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Case report

# Primary multiple tumor with affection of the thyroid gland, uterus, urinary bladder, mammary gland and other organs

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ABSTRACT

*Background:* Nowadays multiple primary tumor is characterized by growth and development of two or more tumors in one patient. The total world sickness rate ranges from 1% to 37%. The presence of four or more tumors in one patient is rare case and presented as casuistry.
*Case presentation:* We showed a case of multiple primary tumor with metahronic lesion of the thyroid, uterus and breast, followed by synchronous benign tumors of the subcutaneous fat, urinary bladder and gallbladder were considered. The development of all malignant tumors in all cases was accompanied by the presence of benign precancerous processes. Analysis of neoplasia histology shows the predominance of poorly differentiated forms of cancers in women with increased aggressiveness of cancerous tissue in each subsequent case and the growth of metastatic ability. The influence of heredity on the tumors progress is confirmed by immunohistochemical characteristics of cancer cells. Steroid-sensitive tissue of the uterus and breast in both cases didn't express ER and PR, in all cases the tissue had overexpression of Ki-67, p53, bax and bcl-2 receptors. The results of DNA testing for determination the Lynch syndrome revealed the presence of microsatellite instability in genetic material. The results of studies revealed the absence of mutations in these genes (MLH1, MSH2 and MSH6). Despite the negative results of the study, it doesn't exclude the possibility of Lynch syndrome for 100%, and its presence may be caused by the mutations of other genes (PMS1, PMS2 and MLH3), responsible for DNA repair. Unfortunately there wasn't any opportunity to study their mutations.
*Conclusions:* While studying the anamnesis of life and disease of women it was revealed that she had multiple primary tumor with lesions of the breast, urinary bladder, thyroid, uterus and other organs. This study shows that neoplastic tissue in all cases had high rates of cell proliferation, their antiapoptotic stability, expression of prognostically unfavorable-receptors, and absence of favorable prognostic markers. Histological study revealed high rates of malignant neoplastic tissue. It indicates to the existence of common mechanisms of malignant tumors and their genetic predisposition that can be clearly observed in many generations of patient.

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## 1. Introduction

The first documented case of a primary multiple tumor (PMT) was found in the works of Avicenna. He described bilateral affection of mammary glands. In 1793 John Pierce described a patient who consistently had cancer in the right and then in the left mammary gland and then uterus cancer. Billroth made special contribution to the study of this issue. In 1869 he identified the following requirements to PMT: tumors should be located in different organs, they should have different morphological structure, and each tumor

*Abbreviations:* MPT, Multiple primary tumor; ICD, International Statistical Classification of Diseases.

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must give its own metastases. In 1932, Warren and Gates published the first study in 1259 patients with PMT [1].

PMT is now understood as an independent appearance and development of two or more tumors that arise simultaneously (synchronous PMT) or at regular intervals (metachronous PMT) in one patient. The total morbidity in the world ranges from 1% to 37%, depending on the type of used analyses, the time of carrying out the investigations and the ethnicity of patients [2–4]. Cases of triple localization occur in 5–8% of cases. The presence of four or more tumors in one patient is a rare case and is considered as a casuistry [5].

There is no common statement of PMT appearance reasons in scientific reports [6]. Age, gender, ethnicity, obesity, smoking, topography and histological type of tumor, its pre-treatment, the impact of the environment are described among these reasons [7]. But genetic predisposition [8] is recognized to have the most significant influence on the PMT appearance. It is manifested by the presence of certain genes (BRCA1, BRCA2, p16/CDKN2A, hMSH2, hMLH1) and their polymorphism. These genes are responsible for proapoptotic and antiapoptotic function of cells [7–9]. Data about the participation of P53 gene and its mutations in multiple tumor genesis were repeatedly highlighted in publications. We can not exclude the multi-faceted impact of P53 gene on the initiation of carcinogenesis [10,11].

There are cases in which the cause of PMP is a disorder in the system of DNA reparation. Lynch syndrome is one of such examples. It is a hereditary disease that occurs in case of a mutation in one gene of DNA mismatch repair (MMR) [12]. It is characterized by the presence of microsatellite instability and mutations in MLH1, MSH2, MSH6, PMS1, PMS2 and MLH3 genes [13].

The survival of patients with PMT varies and depends on many factors (localization of the primary center, synchronism or metahronnism of a tumor etc.). More and more data about the survival of patients with PMT appears in the reports, comparatively with patients who have a neoplasia of one localization [14]. It is connected with the presence of more differentiated forms of cancers in case of PMT which requires less aggressive therapy.

## 2. Case presentation

A 62-year old woman was born in Russian city of Voronezh in 1953. Her family lived near a chemical plant, where her parents worked throughout their lives. From anamnesis we have known that her grandfather (on her father's side), her father and brother died of malignant neoplasms in the intestines at the age of under 50. Also we have known that her uncle (on her mother's side) died of urinary bladder cancer at the age of 61.

The woman was treated for such non-neoplastic diseases as pneumonia, chronic obstructive pulmonary disease, hastropathy, chronic tonsillitis, hepatosis and cystitis throughout her life.

For the first time our patient addressed doctors concerning the neoplasm of subcutaneous fat at the age of 16 in 1969, and it was only the beginning of her oncological sickness.

### 2.1. Forearm tumor

The neoplasm of left forearm was removed in patient at the age of 16 in 1969. This tumor was relapsed twice in 1985 and 2015. In the latter case, the tumor had oval shape, it was of yellow colour with hemorrhages, and its size was $6 \times 4 \times 3$ cm. The tumor was represented by typical adipose tissue surrounded by a thin fibrous capsule. In all cases, left forearm lipoma (International Statistical Classification of Diseases 10 (ICD) – D17.2) was diagnosed after histopathological study.

### 2.2. Thyroid tumor

For the first time hypoechoic nodular formation on the front surface of the right part of the thyroid gland was revealed during the ultrasound investigation in 2008. Its size was $16 \times 13 \times 24$ mm. On the back surface of the same part of the thyroid gland isoechoic formation with $11 \times 8 \times 14$ mm hydrophilic rim was revealed. As a result nontoxic multinodular goitre of the 1st stage was diagnosed in our patient (ICD 10 – E04.2). We have known that our patient's mother also suffered from goitre of the thyroid gland.

This disease has eventually progressed:

- additional isoehoic formation with a hydrophilic rim was revealed in the right part of the thyroid gland in 2009. Its diameter was 5 mm;
- the center which size was $16 \times 13 \times 24$ mm, increased to $16 \times 17 \times 28$ mm in 2011 and eventually it obtained moderately reduced echogenic lobulated structure in 2013;
- the center on the back surface of the right part of the thyroid gland which size was $11 \times 8 \times 14$ mm, increased to $12 \times 10 \times 16$ mm. Hydrophilic area without clear contours appeared at the periphery. Its size was $8 \times 6 \times 5$ mm;
- hypoechoic formation with irregular and indistinct contours appeared on the back surface of the left part of the thyroid gland. Its size was $10 \times 8 \times 16$ mm;
- a reaction from anterior jugular lymph nodes appeared on both sides. These lymph nodes with preserved echoic structure increased to $13 \times 5$ mm.

The results of puncture biopsy research of the thyroid gland lumps also had negative dynamics. In 2012 cytogram corresponded to a nodular goitre. In 2013 cytogram of punctates corresponded to a follicular neoplasia of the thyroid gland. There were layers and groups of epithelial cells with signs of atypia in the received material; they were presented in the form of microfollicular structures.

Surgeons performed subtotal resection of the thyroid gland with the purpose of treatment. Histological examination revealed that the tumor had been presented with tumor cells in the form of solid clusters with a single follicles formation. Follicular cells had various degrees of cellular atypia, there was invasion into blood vessels and surrounding tissues (Fig. 1A). Follicular thyroid cancer, stage III T3N0M0 (ICD 10 – C73) was diagnosed after intraoperative and histopathological investigation.

### 2.3. Uterus tumor

As a result of the uterine bleeding fractional scrapping of the walls of the uterus cavity was made in patient for diagnostic and therapeutic purposes in 2011 (the patient has had menopause since 2006). Endometrial glandular hyperplasia (ISD 10 – N85.0) was diagnosed. There was a relapse of bleeding 5 months later the same year. The results of histopathological study showed the growth of moderately varied adenocarcinoma in the uterus cavity. Hysterectomy with adnexas was performed in woman according to the health reasons. The results of macroscopic investigation showed that the uterus was not enlarged. When the uterus was cut an endometrial tumor (3 cm in diameter) was revealed in the right corner. Left uterine tube was in the form of a tumor, which was not united with the outer surface of the uterus. Histological examination of endometrial tumor showed its growth. The tumor consisted of glandular-papillary structures with the presence of solid areas. Tumor cells were polymorphic, hyperchromic, there were numerous mitotic figures (Fig. 1B). The investigation of the left fallopian tube tissue revealed the presence of tumor growth from the side of adventitia. That tumor had the same histologic characteristics as the uterus tumor. Moderately varied uterine adenocarcinoma

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