



Editorial

## The Carney Triad: A Lesson in Observation, Creativity, and Perseverance

The triad described by Carney in this issue of *Mayo Clinic Proceedings* (pages 543 to 552) has special historical interest for me. Twenty-two years ago, the medical community was introduced by Dr Aidan Carney to a syndrome that included gastric sarcomas, pulmonary chondromas, and extra-adrenal paragangliomas that were likely to be functional and cause hypertension. All of these components tended to be multiple.<sup>1</sup> This complex has subsequently been designated the Carney triad, which exists thanks to the amazing degree of perseverance by Aidan Carney.

I began studying gastrointestinal stromal tumors (or GISTs) 30 years ago when I reviewed all the cases accessioned at the Armed Forces Institute of Pathology. My review included 3 malignant gastric tumors composed of round cells that formed multiple separate nodules. One patient was a 12-year-old girl, the second was a 24-year-old woman, and the third was a 30-year-old man. The 2 females had long survival times, but the man died of metastatic disease about 2 years after diagnosis. I did not recognize them as being anything special, and I buried them in the data covering all 127 GIST cases that were subsequently published.<sup>2</sup>

Aidan Carney somehow found these 3 cases hiding in that article, and he called me to discuss them. This situation was not unique; he was dedicated to tracking potential sources, a trait that has continued to this day and has resulted in his identification not only of this syndrome, but of others as well. He had found something about the tumors that I had missed, a subset of those tumors that formed part of a syndrome. They occurred in young women, were multiple, and had slow progression of their metastases. In contrast, the typical gastric stromal tumor is solitary, it occurs in patients with a mean age in the fifth or sixth decades, and the malignant tumors are aggressive.

Carney's original publication in 1977 included 4 cases from the Mayo Clinic and 3 more from the literature, a total of 7.<sup>1</sup> In the next report in 1979, the number was 15,<sup>3</sup> and the 5-year review in 1983 included 24 cases.<sup>4</sup> The latest compilation, published in this issue, comprises 79 cases

from Dr Carney's experience and from the literature, about 3½ cases a year. These are not the numbers of epidemics. Yet, this syndrome has been a catalyst for case reports and small series reports, and it has become a topic for surgical pathology slide seminars. Why do diseases such as the Carney triad appeal to surgical pathologists? Part of the appeal is that it is esoteric, and esoteric things in general seem to generate more interest and excitement than they deserve medically. Pathologists and, I suspect, other physicians enjoy reading about, hearing about, and discussing medical conditions that are both rare and complex, and these days, such conditions become even more interesting if they are associated with specific genetic abnormalities.

The Carney triad also appeals to pathologists because the most frequent component of the triad is a gastric stromal tumor. GISTs are uncommon mesenchymal neoplasms that have neither mature smooth muscle nor Schwann cell differentiation. They occur almost exclusively in the gut, although a few pop up in other sites, such as the omentum, mesentery, and retroperitoneum. They differ in cell type and growth pattern by site, so that gastric tumors bear little resemblance to small intestinal or rectal tumors. Gastric stromal tumors, the largest group of GISTs, come in several varieties.<sup>5</sup> Some are composed of spindle cells, while in others, the cells are round or epithelioid, and there are benign and malignant variants of both cell types. Initially, all these were thought to be smooth muscle tumors, but numerous studies using electron microscopy, immunohistochemical techniques, or both have proved that the tumor cells were not smooth muscle but were other cells with occasional muscle or Schwann cell or even neuronal features.<sup>6-10</sup> As a result, the smooth muscle designation has usually been dropped, and the nonspecific label "stromal tumor" was substituted. Numerous studies covering GISTs have been published in the past 10 years. In fact, at the March 1999 annual meeting of the United States and Canadian Academy of Pathology, an organization largely of academic surgical pathologists, these tumors were the subject of 1 of every 9 abstracts in the field of gastrointestinal pathology, a number similar to that for Barrett esophagus, colorectal cancer, and gastric cancer, diseases that are far more common and far more important than stromal tumors.

Why is so much time and energy expended studying GISTs? First, these tumors have had a reputation for unpredictable clinical behavior, so it would be wonderful if there were morphologic features that always predicted malignant behavior. So far, numerous mitoses and dense cellularity seem to be the best markers. Second, since the tumors contain neither mature smooth muscle nor Schwann cells,

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it would be a coup to identify the cell type. Recent studies have proven that the tumor cells express the *c-kit* protein often in conjunction with the CD34 antigen and have ultrastructural features of specialized pacemaker cells in the gut nerve plexuses known as interstitial cells of Cajal (ICCs).<sup>11,12</sup> Some GISTs also have mutations in the *c-kit* gene. The ultrastructural features include a mix of a few smooth muscle, Schwann cell, and neuronal characteristics, features that were observed for years before the ICC became the cell of the moment. These same features have been observed in Carney tumors, so they fit in nicely.<sup>13-15</sup> We await the definitive study of Carney tumors to prove that they contain ICCs like all other GISTs, although we have little doubt that they do.

The Carney triad has 3 anatomic components, but from the beginning, it was obvious that this was more than a triad, because it had 2 unusual clinical features, female sex and young age, thus making it a syndrome. As this syndrome has matured, more components have come to light, including adrenal cortical adenomas in one eighth of the patients, duodenal stromal tumors, and possibly esophageal leiomyomas. The peculiarities of this syndrome, including the unusual combination of tumors and their multiplicity, suggest that there should be a specific genetic defect, but as Carney reports, the evidence of possible familial occurrence is limited to siblings of 2 patients who had only paragangliomas. These new details, published in this issue of *Proceedings*, are part of the exhaustive review of the cases Dr Carney has collected. Of course, this is only a fraction of the cases that really have occurred. For example, in the past 20 years, I have seen in consultation several patients in their teens and 20s with gastric stromal tumors; some of the tumors were multiple, and most were composed of epithelioid cells. None of these patients has been described in the literature or seen by Dr Carney. For all these cases, I suggested to the contributing pathologists the likelihood of the patients' having the Carney triad. Unfortunately my follow-up is not nearly as complete as Dr Carney's, so I don't know if those patients have other manifestations of the triad. I bet they do!

From the data in this report, it appears that there is a typical Carney syndrome patient: female (85% were), less than 30 years old (82% were), with both gastric and pulmonary tumors (75% did), and with survival for about 20 years after diagnosis, even with hepatic metastases (81% were in this survival group). However, according to Dr Carney, few patients have all of the most common components, the 3 anatomic disorders, and the 2 clinical features. Fewer than a quarter had all 3 tumors. The gastric tumors, although mainly multiple, small epithelioid stromal tumors, also include big ones, single ones, and those composed mainly of spindle cells. An example is a man I saw in his

late 20s who had a single, huge gastric spindle cell sarcoma resected more than a year before he presented to our thoracic surgery department with masses in his lungs, which were thought to be metastases from the gastric sarcoma. One of these pulmonary masses was resected, and it was a chondroma. Did this patient have the syndrome? He was the wrong sex, but the right age. He had a malignant gastric stromal tumor, but the wrong cell type. He had pulmonary chondromas, but no paragangliomas. The Carney triad seemed likely, but there were no diagnostic rules to make that determination. Perhaps it is time for Dr Carney to establish the specific minimal diagnostic standards. He deals with this indirectly in his report when he mentions that long-term follow-up may be necessary in a patient with 1 of the features, because it may be many years (in 1 case, 26 years) before a second manifestation becomes apparent.

Has the Carney triad had a clinical effect? It is a rare condition, so rare, in fact, that Dr Carney has been able to collect only 79 cases from his own experience and from the literature in the 22 years since the first article on the subject appeared. The condition is not well known among pathologists and other clinicians. However, Aidan Carney, with intelligence and perseverance, recognized that not all gastric stromal tumors are the same and that there is more to them than simply determining the cell types within them or finding features that distinguish the benign ones from the malignant. He observed that a small group of them occurred in a specific clinical setting and that they had a peculiar clinical behavior. He scoured the literature for similar cases and tracked down the authors of most such reports with almost religious fervor to see if those cases were like his. The Aidan Carneys of the world are insightful and creative, and they force those of us who are neither to keep our eyes open, observe things carefully, and question dogma frequently. The Carney triad is not so much a medical issue as it is a medical lesson.

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