Recurrent Pancreatitis in Gardner Variant Familial Polyposis

Etiology, Diagnostic Approach, and Interventional Results

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Hypothesis: Pancreatitis arising from an obstructing ampullary neoplasm in patients with Gardner variant familial polyposis is an infrequently described clinical entity. We reviewed all patients with Gardner variant polyposis presenting with pancreatitis during a 12-year period in our institution, hoping to better define etiology and the appropriate diagnostic and interventional approach.

Methods: A retrospective record review (1986-1998) defined patient demographics, presenting features, initial and subsequent endoscopic retrograde cholangiopancreatography (ERCP) findings, subsequent treatments, and both immediate and long-term outcomes. Particular consideration was given to initial post-ERCP diagnosis and to endoscopic interventions undertaken at that time. We also looked at those patients who eventually required surgical intervention after long-term failure of medical and endoscopic therapy, the indications for surgery, final pathological characteristics, and follow-up results.

Results: Eight patients (6 women and 2 men), with a mean age of 42 years at initial presentation, were found. Each patient was known to have Gardner variant familial polyposis at the time of the initial bout of pancreatitis. All had undergone prior colectomy and 4 of 8 had undergone prior cholecystectomy. None were known to be taking medications or ingesting pancreatoxic substances. Five of 8 patients had obstructing focal or diffuse adenomatous disease involving the ampulla. Two of 8 patients had pancreatitis attributed to other causes (divisum, stones) and a single patient had no clear etiology. Three of 5 patients with ampullary adenomatous disease underwent pancreaticoduodenectomy for recurrent adenomatous encroachment and ampullary stenosis, despite repetitive snare resection and papillotomy. All of these patients had ampullary and other duodenal adenomas, and none had malignant disease.

Conclusions: Patients presenting with pancreatitis in the setting of Gardner variant familial polyposis will frequently have an obstructing ampullary neoplasm, although additional etiologies should be sought. Initial endoscopic therapy affords transient relief but may not be definitive. The abnormal scarring and fibrosis (keloid formation, desmoid reaction) that characterize this disease likely play a large role in endoscopic or subsequent surgical failure. A significant number of these patients will go on to require surgical referral and intervention.

Arch Surg. 1999;134:311-315

GARDNER SYNDROME was initially described as one of the familial polyposis syndromes; however, it also has extensive extracolonic manifestations. These include osteomas of the skull, jaw, and other bones as well as desmoid tumors and other soft tissue lesions.1,2 Also well described are gastric and small-bowel polyps.3,4 This syndrome is now known to be an expressionional variant of the same dominant, autosomally inherited gene mutation that characterizes familial adenomatous polyposis. Frequently mentioned in the discussion of upper gastrointestinal tract polyps is their malignant potential, reported to be as high as 12% in some series.5,6 Less often discussed, and found in the literature only as sporadic case reports, are the obstructive problems these neoplasms can create in the region of the ampulla—specifically, obstructive pancreatitis. Our review of the literature to date revealed only several single-case reports of obstructive pancreatitis secondary to ampullary neoplasm and prompt surgical intervention was undertaken in most cases.8,10 We reviewed our own experience to help define the frequency of obstructing lesions in this setting and to establish the role of endoscopic and surgical treatments.

RESULTS

Eight patients (6 women and 2 men), with a mean age of 42 years, were found. All had GV familial polyposis at the onset of
PATIENTS AND METHODS

We retrospectively reviewed all admissions for pancreatitis during a 12-year period that included a diagnosis of gastrointestinal tract tumor at the time of discharge or preexisting at the time of admission. We found 8 patients who had a diagnosis of Gardner variant (GV) familial polyposis that preceeded the diagnosis of pancreatitis. In each case, midgastric abdominal pain and tenderness, an elevated amylase level, and abdominal ultrasonography and computed tomography of the abdomen established the diagnosis. All patients ultimately underwent diagnostic endoscopic retrograde cholangiopancreatography (ERCP). The results of these initial studies were reviewed and findings confirmed the etiology of the pancreatitis. Patients found to have obstructive ampullary adenomas were noted to have either a focal or diffuse pattern of disease.

Endoscopic interventions were then reviewed and outcomes noted by status of symptoms after treatment. For those patients who underwent initial endoscopic sphincterotomy, we noted the type (biliary vs pancreatic) and presence or absence of stenosis at these sites on repeated ERCP.

Follow-up endoscopic findings, particularly in the setting of pancreatitis recurrence, were also noted. We looked at those cases that eventually required surgery, the indications for that surgery, and long-term outcomes. No statistical analysis was attempted given the small number of patients involved.

initial pancreatitis. All had undergone previous colectomy and 4 of 8 patients had undergone prior cholecystectomy. No patients were taking medications or ingesting substances known to be pancreatotoxic and all noninvasive abdominal imaging procedures were negative for stones or tumor. All patients underwent ERCP by a single endoscopist at the time of initial presentation. Findings and treatment results are summarized in the Table. Five of 8 patients were found to have obstructive annulmonary adenomatous disease at ERCP. Two of the 8 patients had other ERCP findings thought responsible for their presentation (stones and divisum) and a final patient had no abnormalities noted at ERCP.

Of the 5 patients noted to have obstructive adamantous disease, 4 had diffuse adenomatous changes and 1 had a focal adenoma compressing the ampulla. An example of each is shown in Figure 1 and Figure 2. Four of the 5 patients with ampullary adenomatous disease underwent initial biopsy with snare resection and biliary sphincterotomy. Resection was by piecemeal snare cautery and sphincterotomy was done using a blended current 30-mm wire sphincterotome. Initial resolution of symptoms was observed. The final patient had adenomatous changes high within the ampulla and underwent initial stenting only. On final pathological examination, malignant disease or carcinoma in situ was not found, although several patients were noted to have adenomatous hyperplasia with mild atypia.

The 2 patients with nonadenomatous etiologies (stones, divisum) underwent biliary sphincterotomy with stone extraction and endoscopic dorsal pancreatic duct sphincterotomy, respectively. The patient with no endoscopic abnormalities other than a mildly dilated pancreatic duct (upper-limit normal) was thought by exclusion to have probable major papillary sphincter dysfunction and underwent major pancreatic duct sphincterotomy.

All 3 of the patients with nonadenomatous etiologies improved initially. The patient who underwent common bile duct stone extraction had lasting relief with no recurrence to date. The other 2 patients had recurrent pancreatitis within 3 months and underwent repeated ERCP and repeated pancreatic duct sphincterotomy at stenosed sphincterotomy sites. Both again experienced symptomatic relief for 3 to 6 months but ultimately had recurrence of symptoms. Each underwent eventual pancreaticoduodenectomy for recurrent sphincterotomy stenosis and recurrent pancreatitis. One of these patients had desmoid reaction pathologically. The patient with divisum continues to have chronic pain problems and has been diagnosed with recurrent pancreatitis at an outside institution. The final patient in this group has undergone 2 pancreaticojejunostomy revisions for stenosis heralded by relapses of pancreatitis and is now symptom free.

The patients with ampullary adenomatous disease who underwent biliary sphincterotomy and snare resection also had initial resolution of symptoms, followed by attacks of recurrent pancreatitis within 6 months of initial endoscopy. The single case of focal adenomatous disease had further encroachment and obstruction requiring 2 more endoscopic sessions of snare piecemeal resection, followed by complete and lasting resolution of symptoms. The patient who had only a stent placed at initial ERCP had a questionable filling defect in the distal common bile duct and brush cytological test results consistent with a malignant stricture, which prompted surgical referral in the absence of a recurrent attack. This patient underwent transduodenal sphincteroplasty and cholecodochoscopy. Diffuse ampullary adenomatous hyperplasia was noted, no neoplasm was found, and pancreatitis has not recurred.

The 3 other patients with a diffuse pattern of disease had varying degrees of stenosis and scarring at the previous sphincterotomy site. Some progression of the adenomatous disease at the ampulla had also occurred, and further snare resection, along with pancreatic duct sphincterotomy and extension of biliary sphincterotomy, was carried out (Figure 3). These 3 patients, 1 of whom had a minor papilla adenoma and cystic dilation of the duct of Santorini (Figure 4), continued to have recurrent bouts of pancreatitis, and went on to surgical referral and eventual pancreaticoduodenectomy. One of these patients had initial transduodenal sphincteroplasty with recurrent stenosis despite multiple revisions and a second had a desmoplastic reaction in the resected specimen. All of these patients have denied recurrent pancreatitis since surgery with a mean follow-up time of 3 years (range, 1-4 years). Characteristics of pathology specimens obtained at operation remained benign and consistent with endoscopic biopsy specimens in all cases. Of note, sphincter manometrics were
not uniformly performed at initial or subsequent ERCP. When recorded (1 patient), readings were below 20 mm Hg and no sphincter dysfunction was noted. To summarize, 6 of 8 patients underwent surgical referral and intervention. Of those 6 patients, 5 underwent eventual pancreaticoduodenectomy without major complications and 3 of those 5 are free of recurrence, with a mean follow-up time of 36 months.

<table>
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* DAA indicates diffuse ampullary adenoma; ES, endoscopic sphincterotomy (biliary, pancreatic, or both); SR, snare resection; ST, stenosis; AE, adenoma encroachment; PD, pancreaticoduodenectomy; FAA, focal ampullary adenoma; NA, not applicable; TDDS, transduodenal sphincteroplasty; Pdiv, pancreatic divisum; and UNK, unknown.
† Multiple times.
‡ In both cases transduodenal sphincteroplasty failed and was followed by pancreaticoduodenectomy.
§ Patient underwent multiple revisions of pancreaticojejunostomy due to recurrent stenosis.

A marked increase in the frequency of upper gastrointestinal tract neoplasms, forming in the stomach, duodenum, and even more distal small bowel, is well known as one of the extracolonic manifestations of familial polyposis. The much heralded increased risk of malignant neoplasms, generally considered to range between 2% and 10%, has resulted in widespread recommendation for frequent endoscopic surveillance and biopsy to detect malignancy early. Medications such as sulindac have been routinely used in hopes of halting progression of C-loop adenomas to invasive cancer, but data supporting its efficacy are sparse.

Less frequently described are the potential nonmalignant complications of adenomatous disease in the periampullary region. Pancreatitis in the specific setting of GV familial polyposis is distinctly uncommon. However, when it does occur, obstructive ampullary adenomatous disease may be the cause. In fact, pancreatitis may be the presenting manifestation of upper gastrointestinal tract neoplasm in these patients. Also additional and unrelated etiologies, such as gallstones or ana-
tomical ductal abnormalities, may be causative in these patients and should be ruled out early in the workup.

As noted earlier, endoscopic intervention in these patients has not been previously described. The few case reports in the literature generally discuss endoscopic biopsy and prompt surgical referral. Our review demonstrates that patients can often be palliated with piecemeal resection and sphincterotomy but that relief will be temporary, will require close endoscopic follow-up, and will be somewhat dependent on the pattern of disease. The single patient who was “definitively” treated with serial snare resection had a single, large, obstructing ampullary mass rather than diffuse adenomatous disease, a pattern that frequently extends up and into the ampulla, making it difficult to resect. This group has a near 100% eventual failure rate of endoscopic sphincterotomy alone. Stenosis of the biliary sphincterotomy orifice outside of this patient subset has a much lower incidence (1%-5% in most published series) but does seem to be higher for pancreatobiliary sphincterotomy. For example, we have previously reported a 14% incidence of stenosis with pancreaticobiliary sphincterotomy in this institution.17

A question might be raised regarding the evidence that ampullary adenomas are the cause of pancreatitis in the 5 patients reviewed here. While we acknowledge that the evidence is somewhat indirect, we maintain that ampullary tumors as a cause of obstructing pancreatitis is reasonably well established in the literature and has been described not only in patients with familial polyposis but in the general population as well.18 A single patient in this series had curative therapy with snare resection and debulking of a solitary ampullary adenoma. Another patient with a diffuse pattern of ampullary disease, involving not only the ampulla but the accessory duct as well, was found to have cystic dilatation of the duct of Santorini (Santorinicele), a finding indicative of obstruction (Figure 4).

The extracolonic manifestations classically described with GV familial polyposis, keloid reaction and fibromas in the form of desmoid tumors and osteomas, belies the abnormal scarring and fibroblast activity of these patients.2 Unusual in the general population, desmoid tumors are seen in many patients with GV familial polyposis and desmoplastic reactions were noted in 2 of the patients in the current series. The latter are typically found intra-abdominally in areas of previous surgery or trauma and can be thought of as a marker of defective fibroblast control.20 This may account for the failure of conventional sphincterotomy techniques in this setting. The patient in this series who failed transduodenal sphincteroplasty because of recurrent stenosis, despite several revisions, and the patient who required repetitive pancreatobiliary sphincterotomy revision, emphasize this. Some debate exists regarding the ability of sulindac to induce regression of C-loop adenomas,12,13 but both sulindac and the antiestrogen analogue, tamoxifen, have been shown to limit desmoid growth and recurrence in patients with GV familial polyposis.21,22 Although not used in the current series, it seems reasonable to extrapolate that one or both of these agents might have a similarly protective effect on scarring and stenosis at the sphincterotomy site if dosage and timing are appropriate for the initial procedure.

Despite the fact that no patient in this series was found to have malignant adenomatous disease, 60% of patients with obstructive adenomas ultimately underwent pancreaticoduodenectomy. The indication in all cases was recurrent or chronic pancreatitis plus failure of endoscopic sphincterotomy. Mean follow-up, to date, is 36 months with full symptom resolution. The question is whether these patients should be immediately referred for surgical evaluation. The patients with a diffuse pattern of adenomatous disease likely would have benefited from earlier surgical consideration. However, the diagnostic and, at least, temporizing role of initial ERCP in these patients is clear. Early relief with snare resection and sphincterotomy is common and could be particularly useful in a sick patient. Longer-lasting results may or may not be observed with the use of either sulindac or tamoxifen. Patients with large, focal, periampullary adenomas may also do well with therapeutic ERCP maneuvers alone, as may other patients with nonadenomatous etiologies, such as the sole patient with cholelithiasis in this series. However, the need for surgical intervention may be inevitable in most of these patients. The results of pancreaticoduodenectomy have been superior in this series and it would clearly be the operation of choice for malignant disease. Surgical sphincteroplasty can be successful but does not remove the long-term risk of progression to malignant disease or prevent cicatrization from progressive desmoid reaction.

In conclusion, pancreatitis occurring secondary to obstructive adenomatous disease in the patient with known familial polyposis is relatively uncommon. Despite the small body of information in the literature, some clear management recommendations can be made. Careful questioning into patient background and medications, along with the use of noninvasive imaging modalities (such as ultrasonography and computed tomography), should always be done to rule out other common causes of pancreatitis. These patients should all undergo upper endoscopy and ERCP. If obstructive ampullary adenomas are found, then biopsy specimens should be obtained and snare resection with sphincterotomy considered. We advocate snare resection at initial ERCP if the lesion is low in the ampulla and not part

Figure 4. Cystic dilatation of the accessory duct of Santorini (arrow) from obstructive ampullary adenomatous disease involving both the major and minor papillae. This patient ultimately underwent pancreaticoduodenectomy.
of a diffuse adenomatous hyperplasia. We also recommend sphincterotomy at initial ERCP unless the endoscopist believes the obstructive lesion is extra-ampullary and amenable to snare resection alone. A postinstrumentation regimen of sulindac should be considered. For patients with malignant disease at biopsy or diffuse adenomatous disease involving the ampulla with recurrent encroachment and stenosis at the sphincterotomy site, prompt surgical referral should be strongly considered.


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REFERENCES