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HISTOLOGY IN MIXED GERM CELL TUMORS. IS THERE A FAVORITE PAIRING?

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ABSTRACT

Purpose: Mixed germ cell tumors account for approximately 30% to 50% of testicular tumors. To our knowledge a systematic review with statistical analysis of the associations of histological subtypes in mixed germ cell tumors has not been done previously. It was our impression that such associations exist. Delineating concordant histological types may provide insight into the ontogeny of testicular tumors and also have important clinical implications.

Materials and Methods: We retrospectively reviewed the testis cancer data base at our institution. The primary tumor of orchiectomy specimens was examined in 2,589 patients. Of these patients mixed histology was noted in 1,765 (68.2%). ORs were calculated for all possible combinations of teratoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma and seminoma. In addition, we evaluated the association of various histological types with teratoma at post-chemotherapy retroperitoneal lymph node dissection.

Results: Of 10 possible combinations of histological types in the primary tumor, positive correlations were noted in 4. The strongest correlation was found between teratoma and yolk sac tumor (OR 2.58, $p < 0.001$). Teratoma or yolk sac tumor in the testis was associated with teratoma in the pathology specimen at post-chemotherapy retroperitoneal lymph node dissection.

Conclusions: The strongest associations of histological subtypes in mixed germ cell tumors were seen between yolk sac tumor and teratoma. Similar associations are seen in late relapse and in some cases of prepubertal tumors. Further study of these associations may prove valuable in understanding the biology and clinical behavior of germ cell tumors.

KEY WORDS: testis, testicular neoplasms, germinoma, neoplasms by histological type, neoplasm metastasis

Germ cell tumors account for the majority (greater than 95%) of testicular neoplasms. Of these lesions 30% to 50% are classified as mixed germ cell tumors (MGCTs), denoting a combination of different germ cell tumor elements.[1] In a number of studies certain combinations of germ cell elements were noted to occur frequently, such as the combination of embryonal carcinoma and teratoma in the series of Mostofi,[2] and von Hochstetter and Hedinger.[3] However, to our knowledge a systematic review with statistical analysis of the associations of histological subtypes in MGCTs has not been done previously. In the current study a large series of MGCTs was analyzed to define possible associations among the various histological elements in these tumors. Delineating concordance among histological types may provide insight into the ontogeny of testicular neoplasms. It may also have important implications in clinical and management aspects, such as predicting the pathology of post-chemotherapy residual masses.

MATERIALS AND METHODS

A review of the testis cancer data base at our institution identified 2,589 patients with primary testicular tumors, of whom 1,765 (68.2%) were diagnosed with MGCTs. The frequency of each germ cell element was noted. Using chi-square tests possible correlations were defined by calculating ORs and CIs for all possible combinations of teratoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma and seminoma. In addition, chi-square tests and Cox proportional hazards models were used to evaluate the associations among various histological types and their different combinations with teratoma at post-chemotherapy retroperitoneal lymph node dissection (RPLND).

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RESULTS

Table 1 lists the frequency of individual histological types in the 1,765 patients with MGCTs. The most frequent histological element in MGCTs was embryonal carcinoma in 84.4% of cases, followed by teratoma in 69.7% and yolk sac tumor in 60.1%.

Table 2 shows the correlations between histological types in all 10 possible pair combinations. Overall statistically significant positive correlations were noted in 4 combinations. The strongest correlation was found between teratoma and yolk sac tumor (OR 2.58, $p < 0.001$). The other positive correlations were noted between teratoma and choriocarcinoma (OR 1.47, $p = 0.002$), embryonal carcinoma and yolk sac tumor (OR 1.42, $p < 0.001$), and choriocarcinoma and yolk sac tumor (OR 1.38, $p = 0.007$).

Of the 2,589 patients in the study 1,229 underwent post-chemotherapy RPLND. There were 659 patients (53.6%) harboring teratoma without other cancer in the resected lymph nodes. Teratoma or yolk sac tumor in the primary tumor was associated with teratoma in the pathology specimen at post-chemotherapy RPLND (OR 3.07, $p < 0.001$ and OR 1.48, $p < 0.001$, respectively). Table 3 lists the associations of histological types in the primary tumor with teratoma at post-chemotherapy RPLND. Table 4 shows the associations of the different combinations of histological types with teratoma at RPLND. Again, teratoma combined with other histological types was strongly predictive of teratoma at RPLND.

TABLE 1. *Individual histological types*

Histological Type	No. Pts (%)
Embryonal Ca	1,490 (84.4)
Immature and/or immature teratoma	1,230 (69.7)
Mature teratoma	772 (43.7)
Immature teratoma	577 (32.7)
Yolk sac tumor	1,060 (60.1)
Seminoma	697 (39.5)
Chorioca	314 (17.8)

TABLE 2. *Correlations between histological types*

Combination		No. Tumors*	OR	p Value
Teratoma	Embryonal Ca	987	0.48	<0.001
Teratoma	Chorioca	208	1.47	0.002
Teratoma	Yolk sac tumor	753	2.58	<0.001
Teratoma	Seminoma	395	0.71	<0.001
Embryonal Ca	Chorioca	259	1.23	0.149
Embryonal Ca	Yolk sac tumor	875	1.42	<0.001
Embryonal Ca	Seminoma	542	0.55	<0.001
Chorioca	Yolk sac tumor	164	1.38	0.007
Chorioca	Seminoma	78	0.65	0.002
Yolk sac tumor	Seminoma	338	0.95	0.552

* Including tumors with more than 2 histological types.

TABLE 3. *Histological primary tumor types with teratoma at post-chemotherapy RPLND*

Primary Tumor Histological Element	No. Tumors	OR	p Value
Teratoma	693	3.07	<0.001
Yolk sac tumor	484	1.48	<0.001
Chorioca	164	1.33	0.091
Embryonal Ca	816	1.25	0.062
Seminoma	379	0.59	<0.001

DISCUSSION

The current study is an analysis of the possible associations and relationships among different histological elements in a large series of patients with MGCTs. The high percent of MGCTs observed (1,765 of 2,589 patients or 68.2%) reflects the fact that this series is surgical with the nonseminomatous germ cell tumors and primary or post-chemotherapy RPLND in the majority of patients.

A number of studies have assessed at the frequency of the various histological elements in MGCTs.[2–5] In classifying more than 6,000 testis tumors Mostofi found that in about 60% more than 1 histological pattern was identified.[2] The most frequent combination was embryonal carcinoma, yolk sac tumor and teratoma. In a review of 324 testicular neoplasms von Hochstetter and Hedinger found that 100 tumors (30.9%) had more than 1 histological type with a combination of embryonal carcinoma and teratoma in 33 (10.2%), a combination of seminoma with other elements in 46 (14.8%) and choriocarcinoma with other elements in 21 (6.5%).[3] In a report from the Danish Testicular Carcinoma Study Group Krag Jacobsen et al found that 352 of 1,058 testicular germ cell tumors were mixed.[4] Of the various subtypes of nonseminomas embryonal carcinoma, yolk sac tumor, teratoma and choriocarcinoma were recorded in 87%, 22%, 55% and 17% of cases, respectively.

TABLE 4. *Combinations of histological primary tumor types with teratoma at post-chemotherapy RPLND*

Combination		No. Tumors	OR	p Value
Teratoma	Embryonal Ca	426	6.11	<0.001
Teratoma	Chorioca	106	3.80	<0.001
Teratoma	Yolk sac tumor	337	3.48	<0.001
Teratoma	Seminoma	167	2.14	<0.001
Embryonal Ca	Chorioca	115	1.51	0.058
Embryonal Ca	Yolk sac tumor	376	1.67	0.001
Embryonal Ca	Seminoma	216	0.73	0.096
Chorioca	Yolk sac tumor	70	1.69	0.042
Chorioca	Seminoma	40	1.12	0.737
Yolk sac tumor	Seminoma	133	0.95	0.785

However, to our knowledge a systematic statistical analysis of the possible concordance among the various elements in MGCTs has not been previously reported. The most frequently observed combination of elements in our series was the combination of embryonal carcinoma and teratoma in 987 tumors, followed by embryonal carcinoma and yolk sac tumor in 875. This finding reflects the high frequency of embryonal carcinoma in MGCTs, which appeared in 84.4% of our cases. However, the highest concordance and strongest correlation between histological elements was seen between teratoma and yolk sac tumor (OR 2.58, $p < 0.001$). This observation was interesting, especially since it mirrors the association of teratoma and yolk sac tumor in cases of late relapse[6] and in certain prepubertal testicular tumors.[7]

The relationships among histological elements in the primary tumor and pathological findings in resected masses in patients undergoing post-chemotherapy RPLND have important clinical implications. It is well known that teratoma is a chemoresistant tumor that is more amenable to surgical extirpation. Therefore, the prediction of teratomatous elements in the retroperitoneum is an important factor in planning the management of these cases. Previous studies have identified teratoma in the primary tumor as a predictor of teratoma in post-chemotherapy residual masses.[8–10] The current study confirms this observation, in addition to suggesting a statistically significant correlation between yolk sac tumor in the primary tumor and teratoma at post-chemotherapy RPLND. This finding may be incorporated with other factors, such as the volume of retroperitoneal disease and percent change in volume in response to chemotherapy, in refining the algorithm for managing post-chemotherapy residual masses in patients with MGCTs.

Many theories have been proposed for testicular germ cell tumor histogenesis. One concept is that all such tumors take their origin from totipotential germ cells and the neoplastic germ cell line may proceed along 1 of 2 basic avenues of differentiation. In 1 direction differentiation goes no further than seminoma. In the other direction differentiation proceeds to or through embryonal carcinoma, a tumor of pluripotential cells with the capability for further differentiation along extraembryonic pathways, giving rise to choriocarcinoma and yolk sac tumor, or intraembryonic pathways, giving rise to teratoma. Although this general scheme was widely accepted, recent lines of evidence call into question at least some of its aspects.[11] Our observations point to a possible stronger link between yolk sac tumor elements, which recapitulate the loose extraembryonic mesodermal and endodermal tissue of the 2-week-old blastocyst, and teratomatous elements, which reflect somatic differentiation.

CONCLUSIONS

The strongest associations of histological subtypes in MGCTs were seen between yolk sac and teratoma. In addition, teratoma or yolk sac tumor in the testis was associated with teratoma at post-chemotherapy RPLND. Further study of these observations may provide insight into the ontogeny of germ cell tumors as well as refine management decisions in patients with testicular cancer.

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