Is it possible to use the serum levels of alpha 1-antitrypsin as a serum biomarker to distinguish endometriosis and endometriosis-associated epithelial ovarian cancers?

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Clear cell carcinoma of the ovary (ovarian clear cell carcinoma [OvCCC]), one of subtypes of epithelial ovarian carcinoma (EOC), is often accompanied with endometriosis, which is also called as endometriosis-associated EOC (EAEOC) and frequently occurs in younger women.[1–5] Unsimilar to other subtypes of EOC (high-grade serous carcinoma of the ovary as an example) which are considered as a "silent killer" because symptoms of patients are often vague or asymptomatic, of short duration, often misdiagnosed as less deadly gastrointestinal diseases, and absence of an effective screening strategies, and additionally heterogeneous in nature, accounting for late diagnosis in their advanced stages, the majority of patients with OvCCC are detected in the early stage (the International Federation of Gynecology and Obstetrics stage I, especially for those patients are accompanied with endometriosis).[5–8] However, an early stage of OvCCC is not reflective of a better prognosis, since compared to other subtypes of EOC, OvCCC is always presented with its hereditary chemo-resistance status, contributing to worse prognosis.[5,9] The mechanisms of chemo-resistance status of OvCCC are extensively studied, including basic genetic changes, epigenetic modification, glycosylation, and tumor microenvironment (TME), and all of them attempt to provide a more reliable, sensitive, and specific biomarker to facilitate the purpose of screening, prompt diagnosis and/or predicting untoward outcome for patients with OvCCC, especially to distinguish OvCCC or EAEOC from pure endometriosis.[7,8,10,11] In the current issue of the *Journal of the Chinese Medical Association*, Dr. Chen and colleagues tried to use serum level of alpha 1-antitrypsin (AAT) isoforms (isoAAT) to examine whether this serum biomarker can be used for the aforementioned purpose.[12]

The authors retrospectively enrolled 103 patients (27 OvCCCs, 44 endometrioses and 32 benign ovarian tumors) to compare the pretreatment sserum level of isoAAT among three groups, and found that patients with OvCCC had a statistically significantly higher serum level of isoAAT than the other two groups (benign tumors) did, with a median of 161 ng/mL in OvCCC compared to 125 ng/mL of both benign tumor groups.[12] Additionally, after adequate debulking surgery and/or complete staging surgery, the patients with OvCCC had a dramatically drop of serum level of isoAAT from 161 ng/mL to 113 ng/mL, supporting that tumor burden of OvCCC is partly corrected with serum levels of this biomarker. Moreover, of the most impressive findings, when patients had preoperative serum levels of isoAAT ≤130 ng/mL, none of them (number as nine) died of OvCCC disease.[12] The current study is interesting and worthy of further discussion.

It is well known that serum marker of CA125 is a gold standard tool to monitor the therapeutic response and detection of recurrent disease in patients with EOC.[7,8,10] Although many efforts have been attempted to discover new cancer biomarkers to apply to patients with widespread cancer, there is still absence of any single biomarker which shows a satisfactory sensitivity and specificity for both screening or identifying the most common cancers, and additionally, nearly all biomarkers are ineffective for the detection of early-stage cancers,[8] suggesting the specific cancer-related biomarker is not in hand yet. Therefore, the authors' conclusion about the value of isoAAT in distinguishing OvCCC from benign ovarian tumors or serving as a potential prognostic biomarker is overestimated, and in fact, their belief is far away from reality. That is to say, their finding may present statistical significance, but not clinical significance, although their efforts are still worthy of congratulation and applause. As shown by authors that the measurement of their isoAAT for distinguishing benign to malignant ovarian lesions is a product after postmodified process,[12] the authors did not mention what is post-modification of this isoAAT in their study. We believe that this post-modification needs glycosylation changes of AAT. However, the glycosylation changes of AAT are relatively complicated, including agalactosylation, sialyation, fucosylation, and so on.[8,13] It is well known that AAT is an acute-phase protein with strong inhibitory activity towards proteolytic enzymes, mainly elastase but also trypsin, chymotrypsin, and thrombin, and its deficiency most often affects the lungs and livers, resulting in the development of early-onset emphysema, chronic obstructive lung disease and/or jaundice and liver cirrhosis.[14] Although some studies tried to use AAT to distinguish benign from malignant diseases, majority of them focused on

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AAT-targeted organs, such as lungs and livers.[13] Even though the aforementioned studies applied to evaluate the role of AAT as potential serum biomarkers have been found, the detailed information of glycosylated status of AAT is recommended for further exploring its value.[13] Without the adequate evaluation of this isoAAT by glycobiology methods, it is difficult to claim that this "isoAAT" can be tested in the future studies.

Additionally, during the acute stage of disease (often inflammation), caused either by pathogens or tissue damage, immune cells and stromal cells (TME) play a crucial role in the recognition and elimination of the inflammatory trigger. The release of various kinds of cytokines, enzymes, and mediators is often tightly controlled and orchestrated by certain types of cells.[7,8] Acute phase protein, based on its word meaning, appears in the early phase of the diseases, and of course, the cancer is also included. Therefore, the timing to measure acute phase protein is critical.

Moreover, as shown by our previous comments before,[15,16] cancer development and progression is associated with local (TME) and systemic inflammation as well as alternation in antitumor immunity, various kinds of cytokines, such as interleukin and acute-phase proteins, as well as immune cells and others, including tumor-infiltrating lymphocytes, tumor-associated neutrophils, M2 polarized macrophages, FOXP3 positive regulatory T cells, and platelets, which subsequently affect the peripheral circulation, resulting in the concept about the close correlation between these peripheral blood parameters, including serum biomarkers and outcome of cancers. However, changes of the peripheral blood parameters are dynamical and it is hard to find its clinical significance only based on one blood sample collected at a specific point. Additionally, as shown by the previous paragraph, acute-phase protein means that the disease stays in acute stage. Cancer is often considered as chronic illness which is involved in chronic inflammatory process. That is why we doubt the value of using acute phase protein as a tool (Dr. Chen's isoAAT for OvCCC) to study its association with cancer, although systematic inflammatory response is easily evaluated and its predictor value is widely accepted. However, the later should be well informed that its predictor value is only present in certain clinical situations.

Although we argue the clinical application of isoAAT to distinguish EAEOC, such as OvCCC from benign ovarian tumors, such as endometriosis, we welcome all studies which focus on this topic, since single biomarkers with satisfactory sensitivity and specificity have not been identified for the most common cancers and some biomarkers are ineffective for the detection of early-stage cancers.[13] To overcome the big gap between the early diagnosis and late diagnosis of EOC, and to distinguish from endometriosis and EAEOC, any attempt should be encouraged.

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