CASE REPORT

Primary hepatic neuroendocrine carcinoma with nonbacterial thrombotic endocarditis: A case report

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Received 22 February 2010; accepted 4 June 2010

KEYWORDS
Nonbacterial thrombotic endocarditis; Primary hepatic neuroendocrine carcinoma

Abstract
Nonbacterial thrombotic endocarditis (NBTE) is occasionally found in patients with carcinoma (lung or gastrointestinal) or debilitating diseases. Definite diagnosis of NBTE should be performed by autopsy. It is difficult to diagnose NBTE if patients have no clinical signs of thromboembolism. Here, we present a case of primary hepatic neuroendocrine carcinoma with NBTE as proven by autopsy.

Introduction
The incidence of primary hepatic neuroendocrine carcinoma is extremely rare; fewer than 300 cases have been reported in the literature [1]. Nonbacterial thrombotic endocarditis (NBTE) is occasionally found in patients with carcinoma (commonly in lung or gastrointestinal carcinoma, especially in mucin-producing adenocarcinoma) or debilitating diseases [2]. No case report has been described in this association. We
present here a case of primary hepatic neuroendocrine carcinoma with NBTE as proven by autopsy.

Case presentation

A 49-year-old woman had suffered from right upper quadrant discomfort, with radiation to her back, and chillness for 1 week. She visited Taipei Tzu-Chi Hospital on February 22, 2008. Abdominal computed tomography showed one huge tumor measuring $8.0 \times 6.0$ cm in dimension at Segments 5 and 6, and segmentectomy was performed on March 19, 2008. The pathology report indicated it to be a poorly differentiated hepatocellular carcinoma. Two months later, she felt a right upper quadrant pain again. An abdominal computed tomography revealed tumor recurrence with multiple lesions at Segments 7 and 8, and metastasis to rib and right lower lung was noted. Transarterial chemoembolization was done on May 28, 2008, and radiotherapy for rib metastasis (3,000 cGy/10 fractions from June 11 to June 24, 2008) was done. During this period, she suffered from right upper quadrant pain and frequent vomiting, and had to take painkiller and antiemetic drugs for symptomatic control. She visited Hualien Tzu-Chi Hospital for a second opinion on July 1, 2008. After admission, she felt drowsy and disoriented. She was later transferred to hospice care on July 11, 2008. Only supportive care and pain control were given. She died of hepatic failure on July 20, 2008.

On autopsy, the main tumor showed moderate differentiated neuroendocrine carcinoma of liver, characterized by spindle- or epithelioid-like cells with moderate pinkish cytoplasm, pepper–salt-like nucleus and prominent capillary stroma. The tumor was arranged in trabecular pattern accompanied by frequent atypical mitosis (Fig. 1A). Immunohistochemistry stain showed that the cancer cells were strongly positive for Cytokeratin, Cytokeratin 7, synaptophysin (Fig. 1B), and CD56, but negative for Chromogranin A. A diagnosis of neuroendocrine carcinoma was made.

The tumor disseminated into the right seventh rib, lungs, kidneys, and bone marrow of her vertebral bone. No evidence of any other primary lesion was found. Therefore, we considered this case as a primary neuroendocrine carcinoma of liver. In addition, we also noted small vegetation in the surface of the aortic valve (Fig. 2A). Microscopically, the vegetation was composed of fibrins and platelets (Fig. 2B) without any inflammatory cells, which suggests the diagnosis of NBTE. No evidence of embolic lesion was noted in the internal organs.

Discussion

Based on our light microscopic observations, immunohistochemical studies, autopsy findings, and the classification of Capella et al. [3], we think that the present hepatic neoplasm
may be classified as a primary neuroendocrine carcinoma. No obvious hepatocellular carcinomatous or cholangiocarcinomatous elements were identified in the tumor. The tumor cells were positively stained for synaptophysin and CD56, which are immunological markers for tumors derived from the neuroendocrine system, and negative for alfa-fetoprotein. The tumor was classified as malignant based on histological observations showing significant pleomorphism, numerous mitoses, and tumor necrosis foci.

The incidence of NBTE is largely unknown. The largest autopsy series published more than 30 years ago included 65 cases of NBTE discovered during a 10-year period of autopsy, giving an incidence of 1.6% in the adult autopsy population [4]. In the 51 cases, one or more malignant neoplasms were found in association with NBTE. Adenocarcinoma is the most frequently observed histological type of the related neoplasm. Lung, pancreas, and gastric cancer, and adenocarcinoma of unknown primary site are the most common cancer locations associated with NBTE [4]. Two cases of malignant tumors of liver associated with NBTE had been reported, one with hepatocellular carcinoma [5] and the other was a cholangiocarcinoma [6]. However, no neuroendocrine carcinoma of liver-associated NBTE had been reported previously. As far as we know, this is the first case report of this association. The vegetations in NBTE, consisting of degenerating platelets that were interwoven with strands of fibrin without evidence of inflammatory reaction, were reported earlier [7,8].

To date, the pathogenesis of NBTE is not completely understood. The most important factor in the formation of the valvular vegetations, perhaps, is the hypercoagulable state associated with malignancies. NBTE is most commonly found to be associated with mucin production of adenocarcinoma, indicating that intravascular mucin may be responsible for NBTE [9]. However, in our case, no mucin production was observed. Nevertheless, several clues to the etiology of NBTE can be gathered from the results of previous pathological investigations in animal and human models. The lesions of NBTE are classically recognized in the vicinities of valvular leaflets with high blood flow; therefore, high blood flow may be one of the factors contributing to the location if not the initiation of these valvular lesions. Furthermore, elevated levels of circulating cytokines associated with cancers, such as tumor necrosis factor or interleukin-1, may also cause local tissue damages that instigate vegetation formation. A study in an animal model of NBTE found increased levels of circulating tissue factor and increased expression of tissue factor mRNA in valvular monocytes and were considered to be closely associated with vegetation formation [10]. These revelations suggest that synergy between local physical and cytokine-mediated valvular damage and excessive platelet and coagulation factor activity are likely to contribute to the pathogenesis of NBTE. Recently, an investigation has indeed offered a direct genetic evidence for the connection between oncogene activation and thrombosis, whereby transcriptional response to the MET oncogene resulted in prominent upregulation of plasminogen activator inhibitor Type 1 and cyclooxygenase-2 genes. This observation provided the first direct genetic evidence for the relationship between oncogene activation and hemorrhage [11].

In conclusion, this is a rare case of primary neuroendocrine carcinoma of liver in association with NBTE based on our autopsy investigation.

References