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A Case of Pancreatic Ductal Adenocarcinoma Arising From Atypical Flat Lesions

To the Editor:

Atypical flat lesions (AFLs) in the pancreas have been suggested a potential precursor to pancreatic ductal adenocarcinoma via acinar-to-ductal metaplasia (ADM) in mouse model studies. Still, the role of AFLs in human pancreatic cancer is unknown. Here, we present a case of *KRAS*-mutated pancreatic ductal adenocarcinoma arising from AFLs based on clear histopathological findings. This incidental finding highlights the need for further investigation of the prevalence and role of AFLs in human pancreatic ductal adenocarcinoma (PDAC) development.

CASE REPORT

A woman around 70 years old presented with abdominal pain and jaundice. No solid tumor was found on radiology, but suspicion of a malignant lesion was raised because of the presence of double duct sign,[1] and the patient subsequently underwent pancreaticoduodenectomy. Perioperatively, the pancreas was soft in texture and absent of macroscopic tumor signs.

Histopathological evaluation revealed *KRAS*-mutated PDAC with both a ductal growth pattern and a low differentiated growth pattern. The nonneoplastic pancreas was marked by chronic atrophic pancreatitis with extensive ADM positive for the ductal marker cytokeratin 7 (Fig. 1A). The metaplastic ductal epithelium consisted of inconspicuous cuboidal cells with centrally placed homogenous nuclei and a low proliferative activity indicated by less than 10% of Ki-67–positive nuclei (Fig. 1A). Only in 1 single acinus with ADM, pancreatic intraepithelial neoplasia (PanIN) grade I was observed.

Several acini with metaplastic ductuli displayed dysplastic changes of the epithelium with pleomorphic hyperchromatic nuclei and a high proliferative activity with more than 50% of Ki-67–positive nuclei indicative of AFLs (Fig. 1A). In addition, some ducts showed back-to-back formations and shift toward a cribriform growth pattern. In 1 acinus with AFL, an outgrowth of a dysplastic gland into the surrounding connective tissue was detected as a clear sign of transition from AFL into infiltrative cancer growth (Fig. 1B).

DISCUSSION

Here, we present a case of PDAC that presents with extensive parenchymal atrophy and ADM as well as AFLs clearly progressing into infiltrating cancer. This case report shows that AFLs can progress to PDAC in human and probably via a sequence from chronic pancreatitis toward acinar atrophy and ADM (Fig. 1C).

Acinar-to-ductal metaplasia is defined as the metaplastic transformation of pancreatic acinar cells into small intra-acinar ductal CK7-positive cells. It can be induced by stress and inflammation including pancreatitis, *KRAS* mutation, and epidermal growth factor receptor activation.[2] In mice with *KRAS* mutation, ADM formation is an early event in PDAC progression.[3] In humans, ADM is commonly found close to PanIN lesions, but its role in PDAC progression is not clear. Shi et al[4] showed that ADM near PanIN lesions often shares the same *KRAS* mutation, whereas isolated ADM without adjacent PanIN foci is of wild-type *KRAS*. The authors argue against acinar cells being the cell of origin in PDAC but that ADM with *KRAS* mutations is more likely a retrograde expansion of PanIN lesions. An alternate interpretation is that ADMs that acquire a KRAS mutation develop into PanIN lesions.[2] The latter has been experimentally supported in mouse models.[5,6] We find it unlikely that the present PDAC case arose from PanIN lesions as only 1 low-grade PanIN was observed in an ADM area.

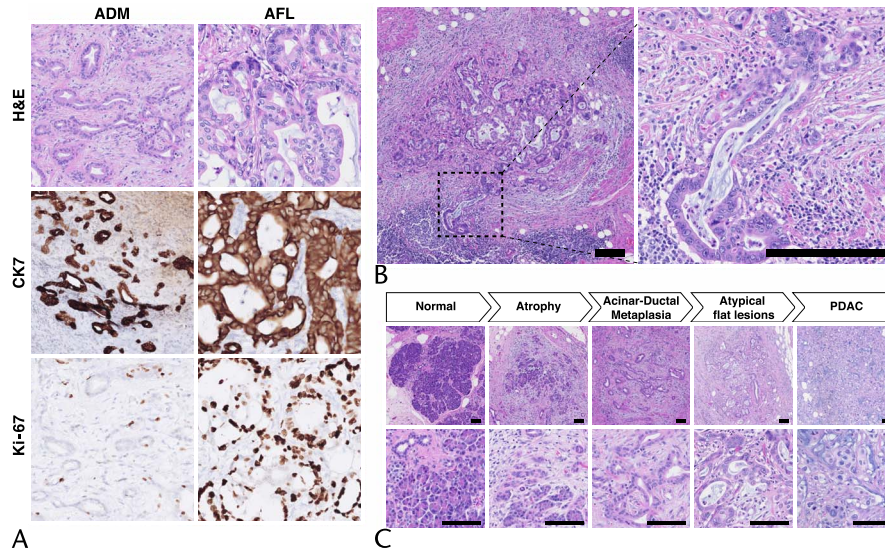

FIGURE 1. A, Acinar-to-ductal metaplasia and atypical flat lesions (AFLs) stained with hematoxylin and eosin, the ductal marker cytokeratin 7 (CK7), and the proliferation marker Ki-67. Acinar-to-ductal metaplasia exhibits small CK7-positive glands without dysplasia and with a low Ki-67 proliferation rate. The AFL displays irregular CK7-positive gland formations with highly pleomorphic epithelial cells and a high Ki-67 proliferation rate. Original magnification ×200. B, Overview over an acinus with AFL (right) and a magnification showing the transition into invasive growth into the surrounding stroma (left). Original magnifications ×50 and ×400. Scale bars, 200 μm. C, Theoretical progression from normal exocrine pancreas parenchyma into invasive ductal adenocarcinoma. Original magnifications ×50 (top panel) and ×400 (bottom panel). Scale bars, 200 μm.

Alternatively, human PDAC might arise from ADM via AFLs, which has been recently shown in mouse models.[7,8] The presence of AFLs has also been demonstrated in human pancreas tissue, but without evidence of AFLs progressing into invasive carcinoma. Aichler et al[8] reported the presence of AFLs in 3 familial pancreatic cancer cases but could not find AFLs in any sporadic PDAC case. On the contrary, Morita et al[9] reviewed slides from 371 pancreatic specimens with different sporadic PDAC forms or benign lesions and identified AFLs in 18 cases. However, these findings do not clarify whether AFL is a precursor or only a bystander. In this case report, there is a clear progression from AFL into invasive carcinoma, which strongly suggests that AFL is the precursor lesion.

In summary, this case report shows for the first time in humans that PDAC can arise from AFLs. The prevalence of AFLs and its pathophysiological role in pancreatic cancer need further investigation.

The case report complies with the Declaration of Helsinki. The patient was contacted and gave oral and written informed consent.

The authors declare no conflict of interest.

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Coronavirus Disease 2019 Pandemic *Potential Collateral Damage on Patients With Operable Pancreatic Cancer*

To the Editor:

The emerging epidemiological data underscore the global impact of the coronavirus disease 2019 (COVID-19) pandemic. Since the first case was reported in December 2019, in Wuhan, China, the subsequent 4 months have seen the virus spread to every continent. In tandem with increasing infection rates, the mortality associated with the infection continues to rise, with over 90,000 deaths reported worldwide with most authorities recognizing that this does not reflect the actual level of infection or mortality.[1] Research towards a vaccine and effective antiviral therapy is underway with much of the effort in the Western world being targeted towards manufacture of mechanical ventilators to ensure timely treatment of COVID-19 patients.[2]

The pandemic has, in addition, at least had significant short- to medium-term effects upon social activities, education, and the economy, although positive environmental effects have been noted.[3] The initial and on-going media focus has predominantly and rightly focused upon tracking the spread of the virus, its associated health indices, and the ensuing economic downturn.[4]

With the focus continuing to be centered upon COVID-19 as a health emergency, sparse attention is currently being paid to the inevitable effects upon management of other diseases during this time. The rapidity of viral spread has forced a speedy redistribution of resources in almost all health care systems around the world with priority being centered on ensuring intensive care unit (ICU) capacity, which in some instances has meant that operating rooms are being used as additional ICU beds meaning that anesthetic staff are being deployed to care for these patients.

As a result, surgical services have reduced their workload with most elective surgery being postponed. The 4 surgical Royal Colleges of the United Kingdom and Ireland have released a joint consensus statement providing guidance for emergency general surgery, but the same has not been published for cancer surgery.[5] A negative effect can be anticipated for patients with almost all cancers but particularly pancreatic cancer because most of these patients will require preoperative anesthetic input and require ICU stay postoperatively. Several studies have demonstrated the adverse impact of delay to surgery in patients with pancreatic cancer.[6] Sanjeevi et al[7] demonstrated that a waiting time from diagnostic imaging to surgery of more than 32 days doubles the rate of irresectability in patients with pancreatic ductal adenocarcinoma. Moreover, emerging data from the "fast track" pancreatic surgery pathway suggests that this rapid assessment process increases rates of curative resection.[8]

As a result of the COVID-19 pandemic, Kutikov et al[9] have proposed guidelines for triaging patients with various tumors, including pancreatic cancers. The authors suggested that in cancers where treatment delay may increase, the risk of disease progression provision should be made to offer immediate surgical intervention in such patients who are younger than 70 years.[9] Although pancreatic cancer clearly falls into this remit on current forecasts of ICU bed occupancy, there will be an inevitable delay in surgery for patients with operable pancreatic cancer.

Patients with resectable pancreatic cancers awaiting surgery for longer than necessary may be offered chemotherapy as a method of disease control and bridge to surgery despite an evidence base. Extrapolating data for this approach in resectable disease from those patients receiving