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EDITORIAL

The Natural and Unnatural History of Pancreatic Fluid Collections Associated with Acute Pancreatitis

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An exponential expansion of medical knowledge has occurred within the past two generations of physicians, largely fueled by advances in technology, combined with dedicated adherence to the principles of evidence-based medicine. Indeed, the volume and quality of currently available medical information can be viewed as one of the more significant human achievements of the last 50 years. The pancreas and its associated conditions have been one of the principal beneficiaries of this information *tsunami*. Once considered to be the last frontier of organ pathophysiology, the enigmatic "piece of flesh" is increasingly surrendering its secrets to ever more comprehensive investigation.

As a case in point, fluid collections resulting from acute pancreatitis were once thought to be quite rare. The late Dr. Robert M. Zollinger Sr., then dean of pancreatic surgeons, once told me that "The number of authors and articles about pancreatic pseudocysts far exceeds the actual incidence!" Moreover, the management of acute pancreatitis-induced fluid collections was problematic. For most of the 20th century, all peripancreatic fluid collections were considered to be "pseudocysts" treated by surgical drainage in order to prevent the excessive morbidity and mortality from complications such as rupture, hemorrhage, and infection. Nevertheless, the diagnosis of a "pancreatic pseudocyst" in the setting of acute pancreatitis was notoriously difficult at that time, being based primarily on the demonstration of an upper abdominal mass, often combined with anterior displacement of the stomach visualized radiographically with barium. Whether or not the mass was actually a pseudocyst, or was caused by the marked edema of the pancreas and surrounding tissues (so-called "pseudo-pseudocyst"), could not be determined, and often necessitated exploratory laparotomy for definitive resolution.

In the early 1970s, we discovered that transabdominal ultrasound was capable of reliably identifying pancreatic fluid collections as a complication of acute pancreatitis, thereby obviating the need for diagnostic laparotomy. Dynamic size changes in these collections, including complete resolution, were documented by serial sonographic studies [1]. Using this non-invasive modality, we set out to determine the natural history of acute pancreatitis-induced fluid collections in a series of prospective studies [2, 3]. In largely alcoholic populations admitted with severe acute pancreatitis and clinical findings suggestive of an acute pseudocyst, we found that 52 of 92 patients (56 %) exhibited the characteristic sonographic findings of a fluid collection in or near the pancreas. Surgical intervention for unrelated complications of acute pancreatitis was deemed necessary in 14 of these cases. Nonetheless, 40 % of the remaining cases underwent spontaneous resolution of the fluid collection within 3 weeks after the onset of pancreatitis. Accordingly, we concluded that conservative management of these early fluid collections was reasonable.

Although the need for clinically-based definitions of the various types of fluid collections associated with acute pancreatitis had long been recognized as necessary for appropriate diagnosis and therapy, it was not until 1992 that precise clinical definitions of these fluid collections were proposed at the Atlanta Symposium [4], and subsequently adopted by the worldwide medical community. As a result of continuing investigations over the ensuing 20 years, however, two additional acute pancreatitis-induced fluid collections, "acute necrotic collections" (ANCs) and "walled-off necrosis" (WONs), have recently been recognized by an International Consensus [5], and added to the Atlanta

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Table 1 Clinical definitions of fluid collections associated with acute pancreatitis

Acute pancreatic fluid collection (APFC): Resulting from interstitial edematous pancreatitis, without evidence of necrosis, and only occurring within the first 4 weeks after onset of pancreatitis. No definable wall, and often irregularly shaped on CT. Usually resolves spontaneously
Acute pseudocyst (AP): An APFC that has become encapsulated with a well-defined wall, and no evidence of necrosis. Only seen more than 4 weeks after onset of pancreatitis, and due to maturation of fibrous tissue surrounding the collection. Global in shape, with a homogeneous internal density. Approximately half undergo spontaneous resolution over time, but may also develop complications
Acute necrotic collection (ANC): A mixed collection of variable amounts of necrotic tissue and pancreatic fluid resulting from documented necrotizing pancreatitis. May present within the pancreatic parenchyma, or in the peripancreatic region. No encapsulating wall. Usually seen early in the course of necrotizing pancreatitis. Accurate diagnosis requires US or MRI to distinguish from AP. Natural history not well established. May become complicated
Walled-off necrosis (WON): An ANC that has undergone fibrous encapsulation. Occurs more than 4 weeks after development of necrotizing pancreatitis. Natural history not well established. May become complicated, but marked decreases in size have also been observed over time

Modified by the author from [4, 5]

definitions. I have proposed the term "necrocyst" for these two latter additions, as it more accurately expresses both the cyst content and the radiologic appearance (Table 1).

Considering the prospective, multicenter, well conducted natural history study by Cui and his internist co-workers from Yeungnam University in Korea [6], we note that 302 patients admitted with documented acute pancreatitis underwent serial CT scans beginning 3–4 days after onset. Peripancreatic fluid collections were documented by computed tomography in 129 (42.7 %) of these cases. Of these 129 patients, acute pancreatic fluid collections (Atlanta definition) occurring in 110 (85 %) all resolved spontaneously. Nineteen patients (15 %) developed an acute pancreatic pseudocyst (Atlanta definition). Five of these 19 acute pseudocysts resolved spontaneously with 11 decreasing in size during follow-up. Complications (infection requiring drainage and pseudoaneurysm) developed in 4 of the 19 patients (21 %). Twenty patients were lost to follow-up, a common event in alcoholic populations, but with unknown consequences for the data presented. Forty-eight-hour C-reactive peptide and lactate dehydrogenase measurements were significantly predictive of acute pancreatic fluid collections and acute pseudocysts, respectively. Based on these observations, the authors advocated conservative management of fluid collections associated with acute pancreatitis. These results and recommendations are comparable to those obtained by ultrasonography in our studies almost 40 years ago. Differences in the frequency of findings between our studies and the current one may reflect differences in population composition or overall severity (see below).

The question before us now is not whether we can accept the findings and recommendations of Cui et al., but rather whether or not these findings can be considered representative of the wide spectrum of presentation of fluid collections associated with acute pancreatitis? I have several concerns that give me pause. First, and perhaps most importantly, the severity of the underlying acute pancreatitis in the Korean study could best be described as "mild" to "moderate." The overall mortality rate was 1.3 %, the average Ranson score was less than 3 in 60 %, and the average APACHE II score was less than 8 in 70 %. The values of each one of these parameters in the Korean study is inconsistent with severe acute pancreatitis. Moreover, none of their patients seemed to develop necrotizing pancreatitis, although it is not clear that intravenous contrast was part of their computed tomography protocol. Neither sonography nor magnetic resonance was used to determine the possible existence of necrocysts in their population of "acute pseudocysts." Accordingly, the authors can make no comments regarding the natural history of the two recently defined fluid collections, ANCs and WONs.

All of these issues suggest a milder form of acute pancreatitis in the Korean study, and begs the question of whether a study population enriched with severe acute pancreatitis would increase the incidence and type of fluid collections. It seems reasonable to expect that milder pancreatitis would be associated with fewer fluid collections of any type. Presumably, the converse may also be true. Secondly, due to the magnitude of radiation dosage attendant upon repeated CT exams, I doubt that serial CT scans would currently be recommended to serially assess fluid collections in acute pancreatitis, when the affordable and safe option of serial sonography is widely available. Finally, the 21 % incidence of significant complications in patients with acute pseudocysts (APs) experienced in this study, while under persistent observation, should not be ignored.

Where are we now, and where should we seek to go? Cui et al. cited numerous articles that reported that acute pancreatic fluid collections (APFCs) occur in approximately 40–60 % of prospective studies of admissions for acute pancreatitis. Fortunately, APFCs undergo spontaneous resolution in more than 90 % of cases, and can therefore be regarded more as a common consequence of interstitial pancreatitis, rather than being considered an actual complication. In contrast, APs develop in only 5–15 % of patients with acute pancreatitis, but have at least a 20 % chance of developing significant complications [3, 6]. Because at least half of these acute pancreatic pseudocysts also resolve spontaneously, serial sonographic observation is a reasonable approach to this group as well, prepared at all times to abandon conservative therapy whenever a complication is

encountered. Little natural history information is available for ANCs and WONs. Although we, and others, have documented many instances of gradual contraction of uncomplicated ANCs and WONs, the actual incidence of spontaneous resolution is unknown. Needle biopsies of the contracted necrotic collections in several patients have revealed fibrous incorporation. On the basis of our prior experience and numerous publications, we conclude that the natural history of each type of necrotic collection remains unavailable, and that intervention in uncomplicated necrotic collections is not supported by current information.

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