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Severe Forms of Acalculous Acute Pancreatitis in Young Female Patients. A Preliminary Study

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Rezumat

Forme severe de pancreatită acută alitiazică la pacienți tineri de sex feminin; un studiu preliminar

Context/Obiective: Pancreatita acută (PA) este o boală severă care implică de obicei spitalizarea şi o terapie personalizată. Progrese remarcabile s-au înregistrat până acum în stabilirea etiologiei, diagnosticului şi terapiei acestei afecțiuni. De exemplu, este bine documentat faptul că evoluția PA constă din două faze fizio-patologice distincte. Prima fază durează aproximativ 1-2 săptămâni, implicând doar modificări inflamatorii locale şi eventual un sindrom SIRS tranzitoriu, care necesită terapie conservatoare. A doua fază este reprezentată fie de remisiunea bolii la pacienții cu forme uşoare de PA, fie de persistența sindromului SIRS şi apariția complicațiilor locale la pacienții cu forme moderate. Prin urmare, complicațiile locale apar de regulă în cea de-a doua fază, când terapia trebuie personalizată în funcție de complicațiile locale pancreatice, precum şi pentru a oferi un suport sistemic adecvat.
Metode/Rezultate: Formele severe sunt mai rar întâlnite şi în general asociază MSOF, care se poate dezvolta în orice moment în evoluția PA. MSOF agravează sindromul SIRS preexistent şi complicațiile locale, făcând tratamentul mai dificil şi crescând semnificativ morbiditatea şi mortalitatea. Acest studiu prezintă evoluția unui grup de pacienți cu PA alitiazică, care nu au prezentat în primă fază nici un determinant sistemic al sindromului SIRS. În consecință, prognosticul nostru inițial a fost favorabil, dar evoluția unora dintre pacienți a fost neaşteptat de severă.
Concluzii: Astfel de cazuri cu evoluție imprevizibilă sugerează necesitatea unei monitorizări atente la toți pacienții cu PA, chiar

dacă datele preliminare sugerează o formă uşoară a bolii. Studii suplimentare vor fi necesare în viitorul apropiat pe această temă, atât pentru îmbunătățirea terapiei cât şi pentru a stabili un scor prognostic cât mai bun, eventual prin includerea de noi elemente de diagnostic şi monitorizare.

Cuvinte cheie: pancreatită acută, forme alitiazice, evoluții severe, pacienți tineri de sex feminin

Abstract

Background/Objectives: Acute pancreatitis (AP) is a severe disease that usually involves hospitalization and a customized therapy. To date, remarkable progress has been made in establishing the etiology, diagnosis and therapy of this condition. For example, it is well documented that the AP course consists of two distinct pathophysiological phases. The first phase lasts about 1-2 weeks, involving only local inflammatory changes and possibly a transient SIRS syndrome, which require conservative therapy. The second phase is represented either by disease remission in patients with mild forms of AP, or by the persistence of SIRS syndrome and the occurrence of local complications in patients with moderate forms. Local complications therefore often occur in the second phase, when therapy must be customized according to the complications of the pancreatic area, as well as to provide adequate systemic support.

Methods/Results: Severe forms are less common and generally associate MSOF, which can develop at any time in the evolution of AP. MSOF worsens preexisting SIRS syndrome and local complications, making treatment more difficult and significantly increasing morbidity and mortality. This study presents the evolution of a group of patients with acalculous AP, who did not present in the first phase any systemic determinant of SIRS syndrome. Consequently, our initial prognosis was favorable, but the evolution of some patients was unexpectedly severe.

Conclusions: Such surprising cases in terms of the evolution may suggest that increased caution is required in all AP patients, even if preliminary data suggest a mild form of the disease. Additional studies are necessary in the near future on this topic, both to improve therapy and to establish a better prognostic score by using new diagnostic tools.

Key words: acute pancreatitis, acalculous forms, severe evolutions, young female patients

Introduction

Acute pancreatitis (AP) is a relatively common digestive disease, caused by a critical inflammation of the pancreatic gland. In order of frequency, the etiological factors are represented by: gallstones, excessive alcohol consumption, trauma, metabolic conditions (hypertriglyceridemia, hypercalcemia, etc.), viral infections, iatrogenic (post endoscopic retrograde cholangiopancreatography), autoimmune, drug induced, and idiopathic. All these etiological factors lead to a common pathological mechanism, represented by inflammation and autodigestion of the pancreatic gland (1-3).

Regarding the evolution, AP may manifest as a single clinical event or may be recurrent. Most patients show a favorable evolution, while a small number of cases develop moderate or severe forms. Such complicated evolutions either associate local and systemic complications (some fatal), or progress to chronic pancreatitis. Therefore, the evolution of AP may be unpredictable, requiring a constant monitoring to be able to administer the most appropriate treatment (4,5).

The diagnosis of AP is generally based at least on two of the three following elements: abdominal pain (persistent and severe, radiating to the back), biochemical documen-

tation of pancreatitis (serum lipase and/or amylase levels three times higher than the normal limit), and suggestive data from abdominal imaging (computed tomography, magnetic resonance imaging, or transabdominal ultrasonography). Generally, the onset of acute pancreatitis is thought to be at the time of abdominal pain. For most patients, the onset of abdominal pain is not the same as the time of admission (6,7).

Mild cases are usually treated by conservative measures: hospitalization, pain therapy, intravenous fluid rehydration, electrolytes, nutritional support, etc. Severe forms of AP often require admission in an intensive care unit, to properly monitor and treat possible complications of the disease (removal of etiological factors such as choledocholithiasis, surgical treatment for local complications, therapy of SIRS and MSOF, etc.). Such complications are often associated with high mortality in patients with AP, even if optimal and timely therapy is administered (8-10).

Relatively common for our surgical department, APs in women are generally caused by lithiasis, while in men the etiology is primarily toxic-ethanolic. However, in the last two years, a significant number of women with alithiasic but severe AP forms have been hospitalized and treated in our clinic. It is an unusual situation compared to the previous period, so a retrospective study was conducted on this topic. We consider the Covid-19 pandemic period as a possible indirect contributing factor, as presented in this article.

First, there are cases of AP that occur either during or after Covid-19 infection, the potential of such infections to induce AP being already described in the literature (11-14). Second, isolation and loneliness have predisposed some people to excessive alcohol consumption. Finally, we identified cases of AP, apparently without excessive alcohol consumption, but with a significant weight gain. On the one hand, weight gain could be caused by a sedentary lifestyle, which may be associated with metabolic dysfunctions capable of inducing AP. On the other hand, weight gain can also be explained by overeating, which may justify the episode of AP especially in the case of highly processed foods with additives (15,16).

Materials and Methods

This is a retrospective study conducted on a group of 12 female patients with acute alithiasic pancreatitis, hospitalized and treated in our clinic in the last two years, between January 2020 and December 2021.

We extracted and noted the data for these patients from the observation sheets. The diagnosis and treatment of each patient was revised, in order to determine the evolution over time of distinct forms of AP, especially in terms of severity. We studied both the data related to the principles and outcomes of the conservative therapy, as well as the surgical treatment in the case of patients with local complications.

Thus, data related to the surgical procedure (occurrence/ nature of local complications in severe AP forms), the general condition of patients (SIRS, MSOF, preexisting comorbidities, etc.) appropriate supportive therapy, as well as the general condition at discharge, were noted and compared using SPSS (Statistical Package for Social Sciences) version 17 for Windows. Due to the limited number of cases, this presentation was focused on essential data, considered not only relevant but also able to determine the design of more representative studies in the near future.

Results

Patients with severe PA were treated in the intensive care unit, either at admission or later, when the evolution worsened. In the intensive care unit, surgical therapy was restricted in the first week, as this approach is known to decrease the mortality of severe AP forms. Delayed surgery allows local tissues the necessary time to delimit/ encapsulate possible areas of necrotic pancreatic tissue, which in about 5-7 days tends to progress to liquefaction. In this way, not only the necrotic tissue is easily removed by surgery, but also

the remaining cavity is better delimited and can be drained/ treated more efficiently.

From a total of 76 female patients hospitalized for AP between January 2020 and December 2021, we selected 12 female patients with alithiasic AP. The exclusion criteria were represented by the absence of gallstones and/ or acute cholecystitis, recent history of acute or chronic pancreatitis, pre-existing traumatic factors, excessive alcohol or drug use. Of these 12 female patients, 8 were treated surgically for local complications one week or more after admission, as presented in the *Table 1*.

Starting from our previous activity in the therapeutic management of AP, the evolution of cases 2, 7 and 8 (see *Table 1*) was unexpected, and determined us to conduct the current investigation. These three cases were represented by relatively young patients, who did not present with SIRS either at admission or after the first week of hospitalization. According to the existing AP scores, patients without SIRS or with transient SIRS should not develop a severe form of AP, so our initial prognosis was good. However, after approximately 6-10 days of evolution, all three patients developed severe forms of AP, including late MSOF and local complications that required surgical therapy.

The course of these three patients contrasts with our initial expectations, as well as with the evolution of the other patients included in this study. In addition, although the rest of the patients had comorbidities at admission, they still developed milder forms of AP. We interpret the unexpected/unfavorable evolution of the three patients with AP in the discussion section, being most probable caused by an inappropriate biological reactivity.

Discussions

The definition and diagnosis of AP are relatively clearly established at present. Instead, the assessment of AP severity and the prediction of the evolution are still issues for discussion. Consequently, several diagnostic and prognostic scores have been proposed over time. Such scores aim to establish not only the severity/ prognosis but also the appropriate therapy of the disease, being related to clinical and imaging data that tend to be integrated and interpreted algorithmically (17,18).

Clinical and Biological Scoring Systems

Ranson and colleagues described in 1974 the first clinical scoring system for AP, which includes 11 prognostic parameters of the patient. At admission, the age (>55 years), WBC (>16,000/mL), glucose (>200 mg/dL), LDH (>350 IU/mL) and AST (>250 IU/mL) should be noted. After 48h, hematocrit (decreas e>10%), BUN/ blood urea nitrogen (increase >5 mg/dL), calcium (<8 mg/dL), PaO 2 (<60 mmHg), base deficit (>4 mEq/L) and

Table 1. The main parameters of the patients treated surgically for local AP complications

	Age	SIRS at admission	SIRS after the first week	MSOF during hospitalization	Hospitalization days	Comorbidities	Mortality	Surgical therapy
1.	43	+	+	+	48	Covid-19	-	SPN
2.	29	-	-	+	27	-	-	SWPN
3.	57	+	+	+	24	HTA, cirrhosis	+	PNB
4.	41	-	+	-	36	-	-	SWPN
5.	43	-	+	+	31	Diabetes mellitus	-	SWPN
6.	49	+	+	+	35	Ulcerative colitis	-	PNB
7.	36	-	-	-	29	-	+	SPN
8.	35	-	-	+	33	-	-	SWPN

SPN: superinfected pancreatic necrosis – open surgery, cases 1 and 7
PNB: pancreatic necrosis with bleeding – open surgery, cases 3 and 6
SWPN: sterile walled-off pancreatic necrosis
-laparoscopic surgery - cases 4, 5 and 8
-percutaneous drainage - case 2

fluid sequestration (>6 L) complete the score. However, multiple studies suggest that the Ranson score would be a moderate predictor of AP. In addition, the completion of the score requires a period of at least 48 hours, a relatively long period of time for critically ill patients, in which treatment must be established and started from the admission (19-21).

The Glasgow score is relatively similar to the Ranson evaluation in that it takes at least 48 hours to complete, being initially described by Blamey and col. in 1984. For this score, the data recorded both at admission and after 48 hours are represented by: age (>55 years), WBC (>15,000/mL), glucose (>180 mg/dL), BUN (>45 mg/dL), PaO2 (<60 mmHg), calcium (<8 g/dL), albumin (<3.2 g/dL), and LDH (>600 IU/L) (22,23).

The APACHE-II (acute physiology and chronic health evaluation II) scoring system was developed in 1989, being extensively used to assess the AP severity. It is a complex score, that can be updated daily during the hospitalization. APACHE-II score includes essential data related not only to AP (vital signs, blood studies, neurologic assessment, etc.) but also to possible chronic illness. Due to its complexity, the APACHE-II score is difficult to calculate (especially daily), and some of the required variables are not usually recorded outside the intensive care unit. In fact, APACHE-II score is not specific for AP, being designed for patients in need of critical care. Several studies show that the Ranson, Glasgow and APACHE II scoring systems have demonstrated similar accuracy in predicting AP severity (22, 24-26).

Other tests used to assess the severity of AP are represented by SIRS score /2006 (the systemic inflammatory response syndrome), which is based on temperature, white blood cell count, heart and respiratory rates), Panc-3 /2007 (related to hematocrit, BMI, and pleural effusions), POP-b /2007 score (age, MAP, PaO2, arterial pH, BUN, calcium), BISAP /2008 (bedside index of severity in acute pancreatitis) including age, blood urea nitrogen, Glasgow Coma Score <15, SIRS ≥ 2, presence of pleural effusion), JSS score /2009 (age, PaO2, base excess, BUN, LDH, calcium, platelet, CRP, SIRS), HAPS /2009 especially for patients with a mild course of the disease (abdominal tenderness, hematocrit and creatinine) (27-30).

Imagistic Scoring Systems

Imaging changes (related to pancreatic, peripancreatic and extrapancreatic data) are often significant in AP, so several scores based on computed tomography/ CT and nuclear magnetic resonance/ MRI have also been designed. Unfortunately, the ultrasound is generally of limited value in evaluation of AP severity, due to the overlying intestinal gas that often hides large portions of the pancreas. Even so, ultrasound has been shown to be useful in detecting gallstones as well as pancreatic fluid collections (31).

The Balthazar CT score was developed in 1985, focusing mainly on the presence and nature of possible fluid collections. The need for such imaging score was imposed by the observation that patients with peripancreatic collections generally had higher rates of morbidity and mortality. Other relatively similar scores (based on non-contrast CT scanning results) emerged shortly thereafter, such as: Schröder index (extrapancreatic score/ 1985), PSI (pancreatic size index/ 1989), CTSI (CT severity index/ 1990), MOP (the mesenteric edema and peritoneal fluid/ 2003) and EPIC (extrapancreatic inflammation on CT/ 2007) (32-35).

The CTSI score is based on contrast CT, thus highlighting not only inflammatory changes, but also the presence of a possible pancreatic necrosis. Even so, data from the literature show that the specific sensitivity and specificity of CTSI in the diagnosis of AP appear to be limited, but still comparable in terms of performance with other scores, such as Ranson, APACHE-II and BISAP (36,37).

Atlanta Classification of Acute Pancreatitis

The Atlanta classification was introduced in 1992, in an attempt to standardize globally

both the terminology and the protocols used in the diagnosis and therapy of AP. This classification was in fact a work in progress related to the evaluation of AP, being perfectible as many data were either not addressed or lacked clarity. Just an example, the Atlanta classification did not initially include a defined serological threshold for pancreatic enzyme levels. In addition, this classification did not make any specification for organ failure (whether transient or persistent), nor did it include peripancreatic collections with and without necrotic debris (38).

All these shortcomings have been solved in 2013, being included in a revised and published form of the Atlanta classification. This revision was not only a process of completion, but also an opportunity to make the classification easier to implement. Thus, distinct entities like subacute/ organized pancreatic necroses, pancreatic sequestration, and pseudocyst associated with necrosis were assimilated and collectively defined as walled-off necrosis. The revised form of the Atlanta classification is based on clinical, biological, imaging data (including the modified Marshall Organ Failure Score), being thus related to either local or systemic determinant factors of AP severity. The degree of severity of AP (mild, moderate, severe and critical) is therefore based on the resulting combinations of these determinants (39-41).

Determining Factors for the Evolution of AP

All of these scores and data mentioned above are valuable and often comparable, so it is not yet clear which of the scores would be most appropriate for diagnosing and monitoring AP. In order to establish this, two distinct phases related to the evolution of acute pancreatitis should be described, as in the revised form of the Atlanta classification.

The early phase usually lasts 1-2 weeks, its evolution being strongly influenced by the presence or absence of SIRS syndrome. The modified Marshall score assesses the respiratory, renal and circulatory systems to determine the SIRS syndrome. SIRS syndrome is caused by the cytokine cascade released as a result of local pancreatic inflammation, and implies the presence of at least two of the four basic criteria. These criteria refer to temperature (greater than 38°C, or less than 36°C), heart rate (over 90 beats/min), respiratory rate (greater than 20 breaths/min) and leukocyte count (either less than of 4.000/mm^3 or more than 12.000/mm^3, or even the presence of more than 10% immature neutrophils). The presence of SIRS syndrome since admission, especially if it is persistent and severe, could lead to transient or persistent organ failure. Persistent organ failure is defined when it lasts more than 48 hours, being a reliable indicator of AP severity in the first phase (42-45).

Acute pancreatitis is therefore a dynamic disease, with both local and systemic evolution. Although local complications begin to develop in the first phase, they are either incipient (small in size) or not mature enough to be early detected by imaging (necrosis gradually liquefy, becoming later heterogeneous and evidently radiological). In addition, such inceptive/ evolving local complications are generally not proportional to the extent of systemic organ dysfunction. For all these reasons, imaging-based investigations (such as CT and MRI) are not able (and therefore not useful) in determining the severity of AP during the first stage (46,47).

The second phase follows the first week, being influenced by systemic organ failure (when it was present in the first phase, and still persists), as well as by the possible development of local complications. Such local complications are more evident in the second phase, so imaging investigations become essential at this stage (48,49).

From a morphopathological perspective, the revised classification (Bologna) divides AP into interstitial edematous pancreatitis (about 80-90% of cases), and necrotizing pancreatitis. Necrotizing pancreatitis may be in the form of parenchymal necrosis, peripancreatic necrosis, and an associated (peripancreatic and parenchymal) necrosis form. When present, necrotizing pancreatitis can be either sterile or infected. Gas imaging signs suggest an

infection, which can be confirmed by culture (image guided FNA) of the necrotic tissue. In the second stage, the treatment strategy is therefore related to both local / morphological changes and systemic evolution, thus being more dependent on radiological evidence (50).

Therefore, the main local complications in AP are represented by pancreatic pseudocysts, acute necrotic collections, acute peripancreatic fluid collection, and walled-off necrosis. Other possible local complications include gastric outlet dysfunction, colonic necrosis, and splenic and portal vein thrombosis (51-53).

Interpretation of this Study and Possible Perspectives

Several studies show that AP that evolves with local complications but without MSOF, had high morbidity with low mortality rates. This means that the evolution of AP can be unpredictable and should be treated with caution, even if SIRS and MSOF were not diagnosed in the first phase of evolution. Taking into account the presence or absence of local and/or systemic complications, a classification of AP into three degrees of severity was proposed.

Mild acute pancreatitis is a poor form of evolution, that is without organ failure and local complications. Its monitoring does not necessarily require advanced pancreatic imaging for morphological evaluation, and usually its symptoms subside from the first week (54).

Moderately severe acute pancreatitis is represented by forms that evolve with SIRS/ transient organ failure and/ or local complications, but in the absence of MSOF. The treatment strategy should target the type of local complications as well as appropriate systemic support (55).

Severe acute pancreatitis is characterized by the presence of MSOF, which amplifies a severe and persistent SIRS, either in the early phase or in the second phase of AP. The occurrence and persistence of MSOF is usually caused by severe local complications, usually infected pancreatic necrosis or severe extrapancreatic infections. Accordingly, it is recommended to treat a patient with AP and persistent SIRS as a potentially severe disease, even in the absence of MSOF (56, 57).

The peculiarity of our three cases is represented by the fact that they evolved in the end as severe forms of AP (one of them with death), but without specific signs for SIRS syndrome. This means that our initial data did not allow us to predict such a critical evolution. As possible explanations, the patient who died gained weight over 20 kilograms in the last year, so metabolic and dietary deficiencies not identified by us are suspected. Current studies show that overweight and obese patients with AP have a significantly increased risk of morbidity and mortality (58,59). For the other two patients there are no additional data, but we can still provide some theoretical perspectives.

Thus, AP is defined as an inflammation of the pancreas, mainly caused by a process of autodigestion (60). Probably the local physiological mechanisms that oppose this phenomenon are still insufficiently explained, while the etiology of AP differs considerably from one country to another (61). Individual characteristics related to vascularity, immune and metabolic pathways (which are difficult to assess in all forms of AP) could also contribute to a particular evolution of the disease. Recent studies show that there are significant genetic and immunological differences between patients, which determine the severity of AP (62,63). Finally, we cannot exclude the consumption of forbidden foods/substances, which are usually difficult to communicate during or after the anamnesis.

Recent data show that the assessment of risk factors (age, sedentary lifestyle, obesity, excessive alcohol consumption, prohibited substances) should not be neglected in the assessment of a patient with PA (58,59). Also, the use of new laboratory markers (calcium, procalcitonin, pH value, free triiodothyronine, Interleukin-6, Interleukin-10, etc.) seems to be extremely useful in assessing the severity of this disease (64-66).

Anatomical features should be considered

(67), while the minimally invasive surgical treatment must be used whenever possible, as it has been demonstrated to lead to the best therapeutic outcomes (66,68). Finally, depending on the etiology, new forms of treatment seem to become available, as is the case of alcoholic AP (69). In addition, the multidetector row CT appears to be able to discriminate between interstitial edematous pancreatitis and necrotizing pancreatitis from the first week of AP (70).

Conclusions

The risk stratification of AP patients since from the first days of hospitalization is essential for establishing the appropriate therapy and care setting. Unfortunately, an ideal prognostic score system (easy to use in clinical practice, to be applicable from the admission and repeatable, accurate enough in differentiating mild to severe forms of AP) is difficult to establish by current (clinical, biochemical, imaging) methods of investigation. It is in part a consequence of the fact that some complications of PA are even unpredictable and, therefore, difficult to anticipate from admission (abdominal compartment syndrome, perforations, arterial pseudoaneurysm, intestinal ischemia, etc.).

The current scores have proven their validity on multiple and extensive studies, which makes them extremely useful for most patients with PA. However, particular forms of evolution cannot be ruled out, so that we recommend treating each case with great caution. In the case of systemic complications, we recommend a clear delineation between preexisting comorbidities of the patient and SIRS/ MSOF syndromes related to AP.

Conflicts of Interests

The authors declare no conflicts of interests.

Ethical Statement

All procedures performed were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments.

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