Thymic Carcinoma with Neuroendocrine Differentiation in a Calf

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(Received 27 January 1999/Accepted 26 March 1999)

ABSTRACT. A neuroendocrine carcinoma originating in the thymus was found in a 7-month-old, castrated male, Japanese Black calf. The neoplasm consisted largely of very primitive cells, characterized by the paucity of cytoplasmic organelles, but a few cells were immunoreactive for somatostatin or neurofilaments. The expression of both cytokeratin and neurofilament protein was a feature of neuroendocrine differentiation. This neoplasm considered to be a tumor of a thymic stem cell, with little but indubitable evidence of differentiation into somatostatin-producing cells. —KEY WORDS: bovine, somatostatin, thymic carcinoma.

Thymic carcinoma is rare in domestic animals, and is associated with epithelial-reticular cells [4]. Thymoma and thymic carcinoma have been reported in adult cattle [6, 8, 10]. In human beings, carcinoid or neuroendocrine tumors occur as primary tumors in the thymus [11]. The present report describes the histological, immunohistochemical and ultrastructural features of a thymic tumor composed of immature cells in a calf. A slight indication of neuroendocrine differentiation was by far the most important feature.

In a 5-month-old, castrated male, Japanese Black calf, the right shoulder appeared slightly raised in height as compared with the left one. Two months later, a swelling was detected apparently on the right shoulder, and the animal took a dislike of rising. Because of this tumor mass, the animal was euthanatized.

At necropsy, the cervical thymus was replaced by a 20 × 13 × 12 cm unencapsulated tumor mass, which was yellowish cream in color and firm and fibrous in consistency. This tumor adhered to the pulmonary pleura, and was continuous with a 20 × 15 × 15 cm tumor mass, which was present among longest muscles near the right shoulder blade and invaded surrounding muscular tissues. The superficial cervical, pulmonary, and caudal mediastinal lymph nodes were enlarged, and on cut section the tissues bulged and were uniform brownish red.

Tissue samples were fixed in 10% neutral buffered formalin, embedded in paraffin wax, and routinely processed for histological examination. Sections were stained with hematoxylin and eosin (HE). Paraffin sections were also stained by the avidin-biotin-peroxidase complex. Paraffin sections were also stained with hematoxylin and eosin (HE). Paraffin sections were also stained by the avidin-biotin-peroxidase complex. The following were used as primary antibodies: mouse monoclonal antibody to cytokeratin (Dako Corporation, Glostrup, Denmark) and rabbit polyclonal antibodies to chromogranin A (Nichirei Corporation, Tokyo, Japan), cytokeratin, serotonin, secretin, neurotensin (BioGenex Laboratories, San Ramon, CA, U.S.A.), glucagon, somatostatin (Biomedica Corporation, Foster City, CA, U.S.A.), and neuron-specific enolase (NSE) (Lipshaw Corporation, Detroit, MI, U.S.A.). Subsequent procedures were carried out by means of an immunoperoxidase labeling system (BioGenex). For electron microscopical examination, small blocks taken from formalin-fixed tissues were post-fixed in 1% osmium tetroxide, embedded in epoxy resin, stained with uranyl acetate and lead citrate, and examined by electron microscopy.

Histologically, the neoplastic tissue in the mediastinum consisted of clusters or sheets of closely packed neoplastic cells, enclosed by variously developed collagenous fibrous tissue (Fig. 1), and was accompanied with necrotic or hemorrhagic areas. Neoplastic cells invaded the pleura and were present mainly within lymphatics, but only few neoplastic cells were detected within pulmonary alveoli. The neoplastic cells were large and polyhedral, and on occasion very large cells were detected. The nuclei were large and oval, with prominent or moderately prominent nucleoli and finely clumped chromatin. The cytoplasm was eosinophilic and relatively narrow. Mitotic figures were occasionally seen. Similar morphological features were observed in the other invasive or metastatic lesions.

Immunohistochemically, somatostatin-, chromogranin-, or NF-positive cells were found in the neoplastic tissue albeit extremely rare (Fig. 2). Many neoplastic cells were positive for cytokeratin (Fig. 3) or NSE.

Ultrastructurally, the neoplastic cells had ovoid nuclei containing plentiful euchromatin, but at times showed indented nuclear contours. There were poorly developed organelles in the cytoplasm. It was rare to find cells containing small numbers of dense-core secretory granules (Fig. 4), sparsely distributed glycogen granules, one or more low density lipid droplets, or globular bodies composed of intermediate filaments. Tight junctions and immature desmosomes were detected between adjoining cells. Cell borders were smooth, but on rare occasions intercellular lumina bearing microvilli were formed (Fig. 5).

A diagnosis of thymic carcinoma should be made only after exclusion of other primary sites, particularly the lung [11]. In our case, a tumor mass was formed in the mediastinum, and extended to longest muscles. The other neoplastic tissues, which were located in some lymph nodes, appeared apparently metastatic, and the present neoplasm was considered to be of thymus origin.

It is thought that multipotential stem cells capable of...
Fig. 1. In this area the tumor is composed of compact groups of closely packed cells, enclosed by delicate strands of fibrovascular stroma. Cellular atypia or pleomorphism is inconspicuous, but there is considerable mitotic activity (arrows). HE stain. ×200.

Fig. 2. Although there is no detectable NF in most neoplastic cells, intense (arrows) or weak (arrowheads) dot-like staining is seen in a small proportion of cells (arrows). Immunostaining. ×400.

Fig. 3. Many neoplastic cells are cytokeratin positive with variation in intensity of staining. Immunostaining. ×200.

Fig. 4. This neoplastic cell with few neurosecretory granules (arrows) is in mitosis. ×7,500.

Fig. 5. A few microvilli are seen protruding into the intercellular lumen bounded by neoplastic cells linked by immature desmosomes (arrows). ×9,000.
showing squamous and neuroendocrine differentiation exist in human and animal thymuses [5]. Sensaki et al. [12] found an undifferentiated thymic carcinoma containing areas of carcinoid cells in a 52-year-old man. The presence of such a tumor could be explained by stem cells showing divergent lines of differentiation, but another possible explanation was focal dedifferentiation of carcinoid tumor. In the earliest stage of human thymic development, the epithelial cells displayed ultrastructural features such as intercellular lumens, immature desmosomes and poorly developed RER [7]. The present neoplasm was composed of very primitive cells having similar ultrastructures, and many neoplastic cells showed positive reactivity for cytokeratin, but only few cells were positive for chromogranin, somatostatin or NF. These findings strongly suggest that this tumor arose from a stem cell and denoted incipient neuroendocrine differentiation. In human beings, neuroendocrine tumors have features of both neuronal and epithelial differentiation [3], and coexpression of cytokeratin and NF has been demonstrated in some cases [2]. The presence of many NSE-positive cells in our case is explainable by the fact that NSE takes place in earlier stages of neuronal differentiation than NF [1, 9].

REFERENCES