Is Alpha-Fetoprotein a New Biomarker for Fetal, Infant and Juvenile Anemia? A Commentary

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Abstract: Alpha-fetoprotein (AFP) is well known as a biomarker for certain cancers and fetal birth defects. However, AFP has long been overlooked as an indicator for the presence of anemia in various diseases of fetal, neonatal, and juvenile individuals. A survey and meta-analysis of the biomedical literature revealed that elevated levels of serum AFP may serve as a viable biomarker of moderate to severe anemia at various stages of ontogeny. Such conditions of anemia could include bone marrow failure, pancytopenia, macrocytosis, microcytosis, and aplastic anemia. Since many congenital diseases that result in anemia are progressive and lethal, the need for a biomarker that could predict and parallel the advancing anemic state in disease would be of utmost importance to the biomedical community.

Keywords: Alpha-fetoprotein, paravirus, anemia, bleeding, folate deficiency, fanconi anemia, hemoglobin, bart's disease.

1. INTRODUCTION

Alpha-fetoprotein (AFP), a tumor-associated fetal protein, has long been utilized as a biomarker for various cancers and fetal birth defects. During pregnancy AFP has served as a reliable biomarker for neural tube defects, aneuploidies, and chromosomal abnormalities. However, its role in anemia and erythropoiesis is less recognized. Although elevations in maternal and fetal serum (MS and FS) AFP are known to occur as a result of fetal-maternal bleeds; other diseases of elevated AFP involving anemia in the fetus/infant are not widely studied. Such conditions include bone marrow failure, pancytopenia, macrocytosis, myelodysplasia, and hypochromatic, microcytic, and aplastic anemias. Many such anemic disorders are inherited recessive disorders which are progressive, lethal, associated with congenital abnormalities with a predisposition to develop malignancies in later life. Hence, it is of utmost importance to the biomedical community that reliable biomarkers are sought and utilized in predicting anemias during fetal, infant, juvenile, and even adult periods of life. Since anemias can be lethal, such a biomarker with predictive ability would meet a worldwide medical and public health need.

In order to assess the value of AFP as a biomarker for anemia, one must first examine the relationship of AFP to various components of the hematopoietic process following embryo/fetal development. In the course of embryonic development, AFP is first synthesized in hematopoietic organs such as the yolk sac and fetal liver and later in the stem cells of bone marrow and oval cells in the adult liver. During pregnancy, it is of interest that both MS-AFP and FS-AFP are significantly correlated with multiple components of the hematopoietic system. Such components include fetal hemoglobin, hematocrit, red blood cell numbers, erythroblasts, erythropoietin, serum iron, transferrin, and ferritin [1]. MS-AFP and FS-AFP appear to play a regulatory role in both fetal hematopoiesis and erythropoiesis. Failure of the hematopoietic processes due to disease and fetal malformations lead to advancing stages of anemia in fetuses and infants. One such example reported by Bartha *et al*. [2] demonstrated that FS-AFP and amniotic fluid AFP (AF-AFP) levels were higher than normal in anemic cases of red blood cell (Rh) alloimmunization. In other instances, AFP levels were found to increase during late hematopoiesis and in early stages of anemia. These data suggested that increasing levels of AFP might be valuable in predicting fetal anemia in certain instances (see below).

At present, there are at least five situations during pregnancy and three in infancy and juvenile stages in which elevated levels of AFP occur concurrent with moderate to severe anemias. The pregnancy examples are discussed first followed by the infant, juvenile, and in one instance of adult anemia. First, it was reported that P19-paravirus infections during 16 to 26 weeks' gestation induced fetal anemia, edema, hydrops, and accumulation of abdominal ascites fluid [3]. Significant elevations of MS-AFP (74 to 560ng/ml) were detected in 13 of 35 (37%) paravirus infected women with fetal complications including aplastic anemia. Secondly, in

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47 cases of fetal hemoglobin Bart's disease, MS-AFP levels (MOM = 2.09; 74-171ng/ml) were elevated at 18-22 weeks' gestation [4-6]. The fetuses exhibited localized edema and hydrops fetalis accompanied by bone marrow failure and moderate anemia. Thirdly, in several pregnancy cases of erythropoietic porphyria (Gunther's disease) at 15-17 weeks' gestation, elevated MS-AFP levels (MOM = 2.87) were accompanied by abnormal ultrasound scans showing ascites, pericardial effusions, and skin edema [7]. In Gunther's disease, an enzyme mutation in uroporphyrin synthesis causes abnormal development in multiple organs, accompanied by severe fetal anemia. Fourthly, FS-AFP levels were found higher than normal in anemic fetuses (200-340ng/ml) from pregnancies with red blood cell (Rh) alloimmunization after the 26th week of gestation [2]. In this regard, failed hematopoiesis occurred during 30-35 weeks of pregnancy in Rheusus immunized women causing complications which led to advanced stages of anemia. Fifth, in folate deficiencies at 30-40 weeks' gestation, high levels of MS-AFP (150 mg/ml) were present during a steady decline of maternal serum folate which is accompanied by a mild physiologic anemia [8]. In the folate deficient pregnant women, there occurs a high incidence of the megablastic-type anemia.

In the infant and juvenile periods, there was found three reported cases in which elevated serum AFP levels correlated with the anemic state. First, a French study of elevated AFP levels was observed in 60 patients with Fanconi Anemia (FA) (ages 1.0 to 53.0 years, median age 13 years). Serum AFP levels in the FA patients ranged from 10.0 to 69.0ng/ml, while 27 control patients (median age 15 years) displayed values less than 8.0ng/ml [9]. The FA condition first manifests as bone marrow failure, followed by pancytopenia, and culminating in aplastic anemia. Secondly, a study of 33 patients (ages 1.0 to 28.0 years; median age 11.6 years) with a Turkish variant FA was reported which utilized 110 control patients (ages 1.5 to 50.0 years; median age 21 years) [10]. Elevated serum AFP levels in FA ranged from 8.0 – 26.0ng/ml, while all control sera were less than 8.0ng/ml. The FA patients exhibited macrocytosis and eventually aplastic anemia. Thirdly, a study comprised of 60 adults with acute bleeding anemias and 75 healthy adult control patients was performed to ascertain AFP serum levels [11]. The anemic patients displayed normal liver function but no other overt disease. Using a modified radioimmunoassay to detect differences in the normal adult AFP range, anemic patients without disease displayed AFP levels of 1.8–3.3ng/ml, while control levels were from 0.25 to 1.2ng/ml. The anemic patient population displayed mainly hypochromatic and microcytic anemias, while hyperchromatic and macrocytic anemias were less prevalent.

From the above discussion, there is no doubt that a relationship exists between elevated serum AFP levels and anemias in fetal, infancy, juvenile, and adult stages. In amniotic fluids (AF), a significant positive correlation was found between the levels of AF-AFP and a cytokine termed Stem Cell Factor, but not in other AF cytokines [12]. MS-AFP levels have further been correlated with fetal hemoglobin, and Doppler cerebral artery velocity measurements in fetal anemia concurrent with alloimmunization during pregnancy. Thus, small to moderate elevations in MS-AFP, FS-AFP, and AF-AFP appear to serve as reliable biomarkers to foreshadow and predict both the state of erythropoiesis and of developing anemias. Although AFP may not be the ideal biomarker for anemia, it is one of the few (perhaps the only one) that is useful in predicting anemia in multiple stages of human ontogeny.

DISCLOSURES

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LIST OF ABBREVIATIONS

AFP – alpha-fetoprotein

FA – Fanconi anemia

MS – maternal serum

FS – fetal serum

AF – amniotic fluid

MOM – multiple of median

Rh – Rhesus

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