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Carcinoid tumor of the appendix during pregnancy. A rare case and a review of the literature

M. Pitiakoudis[1], M. Kirmanidis[1], A. Tsaroucha[1], E. Christianakis[2], D. Filippou[2,3], E. Sivridis[1], C. Simopoulos[1]

[1]2nd Surgical Department, Medical School, University of Thrace, Alexandroupolis; [2]1st Department of General Surgery, "Tzaneio" General Hospital, Piraeus; [3]Department of Anatomy, Nursing Faculty, University of Athens, Athens, Greece

Summary

We present a rare case of a carcinoid tumor of the appendix that was diagnosed during pregnancy in a 24-year-old female. The patient was admitted to our department for acute abdominal pain localized on the right half of the abdomen, mimicking acute appendicitis. Open appendectomy was carried out and at the histological examination carcinoid was found in the surgical specimen. Only few similar cases were found in the literature reporting appendiceal carcinoid tumor during pregnancy.

Key words: acute appendicitis, carcinoid, pregnancy

Introduction

Carcinoids are derived from primitive stem cells located in the intestinal wall. As Broaddus et al. [1], Moraes et al. [2], Soga et al. [3] and Piura et al. [4] have reported, carcinoid tumors can be found in different organs [1] including the lungs [2], mediastinum, thymus [3] liver, pancreas and ovaries [4]. Carcinoid tumors of the appendix are the most common [5,6]. Doede et al. found 0.169% carcinoid tumors in 4747 appendectomies [7].

Considering that carcinoids are rare and that many authors have tried to establish some kind of treatment for this neoplasm, it is interesting to study this condition in the rare case of its occurrence during pregnancy.

Case presentation

A 24-year-old pregnant woman (32nd week) presented at our emergency room with symptoms of acute appendicitis. The patient was complaining of vomiting and pain on the right iliac fossa. On physical examination there was tenderness in the right abdomen and rebound in the right paraumbilical region. On auscultation the bowel sounds were normal. Arterial blood pressure was 105/80 mm Hg, and the heart rate 79 bpm. The patient's temperature was 36.9° C. From the blood analysis hematocrit was 29.1%, white blood cells 15,200/ml, with a neutrophils prevalence (85.2%).

Gynecological examination showed no abnormal findings. A live fetus of about 33 weeks and 3 days with normal amniotic fluid was seen on ultrasound. The fetal weight was 1862 g, the fetus presented cephalic prominence, the placenta was in the posterior uterine wall and the non stress test (NST) was reactive. The dilatation was about 1 cm, just like a multi-gravida.

An enlarged McBurney incision was performed. The appendix was inflammatory, especially on its peripheral part. A typical appendectomy was performed. The resected specimen was about 7×1 cm. Histological examination of the resected appendix revealed carcinoid, 0.5 cm in diameter, on the tip of the appendix. The tumor was consisted of small uniform neoplastic cells

Correspondence to: Dimitrios K. Filippou, MD, PhD. 14 Agias Eirinis Street, 11146 Galatsi, Athens, Greece. Tel: + 30 6944 287125, Fax: + 30 210 2220892, E-mail: d_filippou@hotmail.com

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that were arranged in islet formations and infiltrated few areas of the muscular layer. The mitotic activity was insignificant. There was a coexisting acute appendicitis and periappendicitis (Figure 1).

The postoperative period was uncomplicated and the patient was discharged on the 12th postoperative day with no clinical symptoms and with good laboratory exams. The patient had a normal delivery at the 39th week of gestation. The infant's weight and height were 3300 g and 50 cm, respectively.

Discussion

The first case of carcinoid tumor of the appendix was officially reported by Beger in 1882 [8,9]. Appendiceal carcinoid is a special Kultschitzky-cell carcinoma and differs from the rest of the carcinoids found throughout the gastrointestinal track. It is considered to compose 32-57% of all the appendiceal tumors [10-12]. On the other hand, it comprises 18.9% of all carcinoid tumors in the body according to a retrospective analysis of 8305 carcinoid tumors of which 1570 in the appendix [10]. These tumors occur earlier than other carcinoids of the gastrointestinal system (average age 42.2 years, comparing to 62.9 years, respectively). The tumors seem to appear more frequently in women (M/F ratio: 0.47) [10], possibly due to their incidental discovery during gynecological or gallbladder procedures [13-15]. Apparently, they are most commonly found at the tip of the appendix (up to 70%) [13-16]. In 14.6% appendiceal carcinoids are accompanied by other non-carcinoid tumors at other sites of the body [3].

The histological origin of the tumor, known as argentaffin cell tumor, is not yet clarified [13,17]. Lundqvist and Wilander compared the histopathogenesis of appendiceal carcinoids with those of the small intestine and suggested that the carcinoids of the appendix arise from subepithelial endocrine cells (SNC), while those of the small intestine come from intraepithelial endocrine cells (ENC) [18]. In order to enlight the histogenesis of appendiceal carcinoids Shaw investigated the density of both ENC and SNC in 50 healthy appendices. The results revealed that although ENC density was the same throughout the appendix, most of the SNC were located towards the tip of the appendix, where carcinoid tumors are usually located, as well as that their density was maximal in young adults. As a conclusion, age and SNC topographical distribution suggest that most appendiceal carcinoids develop from SNC [19].

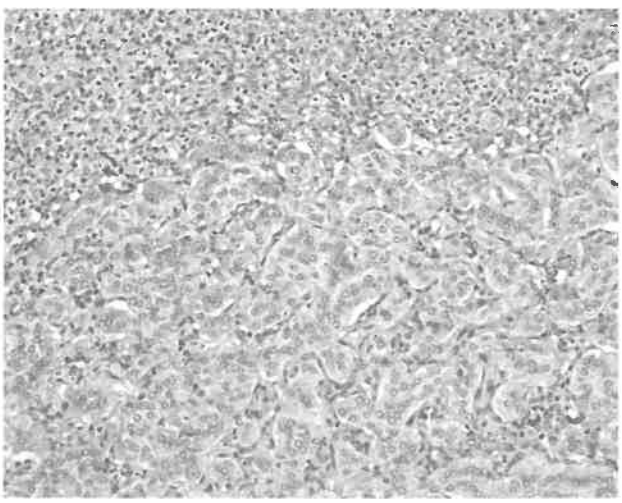


Figure 1. Histological appearance of the specimen (H&E × 40).

Macroscopically, appendiceal carcinoids appear as firm, solid, yellow nodules in the submucosa. Sometimes they invade the muscular and serosal layers and extend to the mesoappendix, which is strong evidence of malignancy. The lumen and architecture of the appendiceal wall disappear in the region involved. Microscopically, carcinoid tumors are formed from small uniform cells, with centrally placed round nucleus, clearly defined by a nuclear membrane. The cytoplasm is redundant and eosinophilic, containing argentaffin granules. The cells form small nests or large clusters and occasionally glandular pattern can be observed. Mitotic activity is actually rare, supporting the benign character of such tumors [9,20]. However, some investigators claim that carcinoids are not really benign because the frequent obstruction of the appendiceal lumen with consequent inflammation leads to early surgery; on the other hand, a large number of appendices is removed incidentally during other procedures, proving that the tumor would possibly metastasize if given enough time [16].

The carcinoid of the appendix has no particular clinical symptoms and it usually presents as acute appendicitis. Most of the times it is diagnosed incidentally during an irrelevant operation (appendectomy, cholecystectomy, salpingectomy, cesarean section) [11]. Its coexistence with pregnancy makes the diagnosis even more difficult. During the first trimester abdominal pain and digestive symptoms may be attributed to pregnancy-related symptoms. On the other hand, the gestation during the second and third trimester makes the clinical examination of the abdomen almost impossible. As a result the disease is diagnosed during a cesarean section or on ultrasound [20].

The malignant potential of carcinoid is determined by 3 criteria: a) the size of the tumor. The calculated risk of metastasis from tumors less than 1 cm is zero, but

increases when the tumor size exceeds 2 cm and lies between 20 to 85% [21,22]; b) histological type; and c) invasion of the mesoappendix, lymph nodes or distant metastasis [23]. In less than 10% of the patients with carcinoid tumors carcinoid syndrome, including diarrhea, abdominal cramps, malabsorption, flushing, bronchoconstriction and right-sided cardiac valve fibrosis, is present [11,12]. An important question expected to be answered is whether the tumor's hormonal activity can actually affect pregnancy. Animal studies have shown that serotonin decreases the uterine blood flow, thus obstructing fetal nutrition. This doesn't seem to apply to humans, however further studies are needed to elucidate this point [21,22].

Apart from the clinical symptoms the diagnosis is also based on biochemical and imaging examinations. Plasma chromogranin A is the currently available most accurate blood marker with its level being increased in 80-100% of patients with neuroendocrine tumors [11,23]. Assessment of 5-hydroxyindoloacetic acid (5-HIAA) and serotonin levels in the blood and urine and the 24 h urinary levels of 5-HIAA are the basic biochemical examinations for the diagnosis of a carcinoid tumor [11,21]. The intermittent character of this tumor's secretions demands multiple determinations of the levels found. Imaging methods may help the preoperative diagnosis. Ultrasound, CT or MRI may show intraperitoneal mass, enlarged lymph nodes or liver metastases. In our case CT could not be used as it is responsible for fetal malformations and carcinogenesis until the 15th week of gestation. For these imaging modalities it is necessary to request consent from the mother and also to make sure there is no other way for accurate diagnosis [20]. Scintigraphy with ^{111}In-labeled octreotide is used for the surveillance of carcinoid or its metastases, but it is contradicted during pregnancy [11,20].

Appendiceal carcinoid is on its own a rarely found entity. Its coexistence with pregnancy is even more uncommon and deserves special report and thorough search of the medical literature. The following 19 incidents with carcinoid during pregnancy have been mentioned in the last 60 years (Table 1).

The first report is dated in 1945 when Banner et al. described 3 patients with carcinoid tumor of the appendix. Appendicectomies were performed in all 3 cases. Along with the carcinoids one of the gestations was ectopic, so it led to abortion and the other two infants were born in perfect health [21,22].

In 1957 Duturmeny and Ruf described a single case that had an spontaneous abortion at the 15th week of gestation [21,23]. One case was mentioned in 1961 by Betson and Golden where the appendiceal carcinoid was diagnosed one month after labor [24]. In 1963 4 cases were described by Berrios et al; one of them presented with bleeding of corpus luteum cyst and aborted on the 10th week of gestation, while the other 3 delivered normally and uneventfully [25]. Methfessel et al. presented one case in 1973 with genetic abnormality and normal delivery [26]. Two cases were reported by Sommer et al. in 1984 without any complications [27]. In 1986 Parsons et al. described one case with delivery without any complications or difficulties [28].

Jurica and Baumgarden presented in 1989 a case with simultaneous occurrence of *C. trachomatis* infection that led to spontaneous abortion [29]. McLean et al. mentioned in 1994 one case that ended with the

Table 1. Reported cases of appendiceal carcinoid tumor during pregnancy, and results during the last 60 years

No	*Authors [Reference]*	*Year*	*No of cases*	*Results*
1	Banner et al. [22]	1945	3	One ectopic gestation, two normal births
2	Duturmeny and Ruf [23]	1957	1	Abortion at 15 weeks of gestation
3	Betson and Golden [24]	1961	1	Normal gestation
4	Berrios et al. [25]	1963	4	3 normal gestations, one abortion
5	Methfessel et al. [26]	1973	1	Normal gestation
6	Sommer et al. [27]	1984	2	Normal gestation
7	Parsons et al. [28]	1986	1	Normal gestation
8	Jurica [29]	1989	1	Abortion
9	McLean et al. [30]	1994	1	Normal gestation
10	Perez Villabona et al. [31]	1996	1	Normal gestation
11	Gokaslan et al. [32]	2002	1	Normal gestation
12	Korkontzelos et al. [33]	2004	1	Normal gestation, colectomy
13	Louzi et al. [20]	2006	1	Normal gestation, colectomy
14	Our case	2007	1	Normal gestation

delivery of a healthy infant [30]. In 1996 Perez Villabona et al. presented one case without complications in labor [31]. Gokaslan et al. reported one case that went through uneventfully in 2002 [32]. In 2004 Korkontzelos et al. presented one case that led to the birth of an infant without abnormalities [33]. The most recent case mentioned in the literature was in 2006 by Louzi et al. where carcinoid and pregnancy coexisted with a mucocele of the appendix [20].

Most of these cases were presented in emergency rooms with the clinical picture of acute appendicitis. The abortions took place later than the appendectomies. In almost all of the cases appendectomy was enough although Korkontzezos et al. [33] and Louzi et al. [20] suggest that it was necessary to perform right hemicolectomies.

The therapeutic strategy depends on the size of the tumor and evidence of invasion. Appendiceal tumors less than 1 cm in diameter are usually non metastatic and so it is recommended to be dealt with simple appendectomy. Because complete mesoappendix resection must be considered during appendectomy, reoperation might be needed if histology shows incomplete mesoappendix. Tumors more than 2 cm have an increased risk of regional spread and distant metastasis, so formal right hemicolectomy is recommended [11]. A grey area concerning therapy is when carcinoid measures 1-2 cm. Goede et al. [34] suggested right hemicolectomy when mesoappendiceal extension is evident, when the tumor is located at the base of the appendix with invasion of the caecum or when the tumor is high-grade, expressed by a large number of mitoses.

Metastatic tumors and carcinoid syndrome are treated with chemotherapy and pharmacologic control of the bioactive substances secreted by the tumors. The poor results of systemic chemotherapy suggest to avoid its use in progressive disease or in patients with uncontrolled hormone-mediated symptoms despite treatment. Octreotide, a somatostatin analog, is the only pharmacologic agent that can improve clinical and biochemical symptoms in up to 60% of the cases. It actually keeps the tumor stable and relapse is noted in only 3-5% [11,34-38].

After surgical excision the 5-year survival of appendiceal carcinoid is up to 85.9% and is the highest among all types of carcinoid tumors [10]. Patients should be followed up regularly since there is a high frequency of associated synchronous and metachronous colorectal cancer (13-33%) [10,11,39,40].

As a conclusion, it seems that pregnancy may not be incompatible with the coexistence of carcinoid tumors of the appendix and hopefully can be preserved, but the risk of abortion may be increased.

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