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Poorly cohesive cell (diffuse-infiltrative/ signet ring cell) carcinomas of the gallbladder: clinicopathological analysis of 24 cases identified in 628 gallbladder carcinomas☆

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Summary Signet ring cell carcinoma is an extremely rare type of gallbladder carcinoma. In the gastrointestinal system, carcinomas with single-cell or cord-like infiltration, previously called "diffuse-infiltrative" type or "signet ring cell," are now designated as "poorly cohesive cell" (PCC) type (regardless of with/without signet ring cells) in the World Health Organization 2010 classification. Six hundred twenty-eight primary invasive gallbladder carcinomas were reviewed for the PCC pattern. Twenty-four cases in which classical PCC pattern constituted greater than 50% of the tumor were included in the study. The mean age was 63 (range, 44-84) years. A strong female predominance was present (female/male ratio, 6.3 versus 3.9 for all gallbladder carcinomas). Most cases (79%) had advanced carcinoma (pT3+) in comparison with 51% of usual carcinomas ($P < .01$). All cases (100%) showed at least focal signet ring morphology (intracytoplasmic mucin), and this was predominant in 50%. Twelve cases (50%) demonstrated a focal invasive glandular component of the usual type. Overlying focal high-grade dysplasia was identified in 11 (46%). Due to block loss, immunohistochemistry could be performed in only 5 cases and revealed a profile similar to upper gastrointestinal carcinomas CK7++/CK20−+/CDX2+−/p53+−. E-cadherin was decreased in the PCC

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component of all cases. The clinical course appeared to be more aggressive than ordinary gallbladder carcinomas, with median survival of 3.3 months versus 11.8 months, which did not reach statistical significance (P = .06 by log-rank test). In conclusion, PCC carcinoma originating in the gallbladder should be kept in mind for the differential diagnosis of disseminated poorly differentiated carcinomas in the abdomen.

1. Introduction

Gallbladder carcinoma is the most common tumor of the biliary tract [1,2]. The prevalence of the neoplasm changes widely according to the population studied: for instance, in the United States, the frequency is 1.43/100 000, whereas in countries like Chile, the frequency increases up to 17.8/100 000 [3-6] The prevalence also varies within the different groups and in different areas within the same country, which suggests that genetic and environmental alterations have significant importance on the development of the disease [7]. Gallbladder cancer has an obvious predominance in the female population (2-6 times more common than men) [3,8-10], and the incidence shows the tendency to increase with age [1,11-13].

Adenocarcinoma of the tubular type is the most common type of malignant gallbladder lesion, which constitutes 90% to 95% of all cases [3]. Little is known on the other histologic types of carcinomas occurring in this organ; most are reported as case reports or analyses of small case series. This includes the so-called signet ring cell carcinomas as well [14-27] .

In the gastrointestinal system, carcinomas with single-cell or cord-like infiltration, previously called "diffuse-infiltrative" type or "signet ring cell," are now designated as "poorly cohesive cell" (PCC) type in the World Health Organization (WHO) 2010 classification [28] In the stomach, recent studies on cases with *CDH1* mutation (with related E-cadherin anomalies) have brought about a new perspective on carcinomas of this phenotype including familial aspects, specifically, the possibility that it is not necessarily the signet ring cytology, but the dyshesive spread of the tumor cells that defines this entity. [29]. It is believed that the molecular/genetic and environmental factors that lead to this distinctive dyshesive spread of the cells also confer the tumors' distinctive biologic and clinicopathological characteristics and outcome [7] .

There are tumor types in other organs as well that can be regarded under this category of PCC, with its refined definition. These include "plasmacytoid" variant of urinary bladder carcinoma [20] and "invasive lobular carcinoma" of the breast. These PCC tumors often demonstrate unique clinicopathological characteristics, including peculiar patterns of dissemination and a propensity for aggressive clinical course.

PCCs (of any site) also often present with disseminated disease in the abdomen, in which case the determination of the primary site is notoriously problematic. Considering that the primary tumors of such cases are also often subtle due to the growth characteristics of PCCs, the diagnosis and management of such cases and the determination of their primary site become a major challenge.

There are virtually no data regarding the clinicopathological characteristics of gallbladder PCC in the literature. The information on "PCCs of gallbladder" is composed of rare individual case reports [14-27] or opinions of authors presented in textbooks [30-32].

This study was undertaken to determine (1) the incidence of PCC differentiation in invasive gallbladder carcinomas, (2) the clinicopathological characteristics of those that qualify as PCC-type carcinoma of the gallbladder by the current definitions, (3) the prognosis of these tumors and compare them with other gallbladder carcinomas.

2. Materials and methods

This study was conducted in accordance with the institutional review board requirements.

2.1. Cases

All pathology materials available on 628 cholecystectomies with invasive gallbladder carcinoma identified in the institutional surgical pathology files of Emory University (Atlanta, Georgia; 1997-2013; 96 cases), Wayne State University (Detroit, Michigan; 1985-2007; 60 cases), and University de la Frontera (Temuco, Chile; 1994-2004; 472 cases) were retrieved and reviewed.

2.2. Definitions

The presence of dyshesive cell invasion pattern, that is, individual cell or cord-like infiltration into the stroma with/without signet ring cell morphology, as defined in the other organs of the gastrointestinal system as "PCC" type in the WHO 2010 classification [28] was defined as PCC pattern.

Cases with PCC pattern constituting greater than 50% of the tumor were classified as PCC carcinoma. Those in which this pattern was less than 50% were regarded as "focal PCC pattern" and were not included in the analysis. Similarly, cases with dyshesive signet ring cells floating within the mucin without stromal infiltration by PCC pattern were also excluded.

2.3. Histopathologic analysis

After the study cohort was verified based on the definitions provided above, it was then investigated for other morphologic manifestations including signet ring cell formation, plasmacytoid cells, anaplastic signet ring cell patterns, and high-grade dysplasia/carcinoma in situ.