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Seminoma With Syncytiotrophoblastic Giant Cells

A Special Form of Seminoma *

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Summary. Testicular seminomas may occur in various forms, of which the classical and spermatocytic are distinct, the anaplastic or atypical seminomas, however, less clearly defined. Lately, a separate group of particular clinical significance, comprising seminomas with syncytiotrophoblastic giant cells (STGC), has been specified. Although this type of seminoma had been recognized morphologically long ago, recent investigations have shown its ability to secrete HCG, a fact that raises serious difficulties in its differential diagnosis with combined seminomas and choriocarcinomas. Two cases of seminomas with STGC are presented and pertinent clinical and morphologic problems discussed.

Key words: Seminoma – Syncytiotrophoblastic giant cells – Human chorionic gonadotropin (HCG).

Introduction

Of all testicular germ cell tumors, seminomas represent the most frequent and most clearly defined form. Subject to controversy, however, are incidence, differentiation and clinical implication of some seminoma subgroups. The *classical seminoma* is characterized by large nests of relatively monotonous tumor cells with abundant clear cytoplasm and large, roundish nuclei containing coarsely dispersed chromatin. Other typical features include interstitial lymphocytic and plasmacytic infiltrates and lymphoid follicles, while granulomas with epitheloid and giant cells of the Langhans type are not infrequent.

An equally characteristic group, the *spermatocytic seminoma*, was first distinguished by Masson (1946). Its cytologic aspect is considerably more unruly:

* Dedicated to Professor E. Uehlinger on the occasion of his 80th birthday

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large or giant tumor cells are found intermingled with smaller elements reminiscent of the various stages of spermatogenesis, a feature that led to the tumor's name. Interstitial infiltrates and granulomatous reaction are absent. According to Thackray and Crane (1976), the mean age of patients with spermatocytic seminoma is 50 years, but only 41 years for patients with typical seminomas. In Mostofi and Price's series (1973), the spermatocytic group accounts for 9% of all seminomas in patients over 50 years, while Thackray and Crane (1976) cite their incidence as 3.7% of seminomas in all age groups. In spite of the diverse cellular composition, the prognosis of spermatocytic seminomas is quite favorable, and metastases are the exception rather than the rule.

The so-called *anaplastic or aggressive seminomas* (Mostofi and Price, 1973) are less clearly defined and most probably correspond to Thackray and Crane's (1976) atypical seminomas. In contrast to typical seminomas, these tumors display a degree of cellular and nuclear atypia that may render their distinction from embryonal carcinomas of the testis quite difficult. Round cell infiltrates are sparse and a granulomatous reaction may be lacking. According to Mostofi and Price (1973), the mitotic activity is of prime importance in separating the anaplastic from other seminoma groups: three or more mitoses per high power field indicate the anaplastic form, a criterion that von Hochstetter (1979) has shown to be unreliable. Anaplastic seminomas imply a significantly worse prognosis than spermatocytic or even typical seminomas. That their histologic distinction is complex is reflected by the disparate figures of incidence given in large published series. Thus Mostofi and Price (1973) found that 10%, Thackray and Crane (1976) that 3% of their pure seminomas were anaplastic.

A fourth group of seminomas which merits particular attention is one that has been described for quite some time, but has been recognized just recently as a separate clinical form. It is constituted by seminomas with giant cells, not of the type found often in association with granulomatous reactions, but of the *syncytiotrophoblastic type*. Dixon and Moore had indicated in 1952 the relatively frequent occurrence of syncytiotrophoblastic giant cells (STGC) in otherwise typical seminomas. The authors cited an incidence of 14% among seminomas and drew attention to the intimate association between STGC and vascular channels in an illustration later reprinted by Mostofi and Price (1973). Syncytiotrophoblastic giant cells have aroused the curiosity of pathologists for some time; earlier works are referred to in the discussion. The peculiarity and clinical significance of this type of seminoma, however, were recognized only through the investigations by Kurman et al. (1977) and Javadpour et al. (1978). The authors were able to demonstrate high serum human chorionic gonadotropin (HCG) levels in patients suffering from such seminomas, while ruling out the suspected presence of choriocarcinomas in most cases. It is precisely this difficulty in the differential diagnosis that demands scrupulous attention, since combined seminomas and choriocarcinomas share with pure choriocarcinomas a similarly sombre prognosis, while seminomas with STGC do not.

We had the occasion to study two cases of seminomas with STGC. Our observations are presented in the following, and clinical and morphologic problems discussed.

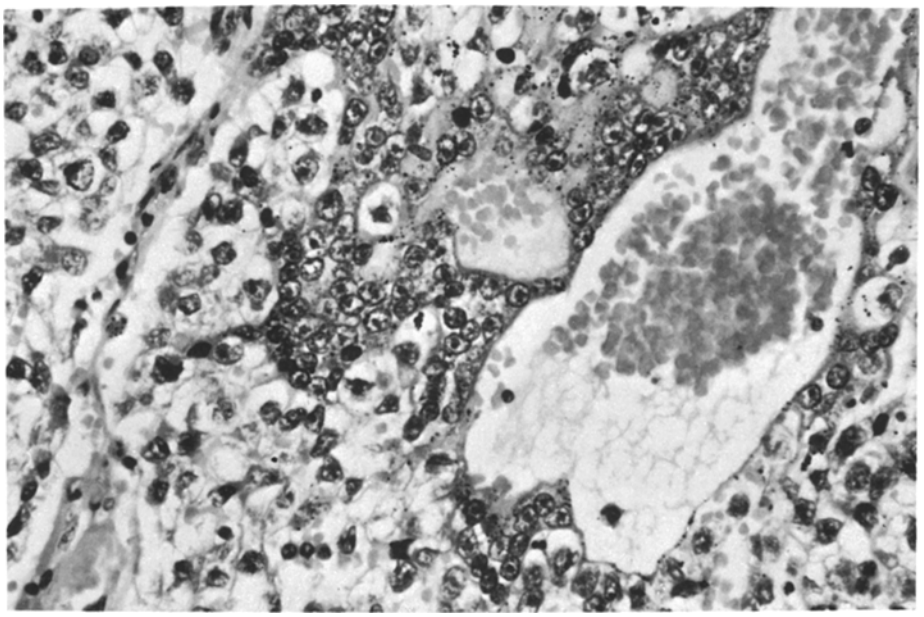

Fig. 1. Seminoma with syncytiotrophoblastic giant cells around vascular spaces (case 1, HE, ×350)

Case Reports

Case 1

A 27-year-old man without previous medical history is involved in a fight in which he suffers lacerations to the lower lip and buccal mucosa, as well as blunt trauma to the scrotum. Physical examination reveals a right testis twice the normal size. Six months later, the swelling is found to persist. Serum levels of both AFP and HCG are elevated at 20 ng/ml and 0.33 IU/ml, respectively. The suspicion of a testicular neoplasm leads to prompt scrotal exploration, where a testis markedly enlarged by tumor tissue is found and removed (Prof. G. Mayor, Urology Clinic, University Hospital, Zürich). The patient is submitted to postoperative radiation therapy to inguinal and para-aortic fields. There were no metastases. On follow-up 3 weeks and 3 months postoperatively, the patient is free of complaints. On both occasions serum AFP levels are within normal limits and serum HCG is negative.

The surgical specimen (HZ 30551/78) consists of a testis measuring $8 \times 6 \times 6$ cm. The tunica albuginea is intact and the epididymis and spermatic cord are grossly free of tumor. Nearly the entire testis, however, is replaced by a homogeneous, yellowish-white tumor mass with centrally hemorrhagic areas. Microscopic examination reveals typical seminomatous tissue with scanty lymphoplasmacytic infiltrates. Occasional areas are populated by giant cells reminiscent of syncytiotrophoblasts lining vascular channels in an endothelial-like fashion. They contain countless, partly overlapping vesicular nuclei (Fig. 1). Cytotrophoblastic elements and other teratomatous formations are absent. In order to rule out the presence of choriocarcinoma, numerous additional tissue blocks were prepared. Although only seminoma was found, it was repeatedly observed, however, that only areas with circumscribed petechiae were the site of STGC, while those with diffuse hemorrhagic suffusion were not. The epididymis, spermatic cord, and two inguinal lymph nodes were free of tumor.

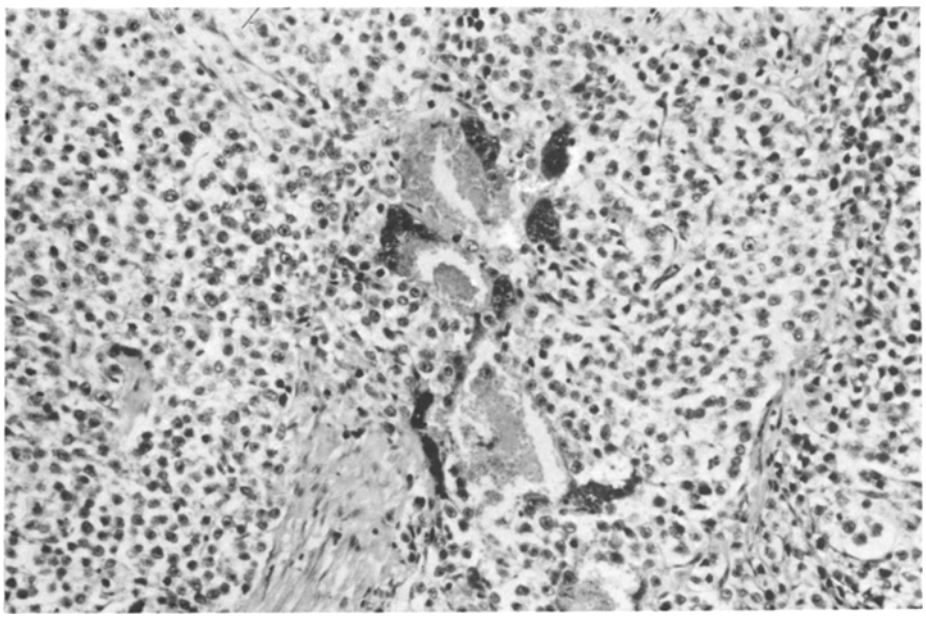

Fig. 2. Seminoma with syncytiotrophoblastic giant cells. Typical perivascular configuration (case 2, HE, ×150)

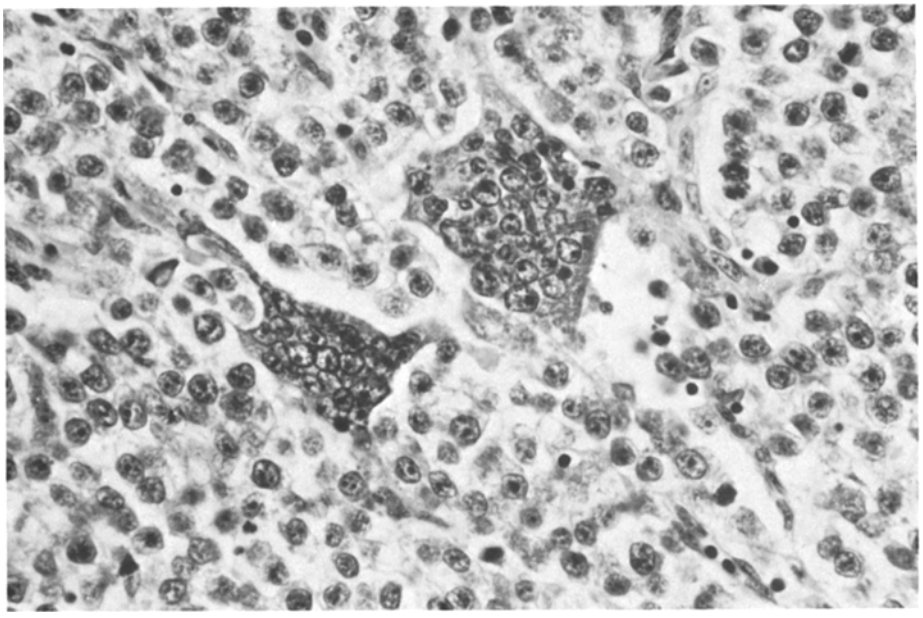

Fig. 3. Typical syncytiotrophoblastic giant cells in a seminoma (case 2, HE, ×350)

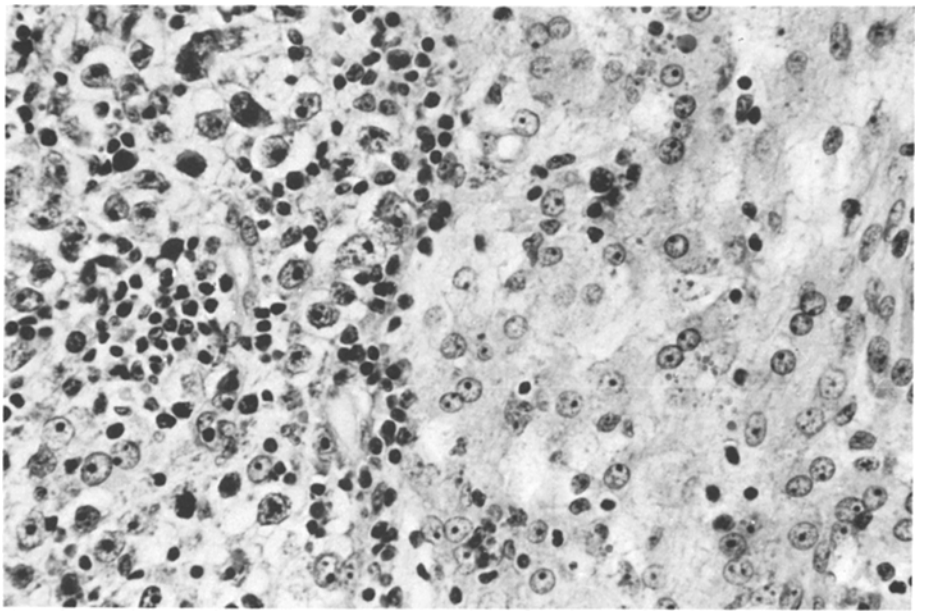

Fig. 4. Leydig cell hyperplasia (right) in the tumor-adjacent testicular tissue (case 2, HE, ×350)

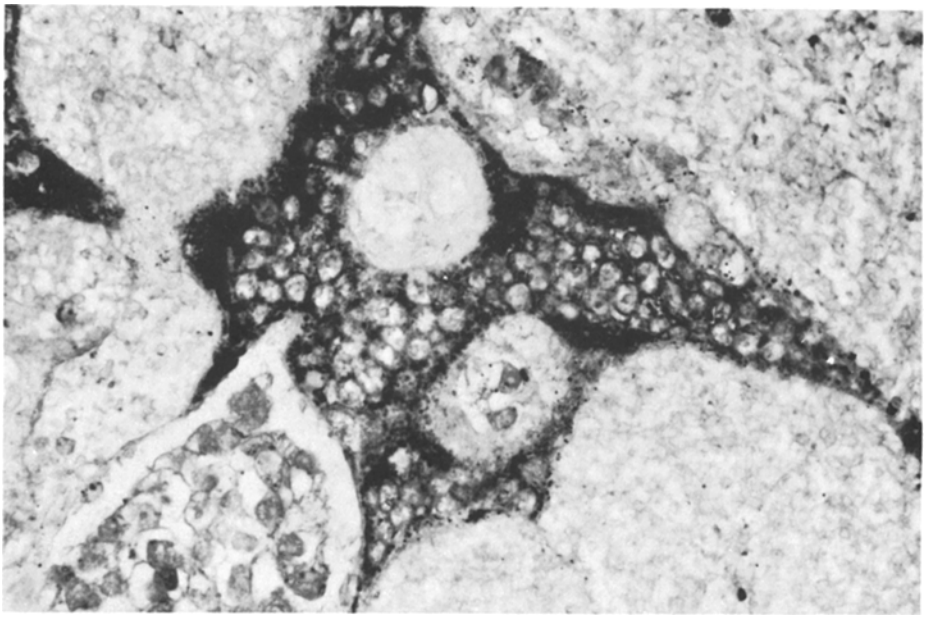

Fig. 5. HCG positive syncytiotrophoblastic giant cell following peroxidase immunohistochemical staining (case 1, ×350)

Case 2

A 25-year-old man with a rapidly increasing right testicular mass is admitted to surgery. Serum AFP levels are negative pre- and postoperatively, while HCG assays in 24 h urine collections of 2,600 and 3,600 IU correspond to levels normally encountered in pregnancy. Although no metastatic lesions are demonstrable on lymphangiography, the patient receives postoperative radiation therapy to inguinal and para-aortic fields. A chest X-ray is unremarkable. On two occasions, 3 and 15 months after orchiectomy, HCG levels in 24 h urine collections are below 1,000 IU. On the last follow-up, $1^1/_2$ years after surgery, the patient is free of complaints.

The orchiectomy specimen (BW 5643/77), measuring 8 cm in greatest diameter, is taken up almost entirely by brownish tumor tissue. Histologic examination reveals a widely necrotic seminoma containing perivascular foci of STGC (Figs. 2, 3), similar in aspect to those of case 1. In the adjoining parenchyma there is pronounced Leydig cell hyperplasia (Fig. 4). Epididymis and spermatic cord are free of tumor. Electron microscopic studies were done in case 1 but yielded insufficient results, due to inadequate fixation. Peroxidase immunohistochemical technique was applied to both cases with positive results (Fig. 5).

In summary, the tumor of both cases was a typical seminoma comprising foci of variably abundant STGC, whose association with dilated vascular channels was particularly conspicuous. The discrete, punctate hemorrhages in the otherwise unremarkable, though in part hemorrhagically suffused seminoma in the first case, indicated on gross examination the localization of STGC groups. In these giant cells HCG could be demonstrated immunohistochemically by the peroxidase method. In both cases, HCG values were abnormal, whereas AFP levels were minimally elevated only in case 1 prior to surgery. Both patients received postoperative radiation therapy and are free of complaints on 6 and 20 months follow-up examinations.

Discussion

Seminomas may occur in combination with choriocarcinomas, any other type of teratoma, embryonal carcinomas or with so-called yolk sac tumors. Combined tumors of this sort will not be treated here. Nor does the problem of reactive giant cells found in association with relatively frequent granulomatous formations in seminomas pertain to the present discussion. It is rather the presence of tumor giant cells of the syncytial type in otherwise pure seminomas that is the subject of our attention.

Seminomas with syncytial giant cells have been known to exist for some time. It is likely that case 124 in the monograph by Chevassu (1906) corresponds to such a tumor, although unfortunately no illustration accompanies it. Nevertheless, the author describes a typical seminoma, adding: "Beaucoup de cellules néoplasiques présentent des signes de dégénérescence; on les voit alors s'agglomérer de façon à constituer de très nombreuses cellules géantes, ou des traînées plasmodiales. Ces agglomérations de cellules à forme syncytiale se font toujours au contact des vaisseaux. Sur des coupes en série, on arrive toujours à reconnaître que les vacuoles remplies de sang que l'on rencontre dans certaines cellules géantes ne sont que des diverticules des vaisseaux voisins. Il semble que ces vaisseaux bourgeonnent au contact des amas néoplasiques et transforment à leur contact ces cellules en vernis syncytial; inversement, il est possible que

ce soient, au contraire, les amas syncytiaux qui, se désagrégeant au contact des vaisseaux, permettent à ceux-ci de déverser leur sang dans des cavités ainsi préformées".

Chevassu (1906) interprets the lesion as a "placentoma", i.e. a choriocarcinoma. The fact that the patient in question, however, remained free of metastases, renders the diagnosis of choriocarcinoma unlikely. Particularly demonstrative illustrations of a seminoma with STGC are given by Dixon and Moore (1952) – a picture that reappears in Mostofi and Price's second edition of the same work (1973) – and by Thackray and Crane (1976). While the four first mentioned authors speak of syncytiotrophoblastic giant cells, Thackray and Crane (1976) term them syncytiotrophoblast-like tumor giant cells. All authors point out the cells' close association to blood vessels. To quote Thackray and Crane: "Giant cells tend to be close to small blood vessels, and an appearance suggestive of bridging of the vessel wall with consequent hemorrhage is occasionally seen". This peculiar relationship between giant cells and vessels is confirmed by our own observations and seems to be so characteristic as to aid in the search for giant cells in seminomas. In fact, in our extensive subsequent examination of the tumor bulk in case 1, hemorrhagic foci invariably indicated the localization of STGC. It is thus advisable to scrupulously search for small, discrete hemorrhages in all cases of seminomas, lest STGC be missed.

The figures pertaining to the incidence of STGC in seminomas vary widely. Dixon and Moore (1952) quote 14%, Thackray and Crane (1976) 6%, while Wurster (1976) found but a single such case among 50 seminomas (2%). Our own material of 38 pure seminomas within the last two years, examined with particular scrutiny for the presence of such giant cells, holds only the two presented cases. Our incidence of 5.6% thus coincides with that of Thackray and Crane (1976).

The association of elevated levels of gonadotropins with apparently pure seminomas has been known for some time as well. Hobson (1965), for instance, describes high HCG levels in the urine of 8 patients with seminomas, assuming the pathologist's failure to recognize occult choriocarcinomas, rather than suspecting a particular type of seminoma. Since 7 of the 8 patients did poorly, the author's assumption may have been well founded, but one patient survived. Heyderman and Neville (1976) and Kurman et al. (1977) were able to demonstrate the presence of HCG in these giant cells of seminomas by the use of immunochemical tissue stains, as Pierce and Midgley (1963) had done in STGC of choriocarcinomas in male and female patients years before. In a prospective study involving 130 seminoma cases, Javadpour et al. (1978) found markedly elevated serum levels of beta-HCG in 11 patients. Subsequent histologic examination revealed the additional presence of choriocarcinoma in one of the 11 cases. In another patient with voluminous metastases, HCG levels dropped to normal after orchiectomy, surgical debulking of the metastases, and radiation therapy; a combined tumor, however, could not be ruled out with certainty. In the remaining 9 cases with elevated serum HCG levels, histologic examination revealed only seminoma with STGC in which HCG could be localized by immunoperoxidase tissue stains. In these patients, serum HCG dropped to normal levels following radiation therapy. Obviously, this particular type of tumor,

characterized by the association of seminomatous cells and STGC does not correspond to the combined seminoma and choriocarcinoma.

The prognostic significance of seminomas with STGC remains unclear. Although Thackray and Crane (1976) found a significantly worse survival rate in seminoma patients with tumor giant cells than in those without, their numbers are too small to be statistically significant. In their published series of 15 patients, comprising combined tumors, i.e. seminomas and trophocarcinomas – a term the authors reserve for embryonal carcinomas – Friedman and Pearlman (1970) present illustrations that may well depict seminomas with STGC. Additional cases in the literature, such as a few of the so-called pseudoseminomas (Schnyder, 1951, 1952; von Albertini and Schnyder, 1951; von Albertini, 1974), in which histologically seminoma-like tumors were associated with elevated serum HCG levels, may belong to our group in question. These authors describe a particularly aggressive clinical course, however, and consider the tumors to be seminoma-like embryonal carcinomas. Thus, the prognosis of seminomas with STGC is as yet uncertain.

The differential diagnosis of these tumors is of prime significance. Their histologic confusion with combined seminomas and choriocarcinomas and vice versa is understandably easy and carries a high risk, as an observation by Javadpour et al. (1978) clearly demonstrates. The diagnosis of seminoma with STGC should be made with extreme circumspection and is, in fact, confirmed only by the subsequent clinical course. Moreover, these tumors are of great theoretic interest since they suggest a close relationship between seminomas and teratomas. They raise the question of an unusual association in an incompletely developed combined tumor, or even the possibility that seminomatous cells may give rise to STGC. Since syncytial giant cells are capable of elaborating other hormones, e.g. human placental lactogen (HPL), the possibility that seminomas with STGC may secrete other hormones must seriously be considered. In this connection, it is of particular interest that Currie et al. (1966) and Porteous et al. (1968) were able to demonstrate by immunochemical methods the presence of a growth hormone-like substance, which they termed human placental factor (HPF), in syncytial giant cells of various testicular neoplasms.

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