CA-125 in the Diagnosis of Pulmonary Tuberculosis

Dear Editor: I have read with interest the article published by Ozsahin et al. (1) focused on the validity of the cancer antigen-125 (CA-125) in the differential diagnosis of active pulmonary tuberculosis (TB). In accordance with a previous study by Yilmaz et al. (2), they reported higher serum CA-125 levels in active pulmonary TB than in inactive pulmonary TB. However, the authors found lower sensitivity and specificity values, and drew attention to the increased CA-125 level in patients with other pulmonary pathologies confused with TB. It seems plausible to suggest that TB must be considered in the differential diagnosis of patients with elevated serum CA-125 concentration; however, further well-designed studies are needed to define the precise role of CA-125 in the diagnosis and follow-up process of TB.

CA-125 is primarily used as a tumor marker for the diagnosis of ovarian carcinoma; however, it is known to increase in various non-malignant inflammatory conditions. The clearest evidence of the association between CA-125 and TB is seen in the cases of peritoneal TB exhibiting highly elevated serum CA-125 levels. A retrospective review of 22 cases of peritoneal TB showed that these cases had elevated CA-125 levels up to 2,021 U/ml (3). These cases represent an important diagnostic problem because it may lead to misdiagnosis as ovarian carcinoma. Furthermore, serum CA-125 levels were studied in patients with tuberculous peritonitis in a case-control study by Mas et al. (4), and were found to be elevated in all patients with tuberculous peritonitis; there was also a significant decrease after treatment. The authors concluded that serum CA-125 level might be used as an effective marker in the diagnosis and follow-up of peritoneal TB.

Another interesting study by Kalantri et al. (5) was carried out to evaluate CA-125 levels in conditions associated with pleural effusion and ascites. Their data showed raised CA-125 levels in most of the cases of ascites and pleural effusion, both transudates and exudates, irrespective of the pathology. However, the tuberculous ascites cases had higher CA-125 levels compared to tuberculous pleuritis. Their findings showed that both pleuriticum and pleural epithelium have the capacity to secrete CA-125, and the secretion occurs following inflammation or mechanical distress. However, they claimed that pulmonary TB as a closed lesion without involvement of the pleural epithelium does not evoke high CA-125 release.

In conclusion, a vast majority of evidence suggests that CA-125 is found increased in tuberculous peritonitis. Nevertheless, the validity of CA-125 is not clear in pulmonary TB without pleural epithelium involvement. The findings reported to the present encourage the further evaluation of this tumor marker in clinical trials to clarify its application in both the diagnosis and follow-up process of this disease that remains highly fatal worldwide.

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Ribavirin Treatment for Crimean-Congo Hemorrhagic Fever

Dear Editor: I read the manuscript entitled “Evaluation of the efficacy of ribavirin therapy on survival of Crimean-Congo hemorrhagic fever (CCHF) patients: a case-control study” by Izadi and Salehi (1) with great interest. They investigated the effectiveness of ribavirin at the capital of the Sistan-va-Baluchestan province which is the main endemic region of CCHF in Iran. They found that there was a positive impact of ribavirin on the prevention of death and also relationship between age and survival. They concluded that all suspected cases of CCHF should be treated with ribavirin as early as possible, until a definitive diagnosis is made available.

There is an ongoing debate over whether to treat CCHF with ribavirin. Ribavirin, a nucleoside analog, has some in vitro activity against CCHF and some experts recommend to use it based on retrospective observational studies. However it is not approved for treatment of CCHF by US Food and Drug Administration (FDA) and most of other official authorities including Ministry of Health of Turkey, another country having great experience on this disease.

I would like to raise a few points about the methods of the study. Ergonul (2) stated that the severity of infection, number of days from onset of illness, and severity of gastrointestinal symptoms are three leading confounders for interpreting the observational studies and if these factors are not properly controlled, there will be misclassification bias. At the study by Izadi and Salehi (1), the severity of the cases at both arms was not given including the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) which are important for determining the severity of disease. The weakness of this study is to include only CCHF IgG positive cases (21 of the 63 cases) into the analysis. Specific IgM declines to undetectable levels by 4 months after acute infection, but IgG could remain detectable for at least 5 years (3). Also the seroprevalence (IgG positivity

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against CCHF) of high risk populations who do not have acute infection could be as high as 12.8% in endemic areas (4). Rickettsiosis, Q fever, brucellosis, leptospirosis, relapsing fever, Lyme disease, viral hepatitis, meningitis, sepsis, meningococcal infection, malaria, hantavirus hemorrhagic fever and other hemorrhagic virus infections (5), and hematological disorders such as idiopathic thrombocytopenic purpura, leukemia (6) may mimic the manifestations of CCHF, hematological disorders such as idiopathic thrombocytopenic purpura, leukemia (6) may mimic the manifestations of CCHF, therefore using the only CCHF IgG positivity for diagnosis may cause misdiagnosis. Although the authors found a positive impact of ribavirin on survival of patients with CCHF, their report is biased and nonconclusive because of such misclassification. Therefore the data should be reanalyzed without the 21 cases that seropositive for only IgG or the cases could be categorized as confirmed versus suspected cases to get accurate results.

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In Reply: Many thanks for your careful attention to the article. We are very pleased that our efforts have attracted the attention of the other researchers in the region to the important issue of CCHF treatment. With regard to your comments about the flaws in the design of our study, please kindly let us to remind you some points:

(i) Based on most references, the judgment on the severity of the CCHF is usually based on a constellation of clinical and para-clinic findings, mostly mentioned in the Tables 2 and 3 of the original article and no clinician merely judges the severity of CCHF based on the AST or ALT levels (1-4).

(ii) We think there is a misunderstanding about the design of the study as follows. “The weakness of this study is to include only CCHF IgG positive cases (21 of the 63 cases) into the analysis.” As it has been explained clearly in the results section of the article, “10 out of 63 selected cases were seropositive for IgM only, 32 were seropositive for both IgG and IgM, and 21 were seropositive for IgG only. For the latter 21 cases seropositive for IgG alone, the IgM ELISA test results were not reported.” (2). However, we understand that our dear colleague is arguing about occurrence of misdiagnosis of other diseases mentioned in his letter and misclassification due to missing IgM results. About misdiagnosis we have to remind you that as it has been mentioned in the materials and methods section of the article, all the patients have been examined and managed carefully by an infectious disease specialist and all the other diseases other than CCHF have been excluded for them based on appropriate lab tests (diseases such as malaria, relapsing fever, leukemia, typhoid fever, meningitis, viral hepatitis, sepsis, and brucellosis).

(iii) With regard to misclassification and exclusion of the 21 cases without reported anti-CCHF IgM levels there is another story. First and foremost misclassification is the flaw of all types of studies (not merely the case-control ones) and all researchers do their best to decrease its level as much as possible. As it has been mentioned in the materials and methods section and also in the results section of the article, in the instance of patients without anti-CCHF IgM results, only those patients were entered the study “who had the typical clinical, laboratory, and epidemiologic presentation of bleeding CCHF” and no one was entered merely based on a positive anti-CCHF IgG result (2). As another important point, based on most published studies (5-7), during the study period (“the time interval between 2000 and 2006”) the seroprevalence of anti-CCHF antibodies in the study population (i.e., the population of Sistan and Baluchestan province, the most important endemic region of Iran) was not more than 7%, and it is too pessimistic to exclude all those 21 patients from the study to make it certain that there is no misclassification. In the worst situation, even if we consider about 10% misclassification (a bit above the upper 95% confidence interval limit of the highest reported seroprevalence in the region) (5,6), at most 2 of those 21 cases might have been misclassified and misclassification at such a level is not an excuse for disregarding all the results.

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