

COMMENTARY

Is There a Proper Type of Management for Branch-Duct Intraductal Papillary Mucinous Tumors of the Pancreas?

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The Dr. Tolstunov's letter published in the present issue of JOP. Journal of the Pancreas [1] is very interesting, because it pointed out the controversial management approach for the branch-duct intraductal papillary mucinous neoplasms (IPMNs) of the pancreas, even in high volume centers for pancreatic disease. The final questions, "Have I been correct with my decision so far in delaying the surgery?" and "Should my mother have had her surgery a long time ago?" pointed out the real problems both for patients (and her/his relatives) and surgeons.

In this letter, an 83-year-old relatively healthy woman with a branch-duct IPMN of the pancreatic neck is reported.

In our opinion, two factors have to be considered: the disease and the patient.

The Disease

The cystic lesion was incidentally diagnosed in 2010 by ultrasound (US), computed tomography (CT) scan and endosonography (EUS) plus fine needle aspiration (FNA). The cystic lesion was localized in the neck of the pancreas and was approximately 2x1 cm in size, with no pancreatic duct dilatation or communication. Fine needle aspiration showed an elevated level of CEA in the cystic fluid. A diagnosis of branch-duct IPMN of the pancreas was made. The patient was subsequently closely followed with EUS plus FNA until July 2013. During this period, the CEA value increased in the cystic fluid and the last

cytology examination showed a "scant atypical mucinous epithelium". Nevertheless, the characteristics of the cystic lesion had not changed (no increase in size, no dilation of the Wirsung duct, no mural nodules), and the patient remained asymptomatic.

A branch-duct IPMN is a precancerous pancreatic lesion and invasive carcinoma has been reported in 11-30% of cases in large series of resected branch-duct IPMNs [2]. The risk factors predicting the presence of malignancy in branch-duct IPMNs are well-known and they have been reported in three consensus conferences [2, 3, 4]. In particular, the consensus conference held in Fukuoka in 2012 [4] recognized high-risk stigmata for malignancy and worrisome features. The high-risk stigmata were considered to be: 1) obstructive jaundice in patients with a cystic lesion of the pancreatic head; 2) an enhancing solid component within the cyst and 3) a main pancreatic duct equal to, or greater than, 10 mm in size. The worrisome features were the following: 1) pancreatitis; 2) a cyst equal to, or greater than, 3 cm in size; 3) thickened/enhancing cyst walls; 4) main duct size 5-9 mm; 5) non-enhancing mural nodules and 6) an abrupt change in the caliber of the pancreatic duct with distal pancreatic atrophy. In young (less than, or equal to, 65 years of age), fit patients with cystic lesions greater than 2 cm in size, surgery could be considered instead of prolonged surveillance.

The European consensus statement in 2013 [2] added that other risk factors have to be considered: 1) the growth rate of the cyst over time (2 mm/year) and 2) the presence of symptoms as well as abdominal pain and new onset diabetes, and increased serum levels of CA 19-9. Finally, a recent meta-analysis regarding cyst features and risk of malignancy in IPMNs of the pancreas has confirmed that the cyst features proposed by the International

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guidelines for the resection of IPMNs were highly associated with malignancy [5]. Among the different risk factors (cyst size greater than 3 cm; presence of mural nodules and dilatation of the main pancreatic duct), the meta-analysis pointed out that a cyst size greater than 3 cm was most strongly associated with malignant IPMNs [5]. According to these consensus conference guidelines, branch-duct IPMNs less than 3 cm in diameter without signs of malignancy should be managed conservatively. Nevertheless, Fritz *et al.* suggested pancreatic resection even in patients with branch-duct IPMNs less than 3 cm without any risk factors for malignancy. In fact, the authors reported an incidence of 25% of malignant tumors in these patients [6].

In our experience, we have noted that the presence of symptoms significantly increased the risk of malignancy [7], and that the indications for surgery were more frequent in young, fit, symptomatic patients with cystic lesions greater than 3 cm [8].

The Patient

The patient was a 80-83-year-old “relatively healthy” woman. We do not know if the patient had one or more co-morbidities, or cardiovascular, pulmonary or metabolic (diabetes mellitus, cirrhosis, etc.) diseases at the time of diagnosis of the disease or if one or more co-morbidities appeared during the follow-up period. These data would be very important in establishing or not a surgical approach. A recent meta-analysis regarding pancreaticoduodenectomy in patients over 80 years of age showed that patients over 80 years of age had significantly higher postoperative mortality and morbidity than patients under 80 years of age [9]. However, when we considered patients under 80 years of age and patients over 80 year-old without differences in co-morbidities, we noted that there were no differences in postoperative mortality and morbidity. In summary, in order to avoid increased postoperative mortality and morbidity in patients over 80 years of age who are candidates for pancreatic resection, selection should be carried out on an individual basis .

Discussion

In the case in the letter, an elderly, relatively healthy, asymptomatic woman with a cyst in the pancreatic neck less than 3 cm was reported. The features of the cyst did not reveal risk factors for the presence of malignancy: cyst size less than 3 cm, no mural nodules and no dilatation of the main pancreatic duct. The characteristics of the cysts remained the same over time and the patient remained asymptomatic. The only parameter which changed was an increased CEA level in the cystic

fluid. The last cytologic examination of the cystic fluid showed the presence of a scant atypical mucinous epithelium. The CEA level in the cystic fluid is considered important in the differential diagnosis between non-mucinous (especially serous tumors) and mucinous tumors [10]. However, there is no direct correlation between the risk of malignancy and the concentration of CEA [11]. Finally, an atypical mucinous epithelium is not synonymous with carcinoma. These considerations, regarding the characteristics of the disease, should be sufficient to plan conservative management.

To these evaluations, we have to add the type of patient. She was over 80 years of age and we do not know if she was fit for surgery because we do not know her co-morbidities. However, we think that patients over 80 years of age usually have more co-morbidities than younger patients. Thus, the postoperative risk for a Whipple procedure or another pancreatic resection has to be considered to be greater in this patient.

In conclusion, our opinion regarding this interesting case is:

- 1) at diagnosis (2010), a surveillance program every six months with MRI and EUS, alternatively, for two years was the correct management;
- 2) presently (August 2013), we agree with what was suggested by the Mayo Clinic, namely, observe, MRI (or EUS) once a year.

The answers to the two final questions are surely very difficult considering the scant information presently available in the literature regarding branch-duct IPMNs (this entity was clearly defined only in 2004; what is its natural history?; Could we recognize more accurate tumors markers?; Why do only 20% become cancerous?, etc.). We can answer the question “Have I been correct with my decision so far in delaying the surgery?” as follows. Yes, we think your decision in delaying the surgery was right. Your mother is still alive and well, and her quality of life is the same as the time of diagnosis. Thus, your decision was correct.

Regarding the question “Should my mother have had her surgery a long time ago?”, the answer is no because there were no surgical indications, the cystic lesion did not show signs of malignancy and the patient was asymptomatic. If she had had surgery, there would have been a 15% chance of death and a 50% chance of being discharged to a health care facility where she would have a poor quality of life.

Conflict of interest The authors have no potential conflict of interest

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