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Atypical presentation of acute pancreatitis: a single center case-match analysis of clinical outcomes

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Abstract. – OBJECTIVE: Acute pancreatitis (AP) may present an aspecific clinical picture without abdominal symptoms (atypical AP). We compared clinical outcomes between typical and atypical AP.

PATIENTS AND METHODS: Thirty out of 1163 patients (2.6%) presented an atypical AP. Demographic, clinical data, laboratory and radiological findings, management type, length of hospital stay (LOS) and mortality rate were retrospectively reviewed. A case match analysis 2:1 was performed. The final groups comprised 50 typical APs (TAP group) and 25 atypical APs (AAP group).

RESULTS: The AAP patients presented fever (36%), syncope (32%) and dyspnea (16%) as the most frequent symptoms. Laboratory values showed similarity between the two groups. We noted a comparable edematous AP rate in both groups (p=0.36). Ten (20%) TAP and 3 (12%) AAP patients needed ERCP, respectively (p=0.38). Cholecystectomy was similarly performed in both cohorts (p=0.81). One TAP patient underwent a percutaneous drainage and subsequent surgical necrosectomy compared to none in the AAP cohort (p=0.47). LOS and mortality rate were comparable (p=0.76 and 0.3, respectively).

CONCLUSIONS: Similar outcomes have been reached in the two groups. Routine evaluation of the serum amylase values fundamentally contributed to early diagnosis and appropriate treatment.

Key Words:
Acute pancreatitis, Abdominal symptoms, Amylase, Atypical pancreatitis, Clinical outcomes.

Introduction

Acute pancreatitis (AP) is one of the most frequent hospital admission causes for gastrointestinal disorders, which accounts for up to 274.000 annual hospitalizations, with approximate costs of 2.6 billion US dollars[1-5]. Notably, severe and persistent epigastric pain associated with nausea and/or vomiting are typical pathognomonic symptoms.

According to the Revised Atlanta Criteria of 2012[6], this typical symptomatology together with serum amylase and/or lipase ≥3 times the upper normal limit is diagnostic of AP, while radiological imaging is generally recommended in unclear cases or in patients who fail to improve after 48-72 hours from symptoms onset.

Early diagnosis and severity prediction are crucial for proper patient management to decrease related morbidity and mortality[7,8]. Diagnostic delays are generally due to late emergency care/medical counseling or to normal amylase and lipase levels in blood tests[9,10]. These factors lead to severe AP in almost 30% of patients, consequently increasing the life-threating complications rate and dramatically rising the disease-related mortality rate up to 30%[11].

More rarely, the absence of abdominal pain, or the presence of symptoms not related to the gastrointestinal system, could be an additional and dangerous cause of misdiagnosis. Diagnosis of AP in these patients could be very challenging for the emergency physician, and could delay appropriate treatment. It has been reported that this atypical clinical presentation of AP generally presents in elderly patients[12-14], or in the context of pre-existing systemic diseases (i.e., systemic lupus erythematosus)[15] or as post-operative subclinical complication[16]. However, despite prognostic relevance of detecting AP early, no case series in literature analyzes the clinical course of

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unusual AP patients without gastrointestinal-related symptoms compared with conventional AP.

We aimed at determining atypical AP (AAP) incidence and clinical outcomes, with particular focus on global mortality, hospital length of stay (LOS), and need for operative procedures.

Patients and Methods

This monocentric study was approved by the Local Ethical Committee and conducted according to the Declaration of Helsinki. A retrospective analysis based on clinical records of patients admitted to our ED from January 1st 2008 to December 31st 2017 was performed. All patients with AP diagnosis were identified and included in the analysis from which we identified patients with AAP. Patients with AAP were compared to patients with "classic" AP in terms of LOS, need for surgical procedures and overall mortality. We performed a case-match analysis to avoid comparison bias since AAP patients numbers compared to the general AP population were smaller, and presented a higher mean age.

Data Collection

Only patients aged 18 years or older hospitalized at our institution after ED evaluation were considered for analysis. The clinico-demographic data collected were: age, gender, symptoms, laboratory values (hemogram, kidney and liver function test, serum electrolytes, serum amylase and lipase) and abdominal ultrasonography (US) and/or computerized tomography (CT) results. We recorded additional examinations during hospitalization, including endoscopic and/or surgical procedures. LOS and in-hospital mortality rates were additionally registered. AP severity was classified according to the Ranson criteria[17] within the first 48 hours after admission.

Pancreatitis Diagnosis, Definition of Atypical Pancreatitis and Clinical Management

As previously reported[14], amylase serum levels are always required as part of the chemical examinations at our ED, while serum lipase determination is prescribed when serum amylase values are equal or higher than 1.5 times the upper normal level.

AP was diagnosed according to the Revised Atlanta Criteria of 2012[6], and, thus, based on at least two concomitant following criteria: 1. epigastric pain generally radiating to the back, 2. amylase and/or lipase activity more than three times the upper normal value, 3. peculiar abdominal US and/or CT scan findings. AP diagnosis before 2012 was revised according to the Revised Atlanta Criteria of 2012.

AAP was defined as abnormal lipase/amylase level, characteristic radiological features, but absent abdominal pain, nausea, and/or vomiting.

Clinical management has been previously reported[14]. Briefly, crystalloids were firstly used for resuscitation, while colloids were additionally employed in case of unresponsiveness to crystalloids. A central venous catheter to administer additional fluids and to monitor central venous pressure was mandatory in case the initial therapy failed. ERCP was selectively performed in case of biliary AP.

Pancreatic necrosis was treated with percutaneous drainage in case of medical therapy failure.

All cases of unsuccessful percutaneous drainage were treated with surgical drainage and necrosectomy.

Study Endpoints

The primary outcome was a comparison between patients with typical and atypical AP symptoms in terms of LOS and mortality.

The secondary outcome was to compare the two groups regarding surgery and endoscopic procedure need.

Statistical Analysis

AAP was compared to "classic" AP patients in a case matching 2:1 (typical:atypical) analysis. Patients were matched for age, gender and AP severity (according to Ranson score) to reduce potential biases from confounding variables.

Categorical variables were statistically compared with Chi-square test. Continuous variables were compared with *t*-test.

Categorical variables are presented as numbers and percentages, and continuous variables are presented as mean ± standard deviation. A *p*-value of 0.05 or less was considered significant. All data were analyzed with SPSS v25® (IBM, Armonk, NY, USA).

Results

From January 2008 to December 2017, 1163 AP patients (633 males and 530 females) with a mean age 56.9±19.3 years were admitted to the

ED of the Fondazione Policlinico A. Gemelli IRCCS of Rome. Among them, 1133 (97.4%) presented a typical AP symptomology (TAP group), while 30 patients (2.6%) presented an atypical clinical presentation (AAP group). Considering the overall population, 279 patients (24%; 274 in the TAP group and 5 in the AAP group) were hospitalized in other hospitals and, thus, lost at follow-up. Hence, the final study population comprised 884 patients (76% of the whole population): 859 (97.2%) in the TAP and 25 (2.8%) in the AAP groups, respectively, with a mean age of 57.7 ± 19.1 years and a male-to-female ratio of 1:1.5. The overall LOS was 10.7 ± 10.9 days while the overall in-hospital mortality rate was 2.7% (25 patients).

After a 2:1 case matching for gender, age and Ranson score, a comparison between 50 patients with TAP and 25 with AAP for the above-mentioned outcomes was performed (Figure 1).

Table I reports patients' demographic and clinical characteristics. No difference was detected between the two groups regarding age, gender, comorbidities and laboratory tests values, including serum amylase and lipase levels. Comparable Ranson scores were also reached between typical and atypical cases. Amylase values were 3-fold the upper normal value (normal values 7-45 U/l) in 72% (18/25 patients) and 66% (33/50 patients) of cases in the AAP and TAP groups, respectively. A value 1.5 times the normal upper limit was detected in all the remaining cases leading to the execution of serum lipase evaluation in all patients. Regarding AP symptoms, all patients with TAP presented persistent epigastric pain associated to vomiting in 22 (44%) and fever in 7 (14%) cases. Conversely, no patient in the AAP group reported abdominal pain. Patients with an atypical AP symptomatology reported fever (9 patients – 36%) and syncope (8 patients – 32%) as the most frequent cause to access the emergency department, followed by dyspnea in 4 (16%) cases and jaundice and diarrhea in 2 (8%) cases, respectively. Table II reports details of symptomatology. Interestingly (even if not statistically significant), no patients in the AAP group referred previous pancreatitis episodes, while 5 (10%) patients in the TAP group reported one or more previous Emergency Department accesses for AP (p=0.1). In these 5 cases, first episodes of pancreatitis were documented as typical epigastric pain.

All patients underwent CT scan, after a first ultrasound evaluation, with choledocholithiasis evidence in 21 (42%) TAP group patients and 11 (44%) AAP group patients, respectively (p=0.9). An associated cholecystitis was encountered in

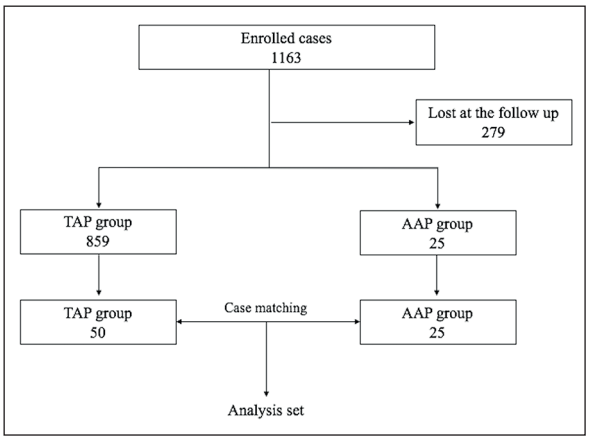

Figure 1. Flow diagram of patients' selection. For case matching: gender, age and Ranson score.

Table I. Patients' demographic and clinical characteristics.

	TAP (n = 50)	AAP (n = 25)	p
Age, years (± SD)	75.54 (± 11.8)	76.92 (± 10.5)	0.7
Gender, n (%)			
Male	26 (52)	13 (52)	1
Female	24 (48)	12 (48)	
Cardiovascular comorbidities, n (%)	31 (62)	15 (60)	0.6
Pulmonary comorbidities, n (%)	11 (22)	6 (24)	0.7
Renal comorbidities, n (%)	5 (10)	2 (8)	0.1
Leukocytes/mm3 (± SD)	11096 (± 6069)	11096 (± 4066)	0.5
LDH, U/l (± SD)	288 (± 132)	312 (± 157.7)	0.6
AST, U/l (± SD)	107 (± 133)	90 (± 90)	0.6
Glycemia, mg/dl (± SD)	132.3 (± 52.2)	155 (± 75.1)	0.3
Serum amylase levels, U/l (± SD)	1114.8 (± 1191.5)	990.2 (± 1101.9)	0.5
Serum lipase levels, U/l (± SD)	2134 (± 2996.6)	1597.9 (± 2644.3)	0.3
Ranson score, mean (± SD)	1.64 (± 0.82)	1.67 (± 0.91)	0.5

Table II. Symptoms of AP presentation for the TAP and AAP groups.

Variable, n (%)	TAP (n = 50)	AAP (n = 25)	p
Vomiting	22 (44)	0	.0001
Fever	7 (14)	9 (36)	0.03
Diarrhea	3 (6)	2 (8)	0.7
Jaundice	3 (6)	2 (8)	0.7
Dyspnea	1 (2)	4 (16)	0.02
Thoracic pain	2 (4)	0	0.3
Syncope	1 (2)	8 (32)	.0001

10 (20%) TAP cases and in 5 (20%) AAP cases (p=1). An underlying pancreatic neoplasia was accidentally detected at the CT scan in 2 (4%) TAP cases and 1 (2%) AAP patient (p=1). Table III reports the main causes of pancreatitis.

Radiological imaging revealed an acute edematous pancreatitis in 24 (96%) patients affected by AAP as compared to 45 (90%) patients in the TAP group (p=0.36). Similarly, necrotic pancreatitis presented a comparable incidence in the two groups (5 and 1 in the TAP and AAP cohorts, respectively; p=0.14). Conservative treatment completely resolved AP in most cases; however, one (2%) TAP patient needed a percutaneous drainage of the necrotic areas. Surgery was performed in 11 (14.7%) patients. Exploratory laparotomy and necrosectomy were needed in only one (2%) TAP patient after drainage failure. Cholecystectomy was performed in 3 (12%) AAP patients and in 7 (14%) TAP group patients (p= 0.81). Of these, 4 (40%) patients underwent a pre-operative ERCP (3 in the TAP group and 1 in the AAP group). In 9 (12%) cases (7 in the TAP and 2 in the AAP cohort) ERCP was the only procedure performed. No intraoperative complications were registered in any case. The mean length of hospital stay was 9 (±7.1) days and no difference was noted between the two groups (9.4 (±6.7) days in the TAP group and 8.9 (±7.4) in the AAP group; p= 0.76). During hospitalization, the overall mortality rate was 6.7% (5 patients): 3 in the AAP and 2 in the TAP cohort (p=0.2). Multiple organ failure was the main cause of death in 1 AAP and TAP case, respectively. The other 2 patients in the AAP group died of heart failure, while the remaining patient in the TAP cohort died of respiratory failure. Table IV reports details of treatment procedures, LOS and mortality rates.

Discussion

AP is a potentially life-threatening condition with a mortality rate ranging from 5% for the mild presentation up to 30% in the severe grade[11]. As consequence, early diagnosis and adequate treatment are widely recognized as crucial factors to avoid disease evolution and related complications[18,19]. Multiple scoring systems and revised classification criteria have been widely proposed over time[6,20-25]. As general acceptance, at least two of the following criteria should be fulfilled for an AP diagnosis: 1. typical severe epigastric and persistent pain, 2. amylase and/or lipase serum level more than 3 times the normal upper limit, 3. characteristic radiological imaging results[6].

As a matter of fact, clinical history represents the first and most important step in AP diagnosis. Patients generally describe dull pain in the epigastrium, which usually radiates into the back. Its severe course often necessitates opioid therapy[26-28].

Table III. Main causes of AP for the TAP and AAP groups.

Variable, n (%)	TAP (n = 50)	AAP (n = 25)	p
Gallstones	21 (42)	11 (44)	0.9
Idiopathic	16 (32)	8 (32)	0.8
Alcohol-induced	10 (20)	5 (20)	0.5
Drug-induced	1 (2)	0	0.15
Other	2 (4)	1 (4)	0.2

Table IV. Treatment procedures and in-hospital course.

Variable, n (%)	TAP (n = 50)	AAP (n = 25)	*p*
Conservative treatment	35 (70)	19 (76)	0.58
Operative treatment	15 (30)	6 (24)	0.18
ERCP	10 (20)	3 (12)	0.38
Percutaneous drainage	1 (2)	0	0.47
Cholecystectomy	7 (14)	3 (12)	0.81
Necrosectomy	1 (2)	0	0.47
In-hospital course			
LOS, days (± SD)	9.4 (± 6.7)	8.9 (± 7.4)	0.76
Mortality	3 (6)	2 (8)	0.2

Atypical AP, defined as any symptomatology in the absence of abdominal pain, is generally related to pre-existing systemic diseases (i.e., lupus erythematosus)[15], advanced age[12-14] and rarely, as post-operative subclinical complication[16]. Diagnosis occurs in these cases accidentally and is mainly based on biochemical abnormalities or characteristic radiologic results (CT scan) performed for other clinical reasons.

To our knowledge, we presented the largest series in the literature on unconventional clinical AP. Case match analysis significantly reduced potential biases comparing the APP with the TAP cohort.

AAP, as compared to the overall AP population of 1163 patients admitted to the ED, accounted for 2.6%, was more often encountered in elderly patients (57.72±19.12 *vs.* 76.92±10.5; $p<0.0001$) and fever (36%), syncope (32%) and dyspnea (16%) were the most frequent symptoms referred. The relation between advanced age and atypical AP symptomatology has been already reported. Of note, two post-mortem studies[29,30] demonstrated an AP diagnosis rate up to 42% in patients older than 60 years without abdominal symptoms. These and our results confirm the well-known "frailty" of the elderly population. Increasing age might relate to a pro-inflammatory status or organ-specific alteration that could increase systemic inflammation and respiratory distress, particularly in acute clinical events such as AP[31]. The consequent higher cytokine production[32] may potentially lead to a primary systemic manifestation of the acute inflammation in form of fever, tachycardia, hypovolemia, dyspnea.

Serum amylase and lipase level measurement, as well as radiological examinations play a crucial role for AP diagnosis, considering this aspecific clinical picture.

However, the diagnostic value of the serum amylase and lipase levels has been widely questioned. Their sensitivity and specificity are strictly dependent on the detection method used. For serum amylase, ranges lie between 70% and 100% and between 33% and 89%, respectively, while serum lipase sensitivity/specificity ranges between 74% and 100% and 34% and 100%[9]. Additionally, multiple factors such as hypertriglyceridemia, extensive pancreatic necrosis or very early pancreatic inflammation without pancreatic acinar cell destruction can correlate to normal amylase and lipase levels[9,10]. These main factors clinically lead to a contrast-enhanced CT-proven diagnosis of AP in up to 19% of patients with normal amylase levels[33]. Regarding our study cohort, a 3-fold the upper limit value of amylase was documented only in 72% and 66% of patients in the AAP and TAP group, respectively. Those results confirm the non-specific diagnostic role for AP. Conversely, a 1.5-fold the normal value was encountered in the 100% of cases, for which we performed a consequent serum lipase concentration evaluation. A significant increase above the normal limit was documented in our cohort despite no consensus is present on the lipase optimal diagnostic cut-off value[34].

A subsequent CT scan exam was considered mandatory for all patients. According to multiple guidelines, routine CT imaging in the initial AP management is not recommended[35,36]. However, a recent retrospective series did not observe any relevant decrease in early CT scan (within 24 hours of care) use comparing data from 2014-2015 with data from 2006-2007, reflecting the need of quality improvement initiatives to reduce the overuse of imaging[37]. Radiological evaluation in our AAP population was mainly related to the legitimate concern for an alternative diagnosis in the absence of abdomi-

nal pain. Advanced age, multiple comorbidities, excessive abdominal pain associated to relevant increase of amylase and lipase serum levels were the main indications in TAP patients. A definitive radiological diagnosis was consequently obtained in 100% of our cohort, evidencing an edematous pancreatitis in 24/25 (96%) and 45/50 (90%) patients in the AAP and TAP groups, respectively (p=0.36). Gallstones were the most frequent cause of AP with a similar rate between the two groups (42% in the TAP *vs.* 44% in the AAP groups; p=0.9) followed by an idiopathic origin in 32% of both cohorts (p=0.5). We reported a significantly higher prevalence of both these main AP causes, as compared to other case series. Even in this case, patients' age could justify our data. Elderly patients generally have a higher prevalence of gallstones associated to an increased diameter of the common bile duct as compared to the general population[38,39]. This makes older patients more susceptible to biliary AP. Similarly, the incidence of idiopathic AP in elderly patients ranges between 23% and 30%, significantly higher as compared to patients younger than 60 years[13]. Most of these idiopathic episodes are *de facto* caused by biliary microlithiasis[40]. This is observed by Ortega et al[41] that identified a biliary cause at the endoscopic ultrasound or MRCP in up to 57% of patients with an idiopathic AP origin. Another reason for the high incidence of idiopathic pancreatitis may be the patients' denial of heavy alcohol intake. Previous studies[42,43] have demonstrated that alcohol assumption is frequently underreported in clinical settings, contributing to mislabeling alcohol related AP as idiopathic AP.

In terms of clinical management, similar rates of conservative and surgical treatments were evidenced in the two groups. The only difference was the need of a percutaneous drainage and surgical necrosectomy in one TAP patient as compared to none in the AAP group. These comparable outcomes may be related to early diagnosing in all cases and to the low severe pancreatitis rate encountered. Consequently, similar LOS was documented in both groups (9.4 ± 6.7 days in the TAP population *vs.* 8.9 ± 7.4 days in the AAP cohort; p=0.76). Additionally, only one case of surgical management is unlikely to affect significantly the LOS of the whole population.

With regard to mortality rate, a value of 6.7% (5/75 patients) was registered, without any statistical difference between the two groups. A higher mortality rate would have been expected in consideration of the advanced age of our study population. For long time, it was thought that the pre-existing cardiocirculatory, renal or pulmonary disease would negatively affect clinical outcomes in case of pancreatic infection, leading more easily to organ dysfunction[13].

Previously, Xin et al[44] and Somasekar et al[45] reported a mortality rate between 17% and 25% for elderly patients. However, these high values may be due to the enrollment of octogenarians and patients affected by severe AP. When a more heterogeneous population for age and AP grade has been analyzed[12,46], the presence of comorbidities did not correlate with an increased risk of pancreatic necrosis, need for surgery, as well as overall mortality. These last two studies[12,46] would consistently support our results.

Regarding the potential correlation between the absence of abdominal symptomatology and mortality, Parniczky et al[19] demonstrated an increased mortality rate in case of atypical AP presentation. This is in contrast with the data we obtained and may be justified by the early diagnosis and the consequent higher rate of mild pancreatitis we obtained, leading to comparable results in terms of AP-related mortality between the two groups.

Despite the case-match analysis performed, the monocentric and retrospective evaluation of our study represents its main limitation.

From a clinical point of view, the routine execution of the serum amylase levels significantly contributed to an early diagnosis and management of AP. However, its execution is not routine in most of the other emergency departments. This factor could have affected the results of our comparison. Therefore, further multicentric studies on AAP would be needed in order to confirm or refute the outcomes we obtained.

Conclusions

Despite the unconventional AP interested only the 2.6% of the whole population, an early diagnosis is essential to avoid a life-threatening evolution of the disease. Fundamental contribution can be given by the routine measurement of the serum amylase levels, leading to additional examinations and to the early diagnosis of AP. As final result, the AAP did not report any significant difference in terms of type management, LOS and mortality as compared to the TAP.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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