Carney complex and teratoma maturum ovarii - a case report

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Summary

This is a case report of an extremely rare Carney complex (CNC) syndrome in a 17-year-old patient. After the decision made by a team of cancer specialists, the patient was admitted to the hospital for surgery because of adnexal tumor associated with ascites and increased Ca 125 tumor marker level. The patient underwent cardiac surgery twice. Adnexal mass and ascites, revealed by transvaginal ultrasound (TVUS) and confirmed by magnetic resonance imagings (MRI), indicated the malignant alteration. Surgery was performed and surgical pathological staging was refined according to the FIGO guideline and included a staging laparotomy. After surgery, general condition of the patient was good, without ascites and pain, with Ca 125 marker levels within reference ranges.

Key words: Carney complex; Teratoma ovarii maturum.

Introduction

Carney complex is a syndrome named after A.J. Carney who first described it in 1985. According to NIH - Mayo Clinic and Cochin Centre data, there are approximately 500 cases who have undergone surgery to date. The latest research findings have proved that certain genetic changes may cause this syndrome and confirmed that malignant diseases and cell proliferation within the body are genetically induced [1-3].

This syndrome is characterized by tumor formation affecting different organs, such as: heart, breasts, endocrine organs including pituitary and thyroid glands, ovaries, gonads, adrenal glands, and includes skin and mucous membrane alterations [4].

It is an autosomal dominantly inherited syndrome, with overall penetrance of up to 70%. There are two types of chromosome mutations – type I mutation of the PRKAR 1A gene coding for the regulatory type I-α subunit of protein kinase A (PKA), located in 17q22q24; type II mutation located in chromosome 2 [5-7].

Two subtypes – type I and type II contain NAME – nevus, heart myxomas, myxoid neurofibromas and ephelide, and LAMB – (lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi syndrome). Mucosal and skin lesions (spotty pigmentation) occur in the face, hands, and lips [8, 9] .

Tumors affecting endocrine system, heart, and skin are primarily heart myxomas which, due to their enhancement, lead to changes in heart functioning, embolisation, and strokes [10]. Myxoma symptoms are similar to fever – temperature accompanied by arthralgia and rash, and followed by increase in temperature. Changes in gland function can cause some ovarian disorders followed by enlarged adnexal mass and ascites, which can be of malignant nature [11-14].

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Case Report

The authors report a 17-year-old patient with the diagnosis of CNC who was admitted to hospital for the surgery of malignant ovaries, after it had been decided by a team of cancer specialists.

She underwent heart surgeries in 2006 and in 2007. Since then she has had regular gynecological, endocrinological, ophthamologic, neurological, and cardiovascular check-ups. She had been first hospitalized for cerebrovascular insult and it was then that the heart tumor was confirmed.

Genetic test results, confirmed by the Institute of Health Bethesda (USA), proved that she was the carrier of *de novo* mutation c418-419 delCa in egzon 4 of PRKAR 1A gene, which is characteristic of CNC syndrome and associated diseases [5, 6, 15].

Neurologist described left hemipareses including increased tone in the left arm, diminished tone in the left leg, negative Romberg test, Babinski's sign was present on the left, meningeal signs were negative, brisk deep tendon reflexes, reduced power of the left arm, and weakness in the left leg. The patient was recommended spa rehabilitation. She also suffered from severe headaches and was treated with magnesium and zinc.

Laboratory and biochemical tests were performed as preoperative preparation and resulted within the reference ranges.

Abdominal ultrasound findings revealed that the liver, spleen, and pancreas were normal without focal lesions.

Furthermore the TVUS revealed substantial amount of fluid in the abdomen, heterogenous mass (74 x 56 x 52 mm) in the left ovary and a right ovary with tumoral aspect (43 x 34 x 40 mm). The MRI imaging showed normal urinary bladder and ureters. Uterus corresponded to the patient's age. There was a lesion, over 100 mm in diameter, arising from the left ovary above the uterus and vesica urinaria. Tumor mass was heterogenous and cystic in shape. The right ovary was 30 mm in diameter, its structure similar to tumor mass. No signs of retroperitoneal lymphadenopathy. Color doppler chest X-ray ultrasound of breast and thyroid and echocardiogram (ECG) were normal.

The management of the case was discussed with a multidisciplinary team.

The diagnosis was the following: obesity; malignant ovarian

Fig. 1

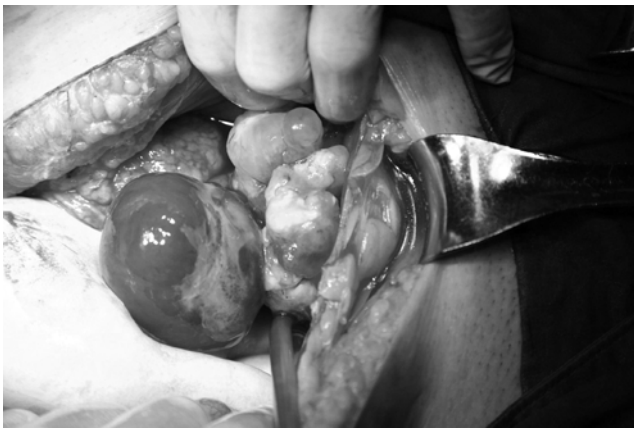

Fig. 2

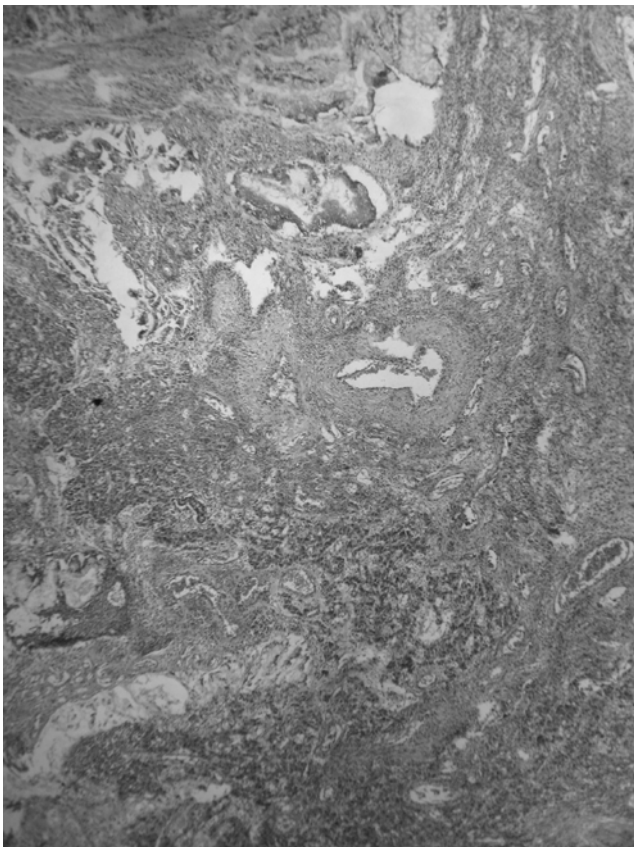

Figure 1. — Left ovary intraoperationem - teratoma maturum.
Figure 2. — Histopatological findings - teratoma maturum ovarii.

neoplasia with ascites; left lateral hemiparesis and naevus pigmentosous.

The patient underwent exploratory laparotomy with aspiration approximately three iters of fluid, ovariectomy sin, appendectomy, multiple biopsies of the peritoneium and omentum.

Staging was done according to FIGO guidelines for ovarian carcinoma, ascites sample was sent to cytological analysis, as well as smears from paracolic gutter and subphrenic space with results that showed no malignant cells.

Ovariectomy was performed on the left side and tissue was sent to frozen histopathological analysis. The findings showed benign alteration on the left ovary – teratoma solidum maturum ovarii (Figure 1).

Appendectomy was performed and was normal. Multiple peritoneal biopsy revealed – hyperplasia of the mesothelium. Partial resection of omentum was carried out and no disease was found. The surgery was completed and the pathology report then showed benign nature of the removed tissue – teratoma maturum ovarii, in a usual manner (Figure 2).

The post- operative course was uneventful. Bowel peristalsis was normal and the patient was discharged five days after surgery. Ca 125 tumor marker level was within reference ranges one month after the surgery. Abdominal postoperative ultrasound findings were normal.

Discussion

Carney complex is an extremely rare syndrome and so far there have been 500 reported cases of this syndrome in the world. According to the latest data there are 160 cases [16].

It is a genetically determined syndrome, although it can appear as a *de novo* mutation on PRKAR1A gene in up to 30% [16, 17].

The diagnosis of CNC and *de novo* mutation c 418-419 del<Ca in egzon 4 PRKAR1A had just been confirmed in the patient reported.

This syndrome may include tumors of the central nervous system (CNS), endocrine organs, and heart, as well as spotty pigmentation of skin and mucous membranes and bone tumors [1, 4, 9, 10]. Myxoma cordis had been confirmed and the patient had undergone surgery twice.

About 7% of heart tumors, myxoma cordis, which were confirmed by ultrasound images, coexist with CNC [10]. Heart tumor is very likely to be associated with CNC in patients less than 40 years old. Surgical resection of the affected tissue was certainly the matter of choice, and it was performed in the case reported [10].

Cases of bone tumors, osteohondromyxoma, coexisting with CNC have rarely been described in literature, only 1% [10]. There is evidence on coexistence of bone tumors and CNC in up to 10% of cases [16]. In certain cases ovarian cysts can become malignant [12, 14].

Cysts on a bizarre shape ovaries are usually followed by ascites and increased Ca 125 tumor marker level, which indicates to ovarian malignant cancer.

The patient presented symptoms of ascites and adnexal tumor.

The CNC patients are usually related and their average age is 20 years [10]. The patient reported is 17-years-old and the diagnosis was confirmed when she was 12.

In order to confirm genetic mutation and the diagnosis, PRKAR1A gene mutation must be checked which can be altered in up to 50% of all the patients [10].

Surgery is to be performed according to the guidelines for ovarian cancers. Regardless of the symptoms prevailing in the patient, the authors decided to perform staging according to FIGO guidelines and preserve fertility after ex-tempore histopathological evaluation had confirmed benign nature of disease.

There is almost no evidence in literature on coexistence of ovarian cancers with CNC [13, 14, 18, 19]. In most cases serous and mucinous cystadenomas and simple ovarian cysts can be reported. There have been some cases of serous papillary ovarian carcinoma coexisting with CNC [11, 12,]. There are no data on mature teratoma coexisting with CNC, as in our case.

Ascites evacuation, pain disappearance, opstipation and nausea with bloating, followed by laboratory and biochemical results within reference ranges, and subsequent return of Ca 125 tumor marker levels to reference ranges as well, were the result of well-performed operation.

Preoperative diagnostics - TVUS and MRI findings, together with the increase in tumor marker, had indicated a malignant nature of the tumor, but was then proved wrong. The only confirmation may come from intraoperative histopathological examination that is mandatary in these cases in order to preserve fertility in young patients.

The patients are advised to have regular check-ups every three months by a neurologist, cardiologist, and endocrinologist together with ultrasound examination of abdomen [16, 17].

References

[1] Losada Grande E.J., Al Kassam Martinez D., Gonzalez Boillos M.: "Carney complex". *Endocrinol. Nutr.,* 2011, *58,* 308.

[2] Almeida M.Q., Stratakis C.A.: "Best Carney complex and other conditions associated with micronodular adrenal hyperplasia". *Pract. Res. Clin. Endocrinol. Metab*., 2010, 2*4,* 907.

[3] Bertherat J., Horvath A., Groussin L., Grabar S., Boikos S., Cazabat L. *et al*.: "Mutations in regulatory subunit type 1A of cyclic adenosine 5'-monophosphate-dependent protein kinase (PRKAR1A): phenotype analysis in 353 patients and 80 different genotypes". *J. Clin. Endocrinol. Metab.,* 2009, *94,* 2085.

[4] Kacerovska D., Michal M., Sima R., Grossmann P., Kazakov D.V.: "Carney complex". *Cesk. Patol.,* 2011, *47,* 192.

[5] Peck M.C., Visser B.C., Norton J.A., Pasche L., Katznelson L.: "A novel PRKAR1A mutation associated with primary pigmented nodular adrenocortical disease and the Carney complex". *Endocr. Pract*., 2010, *16,* 198.

[6] Cazabat L., Ragazzon B., Groussin L., Bertherat J.: "PRKARA1 mutations in primary pigmented nodukar adrenocortical disease". *Pituitary*, 2006, *9*, 2011.

[7] Mavrakis M., Lippincott-Schwartz J., Stratakis C.A., Bossis I.: "Depletion of type Ia regulatory subunit (RIalpha) of protein kinase A (PKA) in mammalian cells and tissues activates mTOR and causes autophagic deficiency". *Hum. Mol. Genet*., 2006, *15,* 2962.

[8] Mateus C., Palangiae A., Franck N., Groussin L., Bertagna X., Avril M.F. *et al*.: "Heterogeneity of skin manifestations in patients with Carney complex". *J. Am. Acad. Dermatology,* 2008, *59*, 801.

[9] Horvath A., Stratakis C.A.: "Carney complex and lentiginosis". *Pigment Cell Melanoma Res.,* 2009, *22,* 580.

[10] Borkar S.S., Kamath S.G., Kashyap N., Sagar C.V., Rao L., Warrier R., Chauhan A.: "Carney complex report and review". *J. Cardiothor. Surg*., 2011, *5,* 25.

[11] Stratakis C.A., Papageorgiou T., Premkumar A., Pack S., Kirschner L.S., Taymans S.E. *et al*.: "Ovarian lesions in Carney complex: clinical genetics and possible predisposition to malignancy". *J. Clin. Endocrinol. Metabol.,* 2000; 85(11):4359.

[12] Carney J.A., Stratakis C.A.: "Virilizing ovarian stromal tumor in a young woman with Carney complex". *Am. J. Surg. Pathol.,* 2011, *35,* 1592.

[13] Papageorgiou T., Stratakis C.A.: "Ovarian tumors associated with multiple endocrine neoplasias and related syndromes Carney complex, Peutz-Jeghers syndrome, von Hippel-Lindau disease, Cowdens disease". *Int. J. Gynecol. Cancer,* 2002, *12,* 337.

[14] Lytras A., Tolis G.: "Reproductive disturbances in multiple neuroendocrine tumor syndromes". *Endocr. Relat. Cancer,* 2009, *6,* 1125.

[15] Kirschner L.S.: "Use of mouse models to understand the molecular basis of tissue- specific tumoriogenesis in the Carney complex". *J. Intern. Med*., 2009, *266,* 60.

[16] Bertherat J.: "Carney complex (CNC)". *Orphanet. J. Rare Dis.,* 2006, 21.

[17] Halaszlaki C., Takacs I., Patocs A., Lakatos P.: "Novel mutation in patient with Carney complex". *Orv. Hetil*., 2011, *152*, 802.

[18] Shetty Roy A.N., Radin M., Sarabi D., Shaoulian E.: "Familial recurrent atrial myxoma: Carney complex". *Clin. Cardiology,* 2011, *34,* 83.

[19] Jabbour S.A., Davidovici B.B., Wolf R.: "Rare syndromes". Clin. Dermat., 2006, 2*4,* 299.

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