

## B6C3F1 マウスに認められた悪性卵黄嚢腫瘍

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## Yolk Sac Carcinoma in a B6C3F<sub>1</sub> Mouse

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Yolk sac carcinoma or endodermal sinus tumor is a well-known tumor in human pathology [4-6]. In rodents this carcinoma has been produced experimentally by transplantation of the extraembryonic portion of an 8 or 9-day-old egg [1, 2], by serial passages of testicular teratocarcinoma [9] and by fetectomy and displacement of the visceral yolk sac to an extrauterine site [12, 13]. Spontaneous yolk sac carcinomas are seldom found in rats and mice, and the first case was reported in 1970 [8]. Stewart *et al.* [14] reported 8 cases of yolk sac carcinomas in murine uteri. More recently, Majeed *et al.* [7] described 15 ovarian yolk sac carcinomas in B6C3F<sub>1</sub> mice, which were found during a review of ovarian neoplasms covering over 40,000 B6C3F<sub>1</sub> mice in the archives of the National Cancer Institute/National Toxicology Program Carcinogenesis Bioassay Program. We encountered an ovarian yolk sac carcinoma with multiple metastases in a 75-week-old B6C3F<sub>1</sub> female mouse.

At necropsy, more than 6 ml of reddish fluid and various-sized masses or nodules were found in the abdominal cavity. The largest dark red mass measured 5 cm in diameter and was adhered to the right lateral lobule of the liver and the right kidney which was compressed and deformed. This tumor mass was encapsulated, soft and friable, and accompanied the necrotic cavity which were filled with villous structure and contained serosanguinous fluid. The second largest mass was 2 cm in diameter and occupied the right ovary. The ovary was mostly brown (necrotic) and partially whitish on the cut surface. Many other small nodules measuring up to 0.5 cm in diameter were scattered on the peritoneal surface.

On microscopic examination, the largest mass attached to the renal hilus and was found to be encapsulated with thin loose connective tissue. In the second largest mass, the tumor had replaced the original ovarian structure and was mostly

necrotic and hemorrhagic. The characteristic feature of the tumor was a predominantly eosinophilic hyaline matrix which was intensely positive to periodic acid-Schiff reaction (PAS) but negative to alcian blue staining. Generally small and uniform cells were arranged in nests, ribbons or a small acinar pattern (Fig. 1). Most of these small-sized cells were round or oval and had hyperchromatic nuclei. Occasionally polygonal or irregular-shaped trophoblastic giant cells were scattered individually throughout the matrix. The giant cells had large elliptic or bizarre-shaped nuclei with one or more prominent nucleoli (Fig. 2). The cytoplasm of both types of cells was amphophilic, granular and/or vacuolated. Sometimes there were eosinophilic cytoplasmic inclusions which were positively stained by the PAS reaction. Small-sized cells with large vacuoles assuming a signet ring cell were also present occasionally. Mitotic figures were seldom found. In the central necrotic areas of the tumor mass, only copious hyalinous substances with shadowy cells were seen. The tumor partially invaded the adjacent tissues through the thin loose capsule with an occasional vascular invasion (Fig. 2). Implantation metastases were present on the peritoneal surface of the liver, pancreas, diaphragm and mesenterium, and in the bursa of the ovary on the opposite side. Remote metastases were seen in the lung. By the peroxidase antiperoxidase method for alpha fetoprotein (AFP) using antisera of rabbit anti-mouse AFP (ICN Immuno Biologicals, Lisle, IL, USA), the cytoplasm of most tumor cells, including the giant cells, showed homogeneous reactivity (Fig. 3), but about one-fourth of all tumor cells and the hyaline matrix were negative.

The ultrastructural examination revealed the hyaline matrix of the tumor composed of homogeneous electron dense materials with partial areas of fine-lamellar structure. The neoplastic cells which were distinctly bordered by the matrix (Fig. 4) had poorly developed microvilli on surface and a few desmosomes between

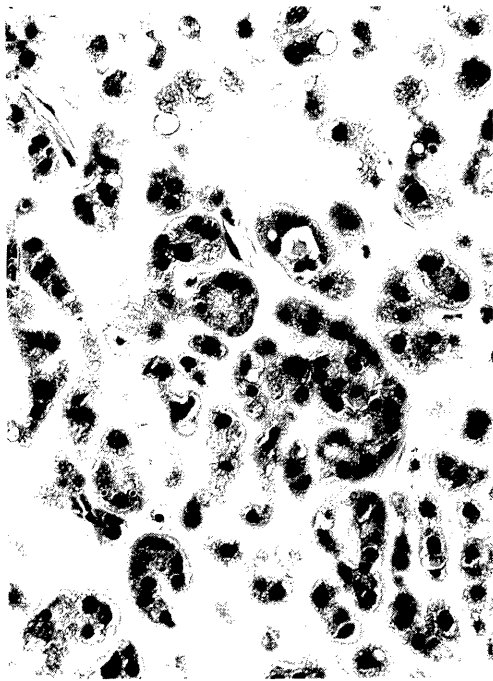


Fig. 1. Small-sized tumor cells arranged in nests, ribbons or a small acinar pattern. They are surrounded by an abundant hyaline matrix. HE stain.  $\times 250$ .

adjacent cells. Pinocytotic vesicles were rarely observed. In the cytoplasm, there were dilated cisternae of rough endoplasmic reticulum which contained a homogeneous or slightly granular moderately electron-dense material similar to the extracellular matrix (Fig. 5). Mitochondria and other organelles were few. Some tumor cells had abundant free-ribosomes and various lengthened tubular structures which were thought to be immature endoplasmic reticulum. In addition, virus-like particles resembling those described in previous reports [2, 10] were frequently observed in the cisternae of rough endoplasmic reticulum (Fig. 4). Most of them were doughnut-shaped and measured 120–180 nm in diameter. Several elongated forms consisting of two or three of those particles were also found.

The characteristic pattern of this tumor was predominantly eosinophilic hyaline matrix containing tumor cells composed of small-sized cells variously arranged and scattered trophoblastic giant cells. These findings corresponded to those from spontaneous and experimental yolk sac tumors of rodents [1, 2, 7–14], and it was



Fig. 2. A tumor thrombus within a vessel. Note the trophoblastic giant cells. HE stain.  $\times 500$ .



Fig. 3. Tumor cells including the giant cell (arrow) show intense reactivity to AFP. Immunohistochemical staining for AFP counterstained with hematoxylin.  $\times 500$ .

diagnosed as primary ovarian yolk sac tumor. The rodent yolk sac has a visceral layer and a parietal layer [10]. The parietal yolk sac cell lies on the interior surface of a thick basement membrane, Reichert's membrane [11]. Therefore, the hyaline matrix in the present case, similar to Reichert's membrane of the embryo, is considered to have been synthesized and secreted by the neoplastic parietal yolk sac cells. Trophoblastic giant cells have also been studied by some investigators [7, 11, 12, 14], and Pierce *et al.* [11] maintained that the trophoblastic giant cells originate from the exterior surface of Reichert's membrane.

By the immunohistochemical method, the tumor cells in the present case were shown to have both positive and negative reactivity for AFP. Such immunohistochemical heterogeneity may indicate that this tumor is a biphasic parietovisceral yolk sac carcinoma, for AFP is produced by the viscera as opposed to the

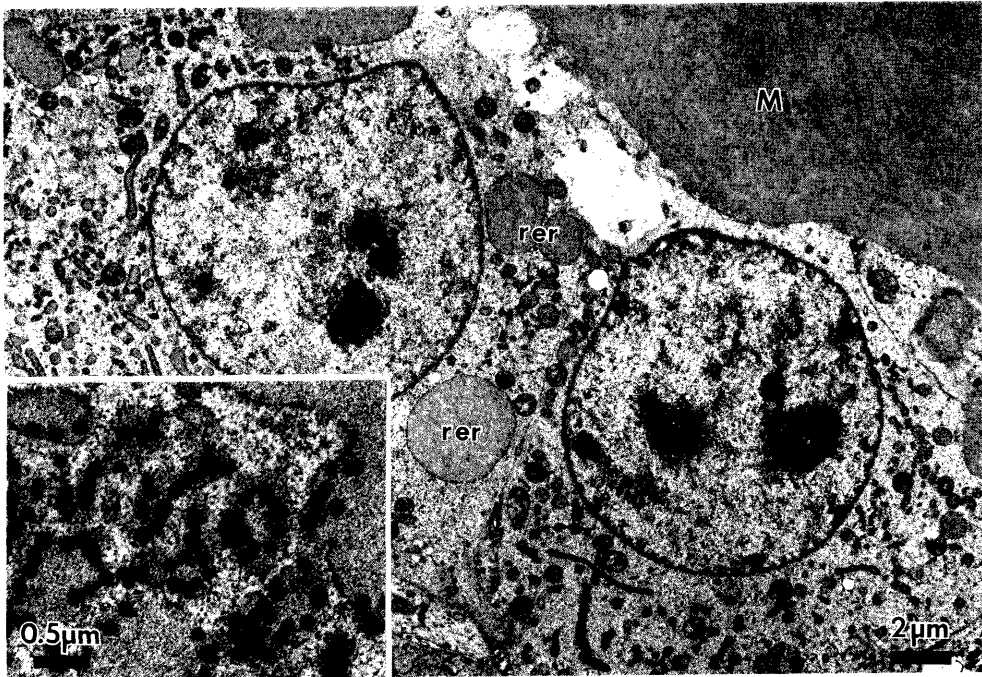


Fig. 4. Yolk sac tumor cells and electron-dense matrix (M). rer; rough endoplasmic reticulum.  $\times 4,000$ . Inset: Virus-like particles inside the cisternae of endoplasmic reticulum.  $\times 14,900$ .

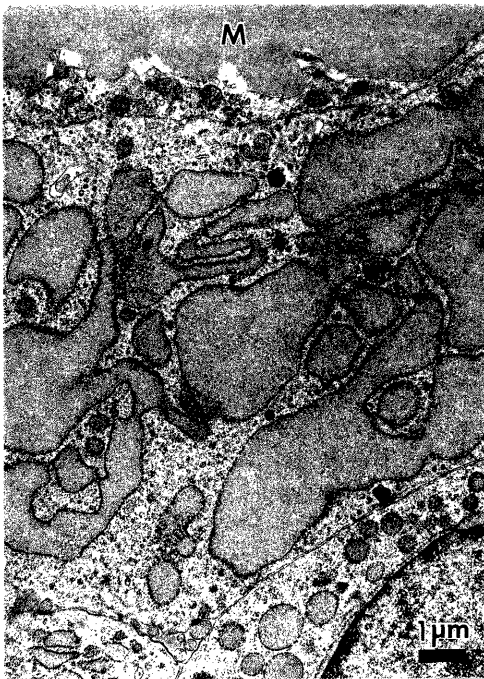


Fig. 5. Dilated cisternae of endoplasmic reticulum containing slightly granular material similar to the extracellular matrix (M).  $\times 6,850$ .

parietal yolk sac [3], Damjanov [1] distinguished two cell types, those containing AFP and those devoid of AFP, during his immunohistochemical and electron microscopic study of an experimentally produced parietovisceral yolk sac carcinoma in a rat. The immunohistochemical findings in the present study correspond to the results of his study [1].

The ultrastructural study of the tumor cells showed distended cisternae of rough endoplasmic reticulum with granular electron-dense material. This is similar to the features of an experimentally produced murine yolk sac tumor previously described [2, 10] as well as to human yolk sac tumor cells [4].

As to the virus-like particles, there is no evidence that they play any role in the development of these tumors [2], and it is uncertain whether or not these particles are true viruses for their noticeable diversity in size and form.

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要 約

B6C3F<sub>1</sub>マウスに認められた悪性卵黄囊腫瘍（短報）：勝田 修・田子 穰・山岸保彦・土谷 稔（株式会社三菱化成安全科学研究所）——卵巣原発の卵黄囊腫瘍を病理学的に検索した。光顕的にはPAS染色強陽性の豊富な硝子様基質と、その中に包埋されたような腫瘍細胞を特徴としていた。腫瘍細胞には類円形を呈する小型細胞とトロホプラスト様巨細胞が認められた。これらは、両染色で微小空胞状の細胞質とクロマチンに富む核を有していた。また免疫組織化学的にAFP陽性と陰性の細胞が認められた。電顕的には腫瘍細胞内で粗面小胞体の著しい拡張が認められた。