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Cancer Prone Disease Section

Mini Review

Carney triad

J Aidan Carney, Constantine A Stratakis

Department of Laboratory Medicine and Pathology (emeritus member), Mayo Clinic, Rochester, Minnesota 55905 USA (JAC), Section on Endocrinology and Genetics (SEGEN), NICHD, NIH, Bethesda, Maryland 20892 USA (CAS)

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Identity

Note

Carney triad (CT) is a multiple neoplasia syndrome featuring gastric gastrointestinal stromal tumor (GIST), pulmonary chondroma and paraganglioma, and other tumors including adrenocortical adenoma and esophageal leiomyoma. The syndrome is likely a developmental disorder. The component tumors tend to be multifocal in affected organs (Carney et al., 1977; Carney, 1983; Carney, 1999). The disorder is different from the familial paraganglioma and gastric stromal sarcoma syndrome (Carney et al., 2002).

Clinics

Phenotype and clinics

Definitive diagnosis of CT requires the presence of 3 of its component tumors (20% of patients). Tentative diagnosis may be made when two (usually gastric GIST and pulmonary chondroma) are found (80% of patients) (Carney, 1999). The presence of any one of the tumors, particularly if multifocal and in a young woman, should raise suspicion of CT. The interval between detection of the first and second component tumor may be as long as 25 years (Carney, 1999).

Most affected patients (75%) present with gastric GISTs (Carney, 1999). The tumor(s) cause mucosal ulceration and gastric bleeding that results in iron-deficiency anemia, and melena or hematemesis or both. Less commonly (15%), a routine pulmonary radiographic examination reveals one or more masses with pop-corn type calcification. Paraganglioma, manifested by a symptomatic or asymptomatic mass or "spells" with episodic hypertension, is occasionally the first component found. The adrenal adenomas are nonfunctioning and generally detected on abdominal computerized tomographic examination performed for other purposes. The esophageal leiomyomas are small and symptomless and generally incidental findings during gastric endoscopy. Formerly, the GISTs were interpreted as epithelioid leiomyosarcomas and were presumed to arise from gut musculature (Carney et al., 1977; Carney, 1983); they are now thought to arise from the interstitial cells of Cajal, the pacemaker cells of the gut, with which they show phenotypic similarity (Kindblom et al., 1998). The tumors metastasize to liver, peritoneum and gastric lymph nodes, rarely outside the abdomen. Additional gastric tumors commonly occur after subtotal gastrectomy or tumor enucleation, and secondary and tertiary gastric surgery may be required.

About 75% of patients with CT have one or more pulmonary chondromas (Carney, 1999). The neoplasms are usually detected during evaluation for the gastric tumors and often misinterpreted as metastatic GIST and treated as such. The lesions may be detected in early teenage or as late as 50 years. They are benign neoplasms that are cured by enucleation. Diagnosis is usually made following surgical resection; needle biopsy may provide the diagnosis. New tumors commonly develop. The chondromas need not be excised unless they cause symptoms resulting from bronchial compression.

The paragangliomas are usually found in extra-adrenal location and occur with equal frequency in the neck, mediastinum where the aortopulmonary body is commonly affected, and abdomen (Carney, 1999). The adrenal medulla is occasionally affected (pheochromocytoma). The neoplasms may be functional and cause episodic hypertension associated with catecholamine excess. Treatment is surgical.

Neoplastic risk

Metastasis occurs in more than 50% of the GISTs and thus the lesions should be regarded as malignant (sarcomas) or potentially malignant (Carney, 1999). The pulmonary chondromas are benign tumors (Carney, 1999; Rodriguez et al., 2007). Most of the paragangliomas are benign but 10% are malignant. An additional number are locally invasive and not resectable (Carney, 1999).

Treatment

Treatment of the CT tumors is surgical (Carney, 1999). The GISTs require a generous gastrectomy because of the likelihood of development new tumors in the stomach remnant. The tumors do not respond to kinase inhibitors (Rodriguez et al., 2007). The pulmonary chondromas do not require treatment once their nature has been established. Primary treatment of the paragangliomas is surgical.

Evolution

Most patients have two of the three major component tumors at initial presentation (Carney, 1999). In those who present with one component, the average interval to development of another component is 6 years but it may be as long as 25 years. No patient has had all of the five component tumors; the maximum was four.

Prognosis

CT is a chronic, persistent and indolent disease (Carney, 1999). The majority of patients survive for many decades either apparently disease-free or with hepatic or peritoneal metastasis. Occasional patients have died under 35 years of age, usually as a result of massive intra-abdominal GIST metastasis. Rarely, the tumor spreads to lung and bone.

Genes involved and proteins

Note

Although the absence of patients with similarly affected relatives is against CT being a genetic disorder, there is a distinct possibility that this is the case because of 1) the rarity of the individual tumors renders their coexistence by chance even in one individual unlikely and 2) their occurrence at an age (young) when tumors are unexpected (Carney, 1999; Diment et al., 2005). These considerations have led to molecular genetic study of the component tumors. Analysis of DNA from the tumors has shown no abnormal coding sequences of the SDHB, SDHC, SDHD, KIT and PDGFRA genes that are involved in the pathogenesis of familial paragangliomas (Diment et al., 2005; Stratakis et al., in press; Colwell et al., 2001; Spatz et al., 2004). Comparative genomic hybridization performed to identify chromosomal locations associated with the CT tumors show frequent deletion of the 1 cen-q21 chromosomal region that involves the SDHC gene (Matyakhina et al., 2007). Other chromosomal abnormalities include loss of the 1p region.

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