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**PECULIARITIES OF POLYNEUROPATHY  
IN THE PERIPHERAL T-CELL LYMPHOMA WITH CYTOSTATICS**

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**Abstract.** The number of patients with malignant tumors has increased steadily. Every year more than 12 million new cases are registered, including non-Hodgkin's lymphoma. A modern problem in medicine consists of not only paraneoplastic processes accompanying the tumor, but a complication of anticancer therapy – neurotoxicity. This paper presents data on the occurrence and form of polyneuropathy in the peripheral T-cell lymphoma, and its main pathogenesis elements. Here the toxic effects of cytotoxic drugs and their role in the impairment of the nervous system have been described.

**Key words:** polyneuropathy; cytostatics; vincristine; peripheral T-cell lymphoma; onconeural antigens; nephrotoxicity.

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**ОСОБЕННОСТИ ТЕЧЕНИЯ ПОЛИНЕЙРОПАТИИ  
ПРИ ПЕРИФЕРИЧЕСКОЙ Т-КЛЕТОЧНОЙ ЛИМФОМЕ  
НА ФОНЕ ТЕРАПИИ ЦИТОСТАТИКАМИ**

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**Аннотация.** Число больных со злокачественными новообразованиями неуклонно возрастает. Ежегодно регистрируется более 12 миллионов новых случаев, среди которых не последнее место занимают неходжкинские лимфомы. Современной проблемой для медицины являются не только паранеопластические процессы, сопровождающие опухоль, но и осложнение противоопухолевой терапии – нейротоксичность. В статье приведены данные о встречаемости и форме полинейропатии при периферической Т-клеточной лимфоме, ее основных звеньях патогенеза. Описано токсическое действие цитостатиков и их роль в поражении нервной системы.

**Ключевые слова:** полинейропатия; цитостатики; винкрестин; периферическая Т-клеточная лимфома; онконейральные антигены; нейротоксичность.

An impairment of the peripheral nervous system in malignant tumors, regardless of patient age, is still a significant problem with many unresolved issues the neurologists have faced with. In particular, there is the question remaining open of the differential diagnosis of paraneoplastic and post-chemotherapeutic disorders of the peripheral nervous system.

The number of patients with malignant tumors has increased steadily worldwide. According to the experts'

calculations, more than 12 million new cases are detected yearly. Consequently, the overall death rate from cancer is expected to reach 7.6 mil. people annually (about 20,000 deaths from cancer a day) [33]. It is known that lung cancer ranks first in male mortality, both in the Russian Federation and worldwide. Breast cancer ranks first in the female cancer morbidity in Russia [11]. However, one should not forget about less common cancer formations such as T-cell lymphomas, which are 12-15% of all types

of lymphomas, while the share of peripheral T-cell lymphomas accounts for 4-7% [15, 18]. According to statistics, peripheral T-cell lymphoma is detected in 1 case out of 100 thousand people per year [22]. Regardless of the features of the tumor development and progress, with rare exceptions, it is an aggressive type: the median overall survival of patients with the peripheral T-cell lymphoma in the basic CHOP-therapy (Cyclophosphamide, Hydroxyldaunomycine, Oncovin, Prednisolone) is 11-34 months [3, 19, 22]. A T-cell phenotype is an independent factor of unfavorable prognosis [34].

Paraneoplastic polyneuropathy is approximately 1% of all types of polyneuropathy, but currently there is no sufficient data to confirm such a low statistics of this disease [6, 7, 9, 11, 13, 29, 31]. Thus, paraneoplastic polyneuropathy occurs in 5% of patients with cancer [6, 30, 31]. On the other hand, after analyzing the data from the literature, it was found that the impairment of the nervous system against lymphomas occurs quite often and reaches 5-29% of cases, and about 5-10% impairs the peripheral nervous system (although, there are still no exact data on the statistics of peripheral T-cell lymphoma) [15, 30].

It is known that the development of paraneoplastic polyneuropathy is associated not only with one of the following factors, such as compression of the nerves by the tumor itself, the impairment of the nervous system with either metastasis or side effects of radiotherapy, chemotherapy, or metabolic, vascular, hormonal changes, or opportunistic infections [1, 5, 7, 11, 31, 32]. It is more reasonable to stick to the multifactorial nature of the impairment of the peripheral nervous system. It is necessary to consider the fact that patients by the time of having recourse to the neurologist, in most cases, have already received at least one course of chemotherapy, because an immune mechanism of impairment occurs inseparably with both the toxic effects of drugs, and under the developed microcirculatory endothelial dysfunction that resulted in the nervous tissue hypoxia with further demyelination and axonal degeneration [4].

L. Thomas and F. Burnet described the basis of the pathogenesis of the cancer and nervous system interaction back in the mid-1950s in their concept of the immune response under cancer. They suggested that immune mechanisms have an effect on tumor cells, inducing thereby the formation of anti-tumor antibodies, which damage the nerve cells [31].

Based on the current visions of the immune system, it is assumed that paraneoplastic lesion of the peripheral nervous system can be caused by immunological processes that are provoked by the presence of tumor formation in cells and the cross-reactive antigens in the nervous system [1, 7, 9, 10, 11, 21, 29]. In some cases, the cells of malignant tumors start inexplicably to synthesize foreign substances (proteins), which are produced in normal conditions either within or on the surface of nerve cells. As a result, a synthesis of such neuronal proteins (so-called paraneoplastic antigens) in the tumor cells lying outside the nervous system causes the activation of the immune system, which in turn leads to the autoimmune response,

i.e. to both production onconeural autoantibodies against the paraneoplastic antigens and, possibly, appearance of specific T-lymphocytes. Further, antibody-specific T-cells generated under the autoimmune response interact with the structures of the nervous system, which contain normal proteins identical in their structure to paraneoplastic antigens, that ultimately damages the neurons (including motor neurons of the anterior horns, and the spinal ganglia cells), and peripheral nerve fibers [1, 9, 10, 11, 12, 24, 31]. Onconeural autoantibodies are IgG, which, circulating in the patient's blood, penetrate into the cerebrospinal fluid by passive diffusion, where they can attack the normal proteins identical to onconeural antigens, causing thereby the specific degeneration of the nervous system [8].

E. Day was the first to describe in 1965 the appearance of antigens specific to normal, non-homologous to tumor, tissues in the malignant cells [25, 30]. He called this phenomenon of antigenic divergence. Independently from E. Day, the researches of Institute of Cytology RAS also detected this phenomenon (Fel et al., 1965, 1966) [25]. Antigens, which ensure the antigenic divergence, were identified as heteroorganic (in our case – onconeural antigens), namely the antigens typical of the tissues non-homologous to the tumor [30]. Currently, there is an active detection and investigation of onconeural antigens and the «response» antibodies synthesized by the immune cells. This is due to the fact that antibodies to onconeural antigens may appear in the blood well before a patient is diagnosed with cancer, and may thus serve as a very early diagnostic indicator of cancer formation and its possible paraneoplastic manifestations, both in the central nervous and in peripheral system [25].

Some literature describes neurological deficit on the background of lymphomas (particularly, of peripheral T-cell lymphoma) as a subacute, progressive flaccid tetraparesis that is a result of damage to the motor neurons of the spinal cord, followed by typical motor impairment, but with a much slighter manifestation of muscle fasciculations. There may also be the segmental damages to motor neurons with the development of paresis in individual muscle groups. More often phenomenon observed under peripheral T-cell lymphoma is an impairment of somatic nervous system [28, 31]. In this case, the clinical pattern includes motor polyneuropathy, for which the presence of pain and damage to the cranial nerves is unusual, with minimal sensitive dysfunction. Very rarely, the upper motoneuron of motor cortical areas may be involved in the process with the development of hyperreflexia, pathological appearance of symptoms (extensor stopnye symptoms, such as Babinski), and clonuses, even in the absence of metastases [28].

Speaking about the impairment of the peripheral nervous system on the background of malignancy, we should remember the specific systemic complications of chemotherapy such as neurotoxicity [8, 11, 20]. A large group of modern, highly effective anticancer drugs used in the treatment of cancer pathognomonic for paraneoplastic polyneuropathy, leads to clinically significant, dose-limiting neurotoxicity, which requires the adjustment and

timely correction of dose, delay of the next cycles of chemotherapy, or discontinuation of treatment [11, 13, 23, 26, 27]. According to the literature, 15-77.8% of cancer patients undergoing chemotherapy (and up to 100% of cases when treated with Vincristine) have the developing toxic polyneuropathy, which significantly complicates the prognosis for the underlying disease [2, 20].

Unfortunately, the mechanisms of peripheral neurotoxicity have not been fully determined yet. The most reasonable assumption is that the neurotoxicity manifestation is usually the result of an impaired axonal microtubular architectonics along with direct damage to the distal parts of axons (development of destructive axonopathy) [8, 9, 11, 13, 23, 26]. A diffuse or segmental demyelination of neurons – mielinopatiya, or degeneration of neuron bodies – neyronopatiya are observed less commonly [11, 16, 23, 26].

The main pathogenetic element of the peripheral axonopathy is a damage to intracellular protein – tubulin, which plays a leading role in ensuring normal physiology of the nervous system [7, 8, 9, 13, 23, 26]. There is also evidence of involving the proteins such as kinesin and actin in the pathological process, with their subsequent damage [13, 23]. Comprehension of the pathogenesis of axonal degeneration of nerve fibers is based on the fact that the peripheral axons and spinal ganglia have no blood-brain barrier, in contrast to the CNS. The cytostatic metabolites penetrate by direct diffusion into the nerve fibers from the surrounding interstitial fluid with their further accumulation there and damage to tubulin [7, 8, 9, 13, 23, 26]. As a result, both the structure and function of microtubules is impaired and, consequently, axonopathy of sensory fibers occurs.

The above pathological process explains also a preferential manifestation of neurosensory disorders in comparison with lack of motor activity during chemotherapy. The bodies of motor neurons are located in the anterior horns of the spinal cord, defending them from the influence of metabolites of antitubulin cytostatic agents with the use of blood-brain barrier mechanisms [23].

Antineoplastic drugs from the group of vinca alkaloids, one of which is vincristine that causes depolymerization of microtubule tubulin, have serious damaging effect on the peripheral nervous system [14, 20, 23, 26, 35]. Chemotherapy-induced peripheral sensory (sensorimotor less when high doses of the drug) polyneuropathy occurs as a result of vincristine therapy in 43% -100% of patients undergoing a specific treatment of the underlying disease under basic treatment (in particular, peripheral T-cell lymphoma). This is a degenerative axonal neuropathy by the nature of damage. The literature also mentions an extremely rare, empirically proved axonal-demyelinating neuropathy, occurring under vincristine therapy: a cytostatic agent can affect Schwann cells and myelin sheath, as well as cause «pseudoaxonal» neuropathy with the axon-»ingrowing» Schwann cells with their further segregation into individual parts. The involvement of the nodes of Ranvier in the pathological process with their subsequent degeneration was

experimentally recorded. Probably, the myelin sheath of the nerve can be damaged due to the toxic effect of cytostatic agent, secondary to axonopathy due to the autoimmune destruction and imbalance between demyelinating and reparative processes [20].

The stimulation electroneuromyographic examinations of patients with malignant tumors, undergoing chemotherapy, allow clarifying the nature and degree of damage to peripheral nerve fibers. The most commonly revealed signs are ones of axonal damage to sensitive fibers in the form of reduced amplitude of sensory response and/or M-response under motor fibers lesion [20]. We should clarify that the motor disorders and, consequently, damage to the motor fibers detected at the stimulation electroneuromyography in vincristine-receiving patients, were recorded 10 years after the end of the therapy [20, 36]. Increase in drug doses can lead to the demyelinating lesion of the nerve fibers manifesting itself in the reduced speed of nerve impulse and increased duration and latency of M-response [20].

Clinical signs of chemoinduced peripheral polyneuropathy occur a few weeks after the start of the chemotherapeutic treatment of the malignant neoplasm. Unlike most of other chemotherapy complications, the clinical signs of neurotoxicity are subjective and relate to neurosensory disorders in patients [11, 13, 23]. Peripheral neurosensory dysfunction may manifest itself as hypoesthesia, dysesthesia, numbness, paresthesias in the distal extremities, deterioration of proprioceptive, vibration, temperature and tactile sensitivity, sometimes with pain syndrome [11, 13, 20, 23]. The most typical of toxic damage to the peripheral nervous system with metabolites of cytostatic agents is a symmetric sensory neuropathy with lower extremities predominance. There may be development of a substantial limitation of routine activity of the patient, which is due to advanced cases of an underlying disease (inability to walk, write, using cutlery, etc.). Long after, there occur related disorders of motor function in the form of mild to moderate muscle weakness and muscle atrophy [23].

The direct damage to the cerebrospinal ganglia with metabolites of cytostatic agents leads to earlier appearance of neuronopathy symptoms rather than of axonopathy ones [26]. Timeframes differ significantly – a few hours or days after administration of cytostatics. Neurological deficit under neuropathy consists in both the lower and upper extremities impairment, a rapid loss of deep reflexes, muscle weakness, and there may be typical herpes sores in the corresponding dermatomes in this situation. Typically, damage to the spinal ganglia is associated with high doses of cisplatin and taxanes, especially when combined [23].

The action of the metabolites of anticancer drugs, particularly vincristine, along with peripheral neurotoxicity may result also in central neurotoxicity [23]. Several foreign and domestic authors describe its appearance in the clinical signs of cranial nerve impairment [14, 23, 35]. According to Bay A., a bilateral ptosis and an ophthalmoplegia may occur [35]. Dixit G. also describes the involvement of the cranial nerves into pathological

process during vincristine therapy, citing the specific anatomical structures such as optic, return, guttural, oculomotor, trochlear, and abducens nerves, as well as the symptoms upon their impairment in the form of a bilateral outer ophthalmoplegia, hoarseness, and short-term visual acuity reduction [17]. Perhaps, in this situation, an additional cranial pathology is a predictor of the chemoinduced polyneuropathy, which will allow the dedicated experts to adjust further treatment.

**Summary.** After analyzing the literature data and the clinical case, we can state with assurance that it is quite difficult to determine the leading damaging component in the nervous system in patients undergoing chemotherapy for peripheral T-cell lymphoma.

The emergence and rapid progression of neurosensory disorders in the extremities and occurrence of additional multiple craniopathy may be a predictor of clinical signs, being indicative of a toxic component of cytostatic agents in the development of chemoinduced polyneuropathy.

As a rule, a polyneuropathy under peripheral T-cell lymphoma is of mixed nature, including both paraneoplastic and toxic components.

The prognosis for axon-degenerating, chemoinduced peripheral polyneuropathy is unfavorable.

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