

## Pitfalls in neuroendocrine tumor diagnosis

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Carcinoids, originating from cells of the diffuse endocrine system (DES), account for 0.7% of all malignancies and are characterized by a slow growth rate and the presence of nonspecific signs and symptoms often making their detection rather difficult. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) represent the majority (~70%) of DES tumors. Historically they account for about 2% of all gastrointestinal tumors but their incidence and prevalence have increased recently, likely owing to the advances accomplished with new endoscopy procedures and diagnostic tools, and to the achievement of long survival rates fostered by the indolent evolution of the disease. Currently, according to the algorithm proposed by Modlin<sup>1</sup> for diagnosis and management of GEP-NETs normally accepted by clinicians in routine clinical practice, the first action after clinical suspicions of a NET comprises the measurement of circulating markers such as CgA, NSE, serotonin, gastrin, or urinary 5-hydroxyindoleacetic acid (5-HIAA). In the case of positive findings, the subsequent action lies in the octreoscan, which allows the topographic localization of the primary lesion or of metastatic disease. Finally, the diagnosis is completed through the surgical resection of the primary tumor or the biopsy of the reachable metastases. However, neither laboratory tests nor octreoscans are completely reliable diagnostic tools because other clinical disorders or atypical radiological findings may mimic a carcinoid, hence leading to an erroneous NET diagnosis. Consequently, the distinct possibility of false positive findings exists, being the lack of experience with the disease the major reason for an incorrect diagnosis. Indeed, with the exception of some sporadic case reports,<sup>2</sup> it does not seem that the matter of the occurrence of false positive NETs has been taken into consideration systematically. Based on two years' experience, we report the occurrence of eight cases previously clinically diagnosed as NETs elsewhere, and then referred to our specialized reference center for pathological substantiation. After investigation, the following diagnoses were made: chronic atrophic gastritis (CAG) with enterochromaffin-like cell (ECL) hyperplasia (4 cases), estrogen-deprivation syndrome (1), hypochondriac disorder (1), metabolic syn-

drome (1), and sarcoidosis (1). Relying on this limited but significant occurrence rate, we deem that some key points should be argued.

Primarily, a frequent mistake concerns the interpretation of abnormal CgA plasma values: this marker, expressed in both functioning and non functioning NET tumors, shows a threshold of sensitivity and specificity depending on tumor histology, extension of the disease, and biological tumor activity.<sup>3</sup> Additionally, the methods used to measure CgA levels are not standardized yet, as appears from the comparison of the three commercially available kits, the outcomes of which may disagree considerably.<sup>4</sup> Other pathological conditions may hinder the specificity because CgA elevations can be detected in some instances in patients with renal and hepatic failure, untreated hypertension, inflammatory bowel disease, and even in the presence of nonendocrine tumors.<sup>5</sup>

Lastly, the use of proton-pump inhibitors may be responsible for the elevations of CgA values, and long-term acid inhibition is a well known cause of CAG with related ECL cell hyperplasia.<sup>6</sup> On the basis of CgA values, it would be best for clinicians to discriminate patients affected by carcinoids from healthy subjects and from those whose abnormal findings depend on hyperplastic lesions of endocrine cells in the context of a CAG. According to our experience,<sup>7</sup> the threshold value of CgA for identifying patients with NETs should be 36 U/L, which gives a specificity of 83-91%. More recently, however, it has been highlighted that there is a need to change the current cutoff CgA values to exclude patients in whom levels are elevated as a result of non-neoplastic conditions.<sup>8</sup> The authors set a 95% specificity, corresponding to cutoff values of 84-87 U/L, arguing that this is essential to exclude patients showing false positive CgA increases from unnecessary examinations specific for endocrine tumors. In our experience, when a borderline or doubtful value is observed, before proceeding to the workup we repeat the plasma assay with the addition of the detection of NSE plasma dosage and of urinary 5-HIAA: the latter, particularly, appears extremely useful and crucial to this purpose.<sup>9</sup>

Another issue critical in making the NET diagnosis easier is the correlation between marker serum values and referred symptoms at presentation. It should be highlighted that at diagnosis the classical carcinoid syndrome of flushing, sweating, diarrhea, abdominal pain, bronchospasm, and right-sided heart failure represents a fairly infrequent event occurring in less than 10% of NETs,<sup>10</sup> because it may depend on the secretion rate of tumor mediators, tumor size, its anatomical location and, chiefly, the extent of liver metastases. Additionally, octreoscan findings should be related to the clinical setting always; consequently, the need of reliable evidence is

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Conflict of interest: the authors report no conflicts of interest.

Received for publication: 31 July 2009.  
Accepted for publication: 14 August 2009.

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Rare Tumors 2009; 1:e32  
doi:10.4081/rt.2009.e32

mandatory. Notwithstanding the fact that octreoscan is carried out routinely in hospitals equipped with nuclear medicine units, the experience of the operators and the adoption of a correct procedure for the image acquisition represent the major issues to achieve reliable results. Based on the largest Italian experience carried out in three hospitals and involving 253 patients, a comparison of different procedures of octreoscan has demonstrated that the best specificity (88%) was obtained when a semiquantitative evaluation was employed.<sup>11</sup> In addition, this procedure showed that bowel preparation is not essential; conversely, when the 24-hour image acquisition shows accumulation in the abdomen possibly because of the radioactive bowel content, it is extremely important to repeat scintigraphy after 48 hours.<sup>12</sup> The capability of recognizing all uptake of physiological tracers and other pathological aspects resulting in a false positive octreoscan response can reduce the false positive results to 3% only.<sup>13</sup> It should be highlighted that the hypophysis, thyroid, liver, spleen, kidneys, bladder, gallbladder, and intestinal tract represent areas of physiological uptake of <sup>111</sup>In-DTPA-octreotide, and that somatostatin receptors are found even in activated leukocytes in granulomatosis processes (sarcoidosis, tuberculosis)<sup>14</sup> and chronic inflammatory processes (inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis).<sup>15</sup>

In conclusion, despite a better general understanding of neuroendocrine disease in terms of natural history, biology, and clinical behavior, differential diagnosis of NETs should be extremely extensive and accurate, needing additional and more definite investigations. Awaiting more specific diagnostic tests, clinical data and radiological findings should be interpreted always by taking the clinical setting, particularly, into consideration. A knowledge of conditions that could mimic a NET is a key factor in the approach to the disease, and close cooperation among dedicated physicians,

pathologists, nuclear medicine specialists, and conventional radiologists is warranted to define the optimal diagnostic protocol. Therefore, to save medical resources and to avoid the patient's impairment, it is appropriate that those patients strongly suspected of having a NET should be referred to and managed in highly experienced centers with the support of a greatly integrated multidisciplinary team.

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