Morphological Lesions Associated with Human Primary Invasive Nonendocrine Pancreas Cancer

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Summary

In 227 cases of human pancreas cancer (100 pancreatectomy specimens and 127 autopsies), pancreas duct epithelium not involved by invasive cancer was examined. Pancreas duct epithelium from 100 autopsies of patients with nonpancreatic cancer, matched by age and sex to the pancreas cancer autopsy cases, was used for control studies. The prevalence of squamous metaplasia, pyloric gland metaplasia, mucous hypertrophy, and focal epithelial hyperplasia was not greatly different in the two groups. Ductal papillary hyperplasia was three times more prevalent in pancreas cancer than in controls. Marked atypia occurred in 20%, and carcinoma in situ, in 18% of the pancreas cancer cases, but neither change was seen in the control cases.

It is possible that focal epithelial hyperplasia was a precursor change but that it was overgrown by the cancer. Papillary hyperplasia could not be properly evaluated as a precursor lesion because of duct obstruction, but practically all cases of marked atypia and carcinoma in situ occurred in papillary lesions.

Marked atypia and carcinoma in situ, by analogy to other cancers, would appear to be precursor lesions, and their presence in association with invasive cancer lends hope to the possibility that there is a significant, recognizable, in situ phase of the disease before invasive cancer occurs.

Introduction

The relatively short clinical course between the appearance of signs and symptoms of pancreas cancer and the death of most patients (less than a year) raises questions about the distinctiveness of the cancer. Is it because the neoplasm arises in an anatomically vulnerable area where there is little disturbance of function until the tumor obstructs a major duct and where there is relatively little barrier to early invasion? Is there a sudden de novo transformation of normal epithelium with higher growth and invasive rates than in most malignant tumors? Or, is pancreas cancer analogous to cancer of other organs with a substantial latent period prior to the growth of the tumor so that earlier diagnosis might become a reasonable possibility?

Recently, we examined histological sections of patients with invasive cancer of the pancreas at Memorial Hospital and found in many of these cases atypical, and markedly atypical, hyperplasias, metaplasias, and carcinomas in situ in pancreas duct epithelium. It is from the last, we believe, that 80 to 90% of pancreas cancers originate (13). Pancreatic duct epithelium was studied in pancreas cancer and in control nonpancreas cancer cases to determine the prevalence of the lesions and their possible precursor relationship to invasive pancreas cancer.

Materials and Methods

From a survey of 787 cases from 1949 through 1973 listed as primary cancer of the pancreas in the Cancer Registry, Clinical Information Center, Memorial Hospital, we have been able to examine histological tissue from 580 cases. Twenty autopsy cases were excluded because of autolysis of pancreas tissue. In 227 cases with nonendocrine primary pancreas carcinoma, there was enough pancreas duct epithelium uninvolved with the primary invasive cancer to provide tissue for histological study. A surgically resected specimen (partial or total pancreatectomy) was available in 100 cases and pancreas autopsy material was available in 127 cases. Pancreas duct epithelium from 100 autopsies of patients with nonpancreas cancer, matched by age and sex to our pancreas cancer autopsies, was used for control purposes. The average number of histological slides per case in the surgical specimens was 5 and in the autopsy cases it was 3.

Tissues were fixed in 10% formalin solution. Slides were stained with hematoxylin and eosin. Meyer’s mucicarmine stain (Ref. 32, pp. 138-139) was used to demonstrate mucin, and the PAS (Ref. 32, pp. 126-128) and Alcian blue, at pH 2.5 (Ref. 32, pp.136-138), stains were used to verify the histological diagnosis of pyloric metaplasia (40). In the “thick” (1 μm) section embedded in Maraglas (13), the tissue mucigen was stained with methylene blue-azure II-basic fuchsin (27).

Clinical and epidemiological data and follow-up studies on these cases are not presented in this report.

Results

The lesions were subdivided into the following groups (Table 1).

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The abbreviation used is: PAS, periodic acid-Schiff.
**Squamous Metaplasia.** This lesion was defined as replacement of the normal mucinous columnar or cuboidal epithelium by squamous (epidermoid) epithelium. Usually, there was little keratohyalin present in the cells, but in some it was abundant (Fig. 1). "Pears" of keratohyalin were not noted. The process was seen usually in the large or intermediate ducts. There was usually considerable hyperplasia of duct epithelium so that the metaplastic area was many cell layers thicker than the single layer of normal epithelium (20, 28). No carcinoma in situ or marked atypia was found in these lesions. In about 10% of the cases in which squamous metaplasia was present, in both the pancreas and nonpancreas cancers, inspissated pale-staining amorphous material was noted in the ducts. The lesion was found in 6% of our pancreas cancer cases and in 12% of our controls.

**Pyloric Gland Metaplasia.** Pyloric gland metaplasia was a process whereby the columnar epithelium of the duct resembles the pyloric glands of the stomach. The staining of mucigen of the cells of the intramural glands, and/or the cells of the large and intermediate ducts, was changed so that it was positive for the PAS reaction and negative for Alcian blue stain (22, 29, 33, 40, 41). The nucleus was more basal and the cytoplasm was more abundant and stained less than in the normal duct epithelial cell. The change most often accompanied the papillary hyperplasia lesion to be described below. The mucous cells of the papillary hyperplastic lesion gave these reactions at the base of the papilla (Fig. 2). The changes were also seen in cases without papillary hyperplasias. No marked atypia or carcinoma in situ was noted in cells showing the metaplasia. In 24% of our cancer cases the lesion was present, whereas, in our controls, it was noted in 17%.

**Mucous Cell Hypertrophy.** A uniform increase in the mucigen of the cell, almost invariably confined to the intramural glands of the large or intermediate ducts, was the feature of this change. Sometimes this was so extensive that it narrowed the lumen considerably (Fig. 3). The cell maintained its cylindrical shape as distinct from the goblet cell (47). Most often the increase in mucigen was associated with papillary hyperplasia, but it did occur independently of it. In some cases there also appeared to be hyperplasia of mucous cells, but no attempt at morphometric analysis was made. No marked atypia or carcinoma in situ was observed in cells with mucous hypertrophy. About 35% of our cancer cases showed this lesion, as did 28% of the control cases.

**Focal Epithelial Hyperplasia.** This change was a focal increase in the thickness of the duct epithelium, usually of 2 to 4 layers of cells, occurring most often in dilated ducts of the large or intermediate size (Fig. 4). The cells were smaller than normal with less mucin per cell and a higher nuclear-cytoplasmic ratio. Little or no keratin was present in the cells. Atypia was present but not prominent (Fig. 4). No marked atypia or carcinoma in situ was seen. The lesion was noted in both pancreas cancer and in the control nonpancreas cancer cases in about the same percentage (5 to 7%).

**Ductal Papillary Hyperplasia.** Papillary hyperplasia consisted of papillae of tall columnar cells growing into the duct lumen (42) (Figs. 2 and 5 to 10). Often the cells contained considerable mucigen. Some lesions were very small projections of epithelium extending slightly above the surrounding normal duct epithelium (Figs. 5 and 6) but, in most cases, the hyperplasia was extensive (Figs. 7 and 10), even, in some circumstances, filling the lumen of the duct. Many papillae contained stalks of vascular and supporting tissues; others did not. Hyperplasia of intramural glands often appeared to be associated with ductal papillary hyperplasia but, because of the extensive atrophy and fibrosis and distortion of ductal architecture, it was difficult to separate intramural glands from accessory ducts. Occasionally, small papillae could be seen in an obvious intramural gland. Usually, there were associated changes, such as pyloric gland metaplasia (Fig. 2) or mucous cell hyperplasia (Fig. 3), in the epithelium of the papilla. A papillary lesion frequently contained minute foci of atypical hyperplasia, marked atypical hyperplasia, and/or, carcinoma in situ (Figs. 7 to 14). Cases of papillary hyperplasia were about twice as frequent in the pancreactomy cases as they were in the pancreas cancer autopsy cases; the average of the 2 groups was 37%. In the autopsy control nonpancreas cancer cases, it was 12%.

**Marked Atypical Hyperplasia.** This lesion occurred in the diagnostic debatable zone between atypical hyperplasia and carcinoma in situ. The change from normal was characterized by loss of polarity of cells, by variation of size, shape, and staining of the nuclei, and by nuclear clumping of chromatin (Figs. 7 to 14). Mitotic figures were noted, and often an increase in cytoplasmic staining was present. In all except 1 case, the cells with marked atypia occurred in association with papillary hyperplasia. In this case, a flat

| Table 1 |
|---------------------|---------------------|---------------------|---------------------|
| **Duct epithelial changes with pancreas cancer** |
| **Surgical** (100 cases) | **Autopsy** (127 cases) | **Combined** (227 cases) | **Control** (100 cases) |
| Squamous metaplasia | 7 | 6 | 6 | 12 |
| Pyloric gland metaplasia | 31 | 18 | 24 | 17 |
| Mucous cell hypertrophy | 48 | 24 | 35 | 28 |
| Focal epithelial hyperplasia | 7 | 6 | 6 | 5 |
| Ductal papillary hyperplasia | 50 | 26 | 37 | 12 |
| Marked atypical hyperplasia | 27 | 14 | 20 | 0 |
| Carcinoma in situ | 24 | 13 | 18 | 0 |

*One hundred autopsies of patients with nonpancreatic cancer matched for age and sex with the autopsy pancreas cancer cases.
lesion, there was also carcinoma in situ. The lesion occurred in about 20% of our pancreas cancer cases but in none of the control pancreases.

**Carcinoma in Situ.** In this lesion, diagnosed by standard criteria (1, 2, 10, 11, 14, 18, 44, 51) allowing for the fact that columnar mucous cells were the site of origin, cells contained nuclei 2 to 4 times the usual diameter, and there were variations in the size, shape, and staining of nuclei. Nucleoli were increased in size and/or number. There was a lack of orderly polarization of cell nuclei. The cytoplasm often stained more heavily than usual and there was an increased nuclear-cytoplasmic ratio. The carcinoma in situ was most often seen in areas of papillary hyperplasia (Figs. 7 to 12) although, in 1 case, “flat” lesions which projected only slightly into the lumen were present (Figs. 13 to 16). In 3 cases, a predominant cribriform pattern (Figs. 9 and 10) and intraluminal bridging of epithelium (Fig. 10), analogous to that present in some cases of intraductal breast carcinoma (31), were found.

In most cases, the carcinoma in situ occurred in tissue taken from within 1 or 2 cm of the edge of the primary invasive pancreas cancer (51). In a small percentage of cases, the lesion was seen in duct epithelium devoid of indication of from which part of the pancreas it came. In 2 of the cases of carcinoma in situ of the pancreas duct, there was, in addition, carcinoma in situ of the adjacent biliary ducts and periampullary areas.

In 4 recent cases not included in this study, in situ cancers were noted in unusual areas. In 2, the in situ lesion was present in the body and tail of the pancreas when the primary lesion was in the head. In the 3rd case, a biopsy of tissue at the periphery of what appeared to be a large primary invading pancreas carcinoma of the body of the pancreas showed only carcinoma in situ. In a 4th case, resection of the tail of the pancreas at another hospital for cancer of the tail showed, at a 2nd operation in our hospital, an in situ carcinoma in the residual body of the pancreas.

In situ carcinoma was found in 24% of our resected pancreas cancer specimens and in 13% of the pancreas cancers found at autopsy, but it did not occur in any of the control nonpancreatic cancer autopsy cases.

**Discussion**

**Limitation of Study.** That the amount of duct epithelium studied has influence on the estimation of the prevalence of lesions is suggested by twice the prevalence of carcinoma in situ in our more detailed surgically resected pancreases, where more tissue was available, than in our autopsy study of pancreas cancer where there were only a few blocks of tissue per case (Table 1).

Because invasive duct carcinoma often grows along ducts replacing normal epithelium and also forms duct-like structures surrounded by a desmoplastic response, it is often difficult to differentiate between a duct with papillary hyperplasia containing marked atypia and/or, carcinoma in situ and a space circumscribed by well-differentiated invasive papillary cancer. The presence of adjacent branching ducts, or ductules, leading to the duct-like structure, or intramural glands, adjacent to the structure (Fig. 11) is helpful in identifying the structure as ductal, as is the presence of a transition from normal-appearing epithelium through atypias to carcinoma in situ (Figs. 11 to 13).

In assessing the possible precursor relationship of lesions to human invasive cancers, it is always hazardous to believe that the absence of a lesion or its low prevalence denies its precursor role, because the growth of the cancer may have obliterated the initial cellular site of origin. Equally cautionary, a high prevalence of a lesion in association with a cancer does not mean a causal relationship. The lesion may be secondary and unrelated, or both it and the cancer may be independent of each other but may be the result of an underlying cause. The neoplastic process may give rise to many phenomena with only one, the cancer, having the more serious implication for the patient.

There was not available to us enough pancreas ductal tissue from cases of duct obstruction without cancer so that we might evaluate the role of obstruction and the resulting degenerative and inflammatory changes on the production of lesions. Some authors have described mostly atrophy of acinar tissue and dilatation of ducts, as well as interstitial fibrosis (26), but others also reported duct epithelial changes (6, 8, 9, 16, 17, 23, 50) secondary to duct obstruction. Edmondson et al. (17) remarked that there was such “remarkable epithelial hyperplasia . . . in chronic pancreatitis, that it . . . would not be surprising to find carcinoma arising in ducts . . . .” Fortunately, there are now available animal models of pancreas cancer (15, 30, 36-38), and these should aid greatly in clarifying the morphological pathogenesis of pancreas cancer.

**Biological Significance of Associated Changes.** It appears that, in our cases, pancreas cancer patients do not have a significantly greater prevalence of squamous metaplasia, mucous cell hypertrophy, pyloric metaplasia, or focal epithelial hyperplasia than do control patients with nonpancreatic cancer.

Squamous metaplasia has been reported in about 10% of noncancerous pancreases (8, 28). However, Rich and Duff (39) stated that the lesion was found in 19% of autopsies in patients over 25 years of age and in 54% of cases of hemorrhagic pancreatitis. Sommers et al. (42) indicated that squamous metaplasia was not part of the hyperplastic process in pancreas cancer cases. Age may be a factor as shown by Korpássy (28) in a study of 500 autopsies where squamous metaplasia of the pancreas was present in 12% but the prevalence in patients over 70 years of age was 29%. The average age of our patients was about 60 years. Korpássy (28) (who called the lesion basal cell hyperplasia) and others believed that the lesion was precancerous. Hackworth and Fisher (25) reported multiple foci of carcinoma in situ in zones of squamous metaplasia of pancreatic ducts.

Walters (47) described goblet cell metaplasia in diseases of the pancreas, and he stated that it was present in 33% of malignancies (presumably, pancreas cancer). Some of these changes would have been classified by us as either mucous cell hypertrophy or pyloric gland metaplasia.

Focal epithelial hyperplasia occurred in only a small percentage of cases, at about the same percentage as in nonpancreas cancer cases, and it would thereby appear not to
be a precursor change in the pancreas. However, a small focal lesion could readily be obscured by an overgrowth of papillary hyperplasia, carcinoma in situ, or invasive cancer. In one of the relatively flat lesions, there was some suggestion of a papillary structure (Figs. 13 and 14) so that it is quite possible that carcinoma originates in flat epithelium and then progresses to a papillary lesion; the lesion illustrated could well be indicative of the early phase of some cancers. Because all of our cases were seen late in the course of their development when extensive invasion and secondary changes had occurred, it was not possible to conclude that the initial cellular configuration at inception was not a focal epithelial hyperplasia.

A prevalence of papillary hyperplasia in our pancreas cancer cases that is 2 to 3 times that found in nonpancreas cancer cases would appear to be a significant statistical difference. However Birnstingl (9) found an incidence of ductal hyperplastic columnar epithelium in 29% of 150 pancreases studied at autopsy. None of these patients had primary pancreas disease but had one of a variety of acute and chronic diseases (9). In a detailed study of 50 pancreases from normal patients in Japan, Yotuyanagi (49) found what he called epithelial metaplasia in 64% of the specimens. This would appear to be a very high figure, except that he used serial sectioning of the whole gland, and the figure is a summary of many morphological entities, including our squamous metaplasia, focal epithelial hyperplasia, and papillary hyperplasia entities. Nakamura (34) reported papillary proliferation of duct epithelium in 2 male babies (a few months old) with colitis but otherwise without evidence of pancreatic disease. Thus, even in the pancreases of patients without primary pancreatic disease there is a relatively high incidence of papillary epithelial changes. In various diseases affecting the pancreas, Yotuyanagi (50) found intraductal epithelial changes in 7 of 18 cases (39%).

Sommers et al. (42) reported that in about 40% of their cases of cancer of the pancreas there was papillary hyperplasia, whereas similar papillary (or adenomatous) hyperplasia of pancreas duct epithelium occurred in about 9% of autopsies of patients without cancer and in 28% of autopsies of diabetic patients. The last is of interest in view of the abnormal glucose tolerance test in pancreas cancer (12) and the increased incidence of pancreas cancer in female diabetics (21). Habán (24) reported a case of multiple papillomatosis of the pancreatic ducts where there were multicentric foci of carcinoma in situ as well as invasive cancers.

Since virtually all atypias and carcinomas in situ of our cases were present in a papillary hyperplastic area, the latter lesion is at least a setting conducive to their development or preservation. With the neoplastic process there may have been set off multifactorial processes, a whole spectrum of events, some leading to hyperplasias, others to metaplasias, and another category may have transformed cells to carcinomas. The association of the increased papillary hyperplasia and carcinoma in situ is not necessarily a causal one, but may be an indirect one in that they both might be the result of the neoplastic process. Duct obstruction may have increased the prevalence of papillary lesions in areas already modified by the neoplastic process.

The finding of markedly atypical hyperplasia in about 20% of the pancreas cancer cases is probably a significant biological finding in terms of carcinogenesis because no such lesion was noted in our control nonpancreas cancer cases. The lesions in our cases were present in areas of papillary hyperplasia (Figs. 7 to 12) in all except one case where the lesion occurred in the flat lesions lining ducts. (Figs. 15 and 16). Often associated with markedly atypical hyperplasias were cells with debatable changes difficult to differentiate from carcinoma in situ (Figs. 7 to 12) and cells obviously fulfilling the criteria of carcinoma in situ. Marked atypia is probably a precursor change which would, in time, progress to cancer in a large percentage of cases, just as an analogous change in the human uterine cervix is followed by cancer of the cervix years later (4, 5).

The carcinoma in situ present in our cases was similar in essential respects to the cancer in situ found in many organs, allowing for the fact that it took place in mucous cells of duct epithelium and was very often associated with papillary hyperplasia. While at this hospital, J. W. Berg (personal communication) had noted the presence of carcinoma in situ in association with pancreas cancer and had used its presence as ancillary evidence in deciding whether the cancer was primary or metastatic. Sommers et al. (42) reported an incidence of about 3% of carcinoma in situ in their autopsy cases from 3 hospitals. Only routine microscopic sections were available to them so that, whether equal amounts of duct epithelium were studied in their and our cases or whether different criteria were used in making the diagnosis, is not known. These authors noted that in 4 cases of carcinoma in situ there were possible transition areas from papillary duct hyperplasia to carcinoma in situ to invasive pancreas duct cancer.

Hartsoock and Fisher (25) believed that, since their case of carcinoma in situ arose in zones of squamous metaplasia, this indicated the neoplastic potential of this metaplasia in the histogenesis of squamous cancer.

In 1 case of giant and spindle cell carcinoma and in 2 cases of adenosquamous carcinoma (13), we found in situ changes in adjacent duct epithelium. All of the other in situ cases also occurred in duct epithelium. Multicentric foci of pancreatic carcinoma in situ have been reported (24, 25, 35). In most of our cases, only one slide containing a focus of in situ carcinoma was present. In some cases more than 1 focus could be demonstrated.

Possible Latent Period of Pancreas Carcinoma in Situ.

From studies on the cervix cancer of the uterus, it is believed that there is a latent period of 5 to 10 years, on the average, from the appearance of in situ lesion to the clinically recognizable invasive cervical carcinoma (4, 5). In many other organs there also appears to be a latent period, varying from months to years, from the morphological recognition of the carcinoma in situ to the clinical fully invasive carcinoma (43). Whether such a circumstance exists in pancreas cancer is unknown. Since only 2 of the 609 pancreas cancers studied by Bell (7) were discovered incidentally at autopsy, it would appear that occult cancers of the organ are very rare. However, these cases were collected from many hospitals, and there is no indication that a detailed search of duct epithelium made for carcinoma in situ.
Sommers et al. (42) stated that, in their 141 autopsies of cancer of the pancreas, 6 were not recognized at gross autopsy examination.

The relative inaccessibility of the pancreatic ducts for clinical examination in the past has contributed to the lack of knowledge about duct epithelium. Retrograde endoscopic pancreatography (46, 48) combined with exfoliated cytology study might increase our knowledge of this neglected tissue. A more vigorous surgical attempt to do total pancreatectomy (19) has provided us with more surgical material for study of duct epithelium (unpublished observations). It would appear desirable to examine pancreatic duct epithelium (obtained at autopsy, by duodenal aspiration, by collection of pancreatic duct epithelium by endoscopy, or by biopsy) in patients at high risk for the disease. Female diabetics, alcoholics, patients with a heavy smoking history, those exposed to occupational hazards, patients with familial pancreatitis, and others who may be assumed to be at higher risk (21) should be examined to determine whether such associated lesions are present in younger age groups than in those in which invasive pancreas cancer occurs.

It would be surprising to us if cancer of the pancreas did not have a significant latent period between the in situ and invasive phases. The demonstration of a latent period would be further impetus for the development of techniques to diagnose the cancer earlier (3, 45, 46, 48) and institute therapy sooner.

References

Fig. 1. Squamous metaplasia of epithelium of a large duct (much of which is still lined by mucinous columnar epithelium) and extensive metaplasia of intramural glands and accessory ducts. × 144.

Fig. 2. Pyloric gland metaplasia in an area of papillary hyperplasia. Dark areas at apex of cytoplasm of cells represent PAS-positive mucigen. Cells lining glands at base of papillae are involved. The cells were Alcian blue negative for acid mucin. PAS (Ref. 32, pp. 126-128), × 127.

Fig. 3. Mucous hypertrophy. Distention of cytoplasm of columnar cells of intermediate ducts or glands by increased amount of mucigen. × 385.

Fig. 4. Focal epithelial hyperplasia. Increase of epithelial cell layer from normal 1-cell layer to 2 to 4 layers. Cell height and mucigen of cytoplasm appear to be decreased. Some slight to moderate nuclear atypia. × 420.

Fig. 5. Varying sized papillae in papillary hyperplasia. Epithelium shows only minimal atypia. × 315.

Fig. 6. Thick (1 μm) section stained with methylene blue-azure II-basic fuchsin of papillary hyperplasia in pancreatic duct of tail of pancreas. Patient had cancer at head of pancreas with biliary and pancreatic duct obstruction. Small uniform papillae with regular nuclei without significant atypia. Black areas at apex of cytoplasm represent mucigen (27). × 410.

Fig. 7. Papillary hyperplasia of duct with foci of atypia, marked atypia, and carcinoma in situ. × 127.

Fig. 8. Higher magnification of Fig. 7. Nuclear pleomorphism, hyperchromicity, loss of polarity, suggestion of intraluminal bridging, foci of marked atypia, and carcinoma in situ × 450.

Fig. 9. Papillary hyperplasia with foci of atypia, marked atypia, and carcinoma in situ × 149.

Fig. 10. Higher magnification of Fig. 9. In addition to usual features of nuclear pleomorphism and loss of polarity, there is some cribiform pattern and intraluminal bridging, carcinoma in situ × 484.

Fig. 11. Multiple ducts with relatively normal cylindrical mucous cells, except in central area, which shows foci of atypia, marked atypia, and carcinoma in situ × 52.

Fig. 12. Higher magnification of adjacent section of Fig. 11. Papilla with marked atypia and carcinoma in situ × 310.

Fig. 13. Dilated duct with normal duct epithelium (right). Rest of epithelium shows atypia, marked atypia, and carcinomas in situ × 44.

Fig. 14. Higher magnification of Fig. 13. Papillae of carcinoma in situ × 360.

Fig. 15. Dilated duct with relatively flat epithelium. Carcinoma in situ with pleomorphism of nuclei, large nucleoli, lack of polarity, and piling up of nuclei. Many cells appear to have mucigen in cytoplasm. × 742.

Fig. 16. Carcinoma in situ of another flat epithelial lesion of duct of same case as Fig. 15. Marked pleomorphism, piling up of nuclei with loss of polarity, and prominent nucleoli; many cells appear to contain some mucigen. × 742.
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