Original article

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NEW CLASSIFICATION AND DIAGNOSIS OF APPENDICEAL CARCINOID TUMORS

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Carcinoid tumours are rare lesions that belong to the APUDoma category having the capacity of Amine Precursor Uptake and Decarboxylase. Gastrointestinal system comprises 90% of all carcinoids in the body and they are the most common type of primary malignant lesions of the appendix. New WHO classification of gastrointestinal carcinoids, diagnostic dilemmas of some carcinoid variants and, sometimes unpredictable prognosis are the reasons for the following study: clinical, macro- and microscopical as well as cytochemical and immunocytochemical examination of the vermiform appendix carcinoids, surgically removed from 16 patients. The appendectomy was induced by acute appendicitis or tumorous mass, without carcinoid syndrome. After two-day fixation in 10% formaldehyde, routinelly processed and embedded in paraffin, laboratory sections were stained with H&E, Fontana-Masson's, Grimelius', FIF and AB-PAS methods. ABC method has been used for immunohistochemical examination. The antibodies for Chromogranin A, NSE, Synaptophysin, Cytokeratin 7, S-100 protein, Ki67 and CEA (primary antibodies) and ABC (secondary antibody) (Dako Kopenhagen) were tested. The patients had no carcinoid syndrome. The most frequent was classic appendiceal carcinoid, well differentiated - NETG1 (8 cases), without metastases; goblet cell carcinoids were rare (3 cases), one case with liver metastases. The second case of goblet cell carcinoid was associated with cystadenoma papillare mucinosum, complicated by pseudomixoma peritonei and the third case was limited only to appendiceal wall. The patient with liver metastases died five months after appendectomy. The patient with goblet cell carcinoid associated with papillary mucinous cystadenoma and complicated by pseudomixoma peritonei had re-operation with both partial cecal and right ovarial resection, associated with washing the peritoneal cavity. The patient was feeling well during six years from the second operation. Based on our results, we have concluded that: the prognosis of the appendiceal carcinoids depends on the stage of the disease in which the carcinoid was discovered; classic carcinoids had the best prognosis, as well as argentaffin and argyrophyl positive characteristics; goblet cell carcinoids have amphicrine characteristics: AB-PAS and argyrophil positive granules, but often, the granules are weakly or argentaffin negative. Tubular carcinoid must be differentiated immunohistochemically from metastatic adenocarcinoma that have the worse prognosis than these carcinoids. *Acta Medica Medianae 2012; 51(1):24-30.*

Key words: *appendiceal carcinoid classification, diagnosis*

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Introduction

Name "carcinoid", was introduced by Obendorfer (1907) for the intestinal tumours which are less agressive than carcinomas and more agressive than the intestinal adenomas (1). Carcinoid tumors of the gastrointestinal tract belong to well-differentiated (G1) neuroendocrine tumors (NET) (2,3). They originate from the enterochromaffin (EC) cells (Figure 1), interspersed throughout the entire gastrointestinal mucosa, forming the largest endocrine cell population in the gastrointestinal system (1-10). The EC cells were also the first gut endocrine cells to be identified (1,2). They were shown to bind chromiun salts and were therefore called " enterochromaffin cells" (1,2). Later, their capacity to bind and reduces silver ions was demonstrated and they were also named "argentaffin cells" (12). Their function was unknown for a long period. However, an endocrine function was early suggested by Feyrter, who proposed a "diffuse neuroendocrine system" in the gut (13). With the introduction of the formaldehyde-induced fluorescence technique, gut endocrine cells were shown to be able to synthesize monoamines, a capacity recognized as APUD (Amine Precursor Uptake and Decarboxy-lation) (2,13). Their argirophyl property, proved by

cytochemical Grimelius' reaction is based on the presence of deposited polypeptide hormones in the cytoplasmic granules, beneath the nucleus (4,5,13). The main secretory product of EC cells is serotonin and the EC cells account for more than 90% of all serotonin synthesized in the body (8,12). Inactivation of serotonine is accomplished by enzymatic degradation (monoamine oxidase-MAO) in the liver and lung, followed by excretion in the urine as the main metabolite 5-hydroxy-indolacetic acid (5-HIAA). Secreted serotonin may influence adjacent cells by a paracrine action or reach distant cells via the circulation (8). Minor amounts of peptide hormones, e.g. tachykinins, enkephalins, motilin, substance P and PP/ PY may also be synthesized in subsets of EC cells (2-12). Physiologically, both serotonin and tachykinins have similar effects on the gastrointestinal tract, i.e. smooth muscle contraction, local vasodilation and secretion water and electrolytes. Certain stimuli from the lumen (acid pH, aminoacids, hypertonic glucose) and noxious stimuli (such as alcohol) and food containing tyramine (nuts, bananas, chocolate) can cause the release of serotonin which evokes adequate mucosal responses like hyperemia, secretion and peristalsis (8).

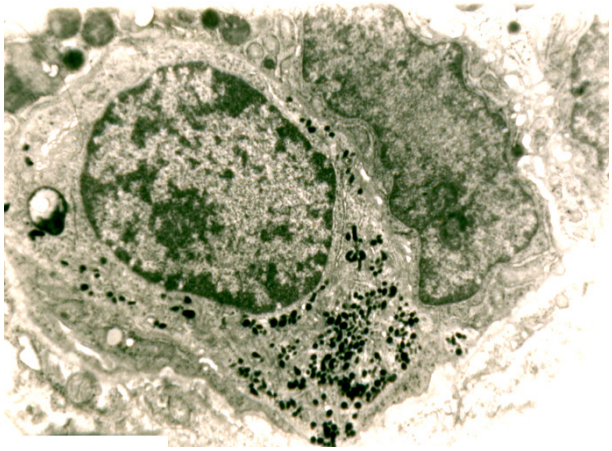

Figure 1. Ultrastructural features of EC cell

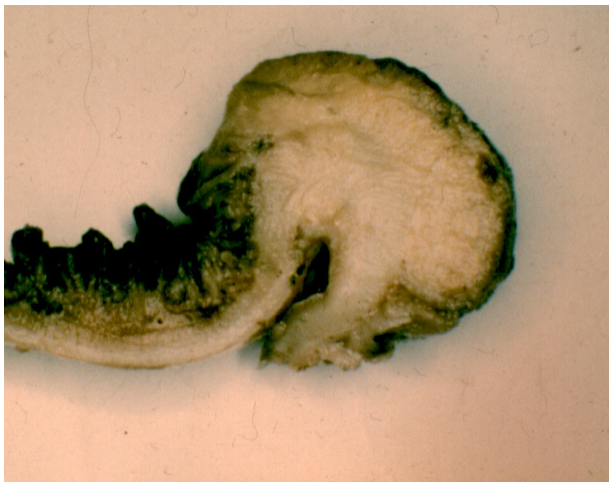

Figure 2. Macroscopical pattern of carcinoid

The new World Health Organization (WHO) classificatio has clarified a number of dilemmas and contradictions, not only in NETs, but also in the domain of carcinoid tumours of the appendix (2). Namely, the carcinoids because of low malignant potential, cellular and nuclear monomorphism were classified as differentiated neuroendocrine tumors, i.e. the NET G1 (Table 1) (2). Increased synthesis or decreased degradation of serotonin induces numerous symptoms in the form of attacks, known as "carcinoid syndrome". However, carcinoid syndrome is rarely manifested in patients with this tumor in the appendix (3-10). Owing to this fact, carcinoid of the appendix are clinically silent for months and possibly years, with sudden appearance of the symptoms of the abdominal cramps, with the attendant appendectomy. In addition, difficult histopathological differentiation of both goblet cell and micoglandular appendiceal carcinoids from metastatic adenocarcinoma and from poorly cohesive signet ring cell carcinoma could explain the constant challenges in the study of carcinoid tumours of the appendix (11–24).

Aim

A retrospective study of clinical, morpho-logical, citohemical and immunocytochemical characteristics of the appendiceal carcinoids.

Material and methods

We analyzed 16 surgical biopsies of the appendix after appendectomy for clinical diagnosis of "acute appendicitis" or "tumoroid appendiceal mass". Five to eight longitudinal slices from the basal, middle and distal segments were taken from each appendix. Taken surgical biopsies were fixed during 24 to 48h (only for FIF metrod) in 10% formaldehyde solution. Fixation in Bouin solution was done only for staining with argiropgylic reaction. Treatment of fixed material was performed in autotechnicon - of Institute of Pathology, Sava Surgery and Human Policlinic in Niš. Paraffin sections of thickness 4/μm were stained with the following methods: conventional H & E technique for histopathologic diagnosis of the present process; Formaldehyde-Induced Fluore-scence (FIF), a specific method for detecting of deposited biogenic amines (serotonin) in tumour carcinoid cells, as well as in the stem EC endocrine cells. The serotonin showed yellow fluorescence in fluorescent microscope; the argentaffine cytochemical reaction (Fontanna-Masson) was based on the properties of serotonin to reduce the silver present in the solution. The reaction is positive if the cytoplasm of carcinoid tumor cells contain deep brown to black granules; Argirophyl method (Grimelius), when the deposited granule were stained in brown color, verified most of the polypeptides, deposited in the cytoplasm of carcinoids.With the development and synthesis of antibodies to chromogranin A, it has become the most important marker for immunocytochemical

carcinoid detection and almost all tumors that origin from neuroendocrine cells. Other immunocytochemical markers for these tumors were also tested: NSE (neuron-specific enolase) synaptophysin, Ki-67, cyrokeratin 7, CEA and S-100, using immunocytochemical ABC (avidin-biotin complex) method. Antibodies were purchased from the manufacturer DAKO (Denmark). Clinical and histopathological results were statistically analyzed and presented in Table 4.

Results

Clinical: Of the 16 patients with tumors of the appendix, incidentally, the carcinoid tumor was detected in 13 patients, after appendectomy, caused by acute appendicitis. Three patients were operated on because of "tumoroid formation" in the appendix. Carcinoid was found more frequently in females than in males (9:7), while the age of patients ranged from 8-69 years. The average age of women was 30.5 years and of men 40.1 years (Table 2).

Localization of " tumour mass" was in 80% in the distal segment, in 14% in the middle segment and the rarest localization (6%) was in the area of the base of the appendix (Table 2).

All patients had no symptoms of carcinoid syndrome, including one patient with liver metastasis. (Table 2). Statistical data associated with with age, sex, standard deviation, average values are shown in Table 4.

Macroscopic appearance: Carcinoid tumour of the appendix was usually presented as a gray-white or gray-yellowish nodules clearly limited, but without the capsule, of submucous localization (Figure 2), stenosing and sometimes filling its entire lumen. Because of infiltrative growth, the wall was partially or completely thickened and of firm consistency. In the largest diameter, the size ranged between 5 and 22mm, localized at the top of appendix. Out of the 16 patients, only one patient with goblet cell carcinoid (24 year-old) had metastasis in the abdominal cavity and in the liver, but without carcinoid syndrome. The remaining two patients with the same type of carcinoid had no regional limph node metastases. However, the patient with goblet cell carcinoid of the basal localization, 7 mm in diameter, associated with papillary mucinous cistadenoma and flegmonous appendicitis, complicated by perforation, had secondary peritoneal pseudomixoma, localized around the cecum and right ovary. During the reoperation, a partial resection of the cecum and right ovary was performed. Today, after five years from the last operation, the patient is healthy, with negative clinical findings in the right lower abdomen. The third patient with goblet cell carcinoid had wided lumen of the appendix and dense glassy mucus (mukocela) and submucous tumor 8 mm in diameter of basal localization, associated with rectal tubular adenoma with dysplasia of grade I.

Table 1. Neuroendocrine neoplasma of the appendix WHO 2010 (Solcia et al.)

Neuroendocrine tumors (NET)
NET G1 (Carcinoid)
NET G2
Neuroendocrine tumors (NEC)
Large cell NEC
Small cell NEC
Mixed adenoneuroendocrine carcinomas (MANEC)
EC cell, serotonin-producing NET
Goblet cell carcinoid
L cell, glucagon-like producing and PP/PZZ-producing NET
Tubular carcinoid

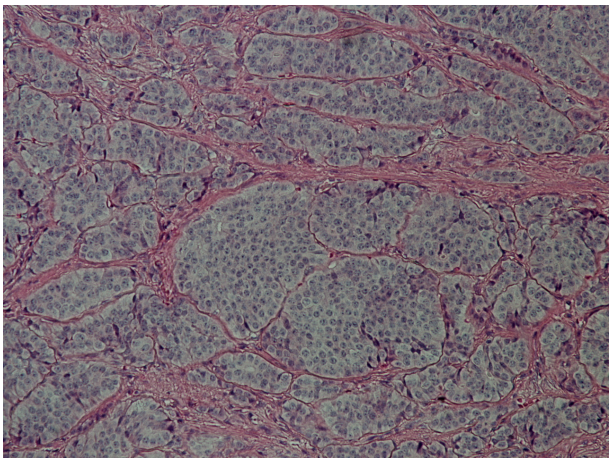

Figure 3. Hystological characteristics of classic carcinoid variant HE x 300

Histopathological, cytochemical and immunocitochemical features: Of the 16 carcinoids, the most common is a classic, well-differentiated variant (8 patients), making 50% of all carcinoids. The tumour cells were arranged in rounded solid nests, or glandular formations, forming a tubular or acinar pattern, surrounded by a thin or rich collagen or hyalin stroma. Tumour cells were uniform, with little or no pleomorphism or mitotic activity (Figure 3) and a Ki67 proliferative index of < 2%, thus mostly belonging to the G1 class. Most of EC cell carcinoids displayed invasion of the muscular wall and subserosal/mesoappendiceal fatty tissue was infiltrated only in one case, but without lymphatic or perineural invasion. The cytoplasm of cells was clear or a bright pink. Cytochemically, serotonin was stained by Fontana-Masson (Figure.4) and peptide hormones by Grimelius (Figure 5) and by chromogranin A (Figure 6). Serotonin presented yellow in the fluorescent microscope (Figure 7); intensity of the color depends on its amount, deposited in the cytoplasm. Tubular carcinoid was a rarer finding of classic carcinoids, with no metastases, i.e. with good prognosis. It was composed of small, discrete tubules, some with inspissated mucin in their lumen. Short trabecular structures also were found,

Table 2. Clinical characterisitcs

Sex	Number	Age (average years)	Localization	Metastazis	Associated with tumours
F M	9 7	30.5 40.1	Distal seg. 80% Mid. seg. 14% Basal. Seg. 6%	1 (in liver)	Mucinous cystadenoma (1) Rectal adenoma (1)

Table 3. Classification of histochemical characteristics

1.	C Type (8)	Grimelius and Chromogranin +; Masson and FIF +: AB-PAS -
2.	Tubular Type (5)	Grimelius and Chromogranin A +, Masson and FIF +; AB-PAS –
3.	Amphycrine (3)	Goblet cell I + Classic carcinoid: Grimelius and Chromogranin +, Masson and FIF - , AB-PAS +

Table 4. Statistical data

	Group	Number	Minimum	Maximum	Average value	Standard deviation
1.	Female	9	8.00	65.00	30.2222	19.11006
2.	Male	7	18.00	69.00	40.0000	19.92486

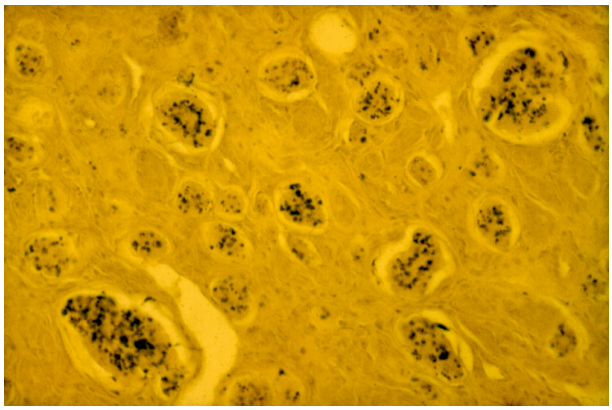

Figure 4. Argentophine reaction of serotonine (Fontana-Masson x 300)

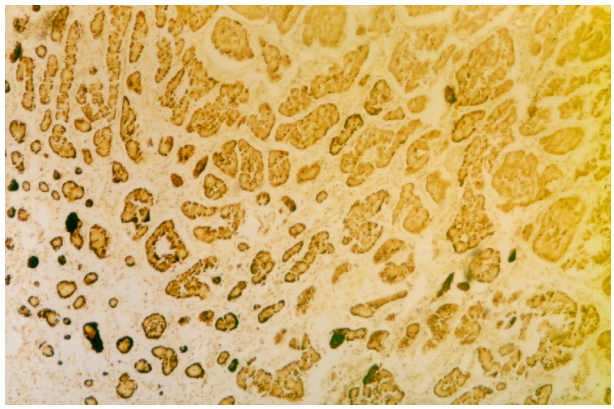

Figure 5. Argirophil reaction of depozited peptide hormones (Grimelius x 200)

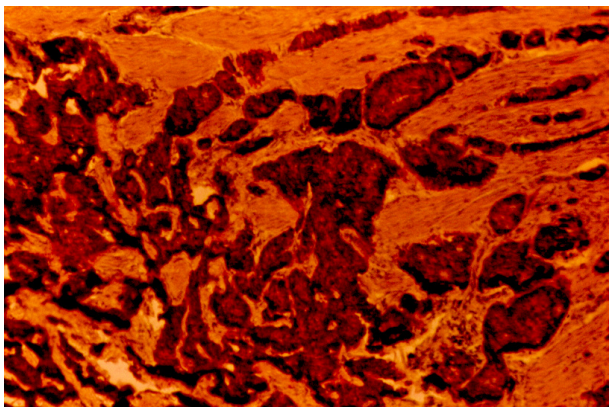

Figure 6. Intensive imunohistochemical cytoplasmatic expression of Chromogranine A (ABC x 250)

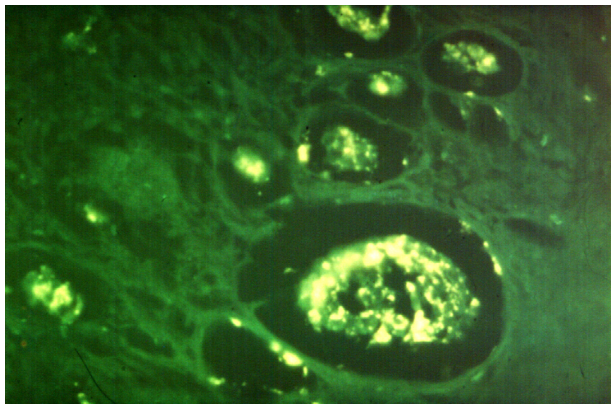

Figure 7. Intensive fluorescenc of serotone, yellow color (FIF x 250)

but the solid nests were absent, as well as both cytological abnormalities and mitoses. Tubular carcinoids were chromogranin A, Grimelius and Fontana-Masson positive tumours. The rarest carcinoid variant (3 patients) was goblet cell variant. It was characterized by predominantly submucous growth, tipically infiltrating the appendiceal wall in a concentric manner, thus producing an ill-defined tumour mass. The tumour was composed of small, rounded nests of signet ring-like cells, resembling normal intestinal goblet cells. The cells showed mild atypia and low mitotic activity with a Ki67 proliferation index (<10%). Mucin staining was intensely positive within goblet cells and extracellular mucin pools. Immunohistochemically, the endocrine-cell compo-

nent was positive for chromogranin A, but rare cells were weakly positive to serotonin, indicating a minimum of serotonin synthesis. Cytokeratin 7 expression (typical of signet ring cell, very agressive, carcinoma) was negative.

Discussion

The carcinoid tumor of the appendix is one of the most common single presentations of this type of tumor and is thereby the most common type of primary malignant lesions of the appendix (2,3). These tumors are often asymptomatic and found by chance during appendectomy or other abdominal operations. The clinical presentation resembled the symptoms of acute appendicitis in almost all cases. They are found in 0.3-0.9% of patients undergoing appendectomy (6), or in one to two cases per 1.000.000 people, or in much higher incidence, including both surgical specimens and autopsies-8.4 cases per 100.000 people (11). The incidence of nodal or liver metastases varies with the size of the primary tumor and it is 20% to 30% in primary tumors less than 1 cm. The incidence increases to 80% for nodal and 50% for liver metastases with tumors greater than 2 cm (11), which was also confirmed by our results. The predominance of female patients is usual in our results – nine to seven. The mean age of this study was 30.5 for female and 40.1 for male, which is lower than in large epidemiological studies (2-8). The younger patients in our results could be explained by very rare sending the appendices (after appendectomy) for pathological analysis with clinical symptoms of acute appendicitis in the old patients.

The second variant of appendiceal carcinoids is goblet cell carcinoid, an enigmatic and rare tumor involving the appendix almost exclusively. The tumor is thought to arise from pluripotent intestinal epithelial crypt-base stem cells by dual neuro-endocrine and mucinous differentiation. We have confirmed worse prognosis of goblet cell carcinoid because one of our three patients had peritoneal and liver metastases and has died some months later. The second patient had at the same time cystadenoma and periappendiceal pseudo-mixoma peritonei. The third patient had enlarged and distended appendix, sausage-shaped, measuring 88mm (longitudinal axis) x 22mm (width). Carcinoid of 16mm diameter was found in the proximal region of the appendix. Its lumen was filled with dense, gellatinous mucus. The present pseudodiverticulum is probably an adjunct to the proximal partial obstruction of the appendiceal lumen by the carcinoid.

Tubular type is also rare carcinoid variant, resembling the metastatic adenocarcinoma. However, its submucous typical glandular structures, covered by monomorph cells, as well as the absence of mitotic activity, are the important characteristics of tubular carcinoid.

Metabolic tumor markers

Carcinoid tumors, like other APUD tumors, contain proteins and release hormones which are metabolized and excreted. Neurosecretory granules within the carcinoid tumor release serotonin that is metabolized into 5-Hiaa and excreted in the urine. In addition, chromogranin A (CgA) has been identified as being contained in the neurosecretory vesicles of neuroendocrine tumor cells and is detectable in the plasma of patients with carcinoid tumors and other peptide hormone-producing tumors (2,3,11). The diagnosis of EC cell and tubular carcinoids is easy and based on serotonin and peptide-hormone in carcinoid cells. Both histochemical and immunohistochemical features of these variants of appendiceal carcinoids are shown in Table 3. The rare, goblet cell variant is more aggressive than classic, resembling the signet ring cell carcinoma, not only histologically, but also immunohistochemically showing strong cytokeratin 7 expression, that we have found in the literature (24-25). Having in the mind that cytokeratin 7 is specific marker for poorly cohesive carcinoma (signet ring cell carcinoma) (WHO, 2010), probably is the mistaken interpretation of the obtained results. Because of that, we pointed out that: histologically, goblet cell carcinoids form insular, trabecular or microglandular structures that are rare and surrounded by dense colagenous stroma; the goblet cells and nuclei are small-sized and typical, without mitotic activity. In contrast, signet ring carcinoma has diffuse structure, with high mitotic activity and atypical nuclei. However, the most important feature of goblet cell carcinoids is its amphicrine histogenesis, which means that goblet cells synthesize mucins and polipeptide hormones, confirmed by AB-PAS and chromo-granine A positive reactions. We also observed that a few neuroendocrine cells, and in small quantity, produce serotonin explaining us the absence of carcinoid syndrome in the patient with metastases in the liver.

Regarding survival, our study confirms that rates for carcinoid tumors are generally favorable, but they vary by tumor size (larger than 2 cm in diameter) and histological variants; however, the most important prognostic factor is the stage of the disease (2–10, 15). The indications for surgical re-intervention are also well known: (1) all lesions larger than 2 cm in diameter, (2) histological evidence of mesoappendiceal extension, (3) timorous at the base of the appendix with positive margins or involvement of the cecum, (4) high grade malignant carcinoids and (5) goblet cell carcinoids.

Conclusion

l. Carcinoid tumor of the appendix, most often present as acute appendicitis.

2. It also emphasizes the value of histo-pathological analysis of every removed appendix.

3. Diagnosis of carcinoid tumors is based on: histological, histochemical and immuno-histochemical results.

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OSVRT NA NOVA SAZNANJA O KARCINOIDNIM TUMORIMA APENDIKSA

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Karcinoidni tumori su retke lezije koje pripadaju grupi APUD-oma jer imaju sposobnost da preuzimaju i dekarboksilišu amino prekursore (Amine Precursor Uptake and Decarboxylase). Oko 90% svih karcinoidnih tumora javlja se u gastrointestinalnom sistemu i najčešći su tip primarnih malignih lezija u apendiksu. Nova klasifikacija gastrointestinalnih karcinoida data od strane SZO, dijagnostičke dileme kod nekih varijanti karcinoida i ponekad nepredvidivi tok razlozi su za analizu savremenih aspekata karcinoidnih tumora apendiksa i prikaz serije slučaja. Serija obuhvata 16 bolesnika sa hirurški otklonjenim verifornim karcinoidom apendiksa, koji su makroskopski, mikroskopski, citohemijski i imunohemijski analizirani. Apendektomija je bila indikovana akutnim apendicitisom ili tumorskom masom bez prisustva karcinoidnog sindroma. Nakon dva dana fiksacije u 10% rastvoru formaldehida, parafinski kalupi su sečeni i bojeni sa hematoksilin eozinom, Fontana-Masson, Grimelius, FIF i AB-PAS metodama. Imunohistohemijsko bojenje vršeno je ABC metodom. Korišćena su antitela na hromogranin A, NSE, Sinaptofizin, Citokeratin 7, S-100 protein (primarna antitela) i ABC (sekundarna antitela) (Dako Kopenhagen). Bolesnici nisu imali razvijenu sliku karcinoidnog sindroma. Najčešće je otkrivan klasičan apendiksni karcinoid koji je dobro diferentovan - NETG1 (9 bolesnika) bez metastaza. Goblet cell karcinoidi su bili ređi nalaz (3 bolesnika), od kojih je jedan imao metastazne promene u jetri; jedan bolesnik je imao udruženi cystadenoma papillare mucinosum, komplikovan sa pseudomiksomom peritoneuma i kod trećeg bolesnika tumor je bio ograničen u zidu apendiksa. Bolesnik sa hepatičnim metastazama imao je petomesečno preživljavanje nakon apendektomije. Kod bolesnika sa karcinoidom udruženim sa papilarnim mucinoznim cistadenomom i pseudomiksomom peritoneuma izvršena je reoperacija sa parcijalnom resekcijom cekuma i desnog jajnika i lavažom peritonealne duplje. Kod ovog bolesnika održava se dobro opšte stanje 6 godina nakon reintervencije.

Na osnovu prikazane serije bolesnika može se zaključiti da prognoza apendiksnih karcinoida zavisi od stadijuma bolesti na otkrivanju. Klasični karcinoidi koji mogu imati i argentafine i argirofilne karakteristike imaju najbolju prognozu. Goblet cell karcinoidi imaju amfikrine karakteristike: AB-PAS i argirofilno pozitivne granule, koje se ponekad mogu prikazati i kao argentafino negativne. Tubularni karcinoidi moraju se imunohistohemijski diferencirati od metastatskih adenokarcinoma koji imaju goru prognozu u odnosu na karcinoide. *Acta Medica Medianae 2012;51(1):24-30.*

***Ključne reči**: karcinoid apendiksa, klasifikacija, dijagnostika*