COLLEGE of AMERICAN PATHOLOGISTS

Testing for Carcinoid Syndrome

SYNOPSIS AND RELEVANCE

There are several biomarkers including 5-hydroxyindoleacetic acid (5-HIAA), chromogranin A (CGA) and serotonin which are used for the evaluation of patients with suspected neuroendocrine tumors (NET) associated with carcinoid syndrome symptoms (eg, flushing and/or diarrhea) as well as for individuals who are asymptomatic with incidental findings that suggest a possible NET from endoscopic or imaging examinations. Application of laboratory systems and interventions for optimal test selection and performance is important to avoid interpretive errors and provide the best diagnostic outcomes in patients with carcinoid syndrome and NETs.

INSIGHTS

Tests used for symptomatic patients. Twenty-four-hour urine 5-HIAA is the primary screening test for symptomatic carcinoid syndrome and suspected NET; repeat testing to confirm previous results is appropriate practice. This test is also appropriate for post-treatment surveillance of NET at 3 to 12-month intervals for up to 10 years if elevated at initial diagnosis. Patients should be carefully instructed about dietary restrictions before specimen collection to avoid false positive test results. Twenty-four (24)-hour urine serotonin testing is indicated for patients with sustained symptoms who have persistently normal 24-hour urine 5-HIAA levels

Tests used for asymptomatic patients Addition of testing serum CGA and 24-hour urine serotonin with 5-HIAA are appropriate for asymptomatic patients with suspected NET based on incidental findings on imaging or endoscopy examinations. However, elevated serum CGA concentrations are associated with many other disorders, and this should be considered before attributing abnormal results to NET unless CGA is extremely high or associated with elevated 5-HIAA levels. Patients on proton pump inhibitors must refrain from taking medication at least 2 weeks prior to CGA testing to avoid false positive results. CGA testing every 3 to 12 months for up to 10 years is appropriate for post-treatment surveillance of NETs while serotonin is not typically beneficial for post-treatment surveillance.

Neuron specific enolase and/or pancreastatin are prognostic and/or post-treatment biomarkers for assessment and monitoring of NETs

BACKGROUND

Carcinoid syndrome is a condition which most commonly causes abdominal pain with recurrent episodes of flushing and/or diarrhea, symptoms due to secretion of vasoactive compounds such as serotonin from low grade neuroendocrine tumors (NET). Asymptomatic NETs are typically detected as incidental findings during endoscopic procedures or imaging examinations.

The single best biomarker for initial evaluation of patients with carcinoid syndrome symptoms is measurement of 5-HIAA in a 24-hour urine specimen. Twenty-four-hour urine 5-HIAA is the final product of serotonin metabolism and in the presence of carcinoid syndrome has greater than 90% sensitivity and specificity for NETs associated with carcinoid syndrome symptoms.[2] However, 24-hour urine 5-HIAA has less diagnostic value in patients with NETs that produce little or no serotonin, and who lack symptoms of carcinoid syndrome. Importantly, 24-hour urine 5-HIAA concentrations increase with certain serotonin-containing foods and pose a risk of diagnostic error if the patient is not properly prepared for testing. Repeat 24-hour urine 5-HIAA testing to confirm initial results is an acceptable practice.

Chromogranin A (CGA), a serum biomarker, is elevated with most NETs and higher concentrations are associated with larger tumor burdens and worse prognosis. However, this is a non-specific marker. Daily serum chromogranin A concentrations vary widely in patients with NETs, and CGA is commonly elevated in many other conditions including endocrine, gastrointestinal, cardiovascular, renal, inflammatory, and neoplastic disorders. Certain drugs such as proton pump inhibitors (eg, omeprazole), which stimulate neuroendocrine cells, are nearly always associated with elevated serum chromogranin A levels. While persistently normal serum chromogranin A levels may help exclude NET tumor as the cause of symptoms, a positive result (eg, greater than 10 times the upper limit of normal) lacks specificity. While serum CGA has limited value for initial diagnosis compared to 24-hour urine 5-HIAA measurements for patients with carcinoid syndrome symptoms, its measurement is useful for asymptomatic patients with suspected NET based on incidental findings detected during endoscopy or imaging examinations. It is also useful at initial evaluation for prognosis and as a baseline for monitoring after a diagnosis of NET is made.

Rarely, elevated urinary serotonin levels may be seen in patients with carcinoid syndrome symptoms who lack elevated 24-hour 5-HIAA concentrations. While not a primary biomarker for initial evaluation, measurement of serotonin in a 24-hour urine may be useful as a secondary test for the occasional patient with persistent carcinoid syndrome symptoms (eg, flushing, diarrhea) of unknown cause. It may also be useful as an adjunct to CGA for asymptomatic patients with suspected NET based on an incidental finding.

Measurement of serum CGA at 3 to 12-month intervals for up to 10 years after treatment for gastrointestinal NET is recommended. Monitoring of 24-hour urine 5-HIAA concentrations is similarly recommended if originally elevated at diagnosis.

Serum neuron specific enolase and pancreastatin are commonly produced by NETs, and levels correlate with tumor mass and metabolic activity. Higher concentrations are associated with poorer prognosis and metastatic spread.

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