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The Morphologic and Biologic Patterns of a Rare Carcinoma *In Situ (CIS)* of Acinar Cells in Azaserine Treated Rats

Azaserin Enjekte Edilmiş Sıçan Asinar Hücrelerinde Az Görülen Karsinoma In Situ'nun Morfolojik ve Biyolojik Özellikleri

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Özet: Karsinoma In Situ'nun sıçan pankreas kanserinin gelişiminde etkili olduğu uzun zamandır bilinmektedir. Bu çalışmada normal koşullarda sıçan pankreasında nadir olarak gözlenen, ancak azaserin uygulaması sonucu sıçan pankreasında meydana getirilebilen bir karsinoma In Situ'nun histopatolojik özellikleri incelenmiştir. Onaltı günlük toplam 10 sıçana vücut ağırlığı esas alınarak (30mg/kg) intra peritonal olarak azaserin enjekte edilmiş ve yavruların 21 günlük oluncaya kadar annelerini emmelerine izin verilmiştir. Yirmibir günün sonunda azaserin enjekte edilen 10 sıçan ve (aynı yaşta) azaserin enjekte edilmemiş 10 tane sıçan (kontrol grubu) normal standart bir diyetle 18 ay süresince beslenmişlerdir. Bu süre sonunda sıçanlar öldürülerek pankreasları çıkarılmış, tesbit edilerek histopatolojik özellikleri incelenmiştir. İnsan ve hayvanlarda kanal (ductal) kaynaklı *karsinoma in situ*'nun yüksek olmasına karşın bu çalışmada gözlenen asinar hücre kökenli karsinoma *in situ*'da desmoplazik ve eozinofilik yapılar izlenmiş olup, proliferatif bir özellik gözlenmiştir. Bu sonuçlar, mekanizması tam olarak bilinmemekle birlikte, *karsinoma in situ*'nun pankreas kanserinin meydana gelmesinde etkili olabileceği yolundaki hipotezi destekler niteliktedir.

Anahtar Sözcükler: Karsinoma *in situ*, azaserin, sıçan

Summary: *The carcinoma in situ has long been indicated to be important in the growth of pancreatic carcinoma of rat pancreas. The present study performed to examine histolopathologic patterns of a rare carcinoma in situ obtained azaserine treated rat exocrine pancreas. Sixteen-days-old, 10 male rats received a single weekly i.p. (30 mg/kg body weight) dose of azaserine for 3 weeks and rats were allowed to continue suckling until 21 days of age. On the day 21 of life, 10 male azaserine-initiated and 10 untreated rats were switched on to a normal standard diet for 18 months. Rats were subsequently sacrificed at the end of experimental process. The entire pancreas was excited at autopsy and histologic patters of pancreases were examined. Although the frequency of ductal carcinoma in situ frequently higher in experimental animals and human than carcinoma in situ of acinar cells. In this study carcinoma in situ of acinar cells characterised by an high degree of desmoplasia, increased cytoplasmic eosinophilia and an increased proliferative capacity than normal acinar cells. This results provide evidence for the hypothesis that carcinoma in situ of acinar cells somehow may play a role in the development of pancreatic cancer, although this remains to be resolved.*

Key Words: *Carcinoma in situ, azaserine, rat*

Pancreatic cancer is one of the most malignant human diseases. In about 80% of pancreatic cancer patients, the tumour has metastased by the time of clinical examination (1). Although the frequency of ductal carcinomas in situ reported 14% incidence by Cubilla & Fitzgerald (2), carcinoma in situ of acinar cells very seldom occurs in human exocrine pancreas (2). It has been estimated that the acinar cell carcinomas of pancreas are rare neoplasms, accounting less than 1% of pancreatic adenocarcinomas, can vary in appearance, from well differentiated to anaplastic structures. However, the morphologic and biologic features of acinar cell carcinoma in situ are largely unknown (3). The acinar cells consider to be origin of some exocrine tumours in rats (3). Almost all of neoplasms may show evidence of acinar cell differentiation. Localised pancreatic lesions displaying significant anaplasia and cytological similarity to fully developed carcinomas are regularly encountered among carcinogen-treated rats. These lesions bears greater histological similarity to carcinomas than to the preneoplastic lesions and these lesions classified carcinoma in situ (CIS) (4,5).

Therefore the purpose of present study was examine the morphologic and biological features of carcinoma in situ obtained from azaserine treated rat pancreas.

Materials and Methods

Animals and Diets: Male inbred Leeds strain rats were obtained from our breeding colony and were housed and kept five animals to a cage under standard conditions (room temperature 23°C; lighting 7am-7pm), on sawdust bedding. Standard diet and tap water were supplied ad libitum.

Treatment: Starting at two weeks of age,10 male rats received a single weekly i.p. (30 mg/kg body weight) dose of azaserine (Sigma Chemicals) for 3 weeks, dissolved in 0.9% NaCl solution to a final concentration of 3 mg/ml. on the day of injection. The pups were then returned to their respective dams and allowed to continue suckling until 21 days of age. On the day 21 of life, 10 male azaserine-initiated and 10 untreated control rats were switched on to a normal standard diet for 18 months, the composition of which has been reported previously (6).

Histology: At the end of 18 months the rats were sacrificed by decapitation. The entire rat pancreas was excised at autopsy and all adherent fat, mesentery and lymph nodes were carefully trimmed off and fixated in 10% buffered neutral formalin for approximately 8-18 h. Sections were then cut at 5 µm on a microtome and stained with haematoxylin and eosin and were examined by light microscopy. Acidophilic foci in the sections were identified and classified according to the established criteria (7,8,9).

Results

By the end of experiment process two azaserine treated rats represented with Carcinoma in situ (CIS) of in various size. However, no carcinoma in situ observed untreated control rats. The major part of the pancreas consisted of acini of variable size, with their collecting ductules.

In the present work acinar cells were eosinophilic owing to the presence abundant zymogen and characterised by rounded nuclei, with prominent chromatin and nucleoli. Also very few basophilic foci were observed in rat exocrine pancreas.

The carcinoma in situ has been observed in the present study characterised with a desmoplastic reaction in acinar cell nodule, was evident for carcinoma, but there not was any sign of a thick fibrous capsule that mostly accompanies to carcinoma in situ (Figure 1). The focal anaplastic changes within nodules (nodule in nodule) was characteristic pattern of carcinoma in situ. A glandular pattern is preserved in the tumour and the degree of anaplasia suggests that this was an early carcinoma.

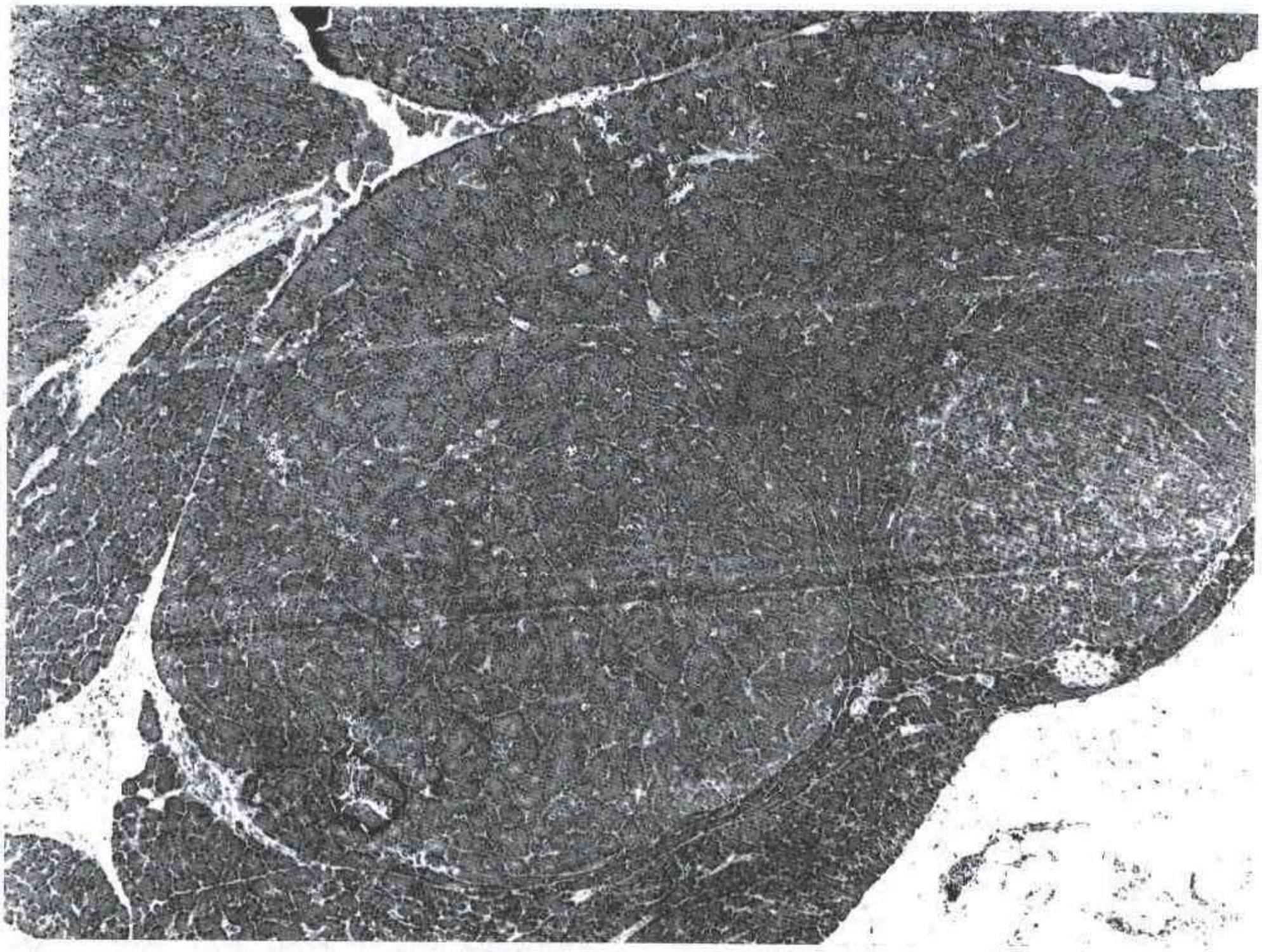

Figure 1. The pancreas from an azaserine-treated rat. This lesion originally classified as an acinar cell adenoma, but may regard as an early stage of CIS because of high degree of anaplasia and localized carcinoma of the pancreas. Magnification X40.

Discussion

Although several morphological and histopathological studies have implicated various grades of carcinoma in situ of acinar cell as a precursor pancreatic adenocarcinomas, the features of this pancreatic neoplasm remains controversial (2,4). The mechanism of CIS in human and experimental animals remain poorly understood. It has been suggested that CIS may be a desmoplastic reaction. In the present study morphologic features of CIS has been characterised with an increased cytoplasmic eosinophilia and greater proliferative capacity than normal acinar cells. The second foci or ì nodule in noduleî appear to be a common features of CIS in rat pancreas that the finding of present work supports previous studies (9).

Anaplastic areas have been seen in acinar cell carcinomas suggests that the uniformly anaplastic carcinomas may also be of acinar cell origin. It has been assumed that a high percentage of these lesions (CIS) would progress with time to invasion and metastasis. However, recognition of this malignant growth potential is difficult because of the high degree of differentiation that is characteristic of these lesions.

In summary, the results of present study suggested that an increased number of CIS may reflect the atypical change of pancreatic acinar cells, this provide strong support for the hypothesis that CIS arising from pancreatic acinar cells may involve in the incidence of pancreatic carcinogenesis in rats.

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