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Review

Diagnosis and management of intraductal papillary mucinous neoplasms of the pancreas

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Summary. *Background and aim of the work:* Intraductal papillary mucinous neoplasms (IPMN) of the pancreas are cystic lesions with malignant potential. Given their increasing incidence in the latest years, a precise characterization and management of these lesions have become more and more crucial: even though the majority of IPMN has a benign and indolent course, it is fundamental to early recognize and stratify patients in order to accurately plan a tailored follow-up and to individuate those that would benefit of surgical treatment. The aim of this paper is to highlight the most recent evidence on IPMN available in the current literature. *Methods:* We performed a review of the recent literature and of the recent guidelines about pancreatic cystic lesions, especially IPMN. *Results:* The incidence of IPMN is now on the rise: an increasing number of patients, possibly because of the increasing diagnostic yield of imaging techniques, is being diagnosed with pancreatic cystic lesions, a great part of which are IPMN. The possibility of malignant transformation requires a careful approach to these patients, in the need of tailoring the follow-up and the therapy. *Conclusion:* A detailed diagnosis, the determination of risk factors for malignant transformation and a multisciplinary approach are of foremost importance for an effective management of IPMN. (www.actabiomedica.it)

Key words: intraductal papillary mucinous neoplasms

Background and aim of the work

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas are mucin-producing cystic tumors, classified as premalignant lesions (1), originating from the pancreatic epithelium of the main pancreatic duct (MPD) or its side branches (2).

The overgrowth of mucin-producing cells usually forms intraductal papillae, along with the production of thick mucus in a variable extension, with a subsequent dilation of the ducts in a grossly visible manner (3). Although the behavior of IPMN can be considered benign, "borderline" and malignant in consideration of the different grade of dysplasia of the involved cells, they always have to be considered as potential precursors of pancreatic ductal adenocarcinoma (PDAC) (4,5).

The reported incidence of IPMN, slightly predominant in males, varies from 0.31 to 4.35/100000, with an average age of 64 at diagnosis (6,7). The marked increase of the incidence in the recent years is probably due to the enhanced accuracy of imaging techniques and to the progress in recognition of the disease (8): up to 15% of patients undergoing abdominal magnetic resonance imaging (MRI) for other reasons are diagnosed with previously unknown pancreatic cystic lesions (9), which can be IPMN in a large number of cases (up to 82%) (10).

Based on the site of the involved pancreatic ducts, IPMN can be differentiated in 3 groups: branch duct (BD)-IPMN, characterized by cyst-forming dilation of lateral branches in communication with a normal MPD; main duct (MD)-IPMN, characterized by dif-

fuse or segmental dilation of the MPD; mixed type (MT)-IPMN, which includes characteristics of both types (1,11). Pancreatic ducts can be involved in a unifocal or multifocal fashion, the latter being more frequent in the elderly (11,12).

Methods

A research of the literature was performed by using Pubmed, Medline, Embase databases.

Cochrane database and google Scholar were searched as well. All types of papers in English, including abstracts and reviews, were included. Considering the year of publication, the research was limited to the last 15 years.

All recent articles were taken into consideration, then a manual search was performed in order to identify all relevant reports. We also considered the reference list from the most relevant articles and guidelines. Articles published as abstracts were also included.

Results

After a detailed evaluation, we included 37 articles in total: 22 were original articles, 6 were reviews, 4 were guidelines, 1 was a consensus of experts, 1 was a case report, 1 was an abstract, 1 was an editorial and 1 was the WHO classification of gastrointestinal tumors.

Clinical appearance

Most patients with IPMN are clinically silent: symptoms such as abdominal pain, weight loss, steatorrhea, new-onset diabetes or jaundice generally occur in the setting of an obstruction of the ductal system or of a complication such as pancreatitis, perforation, hemorrhage or fistulation (13-15).

Diagnosis

Imaging (MRI and CT)

The diagnosis is often incidental. MRI with magnetic resonance cholangio-pancreatography (MRCP) is considered the imaging technique of choice, being more accurate than computed tomography (CT) in the evaluation of pancreatic cysts (11): its sensitivity and specificity in assessing the presence of communication with the MPD are 91-100% and 89%, respectively (7). Indications for CT include the presence of calcifications, assessment of vascular involvement or metastatic disease, suspicion of post-operative recurrence of PDAC (16).

Endoscopic UltraSound (EUS)

EUS, with its high accuracy in the evaluation of the cystic component and the pancreatic parenchyma, should be used in case of suspicious morphological features: based on morphology, EUS is more sensitive (76%) than MRI or CT (34% and 48%) in differentiating neoplastic from non-neoplastic cysts (16,17).

Contrast harmonic enhanced EUS (CH-EUS) can be considered in the evaluation of mural nodules, as in this setting it seems superior than CT or standard EUS, with a sensitivity of 100% and a specificity of 80% (18).

EUS-guided fine needle aspiration (FNA) is of great value, as it allows the possibility of cytological sampling any solid component and aspirating cyst fluid for analysis (19).

Cystic biomarkers

CEA, CA 19.9 and amylase should be tested whenever cystic fluid is available.

CEA values ≥192 ng/mL can distinguish mucinous from non-mucinous cysts; high amylase levels confirm communication with the MPD (as in IPMN) and CA 19.9 helps distinguishing cases in which CEA is indeterminate (7). In a little cohort of patients, glucose outperformed the accuracy of CEA in differentiating mucinous from non-mucinous cysts (20). Next generation sequencing on cystic fluid for KRAS/GNAS mutations is extremely useful in the differential diagnosis of IPMN with other pancreatic cystic lesions, although not widely available yet (7,16).

Serum biomarkers

Serum CA 19.9 values correlate with the presence of malignant IPMN, being therefore considered

a feature of concern (11). Its sensitivity is 79-100%, although a normal value does not exclude malignancy (7).

Natural history

Adequate and tailored surveillance of IPMN patients is fundamental, as it allows the early detection of potentially resectable pancreatic cancer that may develop on this premalignant condition (21). Invasive carcinoma derived from IPMN does not have to be confused with concomitant PDAC arising in a different site from IPMN, which is considered a separate entity (22).

As premalignant lesions, IPMN harbor the potential for progression towards cancer. Although the time for progression is limited in the elderly, IPMN diagnosed in older patients are more prone to degeneration (12). Multifocal cysts correlate with the incidence of PDAC concomitant with IPMN, thus being a possible risk factor for cancer (23).

Risk factors for degeneration are defined, in the Japanese guideline, as "worrisome features" (cyst ≥3 cm, enhancing mural nodule <5 mm, thickened enhanced cyst walls, MPD size of 5-9 mm, abrupt change in the MPD caliber, lymphadenopathy, cyst growth >5 mm/2 years, increased serum levels of CA 19.9) and as "high risk stigmatas" (obstructive jaundice with a cyst in the pancreatic head, enhanced mural nodule >5 mm, MPD size ≥10 mm), the latter being strong indications for surgery (11).

Although it is known that the risk of malignancy in main duct- or mixed type IPMN is higher than in BD-IPMN (1,24), the rate of progression hasn't been clearly defined yet (25). In a recent study of Han and colleagues, a population of 1369 patient diagnosed with BD-IPMN was followed-up for at least 3 years resulting in the detection of high-grade dysplasia (HGD) or invasive IPMN in 13 patients (0.9%): a relation with progression was found with the initial cyst size and a faster cyst growth rate (26). In another study, Pergolini and colleagues highlighted an overall risk of malignancy (including concomitant PDAC) of 8% in a cohort of patients followed up >10 years, supporting the idea of continued surveillance, as long as the patient is fit for surgery (27): this is in contrast with the previous recommendations of the American guidelines, which suggest stopping surveillance after 5 years in cysts without worrisome features if no significant changes are detected (9).

IPMN in liver transplant recipients haven't shown any accelerated pattern of progression, compared to the general population in a large cohort of patients (28).

At this moment, current literature is inconclusive about increased incidence of extrapancreatic neoplasm in IPMN patients, suggesting that standard surveillance should be advised (29).

Treatment

Surgery

The frequency of HGD and cancer in MD-IPMN and MT-IPMN is high: these high rates justify the indication for surgical resection in all patients fit for surgery (11,16).

European guidelines recommend surgery in MPD dilation >5 mm, while Japanese guidelines strongly recommend surgical resection in IPMN with obvious "high risk stigmata": MPD ≥10 mm, jaundice or enhancing mural nodules > 5 mm (11). Enhancing mural nodules < 5 mm, MPD dilation of 5 to 9 mm are considered "worrisome features" with a recommendation of surgical evaluation but not to immediate resection.

If the MPD dilatation affects the entire gland, a pancreatoduodenectomy with frozen section analysis is recommended (16).

A total pancreatectomy is otherwise indicated in case of increased risk for malignancy: familial pancreatic cancer, a mural nodule, involvement of the entire MPD (30-32).

A partial pancreatectomy is indicated in localized IPMN together with frozen section analysis on the resection margins, useful for detecting spread of dysplasia or cancerous lesions and guiding an extended resection, especially in young fit-for-surgery patients.

In cases of multifocal IPMN each lesion should be evaluated as a single entity and a tailored surgical approach is indicated according to the presence of "high risk stigmata" or "worrisome features" (33,34).

Since small BD-IPMN can evolve into HGD or cancer, it is suggested to monitor the presence of rela-

tive criteria for resection and, if multiple, to evaluate for surgery.

Relative surgical criteria, proposed by European guidelines, are: growth rate ≥5 mm/year, CA 19.9 level >37 U/ mL in the absence of jaundice, MPD diameter > 5 and < 9.9 mm, cyst diameter ≥40 mm, symptoms (new-onset of diabetes mellitus or acute pancreatitis), contrast-enhancing mural nodules <5 mm.

Literature reports an increased risk of malignancy from 12% to 47% in cases of a cyst ≥30 mm; European guidelines propose a cut-off point for resection of IPMN, regardless of the absence of clinical symptoms or (other) risk factors, of > 40 mm (16,26,35).

In young patients (< 65 years), surgery has to be evaluated against the burden of life-long imaging follow-up owing to the cumulative risk of HGD and malignancy. Resection can be indicated in young fit-for-surgery patients even in cyst > 2cm without "worrisome features" (11,36).

Post-surgical follow-up is required until the patient is fit for surgery, also because a significant number of recurrences can develop over 5 years after the index operation (37). In the post-surgical setting: patients with PDAC associated to IPMN have to be followed-up as those with PDAC; patients with HGD or MD-IPMN need MRI or EUS monitoring every 6 months for the first 2 years then yearly; patients with IPMN in the remnant pancreas (no HGD left) and patients with low grade dysplasia (LGD) need the same monitoring as the unresected ones (16).

Margin positivity after resection for non-invasive IPMNs is primarily due to LGD and is not associated with developing recurrence in the remnant pancreas or at the resection margin (37).

"Watchful waiting" and follow-up timing

Watchful waiting is justified in patients with asymptomatic BD-IPMN without high risk stigmata (7,9,11,16). In these patients an aggressive approach is not justified, as the low rate of progression of these lesions should be compared with the risk of surgery itself and post-operative mortality (15).

The perfect timing of follow-up is still a matter of debate. European guidelines indicate repetition of imaging every 6 months in the first year after diagnosis and then yearly, in patients with no current indications for surgery and independently of the bigger cyst size. MRI is the preferred imaging modality, whereas EUS has to be used if features of concern show up (16). On the other hand, Japanese guidelines propose a variable timing based on the size of the main cyst; Italian guidelines also take into consideration the possibility to lengthen the intervals if the IPMN is stable in time (7,11). Conversely, patients with a relative indication for surgery need a tighter follow-up, with MRI or EUS scheduled every 6 months (16).

Regarding the possibility of progression even after 5 years, the follow-up should be life-long until the patient is fit for surgery: in this setting, stopping the follow-up after 5 years of stable disease, as suggested by the American guideline, seems too risky (9,25,27).

Conclusions

Due to the increasing incidence and aging of the population, IPMN management is an uprising problem. Given their natural history and the possibility of progression towards malignancy, a life-long surveillance seems the most appropriate management to advise, in a multidisciplinary setting. Follow-up of these lesions is recommended until the patient is fit for surgery, as surgery is the only therapeutic option in patient with high-risk features. The perfect timing for follow-up is still a matter of debate and should be discussed in a tailored manner based on patient's and tumor's characteristics. Further studies are required in order to better assess the behavior of IPMN and to highlight early predictors of malignancy. The molecular profile determination has given, until now, promising results.

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