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Chapter IV

**CARDIAC CONDUCTION SYSTEM INVOLVEMENT
IN METASTATIC PANCREATIC DUCTAL
ADENOCARCINOMA**

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ABSTRACT

While almost all malignant tumors are occasionally found to have metastasized to the heart, the involvement of the heart is not common and is poorly studied. The authors report the histological examination of the heart and conducting tissue on serial sections in a case of sudden death due to a cardiac localization of pancreatic ductal adenocarcinoma. Post mortem histologic examination showed the presence of cardiac metastatic pancreatic ductal adenocarcinoma compressing the atrio-ventricular node and the His bundle. The accurate examination of the cardiac conduction system has been crucial in finding the compression of the conduction system by the tumor as the morphological substrate responsible for lethal electrical cardiac instability and sudden death.

Keywords: sudden death, cardiac conduction system, pancreatic ductal adenocarcinoma, cardiac metastases.

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INTRODUCTION

While almost all malignant tumors are occasionally found to have metastasized to the heart [1-3], the involvement of the cardiac conduction system is not common and is poorly studied [2,4].

For several years we have performed series of studies on the cardiac conduction tissue involvement in cases in cardiac primary or secondary tumors [5,6]. The importance and frequency of sudden death due to cardiac metastatic infiltration prompted us to analyze in more detail the cardiac conduction system localization in tumors. This report will continue a previous study [5] focusing on the histological examination of the heart and conducting tissue on serial sections, as well as the analysis of the ECG recording in a case of sudden death due to a cardiac localization of pancreatic ductal adenocarcinoma.

CASE REPORT

The decedent was a 70-year-old Caucasian man admitted to Hospital for chest pain and gross hematuria. He was a cigarette smokers (8 cigarettes/day). Echocardiography disclosed two cardiac masses of unknown origin or histotype: 1) a mass located in the right atrium, infiltrating the chordae tendineae of the tricuspid valve, 2) a mass in the right ventricle pushed in the right atrium during the diastole and to the right ventricle during the systole. The ECG showed normal sinus rhythm, ventricular premature contractions, and right bundle branch block (Fig. 1). The patient developed hyperpyrexia and disseminated intravascular coagulation. He was treated with antibiotic and anticoagulant therapy, but died suddenly, despite the reanimation attempts. Further clinical details of this case were previously reported [5].

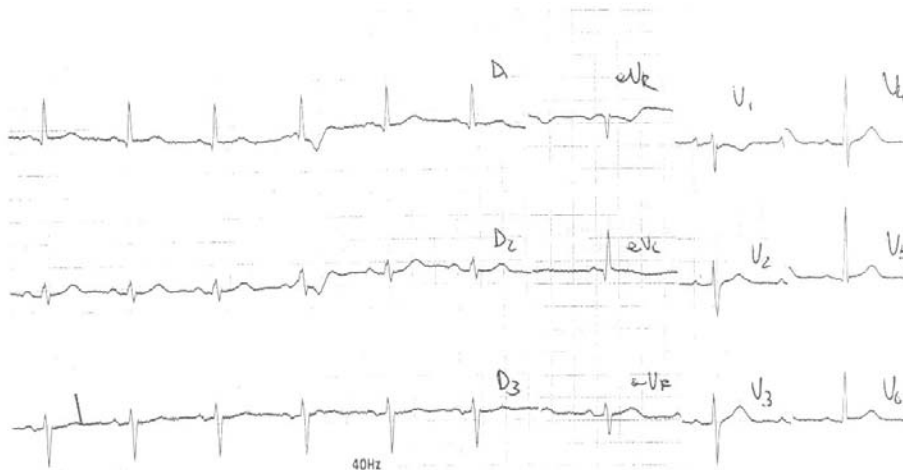


Figure 1. Electrocardiography showed normal sinus rhythm, ventricular premature contractions, and right bundle branch block.

Materials and Methods

A complete autopsy was performed, including particularly the observation of the cardiac conduction system, and of central and peripheral autonomic nervous structures involved in the cardio-respiratory reflexogenesis, according to the protocol routinely followed in our Institute, available on the web site: http://users.unimi.it/~pathol/sids/tecnica_e.html [4-7].

Multiple samples of all organs were fixed in 10% formalin buffer, processed and embedded in paraffin. Four- μ m sections were stained with hematoxylin-eosin.

The heart had been regularly examined for pathologic changes in the atria, septa, ventricles, pericardium, endocardium and coronary arteries. Samples of the common myocardium were stained with hematoxylin-eosin and trichromic Heidenhain (Azan).

To examine the cardiac conduction system, two blocks were prepared. The first contained the junction of superior vena cava and right atrium encompassing the entire area of the sino-atrial node, while the second contained the atrio-ventricular node, His bundle down to bifurcation and bundle branches, with two centimeters of attached septum above and below. The sino-atrial block was cut serially sectioned in a plane parallel to the crista terminalis. The atrio-ventricular junctional block was serially sectioned in a plane parallel to the two atrioventricular valve rings. All sections were cut serially at intervals of 40- μ m. For these intervals, three sections were retained and mounted, and one of the mounted sections was stained alternately with hematoxylin-eosin and Azan. All intervening sections were kept and stained as deemed necessary [7].

As previously reported [5], immunohistochemical stains were performed on formalin-fixed, paraffin-embedded tissue sections of lymph node of the heart using the Avidin-Biotin Complex (ABC) method: epithelial membrane antigen (EMA), cytokeratin 7 and AE3 (CK7, CKAE3), carcinoembryonic antigen (CEA), vimentin (VIM), and S100 protein (Dako, Carpinteria, CA).

Pathological Findings

Post mortem external examination revealed a thin, normally developed elderly Caucasian man.

The heart weighed 430 gm; the cardiac diameters were: 14 cm (transverse) by 12.5 cm (longitudinal) by 5 cm (anteroposterior). The gross cardiac examination revealed cardiomegaly. Dissection of the heart showed the presence of two large masses: 1) A mass measuring 8 by 4 by 2 cm which completely replaced the right atrium and encroached upon the right ventricular chamber. 2) A second tumor, measuring 4 by 3 by 2 cm, was attached to the chorda tendineae of the tricuspidal valve. Similar structures ranging in diameter from 0.5 to 1 cm were located on the endocardium of the septum and of all chambers. The multiple cardiac tumors occurred as circumscribed but nonencapsulated lesions. Their cut surface were reddish-colored, while the remainder of the myocardium was brownish and homogeneous in appearance. The coronary arteries were rigid and open.

Histological examination disclosed a pancreatic ductal adenocarcinoma, with metastatic infiltration in the heart, liver, lungs, thyroid, kidneys, adrenal glands, and in the mesenteric,

periaortic and mediastinal lymph nodes. Nonencapsuled proliferation with mucin-producing glandular structures were observed. Mitotic figures, necrosis and intratumoral hemorrhages, and perineural infiltration (Fig. 2) were also observed. Immunohistochemical stains showed the tumor cells to be EMA, CK7, CK AE3, and CEA positive, VIM and S100 negative.

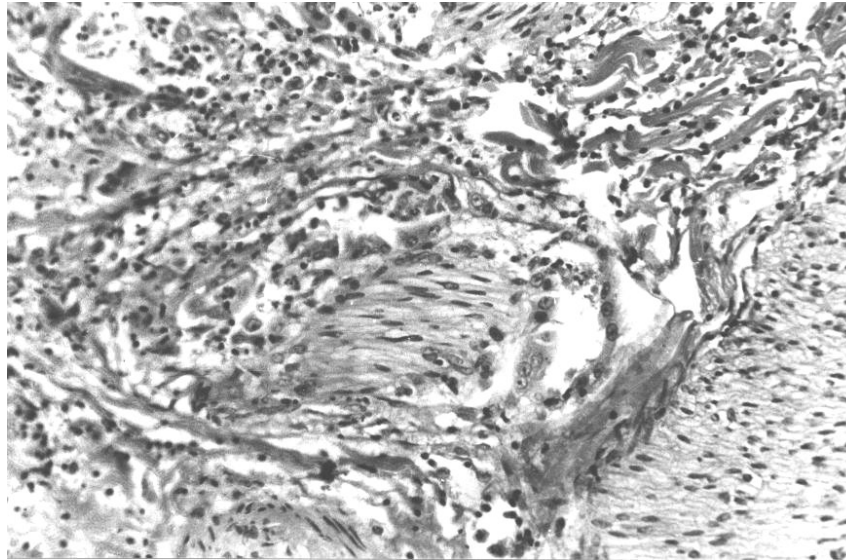


Figure 2. Section of pancreas through the tumor showing perineural invasion. Hematoxylin-eosin, 100x.

Histological examination of the cardiac masses showed a nonencapsuled proliferation with mucin-producing glandular structures, identical to the ones observed in the pancreas and in the other secondary localization of the pancreatic ductal adenocarcinoma. The morphologic aspect, confirmed by immunohistochemical procedures, led to the diagnosis of secondary cardiac pancreatic ductal adenocarcinoma [8].

The cardiac masses compressed the cardiac conduction system (Figures 1-3). The sinoatrial node (Fig. 3), the atrio-ventricular node and the His bundle (Fig. 4) were overstretched by the pancreatic ductal adenocarcinoma metastatic tumor.

DISCUSSION

In a previous study [5] we have already discussed that cardiac tumors can cause hemodynamic and conductive abnormalities resulting in sudden death [3-6,9,10]. In the present work we add that the ECG showed normal sinus rhythm, ventricular premature contractions, and right bundle branch block (Fig. 1). The compression of the cardiac conduction system by the tumor could likely have desynchronized ventricular refractoriness leading to the onset of ventricular fibrillation and sudden death. Cases of sudden death due to a cardiac tumor involvement of the conducting tissue have been reported in the literature [1,6,7,9]. Roberts et al. [11] reported ECG abnormalities (mainly sinus tachycardia and ST-T waves changes) in 24% of cases with secondary cardiac involvement. Allen et al. [12]

reported ECG abnormalities in 50% of the patients with cardiac involvement, concluding that there is a noticeable discrepancy between the presence of a clinically important cardiac dysfunction and the incidence of cardiac involvement. We recently reported a case of sudden death due to a cardiac infiltration of non Hodgkin malignant lymphoma affecting the sino-atrial node and atrio-ventricular node [4]. Dickens et al. [13] reported a case of sudden death associated with a solitary intracavitary right atrial metastatic adrenal cortical carcinoma, but did not analyze morphologically the possible involvement of the cardiac conduction system.

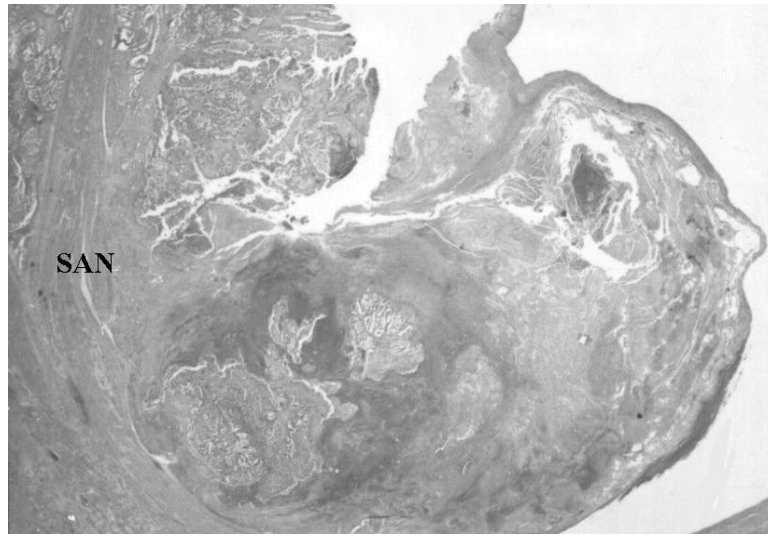


Figure 3. The sino-atrial node compressed by the metastatic pancreatic ductal adenocarcinoma. SAN= sino-atrial node. Hematoxylin-eosin, 10x.

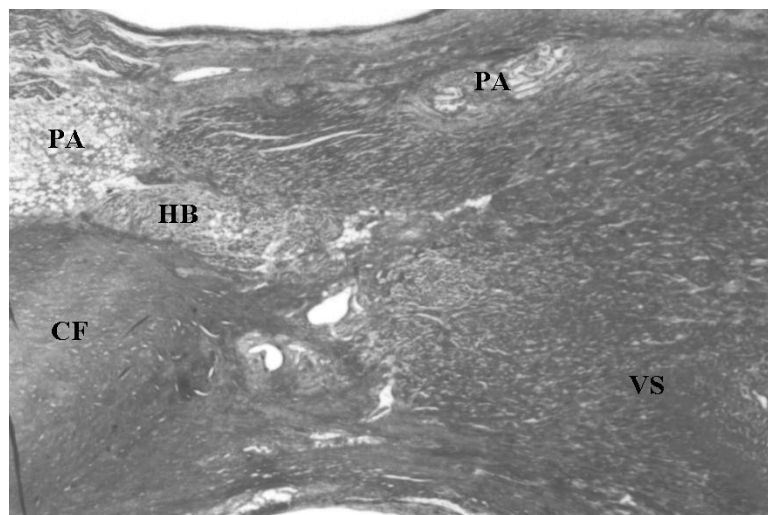


Figure 4. The His bundle compressed by the metastatic pancreatic ductal adenocarcinoma. His bundle= atrio-ventricular node; CF= central fibrous body; PA= metastatic pancreatic ductal adenocarcinoma; VS= ventricular septum. Hematoxylin-eosin, 25x.

In this case, the sudden death could have been due also to a cardiac motility defect caused by the invasion of the common myocardium, as well as to the obliteration of right ventricular outflow tract by the tumor [5].

The pancreatic adenocarcinoma has a poor prognosis and the lowest five-year survival rate [14]. While cause of pancreatic cancer remains unknown, the most prominent risk factor is cigarette smoking [14]. The present case was a cigarette smoker, as the patient reported to smoke approximately 8 cigarettes/day.

Clinical signs and symptoms of a cardiac involvement by a tumor are often non specific so that it can remain undiagnosed while the patient is alive [9]. The present patient presented chest pain and gross hematuria.

When heart is affected, metastatic disease is almost always widespread elsewhere in the body [10]. In the present case, the pancreatic ductal adenocarcinoma had metastasized to the heart and also to the liver, the lungs, the thyroid, the kidneys, the adrenal glands, and the lymph nodes. The tumor showed perineural invasion (Fig. 2).

In the present case, the accurate examination of the cardiac conduction system has been crucial in finding the infiltration of the conduction system by the pancreatic ductal adenocarcinoma as the morphological substrate responsible for the lethal electrical instability of the heart and sudden death.

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