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The Role of Circulating Antigen and Autoantibody in Diagnosing Ovarian Cancer

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Abstract: ***This review will focus on recent knowledge related to circulating autoantigens and autoantibodies in ovarian carcinoma diagnosis. Since autoantigens and autoantibodies have been identified in the circulation of patients with early-stage cancer, it has been speculated that the assessment such panel specific for ovarian carcinoma might hold great potential as a novel tool for early diagnosis of ovarian carcinoma.***
Keywords: Tumor associated antigen, autoantibody, ovarian cancer, serum marker.

I. INTRODUCTION

Ovarian cancer often has no symptoms in the early stages. At later stages, it becomes more difficult to treat and can be fatal. This is primarily because majority of ovarian cancer cases present at an advanced stage (FIGO stage III and IV), with the disease spread well beyond the ovaries [1]. Over the last three decades, despite the advances in treatment of ovarian cancer, the associated poor prognosis and high death rate have not significantly improved [2]. It has been also noted that current therapies for patients with early FIGO stage I/II improves the 5-year survival rates from 73% to 93%. Their usefulness, however, is limited for patients with advanced stage disease where the 5-year survival is only about 30% [3,4]. Till date the diagnosis of ovarian cancer is done by either transvaginal ultrasonography (TVU) and serum levels of the cancer antigen 125 (CA125) or their combination. Both the techniques are inappropriate for screening the populations in general. Previous studies have shown that TVU can provide some degree of high sensitivity; however, its specificity and was found to be unsatisfactory [5]. Although effective at identifying 80% of patients with late stage disease, CA125 is only elevated in less than 50% of early stage ovarian cancer [6]. Another disadvantage to the use of CA125 is its elevated levels in benign conditions including endometriosis, fibroids, pelvic inflammatory disease as well as various other malignancies. Thus, it is very important to detect the disease at its earliest state with high specificity and sensitivity.

II. SERUM TUMOR BIOMARKER

No single biomarker, including CA-125, has sufficient sensitivity at high specificity for the early detection of ovarian cancer. Therefore, it is necessary to identify additional informative biomarkers that complement CA-125 [7].
Tumor markers can be secreted or shed by the tumor more than the normal tissue or cell phenotype. These can occur as re-expression of silenced genes or as an alternative mRNA splicing expression of an already expressed gene product. Some glycoproteins produced by cancer cells have altered glycan structures, although the proteins themselves are ubiquitous [8].
Tumor markers are secreted, released, or leaked through different mechanism into the bloodstream and is detectable in blood samples. To enter the bloodstream directly, proteins are cleaved into truncated forms or fragments, which are sometimes specific to the protease micro-environment of the tumor [9,10].
Serum markers for early detection of ovarian cancer other than highly studies CA 125, that are currently used or under investigation are discussed below.

A. Cancer Antigen 19-9 (CA 19-9)

Serum levels of CA 19-9 (monosialoganglioside antigen widely used in gastrointestinal adenocarcinoma diagnostics) are elevated in 68% to 83% of mucinous ovarian cancers but in only 28% to 29% of non-mucinous types, whereas CA-125 is elevated in 80% of non-mucinous ovarian tumors [11-14] providing a differential diagnostic tool for non-mucinous versus mucinous subtypes. Other markers, alone or in combination, have also been used; serum CA 15-3, CA 72-4, and CEA levels are elevated, respectively, in 50% to 56%, 63% to 71%, and 25% to 50% of patients with ovarian cancer [15-21]. Additionally, these markers did not offer additional clinical benefit for monitoring ovarian cancer, suggesting that the serial measurement of these markers may play a role only in the management of patients with a normal CA 125 assay [21].

B. Human epididymis Protein (HE4)

HE4 has recently been accepted as monitoring method for patient management with ovarian cancer by the U.S. FDA. HE4 showed the highest sensitivity of 72.9% among all single markers, including CA-125, in the detection of ovarian cancer, in both the early (62%–83%) and late (75%–93%) stages by a study done by Li and his group [22].

C. Lysophosphatidic Acid (LPA)

Elevated serum LPA levels, another potentially useful marker, were found in 90% and 98% of ovarian cancer in early and late stages, respectively; however, serum levels of LPA do not correlate well with the stage of the disease, and nonspecific elevation of LPA was detected in healthy and benign gynecologic conditions [23-24].

D. Cell Surface Death Receptor (sFas)

Significantly, elevated sFas levels are detected in some patients with ovarian cancer as compared with healthy women, and serum sFas level was shown to be a statistically significant indication factor for survival, as well as histologic grade, in ovarian carcinomas [25].

E. Mesothelin

Mesothelin [26], is a protein of unknown biologic function, which is present in normal mesothelium and has been detected at elevated levels in the serum of patients with mesothelioma, ovarian cancer, and some squamous cell carcinomas. Through transcriptional profiling, mesothelin was found to be elevated in the serum of 76% of patients with ovarian cancer and was also found to be informatively complementary to CA-125 in early detection of ovarian cancer [27].

F. Haptoglobin-a (HP-a)

Using surface enhanced laser desorption and ionization (SELDI) and mass spectrometric protein profiling, HP-a (a liver protein) has been identified as being a potential tumor marker having a 64% sensitivity and a 90% specificity in ovarian cancer patients [28].

G. Bikunin

Bikunin is a glycosylated protease (glycoprotein) that inhibits tumor cell invasion and metastasis. Recently a report suggested preoperative plasma bikunin as a strong prognostic marker for ovarian cancer. A large study showed that low plasma level of bikunin were associated with late-stage disease, probable suboptimal debulking with a large residual tumor (>2 cm) outcome, low response to chemotherapy, and reduced survival time [29].

H. Ovarian Cancer Related Antigen (OVX1)

OVX1 can be detected by radioimmunoassay. In a study, OVX1 was found to be upregulated in more than 50% of ovarian cancer patients who were CA-125 negative [30,31].

Other marker panels for early detection of ovarian cancers have been investigated. Zhang and colleagues identified a panel of markers that consisted of 3 proteins, including apolipoprotein A-I (apoA-I), a truncated form of transthyretin (TTR), and a cleavage fragment of H4 (inter-a-trypsin inhibitor heavy chain) to detect early-stage ovarian cancer with a sensitivity of 83% and a specificity of 94% [32]. For early detection of ovarian cancer, a multiple logistic regression model (MLRM) was used by Su and his group for CA-125, ApoA-I, transferrin (TF), and TTR [33]. A sensitivity of 89% and a specificity of 97% was provided by this model for early detection of ovarian cancer. The model also distinguished normal and mucinous ovarian cancer samples with sensitivity and the specificity of 95% and 92%, respectively. Nosov and colleagues applied this same MLRM model and marker panel to analyze serous and endometrioid histologic types of ovarian carcinomas; they showed a sensitivity of 94% and a specificity of 94% for serous ovarian carcinoma in its early stage, and a sensitivity of 98% and a specificity of 98% for endometrioid ovarian carcinoma in its early stage [34]. Visintin and colleagues proposed a panel of serum biomarkers that consisted of leptin, prolactin, osteopontin, insulin-like growth factor II (IGF-II), macrophage inhibitory factor (MIF), and CA-125 to discriminate between patients with ovarian cancer and healthy women. The panel had a sensitivity of 95% and specificity of 99% [35]. Not surprisingly, this panel provided a significant improvement over CA 125 alone. However, these studies had similar methodologic limitations of excessive numbers of tumor cases versus small numbers of matched population controls.

One important question remains: how long before the diagnosis of an ovarian cancer does the serum level of various markers begin to rise above background levels as a tumor grows? To answer such questions Anderson and colleagues [36] studied the serum

concentrations of CA125, HE4, and mesothelin in from 0–18 years before the diagnosis of a tumor. They found that the markers may provide some evidence of ovarian cancer up to 3 years before clinical diagnosis, but the more likely lead time for the detection of a change associated with these markers appears to be less than 1 year.
In conclusions, proteomics and bioinformatics-based research hold a great potential promise for finding more accurate and useable biomarkers for early detection of ovarian cancer.

III. AUTOANTIBODY PROFILING IN OVARIAN CANCER

Autoantibodies directed against tumor associated antigens (TAAs) may use as more sensitive diagnostic markers. TAAs are tumor specific proteins and peptides that are subjected to dysregulation, mutation or post translational modification (PTM) during cancer development and have been reported as potential causes of an (auto-)antibody response [37]. There are few characteristics of autoantibodies that make them potential candidates for biomarker validation and screening. First, they are detectable at early stages of disease. Their production by B-lymphocytes can be activated by a single antigen resulting in signal amplification through the humoral immune response. Second, they are resistant to proteolysis and metabolism, hence, half-life of approximately 21 days [38-40]. This stability allows their reliable detection and facilitates their use in the development of diagnostics. Third, they are detectable in the blood serum/plasma, and can therefore be analyzed through well-established techniques [41].

Various methods like serological analysis of recombinant cDNA expression libraries (SEREX), phage display, protein microarray, serological proteome analysis (SEPRA) and immuno-affinity chromatography have been used to identify autoantibody biomarkers in various malignancies. However, reports on the use of these technologies in ovarian cancer are limited.

A. p53

The best characterized autoantigen/autoantibody relationship is tumor suppressor p53. p53 autoantibodies has been detected in approximately in 20-25% in patients with ovarian cancer [42]. Overexpression of mutant p53 in cancer cells results in the production of p53 autoantibodies [43,44]. Indeed, while mutation of p53 appears a seminal event in carcinogenesis and is present in 80% of type II epithelial ovarian carcinoma, it is still unclear why only a subset (20%–40%) of these cases generates anti-p53 autoantibodies [45].
In 2000, Vogl et al. analyzed with use of a newly developed ELISA based on highly purified and re-natured p53 the presence of anti-p53 autoantibodies in the sera of patients with ovarian carcinoma, patients with borderline ovarian tumor, and patients with benign ovarian tumor. The prevalence of anti-p53 autoantibodies in patients with invasive cancer was 19%, whereas no p53 autoantibodies were found in patients with ovarian borderline or benign tumors [46]. p53 mutation are high with type II tumors, thus p53 autoantibodies are associated with high grade tumors.
Tsai-Turton et al. [47] demonstrated that serum p53 autoantibodies levels were significantly higher in patients with type II ovarian carcinoma as compared to those of healthy women ($P < .001$). p53 autoantibodies level are found to be significantly higher in patients with advanced-stage (III/IV) type II carcinoma as compared to patients with early-stage (I/II) type II carcinoma ($P < .001$). Up to 80% ovarian tumors exhibit mutated p53, however investigations are carried out on why only 20% to 40% of these tumors exhibit autoantibodies to p53 [47].

B. Homeobox Proteins

The anti-HOXA7 autoantibodies assay alone allows no distinction between benign and malignant ovarian tumors, it can discriminate patients with well-to moderately differentiated ovarian carcinomas from healthy women. Naora and colleagues showed significant serologic reactivity to the HOXB7 antigen in 33.3% of ovarian carcinoma patients and in only 3.4% of healthy women ($P < .0001$). This observation has to be validated in larger cohort with investigation correlating titers of anti-HOXB7 autoantibodies with stage of disease. Nevertheless, Naora et al.'s data raise the possibility that serologic detection of HOXB7 autoantibodies could have diagnostic potential [48].

C. Heat Shock Protein (HSP)

Autoantibodies to HSP90 has been implicated in autoimmune diseases [49] and in malignancies such as ovarian cancer (50). Vidal et al., have showed that HSP90 autoantibodies are tumor associated and stage specific. By ELISA using a purified recombinant 27-kd heat shock protein (HSP-27), Korneeva et al. [50] demonstrated a significantly higher prevalence of serum IgG autoantibodies to HSP- 27 in patients with ovarian carcinoma 50% and other female genital tract malignancies compared to those in healthy women

3.4%.

With use of SEREX, Luo et al. [51] identified 12 new candidate ovarian carcinoma antigens. One of them, HSP-90, was studied in detail and found to be immunogenic in one-third of the patients with advanced-stage ovarian carcinoma. Based on the finding that anti-HSP-90 autoantibodies are frequently found in advanced-stage epithelial ovarian carcinoma, it has been concluded that anti-HSP-90 autoantibodies s might represent a novel biomarker for epithelial ovarian carcinoma and that HSP-90 might be used as a target for immunotherapy in this disease [51].

D. Cathepsin D

Chinni et al. [52] found that 40% ovarian carcinoma patients produced circulating autoantibodies to cathepsin D. Recently, Taylor et al. [53] showed that the presence of cathepsin D autoantibodies can differentiate between benign ovarian condition and ovarian carcinomas (even stage I carcinoma).

E. NY-ESO-1

NY-ESO-1autoantibodies have been linked with ovarian cancer (type II). The NY-ESO- 1 gene is located on Xq28. Stockert et al. [54] reported an autoantibody response to NY-ESO-1/LAGE-1 antigen in 12.5% of epithelial ovarian carcinoma patients. Serum autoantibodies to NY-ESO-1 and LAGE-1 was investigated by Odunsi et al. They showed that autoantibodies were detected in 30% ovarian carcinoma patients whose tumors expressed either NY-ESO- 1 or LAGE-1 antigens. Detectable autoantibodies were present for up to 3 years after initial diagnosis of epithelial ovarian carcinoma.

Other investigated autoantibodies to detect ovarian cancer include, GIPC-1, IL-8, Ep-CAM and S100A7. One research group [55] hypothesize that detection of serum autoantibodies to GIPC-1 might be a sensitive marker for early-stage epithelial ovarian carcinoma and superior to methodologies based on TAA detection. Combining IL-8 and anti- IL-8 IgG autoantibodies with CA-125 resulted in increased classification power as compared to individual markers analyzed separately. The authors concluded that IL-8 and anti-IL-8 autoantibodies might potentially serve as additional biomarkers for epithelial ovarian carcinoma [56]. Another study showed that autoantibodies to Ep-CAM are less sensitive and specific than CA-125, autoantibodies to Ep-CAM might be complementary to CA-125. By combining autoantibodies to Ep-CAM with CA-125, the specificity is increased as compared with CA-125 alone without lowering the sensitivity [57]. Another study stated that autoantibodies to S100A7 may serve as a useful biomarker for early diagnosis of ovarian carcinoma as it has been observed that increased S100A7 expression may be an early event in ovarian pathogenesis and [58].

IV. CONCLUSION

Thus, at present, there is little to offer for early diagnosis of epithelial ovarian carcinoma, but this is review is first in its type stating the importance of circulating antigen and autoantibody in ovarian cancer. Autoantibodies to TAAs have been shown to be present in the circulation of people with various forms of solid tumor even before TAAs can be detected, and these autoantibodies can be measured up to 5 years before symptomatic disease. We therefore suggest more study with larger cohort of subjects focusing detection of early ovarian cancer based on the relation between the autoantigen and its autoantibody. The immune system recognizes the TAAs as foreign and induces a humoral immune response very early in the disease process [59]. Although measurement of autoantibodies to a single TAA is possible, the low sensitivity and specificity renders single autoantibody measurements of little value for screening and early detection of cancer. There has been some proof, however, that combination of autoantibodies to various TAAs into a panel assay test might provide a reasonable level of sensitivity and specificity for the detection of cancer. Thus, the data holds a great potential of developing a serum assay evaluating the autoantibody response to a panel of TAAs for cancer diagnosis. The implications of this would be that autoantibodies to TAAs would provide a simple blood test for early diagnosis of epithelial ovarian carcinoma. Nevertheless, it must be remembered that measurement of serum autoantibodies to TAAs for early diagnosis of epithelial ovarian carcinoma is still investigational and should be carried out along with traditional diagnostic studies. Thus, there is a need to implement study combining its circulating antigen and their autoantibodies for better diagnostic methods with greater sensitivity and specificity.

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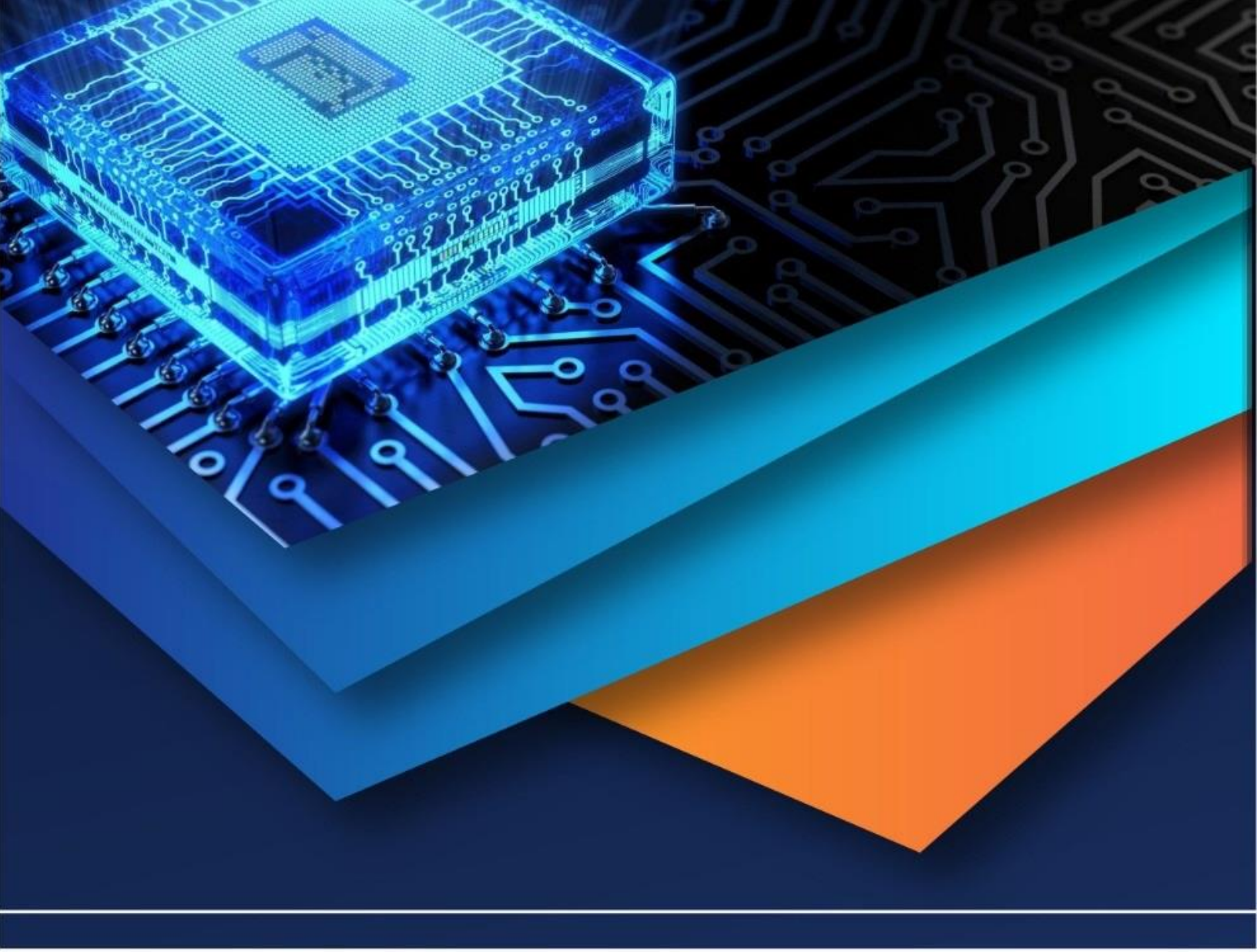

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