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Commentary

Head and Neck Germ Cell Tumors: Effectiveness of Alpha-Fetoprotein as a Diagnostic Biomarker

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Abstract

Germ cell tumors (GCT) represent an assorted group of benign and malignant neoplasms derived from primordial germ cells. Although most GCTs reside in the retro-peritoneal cavity, tumors can also exist in the midline axis of the body including the mediastinum and head and neck regions. The cervical areas encompass the oral cavity, neck region, eye orbits, nasopharynx, and oropharynx. Both benign and/or malignant teratomas (yolk sac) can develop in tissues such as mandible, gingiva, upper lip, epignathus, floor of the month, base of the skull, scalp, lingual, and craniofacial areas. Alpha-fetoprotein (AFP) is a well-known and highly utilized biomarker for teratomas of the head and neck regions. AFP levels have long been employed as a "first response" biomarker for the cervical GCTs because AFP is a marker of aggressive disease. Both serum AFP and the cytoplasmic presence of AFP play a notable role in the diagnosis, follow-up, and monitoring of post-surgical resurgence and/or reduction of GCT mass. Thus, serum levels of AFP have served as an indicator of tumor activity, chemotherapy response, presence of malignancy and cancer cell transformation. In this report, it is demonstrated that AFP presence, in the blood of certain tumor bearing patients, is a superior biomarker to hCG, CEA, and lactate dehydrogenase; while cytoplasmic AFP, together with established histopathological markers, aid in confirming GST diagnosis.

Keywords: Alpha-fetoprotein; Germ cells; Teratomas; Meta-analysis; Biomarkers; Cancers; Head and neck tumors; Malignancies

Introduction

Clinical Background

Germ cell tumors (GCTs) designate masses of tumor growth composites of pluripotent primordial cells derived from all three developmental germ cell layers consisting of ectoderm, endoderm, and mesoderm [1]. Both cystic and solid tissue areas of GCTs originate from toti-potent aberrant germ cells of the blastula and/or morula stages at the 5th to 6th week of embryogenesis [2]. The GCTs are thought to arise due to mis-directed germ cells passaging along the dorsal wall of the embryo near the body midline during their migration from the fetal yolk sac to the gonadal folds [3]. These ectopic germ cells undergo proliferation, differentiation, and transformation into either fetal (immature) tumor or more differentiated (mature) tumor tissues [4]. Miscues in germ cell localization cause the migrating cells to come to rest at or near the midline dorsal mesenteries in regions of the sacral vertebra, retroperitoneum, mediastinum, pineal region, and the head and neck areas. The head and neck regions affected include the oral cavity, cervical areas, eye orbits, nasopharynx, and oropharynx [5].

Types of Germ Cell Tumors

Teratomas are part of the GCT family of tumors that includes seminomas, dysgerminomas, endodermal yolk sac tumors, embryonal carcinomas, gonadoblastomas, and choriocarcinomas [6]. Teratomas represent a mostly benign histologic type of pediatric germ cell tumors. The teratomas have a cystic tissue structure and a solid tissue structure. Following treatment, teratomas have an excellent prognosis [7] and many are curable with multi-agent chemotherapy and complete surgical resection followed by monitoring of serial alpha-fetoprotein (AFP) measurements [8].

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The present commentary is intended to address the overall effectiveness of alpha-fetoprotein (AFP) as a first response biomarker for GCTs in light of other serum and histopathologic markers.

Benign and Malignant Germ Cell Tumors

Many GCTs in childhood occur at mid-axial body sites of the intracranial head and neck areas and comprise about 5-6% of all neonatal tumors [9]. In this subset, cervical/facial teratomas are the most common followed by oropharyngeal and nasophyngeal tumors [10]. The head and neck tumors produce large tissue masses of benign growth causing clinical distress during the perinatal period (i.e. breathing/swallowing/vision difficulties and cosmetic effects), especially in areas of the mouth, throat, nose, temporal bone, info-temporal fossa, eye orbit, and the intracranium [11].

Although many GCTs are benign, malignant ones do occur dependent on tumor type. Most malignant tumors occur in the sacrococcygeal region, but can also occur in the head and neck regions with a GCTs incidence of one in 20,000 to one in 40,000 live births [12]. Moreover, it has been reported that only 2.5% of GCTs in children are malignant compared to 69% in adults [13]. When malignant transformations occur in the migrating germ cells, malignant germ cell tumor tissue can be observed. Endodermal yolk sac tumors (YST) represent a subtype of germ cell tumors that usually grow in the gonads but can also occur in midline body areas as stated above. Yolk sac tumors are malignant cancers that display cytoplasmic Schiller-Duval bodies and elevated AFP levels [11]. The YSTs are very aggressive with a poor prognosis and show early metastatic potential to organs such as the lungs, lymph nodes, liver, and bones [14].

Alpha-fetoprotein as a Biomarker for Head and Neck Germ Cell Tumors

Alpha-fetoprotein (AFP) is the most abundant fetal protein present during embryogenesis. It is first synthesized by the yolk sac and fetal liver, then by gastrointestinal tissues such as fetal stomach and pancreas [15]. Human AFP can be present in two distinct forms, namely, the blood circulating serum secreted form (69 Kd) and a histologically detected non-secreted cytoplasmic (Cy) form (<67 Kd) [16,17]. Both forms can be present together and each is an autocrine growth-promoting entity affecting cell growth, proliferation, signal transduction, and transcription/translation [18]. The cytoplasmic form of AFP (CyAFP) lacks an amino-terminal signal sequence of 19 amino acids and a glycosylation site, while full length serum AFP (SAFP) contains a total of 609 amino acid and a single glycosylation site [17]. Clinicians should take into consideration both functional forms when assessing their presence in head and neck germ cell tumors. It would be advantageous for clinicians to include measurements and observations of both serum and histological AFP as much as possible since both AFP forms are growth promoting factors.

Elevated serum levels of AFP in germ cell tumors are useful for: 1) the differential diagnosis of yolk sac tumors and teratomas; 2) monitoring responses to therapy; and for 3) prognosis [10,9]. Immuno-histochemical presence of AFP in tumor cell is useful in confirming the diagnosis of yolk sac tumors and teratomas and excluding other GC tumors [2,13]. SAFP is highly elevated in most endodermal yolk sac tumors and in certain other germ cell tumors. Many cancer cells display cell surface membrane receptors for AFP, especially tumor cells such as YST and some GCTs [19,20]. The AFP molecule has been demonstrated to be an autocrine growth factor that binds its cognate receptor, entering the cell by receptor-mediated endocytosis, and affecting several signal transduction pathways leading to increased cell cycle progression, cell growth, and cell proliferation. In non-AFP secreting tumors, cytoplasmic (Cy) AFP plays a significant role in upregulating KRAS, cyclic adenosine monophosphate, protein kinase-A, increasing cytosolic Ca++ levels, and cooperating with growth factors and transcription proteins to promote cancer cell growth [18]. Thus, the presence of circulating SAFP and cytoplasmic CyAFP both represent the presence of growth-stimulating entities with the potential to promote tumor progression via growth, proliferation, and metastasis [17,21,22].

Usefulness of AFP as a Biomarker in GCTs

Serum AFP can also play a role in the diagnosis, follow-up, and monitoring by means of post-surgical SAFP determinations. Serum AFP levels can serve as an indicator of disease activity as well as the presence of malignancy and cancer cell transformation [2,6]. AFP levels are also measured following chemotherapy and/or tumor resection. Although monitoring of single AFP determinations are important, more essential is the serial measurements and kinetic plotting of SAFP concentrations over time periods [23,24].

The utility of AFP as a biomarker for GCTs has additional advantages. Upon initial patient presentation, AFP measurements could be used to determine criteria for potential maturity or immaturity of the tumor. As a precaution, it is noteworthy that elevated AFP levels are present in both immature and healthy neonates less than one year of age [1,2]. Moreover, an absence of AFP does not necessarily eliminate a congenital tumor because perinatal AFP levels are directly influenced by both birth (body) weight and gestational/perinatal age. AFP presence further plays a definitive role in surveillance of tumor recurrence and clinical monitoring to predict GCT early recurrence and treatment outcomes. As implied above, reliance should not only depend on the presence of an elevated AFP level, but should be based on the kinetics of serial SAFP determinations. Eventual diagnosis of the GCT should also take into account the immuno-histochemical presence of cytoplasmic AFP observed in frozen and paraffin tumor sections. In addition to SAFP levels, some laboratories have incorporated additional biomarkers such as glypican, CDX2 (a homeobox transcription factor), and serum lactate dehydrogenase with some success [25]. Although beta-human chorionic gonadotrophin (hCG) is not elevated and provides no added value in diagnosing teratomas, it does have value in other GCTs. Histopathological markers have also included LMWCK (a tyrosine kinase) and SALL2 (a

transcription factor) proteins [25,26]. Multiplex immunobead analysis of biomarkers for GCTs involving 60 different markers have been recently reported and employ algorithms for interpretation [27]. Twenty-six of the biomarkers detected in the immunobead assay included proteins such as cytokines, chemokines, growth factors, and tumor antigens in this recent study.

AFP Levels in Various Head and Neck Germ Cell Tumors

Discussed below is a meta-analysis of select patient case studies and their SAFP and CyAFP determinations in teratomas, endodermal yolk sac tumors, embryonal cell carcinomas, and squamous cell carcinomas. This analysis was divided into 5 subgroups based on SAFP concentration (ng/ml) ranges representing 25 case studies encompassing 83 GCT-bearing patients. However, only select tumor-bearing patients have been listed below as examples.

Group I

The first group of GCTs to be addressed is head and neck teratomas that expressed serum AFP concentrations of 100 to 1000 ng/ml. Such tumors are exemplified by three cervical/neck and craniofacial teratomas, two endosomal yolk sac tumors and one squamous teratoma with SAFP levels ranging from 127 to 700 ng/ml [11,6,7,23,24,27]. Cytoplasmic AFP was reported in more than half of the cases. The ages of Group-I patients ranged from newborns to 5 years of age.

Group II

The second group of GCT demonstrated SAFP levels within a range of 1,000 to 10,000 ng/ml. A mature GCT teratoma of the neck displayed a SAFP level of 6,591 ng/ml and another of the scalp (embryonal carcinoma) displaying 1,500 ng/ml [5,7]. Three endodermal yolk sac tumors of the upper lip, sinopharynx and nasopharynx expressed a SAFP range from 1,000 to 3,000 ng/ml, [4,13,7]. Cytoplasmic AFP presence was detected in more than half of the tumor, largely in endodermal yolk sac tumors. The ages of Group-II patients ranged from newborns to 3 years of age.

Group III

The third group of GCT examined displayed SAFP levels over a range of 10,000 to 100,000 ng/ml. The eight tumors included two oropharyngeal, one craniofacial, one thyroid gland, two yolk sac submandibular tumors, and two cervical/neck tumors displaying a SAFP range from 10,800 to 96,000 ng/ml [1,8,14,27-29]. These tumors displayed cytoplasmic AFP in half of the tumors examined including all of the yolk sac tumors. The ages of Group-III patients ranged from newborns to 10 years of age.

Group IV

The fourth group of GCT represented the highest AFP levels measured in patients of the present report. Both patients in this group exhibited SAFP levels that exceeded 100,000 ng/ml. One tumor originated in a patient with an oropharynx (epignathus) tumors displaying a SAFP level of 316,000 ng/ml. The second tumor, a craniofacial teratoma, expressed a level of 220,000 ng/ml [2,28]. Yolk sac tumors were not represented in this group. Neither tumor type had been examined for cytoplasmic AFP. In these two different teratomas, SAFP levels far exceeded those observed in the group-3 yolk sac tumors. The ages of Group-IV patients ranged from newborns to 4 years of age.

Group V

The fifth group of GCT was represented by two squamous cell carcinomas, one displaying a SAFP level of 244 ng/ml [6], while the other tumor patient displayed a SAFP level that was not elevated exhibiting a normal value of 2-4 ng/ml [26]; cytoplasmic AFP presence was reported only in the former tumor patient. Thus, not all squamous carcinomas express aberrant SAFP levels. The ages of Group-V patients were one 2 year old (former) and one 60 year old patient (latter).

Concluding Statements

Germ Cell Tumors (teratomas) are an assorted group of benign and malignant neoplasms derived from primordial germ cells. Most GCTs of the fetus/neonate are benign, except yolk sac tumors; the teratomas can be expressed as either mature or immature. The immature tumors display both the higher SAFP levels and the maximum tumor spacial dimensions than the mature teratomas. Many GCTs contain calcifications and strands of partially differentiated segments of hair, bone, muscle, and other bodily tissues. Tumor masses can also be detected by antenatal and perinatal sonography and by physical exam (palpation). In fact, AFP determinations in the prenatal and perinatal periods have proven invaluable in measuring both maternal serum and amniotic fluid levels [12,14]. The most recently-accepted chemotherapy regimen for GCT patients includes cisplatin, bleomycin, and etoposide [7]. In the past, GCTs have been misdiagnosed as lymphadenopathies and lymphangiomas [2]; however, AFP is not elevated in most lymphatic tumors.

Measurements of AFP serum levels and cytoplasmic presence have proven extremely helpful in the diagnosis of germ cell tumors. Indeed, AFP is a marker of aggressive disease. However, AFP levels should not be considered absolute discriminatory factors of germ cell tumor type or maturity. Serial monitoring of SAFP levels should be performed to analyze the kinetics of serum AFP levels over time periods that could reflect neoplastic growth or lack thereof. Hence, AFP measurements can serve as indicators of response to both surgical measures and chemotherapies. Decreasing AFP levels indicate a neoplastic mass reduction and possibly reduced metastases; whereas, increased AFP levels mark a neoplastic relapse. It was further revealed in the above discussions, that SAFP determinations for GCTs can be superior to serum hCG, CEA, and lactate dehydrogenase measurements in some instances. Moreover, determination of cytoplasmic AFP presence in combination with glypican, placental alkaline phosphatase, and alpha-1-antitrypsin provides a very useful combination for histopathological examination.

Postscript

For further information on childhood germ cell tumor treatment, the reader is directed to reference [30].

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