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Retroperitoneal Histology of Patients with Elevated Serum Alpha-Fetoprotein and Pure Seminoma at Orchiectomy

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Abstract

Objectives—A histologic diagnosis of seminoma at orchiectomy with an elevation in serum alpha-fetoprotein (AFP) indicates the likelihood of unrecognized NSGCT elements. We report the retroperitoneal histology of a contemporary series of patients with pure seminoma at orchiectomy with an elevation in serum AFP that were managed as NSGCT.

Methods—We identified 22 patients between 1989 and 2009 with pure seminoma diagnosed at orchiectomy with an elevated serum AFP (> 15 ng/ml) either pre- or post-orchiectomy. Retroperitoneal histology and relapse data are reported.

Results—Median pre-orchiectomy and pre-chemotherapy serum AFP levels were 248 ng/ml (IQR 48, 4693) and 279 ng/ml (IQR 66, 5311), respectively. Percentage of patients with clinical stage I, II, and III was 5%, 50%, and 45%, respectively. Percentage of patients with IGCCCG good, intermediate, and poor risk status was 32%, 32%, and 36%, respectively. Twenty-one patients had induction chemotherapy followed by PC-RPLND. Overall, 67% of patients had NSGCT elements in the retroperitoneum. Histologic findings were pure teratoma in 38%, malignant transformation in 14%, and viable NSGCT in 14%. Fifty-nine percent had some component of teratoma in the RP. One patient (5%) had any seminoma in the RP, but this patient also had RP teratoma. Seven patients relapsed and received salvage chemotherapy. Actuarial relapse free survival at 5 and 10 years was 76% and 61% reflecting a high percentage of patients with stage II/III disease.

Conclusions—Pure seminoma at orchiectomy with an elevated serum AFP portends a high likelihood of harboring NSGCT elements in the RP.

Keywords

testicular cancer; seminoma; AFP; RPLND

Introduction

Testicular germ cell tumors can be grouped into seminomatous and non-seminomatous germ cell tumors (NSGCT), each of which comprises approximately 50% of diagnosed cases.

Syncytiotrophoblasts can cause elevations in serum HCG in up to 15% of men and LDH can be elevated in up to 80% of patients with seminoma. (1) However, AFP is not secreted by pure seminoma in the absence of other sources of AFP elevation in the absence other sources such as liver dysfunction. Therefore, a histologic diagnosis of seminoma at orchiectomy with an elevation in serum AFP indicates the presence of unrecognized NSGCT elements. Low stage metastatic seminoma to the retroperitoneum can be treated with observation or radiotherapy. (2) (3) (4) In contrast, NSGCTs are not nearly as responsive to radiotherapy and typical treatment consists of chemotherapy and/or surgery depending on stage and risk. While it is known that pure seminoma does not produce AFP, there have been few contemporary studies reporting likelihood of finding NSGCT elements outside the orchiectomy specimen. We report on a cohort of men who were diagnosed with pure seminoma at orchiectomy with an elevation in AFP and report histology of retroperitoneal lymph nodes at either primary or post-chemotherapy retroperitoneal lymph node dissection.

Methods

After obtaining Institutional Review Board approval, we queried the prospective MSKCC Testis Cancer Registry and identified 22 patients between 1989 and 2009 that had pure seminoma diagnosed at orchiectomy that had an elevated serum AFP (> 15 ng/ml) at either pre- or post-orchiectomy. Available pathology slides were reviewed by a pathologist at MSKCC and confirmed to be seminoma. Baseline clinical and tumor features are described (table 1). All 22 patients were treated according to algorithms based on the treatment of NSGCT due to elevations of AFP. Patients that had elevated serum tumor markers after orchiectomy ($n=21$) were treated with IGCCCG risk based chemotherapy which was followed by PC-RPLND. One patient with clinical stage I disease normalized his serum AFP level after orchiectomy and proceeded to primary RPLND. Visible extra-retroperitoneal sites of disease were resected after PC-RPLND. Retroperitoneal histology, relapse data, and subsequent treatment are reported. Kaplan-Meier survival analysis was performed using the Stata® software package 8.2.

Results

Overall 22 patients were identified that had a diagnosis of pure seminoma at orchiectomy and elevated AFP. Baseline patient characteristics are listed in table 1. Median age of treatment was 32 years (IQR 28, 40) and median follow-up time was 4.1 years (IQR 1.1, 7). Median pre-orchiectomy and pre-chemotherapy serum AFP levels were 248 ng/ml (IQR 48, 4693) and 279 ng/ml (IQR 66, 5311), respectively. Percentage of patients with clinical stage I, II, and III was 5%, 50%, and 45%, respectively. Percentage of patients with IGCCCG good, intermediate, and poor risk status was 32%, 32%, and 36%, respectively. Twenty-one patients had induction chemotherapy followed by PC-RPLND. BEP, EP, and VIP was used in 62%, 29%, and 9%, respectively. RPLND histology is listed in table 2. Overall, 67% of patients had NSGCT elements in the retroperitoneum and 33% had fibrosis in the RP. Teratoma was present in 38% of patients. Malignant transformation of teratoma was present in 14% of patients. Viable NSGCT was present in 14% of patients. Fifty-nine percent of patients had some component of teratoma in the RP. While one patient (5%) had seminoma

in the RP after induction chemotherapy, this patient also had teratoma in the RP. This patient received adjuvant chemotherapy with 2 cycles of EP. There was no patient that had pure seminoma in the RP at the time of RPLND despite all patients having pure seminoma on orchiectomy. One patient had an elevation in pre-orchiectomy AFP with a histologic diagnosis of pure seminoma and underwent primary RPLND. RP histology in this patient did not reveal metastatic GCT. Two patients had extra-retroperitoneal resections. The extra-retroperitoneal site histology mirrored the RP histology. The first patient had malignant transformation of teratoma at RPLND and also had malignant transformation in a resected liver mass. The second patient had teratoma at RPLND and had dissection of a neck mass which also showed teratoma.

Overall, 7 patients relapsed during follow-up. The most common site of relapse was the retroperitoneum (71%), followed by the lung (29%), and liver (29%). This is illustrated in table 3. Most relapses (71%) occurred before 1999 when template dissections were used. All patients that relapsed (n=7) received salvage chemotherapy. TIP was used most frequently (71%). Re-operative RPLND was performed in 3 patients, all of whom had teratoma at the time of re-resection. Actuarial relapse free survival at 5 and 10 years was 76% (95% CI 52 to 90) and 61% (95% CI 34 to 80) (figure 1). Actuarial disease specific survival at 5 and 10 years was 100% and 88% (95% CI 39 to 98).

Comment

AFP is a glycoprotein whose production is limited to the liver, gastrointestinal tract, and fetal yolk sac. Relative to testicular cancer, secretion of AFP is limited to the NSGCT histology. For this reason, it is important that patients with a pure seminoma at orchiectomy and an elevated serum AFP are treated like patients with NSGCT. Our study has shown that over two-third of the patients had components of NSGCT histology at the time of PC-RPLND. In fact, there was no patient that had pure seminoma in the retroperitoneum at the time of PC-RPLND. Only 1 patient had any seminoma in the retroperitoneum, and this patient also harbored teratoma in the retroperitoneum. Since treatment paradigms vary greatly between seminoma and NSGCT, proper diagnosis is hallmark towards directing appropriate therapy for both low stage and advanced disease.

The management of low stage (I to IIa) NSGCT and seminoma diverge significantly. Since low stage seminoma is exquisitely sensitive to radiotherapy, cure can be achieved in the vast majority of men with radiotherapy. (2) (3) (4) Teratoma is rarely found after the treatment of seminoma. Radiotherapy for the treatment of NSGCT has had limited success. (5) (6) (7) (8) Excellent success rates associated with treatment of NSGCT with chemotherapy and RPLND preclude radiotherapy as acceptable treatment. This study has shown that NSGCT elements in the RP can be identified in almost 70% of patients with pure seminoma at orchiectomy and an elevated serum AFP.

Limitations of this study warrant discussion. First, an elevated AFP in the setting of pure seminoma is a rare entity. No single institution study will be able to capture all patients that meet this specific criteria. Thus, while it is difficult to know the true denominator of patients who meet this criteria, this study provides valuable information on a significant cohort of

patients with pure seminoma at orchiectomy and an elevated serum AFP. Second, while patients who presented from outside institutions did have their orchiectomy pathology reviewed at MSKCC, pathologic review is sometimes limited by the number of slides provided for analysis. It is possible that small foci of NSGCT in the orchiectomy specimen were not seen for this reason.

Correctly distinguishing between seminoma and NSGCT is also critical in advanced germ cell tumors. Patients with advanced stage testicular cancer (clinical stage IIb or greater), regardless of histology, are treated with risk adapted chemotherapy with platinum based chemotherapy. After chemotherapy, however, patients with pure seminoma are often observed if the residual mass is less than 3 cm in size because the high likelihood of fibrosis in the RP outweighs the risk associated with surgery in this setting.(9) Post-chemotherapy surgery for NSGCT is usually indicated because the RP can harbor viable cancer or teratoma in over 50% of patients. (10) (11) (12) This study illustrates NSGCT elements were found in 60% of patients. Unresected teratoma may grow, invade into adjacent structures, and has the potential to transform into somatic cancers such as sarcoma or carcinoma. (13) (14) (15) (16) Improperly identifying a man with pure seminoma at orchiectomy with an elevated AFP as a pure seminoma patient may leave him vulnerable to unresected harmful NSGCT elements.

Conclusion

A patient with an elevated AFP and a histologic diagnosis of pure seminoma at orchiectomy should be treated like a patient with NSGCT. In our study, NSGCT elements were present in two-thirds of the patients and no patient harbored seminoma alone. Understanding this phenomenon is hallmark because improper identification and treatment of these patients like a pure seminoma can affect relapse and survival.

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Figure 1.
Consort diagram

Table 1

Baseline patient characteristics (N=22)

Age	32 (IQR 28, 40)
Median follow-up (years)	4.1 (IQR 1.1, 7)
Laterality	
Left	16(73)
Right	6(27)
Pre-orchietomy AFP	248(IQR 48, 4693)
Pre-orchietomy HCG	804(IQR 1, 8226)
Ochietomy histology	
Pure Seminoma	22 (100)
Clinical Stage	
I	1(5)
II	11(50)
III	10 (45)
Pre-Chemo AFP	279(66, 5311)
Pre-Chemo HCG	337(12, 13935)
IGCCCG Risk Stratification	
Good	6(32)
Intermediate	6(32)
Poor	7(36)
Chemo Agent	
BEP	13(62)
EP	6(29)
VIP	2(9)
Pre-RPLND Elevated AFP	4 (18)
Pre-RPLND AFP	6 (IQR 5,10)
Pre-RPLND Elevated HCG	4(18)
Pre-RPLND HCG	0 (Range 0, 24)

Table 2**RPLND Histology**

RPLND Histology	
Fibrosis	7(33)
NSGCT Histology	15(67)
Pure Teratoma	8(38)
Malignant Transformation	3(14)
Viable NSGCT	3(14)
Any Teratoma	13(59)
Any Seminoma *	1(5)
Pure Seminoma	0(0)
Adjuvant Chemotherapy	1(5)

*
also had teratoma

Table 3**Relapse Data**

Relapse (n=7)	
Sites of Relapse	
Retroperitoneum	5(71)
Lung	2(29)
Liver	2(29)
>1 site	2(29)
Marker elevation only	1(14)
Any Marker elevation	4(57)
Relapse (n=7, year of surgery)	
Before 1999	5(71)
After 1999	2(29)
Relapse Chemo Agent (n=7)	
TIP	5(71)
TICE	1(14)
Autologous BMT	1(14)
Redo-RPLND (n=3)	
Pathology at Redo-RPLND	
Teratoma	3(100)