Carney et al first described the triad of gastric leiomyosarcoma, pulmonary chondroma and extra-adrenal paraganglioma in 1977, and this condition has been known as the Carney’s triad [1,2]. The gastric leiomyosarcoma is now termed gastrointestinal stromal tumor (GIST). Herein, we present a case with a GIST and upper gastrointestinal hemorrhage as initial presentations of the Carney triad, and a short review of literature.

**CASE PRESENTATION**

A 26-year-old woman complained of dizziness and generalized malaise lasting for 3 days before receiving...
emergency care in November, 2006. A review of her medical history revealed no underlying systemic disease. The patient also complained of several episodes of melena and anorexia during the 3 days before admission. Her hemodynamic status was normal, but physical examination revealed pale conjunctiva and dry oral mucosa. Irrigation by a nasogastric tube obtained a substance resembling ground coffee. Other than a hemoglobin level of 7.4 g/dL, her laboratory results were normal. Gastroendoscopy revealed an antral submucosal tumor over the lesser curvature side with an ulcer over the tumor and stigmata (Figure 1). An abdominal computed tomography (CT) scan after admission showed one antral intramural tumor and three other lesions over segments II/V of the liver and the retroperitoneal space. These lesions were assumed to be metastasized from the antral tumor (Figures 2A–C). A chest X-ray revealed no evidence of lung metastases. After her anemia and overall clinical condition improved, the patient underwent a wedge resection of the antral tumor, partial hepatectomy of the liver segment V lesion, and excision of the retroperitoneal tumor. Subsequent follow up at our hospital revealed an uneventful recovery.

The excised gastric tumor was grayish in color, 3.5 cm in diameter and had a solid parenchyma. Microscopic study revealed spindle cells arranged in fascicles, palisades and whorls. Immunohistochemical studies were positive for CD117 and CD34 (Figures 3A and 3B). The mitosis count was less than 5 per 50 cells in

Figure 1. Upper endoscopy image showing the antral submucosal tumor (double arrows) with a gastric ulcer (arrowhead) and stigmata.

Figure 2. Abdominal contrast-enhanced computed tomography and chest X-rays. (A) Intramural tumor at prepyloric antrum (single arrow)—a suspected gastrointestinal stromal tumor. (B) Liver metastases (arrowhead) in segment V. (C) Retroperitoneal tumor (double arrows) over the aortocaval region. (D) Bilateral lower lung field showing multiple nodular shadows (arrows). (E) Follow-up computed tomography performed 32 months after surgery shows no evidence of local recurrence or progression of the metastatic lesions (arrowhead).
each high-power field, which raised suspicion of gastrointestinal stromal tumor (GIST) with low risk of malignancy. Analysis of a liver specimen showed similar pathologic characteristics and immunohistochemistry findings to those observed in the gastric tumor and confirmed the diagnosis of GIST with liver metastasis. The retroperitoneal tumor was 4 cm in diameter with grayish nodules and well-defined nests of cuboidal cells that were separated by highly vascularized fibrous septa. Immunohistochemical studies were positive for chromogranin and synaptophysin (Figures 3C and 3D). Thus paraganglioma was diagnosed.

This diagnosis prompted further study for other lesions in the Carney triad. Positron emission tomography (PET) CT scans performed 1 month after surgery showed several regions of high fluorodeoxyglucose (18F) (FDG) avidity over liver segments II, III and V, between the right atrium and ventricle of the heart, and over the left subtemporal fossa (Figures 4A and 4B). Postoperative adjuvant therapy with imatinib mesylate (400 mg/day) was started 4 weeks after the metastatic GIST lesion was identified. A chest X-ray taken 5 months postoperatively showed several new nodular shadows over her bilateral lower lung field and were suspected to be metastatic GIST lesions or pulmonary chondromas, which is the third component of the Carney triad. However, the patient was otherwise asymptomatic. Further chest X-ray and an abdominal CT scan at 32 months after operation showed no change in pulmonary lesions or liver metastatic lesions (Figure 2E). Her condition was stable at her 33-month postoperative follow-up visit.
DISCUSSION

In 1977, Carney et al [1] first reported the association between gastric leiomyosarcoma, extra-adrenal para-ganglioma and pulmonary chondroma in seven patients. This synchronous or metachronous condition was later referred to as the Carney triad [2]. In 1999, Carney [3] collected data for a population of 79 patients with this syndrome, which included most of the cases reported worldwide. Important findings included female predominance (85%) and early onset of symptoms before 30 years of age in 82% of cases. Because associated tumors were rare and only 78% patients had one or two of the three components at the onset of symptoms, the presence of at least two of these three rare tumors was considered sufficient for diagnosing the triad. In practice, however, few patients exhibit all three components of the Carney triad, and its clinical presentation is usually chronic, persistent and indolent.

The gastric leiomyosarcomas in Carney triad are now termed GISTs. GISTs are immunohistochemically positive for KIT, which is also expressed by the interstitial cells of Cajal. A GIST is the most commonly observed (99%) component of Carney triad [3]. The most common initial clinical manifestation is a GIST with bleeding and associated symptoms and signs (e.g. anemia, hematemesis, and melena) [4], as noted in our case. Another widely reported characteristic of GISTs, as revealed by upper endoscopy in our case, is an ulcerated submucosal mass in the antrum close to the lesser curvature. Microscopic observation of the masses revealed polygonal and fusiform cells arranged in sheets, clusters and fascicles. In this triad, gastric GISTs are characterized by (1) early occurrence, (2) few local symptoms, (3) an intramural origin with eventual mucosal ulceration, (4) presentation typically in the antrum and the lesser curve, and (5) very slow progression of the metastases [3]. Surgical excision remains the only curative therapy for gastric GISTs associated with Carney’s triad. Although partial gastrectomy may be performed initially, further gastrectomy may be required if the tumors recur [3,4]. However, after initial surgical resection, recurrence of GISTs still occur in 46% of patients and multiple resections are often necessary. Meanwhile, excision is the preferred method for treating accessible hepatic metastatic lesions arising from a GIST.

Alternative therapies for metastases from GISTs are an interesting issue. Chemotherapy, radiation, thermoablation or cryoablation have been proven to be ineffective for treating metastatic lesions. Despite the widespread use of the tyrosine kinase inhibitor imatinib mesylate for treating metastatic GISTs, its role in gastric GISTs in the Carney triad has been rarely reported. Diment et al [5] performed the first molecular analysis of gastric GISTs in Carney triad, which revealed the absence of mutations in c-kit and platelet-derived growth factor receptor-α, with similar findings reported by Knop et al [6] and Stratakis et al [7]. Raffensperger and Krueger [8] shared their
experience in providing adjuvant therapy with imatinib mesylate in a patient surgically treated for liver metastases from gastric GISTs. However, 18 months after starting adjuvant therapy, the patient died of multiple metastases from her gastric GISTs. Stratakis and Carney [7] and Matyakhina et al [9], in their later reports of cases with Carney triad, revealed two chromosomal changes, 1q12-q21 deletion region and the loss of 1p. Both Diment et al [5] and Stratakis and Carney [7] concluded that the poor response of gastric GISTs in the Carney triad to imatinib mesylate may be due to the absence of c-kit and platelet-derived growth factor receptor-α mutations, either of which occur in most sporadic GISTs. The patient in the current study stabilized after 32 months of imatinib mesylate treatment. However, a longer follow-up is needed to exclude possible disease progression. We recommend further studies of adjuvant therapy for Carney triad GISTs to obtain a definite conclusion.

In contrast to the frequent occurrence of gastric GISTs in the Carney triad, extra-adrenal paraganglioma was reported in only 47% of patients [3]. Microscopically, the granular cytoplasm ranges from eosinophilic to clear and is arranged in a trabeculo-alveolar pattern supported by a fibrovascular stroma. Extra-adrenal paragangliomas are usually positive for chromogranin A. Other features include an extra-adrenal location, multifocality, functioning in 35% of cases and benign behavior in most cases [3]. However, four patients also exhibited metastasis from this tumor, which was also observed in the study by Carney. Therefore, the paraganglioma should be resected if it is accessible owing to the possibility of metastasis, the potential for compromised vascular and neural structures by continued growth of the tumor, and the positive outcomes of curative surgery. Vogl et al [10] shared their successful experience in treating paraganglioma non-operatively using transarterial embolization to impede the growth of mediastinal paragangliomas and carotid gangliomas. However, further evaluation of interventional radiology is needed to clarify its role in managing the Carney triad.

Pulmonary chondromas, the third component of the Carney triad, occur in 76% of patients [3]. Chondromatous hamartoma of the lung is believed to be a benign neoplasm derived from peribronchial mesenchyme [11]. Histologically, pulmonary chondromas are composed of mature cartilage, bone and myxoid stroma containing stellate mesenchymal cells [12]. The clinical features of these pulmonary tumors include: (1) appearance early in the disease course; (2) absence of symptoms or deleterious effects in most patients; (3) multifocal, bilateral or peripheral occurrence; (4) coarse calcification; (5) benign course; and (6) can be cured by surgery [3]. The tumor can be excised by thoracotomy or thorascopic approaches [13]. However, the tumor could be left in situ, as in the present case in whom surgical biopsy was not performed because the pulmonary lesions were asymptomatic and indolent [8,12].

Due to the extreme rarity of the triad components occurring individually, patients who are diagnosed with one component of the Carney triad should be assessed for the other components, particularly in female patients younger than 40 years of age. Margulies and Sheps [14] presented an algorithm for the initial assessment and continued follow-up of patients with one component of the Carney triad. In patients with gastric GISTs who also present with symptoms and signs of catecholamine excess, e.g. hypertension, or the presence of metanephrine or vanillylmandelic acid in 24-hour urine samples, the algorithm is an effective screen for biochemically active paragangliomas. If urine assays show abnormal findings, 131I-metaiodobenzylguanidine scans should be performed to localize the tumors. Vogl et al [10] reported the clinical use of 18-fluoro-2-desoxyglucose PET (FDG-PET) as an imaging tool in patient follow-up programs. Their use of FDG-PET in a patient diagnosed with a gastric GIST and pulmonary chondroma successfully identified one mediastinal mass, which was consistent with the presence of paragangliomas later identified by a 131I-metaiodobenzylguanidine scan and 111In octreotide scintigraphy. Kächele et al [15] also reported an epicardial paraganglioma lesion identified by PET CT in a patient who had undergone surgical removal of a GIST 1 month earlier. The above findings emphasize the importance of FDG-PET CT scans in patients with the Carney triad. Metabolically active lesions revealed by FDG-PET CT scans may represent paragangliomas in addition to GIST metastases or other primary tumors. Thus further diagnostic studies and intervention may be justified depending on the lesion location and the clinical condition of the patient. In the patient reported here, PET CT scans performed 1 month after surgery revealed several lesions over the bilateral lobes of the liver, right pericardium and left subtemporal area.
The PET CT scans detected occult lesions that other conventional imaging tools (i.e. standard CT) may not identify in the early postoperative phase. PET CT scans also provide a guide for follow-up after adjuvant therapy. Nevertheless, additional experience is needed to confirm the diagnostic role of PET CT in this triad.

In summary, this case report and literature review of the Carney triad should alert physicians to the possibility of this rare syndrome in young patients who exhibit one of the three components in unusual locations and the need for further diagnostic studies to identify early-stage tumors while curative surgery is still possible. Some patients may require long-term follow-up to detect other components of the Carney triad. Finally, the role of PET CT scans in identifying occult lesions and in guiding adjuvant therapy for gastric GISTs associated with this syndrome need further studies before definite conclusions can be made.

REFERENCES

一位 Carney Triad 病患的臨床表現、影像及病理之特徵：個案報告及文獻回顧

陳欽凡 1  莊捷翰 1  劉孟冠 2  許文鴻 2  林相如 3,4  謝建勳 1,5

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我們報告了一位罹患 Carney Triad 的病患以胃腸道基質腫瘤合併上消化道出血做為初始表現之案例。一位 26 歲的女性病患因為過去三天感覺頭暈以及解數次黑便而來到本院求診。理學檢查發現生命徵象正常，但眼結膜呈現蒼白。上消化道內視鏡檢查發現胃竇黏膜下腫瘤合併黏膜潰瘍及出血的證據。腹部電腦斷層檢查發現有：(1) 胃竇腫瘤(2) 肝臟第二及第五小節病灶(3) 後腹膜腔腫瘤。病人隨後接受了手術，術後恢復良好。病理診斷證實是胃竇胃腸道基質腫瘤合併肝轉移，以及後腹腔副神經節瘤。病患之後針對轉移性胃腸道基質腫瘤而接受 Imatinib mesylate治療，術後 32 個月追蹤電腦斷層檢查並未發現有局部復發或肝轉移病灶擴展之現象，病患在術後第 33 個月仍持續在本院追蹤且情況良好。在文獻記載的近 100 個 Carney Triad 病例中，這是在台灣發現的第一個病例，這個病例彰顯了在罹患胃腸道基質腫瘤、副神經節瘤或是肺軟骨瘤三者其中之一的年輕女性，必須考慮到此種罕見症候群的可能性，並安排進一步的檢查，以期能在腫瘤可以外科手術切除治癒前，早期發現及治療

關鍵詞：Carney Triad，胃腸道基質腫瘤，副神經節瘤，肺軟骨瘤

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