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The significance of giant cells in human testicular seminomas

A clinico-pathological study

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Summary. In order to study the nature and significance of various giant cells encountered in seminomatous tumors of the testis, we reviewed the morphology of 243 consecutive pure seminomas and 107 combined (mixed) tumors, as well as the long term clinical follow-up in 26 patients. Giant cells were grouped into histocytic or neoplastic ones and the latter subtyped according to morphologic and immunocytochemical characteristics. Neoplastic giant cells were found in 34.6% of all pure seminomas and in 11.2% of all combined tumors, i.e. twice as often as histocytic giant cells in either tumor group. The various types of neoplastic giant cells were found alone or in combinations with other types. Giant cells capable of elaborating B-HCG were seen in 19.3% of all pure seminomas and in 9.3% of seminomatous components of combined tumors. These incidences argue strongly against a trophoblastic element infiltrating a seminoma from a concomitant occult choriocarcinomatous focus. Large mononuclear giant cells, seen in spermatocytic seminomas, were observed in 15.6% of all pure seminomas, particularly in combination with B-HCG producing giant cells. Another type, characterized by marginated nuclei and eosinophilic cytoplasm were invariably part of a mononuclear cell population of similar features and encountered focally in 9.1% of all pure seminomas.

Clinical follow-up, particularly in cases with B-HCG positive giant cells, revealed that treatment as for conventional seminomas at an early stage at least is followed by an excellent course.

Key words: Seminoma – Giant cells – Syncytiotrophoblastic giant cell – B-HCG

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Introduction

Giant cells are a frequent finding in testicular germ cell tumours, particularly in the non-seminomatous components. Among them, the syncytiotrophoblastic giant cell (STGC) has been the focus of considerable attention. It is the single most characteristic signature of trophoblastic tumors, provided additional morphological criteria are met (von Hochstetter and Hedinger 1982), and the production site of human chorionic gonadotropin (B-HCG), a sensitive tumour marker of particular value in surveying treatment response and clinical course.

A variety of giant cells also occur in pure seminomas and in seminomatous components of heterogeneous germ cell tumours. The foreign body, Langhans, or histiocytic giant cell is typical of the occasional granulomatoid stroma reaction seen in some cases. Tumour cells several times the size of the usual seminoma cell are at times encountered, especially in spermatocytic seminomas. Moreover, the occurrence of STGC in otherwise typical seminomas has been acknowledged for some time (Chevassu 1906; Dixon and Moore 1953; Mostofi and Price 1973; Thackray and Crane 1976) and recently led to the formulation of a distinct clinico-pathological entity (Kurmann et al. 1977; Javadpour et al. 1978; Hedinger et al. 1979). Its incidence and prognostic significance, however, have remained unclear and controversial (Javadpour et al. 1978; Mauch et al. 1979).

Hence, we undertook to review all cases of seminoma, pure and combined, from our testicular tumour files in order to determine the incidence of the various giant cells, to study their morphological and cytochemical characteristics, and to correlate giant cell type with clinical course and prognosis.

Materials and methods

The testicular tumour files at our Institute of Pathology comprise 500 cases of germ cell tumors registered between 1971 and the end of 1983. Selected for review were all pure seminomas ($N=243$ or 48.6%) and all combined tumors, i.e. those revealing one or more histological types in addition to seminoma ($N=107$ or 21.4%). The specimens had been fixed in 4% buffered formalin and embedded in paraffin. Routine histological slides stained with H&E, van Gieson's, and periodic acid-Schiff were available in each case from an average of 4 to 5 blocks of tumour tissue.

We considered as giant cells all cells
- exhibiting more than one nucleus,
- containing a single nucleus greater than 35 μm in diameter.

This figure was derived as the upper limit for nuclear size in giant spermatogonia, an occasional feature of non-neoplastic germinal epithelium (Sigg and Hedinger 1983).

Morphological classification

Giant cells were recorded either as reactive (histiocytic, foreign body or Langhans type) or as giant cells proper to the neoplastic tissue. The latter were further classified according to cellular and nuclear features detailed below. Attention was paid also to their distribution and relation to capillaries and fibrous septa.

Histiocytic giant cells. Multinucleated giant cells akin to those of sarcoid granulomas measure 25–80 μm and contain up to 15 or so round nuclei with finely dispersed chromatin (Fig. 1a) often in a typical horseshoe configuration.

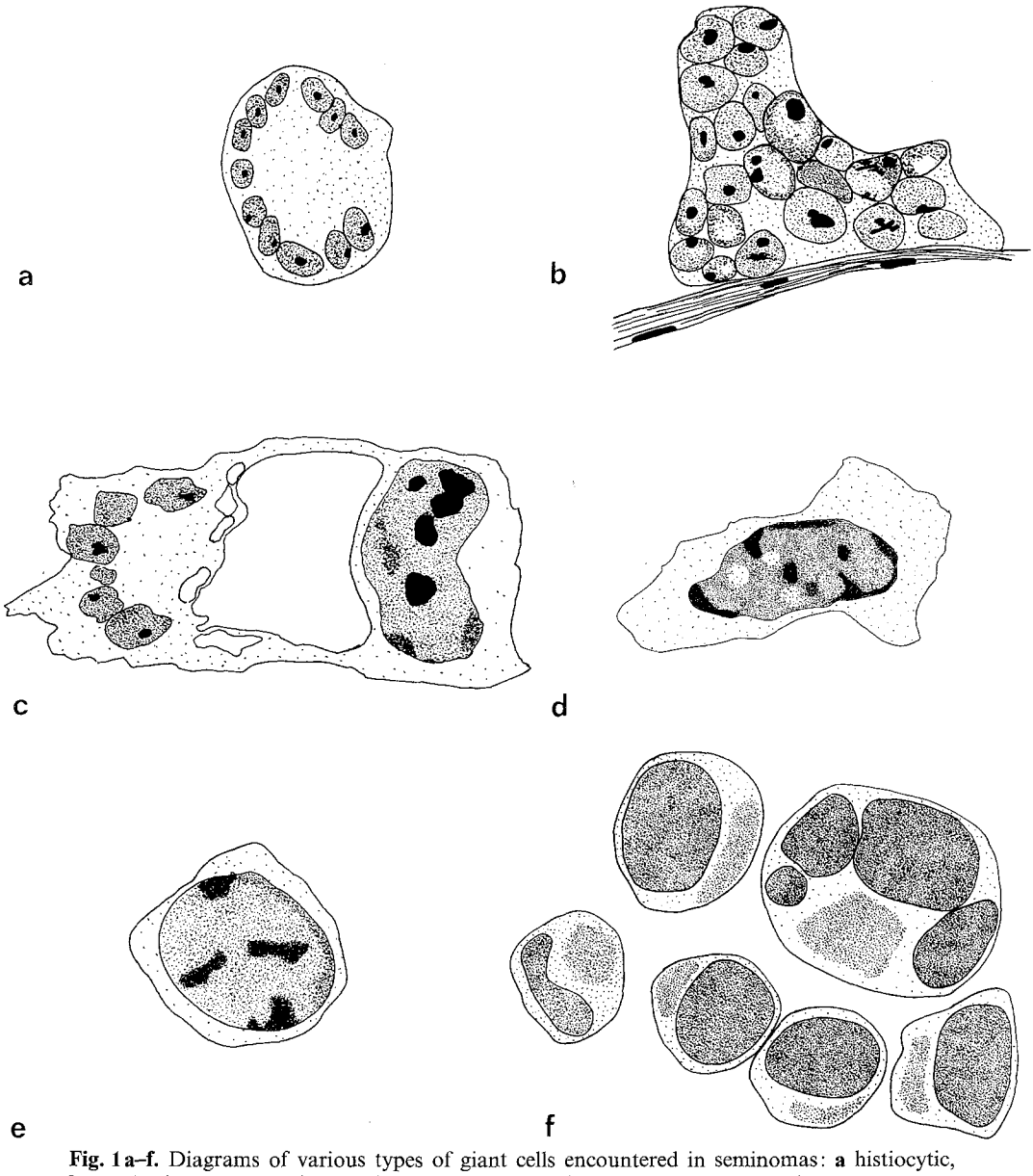


Fig. 1 a–f. Diagrams of various types of giant cells encountered in seminomas: **a** histiocytic, **b** neoplastic type I, **c** and **d** neoplastic type II, **e** neoplastic type III, **f** neoplastic type IV

Tumour giant cells. Four types could be discerned primarily on the basis of number and features of nuclei:

Type I. Multinucleated giant cell that may reach large dimensions (up to 250 μm) containing numerous uniform, densely packed nuclei that leave only a narrow rim of cytoplasm (Fig. 1 b). The nuclei are similar to those of surrounding seminoma cells, displaying a distinct nuclear envelope, granular or coarse chromatin with marginal condensations, and prominent nucleoli. The cytoplasm may contain phagocytosed erythrocytes or white blood cells.

Type II. Giant cells of similar configuration to type I, but with the distinguishing feature of one or several large and polymorphous nuclei (Fig. 1c). The chromatin content and distribution vary. Giant cells with abundant cytoplasm and similar features but with a single giant nucleus (Fig. 1d) were included under the assumption that the plane of section passed through that nucleus only.

Type III. Round to polygonal cells generally about 50 μm in size containing a single roundish nucleus of at least 35 μm with a prominent nuclear envelope and homogeneously dispersed chromatin (Fig. 1e). The narrow rim of cytoplasm is devoid of visible inclusions.

Type IV. Roundish cells, 30 to 125 μm in diameter containing at least two marginated "pince-nez" nuclei with distinct nucleoli and centrally eosinophilic, faintly granular to fibrillar cytoplasm. These giant cells are found among mononuclear cells of similar cytoplasmic features.

Immunocytochemical Screening

Additional sections from many neoplasms revealing these various giant cells were screened by the PAP-method of Sternberger et al. (1970) for the presence of B-HCG, alphafetoprotein (AFP), lysozyme, ferritin, and factor VIII-associated antigen. Antisera were obtained from DAKO (AFP, lysozyme, ferritin), Immulok (factor VIII), and SERONO (B-HCG). Those for B-HCG, AFP and lysozyme were diluted 1:100. Antisera for ferritin and factor VIII were used as supplied.

Clinical follow-up

All patients whose seminomas harboured neoplastic giant cells and who had undergone orchiectomy at least 5 years prior to writing were selected. 41 patients fulfilled these requirements and follow-up information was obtained on 26.

Results

From 1971 to the end of 1983, 500 cases of testicular germ cell tumours were examined at our Institute. Pure seminomas were diagnosed in 243 cases (48.6%) and in another 107 (21.4%) seminoma was one component in tumours of more than one histological type. Included in this group of combined tumours were examples of early, interstitially infiltrating seminomas.

Histiocytic and neoplastic giant cells within seminomas were recorded (Table 1) according to the criteria given above. In pure seminomas, neoplas-

Table 1. Numerical and percentage distribution of neoplastic and histiocytic giant cells in pure seminomas and seminomatous components of combined tumours

		Neoplastic giant cells only	Neoplastic + histiocytic giant cells	Histiocytic giant cells only
Pure S ($N=243$)	N	74	10	32
	%	34.6	17.3	
Comb Tu ($N=107$)	N	10	2	4
	%	11.2	5.6	

Table 2. Immunohistochemical screening of histiocytic and neoplastic giant cells in seminomas and seminomatous components of combined tumors

Giant cell	Beta-HCG	AFP	Factor VIII	Lysozyme	Ferritin
Histiocytic	−/14	−/12	−/12	10/12	−/12
Neoplastic					
Type I	9/17	−/13	−/13	−/13	−/13
Type II	6/9	−/9	−/7	−/7	−/7
Type III	−/17	−/15	−/16	−/15	−/16
Type IV	−/7	−/6	−/6	−/6	−/6

tic giant cells alone were noted in 74 cases, histiocytic ones alone in 32, and in another 10 cases both were present. In combined tumours, 10 cases revealed neoplastic giant cells alone, 4 histiocytic ones alone, and 2 cases contained both.

Hence, both neoplastic and histiocytic giant cells were recorded three times more often in pure than in combined seminomas; in both pure and combined tumours the ratio of the incidences of neoplastic to histiocytic giant cells was 2:1.

Immunocytochemical reactivity

Histiocytic and all types of neoplastic giant cells were represented in the tumours screened immunocytochemically. Table 2 lists the reactions of particular giant cell types whose variably combined occurrence in the individual pure or combined tumour did not affect the pattern of reactivity. Treated with B-HCG antiserum, 9 of 17 cases with type I and 6 of 9 cases with type II giant cells gave a positive reaction while none of the other types did. A tendency to focal distribution was noted: not infrequently a series of step sections would reveal positively reacting giant cells in a few foci of one nodule only. Lysozyme was positive in 10 of 12 cases with histiocytic giant cells and in none of the other types. AFP, factor VIII, and ferritin were negative throughout.

Histiocytic giant cells

Histiocytic giant cells (Fig. 2) were seen in a total of 42 cases of pure seminoma (17.3%) and in 6 (5.6%) of the combined tumours (Table 1). Hence the granulomatoid stromal reaction was found to occur three times as often in pure seminomas as in combined tumors.

In pure seminomas with neoplastic giant cells ($N=84$), the histiocytic type were found in 10 cases (11.9%), while in those without neoplastic giant cells ($N=234-84=159$) they were seen in 32 cases (20.1%). In the group of combined tumours an analogous segregation yields non-significant results, given a total of only 6 cases with histiocytic giant cells.

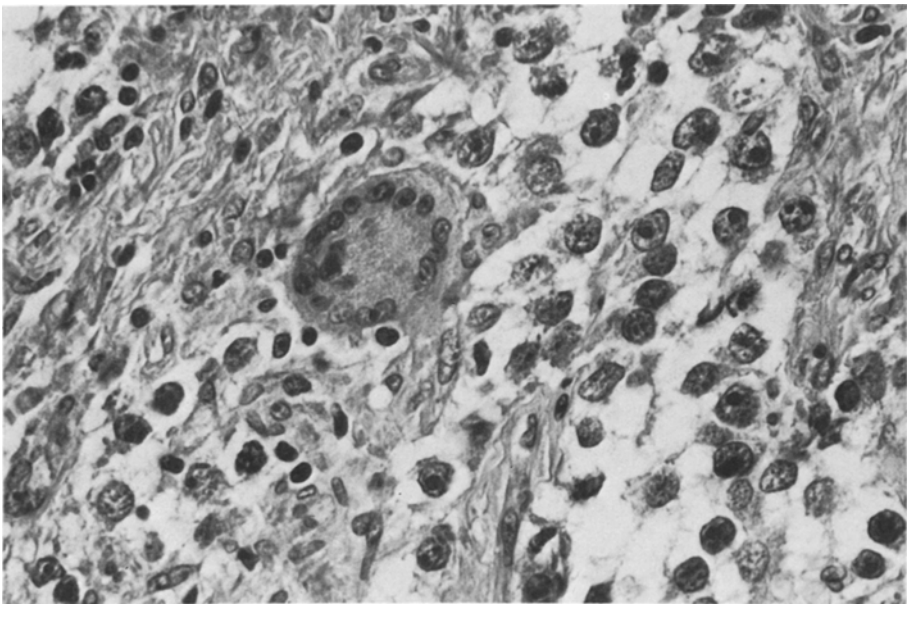


Fig. 2. Histiocytic giant cell of the granulomatoid stroma reaction in seminoma. H. and E., ×440

Neoplastic giant cells

Although all neoplastic giant cell types could be found scattered singly throughout the entire neoplasm, types I and II were encountered more often in one or several tumour nodules only. They are usually clustered about connective tissue septa, capillaries, or haemorrhagic foci and may contain erythrocytes within distended cytoplasmic vacuoles, conveying at times the impression of syncytial endothelial cells lining sinusoidal spaces (Fig. 3–6). In fact, the association of clusters of type I and II giant cells with haemorrhagic foci is so consistent that on gross inspection of a seminoma petechial haemorrhages are a most useful clue and should always be sampled for microscopic examination. Type III giant cell (Fig. 7) occurred singly and sporadically throughout the tumour, as in spermatocytic seminomas. The type IV giant cell (Fig. 8) was invariably part of a particular seminoma cell population that made up one or several nodules, less often the entire neoplasm. The giant cell differs from the surrounding cells solely by its number of nuclei, but otherwise shares the characteristic features of an eosinophilic, faintly granular to fibrillar cytoplasm and marginated reniform nuclei. Unfortunately, we have not yet encountered this peculiar cell in our material freshly sampled for EM.

The results of B-HCG positivity on immunocytochemical screening (Table 2) soon led us to consider types I and II as morphological variants of similarly competent cells. Table 3 depicts the incidences of all the types

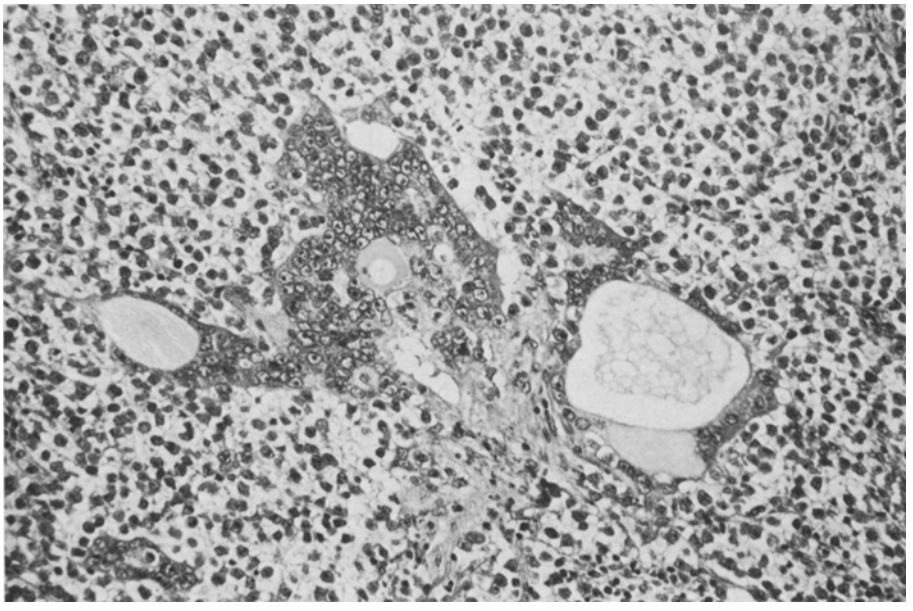


Fig. 3. Large syncytiotrophoblastic giant cell (neoplastic type I) with irregular cytoplasmic extensions, featuring innumerable nuclei and several sinusoidal vacuoles. H. and E. ×160

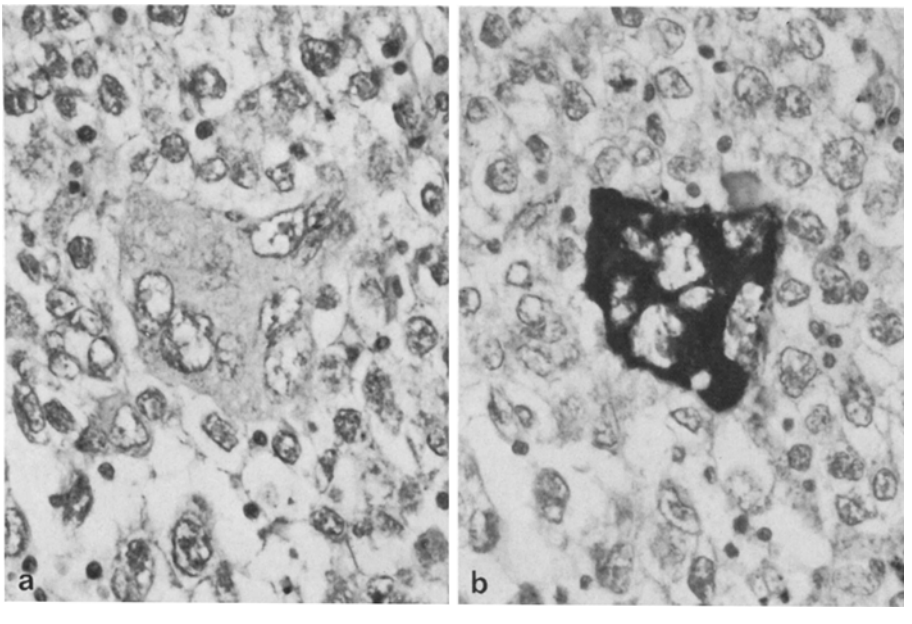


Fig. 4a, b. Syncytiotrophoblastic giant cell (neoplastic type I) **a** H. and E., **b** positive B-HCG stain. Both ×400

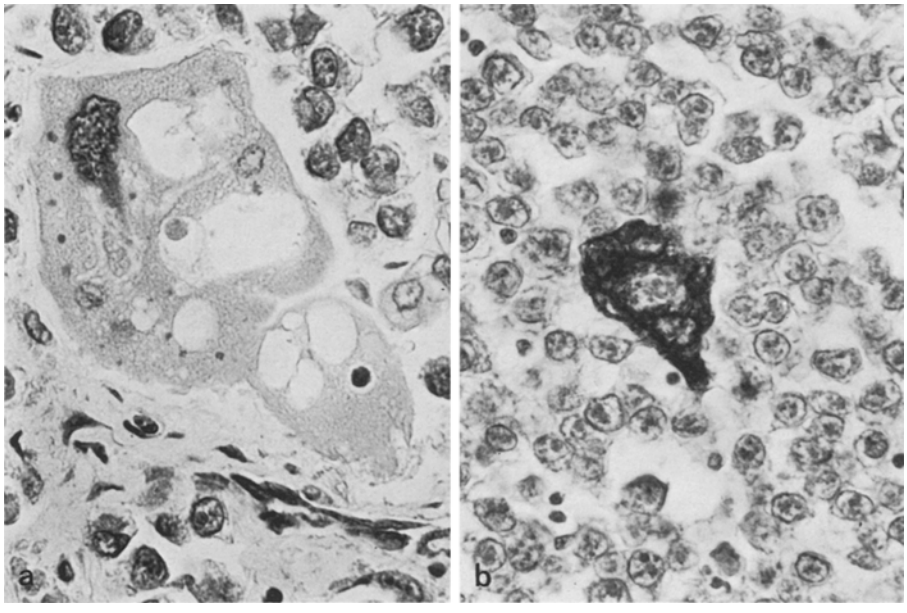


Fig. 5a, b. Syncytiotrophoblastic giant cell (neoplastic type II) with multiple polymorphic nuclei, **a** H. and E., **b** positive B-HCG stain. Both ×400

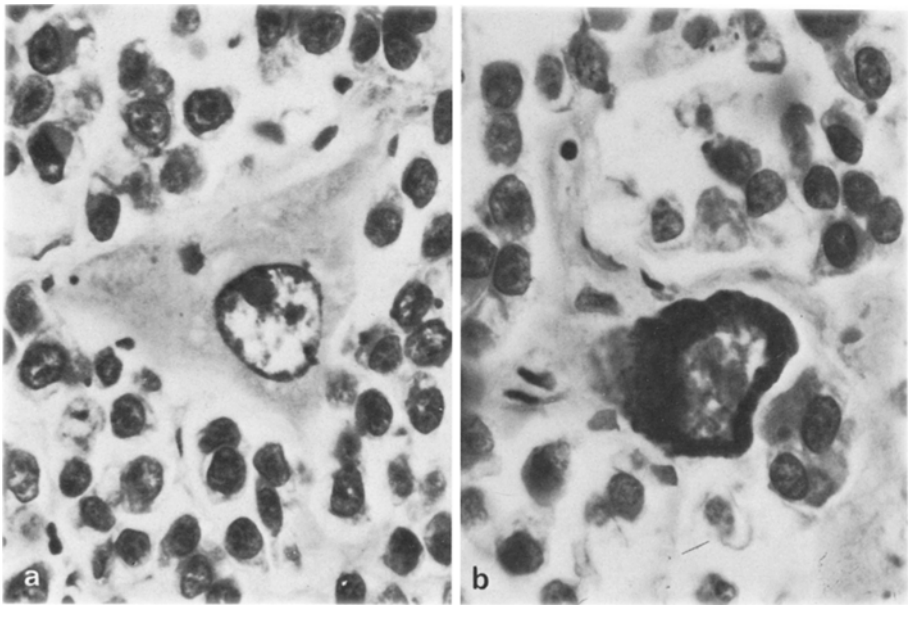
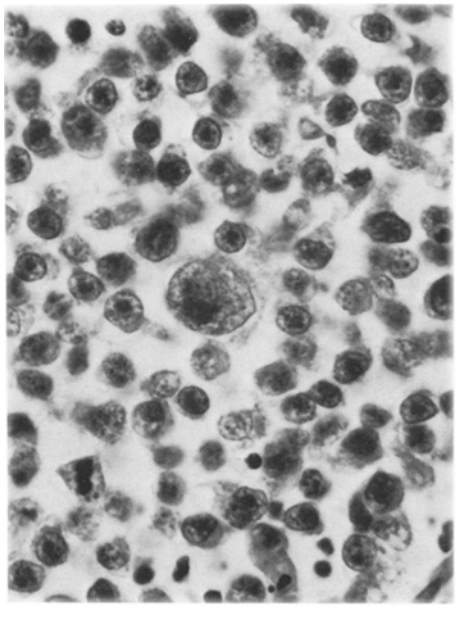


Fig. 6a, b. Large body giant cell (neoplastic type II) with single nucleus, **a** H. and E. ×440, **b** positive B-HCG stain. ×500



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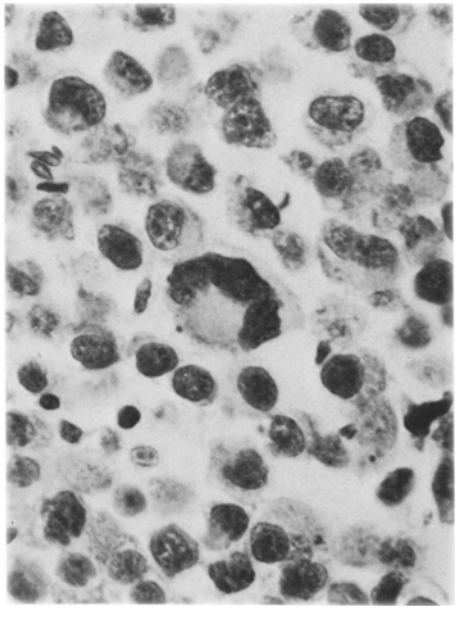

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Fig. 7. Mononuclear giant cell with little cytoplasm (neoplastic type III). H. and E. ×480

Fig. 8. Giant cell with several peripheral nuclei (neoplastic type IV). Note also the granular cytoplasm and excentric nuclei of surrounding mononuclear tumor cells. H. and E. ×400

Table 3. Distribution and combinations of types of neoplastic giant cells in pure seminomas and seminomatous components of combined tumours. Numbers in parentheses express percentages of all pure seminomas ($N=234$)

		I/II	III	IV	All types
Pure	I/II	32 (13.2)			1 (0.4)
Comb		6			–
Pure	III	12 (4.9)	18 (7.4)		
Comb		3	2		
Pure	IV	2 (0.8)	7 (2.9)	12 (4.9)	
Comb		1	–	–	

of neoplastic giant cells alone and in combination when types I and II are taken together.

Of 84 cases of pure seminoma with neoplastic giant cells, 32 contained type I/II alone, another 15 in combination with other types. Thus 47 or 243 pure seminomas (19.3%) revealed this form of giant cell. The type

Table 4. Clinical follow-up in 26 patients with neoplastic giant cells in pure seminomas and in seminomatous components of combined tumours

Patient	Clinical stage	Giant cell type	Therapy	Follow-up period and status
Pure seminoma				
1	I	I	S+RT	36 months NED
2	I	I	S+RT	46 months NED
3	I	I	S+RT	60 months NED
4	I	I	S+RT	60 months NED
5	I	I	S+R	60 months alive with metastases (stage III)
6	I	II	S+RT	47 months NED
7	I	II	S+RT	60 months NED
8	I	II	S+RT	60 months NED
9	I	I, III	S+RT	60 months NED
10	I	I, III	S+RT	60 months NED
11	I	I, IV	S+RT	60 months NED
12	I	IV	S+RT	32 months NED
13	I	IV	S+RT	60 months NED
14	II	I	S+RT+CT	18 months died from metastatic disease[a]
15	II	II	S+RT	52 months NED
16	II	I, II, III	S+RT	24 months died from metastatic disease
17	II	III	S+RT	18 months died from metastatic disease
18	II	III	S+RT	60 months NED gynecomastia
19	IV	I, II, III	S+CT	20 months died from metastatic disease
Combined tumors				
1	I	I	S	60 months NED
2	I	II	S+RT	60 months NED
3	I	I, II	S+RT+CT	24 months died from metastatic disease
4	I	II, III	S+RT+CT	60 months NED
5	I	III	S+RT	60 months NED
6	II	I	S+RT	weeks died from metastatic disease
7	II	II	S+RT+CT	24 months died from metastatic disease

Abbreviations: S = surgery; RT = radiotherapy; CT = chemotherapy; NED = no evidence of disease

[a] Inadequate treatment

III cell was noted in 38 cases (15.6%) of pure seminomas. In 18 of them it was the only type of neoplastic giant cell, in 20 it occurred together with other types. Of seven cases previously classified as spermatocytic seminomas four revealed type III giant cells alone, the other three type III together with type II. Type IV was found alone in 12 cases and in combination with other types in another 10. Among all pure seminomas its overall incidence was thus 9.1%.

When our pure seminomas are grouped into those with type I/II giant cells ($N=47$) and those without them ($N=243-47=196$), the incidence of type III giant cell is 27.7% in the former and 12.8% in the latter. The

chi-square test confirms this difference to be significant ($p < 0.05$). For type IV giant cell the incidences are 6.4% and 9.7% respectively, a difference that is not significant.

The relative paucity of combined tumors does not allow as detailed an analysis. Nevertheless, type I/II giant cell was the most frequently encountered, alone in 6 cases and in combination with other types of neoplastic giant cells in another four. Thus, the overall incidence of this type of giant cell in all combined tumors was 9.4%. Type III was encountered in 5 cases, three times with type I/II, twice alone. Type IV was seen only once, in combination with type I/II.

Clinical follow-up

Forty-one patients had undergone orchidectomy at least 5 years previously for seminomatous tumours with neoplastic giant cells. Information could be obtained in 26 cases, i.e. in 19 with pure seminomas and 7 with combined tumours, and is summarized in Table 4.

In the group with pure seminoma, four patients died within 2 years; one had been treated inadequately and three had presented initially at advanced clinical stages, one of whom had metastatic spread to the cervical spine. Another patient is alive with metastases following post-operative radiotherapy of a type I giant cell-containing seminoma. The other 14 patients, 11 of whom harbored tpye I/II giant cells, did well and are free of tumour up to 5 years and more after diagnosis.

In the group with combined tumours, three patients died from metastatic disease. Two had come to medical attention at clinical stage II. All had embryonal carcinoma (malignant teratoma undifferentiated) as the non-seminomatous component. The four remaining patients have survived at least 5 years with variable therapy and are free of tumour.

Discussion

The results summarized in Table 1 show that histiocytic giant cells are encountered three times more often in pure seminomas than in the seminomatous component of combined tumours. If the granulomatous stromal reaction is an expression of a host immune response, the presence of a highly malignant non-seminomatous component, e.g. embryonal carcinoma, may be considered to reflect an attenuated state of responsiveness.

The considerable difference in incidence of the histiocytic giant cell reaction in pure seminomas without neoplastic cells (20.1%) and in pure seminomas with neoplastic giant cells (11.9%) cannot be explained as easily on the basis of decreased host responsiveness. According to the clinical follow-up we were able to document, the neoplastic giant cells did not constitute a highly malignant component. Moreover, only one of nine spermatocytic seminomas, (11.1%) widely held to be truly benign in behaviour, revealed histiocytic giant cells. It may be added that spermatocytic seminomas typically lack lymphocytic infiltrates, also considered to be a measure of host responsiveness.

Hence, the variable granulomatous stromal reaction may be the indication of altered states of host responsiveness to a malignant component, as in the case of a compound tumour, and/or to tumour tissue of a different antigenicity, as in spermatocytic seminomas and seminomas with neoplastic giant cells generally.

While the overall incidence of the stromal giant cell reaction compares with that of other reports (Mostofi and Price 1973; Thackray and Crane 1976), the frequency with which neoplastic giant cells were encountered is surprisingly high; they are found twice as often as histiocytic giant cells and, like theme, three times more often in pure seminomas than in the seminomatous component of combined tumors. The latter may in part be due to the fact that included among our combined tumors are cases of early, microscopic seminoma, too early perhaps in their development to have developed giant cell forms. However, the possibility that seminomas in pure and in combined forms are not identical neoplasms but are dissimilar in morphological expression, as they are in biological behaviour, cannot be dismissed (von Albertini 1943; Hedinger 1981).

About 20% of pure seminomas display, often focally, multinucleated giant cells capable of elaborating B-HCG. Like the trophoblastic giant cells of non-seminomatous germ cell tumours, choriocarcinoma in particular, they are often associated with distended capillaries or petechial haemorrhages, that serve as an important clue on gross inspection. In seminomas, however, these giant cells are not part of an epithelial or cytotrophoblastic component but pertain undoubtedly to the seminoma. The fact that type I/II giant cells were found in 19.4% of all our pure seminomas and in only 9.3% of all combined tumours argues against a trophoblastic component that infiltrates a seminomatous mass from a concomitant occult choriocarcinomatous focus.

The mononnuclear type III giant cell was found in nearly 16% of all pure seminomas. Although unassociated with b-HCG production, it is more likely to be encountered in seminomas with STGC. In addition, it is a constituent of the polymorphous cell population of spermatocytic seminomas, but may be found in otherwise classical seminomas. Hence, we consider it to be a sporadically occurring variant of the usual tumour cell population whose potential for cellular polymorphism it helps to express.

The occurrence of the type IV giant cell appears to be independent of the presence of other types of giant cells. It is invariably part of a characteristic cell type that displays excentric nuclei, eosinophilic fibrillar cytoplasm and a marked tendency for bi- or multinucleate forms. The significance of these cellular features has remained unclear.

Several publications deal with the clinical significance of STGC in seminomas (Friedman and Pearlman 1976; Javadpour et al. 1978; Mauch et al. 1979; Lange et al. 1980; Morgan et al. 1982). Obviously, B-HCG serves as a valuable tumour marker for diagnosis, evaluation of treatment, and follow-up. In 9 cases with elevated serum HCG related by Javadpour (1978) histological 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 type of tumour, i.e. seminoma with STGC, is not identical to combined seminoma and choriocarcinoma. As far as prognosis is concerned, our study indicates that seminomas with STGC, treated like classical seminomas by orchidectomy and radiotherapy, follow the same favourable course. This certainly applies to cases of low clinical stages at least. Whether at advanced stages the prognosis worsens with respect to comparable classical seminomas cannot be answered here. In the literature, the overall prognosis for seminomas with STGC is often taken to be less than favourable (Dixon and Moore 1952; Hobson 1956; van der Werf-Messing 1971; Wilson and Woodhead 1972; Maier and Sulak 1973; Mauch et al. 1979). But in most of these reports the presence of a non-seminomatous germ cell component was not excluded beyond doubt by appropriately thorough examination and/or measurement of tumour marker levels.

Conclusions

1. Giant cells are a frequent finding in seminomas. Neoplastic giant cells occur twice as frequently as histiocytic ones in both pure seminomas and seminomatous components of combined/mixed tumors. Both kinds of giant cells are encountered three times more often in pure than in combined seminomatous tumors.

2. One-third of pure seminomas contain neoplastic giant cells as they are here defined. Among them, STGC are the most frequent: one pure seminoma in five harbors STGC, often focally. These cells elaborate B-HCG, a tumour marker of considerable value for diagnosis, evaluation of treatment, and follow-up.

3. The presence of STGC in seminomas is not indicative of the sombre prognosis usually associated with trophoblastic or choriocarcinomatous germ cell tumors. As in conventional seminomas, treatment at an early stage with orchidectomy and radiotherapy is followed by a favourable course.

4. Other neoplastic giant cells comprise a mononuclear form found in all our spermatocytic and occasionally in otherwise classical seminomas. It is likely to be the expression of polymorphism and polyploidy that seminomas tend toward generally and spermatocytic ones in particular. Another type of giant cell is associated with a distinct morphologic variant of seminoma cell the significance of which requires further study.

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