

Contrast-Induced Acute Pancreatitis after Cerebral Arteriography

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Abstract

Although kidney failure due to iodinated contrast medium is relatively common, the well-established relation of these agents with pancreatitis is not yet well established. The few reports in the literature associating pancreatitis with radiographic contrasts demonstrate, in animal studies, a possible clinical worsening in an ongoing pancreatitis. Contrast-induced pancreatitis is an extremely rare adverse event, usually presenting with mild symptoms. We report two cases of patients submitted to cerebral digital subtraction angiography due to cerebrovascular diseases, both evolving with pancreatic enzyme elevation with other causes excluded by a multidisciplinary team.

Keywords: Pancreatitis, Contrast medium, Drug-induced abnormalities, Arteriography, Diagnostic imaging, Drug toxicity, Acute kidney injury, complications.

Introduction

Acute pancreatitis is a high morbidity inflammatory disorder of the pancreas, ranging from local lesions to systemic inflammatory response and organic failure [1]. The diagnosis of acute pancreatitis requires at least two of the following: characteristic abdominal pain; biochemical signs (such as elevation of amylase and lipase above 3 times the upper or normal limit); and/or radiographic evidence on imaging examination [2]. Approximately 80% of cases of acute pancreatitis arise from biliary lithiasis and alcoholism [3], with the rest including hypertriglyceridemia, drug reactions, and cystic or solid pancreatic malignancies [4]. The hypothesis of the use of intravenous Iodinated Contrast Medium (ICM) as the cause of acute pancreatitis has always been analyzed by different studies, however most of them analyzed patients receiving intravenous ICM to evaluate an established acute pancreatitis through abdominal Computed Tomography (CT) during their treatment.

Therefore, it has never been clearly demonstrated by clinical data that ICM causes adverse effects on the human pancreas, or whether it is an isolated etiologic agent of acute pancreatitis [5]. To the best of our knowledge, we report the two first cases of acute pancreatitis related to ICM use during digital subtraction angiography (DSA).

Based on clinical staging, several classification were proposed to predict the progression from acute pancreatitis to the very severe necrotizing type, (e.g. Ranson, Glasgow and APACHE II), achieving a sensitivity of 85% [6-8].

Case Reports

Case 1

A 37-year-old man complaining of 7-days sudden-onset headache and vomiting was admitted in the Emergency Room, and presenting

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with mild stiff neck, Glasgow Coma Scale 15, Hunt-Hess scale I, World Federation Neurological Societies grade I. He reported high blood pressure (HBP) treated during 12 years with Amlodipine, and he denied head trauma, infection affecting the central nervous system, addiction or family history of cerebrovascular event. Head CT scan and MR showed subarachnoid hemorrhage in skull base cisterns and fourth ventricle, Fisher scale IV. A head and neck DSA was performed using 140ml of low osmolarity iodinated non-ionic contrast iohexol (Omnipaque®, GE Healthcare Inc., Marlborough, Massachusetts, USA), and evidenced a dissecting aneurysm in V3 segment of the left vertebral artery and a “string-of-beads” pattern in both internal carotid arteries and in both V2 segments, as well as right renal artery ectasia, being diagnosed multifocal type fibromuscular dysplasia. In the same day, clinical worsening occurred and required mechanical ventilation due to urinary focus sepsis. He evolved with grade II bilateral hydronephrosis, transient thrombocytopenia, pancreatitis and acute renal failure. Laboratory tests with reference value are described in Table 1. The diagnosis of pancreatitis was made by laboratory alterations and by diffuse pancreas increase in abdominal CT. The patient received Ceftriaxone 1g daily for 14 days and remained intubated receiving parenteral diet during 25 days. Lipase and amylase normalization only occurred after day 18th, and no dialysis was needed. Thus on 37th-day post-ictus, after clinical improvement, a transluminal percutaneous angioplasty (TPA) of dissecting aneurysm was performed uneventfully. Laboratory tests and neurological examination became normal and the patient was discharged asymptomatic. He undergone several endovascular procedures using ICM due to fibromuscular dysplasia complications, and no pancreatic alteration was seen during the 3years follow-up.

Case 2

A 33-year-old male with epilepsy secondary to intracranial hemorrhage occurred 6-years before due to a left parieto-occipital Spetzler-Martin grade III arteriovenous malformation (AVM), was treated by four sessions of embolization, without any complications. He reported HBP, type 2 diabetes melitus, dyslipidemia, and grade I obesity in current continuous use of Phenytoin 300mg, Metformin, Simvastatin, and Atenolol and addictions smoker 10 pack years and ex-alcoholic (stopped 6 years ago). History of pancreatitis 8 years ago, with no complications or need for surgical treatment. He underwent new follow-up head and neck DSA using 90ml of ICM (Omnipaque®). About 7 hours later he complained of upper abdomen pain, and abdominal ultrasound and CT discarded cholelithiasis, appendicitis, free fluid, and masses. Laboratory tests were described in Table 1. The diagnosis of mild acute pancreatitis was done and the patient remained fasted for 6 days, receiving diet and parenteral hydration, as well as analgesics and antiemetics. No antibiotic therapy was required and clinical improvement occurred after 72 hours. The patient was discharged asymptomatic and laboratory tests were normal after 10 days. During the 5-year follow-up, one DSA was performed and there were neither pancreatic changes, nor new neurological deficits.

Discussion

Our both cases refer to acute pancreatitis without severity criteria associated with the use of the ICM Iohexol, which is widely used in diagnostic and therapeutic procedures. Both patients received contrast due to cerebral angiograms. The viscosity of the Iohexol-300 at 37 °C is 6.3 cP, whereas the human plasma viscosity is equilibrated at 1.72 cP. This suggests that the intravascular use of Iohexol increases plasma viscosity, reducing blood flow [9]. This effect on tissue perfusion has been considered as the main cause of contrast-induced nephropathy [10-12]. In addition to the hemodynamic effect on tissue perfusion, contrast agents are known to cause acute renal damage in high-risk patients also by the direct toxic effect on renal cells [13]. Patients with diabetes mellitus, kidney failure, shock, and the elderly are considered to be more susceptible to contrast-induced nephropathy, possibly due to the precarious organic reserve of renal function [12,14]. Likewise, patients undergoing contrast tests, but with normal renal function, do not develop contrast-induced nephropathy [15]. In the reported cases, risk factors may have contributed to the micro-hemodynamic pancreatic damage, as has been shown in relation to renal damage.

Experimental studies in animal models showed an association between the reduction of pancreatic capillary flow and necrotizing pancreatitis, as well as heterogeneous alterations of perfusion in the organ [16]. These pancreatic microcirculatory changes would contribute to an interstitial inflammatory condition that could progress to necrosis [5]. Other experimental models have shown increased necrosis in acinar cells, induced by contrast endovenous media [17]. Yet another study has demonstrated that the exposure of human and rat acinar cells to radiocontrast agents such as Iohexol induced pancreatic inflammatory changes mediated by NF-κB activation, cytosolic Ca²⁺ and calcineurin signaling [18].

In humans, indirect evidence has been demonstrated in a retrospective study of 57 patients with acute pancreatitis [19]. The 31 patients submitted to contrast-enhanced CT had a longer duration of symptoms, suggesting a deleterious effect of intravenous contrast. In another retrospective study, patients with mild pancreatitis and BMI greater than or equal to 25, when submitted to contrast-enhanced pancreatic CT, had a higher rate of local and systemic complications, suggesting local and systemic effects by contrast [5].

In the first case reported here, the same pathophysiological principle could explain the renal and pancreatic lesions induced by Iohexol. The incidence of Iohexol-induced

Table 1: Laboratory tests of the two case reports. The values refer to the worst result during treatment. All tests were normal previous to the contrast use.

Test	Case 1	Case 2	Reference Value
Lipase	2042	555	23-300
Amylase	472	902	38-126
Creatinine	3.54	0.83	0.6-1.2
Urea	142	29	19-43
Potassium	6.0	3.6	3.5-5
CPK	-	16176	30-130
Triglycerides	92	793	<150

nephropathy in angiograms comparing Ioxol and Iodixanol was reported in 26% [10]. There are no case reports in the literature of acute pancreatitis after exposure to Ioxol, mainly preceded by acute renal injury.

The second case follows an alternative course. It is a patient with risk factors for acute pancreatitis, a history of prolonged intense alcoholism and dyslipidemia. The main questioning concerns the possible predisposition to the development of contrast-induced pancreatitis such as Ioxol in patients who previously had acute pancreatitis of a non-contrast-induced etiology, in addition to the associated factors. Again, no similar reports have been found in the literature with such specificities.

The striking CPK elevation concomitant with pancreatic disease, with no evident etiology, is still striking. Perhaps we could extrapolate the pathophysiological mechanisms of renal and pancreatic aggression by extending it to muscle tissue. The lack of data in the literature points to the demand for studies that may clarify this finding.

We note that the reported cases of acute contrast-induced pancreatitis are rare. Considering the wide use of non-ionic contrasts such as Ioxol in diagnostic procedures such as cerebral DSA, knowledge about risk factors leading to acute pancreatic injury has important implications. The first one concerns the elaboration of prophylaxis protocols that avoid or minimize deleterious effects, considering risks and benefits in their use in these procedures. The second refers to the therapeutic possibilities from the structured understanding of the precise pathophysiological mechanisms. In this sense, prospective randomized studies are necessary for a better understanding of the topic.

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