Mildly elevated serum alpha-fetoprotein (AFP) among patients with testicular cancer may not be associated with residual cancer or need for treatment

Serum tumor markers (STM) play a key role in diagnosis, prognosis, management, and follow up of testicular cancer [1–3]. However, the specificity of STM is limited and false positives can occur. Specifically, elevated AFP in adults can be associated with a variety of underlying processes [3–5]. It is important for physicians to recognize these alternatives, particularly when AFP is only mildly above normal. We review a cohort with testicular germ cell tumors from three geographically distinct referral centers in the United States to identify a large case series with persistently elevated AFP not reflecting the presence of testicular cancer (Figure 1).

A total of 705 consecutive patients presenting with testicular cancer to the University of Chicago Medical Center (n = 209) and University of Southern California (n = 422) from 2007 to 2016, and the Johns Hopkins Hospital (n = 74) from 2013 to 2015 were reviewed. Patients with non-germ cell primary testicular tumors, benign testicular tumors, metastases from non-testicular primary tumors, and insufficient medical records were excluded. Among these, we identified patients with AFP levels above normal but below 30 ng/ml, persistent for at least 6

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References


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Letters to the editor

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Figure 1. Serum AFP values for patients based on time from diagnosis with additional interventions noted. Patient 5*—time is from AFP elevation 11 years after original diagnosis. Patient 7*—time is from identification of enlarged RP lymph node 4 years after diagnosis.

Table 1. Details regarding the 10 patients with stable mild AFP elevation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Histology</th>
<th>Stage</th>
<th>Disease and treatment course</th>
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<tbody>
<tr>
<td>1</td>
<td>NSGCT (100% teratoma)</td>
<td>IA</td>
<td>• 30-year-old&lt;br&gt;• Pre-orchiectomy: AFP 18.8 ng/ml, hCG, and LDH normal. Post-orchiectomy: AFP 18 ng/ml, hCG normal&lt;br&gt;• AFP has ranged from 15 to 18 ng/ml over the subsequent 15 months with no clinical or radiographic evidence of disease</td>
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<td>2</td>
<td>NSGCT (75% embryonal, 15% yolk sac, 10% teratoma)</td>
<td>IB</td>
<td>• 35-year-old&lt;br&gt;• Pre-orchiectomy: AFP 38.3 ng/ml, hCG 6.6 mIU/ml, LDH 202 U/l&lt;br&gt;• Post-orchiectomy: AFP 9 ng/ml, hCG, and LDH normal&lt;br&gt;• Underwent RPLND (for IB NSGCT) with 26 negative lymph nodes&lt;br&gt;• AFP ranged from 9 to 11 ng/ml over the subsequent 29 months with no clinical or radiographic evidence of disease</td>
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<td>3</td>
<td>NSGCT (95% teratoma, 5% yolk sac, &lt;1% embryonal)</td>
<td>IIB</td>
<td>• 28-year-old&lt;br&gt;• Pre-orchiectomy: AFP 559 ng/ml, hCG normal&lt;br&gt;• CT revealed a 3.8-cm retroperitoneal lymph node&lt;br&gt;• Post-orchiectomy tumor markers: AFP 106 ng/ml, hCG within normal limits&lt;br&gt;• Received four cycles of etoposide and cisplatin with AFP 12 ng/ml following chemotherapy&lt;br&gt;• Retroperitoneal lymph node remained enlarged following chemotherapy and patient underwent RPLND in November 2012 with 1 lymph node (of 22) with teratoma&lt;br&gt;• AFP 10–13 ng/ml over the subsequent 24 months with no clinical or radiographic evidence of disease</td>
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<td>4</td>
<td>NSGCT (55% teratoma, 40% embryonal, 5% yolk sac)</td>
<td>IB</td>
<td>• 18-year-old&lt;br&gt;• Pre-orchiectomy: AFP 301 ng/ml, hCG 36 mIU/ml&lt;br&gt;• Post-orchiectomy: AFP 90.9 ng/ml, hCG 3.5 mIU/ml&lt;br&gt;• AFP decreased to 9 ng/ml over next 8 weeks&lt;br&gt;• Underwent RPLND (for IB NSGCT) and was found to have 6 positive nodes (of 53) (yolk sac, embryonal, and teratoma).</td>
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| 5       | Seminoma  | IB    | - AFP 9 ng/mL following RPLND. Received BEP ×3  
- AFP 8–11 ng/mL over the next 43 months with no clinical or radiographic evidence of disease  
- 31-year-old  
- Pre-orchiectomy: AFP <5 ng/mL, hCG and LDH normal  
- Post-orchiectomy: normal tumor markers  
- Over the next 11 years, the patient had no clinical or radiographic evidence of disease  
- AFP became elevated to 10.8 ng/mL and fluctuated from 11 to 18 ng/mL with no clinical or radiographic evidence of disease  
- Most recent AFP 13 years after diagnosis was 22.2 ng/mL |
| 6       | NSGCT (90% teratoma, 8% embryonal, 2% choriocarcinoma) | IA    | - 32-year-old  
- Pre-orchiectomy: AFP 143 ng/mL, hCG 1854 mIU/mL, LDH 137 U/L  
- Post-orchiectomy: AFP 14.5 ng/mL, hCG normal  
- Recommended to monitor AFP; however, oncologist at an outside hospital administered three cycles of BEP. AFP 14.7 ng/mL following chemotherapy  
- AFP ranged from 14.7 to 15.8 ng/mL over the next 9 months with no clinical or radiographic evidence of disease |
| 7       | Seminoma  | IA    | - 52-year-old  
- Pre-orchiectomy: AFP 24.4 ng/mL, hCG <1 mIU/mL, LDH 209 U/L  
- Post-orchiectomy: AFP 27.6 ng/mL, hCG 2.4 mIU/mL, LDH 155 U/L  
- AFP ranged from 21.3 to 29.3 ng/mL over the next 48 months with no clinical or radiographic evidence of disease  
- Five years following diagnosis, new 15 mm para-aortic lymph node  
- Received three cycles of BEP with resolution of the lymph node. AFP following chemotherapy was 26 ng/mL  
- AFP has fluctuated from 24 to 40.2 ng/mL over the subsequent 24 months (most recently 31.1 ng/mL) with no clinical or radiographic evidence of disease |
| 8       | NSGCT (100% embryonal) | IS    | - 21-year-old  
- Pre-orchiectomy: AFP 18.2 ng/mL, hCG 2.6 mIU/mL, and LDH 154 U/L  
- Post-orchiectomy: AFP 61.7 ng/mL, hCG and LDH normal  
- Treated with three cycles of BEP with AFP decrease to 7.8 ng/mL  
- AFP ranged from 7.9 to 8.6 ng/mL over the next two months with no evidence of disease  
- Underwent RPLND with no lymph nodes containing viable cancer  
- Following RPLND, AFP normalized to 6.4 ng/mL  
- AFP ranged from 7.9 to 94 ng/mL over the next 24 months with no clinical or radiographic evidence of disease, most recently 7 ng/mL |
| 9       | Seminoma  | IB    | - 33-year-old  
- Pre-orchiectomy: AFP 14 ng/mL, hCG <0.5 mIU/mL, and LDH 219 U/L  
- Post-orchiectomy: AFP 17.6, hCG <0.5 mIU/mL, and LDH 181  
- 1.3 cm right retroperitoneal lymph node  
- RPLND with no positive lymph nodes (of 36 total)  
- Following RPLND, AFP remained elevated at 15.6 ng/mL  
- AFP ranged from 12.6 to 14.9 ng/mL over the next 9 months with no clinical or radiographic evidence of disease |
| 10      | Seminoma  | IA    | - 45-year-old  
- Pre-orchiectomy: AFP 11.3 ng/mL, hCG 1.0 mIU/mL  
- Post-orchiectomy: AFP 10.9 ng/mL, hCG <1.0 mIU/mL  
- 4 months following diagnosis, new suspicious left external lymph node on CT scan with biopsy positive for seminoma. AFP of 10.9 ng/mL  
- Received 3 cycles of BEP with resolution of lymph node, with a stable AFP following  
- AFP ranged from 12 to 15 ng/mL over the next 45 months with no clinical or radiographic evidence of disease |
months, and with no additional clinical or radiographic evidence of testicular cancer.

Among 593 patients, 10 (1.7%) met inclusion criteria (Table 1). Median age was 32 years old (IQR 28–35). Three (30%) were diagnosed at a study site, whereas seven (70%) were referred to a study site after initial diagnosis. Nine (90%) had stage I disease at presentation and one (10%) had stage IIB. Six (60%) had non-seminoma and four (40%) had seminoma. Two (20%) ultimately had documented disease recurrence, requiring treatment with chemotherapy, but continued to have unchanged, mildly elevated AFP. The median length of follow-up from diagnosis was 42 months (IQR 16–84). Average length of AFP elevation was 22.6 months (range 9–49).

Three patients received additional interventions based on their elevated AFP: one underwent an RPLND (patient 8) and two received chemotherapy (patients 4 and 6). For all three patients, the post-treatment AFP was unchanged. No identifiable etiology of the elevated AFP was found in any of the 10 patients.

These patients highlight ‘falsely elevated’ AFP can have a significant impact on treatment decisions, requires a comprehensive evaluation to rule out an etiology, but can ultimately be safely managed with continued surveillance. Any new or sustained increase in AFP warrants a thorough evaluation including repeat values, evaluation of the chest/abdomen/pelvis, contralateral testicle (if present), and infused CT scan of the liver. Our findings also provide strong evidence that modest elevations in AFP often have a significant effect on treatment. These interventions, in the form of chemotherapy, radiation, and surgery, are invasive, costly and accompanied by potential morbidity.

We conclude mildly elevated and stable AFP, when not accompanied by any other indication of testicular cancer, should be managed by ongoing surveillance. This would likely reduce unnecessary treatment, morbidity, and cost.