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Synchronous multiple primary tumors in a child. Case report

Abstract. *Diagnostics and treatment of multiple primary tumors remain the acute issue of modern oncology. The growing number of cases of this pathology generates new clinical and pathological problems in differential diagnostics and treatment which require a complex approach to their solution.*

The article presents the case of multiple primary tumors in a child of 8 years old. The two detected tumors differed in histomorphology, immunotype, and degree of malignancy (desmoplastic astrocytoma / ganglioglioma, G = I and anaplastic lymphoma, ALK-positive).

Every clinical doctor has to remember about multiple primary tumors, the difficulties of their diagnostics and treatment. This case is of great practical interest due to the rare occurrence of such pathology.

Keywords: *multiple primary tumors, astrocytoma, lymphoma, pathomorphology, immunohistochemistry (IHC).*

The aspects of clinical and pathomorphological diagnostics of primary multiple neoplasms (PMN) remain the topical, complex and multidimensional problem of modern oncology due to the growing number of patients with that pathology. Primary multiple neoplasms (PMN), also known as polyneoplasia, represent two or more tumors that have simultaneously or sequentially developed in one or more organs and differ in their histogenesis and pathological structure [1]. In most cases, the patients have two tumors; three nodes are detected in 5-8% of patients. The detection of four or more neoplasia is extremely rare and is considered as a casuistic case [1-3]. A sharp increase in the PMN incidence is observed in the last decades. For instance, in the 1970-80s the share of PMN in the overall structure of newly detected malignant tumors was less than 1% vs. over 13% these days [1-4]. In neurooncology, PMN are registered in very rare cases – 5%; in pediatric neurooncology – in no more than 2% of cases [5]. G.G. Nepryakhin presents 10 such cases in his pathoanatomical statistics: in 5 cases, brain tumors were combined with carcinomas of the prostate gland; in other 5 cases, the brain tumors were combined with carcinoma of esophagus, lung, uterus, breast, or penis [5].

PMN were first mentioned in the manuscripts of Avicenna who described the bilateral breast cancer more than a thousand years ago. In the XIX century, the PMN description in specialized literature became increasingly common. The German surgeon Billroth made the most significant contribution to the definition and study of that pathology. He was the first to define such pathological conditions and referred to PMN the neoplasms of various structures, localized in different organs and producing own metastases [6].

Multifactorial genetic mutations are the immediate causes of PMN development. Three main types of neoplasia are defined depending on the specifics of PMN etiology and pathogenesis: caused by 1) spontaneous somatic mutations, 2) induced somatic mutations, 3) inherited genetic mutations. It should be noted that such breakdown is fairly conditional. In practice, it is more possible to pinpoint the basic cause of development which is combined with other less significant factors [7, 8].

The most significant factors inducing the development of PMN include smoking, living in unfavorable ecological areas, occupational hazards (contact with chemical mutagens in some industrial sectors, excess of prescribed loads in radiologists), multiple X-Ray examinations, radiation therapy, and chemotherapy for previous cancers. The likelihood of PMN is also increased in the presence of nutritional disorders, immunodeficiency states, hormonal impairments, and certain endemic diseases [9, 10, 13, 14].

As of today, numerous attempts have been made to classify PMN basing on the classification proposed by V.G. Bebyakin in 1974 (Table 1). Clinically, PMN are divided into synchronous and metachronous PMN and by their histological structure. Synchronous PMN are two or more tumors diagnosed simultaneously or within 6 months. Metachronous PMN are two or more tumors diagnosed within more than 6 months and with no time limit. In terms of histological structure, the tumors can have similar or different histological structure [11, 12, 15].

Table 1 – PMN classification (V.G. Bebyakin, 1974)

Classification feature	Type of tumor
I. By combinations (manifestation character)	1) Benign 2) Benign and malignant 3) Malignant
II. By the sequence of detection over time	1) Synchronous 2) Metachronous 3) Synchronous-metachronous 4) Metachronous-synchronous
III. By functional relationships	1) Functionally dependent 2) Hormone-dependent (hormone-driven) 3) Unsystematized
IV. By tissue attribute	1) Singe tissue attribute 2) Various tissue attribute
V. By histological structure	1) Single histological structure 2) Various histological structure
VI. By localization	1) Single and paired organs 2) Various organs of the same system 3) Organs of various systems

The below case is presented given the rareness of PMN, especially in pediatric neuro-oncology:

A boy N., 8 years old, received hospital treatment at the pediatric neurosurgery department of the National Center for Neurosurgery, JSC (hereinafter – NCN, JSC) for 15 hospital days. According to the medical history, he got a head injury as a result of falling on February 27, 2017. On February 28, 2017, during the school day, the boy presented single generalized tonic-clonic seizures with a short-term loss of consciousness. MRI brain scan results: "Signs of a formation in the left parietal lobe sized 3.2x2.0x2.3 cm with a heterogeneous annular accumulation of contrast." According to the life history: the child of the second pregnancy, second delivery, the development status according to the age. The normal course of pregnancy. The child was vaccinated according to the age. In the past: catarrhal diseases. Upon admission to NCN, JSC, the child was in a severe condition. Neurological status: the level of consciousness on the Glasgow scale – 15 points, the child is cooperative, responds adequately to the examination, executes the given commands, understands the speech addressed to him. His intellectual development corresponds the age. No observed cranial nerves pathology, no movement disorders. The meningeal symptoms – negative. Laboratory and instrumental tests before hospitalization: FBC – hemoglobin 117 g/l, erythrocytes – $5.12x10^{12}$, leukocytes – $4.2x10^{9}$, ESR - 17 mm/h. Blood biochemical parameters and coagulation profile – within normal limits. Surgery on March 16, 2017: "Osteoplastic cranial trepanation of the left parietal region. Microsurgical removal of a glial tumor of the left parietal lobe." During the surgery, the tumor was removed by aspiration and coagulation. The result of intraoperative rapid biopsy: "Suspicion for desmoplastic ganglioglioma." The fragments of removed formation were referred to pathoanatomical department for examination and fixed during one day in 10%-neutral buffered formalin. After standard processing, the preparations were stained by hematoxylin and eosin. The pathological study was carried out using the microscope Axioscop 40, Carl Zeiss, Germany with a total magnification power X 100, X 200. The tumor tissue was represented by a loose glial-fibrillar stroma with the presence of astrocytes with numerous appendices and gangliocytes. The desmoplastic reaction determined in the tumor was manifested by focal expansion of fibrous tissue fibers and vascular sclerosis. Immunohistochemical examination: the tumor was positive in the glial component to the glial fibrillary acidic protein (GFAP), positive in the ganglion cells to the neuron-specific enolase (NSE) and synaptophysin, and positive in the foci of the desmoplastic reaction to the vimentin. The proliferative activity index Ki67 – 3-5%. Pathomorphological conclusion based on the results of histopathological and immunohistochemical studies: "Desmoplastic infantile astrocytoma/ganglioma G = I. ICD-O code 9412/1)" (see figures 1-3). The histological preparations were reviewed at the National Scientific Mother and Child Health Center, JSC in Astana (hereinafter – NSMCHC, JSC) and the Clinical Oncologic Center in Omsk, Russian Federation. The conclusion was confirmed.

The postoperative clinical course corresponded to the performed surgery. The child's status was severe with a positive dynamic. MRI brain scanning carried out on March 17, 2017 as postoperative control showed a partially removed formation with marked perifocal edema in the left parietal lobe. On the post-contrast MRI scans, that zone did not accumulate the contrast.

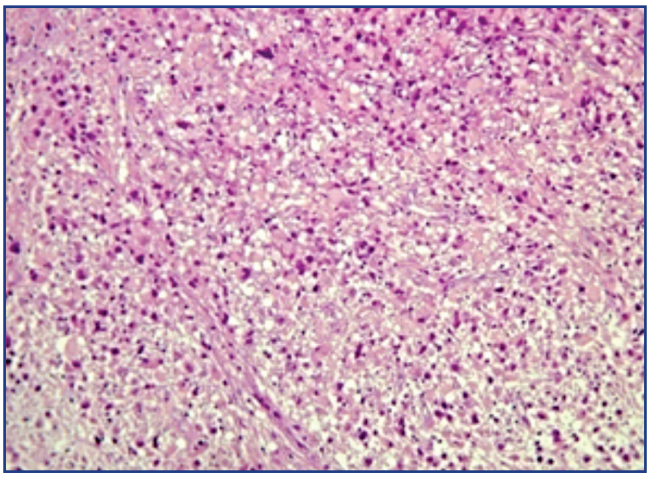

Figure 1 – Desmoplastic infantile astrocytoma/ganglioglioma.
X 100. Stained by hematoxylin and eosin

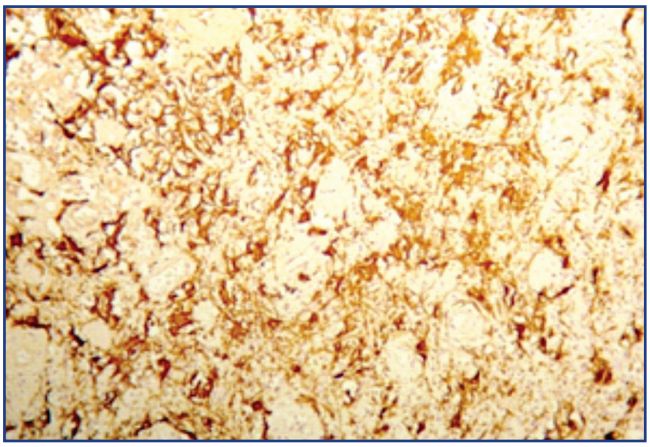

Figure 2 – Positive reaction to GFAP.
X 200. IHC.

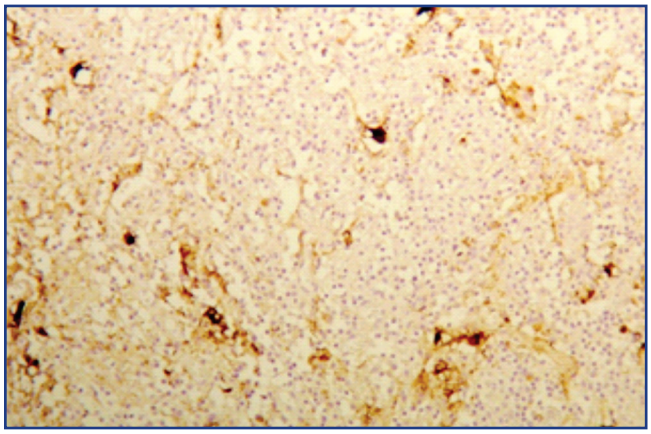

Figure 3 – Positive reaction to NSE.
X 200. IHC

On March 28, 2017, the child was examined by a pediatric oncologist who recommended hospitalization to the oncology department of NSMCHC, JSC for specialized treatment. On March 31, 2017, the child was transferred to the neuro-oncology department No.3 of NSMCHC, JSC where he received a course of radiation therapy with the total boost dose (TBD) of 54 Gy during 5 months of hospital care. The condition of the child did not improve after the course of radiation therapy. On August 10, 2017, the soft tissue formations were found on the left side of

the neck and the rise side of the costal arch, as well as in the left hip area. The CT scan as of August 15, 2017 showed two neoplasms in the left lung (S3 and S6) and the intrathoracic lymph-nodes hyperplasia.

In September 2017, the child was examined in Moscow. In the Russian Cancer Research Center (RCRC) a biopsy sample was taken from the formation of soft tissue of the thigh. "Anaplastic lymphoma, ALK-positive, with proliferative activity index Ki67 - up to 100%" (Figures 4, 5) was verified. The therapy for lymphoma was recommended.

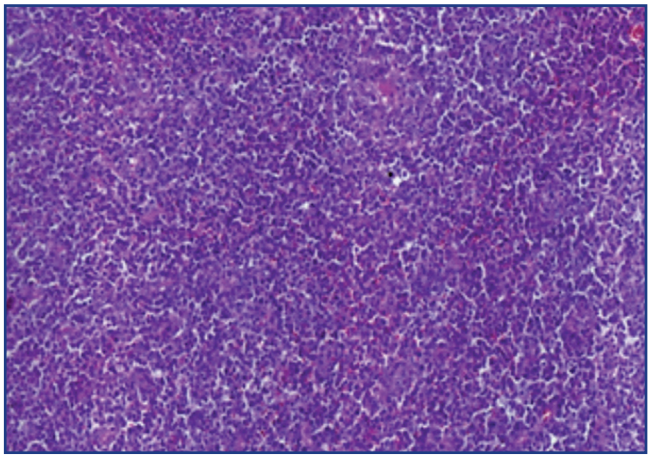

Figure 4 – Anaplastic large cell lymphoma. X 100. Stained by hematoxylin and eosin

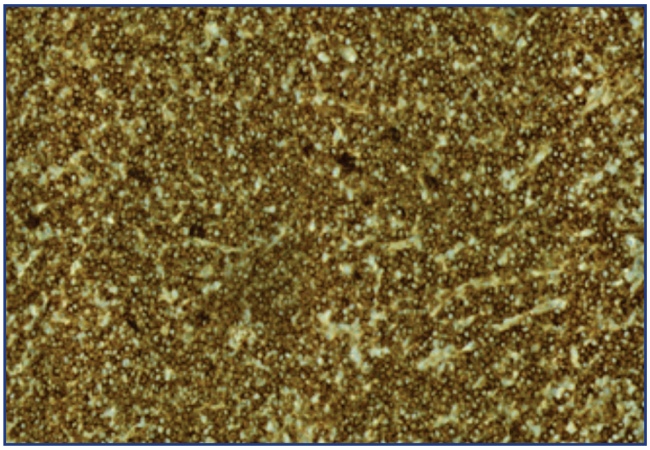

Figure 5 – Positive reaction to CD30. X 200. IHC

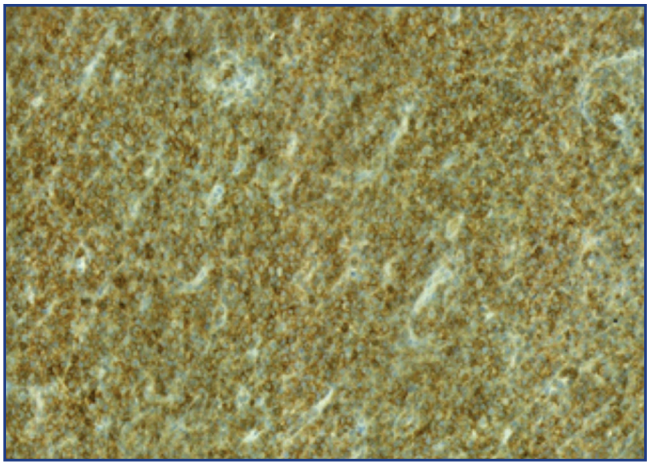

Figure 6 – Positive reaction to CD4. X200. IHC

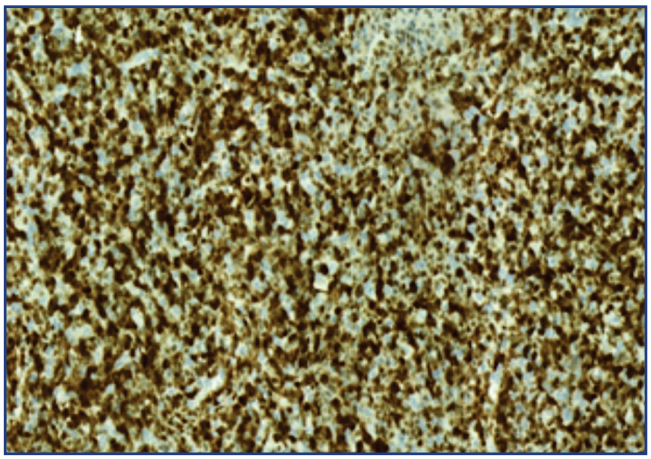

Figure 7 – Positive reaction to ALK. X200. IHC

Subsequent examination revealed multiple tumor foci in the pancreas, para-aortic lymph nodes, lungs, and soft tissue of the body and the extremities. PET as of September 19, 2017: "Numerous foci of increased RPh metabolism in soft tissue of the body and extremities, lymph nodes of the jugular group, mediastinum, left lung root, inguinal region, pancreas, in the lateral segment of the 8th rib rightward, CNS (in the parietal region along the sickle leftward), possibly in the right kidney".

The following clinical diagnosis was established based on the history, clinical and lab examination, as well as histopathological examination of the surgical material of the brain tumor and the biopsy material from the formation of soft tissue of the thigh: "Primary multiple synchronous neoplasms. Desmoplastic infantile astrocytoma/ganglioglioma, G1. State after partial removal of the tumor (S1-3, R3), radiation therapy TBD 54 Gy. ALK-positive anaplastic lymphoma. The condition after the course of chemotherapy".

Thus, in this case the child has PMN which differ in histogenesis, morphology, immunotype, and the degree of malignancy (desmoplastic astrocytoma/ganglioglioma G1, Ki67 up to 5%; ALK-positive anaplastic lymphoma, Ki67 up to 100%). They are not metastases of each other. They developed in synch (were diagnosed within 6 months) and affected two different systems (CNS, lymphatic system with parenchymal organs: lungs, pancreas and soft tissue). Every clinical doctor should be aware of PMN and the challenges associated with their diagnostics and treatment. The presented case study is of great practical interest due to the rare incidence of this pathology.

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