Early Detection of Colorectal Cancer Metastasis and Relapse by Recognizing Nonspecific Cross-Reacting Antigen 2 in Commercial Carcinoembryonic Antigen Assays

To the Editor:

Carcinoembryonic antigen (CEA), one of the first known tumor markers, is still the most useful clinical marker to aid in the diagnosis and monitoring of colorectal cancer. Many commercial assays are available for measuring CEA, but their practical use is complicated by the molecular heterogeneity of CEA. CEA is a heavily glycosylated protein of the immunoglobulin gene superfamily and has several related antigens such as nonspecific cross-reacting antigen (NCA), NCA-2, and normal fecal antigen. Previous investigations have indicated that some commercial assays for CEA cross-react with various CEA antigens owing to the epitope group specificity of the monoclonal antibodies (mAbs) employed in the assay (1, 2). NCA-2 is a member of the CEA gene family and is structurally most similar to CEA. It has been reported that CEA might be increased in the serum of some colorectal cancer patients, and the cross-reactivity to NCA-2 might be a beneficial characteristic of CEA assays with respect to their diagnostic sensitivity in colorectal cancer patients (3).

A patient who had colorectal cancer and underwent a transverse colectomy at our hospital in 1996 suffered relapses of the cancer in 2000, 2002, and 2003 and had chemotherapy and surgical resection each time. In 2006, metastasis was detected in the liver, and surgery was performed to resect the liver metastasis. Serum CEA concentrations, measured using the Beckman Access CEA assay (Beckman Coulter) fell into a lower range (near the lower reference limit) after each surgery, but then increased gradually. We also measured CEA concentrations with the Elecsys CEA II assay (Roche...
Diagnoses) starting in December 2003, and the concentrations of CEA increased at a faster rate than with the Access CEA (Fig. 1A).

We subsequently assayed 1 serum sample from the patient on January 18, 2005, with the following 5 commercial CEA assays: Elecsys CEA II, Architect CEA (Abbott Laboratories), Lumipulse CEA-N (FujiRebio), SphereLight CEA (Wako Pure Chemical Industries), and Access CEA (Fig. 1A). Informed consent was obtained from the family of the patient. The results demonstrated that 2 of the 5 assays, the Elecsys CEA II and Architect CEA, yielded higher concentrations of CEA of approximately 400 µg/L, whereas the others yielded lower concentrations of CEA <100 µg/L. We performed gel-filtration and Western blot experiments with the same patient sample and NCA-2 that was extracted from meconium (3). Gel filtration of the patient’s serum revealed that the small amount of antigen was found by Lumipulse CEA-N, SphereLight CEA, and Access CEA, whereas large amounts of antigen were detected by Elecsys CEA II and Architect CEA, and the antigen was eluted at fractions of slightly smaller molecular size than others. NCA-2 showed the same elution profile as the patient specimen detected by the Elecsys CEA II. In addition, Western blot analysis indicated that the mAb of Elecsys CEA II reacted with both CEA and NCA-2 (lanes 4 and 5 in Fig. 1B) and that NCA-2 was clearly detected, yet CEA was barely detected in the patient’s serum sample (lane 2), although the mAb usually detects both CEA and NCA-2 in sera from patients with cancer of the colon and rectum (lane 3). According to the manufacturer’s documentation and comments, both the Elecsys CEA II and Architect CEA use anti-CEA mAbs cross-reacting with NCA-2, although the other kits use anti-CEA mAbs specific to CEA. This information agrees with the results of our investigations and strongly suggests that in this case the cross-reactivity with NCA-2 caused the substantially higher CEA concentrations with the Elecsys CEA II and Architect CEA. This finding is clinically important, but the recent National Academy of Clinical Biochemistry guidelines on cancer markers (4) do not address differences between CEA assays or the reports on CEA-related antigens (2).

After the patient underwent resection of liver metastasis in 2006, the CEA concentrations measured with both the Elecsys CEA II and Access CEA decreased rapidly, and the Access CEA results fell within the reference interval and remained unchanged in successive determinations. The Elecsys CEA II, however, remained above the cutoff value and rose in successive determinations (Fig. 1A). The patient suffered metastatic relapse of colorectal cancer, which eventually led to the patient’s death. This patient’s history reveals that colorectal cancer may mainly express NCA mRNA, as in this case, and thus monitoring NCA-2 concentrations using mAb with cross-reactivity to NCA-2 might be useful in the early detection of metastasis and relapse of colorectal cancer.

Further studies are clearly needed with additional patients with colorectal and other cancers, as well as healthy individuals, to validate the utility of monitoring NCA-2 in clinical practice.

References

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