Yolk sac carcinoma, also known as endodermal sinus tumor, is a rare spontaneous neoplasm of germ cell origin in rodents, although it can be experimentally induced in rats and mice by implantation of an extraembryonic part or whole egg cylinder under the kidney capsule and by displacement of the visceral yolk sac with or without mouse sarcoma virus into the placenta after fetectomy.

Both spontaneous and induced yolk sac tumors are composed of cells mimicking a parietal and visceral yolk sac. The parietal cells were round to polygonal, contained eosinophilic droplets and were arranged in nests and cords in the eosinophilic matrix. Both the intracytoplasmic droplets and the matrix were stained positively with PAS. The visceral cells were cylindroform, and proliferated in papillary and tubular patterns and occasionally formed Shiller-Duval body-like structures. In the dissemination sites, the neoplastic cells proliferated on the surface of the various tissues and often infiltrated into deeper parts of the tissues. Immunohistochemically, both neoplastic cells were positive for α-fetoprotein and keratin, and the eosinophilic matrix was positive for laminin.

Ultrastructurally, the parietal cells had dilated rough endoplasmic reticulums, which were filled with electron-lucent laminated structures. The visceral cells had poorly to moderately developed intracytoplasmic organelles and were interconnected with desmosomes. Taken together, the present tumor was diagnosed as yolk sac carcinoma arising from the ovary and was characterized by not only high metastasis but also invasive infiltration with biphasic proliferation of the parietal and visceral cells. (DOI: 10.1293/tox.24.81; J Toxicol Pathol 2011; 24: 81–85)

Key words: Yolk sac carcinoma, ovary, highly metastatic, spontaneous, rat
Macropic findings of spontaneous yolk sac carcinoma in a rat. Dark-brownish masses in the ovaries (arrowhead) and numerous yellow-whitish nodules in the abdominal and thoracic cavities.

Histologically, both ovaries were almost completely replaced by neoplastic cells, showing similar histological pictures, and the normal ovarian tissue scarcely remained in the peripheral area of the tumor. The tumors were composed of cells mimicking a parietal and visceral yolk sac (Fig. 2A). Each type of the neoplastic cells proliferated with a characteristic growth pattern. The parietal cells were round to polygonal with a round to pleomorphic nucleus and intracytoplasmic eosinophilic droplets. These cells were arranged in nests or cords in an abundant eosinophilic matrix (Fig. 2B). Both the intracytoplasmic droplets and the eosinophilic matrix were stained intensively by PAS (Fig. 2C). Moreover, mitotic figures were not frequently detected in the parietal and visceral cells, the neoplastic cells invaded both the ovarian capsules and the blood vessels in the periovarian tissues (Fig. 2I). Moreover, the thymus and mediastinal lymph node were involved in the neoplastic cells with focal necrosis. Immunohistochemically, both neoplastic cells were clearly positive for AFP (Fig. 3A, B) and keratin (Fig. 3C, D), and the eosinophilic matrix in the parietal cells was positive for laminin (Fig. 3E).

Ultrastructurally, the parietal cells were characterized by microvilli on the cell surface and by dilated rough endoplasmic reticula (rERs) in the cytoplasm, whereas other intracytoplasmic organelles were not well developed in these cells. The dilated rERs were filled with electron-lucent homogenous, and occasionally laminated, structures (Fig. 4A). The tumor matrix was composed of similar materials to those observed in the dilated cisternae of rERs, but not to those of laminated structures. Conversely, the visceral cells had poorly to moderately developed intracytoplasmic organelles and well developed desmosomes (Fig. 4B). Collagenous fibers were noted in the matrix of the area of visceral cell proliferation.

The morphological characteristics of the present neoplastic cells were generally comparable to those of yolk sac tumors previously reported in rats and mice, while some immunohistochemical differences were pointed out between the present case and the previous ones. Namely, AFP was produced by visceral yolk sac cells in rodent yolk sac carcinoma reported previously, while parietal cells as well as visceral cells were positive for AFP in the present case. The meaning of this is obscure, and therefore, more cases and evidence is needed for discussion. In regard to immunohistochemistry for keratin, both parietal and visceral cells showed a positive reaction in the present tumor. Although there have been no available data on the immunohistochemical nature of the tumor in rodents, it is known that ovarian dysgerminoma with yolk sac components shows a positive immunohistochemical reaction for keratin as well as AFP in humans. Therefore, the present tumor may provide useful information on the immunohistochemical nature of rodent yolk sac tumors.
Fig. 2. Characteristic pictures of spontaneous yolk sac tumor in a rat. A: Ovarian tumors were composed of two types of cells mimicking a parietal and visceral yolk sac. HE stain, Bar = 500 μm. B: Parietal cells arranged in a nest and cords of cells in the abundant eosinophilic matrix. HE stain, Bar = 50 μm. C: Eosinophilic droplets in the neoplastic cells and the tumor matrix were stained positively by the PAS reaction. PAS stain, Bar = 100 μm. D: Parietal cells formed a cyst lined by goblet cells. HE stain, Bar = 100 μm. E: Visceral cells showed tubular and papillary proliferation. HE stain, Bar = 100 μm. F: Metastatic focus in the diaphragm. HE stain, Bar = 500 μm. G: Schiller-Duval body-like structures. MT stain, Bar = 50 μm. H: Trophoblastic giant cells. HE stain, Bar = 50 μm. I: Parietal cells invaded into the blood vessels. HE stain, Bar = 100 μm.
The hyaline matrix observed in the area of parietal cell proliferation showed similar characteristics to those of Reichert’s membrane from a normal embryo, in terms of morphology and staining, and the parietal cells are considered to have that contained similar materials in the dilated rERs.

Biologically, the present tumor was highly malignant, and the neoplastic cells were extensively disseminated in the abdominal cavity and also metastasized to distant organs via blood and lymphatic vessels, but less frequently. The neoplastic cells on the peritoneal surface frequently invaded into the deeper part of the parenchyma. Such highly invasive behavior with biphasic proliferation of the parietal and visceral cells is one of the characteristics of the present tumor. The primary site of the present tumor is considered
to be the right ovary, since the biggest mass was observed there. However, there still remains a possibility that the present tumor developed multicentrically in both ovaries.

Germ cell tumors derived from the ovary are classified into dysgerminoma and embryonal carcinoma. Embryonal carcinoma, a totipotential tumor, is further classified into yolk sac carcinoma or teratoma (ectoderm, mesoderm and endoderm) and teratoma (ectoderm, mesoderm and endoderm)\(^8\),\(^11\). It has been reported that inducible yolk sac carcinoma is composed of endodermal cells and contains mesenchymal, trophoblastic and mesodermal cells\(^7\),\(^12\). Furthermore, in a previous report, a small yolk sac carcinoma-like focus was detected in a large immature ovarian teratoma in a rat\(^13\). From this evidence, it is considered that the tubular and cystic structures lined by goblet cells and trophoblastic giant cells in the present tumor may have resulted from differentiation or dedifferentiation of totipotential or endodermal cells. It is important to examine various regions of the tumor because tumors like this contain several different elements.

Taken together, the present tumor was diagnosed as ovarian yolk sac carcinoma composed of both parietal and visceral components and was characterized by highly disseminated metastasis and invasive proliferation.

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**References**