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Aspiration Cytology of the Osteoclastic Variant of Anaplastic Thyroid Carcinoma: with Special Emphasis on the Undifferentiated Mononuclear Cells

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Anaplastic thyroid carcinoma (ATC) is an uncommon aggressive malignant tumor, and the osteoclastic variant of ATC is extremely rare. We report here on the fine needle aspiration cytology of the osteoclastic variant of ATC in an 83-year-old woman. The smear was composed of many oval to slightly elongated undifferentiated mononuclear cells admixed with multinucleated osteoclast-like giant cells. The mononuclear tumor cells revealed inconspicuous nuclear pleomorphism and the nuclei were characterized by vesicular chromatin and an indented or lobulated nuclear membrane with conspicuous nuclear grooves. A few epithelial clusters suggestive of a papillary carcinoma component were also observed. Making the proper cytological diagnosis of the osteoclastic variant of ATC is helpful to determine the proper treatment modality for these patients.

Key Words : Thyroid neoplasms; Anaplasia; Osteoclastic; Cytology

Anaplastic thyroid carcinoma (ATC) is also called undifferentiated thyroid carcinoma, and this is a highly malignant tumor that constitutes about 10% of all thyroid malignancies.[1-3] Microscopically, ATC reveals three major patterns such as the spindle cell, giant cell and squamoid cell patterns, and sometimes these patterns are combined in different proportions according to the case.[1-3] Some multinucleated giant cells can be associated with ATC. However, the osteoclastic variant of ATC, in which many multinucleated giant cells resembling osteoclasts are encountered, is very rare.[4,5] The aspiration cytology of the osteoclastic variant of ATC has rarely been reported and most of the previous reports have emphasized the presence of multinucleated giant cells.[6-9] We present here the fine needle aspiration cytology (FNAC) of the osteoclastic variant of ATC in an 83-year-old woman, and we place special emphasis on the cytologic feature of the undifferentiated mononuclear cells.

CASE REPORT

An 83-year-old woman presented with pain and swelling of the left neck along with odynophagia and hoarseness that she had experienced for the previous 2 days. On physical examination, diffuse swelling as well as a sensation of heat was noted on the neck. The ultrasonograph exam revealed an ill-defined huge hypoechoic nodule at the left thyroid. The mass measured 3.94 × 3.02 cm in dimension. On computed tomography (CT), the nodule was observed to be an ill-defined heterogenous enhancing solid mass that had invaded into the esophagus and abutted to the trachea (Fig. 1). FNAC and biopsy were performed on the mass.

The aspirate was highly cellular and it was composed of two different major cell populations (Fig. 2A) and one minor component (Fig. 2D). First, many small mononuclear cells were seen singly or in variable-sized loose or syncytial clusters. The mo-

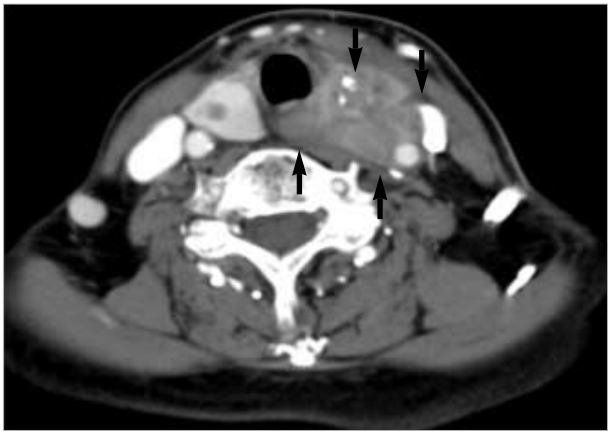

Fig. 1. The neck computed tomography shows an ill-defined heterogeneous enhancing solid thyroid mass (arrows) that has invaded into the esophagus and abuts to the trachea.

nonuclear cells were relatively uniform and not pleomorphic. The cytoplasm of these cells was weakly eosinophilic with irregular and elongated cytoplasmic processes and indistinct cytoplasmic membranes. The nuclei were ovoid or slightly elongated with inconspicuous nuclear pleomorphism, vesicular chromatin and small distinct nucleoli. The nuclear membrane was slightly to markedly lobulated and it was indented with frequent nuclear grooves and occasional intranuclear pseudoinclusions (Fig. 2B, C). Mitotic figures were frequently seen. Second, a large number of multinucleated osteoclast-like giant cells (MOGC) were intermingled with the mononuclear atypical cells throughout the smear (Fig. 2A). The MOGCs were packed with many bland looking uniform-sized nuclei (Fig. 2B). The number of nuclei ranged from several to 30. These nuclei were round or ovoid with a smooth nuclear membrane and fine

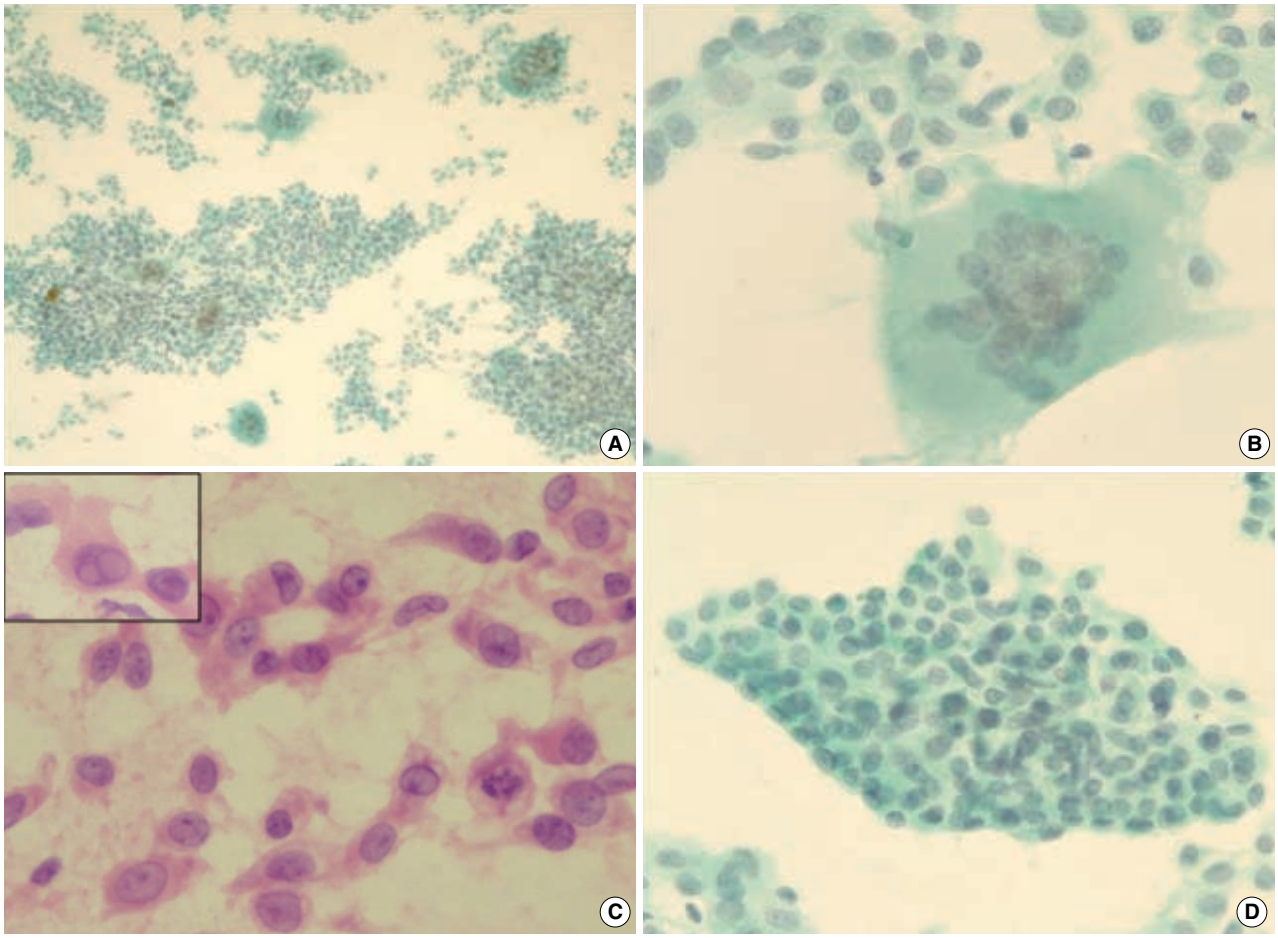

Fig. 2. Fine needle aspiration cytology of the thyroid. (A) The aspirate mostly consists of a mixture of mononuclear cells that present singly or in variable-sized clusters, and multinucleated giant cells. (B) The mononuclear cells reveal ovoid or elongated nuclei with nuclear grooves. The multinucleated osteoclast-like giant cells show dense cytoplasm and multiple bland-looking packed nuclei. (C) The mononuclear cells reveal short cytoplasmic processes, vesicular chromatin, an indented or lobulated nuclear membrane, small distinct nucleoli, nuclear pseudoinclusions (inset) and mitotic figures. (D) The cluster with a smooth contour is composed of follicular cells showing nuclear clearing and nuclear grooves, which suggests a papillary carcinoma component.

chromatin. The cytoplasm was dense and the cytoplasmic membrane was fuzzy. Pleomorphic cells or tumor giant cells were not seen throughout this aspirate. Third, a few clusters of follicular cells were found as a minor component. The follicular cells showed nuclear enlargement, nuclear clearing and nuclear grooves, and this all suggested an associated papillary carcinoma component (Fig. 2D).

The histology of the biopsy specimen revealed a solid proliferation of momonuclear cells intermingled with many MOGCs and minute foci of follicular epithelial nests in a papillary or follicular pattern (Fig. 3A). The mononuclear cells revealed indistinct cytoplasm, conspicuous nuclear indentation and grooves with intranuclear cytoplasmic inclusions, and high mitotic activity (Fig. 3B). The foci of follicular cells revealed nuclear enlargement, nuclear clearing and nuclear grooves, and this all suggested papillary carcinoma. Multifocal necrosis was noted within the tumor. Immunohistochemically, the mononuclear cells and MOGCs stood in contrast to the follicular cells. The mononuclear cells and MOGCs were negative for cytokeratin, epithelial membrane antigen, thyroglobulin and thyroid transcription factor-1, while the follicular cells were positive for these markers (Fig. 3C). In contrast, the mononuclear cells and MOGCs were diffusely positive for vimentin, but the follicular cells were negative for vimentin. The MOGCs diffusely expressed CD68.

The patient was managed conservatively without surgical intervention. She developed dyspnea a month later. The mass had rapidly increased on the follow-up neck CT.

DISCUSSION

ATC is a rare highly malignant tumor that arises from the follicular cells of the thyroid gland.[1-3] Most cases of ATC develop in elderly patients and ATC is a rapidly growing tumor.[1-3] Histologically, the majority of ATCs show spindle cell, giant cell and squamoid cell patterns; these 3 subtypes frequently coexist and they are not predictive of the patient's outcome.[1,2] The osteoclastic variant of ATC is extremely rare,[4,5] and this consists of a mixture of undifferentiated mononuclear cells and multinucleated bland looking osteoclasts-like giant cells, and it is remi-

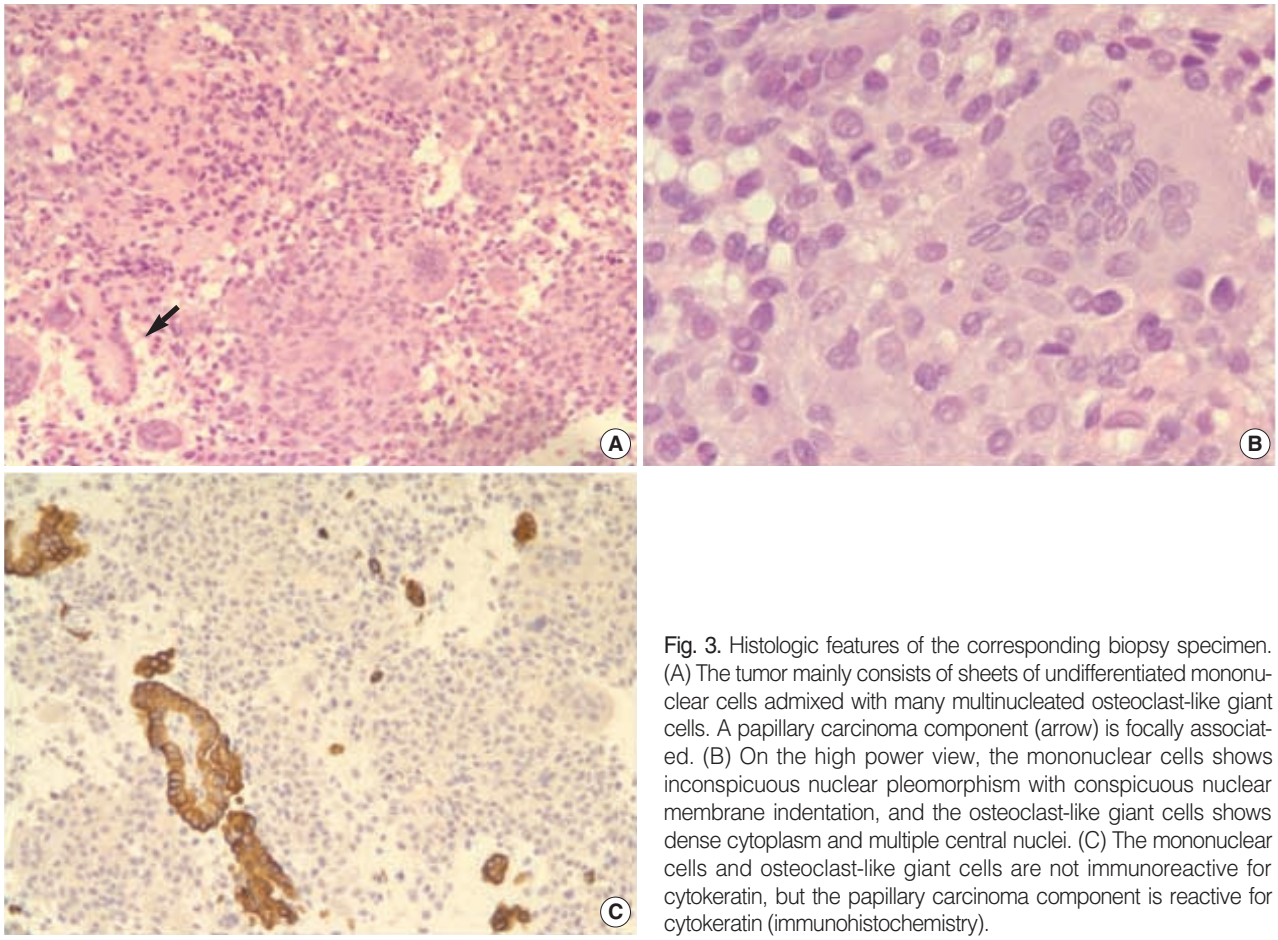

Fig. 3. Histologic features of the corresponding biopsy specimen. (A) The tumor mainly consists of sheets of undifferentiated mononuclear cells admixed with many multinucleated osteoclast-like giant cells. A papillary carcinoma component (arrow) is focally associated. (B) On the high power view, the mononuclear cells shows inconspicuous nuclear pleomorphism with conspicuous nuclear membrane indentation, and the osteoclast-like giant cells shows dense cytoplasm and multiple central nuclei. (C) The mononuclear cells and osteoclast-like giant cells are not immunoreactive for cytokeratin, but the papillary carcinoma component is reactive for cytokeratin (immunohistochemistry).

niscent of giant cell tumor of bone or soft tissue.[4,5] Although there are some histological differences between the variants of ATC, their clinical behaviors are similar.[1]

The FNAC of the osteoclastic variant of ATC is characteristic and it shows a cellular smear with two cell populations: undifferentiated mononuclear cells and multinucleated osteoclast-like giant cells.[6-9] The mononuclear cells are the main neoplastic element. The multinucleated giant cells resemble osteoclasts and they are abundantly admixed with the mononuclear malignant cells. The cytologic characteristics of the mononuclear cells were not so much emphasized in the previous reports. In our case, the mononuclear malignant cells revealed a characteristic undifferentiated morphology with a relatively uniform primitive appearance, a high nuclear cytoplasmic ratio and frequent mitotic figures. Highly pleomorphic cells were not seen in our case, which stands in contrast with conventional ATC. Cytoplasmic processes were easily recognized in the cytologic smear. The nucleus was ovoid or enlongated with powdery ground-glass chromatin, nuclear grooves, nuclear membrane lobulation and occasional nuclear pseudoinclusions; these findings seem so characteristic, but they have not emphasized in the previous reports. Some previous reports have suggested the epithelial origin of the mononuclear cells according to the immunohistochemical and electron microscopy findings. However, in our case, the mononuclear malignant cells immunohistochemically revealed mesenchymal differentiation without any epithelial differentiation.

The multinucleated giant cells, or the so called osteoclast-like giant cells, seen in the osteoclastic variant of ATC contain multiple small bland looking nuclei that are centrally packed. The osteoclast-like giant cells usually reveal dense cytoplasm rather than the foamy cytoplasm of the multinucleated giant cells seen in nodular hyperplasia with cystic degeneration.[10] These cells have been thought to probably be non-neoplastic and rather, they are reactive cells of the monocytic/histiocytic lineage that are derived from mononuclear cells through the mechanism of cell fusion.[4] Immunohistochemically, this idea is supported by the cellular staining for lysozyme as well as CD68 and cathepsin K.[4]

If multinucleated giant cells are found on FNAC of a thyroid, then the main differential diagnoses include ATC, papillary carcinoma, subacute thyroiditis, Hashmoto's thyroiditis, nodular hyperplasia and Langerhans cell histiocytosis. In the conventional ATCs, the giant cells, if seen, are mostly the pleomorhic type and there are not so many osteoclast-like giant cells as in the osteoclastic variant of ATC.[4] The aspirate of papillary carcinoma can also contain multinucleated giant cells, and particularly in the setting of cystic degeneration.[10] However, numerous undifferentiated mononuclear cells are not seen in papillary thyroid carcinoma. The mononuclear cells could be differentiated from the papillary carcinoma cells as the latter usually don't reveal conspicuous cytoplasmic processes, nuclear elongation and nuclear membrane lobulation. Subacute thyroiditis and Hashmoto's thyroiditis can be excluded by the lack of an inflammatory background.[11] Nodular hyperplasia reveals abundant colloid material and some multinucleated giant cells that show foamy cytoplasm rather than dense cytoplasm.[10] Langerhans cell histiocytosis rarely involves the thyroid. Langerhans cell histiocytosis shows numerous Langerhans cells, which are histiocyte-like cells with grooved and indented nuclei, and some multinucleated giant cells. These Langerhans cells have more abundant cytoplasm than the mononuclear cells of the osteoclastic variant of ATC and the Langerhans cells are mixed with many eosinophils and lymphocytes.[12] Many of the giant cells seen in Langerhans cell histiocytosis are not osteoclastic-like.

When we first examined the aspiration cytology, the cytological finding seemed to be so similar to that of giant cell tumor of soft tissue or bone that we wondered if the radiologist or clinician misunderstood that the site of this lesion was the thyroid. Giant cell tumor of soft tissue or bone is rarely associated with pulmonary metastasis,[13,14] yet to the best of our knowledge, there have been no reports of giant cell tumor of soft tissue or bone that have metastasized to the thyroid. Although giant cell tumor of soft tissue usually affects the superficial soft tissue of the upper and lower extremities and trunk, it can occur in the neck.[13] Because the FNAC of the osteoclastic variant of ATC is very similar to that of giant cell tumor of soft tissue, it would sometimes be difficult to discriminate between giant cell tumor of soft tissue and the osteoclastic variant of ATC, and particularly for cases of tumor that has a radiologically undetermined origin. Like the usual ATC, the components of well-differentiated thyroid carcinoma can be identified in the osteoclastic variant of ATC and the identification of the well-differentiated thyroid carcinoma component is helpful to confirm the tumor's thyroid origin. In our case, minute components of papillary thyroid carcinoma supported the tumor's thyroid origin.

In conclusion, the osteoclastic variant of ATC is a rare variant of ATC. Because ATCs, including the osteoclastic variant of ATC, are rapidly growing, highly aggressive tumors, multimodality treatment can be applied.[15] Recognizing the cytological finding of the osteoclastic variant of ATC and making the prompt and proper cytological diagnosis are helpful to determine the treat-

ment plan for the patients who suffer with this malady.

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