Pathology & Oncology Research (2020) 26:1989–1990
https://doi.org/10.1007/s12253-019-00714-0

LETTER TO THE EDITOR

Nuclear Cytoplasmic Inclusions in Lung Adenocarcinoma: Relevance of Immunohistochemistry

Handra-Luca Adriana [1,2]

Received: 30 May 2019 / Accepted: 8 August 2019 / Published online: 19 August 2019

To the Editor,
Sir

New characteristics of nuclear inclusion in lung carcinoma cells have been recently reported [1]. However, their precise nature remains matter of debate, whether drug induced (bleomycin, busulphan), viral infection-related or not [2–4].

We had the opportunity to detect nuclear inclusions in 2 lung adenocarcinomas, one of them showing giant cells. The personal and medical histories were peculiar by the patient's hobbies and treatments: interest for stuffed animals and bird feeding and, radiotherapy (breast cancer), respectively. An excessive smoking history was also reported. At microscopy, on the hematoxylin and eosin stained tissue-sections, the tumor cell nuclei showed meganucleoli and clear rounded structures partially or completely filled by a light-eosinophilic material (Fig. 1). TTF1 was not expressed in the nuclear inclusions. Cytokeratin (CK) CK7 was expressed in several of them. The 2nd tumor showed similar nuclear inclusions. The nuclear inclusion form was round or of varied shapes, possibly result of the diverse forms of atypical nuclei. PDL1, expressed by the 2nd tumor, showed a similar expression pattern to CK7 in the nuclear inclusions.

Here we report CK7 expression in nuclear inclusions of lung adenocarcinoma confirming their cytoplasmic nature, inclusions previously shown to be positive for the PAS-stain and for surfactant protein A immunohistochemistry [5, 6]. Nuclear changes related to noxes (including tobacco-etch virus, radiotherapy) [7] and/or to changes in cytoplasmic proteins, as presence of autophagy-associated proteins in hepatocellular carcinomas (p62, ubiquitin, LC3B, cathepsin B and cathepsin D) [8] could be incriminated. Interestingly the programmed-death-ligand PDL1 protein, was also expressed in the nuclear inclusions.

In conclusion, nuclear inclusions in lung carcinomas may show CK7 and PDL1 expression confirming their cytoplasmic nature. The presence of nuclear inclusion could be suggestive of specific conformational types of nuclear atypia and/or nucleus/cytoplasm interactions, possibly impacting on prognosis [9]. However, the accurate etiopathogenesis remains difficult to precise, further studies are required.

✉ Handra-Luca Adriana
adriana.handra-luca@aphp.fr; adriana.handra-luca@hotmail.comm; adriana.handra-luca@univ-paris13.fr

[1] Service d'Anatomie Pathologique, APHP GHU Avicenne, Universite Paris Nord Sorbonne Cite, 125 rue Stalingrad, 93009 Bobigny, France

[2] University Paris Nord 13, UFR SMBH, Bobigny, France

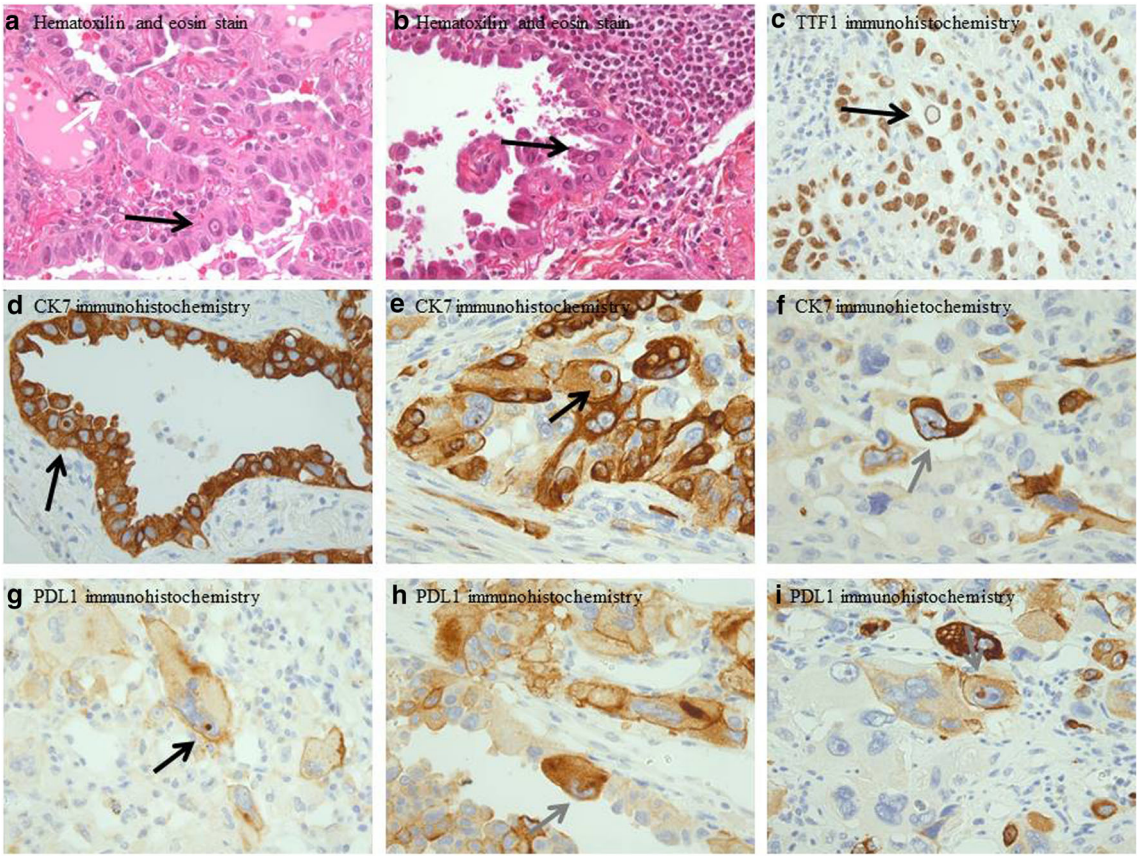

Fig. 1 Intranuclear inclusions in lung adenocarcinoma. Nuclear inclusions were detected in lung adenocarcinoma cells. The nuclei also showed prominent nucleoli (**a**,**b**: black arrows/inclusions, white arrow/nucleolus). The TTF1 protein was not expressed in the nuclear inclusions (**c**: black arrow). Cytokeratin 7 (CK7) was expressed in nuclear inclusions (**d**: black arrow). In the 2nd case, the nuclear inclusions also expressed CK7 (**e**: black arrow). In some tumor cells, the connection between the nuclear "inclusion" and the cytoplasm could be observed (**f**: gray arrow). The nuclear inclusions in this case also showed PDL1 expression (**g**: black arrows). A connection between the PDL1-positive "inclusion" and the cytoplasm could be detected in other cells (H,I: gray arrows). To note would be the different staining intensities in the nuclear inclusion and cytoplasm. Case 1: A-D; case 2: E-I. Original magnification ×40 (A-I). A,B hematoxylin and eosin staining, C TTF1, D-F CK7 and G-I PDL1 immunohistochemistries

Compliance with Ethical Standards

Conflict of Interest None.

References

1. Kobayashi S, Saio M, Fukuda T et al (2019) Image analysis of the nuclear characteristics of emerin protein and the correlation with nuclear grooves and intranuclear cytoplasmic inclusions in lung adenocarcinoma. Oncol Rep 41:133 142
2. Rosai J (2011) *Rosai and Ackman's Surgical Pathology.* 10th edition expert consult. Mosby Elsevier, Philadelphia
3. Torikata C, Ishiwata K (1977) Intranuclear tubular structures observed in the cells of an alveolar cell carcinoma of the lung. Cancer 40:1194 1201
4. Gyorkey F, Gyorkey P, Sinkovics JG (1980) Origin and significance of intranuclear tubular inclusions in type II pulmonary alveolar epithelial cells of patients with bleomycin and busulfan toxicity. Ultrastruct Pathol 1:211 221
5. Singh G, Katyal SL, Torikata C (1982) Carcinoma of type II pneumocytes. PAS staining as a screening test for nuclear inclusions of surfactant specific apoprotein. Cancer 50:946 948
6. Mizutani Y, Nakajima T, Morinaga S et al (1988) Immunohistochemical localization of pulmonary surfactant apoproteins in various lung tumors. Special reference to nonmucus producing lung adenocarcinomas. Cancer 61:532 537
7. Knuhtsen H, Hiebert E, Purcifull DE (1974) Partial purification and some properties of tobacco etch virus induced intranuclear inclusions. Virology 61:200 209
8. Schwertheim S, Westerwick D, Jastrow H, Theurer S, Schaefer CM, Kälsch J, Möllmann D, Schlattjan M, Wedemeyer H, Schmid KW, Baba HA (2019) Intranuclear inclusions in hepatocellular carcinoma contain autophagy-associated proteins and correlate with prolonged survival. J Pathol Clin Res 5:164 176
9. Aida S, Shimazaki H, Sato K et al (2001) Prognostic significance of frequent acidophilic nuclear inclusions in adenocarcinoma of the lung with immunohistochemical and ultrastructural studies. Cancer 91:1896 1904