

## THE CONCEPTUAL AND CLINICAL PROBLEMS OF PARANEOPLASTIC SYNDROME IN ONCOLOGY AND INTERNAL MEDICINE

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Symptomatology of oncological diseases consists not only of local symptoms caused by the primary malignancy or its metastases, but also by general systemic signs that are not directly connected with the tumor. These symptoms are mostly associated with autoimmunity or endocrine influences. In many cases, the source of paraneoplastic syndromes (PNS) is unknown. Nearly 15% of oncological patients demonstrate these syndromes but it is diagnosed much more rarely. The survey of the numerous PNS is offered. The significance of the PNS differs for oncologists and other physicians who encounter it in their practice. The reason of those differences, as well as the connection between PNS and cancer toxicity is discussed. The experience of antitoxic therapy (hemisorption, lymphosorption, enterosorption) used in our clinic in the previous years is overviewed.

**Key Words:** cancer, diagnosis, paraneoplastic syndromes, tumor toxicosis.

Tumors usually produce symptoms by invasion, obstruction and bulk mass on the primary localization of neoplasm and their regional or distant metastases. In addition, tumors can produce signs at a distance from their localization. These are the so-called paraneoplastic syndromes (PNS) [1, 2].

These syndromes are not a direct effect of the tumor or its metastases. They are caused by substances produced by tumor and distributed by circulation. These substances act on the target organs and result in clinical picture named PNS. Most of these substances are polypeptide hormones, autoantibodies, growth factors, cytokines, hormones and their precursors. The etiology and pathogenesis of a number of PNS are unknown till now (e.g. acanthosis nigricans) and require additional investigations [3].

Over the last years, many of these tumor-secreted proteins have been described. The PNS may be the first sign of a malignancy and we can use it for early cancer detection. PNS does not predict the result of treatment of the underlying malignancy [4].

Thus, proteins secreted in PNS may be used as tumor markers. Different PNS caused by diverse reasons (hormonal, immunological etc.) demonstrate various treatment results. A successful treatment of the tumor usually leads to disappearance of the PNS. In many cases, the underlying tumor cannot be treated, but symptoms and complications of the PNS can be successfully managed by nonspecific means which were tried in our institution (Lviv Oncological Center) several years ago [5].

It is believed that appearance of PNS is connected with endocrine, immunological or metabolic influ-

ences of the tumor. Over 600 PNS have already been described so far (Table).

**Table 1.** Most common PNS

Syndrome group	Clinical signs	
Cutaneous	Acanthosis nigricans maligna	
	Erythema gyratum repens	
	Bazex paraneoplastic acrocheiratosi	
	Acquired hypertrichosis lanuginosa	
	Necrolytic migratory erythema	
	Leser-Trélat Sign	
	Paraneoplastic pemphigus	
	Dermatomyositis	
	Sweet syndrome	
	Palmoplantar keratoderma	
	Pyoderma gangrenosum	
	Neurological	Limbic encephalitis
		Subacute cerebellar degeneration
		Opsoclonus-myoclonus
Optic neuritis		
Cancer associated retinopathy		
Subacute sensory neuropathy		
Guillain – Barre' syndrome		
Chronic gastrointestinal pseudo-obstruction		
Myasthenia gravis		
Lambert – Eaton myasthenic syndrome		
Endocrine	Necrotising myelopathy	
	SIADH	
	Hypercalcemia	
	Cushing syndrome	
	Hypoglycemia	
	Hematologic	Eosinophilia
Granulocytosis		
Pure red cell aplasia		
Thrombocytosis		
Thrombocytopenia		
Anemia		
Coagulopathies (thrombophlebitis, thromboembolism, disseminated intravascular coagulation – DIC)		
Rheumatologic		Paraneoplastic polyarthritis
		Remitting seronegative symmetrical synovitis with pitting edema
		Polymyalgia rheumatica
	Palmar fasciitis	
	Multicentric reticulohistiocytosis	
	Tumor-induced osteomalacia	
	Vasculitis	
Renal	Glomerulonephritis	
	Nephrotic syndrome	

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**Abbreviations used:** aPL – antiphospholipid antibodies; CLL – chronic lymphocytic leukemia; DIC – disseminated intravascular coagulation; PNS – paraneoplastic syndromes.

Syndrome group	Clinical signs
Others	Cachexia Fatigue Fever Lactic acidosis Hypouricemia

Their number is constantly increasing, but it is disputable whether all of them can be evaluated as PNS. True PNS satisfy two main criteria: strong association of suspected PNS with malignancy and their parallel course [3].

### PARANEOPLASTIC CUTANEOUS SYNDROMES

For clinicians these syndromes can be of diagnostic value. The attitude of different medical experts to this phenomenon differs: dermatologists observe PNS or similar syndromes in skin diseases. Most important for is to establish a differential diagnosis between dermal PNS and plural dermatosis. Cutaneous manifestations of distant cancer are more frequent than other similar appearances, and an especially wide variety of skin syndromes is associated with malignancies [6]. These are first of all keratinization disorders. The most important PNS of this kind is acanthosis nigricans. It is characterized by grey-brown hyperpigmented velvety plaques that often affect the neck, flexor areas, and anogenital region. It is typically associated with adenocarcinomas of the gastrointestinal tract, predominantly with gastric cancer, but can be associated with other adenocarcinomas (lung, breast, ovarian, and even hematologic malignancies) [7]. In addition, keratinization disorders are represented by tripe palms, usually associated with lung or gastric cancers, acquired ichthiosis (associated with Hodgkin's and other lymphomas, multiple myeloma, Kaposi's sarcoma). Palmar hyperkeratosis is associated with esophageal, breast, and ovarian carcinomas [8].

It is relevant to name several other cutaneous PNS connected with different tumors: acrokeratosis paraneoplastica (Bazex' syndrome), associated with squamous cell carcinoma of the esophagus, head and neck or lung tumors. It precedes the tumor in 60% of cases. Exfoliative dermatitis may be associated with lymphomas and rarely with solid tumors (lung, liver, prostate) [9].

Disorders of cutaneous discoloration and deposition (melanosis, plain xantomias, vitiligo, and leucoderma) are also considered to be PNS associated with different malignancies. Neuroplastic dermatoses constitute an interesting group. Sweet's syndrome presents with acute onset: fever, neutrophilia and appearance of cutaneous plaques on the face, neck, and upper extremities. Association with malignancies occurs in 20% of cases. The other dermatologic PNS is pyoderma gangrenosum appears as a form nonhealing ulcers with a necrotic base.

Pyoderma gangrenosum is associated with hematological malignancies, including cutaneous T-cell lymphomas, gastric carcinomas, and other

gastrointestinal abnormalities. I (here — **B. Bilynsky**) remember a clinical case when during a clinical patient round I, being a young docent, diagnosed gastric cancer due to the presence of black spots on the patient's face (acanthosis nigricans), which was evaluated by my colleagues as melanoma [8, 10].

Vascular abnormalities belong to dermatological appearances. Episodic reddening of the face and neck lasting a few minutes is associated with the carcinoid syndrome, leukemia, medullary carcinoma of the thyroid, renal cell carcinoma, systemic mastocytosis, and pheochromocytoma. Multifocal migratory thrombophlebitis (antiphospholipid syndrome) is associated with numerous malignancies, most commonly with gastrointestinal, but also lung, prostate, ovary tumors, leukemias and lymphomas. It is related to hypercoagulable state accompanying the advanced cancer. A cordlike thrombophlebitis on the thoracic wall (Mondor's disease) may be associated with breast cancer. Pruritus may be the initial feature of an occult malignancy or a clinical manifestation of a previously diagnosed tumor. There are other numerous additional hereditary disorders associated with cutaneous manifestations of malignancy [3, 6].

Dermatologic PNS include also a number of endocrine and metabolic lesions (systematic modular panniculitis or subcutaneous fat necrosis, hyperpigmentation by Addison syndrome), telangiectasia, and scleroderma-like changes in carcinoid syndrome, and others [7, 8].

Bullous disorders, mostly paraneoplastic pemphigus usually occur in the presence of B-cell lymphoproliferative disorders — lymphomas, chronic lymphocytic leukemia (CLL), Castleman's disease, thymoma, Waldenström's macroglobulinemia, and spindle cell neoplasms. Dermatologic PNS can be represented by collagen-vascular diseases, disorders of hair, and some skin neoplasms associated with internal malignancy. To the latter belong such autosomal-dominant syndromes as Muir — Torre syndrome (numerous sebaceous gland neoplasms), Cowden's syndrome (multiple hamartomas), Gardner's syndrome (hundreds of adenomatous colorectal polyps and numerous epidermal cysts and soft tissue tumors), and Gorlin-Goltz syndrome (multiple basal cell carcinomas with numerous bony abnormalities and a strong predisposition for malignancy) [3, 9, 10].

### PARANEOPLASTIC NEUROLOGICAL SYNDROMES

Neurologic manifestations of PNS are close to the dermatologic ones, and often have some common signs and etiological display with the skin syndromes [11].

Neurological symptoms that are not related to the direct effect of malignancies on the neurologic system are defined as PNS. These syndromes include dermatomyositis, Lambert — Eaton myasthenic syndrome, subacute cerebellar degeneration, subacute sensory neuropathy, opsoclonus-myoclonus, sensory

motor peripheral neuropathy, encephalomyelitis, and many others [11, 15]. Such neurologic disorders as PNS are associated with different malignancies in 10–60% of cases. Paraneoplastic disorders are also a rare cause in vision loss in cancer patients [12].

A number of antineural antibodies appear in the case of PNS and cancers. That is why neurologists have to be interested in recognition of the PNS, which would lead to the correct determination of diagnosis and application of an adequate treatment [12, 27].

### **PARANEOPLASTIC ENDOCRINE SYNDROMES**

Once a PNS is diagnosed, an appropriate systemic evaluation for a neoplasm is to be undertaken. The majority of PNS are connected with endocrinological disorders. In their practice, the experts in endocrinology encounter such clinical cases that are frequently associated with a wide variety of common cancers.

A number of PNS are associated with secretion of several hormones and hormone-like substances. The most widespread of them are ACTH (Cushing syndrome), antidiuretic hormone, insulin-like growth factor, erythropoietin, growth factor realizing hormone, parathormone-like protein, etc. [13, 28].

The following tumors are associated with ectopic adrenocorticotrophic hormone: small cell lung carcinoma, bronchial carcinoid, thymic carcinomas, tumors of pancreas, pheochromocytoma, medullary cancer of the thyroid, gastrointestinal carcinoid, adenocarcinoma, etc. [13, 14].

Clinical features of inappropriate antidiuretic hormone production syndrome consist of combination of water retention and secondary solute loss which leads to the fall of plasma sodium concentration. As a rule, the patients have normal volume status, hypothermia with hypoosmolality, elevated renal excretion of sodium, and urine osmolality greater than plasma osmolality. Most common clinical symptoms in these patients are caused by central nervous system toxicity. Patients complain of fatigue, anorexia, headaches, and altered mental status. Further, with the progress of the syndrome the delirium, confusion, and seizures develop. The syndrome may cause a coma, and in rare cases result in death. Most patients have minimal symptoms and during routine laboratory evaluation are diagnosed with hyponatremia [2, 11, 19].

Tumors associated with bone metastases (breast, prostate, lung cancers) lead to hypocalcemia. Those patients have increased skeletal avidity for calcium. Hypocalcemia can also occur in patients, whose tumors secrete calcitonin (medullary thyroid carcinoma, breast cancer, colorectal cancer, lung cancer, carcinoid). Hypocalcemia has many clinical manifestations. It can be asymptomatic, in some cases it demonstrates significant symptoms associated with neuromuscular irritability and cardiovascular changes: peripheral and perioral paresthesia, cramps, tetany, seizures, bronchospasm, laryngospasm, anxiety, confusion, cardiac arrhythmias, and congestive cardiac failure. In extreme

cases hypocalcemia is life threatening, especially if not recognized and untreated [3, 16, 17].

Tumor induced osteomalacia is a rare PNS characterized by hypophosphatemia and very low circulating concentrations of vitamin D<sub>3</sub>. The majority of neoplasms causing this syndrome are benign, but this PNS can coexist with lung carcinoma, multiple myelomas, and prostate cancer. Patients present with bone pain, phosphaturia, renal glucosuria, hypophosphatemia, normocalcemia, low level of 1,25 dihydroxyvitamin D<sub>3</sub>, and increased alkaline phosphatase level [18].

Mesenchymal tumors and hepatic carcinomas are mostly responsible for hypoglycemia as a PNS. Insulomas also frequently produce hypoglycemia. Gastrointestinal stromal tumors, lymphomas and adrenal carcinomas may also be associated with this PNS. Patients may have typical signs of hypoglycemia including generalized neurologic abnormalities. The causes of paraneoplastic hypoglycemia include production of nonsuppressible insulin-like GF-1 and GF-2, hypermetabolism of glucose, production of substances stimulating ectopic insulin release, production of hepatic glucose inhibitor, insulin binding by a monoclonal protein, insulin receptor proliferation or — rarely — ectopic insulin production [4, 11].

We can make a conclusion that in many cases endocrinologists have common problems with oncologists and clinical errors may happen in some unexpected circumstances, when a PNS is evaluated as a hormonal disease.

### **PARANEOPLASTIC HEMATOLOGIC SYNDROMES**

Many PNS of different origin show some hematologic manifestation. They include the following.

Erythrocytosis is mostly associated with renal cell carcinoma. The elevated serum erythropoietin is the chief reason of this PNS. Hepatoma is the next most common malignancy leading to erythrocytosis. The elevation of serum erythropoietin is also the reason of the development of erythrocytosis. Other tumors may be also accompanied by erythrocytosis. They include the following neoplasms: Wilms' tumor, hemangiomas, cerebellar hemangioblastoma, sarcomas, uterine fibrosis, and adrenal tumors [18].

There are obvious cases of polycythemia connected with arterial desaturation associated with hemoglobinopathies, carboxyhemoglobinemia, and chronic hypoxic states [19].

The anemias are typical for many kinds of tumors, especially at advanced stages. They are normocytic normochromic or hypochromic, connected with chronic diseases, with bone marrow invasion, secondary to cytostatic therapy and radiation treatment. Normochromic normocytic anemia in cancer patients is a common PNS.

Paraneoplastic anemia is characterized by low serum iron levels, normal or increased ferritin levels, normal iron stores, and low serum erythropoietin level. Pure red cell aplasia is a rare cause of anemia in cancer

patients. It can be associated with thymoma and hypogammaglobulinemia. This PNS may also be associated with different lymphoid malignancies. It is rarely caused by solid tumors. Warm antibody hemolytic anemia is most commonly associated with lymphomas. Cold agglutinin disease is most connected with Waldenström's macroglobulinemia and lymphomas. Autoimmune hemolytic anemia may be associated with solid tumors, such as ovarian, lung, breast, gastrointestinal and renal cancers.

DIC can follow the microangiopathic hemolytic anemia in metastatic carcinomas [20].

As a PNS, microangiopathic hemolytic anemia may respond to effective anticancer therapy. The mechanism of most PN anemias remains unknown.

Granulocytosis with elevation of white blood cell count without infection or leukemia is common in neoplasms as one of the PNS. Usually, tumors that are accompanied by granulocytosis include Hodgkin's lymphoma, different other lymphomas, and a variety of solid tumors such as stomach, lung, pancreatic, brain cancers, and malignant melanoma. The common mechanism associated with granulocytosis is production of growth factors by the tumor.

Granulocytopenia may appear as a PNS. Except under the influence of chemotherapy, radiation therapy or tumor infiltration of bone marrow, the tumors can rarely produce a factor that would suppress granulopoiesis by interfering with many growth factors. There are several reports about antibodies against granulocytes in patients with Hodgkin's lymphoma. Neutropenia associated with large granular lymphocytic leukemia and lymphoma may be caused by immune dysregulation of T-cells.

In some cases, thrombophlebitis represents an incident of PNS. Oncological patients have a hypercoagulable state. An association between venous thrombosis and malignancy was first suggested by Trousseau in 1865. Clinical thromboembolism occurs in 11% of cancer patients and is the second leading cause of death in patients with overt malignant diseases. Clearly, cancer related thrombosis has a complex of features including different imbalances of coagulation and fibrinolysis. Several studies of patients with venous thromboembolism suggest a higher incidence of malignancy diagnosed within the first 6 months after presentation of thrombosis.

Several paraneoplastic coagulopathies associated with cancer have been reported too. It concerns such localizations of malignancy as gastric and adrenal carcinomas, leukemias and lymphomas [2, 21].

Acquired hemophilia (factor VIII antibodies) has been reported in patients with solid tumors, paraproteinemias and lymphoproliferative disorders. Overt DIC occurs in 7% of patients with solid tumors (primarily adenocarcinomas). Eosinophilia, basophilia, thrombocytosis, thrombocytopenia, and thrombophlebitis also belong to hematologic manifestations of PNS [22].

Hematologic manifestations of cancer include also nonbacterial thrombotic endocarditis. It may lead

to thrombotic or hemorrhagic complications and may occur with or without DIC. Nonbacterial endocarditis should be suspected in cancer patients with ischemic embolic events and is most commonly seen with adenocarcinomas of the lung and pancreas [20, 21].

### PARANEOPLASTIC RENAL SYNDROMES

Renal manifestations often accompany several kinds of malignancy. In 22% of cases membranous nephropathy has been clearly associated with a malignancy. Most common malignancies in this connection are lung, colon, and stomach carcinomas.

Nephrosis-ranged proteinuria, hypertension and microscopic hematuria characterize the syndrome. Immune complexes are thought to play a role in malignancy-associated glomerular disease. The responsible antigens include fetal antigens, autologous nontumor antigens, tumor-associated antigens, and viral antigens [4].

Other glomerular diseases include membranoproliferative glomerulonephritis and minimal-change disease. Hodgkin's lymphoma is the cause of most cases of minimal-change disease with lymphoproliferative disorders, pancreatic carcinoma, and mesothelioma. Approximately 10–15% of cases precede the lymphoma and 40–50% manifest after the tumor is diagnosed. There is a parallel relationship between the activity of the lymphoma and the degree of proteinuria.

Other cancer-associated glomerulopathies include focal and segmental glomerulosclerosis with CLL, T-cell non-Hodgkin's lymphomas, and acute myelogenous leukemia. Immunoglobulin A nephropathy is associated with lung, head, and neck cancer, pancreatic cancer, mycosis fungoides, and liposarcoma. Membranoproliferative glomerulonephritis is connected with chronic lymphoblastic leukemia, Burkitt's and other lymphomas, hairy cell leukemia, and malignant melanoma [3].

Thus, the nephrologists have to do with different PNS that need to be differentiated from non-oncological renal diseases and *vice versa*. Internists encounter the PNS more often than other specialists. In internal medicine clinics classic PNS is encountered in 90% of patients with PNS, the endocrine and metabolic syndromes in 7–10%, the rheumatoid-like — in 25–62%, the cardiovascular — in up to 50%, dermatological — in 14–63%, neurological — in 1%, gastrointestinal syndromes — in 12–22%, hematological — in 35–55% of patients. Consequently, the internists have to remember about the possibility of PNS in their patients.

### PARANEOPLASTIC RHEUMATOLOGIC SYNDROMES

Rheumatologists are of special importance among other representatives of medical professions. In their practice, rheumatologists often encounter the so-called "masks" — typical for rheumatological disorders but sometimes present as a part of PNS.

Rheumatologic diseases and malignancies have many common features — in etiology, diagnostics, and complications, including some PNS.

The peculiarities of paraneoplastic rheumatic syndromes are as follows:

- chronological correlation with oncological diseases;
- frequent occurrence in elderly age;
- asymmetric affection of joints;
- predominant involvement of lower limbs into the process;
- abrupt in onset;
- as a rule, absence of rheumatoid factors and rheumatoid nodules;
- nonspecific alterations in synovial biopsies;
- positive dynamics of PNS during the successful treatment of malignancy;
- “rheumatological” symptoms recurrence caused by metastases or local recurrence of the malignancy.

Rheumatologic PNS include:

- hyperostotic osteoarthropathy (Marie — Bamberg syndrome);
- rheumatoid arthritis;
- dermatomyositis;
- tendovaginitis migrans;
- scleroderma-like syndrome;
- different types of vasculitis including panarteritis nodosa and Wegener’s vasculitis;
- lupus erythematosus;
- palmar hyperkeratosis;
- polychondritis and many other above-mentioned syndromes [2–4].

Malignization is often accompanied by autoimmune processes that are followed by production of a variety (nearly 400 kinds) of antibodies against the bright spectrum of antigens. Oncoproteins controlling the cellular growth and differentiation are best known among them. For example, 50% of patients with breast cancer represent p185, some other proteins are associated with lung cancer, ovaries and colon malignancies. Best known is p53 which prevents cancerogenesis and teratogenous disorders. In the process of mutation, it loses the named properties and is present in many tumors in such form. Its specificity is nearly 96%, so it can serve as a test for early diagnosis in high-risk patients. The antigens connected with cell proliferation are present in every kind of cancer in 2% of cases.

It is known that autoimmune rheumatological disorders are connected with a lot of antibodies — Ro, La, Sm, RNP, and others may be present in patients with malignancies. A high level (22%) of antiphospholipid antibodies (aPL) is detected in 3% of patients with malignancies as compared to healthy contingent. The risk of thrombosis triples in oncologic patients with aPL(+) in comparison with the patients with aPL(–). At the same time, a patient with aPL(+) has a higher risk of cancer development.

The so-called classic PNS which include fever, asthenia, cachexia, and anaemia are worth discussing.

These signs are common for a large number of malignancies and some researchers argue that these symptoms characterize tumorous intoxication.

PNS simulating autoimmune disorders are quite frequent in rheumatological practice. Relation between tumors and autoimmune processes is rather complicated. Many factors take place in those relations.

An allergic reaction often develops on the background of tumors.

Oncoantigens further sensitize the organism. This leads to violation of immunologic tolerance to autoantigens. Anticancer drugs also have influence on the immunological state of the organism. As a result, many rheumatological signs appear also in cancer patients.

Emergence and development of tumors is accompanied by metabolic changes in the organism that lead to disturbance of protein, fat, carbohydrate metabolism, and to infringement of immune system. Clinical signs of such events include weakness, tiredness, hypodynamia, disturbance of sleep, weight loss, hypothermia, and several other symptoms. These facts are defined as endogen intoxication syndrome or tumor toxicosis. These phenomena are present in 70–80% of oncological patients [23].

To compare PNS it is necessary to remember that the same signs can be evaluated as common symptoms of many PNS.

Reports on sorbtion appeared in oncological literature at the end of the previous century [24].

Rheumatoid arthritis or asymmetric polyarthritis may occur with malignancy.

Joint manifestations regress on removal or control of the underlying malignancy in 48% of patients. About 80% of female patients with asymmetric polyarthritis and malignancy had breast cancer. Some 83% of patients with polymyalgia rheumatica are said to develop a malignancy within 3 months and some of these cases may represent arterial embolism of muscle through nonbacterial thrombotic endocarditis. Lymphomas may be associated with systemic rheumatic disease. In Sjögren’s syndrome a spectrum of benign to malignant lymphoproliferations can be seen, but whether this is “at a distance from the tumor” remains to be determined [29].

Metastases to joints can simulate rheumatoid arthritis and cytological examinations should be done in regard to joint effusions in cancer patients [30].

Fever occurs frequently in cancer patients and is usually caused by infection. In addition, there exist other noninfectious causes, with which certain concerns are associated. Main associations are with Hodgkin’s lymphoma, myxomas, hypernephromas, osteogenic sarcomas, and other tumors. Tumor-associated fever is usually defined as “unexplained” fever that coincides with tumor growth, disappears promptly on tumor removal or control and reappears with tumor recurrence. When the fever persists, the tumor is a likely cause of it if other reasonable causes are excluded. In Hodgkin’s disease, fever is a bad

prognostic sign. There are no data on the influence of fever associated with other tumors on prognosis.

The etiology of tumor-associated fever is connected with several “endogenous” pyrogens released by tumor cells [25, 26].

Some malignant cells are able to stimulate the production of “blocking antibodies” against tumor antigens, for example, the production of immunoglobulins of A, E, and D classes which do not activate the complement system and conjugates with tumorous antigens building antigen-antibodies complex on the surface of cancer cell which can cause the so-called immune-complex syndrome similar to PNS or tumor toxicosis [32].

All of these pathologies are characterized by an aggregate of symptoms including weakness, tiredness, hypodynamia, sleep disorders, appetite loss, paleness, hypothermia, and other symptoms. Some decades ago such complexes of metabolic and nonspecific clinical signs were evaluated as tumor toxicosis and a corresponding treatment was proposed [33]. We investigated the possibilities of detoxication treatment, including hemosorption, lymphosorption, enterosorption, and others. We learned that in some cases not only does the sorption treatment give unexpectedly positive results in regard to clinical course but sometimes also facilitates the reduction of the tumor [34].

In particular, plasmapheresis was used in 4 patients with lung cancer, and provided for lessening or even elimination of clinical symptoms influencing clinical, biochemical and immunological manifestations of intoxications, and giving the possibility to finish the course of radio- of chemotherapy [35]. Another study showed positive subjective changes of the patients' condition, lower concentrations of circulating immune complexes and improvement of reactions of cell-mediated immunity (blast-transformation reaction and E-rosetting cell) in patients with extended forms of tumor process after use of hemosorption [36].

Taking into account the previous clinical experience we can state that the so-called tumorous toxicosis is a part of PNS and it is reasonable to discuss the idea of detoxication from the present-day perspective.

Analyzing the problem of PNS and the attitude of different medical professionals to it, we can claim that internists, dermatologists, rheumatologists, neurologists, and other non-oncology professionals encounter PNS in their everyday medical practice. For these specialists the presence of the abovementioned syndromes may be a display of usual diseases (like rheumatism, skin diseases, kidney failure, etc.) that needs a specific treatment. In the case when the disease is not connected with the mentioned conditions but is a manifestation of malignancy (PNS) the treatment of a non-oncological disease leads to the loss of time with corresponding consequences. That is why the correct differential diagnosis is very important for the mentioned experts.

The subject of PNS is not sufficiently covered in special oncology literature, the reason of which lies in the fact that oncologists having a morphologi-

cal confirmation of malignancy interpret all present symptoms as a manifestation of cancer.

According to estimations, PNS does not correlate with the stage of tumor or its prognosis. That is why they stay outside the consideration of oncologists.

The problem of tumor toxicosis (or immune-complex disease corresponding to malignancies) was discussed in special literature several decades ago. As a logical conclusion, a detoxication or deblocking treatment was proposed. Probably it could be reasonable to return to this idea in some patients with PNS.

## CONCLUSIONS

1. PNS are a heterogenous group of phenomena caused by malignancies influencing the endocrine and immune systems, metabolism, and other mechanisms, not all of which have been identified by now.

2. Not all facts that are described as PNS correspond to the identification criteria for PNS. Some of them are not influenced by radical treatment of the tumor, whereas such influence is postulated as obligatory for PNS cases.

3. Some PNS are life-threatening and therefore require active treatment.

4. Tumorous toxicosis or immune-complex disease, which were widely discussed in the past decades, are *de facto* a part of PNS and consequently their respective treatment deserves attention.

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