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Primary Carcinoid Tumor of the Testis: Immunohistochemical, Ultrastructural and DNA Flow Cytometric Study of Two Cases

Primary testicular carcinoid tumor, occupying 0.23% of testicular neoplasm, is a rare and indolent neoplasm with the potential for distant metastasis. We present two cases of primary pure carcinoid tumor of the testis. Both patients were 36 years old. Physical examination revealed testicular mass with and without tenderness. The preoperative serum levels of β-human chorionic gonadotropin and α-fetoprotein were normal and neither patient had carcinoid syndrome. The tumors measured 7.5x6x4 cm and 5.5x5x4 cm in size. Histologically, immunohistochemically and ultrastructurally, the tumors showed typical features of the carcinoid tumor. Case 1 showed extensive tumor necrosis and vascular invasion. DNA flow cytometric analysis showed aneuploidy with DNA index of 1.47 and S+G_2M of 14.0% in case 1 and tetraploidy with DNA index of 1.96 and S+G_2M of 22.1% in case 2. Both patients have been well without any signs of metastasis after operation for 24 months in case 1 and for 16 months in case 2.

Key Words : *Testis; Carcinoid tumor*

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INTRODUCTION

Carcinoid tumors mostly occur in the gastrointestinal tract, especially in the appendix, ileum and rectum, and lung. Five percent of carcinoid tumors occur in various other organs, including the thymus, esophagus, biliary duct, Meckel's diverticulum, breast, ovary, and testis (1). Testicular carcinoid tumor is extremely rare and occupies 0.23% of testicular neoplasms (2). It has been divided into three groups: primary pure testicular carcinoid tumor, carcinoid tumor occurring as a part of a teratoma, and secondary carcinoid tumor metastatic to the testis (3). In 1930, Cope described the first case of metastatic testicular carcinoid tumor from the small bowel and in 1954 Simon et al. reported the first case of primary testicular carcinoid tumor (4, 5). Since then, 71 carcinoid tumors have been reported in foreign literature, 62 of these were primary tumors and 9 were metastases from various sites (6-11). The majority of testicular carcinoid tumors are primary pure carcinoid tumors. Carcinoid tumors occurring as a part of a teratoma and carcinoid tumors metastatic to the testis are unusual. In the Korean literature, only one case of testicular carcinoid tumor was reported by Chun and Suh in 1995 (12).

We report two cases of primary pure testicular carcinoid tumors with immunohistochemical, ultrastructural, and DNA flow cytometric analyses.

MATERIALS AND METHODS

All specimens were fixed in 10% formalin for 24 hours, processed routinely for light microscopic examination. The immunohistochemical stain was performed using a common avidin-biotin-peroxidase complex method. Briefly, formalin-fixed, paraffin-embedded sections were rehydrated and incubated overnight at 4℃ with the diluted primary antibodies. Used primary antibodies were neuron specific enolase (NSE, Dako corp., Carpinteria, CA, U.S.A., 1:50), chromogranin (DAKO, 1:20), cytokeratin (DAKO, AE1/AE3, 1:50), synaptophysin (Zymed laboratories Inc., CA, U.S.A., 1:50), placental alkaline phosphatase (DAKO, 1:50). Biotinylated anti-mouse and rabbit IgG (DAKO) and a complex of peroxidase conjugated streptavidin (DAKO) were added in sequence, and they were reacted with 3-amino-9-ethylcarbazole and then counterstained with hematoxylin. For ultrastructural study, formalin-fixed tumor tissue was fixed in 2.5% buffered glutaraldehyde and processed using standard techniques. Thin sections were stained with uranyl acetate and lead citrate and examined with an electron microscope of Hitachi 600. DNA analysis

using a FACScan flow cytometer (Becton Dickinson, U.S.A.) was from a representative block of formalin-fixed, paraffin-embedded tumor tissue. The selected block contained at least 15% of tumor cells. Preparation of nuclear suspensions was performed using a standard method.

CASE HISTORY

Case 1

A 36-year-old man complained of right lower quadrant pain radiating to the genital area for 3 days. Physical examination revealed a round, firm, and tender mass in the right testicle. Ultrasound examination of the scrotum revealed a 10×9 cm-sized solid mass with heterogeneous echogenicity. A vague calcific shadow was noted within the mass. The epididymis was normal in contour. The left testis was normal in appearance. Testicular scan with Tc-99 pertechnetate (10 mCi) demonstrated increased blood flow to the right testicle. Neither serum beta-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (α-FP) was elevated. Urinary 5-hydroxy-indole acetic acid was normal. Symptoms related to carcinoid tumor were not present. Chest X-ray, intravenous pyelogram, abdominal ultrasonogram, and abdominal CT failed to demonstrate any lesion. A right radical orchiectomy was performed. The patient has been well without metastasis for 24 months after operation.

Case 2

A 36-year-old man was admitted for a painless, slow-growing left testicular mass for 7 years. Physical examination revealed a non-tender and firm mass in the left testicle. Serum β-hCG and α-FP were within normal limits. Chest X-ray showed paracicatricial emphysematous change and bronchiectasis in the left lung. Symptoms related to carcinoid tumor were not present. A left radical orchiectomy was performed. The patient has remained well for 16 months after operation.

PATHOLOGIC FINDINGS

Gross findings

In case 1, the right testis was entirely replaced by the tumor, measuring 7.5×6×4 cm in size. The tumor was well circumscribed. The cut surface showed extensive necrosis with yellowish-gray in color and spotted hemorrhage, except for a yellowish-brown, viable and solid area in the upper portion. The epididymis and spermatic cord were unremarkable (Fig. 1). In case 2, the left testis was almost totally replaced by a yellowish-brown, homogeneous and solid mass with firm consistency (5.5×5×4 cm). There was neither necrosis nor hemorrhage. The epididymis and spermatic cord were unremarkable. The cystic space between the visceral and parietal tunica vaginalis was filled with clear serous fluid (Fig. 2).

Light microscopic findings

The tumors were well demarcated from the surrounding parenchyma. They showed an insular, acinar and trabecular patterns separated by fine fibrous bands (Fig. 3). The tumor cells were relatively uniform having oval to round nuclei with prominent chromatin clumping along the nuclear envelope and eosinophilic granular cytoplasm (Fig. 4). There was some variation in the nuclear size. There were occasional mitotic figures, but atypical mitotic figure was not observed. No teratomatous elements were found in both. Extensive tumor cell necrosis and hemorrhage, and occasional vascular invasion by tumor cells were noted in case 1 (Fig. 5). The residual testicular parenchyma around the tumors was compressed and atrophic. The tunica albuginea was thickened by fibrosis, while the epididymis and spermatic cords were unremarkable.

Immunohistochemical findings

Immunohistochemical stainings for cytokeratin, NSE,

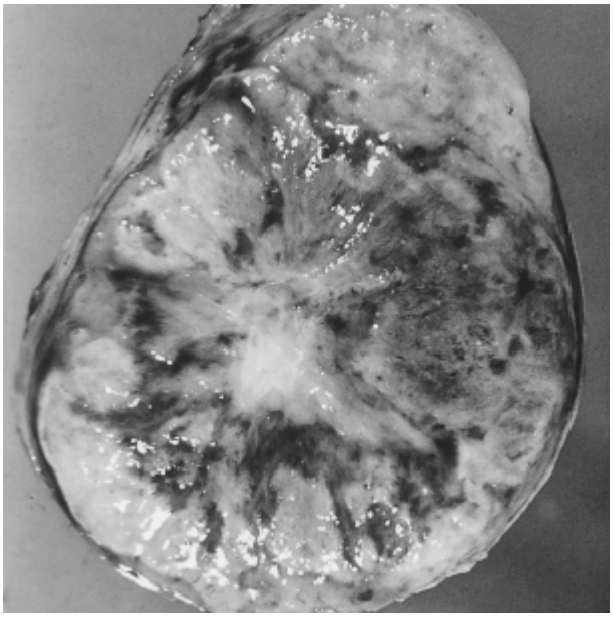

Fig. 1. The testis is totally replaced by a well circumscribed mass with extensive yellowish-gray necrosis and spotted hemorrhage, except for yellowish-brown, viable and solid area in the upper portion (Case 1).

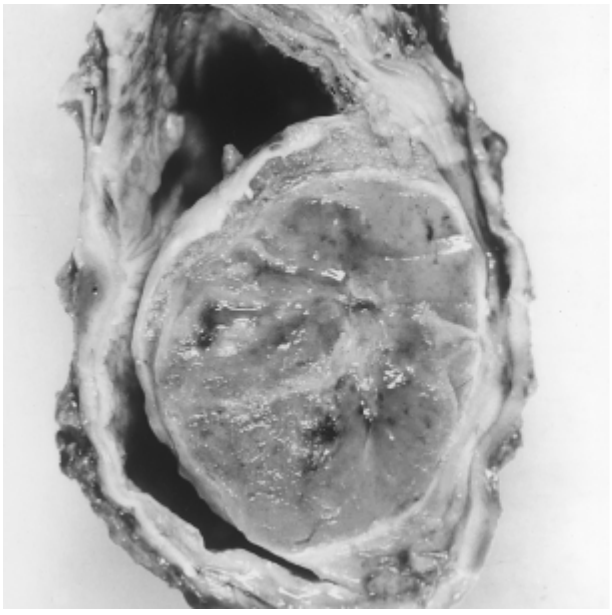

Fig. 2. The testis is nearly replaced by a yellowish-brown solid mass without necrosis and hemorrhage (Case 2).

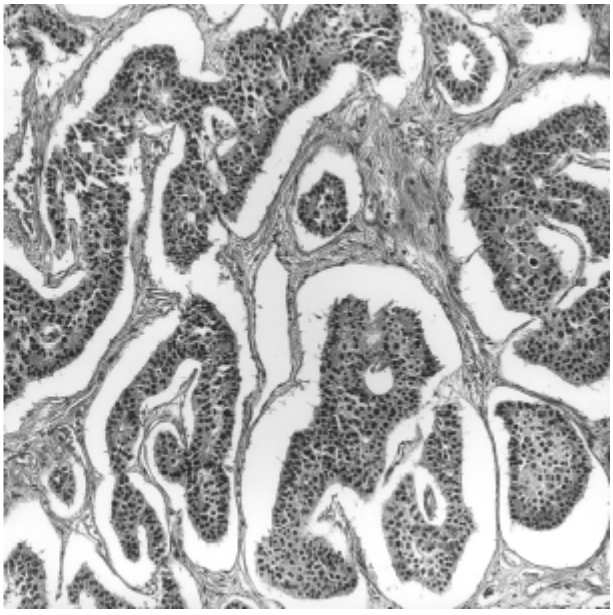

Fig. 3. Multiple solid nests separated by fine fibrous bands (H & E, ×100).

chromogranin, and synaptophysin showed diffuse positivity of the tumor cells in case 1. In case 2, cytokeratin and NSE showed diffuse positivity of the tumor cells, but synaptophysin and chromogranin showed focal positivity. Placental alkaline phosphatase was negative in both cases.

Electron microscopic findings

In case 1, the tumor cells were ovoid to polygonal. Nuclei were ovoid and revealed heterochromatin along the nuclear envelope as well as within the nuclei. In the cytoplasm,

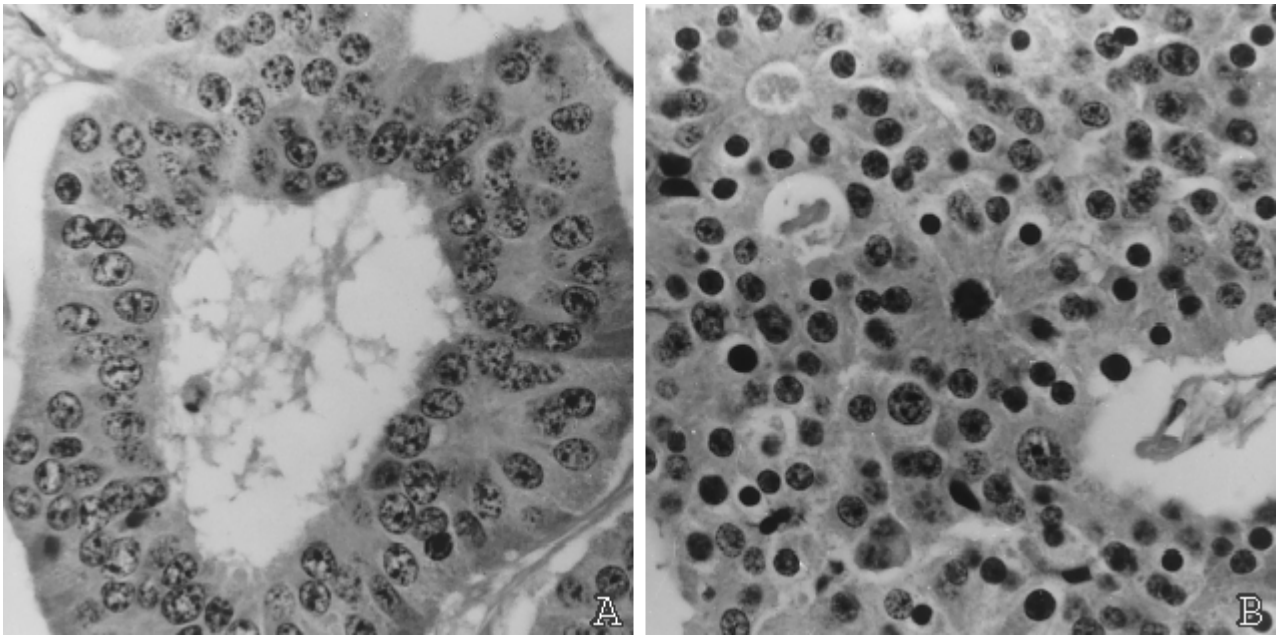

Fig. 4. Tumor cells have relatively uniform oval to round nuclei, prominent coarse heterochromatin, and eosinophilic granular cytoplasm (A: H & E, ×200, Case1, B: H & E, ×400, Case 2).

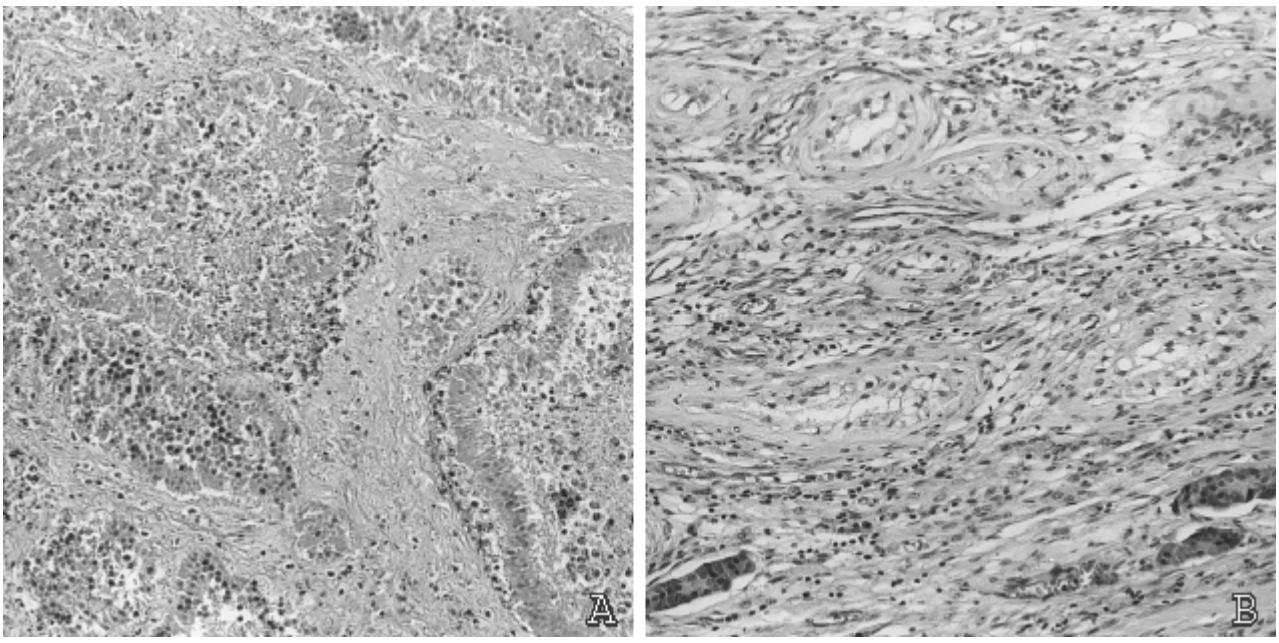

Fig. 5. Extensive tumor necrosis (A) and vascular invasion (B) in Case 1 (H & E, ×100).

numerous various sized, oval to round, electron-dense granules were found. They had a central uniform dense core with a delimiting membrane and a thin peripheral halo (Fig. 6).

The tumor cells of case 2 revealed degenerated change. Most cytoplasmic organelles were washed out and only a few rough endoplasmic reticulum remained. Neurosecretory granules were not found which may explain the focal nature of synaptophysin and chromogranin immunoreactivity. Nuclear morphology was similar to as in case 1 (Fig. 7).

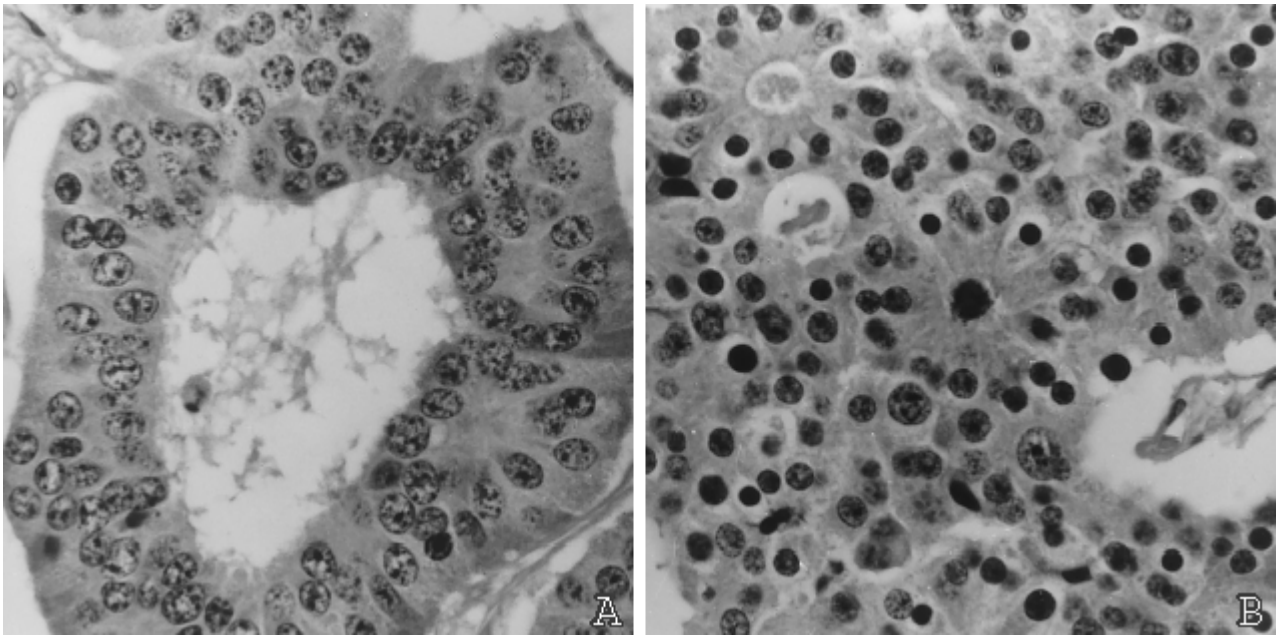

Fig. 6. Electron microscopy of case 1 reveals numerous elec-tron dense neurosecretory granules in the cytoplasm and an oval to round nucleus with prominent heterochromatin (inset: neurosecretory granules) (Uranyl acetate and lead citrate ×600).

Fig. 7. Electron microscopy of Case 2 reveals heterochromatin along the nuclear envelope as well as in the central area of nuclei and a few rough endoplasmic reticulum in the cytoplasm (Uranyl acetate and lead citrate ×23,000).

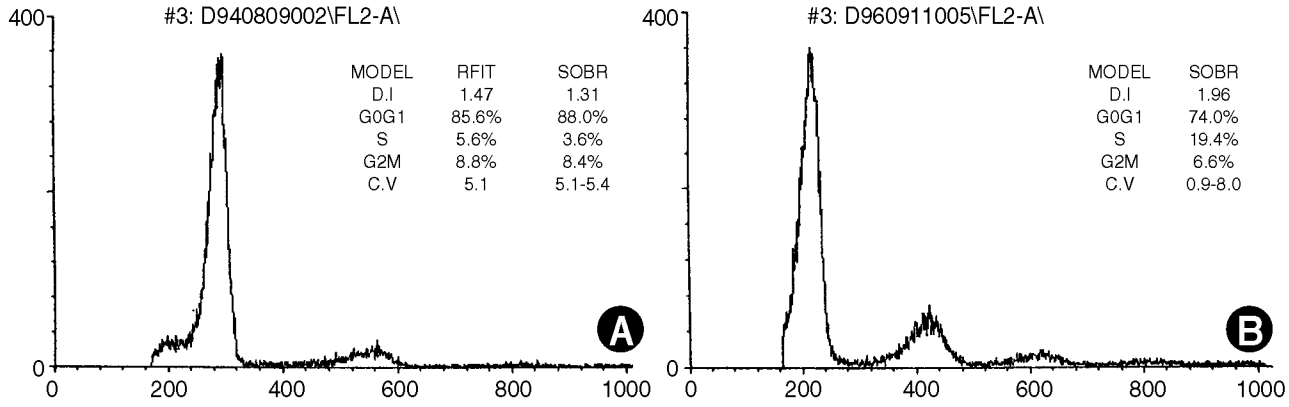

Fig. 8. Aneuploidy with DNA index of 1.47 in Case 1 (A) and tetraploidy with DNA index of 1.96 in Case 2 (B) by DNA flow cytometry.

DNA flow cytometric findings

Case 1 revealed aneuploidy with DNA index of 1.47 and S+G_2M of 14.0% and case 2 revealed tetraploidy with DNA index of 1.96 and S+G_2M of 22.1%. (Fig. 8).

DISCUSSION

Carcinoid tumor is a extremely rare neoplasm of the testis. It is usually well-circumscribed, solid, firm, and yellow to brown. Some reported cases showed small cystic or necrotic foci (13, 14). Clinical presentation is a testicular enlargement or a discrete testicular mass, more commonly in the left. Testicular pain and symptoms related to carcinoid syndrome were present in 12.3% of cases. The duration of symptoms ranges from less than 1 month to 240 months (mean=37.5 months) (6). The age ranges from 10 to 83 years with the majority being in their 5th to 7th decade. The peak age is older than that of most primary germ cell tumors (1). Testicular carcinoid tumors arising in teratoma are rare, unlike ovarian carcinoid tumors which are often associated with teratoma (5, 15, 16). Ovarian carcinoid tumor presents carcinoid syndrome in one-third of the cases despite the absence of metastases (17-19). The reason is that the blood flow from the ovaries goes directly into the systemic circulation (18). Both 5-hydroxytryptamine (serotonin) and substance P have been associated with carcinoid syndrome. The lack of carcinoid syndrome in most testicular carcinoid tumors is thought to be that these hormones may be secreted in an inactive form, or that they are secreted at insufficient levels to cause the clinical syndrome, or that they are rapidly inactivated in the circulation (20).

The ultrasound appearances of testicular carcinoid are not specific and show a well defined hypoechoic intratesticular mass containing dense calcification with the differential diagnoses including testicular germ cell tumors, particularly teratoma and embryonal carcinoma, Sertoli cell tumor, epidermoid cyst of the testis and tuberculous epididymo-orchitis. Therefore, carcinoid tumor should be considered in diagnosis of a testicular mass containing calcifications (1, 3, 13, 21-26).

The histogenesis of primary testicular carcinoid tumor is unclear. The possible origins are the differentiation of the toti-potential germ cells to argentaffin-like cells or the development of a monodermal teratoma without other teratomatous elements (1, 14, 27).

Zavala-Pompa et al. analyzed 63 previously reported cases and their three cases of testicular carcinoid tumors (6). Fifty-seven cases were testicular in origin and 9 were metastatic tumors from extratesticular sites. Of the 57 primary testicular carcinoid tumors, 43 (75.4%) were the pure carcinoid tumors and 14 (24.6%) were carcinoid tumors associated with mature teratoma (mixed carcinoids). Six patients (10.5%) subsequently developed metastases and most of them showed a larger tumor of pure carcinoid type (28-30). Fifty percent of the carcinoid tumors with metastases had carcinoid syndrome, compared with 5.6% of the carcinoid tumor without metastases. Based on the reviewed data, they stated that the features associated with a malignant course were tumor size (average size 7.3 cm) and the presence of carcinoid syndrome. Tumor necrosis was found in 8 neoplasms, only one of them developed metastasis. Vascular invasion or tunica albuginea invasion by the tumor was identified in 10 tumors and only one of them developed metastasis (6).

The treatment of choice for testicular carcinoid tumor is radical orchiectomy. No further postoperative therapy is considered to be necessary. For the carcinoid tumor as a part of a teratoma, the treatment is the same as for testicular teratoma and the prognosis depends on the type of teratomatous elements and the stage of the tumor (14). Serial estimations of serum serotonin and its degradation products in the urine, mainly 5-hyroxy-indole acetic acid, are considered to

be very useful for follow-up of the patients (9).

In testicular carcinoid tumor, DNA ploidy pattern by flow cytometry revealed aneuploidy with near-diploidy DNA index (6). To date, the correlation between the DNA index and the clinical course in testicular carcinoid is not clear. In our cases, case 1 with extensive necrosis and vascular invasion revealed aneuploidy. Case 2 had neither necrosis nor vascular invasion but revealed tetraploidy. Therefore, long-term follow-up seems to be necessary for our cases to determine the significance of DNA abnormalities. The clinical course and prognosis of primary testicular carcinoid tumors are indolent and good, but the carcinoid tumors metastatic to the testis are not. A careful clinicopathologic correlation is required to determine whether the tumor is primary or metastatic.

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