, which exist normally as a major component of nonhiston protein in the nucleus.

At the moment, we do not have any means to elucidate what the filaments are in our case, but we believe they were produced within the nucleus. No hormonal effect is conceivable and no medications such as anticancer chemotherapeutic agents were given in our case. Since they appeared in a tumor cell, we would like to speculate that metabolic derangement in the tumor cell may have had something to do with the development of this material.

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