Falsely Increased Thyroid-stimulating Hormone Concentrations attributable to Interference from Human Anti-mouse Antibodies

To the Editor:

We describe a case of a spurious increase in serum thyroid-stimulating hormone (TSH) attributed to a circulating human anti-mouse antibody (HAMA) in a two-site mouse monoclonal antibody-based assay.

A 71-year-old woman on long-term levothyroxine therapy was referred for investigation of uveits. Her serum TSH had been maintained within the usual reference interval for more than a decade. The initial TSH value by an immunochemical method (assay A) on the Dimension RxL analyzer (Dade Behring) was 7.5 mIU/L (reference interval, 0.34–4.82 mIU/L). Because of this unexpected result, it was checked by another method (assay B), a two-site chemiluminescent immunometric assay (Third Generation TSH on the Immulite 2000; DPC Corp.). The TSH value for the same serum was 0.36 mIU/L (reference interval, 0.25–4.60 mIU/L), and free thyroxine was 18.8 pmol/L (reference interval, 10.3–25.5 pmol/L).

In assay A, chromium dioxide particles are coated with mouse monoclonal antibodies specific for the intact TSH, and detection is by an alkaline phosphatase-labeled mouse F(ab’)2 fragment specific for the TSH subunit. In assay B, the first mouse monoclonal antibodies specific for TSH are bound to a polystyrene bead, and detection is by an alkaline phosphatase-labeled goat polyclonal antibody preparation.

After addition of a blocking reagent composed of binders to inactivate heterophilic antibodies (HBT; Scantibodies Inc.), serum TSH on the Dimension RxL was 0.49 mIU/L. HAMA (IgG) measured by ELISA (Medac Diagnostika) was 253 μg/L (reference values, <40 μg/L).

In two-site (sandwich) immunoassays, HAMA present in serum can interfere by bridging between the mouse immunoglobulin capture antibody and the mouse immunoglobulin conjugate (1). The use of F(ab’)2 fragment eliminates the interference of anti-FC region heterophilic antibodies, but the interference of anti-idiotypic antibodies remains. Interference by HAMA or by an antibody with HAMA activity has been described previously with TSH assays from other manufacturers (2–4). This is the first description of such interference in TSH measurements on the Dimension RxL. Several authors have proposed the addition of nonspecific animal immunoglobulins from the same species or from other species to prevent binding with HAMAs (5,6). We understand that assay A has been reformulated with bovine gamma globulins. We retested the sample with the reformulated assay and obtained a value within the reference interval (0.34 mIU/L). We conclude that the presence of heterophilic antibodies should be considered when measured TSH concentrations are not compatible with either the clinical history or other thyroid function tests.

References

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Editor’s Note: The manufacturer declined to comment.

CA-125 Concentrations in Patients Awaiting Cardiac Transplantation

To the Editor:

CA-125 (cancer antigen or carbohydrate antigen) is a high-molecular weight glycoprotein most appropriately used for monitoring treatment response and recurrence of ovarian carcinoma, with concentrations >35 units/mL indicating residual tumor. Serum concentrations have also been shown to correlate with ovarian tumor mass. Increases, although usually not as marked, have been seen in other conditions such as lung cancer, gastrointestinal cancer, abdominal miliary tuberculosis, endometriosis, pelvic inflammatory disease, and during ovulation in 1–2% of healthy women. Therefore, this serum marker is not recommended as a screening test for ovarian carcinoma (1–3).

Recently, at the University of Pennsylvania Medical Center, CA-125 was inadvertently ordered on a male heart failure (HF) patient awaiting cardiac transplantation, and was found to be markedly increased at 1060 units/mL. The test was repeated and confirmed the marked increase. The patient was also tested for human anti-mouse antibody (HAMA) to rule out possible interference causing a false-positive result. The results of the HAMA test were negative. The CA-125 concentrations decreased after transplantation with improvement in clinical status (538 units/mL). We analyzed multiple sections of the patient’s explanted native heart by use of immunohistochemical staining for CA-125 (1:50 dilution; positive control = ovarian adenocarcinoma; Dako) to determine the source of CA-125 production. No positive staining was detected.
detected in the tissue (cardiac, vascular, and mesothelial cells).

A subsequent literature search revealed one study pertaining to CA-125 in HF patients. That study included 71 patients of all New York Heart Association (NYHA) classes and showed a relationship between advancing HF and progressive increases in CA-125 concentrations [mean CA-125 for NYHA classes: class I = 36 units/mL; class II = 79 units/mL; class III = 210 units/mL; class IV = 502 units/mL (4)].

The authors of this study felt that the elaboration of CA-125 could be from the pericardial mesothelium; however, the exact mechanism is unclear (4–7). In clinical practice, augmentation of HF therapy is based solely on worsening symptoms and echocardiographic findings. However, on the basis of this initial encouraging report and our experience, this pilot study investigated the possibility of using the CA-125 marker to identify patients with worsening HF before they develop clinical symptomatology.

We analyzed serum CA-125 concentrations using the CENTOCOR CA-125 II RIA from blood obtained during a 6-month period from 35 patients (33 males; 30 Caucasians) with NYHA class III or IV HF awaiting cardiac transplantation. Blood was drawn during their routine clinic visits and while they were hospitalized. This study was approved by the Institutional Review Board, and informed consent was obtained from all patients. Clinical stability was based on examination by a HF cardiologist, as well as invasive hemodynamic measurements. Patients with markedly abnormal hemodynamics, or those with signs of low output failure, were considered unstable. Although many of the patients did show increases in CA-125 concentrations, some being quite marked, there was no correlation between clinical status and the concentration of CA-125 (Table 1). There was also no correlation between “confounding” factors, such as pericardial, pleural, or peritoneal effusions.

We were unable to confirm the published correlation and conclude that CA-125 is not a useful marker in predicting cardiac status or managing pretransplant patients. However, perhaps a larger and longer-term study may be able to show a meaningful relationship.

### Table 1. CA-125 in stable and unstable HF patients.

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CA-125 concentrations at one time point in the 35 patients.

### References


### Notes

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### Toward a Laboratory Data Interchange Standard for Clinical Trials

**To the Editor:**

In 2001, an estimated 2.3 million people in the United States participated in and completed a clinical trial: 750,000 in government-sponsored clinical trials, 850,000 in industry-sponsored Phase I to III clinical trials, and 700,000 in industry-sponsored Phase IV clinical trials (1). Major medical center participation in the conduct of clinical trials grew strongly in 2001. More than 65% of...