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Thyroid follicular adenoma with numerous intracytoplasmic lumina mimicking yellow bodies: a case report

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Intracytoplasmic lumina (ICL) are distinct, intracytoplasmic spherical structures enclosed by a cell membrane.[1,2] ICL are usually solitary and are 5–10 μm in diameter. Ultrastructural studies have shown that they are composed of an epithelial membrane bearing apical microvilli.[1,2] ICL sometimes contain inspissated secreted material, have been observed in adenocarcinomas, particularly of the breast,[1–4] and their presence is a cytological clue to indicate carcinoma.[1] In the thyroid, their presence has not always indicated malignancy as ICL have been observed in both benign and malignant thyroid lesions including non-neoplastic Hürthle cell lesions (NNHCLs), Hürthle cell tumours (HCTs), and medullary carcinomas (MCs).[5–7]

Recently, we encountered a case of follicular adenoma (FA) with numerous ICL. To the best of our knowledge, such a case has never been reported. At the time of cytological diagnosis, we confused ICL with yellow bodies (YBs) that are characteristic of hyalinising trabecular tumours (HTTs). Herein, we report our rare case and discuss the distinction between ICL and YBs.

Case history

A 39-year-old woman was referred to our hospital for evaluation of a thyroid nodule. On ultrasonography, the nodule was located in the upper left lobe, measured 1.4 × 0.6 × 1.1 cm, and was oval, well-defined and hypoechoic. Ultrasound-guided fine-needle aspiration cytology (FNAC) indicated atypia of undetermined significance and a follicular variant of papillary carcinoma or a follicular tumour was suspected. Four months later, FNAC was repeated and the findings were similar. Subsequently, a left lobectomy was performed.

Cytological findings

The cytological findings of the two FNACs were similar. The aspirated material was highly cellular. A large number of follicular cells were arranged in small follicular or trabecular patterns. The cytoplasm was faintly stained and the cell membrane was indistinct. ICL with distinct borders were readily observed and they frequently contained secreted material. Some ICL depressed the nuclear membrane (Figure 1). We calculated the incidence of ICL using the WinROOF image processing software (Mitani Corp., Tokyo, Japan) for Windows. ICL was seen in

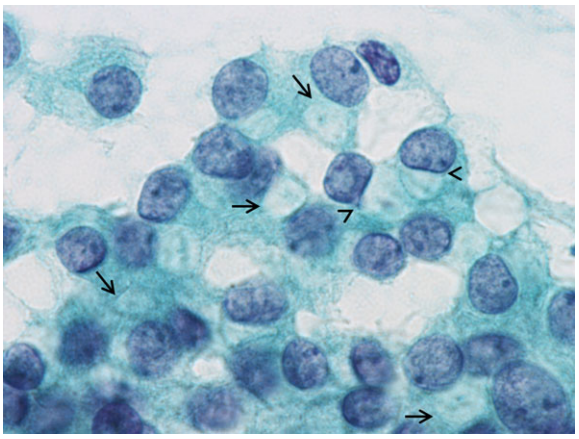

Figure 1. Intracytoplasmic lumina are seen in the follicular cells. Intraluminal secreted material (arrow) and depressed nuclei (arrowhead) are noted (Papanicolaou, ×100).

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12.5% of the follicular cells. The nuclei were enlarged and round to oval in shape. Nuclei with indentation, lobulation, grooves and intranuclear cytoplasmic inclusions (ICIs) were occasionally observed. ICI-like structures were also observed including inclusions not surrounded by a nuclear membrane and inclusions that stained less intensely than the cytoplasm. The chromatin was a fine structure but did not show a typical ground-glass appearance.

Histological findings

Grossly, an encapsulated tumour measuring 1.0 × 0.9 cm was present in the resected left thyroid lobe. On examination of the cut surface, the tumour was solid, homogeneous and tan-yellow (Figure 2). Microscopically, the tumour was composed of follicular cells showing a microfollicular or trabecular growth pattern. The cytoplasm was eosinophilic, amphophilic or slightly clear. A small number of the tumour cells were weakly positive for mitochondria. ICL were readily observed throughout the tumour. The incidence of ICL was 13.7% of the tumour cells. The ICL frequently contained secreted material. The secreted material did not stain with PAS or Alcian blue. Some ICL pushed the nuclei to the periphery of the cell or depressed the nuclear membrane (Figure 3). The nuclei showed nuclear grooves and ICIs, but the nuclear chromatin did not show a ground-glass appearance. Nuclear overlapping was not present. The stroma was scant and vascular. PAS staining did not reveal thick basement membrane material around the microfollicles or trabeculae.

Figure 2. Cut surface of the resected thyroid. An encapsulated solid tumour is seen (resected material).

Immunohistochemical findings

The tumour cells were positive for thyroglobulin (polyclonal; DAKO, Carpinteria, CA, USA) and negative for CEA (COL-1; Nichirei, Tokyo, Japan), cytokeratin 19 (RCK108; DAKO, Carpinteria, CA, USA), HBME-1 (HBME-1; DAKO, Carpinteria, CA, USA) and galectin-3 (9C4; Novocastra, Newcastle upon Tyne, England). Some ICL were positive for thyroglobulin but the ICL did not stain positive for any of the other antibodies listed above. The Ki-67 (MIB1; DAKO, Carpinteria, CA, USA) labelling index was less than 1%. Cell membrane reactivity with Ki-67 was not observed.

Discussion

The tumour, in this case, was well encapsulated and showed a follicular and trabecular growth pattern. Nuclear grooves and ICIs were observed but the chromatin did not have a ground-glass appearance and nuclear overlapping was not present. Immunohistochemically the tumour cells were negative for

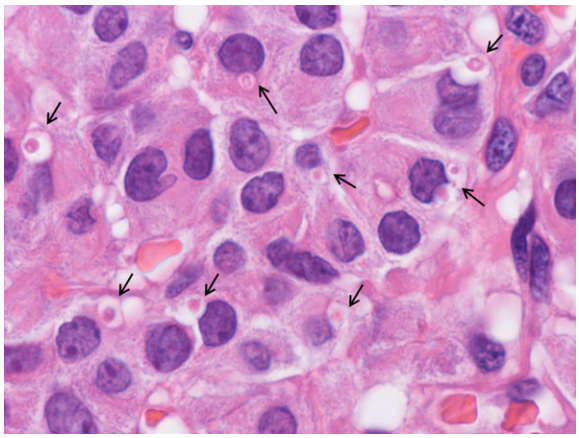

Figure 3. Many intracytoplasmic lumina are seen. Some of them push out the nuclei or depressed the nuclear membrane (arrow) (HE, ×100).

cytokeratin 19, HBME-1 and galectin-3, for which papillary carcinoma shows immunopositivity[8]. Therefore, our case was diagnosed as an FA.

In our case, numerous ICL were observed in an FA. It is well known that ICL are a diagnostic clue for adenocarcinoma, particularly of the breast[1–4], but less attention has been paid to the presence of ICL in thyroid lesions.

Yang and Khurana found ICL in HCTs (70%) and NNHCLs (15%) in the cases studied.[5] They concluded that the presence of ICL is a helpful feature in distinguishing between them. Elliott *et al.*[6] also identified the presence of ICL in HCTs and NNHCLs but the reported frequency was 23% and 17%, respectively and there was no significant difference. In addition, the above two reports did not mention the frequency of ICL in the individual cases. MC cells might bear ICL with CEA-positive granular material.[7]

To the best of our knowledge, the present case is the first case ever reported of a non-Hürthle cell FA showing ICL. Furthermore, numerous ICL were clearly observed throughout the tumour. From this case, it is clear that the presence of ICL may appear in a non-malignant lesion in the thyroid.

The ICL seen in the present case differed from those seen at other anatomical sites, both histochemically and immunohistochemically. The secreted material of ICL seen in breast cancer is positive on PAS staining[3] and immunohistochemically react with CEA,[2] but those seen in our case were negative for both. Thus, we can safely assume that the components of ICL differ depending on the type of tumour cells bearing them.

At the time of cytological diagnosis, we confused ICL with YBs seen in HTTs. HTTs are characterised by a trabecular growth pattern, numerous ICIs, intratrabecular basement membrane material and YBs[9]. YBs are intracytoplasmic inclusion bodies and are round, refractile and often granular. YBs are stained pale light green on Papanicolaou staining and yellow on HE staining[10]. As YBs are usually associated with a halo encircling them, the structure is superficially similar to that of ICL containing secreted material. However, to date, the morphological similarity and difference between ICL and YBs have not been described.

On ultrastructural examination, YBs have been described to be equivalent to giant lysosomes. Therefore, the halo encircling the YBs might be a fixation artefact, and the boundary is indistinct.[10] ICL are proper lumen formed in the cytoplasm, are outlined by a dense rim of cytoplasm and are ultrastructurally characterised by microvilli lining the lumina[11]. We believe that this difference is a clue to distinguishing ICL and YBs. Another clue seems to be the nuclear configuration. Nuclei depressed by ICL were noted in our case. Such a phenomenon has not been described in YBs. Lysosomes are usually PAS-positive. As YBs are equivalent to lysosomes, they should also be positive for PAS staining. The secreted material within the ICL seen in our case was PAS-negative. Therefore, PAS staining may be useful in their differentiation. Additionally, Golgi apparatus may be superficially similar to ICL, but it is observed as a perinuclear clear zone identified in plasma cells and is not surrounded by a cell membrane.

To the best of our knowledge, this is the first report of a case of FA with numerous ICL. We should all be aware that ICL may appear in a non-malignant lesion, unlike those seen in breast cancer. Additionally, ICL should be differentiated from the YBs seen in HTTs on FNAC of the thyroid.

Conflict of interest

We have no conflict of interest in this article.

Financial disclosure

We have no connection to any companies or products mentioned in this article.

Ethical approval

The ethics committee of our hospital and the subject gave informed consent to our study.

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