Early neoplasms of the ampulla and intrapancreatic biliary tract

Deepti Dhall
Maha Guindi
Richard Mertens
Shefali Chopra

Abstract

The classification of precursor lesions arising in the ampullary region and in the intrapancreatic biliary tract has recently evolved. It largely includes adenomas, papillary-tubular neoplasms of the ampulla and intrapancreatic bile duct, and flat dysplasia/biliary intraepithelial neoplasia (BilIN). Ampullary adenomas (AA) arise from the duodenal surface of the ampulla. Exophytic/tumoural neoplastic precursor lesions occurring within the ampullary channel are designated intraampullary papillary-tubular neoplasms (IAPNs), and their counterparts within the bile ducts are called intraductal papillary neoplasms of the bile duct (IPNBs). While AAs are usually intestinal type, IAPNs and IPNBs have different phenotypes, including pancreatobiliary, intestinal, gastric, oncocytic, and mixed types. IAPNs and IPNBs have a high incidence of high grade dysplasia and associated invasive carcinoma. Non-invasive and minimally invasive papillary neoplasms have a much better prognosis than conventional carcinomas. BilIN is presently categorized as BilIN-1, BilIN-2 and BilIN-3. BilIN can be difficult to distinguish from reactive atypia. The role of immunohistochemistry and FISH studies in the diagnostic evaluation of early neoplastic lesions is discussed.

Keywords ampulla; ampullary adenomas; bile duct; biliary dysplasia; biliary intraepithelial neoplasia; intraampullary papillary-tubular neoplasms; intraductal papillary neoplasm of bile duct; intrapancreatic bile duct; precursor lesions

Deepti Dhall *MD Consultant in Gastrointestinal and Liver Pathology, Associate Director of Gastrointestinal Pathology, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA. Conflicts of interest: none declared.*

Maha Guindi *MD Consultant in Gastrointestinal and Liver Pathology, Director of Gastrointestinal and Liver Pathology, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA. Conflicts of interest: none declared.*

Richard Mertens *MD PhD Consultant in Gastrointestinal and Breast Pathology, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA. Conflicts of interest: none declared.*

Shefali Chopra *MD Consultant in Gastrointestinal and Liver Pathology, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA. Conflicts of interest: none declared.*

Introduction

The ampulla is a complex anatomical structure. In the strict sense, ampulla refers to the common channel formed by the distal-most ends of the pancreatic and common bile ducts, which open into the duodenum. However, when discussing ampullary neoplasms,[1] the ampullary region includes the following structures: (1) The distal ends of the common bile duct and the pancreatic duct (present within the duodenal wall). These ducts may either form a common channel before opening into the duodenum or may open side by side into the duodenal lumen; (2) The papilla (the duodenal protuberance surrounding the ampullary orifice which demonstrates transition of pancreatobiliary epithelium to intestinal epithelium and frequently contains some foveolar-type epithelium); (3) The duodenal surface of the papilla; and (4) The accessory pancreatobiliary ducts and mucous glands surrounded by smooth muscle (sphincter of Oddi). A thorough knowledge of the anatomy of this region, which is often variable, and the different histologic features of its component structures is a key to understanding the neoplastic entities involving the ampulla.

Early tumoural neoplastic lesions of the ampulla and intrapancreatic bile duct are endoscopically and grossly visible as discrete raised/exophytic lesions. In addition to tumoural precursor lesions, the intrapancreatic bile duct and rarely the ampulla may also develop flat dysplasia. These early neoplastic lesions can be discussed by their location (duodenal surface of the ampulla, ampullary channel, or intrapancreatic bile duct) or can be grouped by their form (tumoural versus flat). This review will discuss the tumoural lesions first, according to their location, and then separately discuss flat dysplasia. The tumoural lesions often involve more than one region of the ampullary anatomy; for example, an ampullary channel lesion may extend into the distal common bile duct or pancreatic duct and can potentially focally invade in more than one area. Documentation of the topography of these lesions at the time of prosection of the resected specimen is of utmost importance in establishing the site of origin of the tumour, as well as staging the tumour in invasive cases. In some cases with extensive involvement of the ampulla, adjacent duodenal mucosa, and the ducts, it may be impossible to determine the site of origin.

Early neoplastic lesions of the ampulla

In the small bowel, the ampulla is the most common site for the development of neoplastic precursor lesions, perhaps due to its complex milieu. Early tumoural neoplastic lesions arising from the duodenal surface of the papilla are called ampullary adenomas, which are similar to colorectal adenomas. Ampullary adenomas are the most common early neoplastic lesions involving the ampulla.[2] These have also been called "periampullary adenomas" in the literature and recently have been designated "adenomas of the ampullary duodenum" to emphasize that they arise from the duodenal surface.[3] Early tumoural lesions occurring within the ampullary channel have been recently studied by Ohike et al.,[4] who have designated them as intraampullary papillary-tubular neoplasms (IAPNs). Unlike ampullary adenomas, which are mostly intestinal type, IAPNs can have an intestinal, pancreatobiliary, gastric or oncocytic phenotype.

Ampullary adenomas

Intestinal-type adenomas

Clinical features — most ampullary adenomas are sporadic, but some are associated with polyposis syndromes, e.g., familial adenomatosis polyposis (FAP). Most FAP-associated adenomas occur around the ampulla. While sporadic ampullary adenomas occur at a mean age of 61 years, ampullary adenomas in FAP patients occur at a mean age of 41 years. Sporadic ampullary adenomas show a female preponderance, whereas no sex predilection is seen with FAP-associated adenomas. Peutz-Jeghers and Lynch syndromes are also associated with an increased risk of ampullary adenomas. Ampullary adenomas can manifest with features of biliary obstruction, including biliary colic, cholangitis and pancreatitis. Approximately 50% of ampullary carcinomas have an associated adenomatous component.

Pathologic features — macroscopically, ampullary adenomas are polypoid lesions seen within the duodenal lumen on the duodenal surface of the ampulla (Figure 1). They may extend into the ampullary channel and distal ends of the common bile duct and/or pancreatic duct (Figure 2). More than 75% of the lesion should be on the duodenal surface of the ampulla to be classified as an ampullary adenoma. Analogous to colonic and non-ampullary small bowel adenomas, intestinal-type ampullary adenomas are composed of columnar cells having pseudostratified, cigar-shaped, hyperchromatic nuclei. They have tubular, tubulovillous or villous architecture (Figure 3). By definition, they all have at least low grade dysplasia and may have high grade dysplasia. A significant proportion of ampullary adenomas with only adenomatous tissue seen on biopsy will contain carcinoma in the resected specimen. Thus, biopsy sampling error should be kept in mind by the clinician when evaluating these lesions, especially ones that cannot be completely locally excised or are difficult to follow-up endoscopically due to extension into the ampullary channel.

Molecular features — similar to colorectal adenomas, ampullary adenomas often exhibit *Wnt* signalling pathway abnormalities, with nuclear beta-catenin immunostaining and *APC* gene mutations, and *KRAS* mutations. *BRAF* mutations and p53 alterations are rare.[5] Less than 10% of ampullary adenomas show a high level of microsatellite instability.[6]

Differential diagnosis — it is important to distinguish reactive/regenerative atypia associated with surface erosion from an adenoma, particularly in a biopsy specimen. With the advent of interventional endoscopic procedures such as biliary stent placement/removal and stone extraction, the resulting reactive ampullary mucosa may appear prominent endoscopically, mimicking adenoma and prompting biopsy. Reactive/regenerating epithelium tends to mature towards the surface, whereas the epithelium of adenomas does not. Prominent acute inflammation is more often associated with reactive/regenerative atypia.

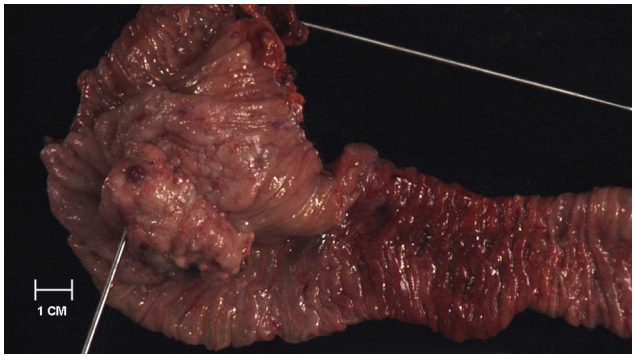

Figure 1 Ampullary adenoma: Polypoid lesion centered on the ampulla (probed) and protruding into the duodenal lumen.

Adenomyoma/adenomyomatous hyperplasia of the ampulla is often clinically misdiagnosed as adenoma. Moreover, endoscopic biopsies from adenomyomas often show surface reactive/regenerative epithelial atypia, which can be mistaken for dysplasia (Figure 4). Adenomyomas are characterized by hyperplastic glandular lobules surrounded by hyperplastic mesenchymal tissue. These glands are lined by single layered cuboidal or columnar epithelium with no atypia or mitotic figures. The epithelial atypia in adenomyomas involves the superficial epithelium and is often focal. Immunohistochemically, positivity for cytokeratin 7 (CK7) and negativity for cytokeratin 20 (CK20) may be helpful in distinguishing adenomyomas from adenomas, which are often positive for both CK7 and CK20.[7]

Pyloric gland adenomas

Pyloric-type ampullary adenomas (PGAs) are rare. They may or may not be associated with heterotopic gastric tissue. Histologically, PGAs are composed of closely packed pyloric gland-type tubules (Figure 5). Dysplasia and associated carcinoma are not uncommon in pyloric gland adenomas.[8,9] The nuclei in PGAs appear bland, rounded and minimally stratified even in dysplastic lesions, as compared to conventional adenomas. Immunohistochemically, PGAs are positive for MUC6 and MUC5AC. Unlike intestinal-type adenomas, activating *GNAS* mutations and associated *KRAS* mutations are frequent in gastric and duodenal PGAs.[10]

Intraampullary papillary-tubular neoplasms

Intraampullary papillary-tubular neoplasm (IAPN) is a term recently proposed by Ohike et al.[4] to describe mass-forming preinvasive neoplasms/adenomatous lesions that occur predominantly (at least 75% of the lesion) within the ampullary channel. IAPNs comprise about 33% of primary ampullary tumours. The WHO terminology for these lesions is non-invasive pancreatobiliary neoplasm and intestinal-type adenoma.[11]

Clinical features: the age range is 27–85 years (mean age 64 years), and the male: female ratio is 2.2, which is similar to ampullary carcinomas. The patients often present with obstructive symptoms, including jaundice.

Pathologic features: these tumours are similar to analogous tumours of the gallbladder, bile duct and pancreas. Macroscopically, IAPNs exhibit exophytic growth on the mucosal surface of the ampullary channel (Figure 6), and they may extend onto the duodenal surface of the papilla and into the distal bile duct and pancreatic duct. They often have a mixture of papillary (villous) and tubular growth (Figure 7) and exhibit a spectrum of dysplasia, with a very high incidence of at least focal high grade dysplasia. They demonstrate different cellular lineages, including intestinal type, pancreatobiliary type, gastric type, and oncocytic type. The intestinal type exhibits histologic features analogous to those previously described for ampullary adenomas (Figure 8).

