JOP. J. Pancreas (Online) 2002; 3(3):62-65.

How Far Are We from the Most Accurate Classification System for Chronic Pancreatitis ?

Generoso Uomo

Internal Medicine Department, 3rd Division, Cardarelli Hospital. Naples, Italy

Chronic pancreatitis (CP) is defined as a continuing inflammatory disease of the pancreas characterized by irreversible morphologic changes which typically cause pain and/or permanent loss of function, evolving over a period of several years into end-stage disease [1, 2, 3, 4, 5, 6]. In clinical practice, this definition distinguishes acute first-onset pancreatitis from advanced CP. However, between these two extremes, it is often difficult to precisely classify pancreatitis for various reasons, including the unavailability of routine means of assessing the early stage of CP [7, 8]. In this regard, pancreatic histology represents the diagnostic gold standard of early stage, but non-surgical access to bioptic specimens of the pancreas still remains difficult [9, 10]. Nowadays we are well aware of the clinical picture of CP, including its various complications, but the current classification systems of the disease give little information about etiology, pathogenesis and outcome.

The classification of any disease has a primary function which is to provide a common language among those caring for the patients. In addition, as for many other chronic diseases, an ideal classification system for CP would be simple, objective, accurate using non invasive procedures**,** and it should include etiology, pathogenesis, structure, function and clinical status in one overall scheme [8]. The proposed classification systems currently available have not met these criteria. These classifications (which basically reflect the *state of the art* at the time of promulgation) include a) the Marseille classification of 1963 [11] with revision in 1984 [12], b) the Marseille-Rome classification of 1988 [13], c) the Cambridge classification of 1984 [14], d) the Zurich classification [10] and e) the Japan Pancreas Society classification for CP [15].

The Marseille and the Marseille-Rome classifications should now be considered inadequate and outdated in the light of the noteworthy understanding in pathophysiology and natural history of the disease obtained over the last fifteen years. The Cambridge classification uses imaging features to provide a grading and severity system but it does not distinguish the different forms of CP on the basis of etiology and clinical outcome. This system proves more useful as a staging system once the diagnosis is made rather than a system for classifying CP [8]. The Zurich classification [10], specifically addressed to the alcoholic form of CP, is quite complex (Table 1), considering diagnosis, etiology, clinical staging, and pain profile separately. This classification emphasizes the *dynamism* of the disease, but is not widely accepted. The Japan Pancreas Society classification for CP (Table 2) [15] is designed to standardize the diagnostic criteria but lacks etiological and pathogenetic features. Thus, this classification is only partially useful in a clinical setting.

Another recent classification is the risk-factor classification system for CP [16], named TIGAR-O from the acronym of the causes of the disease (Table 3). This classification is based upon new developments for diagnosis and recent advances in genetics, providing new possibilities for the accurate, early

Table 1. Zurich classification for alcoholic chronic pancreatitis (CP) [10].

A) Definite alcoholic CP
In addition to a typical history or a history of excessive alcohol intake (≥80 g/day), one or more of the following criteria establish the diagnosis:
- Calcification in the pancreas
- Moderate to marked ductal lesions (*"Cambridge"* criteria)
- Marked exocrine insufficiency defined as steatorrhea (>7 g fat/24 h) normalized or markedly reduced by enzyme supplementation
- Typical histology of an adequate surgical specimen

B) Probable alcoholic CP
In addition to a typical history or a history of excessive alcohol intake (≥80 g/day), the diagnosis of probable CP is likely if one or more of the following criteria are present:
- Mild ductal alterations (*"Cambridge"* criteria)
- Recurrent or persistent pseudocysts
- Pathologic secretin test
- Endocrine insufficiency

Addendum: these diagnostic definitions may also be used for nonalcoholic CP

Etiological Factors
- Alcoholic CP
- Non-alcoholic CP
  - Tropical (nutritional) CP
  - Hereditary CP
  - Metabolic (hypercalcemic, hypertriglyceridemic) CP
  - Idiopathic ("early" and "late" onset) CP
  - Autoimmune CP
  - CP due to miscellaneous causes; e.g. radiation injury, phenacetin abuse
  - CP associated with anatomic abnormalities ("Anatomic CP": periampullary duodenal wall cysts, pancreas divisum, obstructive pancreatitis, post-traumatic pancreatic duct scars)

Clinical Staging
- Early stage: recurrent attacks of clinical alcoholic acute pancreatitis (with or without local complications) without evidence of CP abnormalities
- Late stage: any evidence of probable or definite CP

identification of the risk factors leading to CP; in addition, the relationship between acute pancreatitis and the development of CP, a controversial issue [17], is also considered. Etemad and Withcomb [8], in a recent comprehensive and up-to-date review of new knowledge about CP, emphasize the usefulness, the potentiality and the clinical implications of this classification system. In fact, the *exact knowledge of the* etiology of *CP* remains the basis for understanding the natural and clinical history of the disease and for developing preventive and therapeutic measures [10].

When we are faced with a patient affected by CP, once the diagnosis is made and the

Table 2. Diagnostic criteria for chronic pancreatitis (CP) from the Japan Pancreas Society [15].

Definite CP
1. Ultrasonography: pancreatic stones evidenced by intrapancreatic hyper-reflective echoes with acoustic shadows behind; CT: pancreatic stones evidenced by intrapancreatica calcifications
2. ERCP: a) irregular dilation of pancreatic duct branches of variable intensity with scattered distribution throughout the entire pancreas or b) irregular dilation of the main pancreatic duct and branches proximal to complete or incomplete obstruction of the main pancreatic duct (with pancreatic stones or protein plugs)
3. Secretin test: abnormally low bicarbonate concentration combined with either decreased enzyme outputs or decreased secretory volume
4. Histologic examination: irregular fibrosis with destruction and loss of exocrine parenchyma in tissue specimens obtained by biopsy, surgery or autopsy; fibrosis with an irregular and patchy distribution in the interlobular spaces; intralobular fibrosis alone not specific for CP
5. Additionally, protein plugs, pancreatic stones, dilation of the pancreatic ducts, hyperplasia and metaplasia of the ductal epithelium, and cyst formation

Probable CP
1. Ultrasonography: intrapancreatic coarse hyperreflectivities, irregular dilation of pancreatic ducts, or pancreatic deformity with irregular contour; CT: pancreatic deformity with irregular contour
2. ERCP: irregular dilation of the main pancreatic duct alone; intraductal filling defects suggestive of non-calcified pancreatic stones or protein plugs
3. Secretin test: a) abnormally low bicarbonate concentration alone or b) decreased enzymes outputs plus decreased secretory volume; Tubeless tests: simultaneous abnormalities in BT-*p*-amino benzoic acid and fecal chymotrypsin tests observed at 2 points several months apart
4. Histologic examination: intralobular fibrosis with one of the following findings: loss of exocrine parenchyma, isolated islets of Langherans, or pseudocysts

CT: computed tomography scan
ERCP: endoscopic retrograde cholangiopancreatography

Table 3. TIGAR-O classification system for CP [8, 16].

Toxic-metabolic
- Alcoholic
- Tobacco smoking
- Hypercalcemia
- Hyperlipemia
- Chronic renal failure
- Medications (phenacetin abuse)
- Toxins (organotin compounds)

Idiopathic
- Early onset
- Late onset
- Tropical (tropical calcific and fibrocalculous pancreatic diabetes)
- Other

Genetic
- Autosomal dominant: cationic trypsinogen gene (codon 29 and 122 mutations)
- Autosomal recessive/modifiers genes: CFTR mutations, SPINK1 mutations, Cationic trypsinogen (codon 16, 22, 23 mutations), alfa-1-antitrypsin deficiency (possible)

Autoimmune
- Isolated autoimmune CP
- Syndromic autoimmune CP (Sjogren syndrome-associated CP; Inflammatory disease-associated CP; Primary biliary cirrhosis-associated CP)

Recurrent and severe acute pancreatitis
- Post-necrotic (severe acute pancreatitis)
- Recurrent acute pancreatitis
- Vascular disease/ischemic
- Radiation injury

Obstructive
- Pancreas divisum
- Sphincter of Oddi disorders (controversial)
- Duct obstruction (e.g., tumor)
- Periampullary duodenal wall cysts
- Post-traumatic pancreatic duct scars

SPINK1: serine protease inhibitor, Kazal type 1

contributing etiologic factors are determined, we are well on the way to correctly answering two important questions: "What is going to happen ? " and "What can be done ?".
"Felix qui potuit rerum cognoscere causas" (Vergilius, *Georgica*, II, 490). - “Happy is he who knows the reason why”.

Key words Pancreas; Pancreatitis (classification; etiology; genetics; history; immunology; therapy) Pancreatitis, Alcoholic; Pancreatic Diseases; Pancreatic Ducts; Pancreatic Insufficiency; Pancreatic Pseudocyst; Radiation Injuries

Abbreviations CP: chronic pancreatitis; CT: computed tomography scan; ERCP: endoscopic retrograde cholangiopancreatography; SPINK1: serine protease inhibitor, Kazal type 1

Correspondence
Generoso Uomo
Internal Medicine Department
3rd Division
Cardarelli Hospital
Via Cardarelli 9
80131 Napoli
Italy
Phone: +39-081-747.2101
Fax: +39-081-5090.707
E-mail address: g.f.uomo@digimaint.it

References

1. Sarles H. Definitions and classifications of pancreatitis. Pancreas 1991; 6:470-84. [AN 91343583]

2. Kloppel G, Maillet B. Pathology of acute and chronic pancreatitis. Pancreas 1993; 8:659-70. [AN 94077849]

3. Cavallini G. Is chronic pancreatitis a primary disease of the pancreatic duct? Ital J Gastroenterol 1993; 25:391-6. [AN 94108115]

4. Amman RW, Heitz P, Kloppel G. Course of alcoholic chronic pancreatitis: a prospective clinicomorphological long-term study. Gastroenterology 1996; 111:224-31. [AN 96315564]

5. Freedman SD. New concepts in understanding the pathophysiology of chronic pancreatitis. Int J Pancreatol 1998; 8:24:1-8. [AN 98419020]

6. Clain JE, Pearson RK. Diagnosis of chronic pancreatitis: is a gold standard necessary? Surg Clin North Am 1999; 79:829-45. [AN 99399345]

7. Uomo G, Rabitti PG. Chronic pancreatitis: relation to acute pancreatitis and pancreatic cancer. [ANn Ital Chir 2000; 71:17-21. [AN 20288328]

8. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 2001; 120:682-707. [AN 21100106]

9. Steer ML, Vaxman I, Freedman S. Chronic pancreatitis. N Engl J Med 1995; 332:1482-90. [AN 95258097]

10. Amman RW. A clinically based classification system for alcoholic chronic pancreatitis: summary of an international workshop on chronic pancreatitis. Pancreas 1997; 14:215-21. [AN 97248027]

11. Sarles H. Proposal adopted unanimously by the participants of the Symposium, Marseille 1963. Bibl Gastroenterol 1965; 7:7-8.

12. Singer MW, Gyr K, Sarles H. Revised classification of pancreatitis : report of the Second International Symposium on the Classification of Pancreatitis in Marseille, France, March 28-30, 1984. Gastroenterology 1985; 89:683-5. [AN 85258858]

13. Sarles H, Adler G, Dani R, Frey C, Gullo L, Harada H, et al. The pancreatitis classification of Marseille-Rome 1988. Scand J Gastroenterol 1989; 24:641-2. [AN 90048874]

14. Sarner M, Cotton PB. Definitions of acute and chronic pancreatitis. Clin Gastroenterol 1984; 13:865-70. [AN 85025511]

15. Homma T, Harada H, Koizumi M. Diagnostic criteria for chronic pancreatitis by the Japan Pancreas Society. Pancreas 1997; 15:14-5. [AN 97355292]

16. Chari ST, Singer MW. The problem of classification and staging of chronic pancreatitis: proposal based on current knowledge and its natural history. Scand J Gastroenterol 1994; 29:949-60. [AN 95141031]

17. Uomo G, Manes G, Rabitti PG. Role of hereditary pancreatitis and CTFR gene mutations in the etiology of acute relapsing pancreatitis of unknown origin. How are they important? JOP. J Pancreas (Online) 2001; 2:368-72. [AN 21872331]