Digestive and Liver Disease 46 (2014) 41–44

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Digestive Endoscopy

Complications of endoscopic ultrasound fine needle aspiration on pancreatic cystic lesions: Final results from a large prospective multicenter study

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ARTICLE INFO

Article history:
Received 22 May 2013
Accepted 11 August 2013
Available online 17 September 2013

Keywords:
Cyst of the pancres
EUS-FNA
Pancreatic cystic lesions

ABSTRACT

Background: Endoscopic ultrasound-guided fine needle aspiration of pancreatic cystic lesions has been reported to have a higher complication rate than that of solid lesions, but the real complication rate is unknown. Aim of the study was to identify the complication rate of endoscopic ultrasound-guided fine needle aspiration and related risk factors.
Methods: Prospective multicenter study at four referral centres. Data were collected from January 2010 to July 2012, searching for all adverse events related to guided fine needle aspiration. All complications occurring up to day 90 were recorded.
Results: 298 patients (43.9% male, mean age 63.2 ± 15.4 years) underwent endoscopic ultrasound-guided needle aspiration of pancreatic cystic lesions. Mean size was 34.1 ± 9 mm. Adverse events occurred in 18 patients (6%): mild complications in 12/18 (66.6%), and moderate complications in 6/18 (33.3%). Seven were immediate, 6 early, and 5 late. All resolved with medical therapy.
Conclusions: Endoscopic ultrasound-guided fine needle aspiration of pancreatic cystic lesions has been found to be associated with a higher complication rate than for solid lesions; however, the risk rate is acceptable considering the complication grade and the important diagnostic role of the technique in the management of pancreatic cystic lesions.

1. Introduction

Pancreatic cystic lesions (PCLs) are being diagnosed with increasing frequency, and cover a vast spectrum, from benign to malignant and invasive. Numerous investigations can be carried out to discriminate between benign and non-evolutive lesions and those that require surgery because there is no single test that allows for a correct diagnosis in all cases. Cystic fluid analysis and cytohistology with endoscopic ultrasound-guided fine needle aspiration (EUS FNA) can aid in this difficult diagnosis. In PCLs, EUS FNA allows evaluation of extracellular mucin, cytological and sometimes histological analysis, biochemical tests, tumour markers, and molecular analysis [1]. The EUS FNA techniques for pancreatic cystic lesions are quite simple. The needles normally used are the same as those for solid lesions, 19-, 22-, and 25-gauge. Doppler is recommended to avoid puncture of the intervening vessels, as is crossing the normal pancreatic parenchyma as little as possible to help avoid pancreatitis. Other recommendations include complete drainage of the cyst in a single needle passage, and antibiotic prophylaxis with intravenous antibiotics just before the procedure, followed by the oral route for 3–5 days to reduce the risk of infection (recommendation grade C) [2]. EUS FNA of cystic lesions has been reported to have a higher complication rate than that of solid lesions [2–8]. The incidence of infectious complications in prospective studies that used prophylaxis was low (0–1.4%) [3–5]. No data from

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http://dx.doi.org/10.1016/j.dld.2013.08.134

controlled studies are available on complications, such as bleeding and pancreatitis, related to EUS FNA of cystic lesions. Finally, the risk of seeding after EUS FNA of malignant PCLs appears to be very low, with only one published case of peritoneal seeding after EUS FNA of a PCL [9]. Because of the higher expected rate of complications after puncture of PCLs than that of solid lesions, many centres prefer not to perform the procedure, renounce valuable information for diagnosis. A prospective study by the Mayo Clinic group on complications related to EUS FNA has been published. To our knowledge, this was the first prospective report, but the limitations of the study were that the complication rate was assessed at a single centre, and the number of EUS FNA procedures on PCLs was low [10]. The aim of our present study was to identify, in a large prospective multicenter study, the rate of adverse events of EUS FNA of PCLs, and the risks related to these complications.

2. Patients and methods

This was a prospective clinical study at four referral centres for EUS: ISMETT/UPMC (Mediterranean Institute for Transplantation and Advanced Specialized Therapies/University of Pittsburgh Medical Center in Italy), Palermo; AUSL Bologna Bellaria-Maggiore Hospital; Civico-A.R.N.A.S. Hospital, Palermo; Humanitas IRCCS, Rozzano, Milan. We collected data from January 2010 to July 2012 looking for all adverse events related to EUS FNA of PCLs. The procedures were carried out by one or two attending endosonographers for each centre, each of whom had undergone third-tier EUS training, and had performed more than 1000 procedures each. The Institutional Review Boards of each participating centre approved this study. Prior to EUS, all patients provided a signed informed consent. We required a history and physical examination on the same day of the procedure, and blood tests were performed within 28 days of the procedure. Inclusion criteria were age above 18 years, EUS diagnosis of PCLs, platelet count greater than 50,000/nL, and, finally, a medically stable enough condition from a cardiopulmonary standpoint to undergo moderate sedation or propofol anaesthesia. EUS FNA was not performed in patients who were being treated with oral anticoagulants, thienopyridines, or aspirin and chronic NSAID intake: these drugs were switched to heparin when possible 5 days before the procedure, which was then discontinued 12 h before the procedure. Antiplatelet agents were then restarted the day after the procedure. Patients received one intravenous dose of antibiotic during the procedure (piperacillin/tazobactam 4.5 g IV or ciprofloxacin 200 mg IV) followed by a 5-day course of an oral antibiotic (amoxicillin/clavulanic acid 1 g or ciprofloxacin 500 mg b.i.d.). The choice of the type of sedation was made by an anaesthesiologist on the basis of local policies at each centre and on the medical examination and clinical history. In the case of deep sedation or general anaesthesia, an anaesthesiologist was always present during the procedure. A complete cystic fluid evacuation, with a single needle passage, was attempted in all cases. Collected data were recorded in database templates using specific pick lists designed for this project. The database included demographic characteristics, medical and drug history, morphological features of cysts at EUS, technical information about the EUS procedure (instrument, needle, etc.), sedation, antibiotic prophylaxis, laboratory tests, adverse events and therapeutic measures for correcting them, and patient outcome. Data included all post-procedural adverse events occurring up to day 90. An adverse event was defined as any deviation from the clinical course after the procedure that was believed to be related to the procedure. Adverse events were assessed and recorded by physicians after the procedure while the patient was recovering from sedation or anaesthesia (immediate complications). Beyond the initial 24 h, only complications that were significant enough to lead to an evaluation by a physician were taken into account. At approximately days 30, 60, and 90, patients were contacted by telephone and asked whether they had experienced any symptoms at any time. Telephone calls were made by a physician with extensive experience in EUS. Inquiries were made about any visits to physicians' offices or emergency rooms, and about any hospitalizations during the 90-day period. Complications were defined as early if occurring within 2 days, and late, from the third day onward. A complication was defined as mild if unplanned or prolonged hospitalization for 3 days was required; moderate if 4–10 days of hospitalization were needed, but no intensive care or surgical intervention; severe if requiring surgical intervention or intensive care, or was fatal [12]. The grading of the adverse events was also classified based on Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

2.1. Statistical analysis

Data were analysed using the SPSS 15 software package (SPSS, Inc., Chicago, IL, USA). Continuous variables were summarized as mean ± SD, or range, when appropriate. Categorical variables were summarized as frequency and percentage. For comparison of qualitative variables, a Chi-squared test was performed. For comparison of quantitative variables, Student's *t*-test was used. The complication rate was coded as binary data. Logistic regression was used to analyse significant predictors of complications: patient demographics (gender and age), comorbidity, type of sedation, size of the lesions, location, needle track, and needle size. Differences were considered significant at a p value of <0.05 (two-sided).

3. Results

From January 2010 to July 2012, 298 patients (131 male [44%],), with a mean age of 63.2 years (SD ± 15.4), underwent EUS FNA of PCLs. The mean size of the PCLs was 34.1 mm (SD ± 19 mm). All patients completed the scheduled antibiotic prophylaxis as described in Section 2. Procedures were performed with patients under conscious sedation in 100 of cases (33.6%), deep sedation in 192 (64.4%), and general anaesthesia in 6 (2%). The needles used were: 22-gauge in 199 (66.8%) cases, 25-gauge in 22 (7.4%), 19-gauge in 57 (19.1%), and, finally, a 22-gauge Pro-core needle in 25 (6.7%). In 54 patients (18.1%) the complete cystic fluid evacuation was not achieved because of high mucus density. Adverse events occurred in 18/298 (6%) patients. The degree of these complications was mild in 12/18 (66.6%), and moderate in 6/18 (33.3%). grade 1 in 44.4%, grade 2 in 22.2%, and grade 3 in 33.3% adopting the Common Terminology Criteria for Adverse Events (CTCAE). Seven were immediate (observed by the physician during the procedure), 6 were early (within 2 days), and 5 were late (≥3 days after the procedure). All complications resolved with medical therapy, within 3 days in 16/18 (88.8%), and within 10 days in 2/18 (11.1%). The complications were: fever in 4 patients (1.3%), resolved with antibiotics, (grade 3 as defined by CTCAE): 3 in those patients with complete cystic fluid evacuation (1.2%) and 1 in those with incomplete cystic evacuation (1.8); $p = 0.2$; intra-cystic bleeding (gradually expanding hyperechoic area within the cyst), after complete fluid evacuation, in 4 (1.3%), self-limiting in 3 (grade 1 as defined by CTCAE) and requiring one blood transfusion in 1 (grade 3 as defined by CTCAE); intra-gastric bleeding in 2 (0.6%), treated with adrenalin injection (grade 2 as defined by CTCAE); abdominal pain in 4 (1.3%), resolved with a single dose of pain medication (grade 1 as defined by CTCAE); mild pancreatitis (amylase increased to at least three times the normal value, in addition to abdominal pain) in 2 (0.6%), 1 in a patient with incomplete cystic fluid evacuation, both self limiting (grade 2 as defined by CTCAE); retroperitoneal haematoma in 1 (0.3%),