Polypoid dysplasia in Barrett's Esophagus : case report and qualitative systematic review of the literature

Sushil K. Ahlawat[1], Metin Ozdemirli[2]

(1) Division of Gastroenterology, Department of Medicine, (2) Department of Pathology, Georgetown University Hospital, 3800 Reservoir Road, NW, Washington, DC 20007.

Abstract

Dysplasia in Barrett's esophagus (BE) occurs as a flat, grossly undetectable lesion. Dysplasia growing as a polypoid lesion in BE is extremely rare. Only a handful of cases are reported in the literature. BE associated polypoid dysplastic lesions have been referred to as *"adenomas"* because of their histologic similarity to a colonic adenoma. We describe a patient with esophageal polypoid lesion associated with BE and review clinical and pathological features of other cases of BE associated polypoid dysplasia or *"adenomas"* as reported in the literature. (Acta gastroenterol. belg., **2012**, 75, **49-54**).

Key words : Barrett's ; esophagus ; dysplasia ; polyp ; adenoma ; adenocarcinoma.

Introduction

Barrett's esophagus (BE) is associated with an increased risk of adenocarcinoma (1). Adenocarcinoma is believed to develop through a metaplasia-dysplasia-carcinoma sequence (2). Dysplasia, the main precursor of carcinoma, most commonly occurs as a flat, grossly undetectable lesion. Rarely, dysplasia in BE may grow as a polypoid lesion. Most BE associated polypoid dysplastic lesions have been referred to as *adenomas* because of their histologic similarity to a colonic adenoma. Although much is known about BE- associated flat dysplastic lesions but little is known about BE-associated polypoid dysplasia. Only a handful of cases are reported in the literature. We report a 72-year-old-man with BE-associated polypoid dysplasia and adenocarcinoma along with the review of literature.

Case report

A 79-year-old Caucasian man was referred for an endoscopic ultrasound to evaluate a previously detected esophageal polypoid lesion on upper endoscopy that was performed 2 weeks ago for evaluation of dysphagia. Patient was also noted to have BE that measured C3 M5 according to the Prague C and M criteria. Biopsies were performed according to the standard protocol, 4 quadrant every 2 cm of BE, and additional biopsy of the polypoid lesion arising in the BE. The biopsy from the esophageal polypoid lesion showed high grade dysplasia (HGD). However, no dysplasia was found in the adjacent BE. His past medical and surgical history was unremarkable. An upper endoscopy with endoscopic ultrasound (EUS) was performed under deep sedation using fentanyl, midazolam, and propofol. A large polypoid lesion with villous appearance was seen in the distal esophagus (Fig. 1A and B) in the setting of BE. The lesion appeared hypo-echoic on EUS and was largely confined to the superficial layers of the esophagus (Fig. 2). No local or regional adenopathy was identified. The polypoid lesion was resected en-block using a hot snare (Fig. 1C) with no immediate or late complication. Histological sections revealed a large adenomatous polyp arising in glandular mucosa with focal intestinal metaplasia adjacent to squamous mucosa (Fig. 3A). Focal high grade glandular dysplasia as well as small foci of intramucosal adenocarcinoma was seen (Fig. 3B). No invasion into tunica muscularis or submucosa was identified. Patient declined invasive therapy including surgery. Approximately 1 year later he developed recurrence resulting in near complete obstruction of the esophagus. At this point he opted for hospice care.

Discussion

Adenomas, defined as neoplastic masses of dysplastic epithelium, are found throughout the gastrointestinal tract and have the potential for containing or developing carcinoma. This risk is best established for colon adenomas that are considered the major precursor of colorectal carcinoma. BE is associated with an increased risk of adenocarcinoma (1). Adenocarcinoma is believed to develop through a metaplasia-dysplasia-carcinoma sequence (2). Dysplasia, the main precursor of carcinoma, most commonly occurs as a flat, grossly undetectable lesion. Very rarely, dysplasia in BE may grow as a polypoid lesion (3). Most BE associated polypoid dysplastic lesions have been referred to as *"adenomas"* because of their histologic similarity to a colonic adenoma. Although much is known about BE- associated flat dysplastic lesions but little is known about BE-associated polypoid dysplasia. A retrospective study of 250 cases of BE-associated dysplasia showed only 5 cases of poly-

Correspondence to : Sushil K. Ahlawat, M.D., UMDNJ-University Hospital, Suite E-178, 150 Bergen St Newark, NJ 07103. E-mail : sushilka@aol.com

Submission date : 03/12/2009
Acceptance date : 19/09/2010

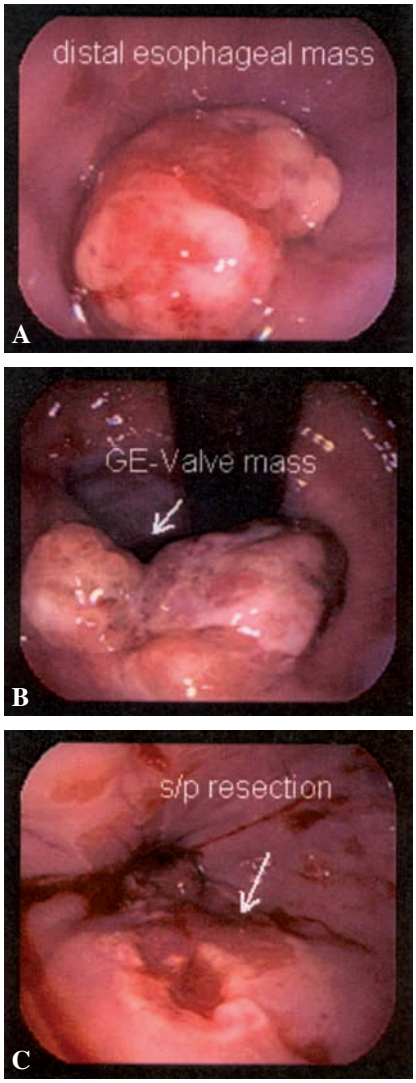

Fig. 1. — Endoscopic views of the distal esophageal polypoid lesion, A. Forward view, B. Retroflexed view, C. Post-resection.

poid dysplasia corresponding to a prevalence rate of 2 percent in a highly selected population (3).

We performed a comprehensive MEDLINE search using MeSH terms, "esophagus", "polyp", "adenoma", "dysplasia" for esophageal polypoid lesions classified as *"adenomas"*. Only English language articles were included. Our review was limited to lesions that were derived from BE. Published articles were reviewed for the patients' demographics, presenting signs and symptoms, endoscopic features, size and location of the polypoid lesion, histological features including a suspicion with BE, treatment and follow-up, where available (3-15). Patients without BE were excluded. These data are shown in Table 1.

Esophageal adenomas are extremely rare and have been reported infrequently. There are no published data on the incidence of polypoid dysplasia in BE because these lesions have been reported only as case reports. Our Medline search revealed 16 manuscripts comprising

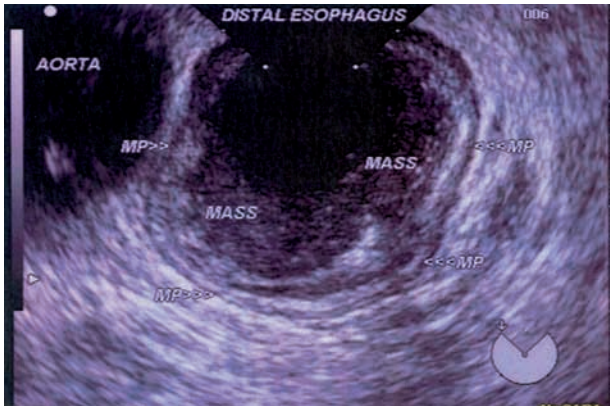

Fig. 2. — Endosonographic image of esophageal polypoid lesion.

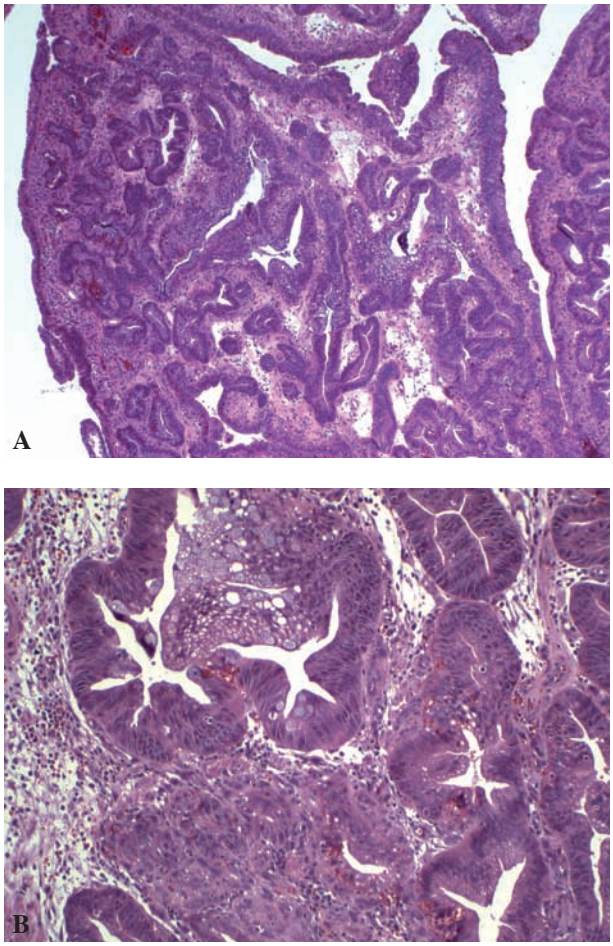

Fig. 3. — A. Section of the esophageal polypoid lesion showing a large adenomatous polyp resembling tubulovillous adenoma (H&E, ×40) ; B. Foci of high grade dysplasia within the polyp (H&E, 100×).

a total of 25 cases. One case report did not describe clinical or pathological information and only the location of the lesion was reported in 3 case reports (16-18). These patients were excluded. Of 21 remaining cases, 76% were male (average age, 59 years ; range, 20 to 81 years). Like our patient, most patients presented with dysphagia

Table 1. — **Summary of clinical and pathological features of patients with esophageal "*adenoma*"**

Authors	year	Age	Sex	Clinical presentation	Endoscopic findings	Location	Size (cm)	BE	Pathological findings	Treatment	Follow-up
Arnold & Mardini (4)	2002	51	M	Follow-up for BE	Nodule	30 cm	1	Yes	Tubular "adenoma" with low and high grade dysplasia and chronic inflammation	Esophagectomy	Alive : 6 months
Cavanaugh *et al*. (5)	1995	59	M	Dysphagia	Pedunculated polyp	35 cm	2.5	Yes	Invasive adenocarcinoma	Esophagectomy and chemotherapy	Alive : 2 months
Kalsbeek and Van Der Wouden (6)	1971	61	F	Dysphagia, vomiting	Obstructing polyp	27 cm	NR	Yes	Intestinal - type BE	Esophagectomy	NR
Lee (7)	1985	68	F	Heartburn	Sessile polyp	NR	1.5	Yes	tubulovillous adenoma	Esophagectomy	Alive : 2 years
McDonald *et al*. (8)	1977	62	M	Hematemesis, weight loss, nausea, vomiting	Multiple nodules	28-38 cm	0.5 - 3	Yes	Villous adenoma with focal adenocarcinoma	Esophagectomy with colon interposition	Died : 45 days post-operation
Stillman and Selwyn (9)	1975	51	M	Dysphagia and weight loss	Multicentric polypoid mass	30	1.5	Yes	Adenoma with superficial carcinoma	Esophagectomy & radiation therapy	Alive : 2 months
Thompson (10)	1983	53	M	Dysphagia, weight loss, epigastric pain	NR	GEJ/ distal esophagus	9	Yes	Villous adenoma with invasive adenocarcinoma	Esophagectomy	NR
Thurberg (3)	1999	81	M	Indigestion, weight loss, anorexia	2 polyps : sessile and polypoid	43 cm	1	Yes	Low and high grade dysplasia with focal intramucosal adenocarcinoma	Esophagectomy	Alive : 6 months
		55	M	Heartburn	Sessile	35 cm	1	Yes	Low and high grade dysplasia with adjacent intramucosal adenocarcinoma	Esophagectomy	Alive : 6 years
		68	M	Postprandial epigastric pain, regurgitation	Pedunculated polyp	GEJ	0.9	Yes	Low and high grade dysplasia with focal intramucosal adenocarcinoma	Polypectomy	Alive : 6 months
		70	M	Epigastric pain, nausea, melena, hematemesis	Nodule	26 cm	0.4	Yes	Low and high grade dysplasia with submucosal invasive adenocarcinoma	Esophagectomy	Alive : 2 months
		79	M	Dysphagia	Pedunculated polyp	GEJ	1.5	Yes	Low and high grade dysplasia with focal intramucosal adenocarcinoma	Polypectomy	Alive : 2 months
Paraf *et al*. (11)	1992	64	M	Dysphagia	Sessile polyp		1	Yes	Villoglandular adenoma, LGD, HGD, focal carcinoma	Esophagectomy	NR
		77	M	Melena	multiple polyps		0.2 to 3.5	Yes	Villoglandular adenoma, LGD, HGD, invasive carcinoma	Esophagectomy	NR
		64	M	Anemia	Two polyps		1	Yes	Villoglandular adenoma, LGD, HGD, invasive carcinoma	Esophagectomy	NR
Keefe *et al*. (12)	1986	40	F	Epigastric pain	Pedunculated polyp	35 cm	1.5	Yes	Tubular adenoma, dysplasia	Polypectomy	NR
Wong (13)	2004	76	F	Hematemesis	Polyp	Lower esophagus	1	Yes	Villous adenoma with moderate dysplasia	Patient declined therapy	NR
Lee (14)	1985	56	M	Dysphagia, epigastric pain	Nodule		1.7	Yes	adenoma with dysplasia	Esophagectomy	NR
Wolfsen (15)	2005	30	M	Asymptomatic	Polypoid changes	Lower esophagus	NR	Yes	Barrett's esophagus, high grade dysplasia	Declined therapy	NR
		59	M	Dysphagia, weight loss	Polyp		2.5	Yes	adenoma with dysplasia	Esophagectomy	NR
		68	F	Heartburn	Polypoid mass		1.5	Yes	adenoma with dysplasia	Esophagectomy	NR
Present case	2007	79	M	dysphagia	Polypoid mass	Lower esophagus	5	yes	adenoma with dysplasia and foci of intramucosal adenocarcinoma	Polypectomy	Alive : 1 year

M : Male ; F : Female ; BE : Barrett's esophagus ; GEJ : Gastroesophageal junction ; NR : Not reported ; HGD : High grade dysplasia ; LGD : Low grade dysplasia.

or epigastric pain. Endoscopically, 14 lesions were present in the distal esophagus or at the gastroesophageal junction, and two were located in the mid-esophagus. Five cases did not report the location of the polyp. The lesions averaged 2.3 cm in size (range, 0.2 to 10 cm). Twelve lesions were polypoid ; one was described as a "multicenteric polypoid mass", 3 as sessile polyps, and 4 as nodules and one as a sessile and polypoid lesion. Our patient didn't have prior known BE ; however, his current endoscopy showed BE. Endoscopically, our patient had large, irregular polypoid mass in the distal esophagus. Endosonographically, the polypoid lesion appeared limited to the superficial layers of the esophageal wall. No EUS information was available in the previously reported cases.

All 21 polyps were associated with BE. Two polyps comprised "intestinal-type" epithelium only (6,15) and the rest of 19 polyps were considered adenomas with foci of adenocarcinoma in 11 polyps (5 invasive, 6 focal and superficial). Several studies have shown hyperproliferative and cell-cycle abnormalities in BE- associated flat dysplasia that precede the development of malignancy. Thurberg et al performed immunohistochemical and molecular study of five cases of polypoid dysplasia in BE (3). The cases were immunostained for MIB-1 and p53 and genotyped for loss of heterozygosity (LOH) at the adenomatous polyposis coli (APC) locus. All polyps showed increased cell proliferation in the form of surface MIB-1 staining and showed positive p53 staining. Three of 3 informative cases showed LOH at the APC locus in the dysplastic epithelium and in areas of adenocarcinoma. All 5 flat dysplasia controls also showed surface MIB-1 staining and p53 positivity, and 3 of 3 informative controls showed LOH for APC. None of the nondysplastic controls showed any of these findings. Thus suggesting that a similar molecular pathogenic pathway probably occurs for both flat and polypoid dysplasia.

Our patient had a large adenomatous polyp resembling a tubulovillous colon polyp with foci of intestinal metaplasia, high grade dysplasia (HGD) and intramucosal carcinoma.

Of 21 patients with adenomas, 16 underwent esophagectomy. Two patients had polypectomy and 2 declined therapy. One patient died 45 days postoperatively from complications related to anastomotic dehiscence, and others were alive from 2 months to 6 years later. Our patient underwent polypectomy because of high surgical risk for esophagectomy. Additionally, patient declined invasive options including complete BE eradication endoscopic mucosal resection.

In our review, out of 22 cases (our patient and 21 previously reported) of BE-associated dysplasia described, all except 1 (95%) had HGD or adenocarcinoma. Flat dysplasia was reported in the adjacent BE in13 cases, however, not all previously reported cases commented on the presence or absence of dysplasia. Biopsy of adjacent BE in our patient did not show dysplasia, however, polypoid lesion showed HGD. Visible lesions in the setting of HGD are more at risk for harboring occult cancer than flat dysplasia (16). Furthermore, the type of lesion is correlated with risk of submucosal invasion (Table 2). Protruding or depressed lesions are at higher risk than those slightly raised or flat areas (17,18). These observation are comparable in some ways to that of dysplasia associated lesion or mass (DALM) in patients with colitis associated dysplasia (Table 3).

Table 2. — **Relative risk of submucosal invasion associated with endoscopic appearance of esophageal lesions in Barrett's esophagus**

Endoscopic appearance	Relative risk of submucosal invasion
Polypoid	Higher
Sessile	Higher
Slightly raised	Low
Flat	Low
Slightly depressed	Higher
Excavated	Very high

EUS with or without fine-needle aspiration (FNA) cytology is a reasonable procedure in patients with polypoid lesion in the setting of BE because of higher risk of occult cancer. Any patient found with lymph node involvement should be referred for esophagectomy. However, EUS is not optimal for differentiation between intramucosal cancer and submucosal cancer in patients with flat HGD (19). Endoscopic mucosal resection (EMR) is better suited for depth staging in this setting. One of the advantages of EMR specimens is that pathologists are better able to stage lesions because they provide large and intact pathological specimens.

Patients with BE who are most likely to benefit from endoscopic eradication therapy are those with esophageal adenocarcinoma (EAC) limited to the mucosa and those with HGD. Esophagectomy has traditionally been the primary treatment in patients with HGD because of high reported prevalence of coexisting EAC (up to 40% in some surgical series) and a high risk of progression of HGD to cancer (20). However, a recent systematic review showed a 12.7% prevalence of invasive EAC among patients undergoing esophagectomy for HGD ; this prevalence was lower than previous estimates (16). There is now acceptance of endoscopic therapy for HGD and intramucosal carcinoma, and esophagectomy is no longer standard of care (21). Endoscopic modalities include tissue acquiring therapies that include focal EMR, complete Barrett's EMR, and endoscopic submucosal dissection. Tissue acquiring modalities are important to stage a polypoid or visible lesion in the setting of HGD or for treatment of intramucosal carcinoma. HGD might also be treated with ablative therapies, such as photodynamic therapy, which has the longest experience of the ablative therapies, radiofrequency ablation, which has demonstrated initial success, and cryoablation, which is a newer therapy (21).

Table 3. — **Clinical characteristics of different type's dysplasia in patients with inflammatory bowel disease and Barrett's esophagus**

Type of dysplasia*	Inflammatory Bowel Disease			Barrett's Esophagus		
	Endoscopic appearance	Risk of cancer	Management	Endoscopic appearance	Risk of invasive cancer	Management
DALM, adenoma-like	Circumscribed polypoid lesion, pedunculated or sessile,, in (previously) inflamed areas of the colonic mucosa	Low	Local excision or colectomy, depending on degree of dysplasia and presence of multifocal flat dysplasia	Polypoid lesions, sessile or pedunculated	High	EUS for staging, if no lymph node involvement then staging endoscopic mucosal resection
DALM, non-adenoma like	Irregular, diffuse masses or plaque-like lesions in active or previously inflamed areas of colonic mucosa	High	Colectomy	Slightly raised or depressed, flat, excavated	Low to high	EUS for staging, if no lymph node involvement then staging endoscopic mucosal resection
LGD in flat mucosa	No gross abnormality	Moderate	Intensification of surveillance of colectomy	No gross abnormality	Low	Endoscopic surveillance twice the first yr and annually thereafter
HGD in flat mucosa	No gross abnormality	Moderate to high	Colectomy	No gross abnormality	High	Staging endoscopic mucosal resection

* Confirmation by 2 expert pathologists.
DALM : dysplasia associated lesion or mass ; HGD : high grade dysplasia ; LGD : low grade dysplasia : EUS : endoscopic ultrasound.

Endoscopic ablation has emerged in recent years and there are ongoing trials combining EMR and endoscopic ablative therapy. Two forms of endoscopic ablation are available : radiofrequency ablation (RFA) and spray cryotherapy. In a recent randomized, sham-controlled trial, RFA completely eradicated intestinal metaplasia in 74% of patients with HGD at 12 months (22). Recently 2 retrospective, multicenter cohort studies evaluated the efficacy and safety of spray cryotherapy for esophageal cancer and Barrett's esophagus with HGD (23,24). Both trials reported a high success rate in eradicating esophageal cancer and HGD (61% to 97%) ; however, both studies were limited by short-term follow-up (mean follow-up 10.5 months. Failure to eradicate intestinal metaplasia either superficial or beneath the neosquamous epithelium ("buried glands") is an issue with ablative therapies (23,24). Ablative therapies are procedures with low mortality compared with esophagectomy ; however, the long-term follow-up data after cryoablation or RFA is not yet available. EMR can both be potentially curative and diagnostic because deeper layers of Barrett's tissue can be staged. Results of ongoing trials combining EMR and endoscopic ablative therapies are awaited.

Conclusions

In conclusion, polypoid and flat dysplastic lesions in BE have similar clinical, pathological, and molecular features. Polypoid dysplastic lesions are usually associated with flat dysplasia and invasive adenocarcinoma. Pathogenetic pathway of carcinogenesis appears similar to that in non-polypoid dysplastic epithelium. EUS should be used to stage polypoid dysplasia and esophagectomy should be considered as treatment of choice for patients with lymph node involvement or invasive cancer. Endoscopic resection is the gold standard for HGD and intramucosal carcinoma.

References

1. HAGGITT R. Barrett's esophagus, dysplasia and adenocarcinoma. *Hum. Pathol*., 1994, **25** : 982-993.
2. HAMEETEMAN W., TYTGAT G., HOUTHOFT H. *et al*. Barrett's esophagus : Development of dysplasia and adenocarcinoma. *Gastroenterology*, 1989, **96** : 1249-56.
3. THURBERG B.L., DURAY P.H., ODZE R.D. Polypoid dysplasia in Barrett's esophagus : A clinicopathologic, immunohistochemical and molecular study of 5 cases. *Hum. Pathol*., 1999, **30** : 745-752.
4. ARNOLD G.L., MARDINI H.E. Barrett's esophagus – associated polypoid dysplasia : A case report and review of the literature. *Digest. Dis. Sci*., 2002, **47** : 1897-1900.
5. CAVANAUGH D.G., CRANDALL L.D., HARRISON L.P., LAYER J.H., WAITS R.K. Jr. Malignant gastroesophageal polyp : A case report. *Wisc. Med. J*., 1995, **94** : 443-445.
6. KALSBEEK H.L., VAN DER WOUDEN A. Barrett's esophagus with papillomatous tumor. *Arch Chir Neerl*, 1971, **23** : 287-296.
7. LEE R.G. Dysplasia in Barrett's esophagus. *Am. J. Surg. Pathol*., 1985, **9** : 845-852.
8. MC DONALD G.B., BRAND D.L., THORNING D.R. Multiple adenomatous neoplasms arising in columnar – lined (Barrett's) esophagus. *Gastro - enterology*, 1977, **72** : 1317-21.
9. STILLMAN A.E., SELWYN J.I. Primary adenocarcinoma of esophagus arising in a columnar lined esophagus. *Am. J. Dig. Dis*., 1975, **20** : 577-582 ?
10. THOMPSON J.J., ZINSSER K.R., ENTERLINE H.T. Barrett's esophagus and adenocarcinoma of the esophagus and gastroesophageal junction. *Hum. Pathol*., 1983, **14** : 42-61.
11. PARAF F., FLEJOU J.-F., POTET F., MOLAS G., FEKETE F. Adenoma arising in Barrett's esophagus with adenocarcinoma. *Path. Res. Pract*., 1992, **188** : 1028-32.
12. KEEFE E.B., HISKEN E.C., SCHEBERT F. Adenomatous polyp arising in Barrett's esophagus. *J. Clin. Gastroenterol*., 1986, **8** : 271-274.
13. WONG W.M., SHEK T.W-H., CHAN C.-K., LAI K.C. Gastrointestinal : villous adenoma of the esophagus. *J. Gastroenterol. Hepatol*., 2004, **19** : 1213.

14. LEE R.G. Adenoma arising in Barrett's esophagus. *Am. J. Clin. Pathol*., 1986, **85** : 629-632.
15. WOLFSEN H.C. Polypoid Barrett's high-grade dysplasia in a patient with familial adenomatous polyposis : A unique association. *Endoscopy*, 2005, **37** : 280.
16. KONDA V.J., ROSS A.S., FERGUSON M.K., HART J.A., LIN S., NAYLOR K., NORTSINGER A., POSNER M.C., DYE C., CISLO B., STEARNS L., WAXMAN I. Is the risk of concomitant invasive esophageal cancer in high grade dysplasia in Barrett's esophagus overestimated ? *Clin. Gastroenterol. Hepatol*., 2008, **6** : 159-64.
17. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. *Endoscopy*, 2005, **37** : 570-578.
18. PETERS F.P., BRAKENHOFF K.P., CURVERS W.L., ROSMOLEN W.D., FOCKENS P., TEN KATE F.J., KRISHNADATH K.K., BERGMAN J.J. Histologic evaluation of resection specimens obtained at 293 endoscopic resections in Barrett's esophagus. *Gastrointest. Endosc*., 2008, **67** : 604-609.
19. YOUNG P.E., GENTRY A.B., ACOSTA R.D., GREENWALD B.D., RIDDLE M. Endoscopic ultrasound does not accurately stage early adenoacrcinoma or high grade dysplasia of the esophagus. *Clin. Gastroenterol. Hepatol*., 2010, **8** : 1037-1041.
20. HEITMILLER R.F., REDMOND M., HAMILTON S.R. Barrett's esophagus with high-grade dysplasia : an indication for prophylactic esophagectomy. *Ann. Surg*., 1996, **224** : 66-71.
21. SHARMA P. Barrett's esophagus. *N Engl J Med*, 2009, **361** : 2548-56.
22. SHAHEEN N.J., SHARMA P., OVERHOLT B.F. *et al*. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N. Engl. J. Med*., 2009, **360** : 2277-88.
23. GREENWALD B.D., DUMOT J.A., ABRAMS J.A. *et al*. Endoscopic spray cryotherapy for esophageal cancer : safety and efficacy. *Gastrointest. Endosc*., 2010, **71** : 686-93.
24. SHAHEEN N.J., GREENWALD B.D., PEERY A.F. *et al*. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high grade dysplasia. *Gastrointest. Endosc*., 2010, **71** : 680-685.