PARANEOPLASTIC SYNDROMES IN GASTROENTEROLOGY

E. Y. Cherevatskaya[1], N. B. Gubergrits[2]

[1]*Donetsk Regional Clinical Territorial Medical Union*

[2]*Donetsk National Medical University n. a. M. Gorky*

Key words: paraneoplastic syndromes, tumors of the digestive organs, pathogenesis, dermal changes, endocrine syndromes, hematological syndromes, osteal-articular-muscular syndromes

"Paraneoplastic syndrome" (PNS) is a disorder caused by the tumor process and became apparent at a distance from the tumor and its metastases.

PNS denote the clinical and laboratory manifestations caused not by local growth in primary or metastatic tumors, but nonspecific reactions of the various organs and systems, or ectopic tumor production of biologically active substances [3].

This term was used in 1948 and came from the Greek word para (near) + neos (new) + plasis (formation).

In 1865, the famous French clinician A. Trousseau first described the development of PNS — migratory thrombophlebitis in patients with gastric cancer, uterine and testicular (later on the basis of unfounded shin vein thrombosis he suggested stomach cancer from which he died) [1].

More than 60 PNS were described later. Their frequency in different tumors varies considerably, suggesting the nosological specificity of PNS. For example, only small-cell lung cancer has in some cases the development of hypercalcaemia and gynecomastia; hypercalcemia is more common in myeloma than other systemic diseases of the blood; autoimmune hemolytic anemia is common in chronic lymphocytic leukemia; amyloidosis — upon lymphogranulomatosis; acanthosis nigricans — gastric cancer, and so on. Many syndromes attributable to paraneoplastic ones occur in non-neoplastic diseases, such as fingers-drumsticks observed in chronic non-specific lung disease, congenital heart disease, liver cirrhosis, and others.

PNS knowledge is important for physicians of all specialties, as tumors of different locations at certain stages prior to local symptoms may occur with non-

specific symptoms, mistakenly treated as a distinct disease of the skin, joints, kidneys, and so on. On the one hand, it may lead to undue therapy, and on the other — to delay cancer search and belated detection of the tumor.

General characteristics of the PNS [3]

Despite the diversity of the nature and severity of the clinical and laboratory manifestations, history of occurrence, further course, there are common features and patterns of PNS:

- pathogenetic mechanisms;
- development only upon the malignant tumors;
- nonspecific clinical and laboratory manifestations;
- lack of parallelism with local symptoms of the tumor;
- possibility of development prior to the local symptoms of the tumor;
- resistance to treatment;
- disappearance after radical treatment of the tumor and re-emergence after relapse.

Currently, the following basic pathogenetic mechanisms of PNS are defined [3]:

- effect of tumor secreted biologically active proteins or polypeptides, growth factors, interleukins, cytokines, prostaglandins, embryonic (carcinoembryonic antigen or α-fetoprotein) and other proteins, such as immunoglobulins, and enzymes;
- development of an autoimmune process or immune suppression;
- formation of ectopic receptors or competitive blocking action of normal hormones by biologically inactive hormones produced by the tumor;
- "forbidden contact", at which enzymes or other products are released, that are normally not present in the bloodstream, but circulating under pathological vascularization of the tumor or the destruction of the basement membranes of tumor cells, which leads to the development of antigenic reactions that do not meet the normal physiological functions;

– other causes, including genetical predisposition to the development of autoimmune processes.

Of the above mechanisms in the pathogenesis of the PNS, immune system reactions in response to the presence of tumor immunologically foreign antigen are the most important. Such a mechanism takes a place upon the development of clinical symptoms of dermatomyositis, rheumatoid arthritis, autoimmune hemolytic anemia, and other systemic symptoms on the background of certain tumors. Another pathogenetic mechanism of PNS is an ectopic production by tumor cells of biologically active substances (hormones, interleukins, etc.), forming one or another manifestation (Cushing's syndrome, fever, erythrocytosis, and others) [3].

Dermal manifestations

Paraneoplastic manifestations are often localized on the skin. There are several variants of dermatoses occurring upon malignant tumors, but not all of them have the same diagnostic value. Among skin PNS, the following ones have clinical significance: acanthosis nigricans, erythema annulare centrifugum Darier; dermatitis herpetiformis Duhring; prurigo of adults; itching; erythema nodosum; panniculitis [4].

Classical PNS with skin manifestations is considered an *acanthosis nigricans (papillary-pigmentary degeneration of the skin)*, detected mainly in cancer of the stomach, pancreas, rectum, rarer — in breast and ovarian cancer (Fig. 1). The presence of black acanthosis is especially suspicious in persons over 40-50 years old, in whom, according to various sources, this dermatosis is associated with tumors of the gastrointestinal tract in 60-100% of cases. Clinically, acanthosis nigricans is characterized by skin pigmentation from gray-coffee to black, warty growths, hyperkeratosis. Approximately half of patients have papillary growth on the mucous membranes of the mouth, labia. The process is localized mainly on the back of the neck, in axillary hollows, the elbows, femoral-inguinal folds, around the navel, anus, on the external genitals [3, 4].

Erythema annulare centrifugum Darier is characterized by the presence of pale pink, swollen, non-peeled (often) red rash on the body, at least on the neck and limb,.

Elements of the rash have towering rim and sunken center with normal skin color. Erythema Darier is prone to peripheral radial growth ("centrifugal" erythema). It often occurs upon the digestive tract cancer and breast cancer [3, 4].

Dermatitis herpetiformis Duhring belongs to the group of so called cystic (vesicular-bullous) dermatoses (Fig. 2). It is clinically characterized by polymorphic rash on erythematous background in the form of nodules, spots, blisters, bubbles, which are grouped into foci, forming sometimes bizarre shapes. Rash is accompanied by severe itching and localized mainly on the symmetric parts of the flexion of the legs, shoulders, and body. Worsening rash is typical upon skin lubricated with iodine-containing drugs. Duhring dermatitis can be observed in many malignant tumors of various localization [3, 4].

Prurigo can appear in the form of multiple small-sized dense nodules, on the surface of which the vial with serous contents is formed (Fig. 3). Because of the severe itching, nodules are sometimes covered by serous-bloody crusts. Excoriation may become infected.

Pruritus without specific skin rash may appear as PNS long before other manifestations of cancer do. Pruritus typically has a generalized character, but may be localized (nose and anus, vulva). In some cases, long continuing itch of shinks, inner thighs, upper trunk and extensor surfaces of the upper extremities is observed in advanced malignancy. With prolonged and intense itching, scratched skin appears, nails get high gloss (a symptom of "polished" nails) due to constant friction of nais. Despite the fact that itching occurs in a variety of non-neoplastic diseases (cholestasis, diabetes mellitus, chronic renal failure, and others.), the presence of causeless pruritus, especially in elderly and senile age, requires the exclusion of tumor [3, 4].

Erythema nodosum refers to the deep skin vasculitis characterized by the appearance of painful bright red dense nodes on the shins (Fig. 4). Often there is fever, pain in the joints. Nodes usually disappear in 2-3 weeks. Relapsing course is quite possible. Along with neoplastic diseases, nodular erythema may occur upon streptococci, rarely in other infections, tuberculosis, sarcoidosis [3, 4].

Weber-Christian panniculitis is a nonspecific focal inflammation of subcutaneous adipose tissue and is characterized by subcutaneous nodules, often localized on the extremities. Hyperemic skin is over them, sometimes nodes become necrotic to form ulcers with further scarring. In a few months nodes may spontaneously disappear and then reappear. It is estimated that 5-10% of patients with panniculitis have tumor disease [3, 4].

Endocrine PNS

Endocrine PNS are caused by the ability of cells of some tumors to secrete biologically active substances that have the properties of various hormones, the excess of which determines the clinical manifestations of PNS.

Among the best known paraneoplastic endocrinopathies is *Cushing's syndrome,* often growing sharply due to ectopic ACTH production by tumor cells (in particular, pancreatic cancer); affects approximately 40% of patients with oatcellular lung cancer. Cushing's PNS differ from the classical and are characterized by acute development, less frequent hyperglycemia, osteoporosis and more frequent hypokalemia and muscle weakness. Along with the increased ACTH production, some tumors secrete melanocyte stimulating hormone, which is manifested in hyperpigmentation [1, 3].

Pancreatic cancer (as well as different variants of bronchogenic, renal, prostate, ovaries cancer) has the ability to secrete parathyroid hormone in the absence of bone tumors (e.g., metastases). During prolonged excessive secretion of parathyroid hormone there may be *calcification* of *organs and tissues* (kidney, etc.), increased gastric secretion. It is also a possibility of production of calcitonin, parathyroid hormone antagonist which is oppressing the mobilization of calcium from the bones and enhances calcium excretion through the kidneys, by certain tumors. As a result, hypocalcemia is being developed with the respective manifestations (in the form of convulsions) [3].

One of PNS variants is the carcinoid syndrome. The basis of the clinical manifestations of PNS is carcinoid tumor tissue production (pancreas, intestine, lung) of serotonin, gastrin, glucagon, insulin peptide, vasoactive intestinal peptides and

other biologically active products. The clinical picture of carcinoid syndrome includes tachycardia, hypotension, tremor, diarrhea disorders, flushing of the face and neck, anxiety. These manifestations may occur in various combinations and to a certain extent are determined by the localization of carcinoid.

In many patients with cancer of the pancreas, stomach, liver, as well as adrenal and lung tumors, hypoglycemia can occur. Paraneoplastic hypoglycemia mechanisms are apparently increased glucose utilization by tumor tissue and insulin secretion peptide [3].

High blood levels of adrenocorticotropic and somatotropic pituitary hormones and corticosteroids may be the cause of paraneoplastic diabetes and hypothyroidism in some cancer patients. Mechanisms of paraneoplastic hyperthyroidism occurring in a number of cases of cancer of the stomach, lung and breast cancer, are poorly understood [1].

Hematologic PNS

The most common "hematological companion" of cancer is anemia, which gives reason in almost all the cases of anemia to suspect the presence of tumor and conduct detection of cancer. However, it is appropriate to recall that anemia in tumor diseases can be caused by different pathogenetic mechanisms. Thus, in tumors of the stomach and intestines iron deficiency anemia develops due to chronic blood loss; anemia upon cancer of the stomach fundus may be associated with a deficiency of vitamin $B_{12,}$ and upon metastasis to the bone marrow it is due to bone marrow insufficiency. Among paraneoplastic anemias, hemolytic anemia is the most common, in particular, autoimmune and microangiopathic one. Autoimmune hemolytic anemia develops upon common lymphoproliferative disease (lymphogranulomatosis, chronic lymphocytic leukemia), but may be in other tumors (cancer of the stomach, lung, ovarian, and others). Microangiopathic hemolytic anemia occurs due to mechanical destruction of red blood cells in the tumor tissue itself or filaments of fibrin in the microvasculature in the development of DIC-syndrome. Paraneoplastic anemia may be also associated with redistribution of iron in the cells of macrophages, as is the case when there is an active anemia on the

background of inflammation of infectious non-infectious origin (anemia of chronic disease) [3].

In addition to anemia, erythrocytosis is revealed in tumors of certain localization (liver, etc.). The basic mechanism of this syndrome is the production of erythropoietin by tumor cells. In these cases, a differential diagnosis with erythema is needed, for which the most typical are the plethora and pancytosis [3].

Changes in platelet germ in malignant tumors occur in the form of thrombocytopenia and thrombocytosis. Thrombocytopenia is of immune nature or the result of consumption of platelets in DIC-syndrome on the background of tumors of different localization (pancreas, stomach, etc.). Thrombocytopenia may be severe and accompanied by hemorrhagic syndrome [3].

Thrombocytosis is considered more typical hematological PNS (cancer of the pancreas, stomach, intestines, etc.). Thrombocytosis is a risk factor for thrombotic complications in patients with malignant tumors.

Generally, one of the PNS in cancer patients is a violation of hemostasis with a penchant for hypercoagulation and development of thrombotic complications (for example, gastric cancer, pancreatic cancer) [3].

Approximately one third of patients with cancer of the body and tail of the pancreas at autopsy have phlebothrombosis. Paraneoplastic phlebothrombosis differs by migratory character, recurrent course, resistance to anticoagulant therapy, is often accompanied by the development of pulmonary embolism. Such a clinical situation should serve as a pretext to conduct the detection of cancer. In cases of early radical removal of the tumor, there may be a persistent cure of recurrent thrombosis. At the heart of thrombotic processes in tumor diseases is thrombocytosis, as well as tumor production of fibrinopeptide A (tumor marker), the amount of which may be proportional to the size of the tumor. Activation of the hemostatic system in cancer patients is realized by an external mechanism of coagulation, i.e. by effect of the tissue thromboplastin on factors VII and X. Many tumor cells produce large amounts of thromboplastin, as well as a special "cancer procoagulant," which are able to

activate VII and X factors. Many cancer patients showed a significant increase in plasma of tissue thromboplastin and activated factor VII [1].

It is necessary to conduct a careful study upon the appearance or frequency of thrombosis, especially in the presence of other manifestations, which may be paraneoplastic ones (fever, arthralgia).

Paraneoplastic thrombotic endocarditis or abacterial warty endocarditis develops in the mitral or aortic valves and is often complicated by embolism of the coronary or cerebral arteries. This syndrome is detected in 1.3% of autopsies of dead from malignant tumors, most often in gastric cancer, pancreatic, colon and lung cancer.

At the same time, there is a possibility of hemorrhagic complications, despite the significant increase in platelet count, since they are functionally defective [3].

Patients with cancer may have hemorrhagic vasculitis as PNS with typical clinical manifestations (symmetrical hemorrhagic rash, raised above the skin, not disappearing when pressed).

Eosinophilia is one of the variants of the hematological PNS. Probably, under the influence of tumor antigens, as well as under the influence of drugs and helminth antigens, activation of eosinoposis occurs, ripening time is shortened and duration of the recirculation of eosinophils in blood increases [3].

Leukemoid reactions develop in some malignant cases. These reactions are both consequence of common actions of neoplastic processes or decomposition products of tumor, and metastasis to the bone marrow. Changes of bone marrow hematopoiesis in these cases affect not only myeloid, erythroid and megakaryocytic sprouts. Leukemoid reaction is often accompanied by anemia, presence erythrokaryocytes (normoblasts) in the peripheral blood, thrombocytosis. In addition, ESR is significantly increased. In the study of bone marrow in patients with malignant tumors (often with stomach cancer, hypernephroma) plasma cell reaction with plasma cell content increased in myelogram up to 20-30% and higher can be detected. In these patients there are considerable difficulties in the differential diagnostics with multiple myeloma. The latter is characterized by the destruction of

flat bones, monoclonal immunoglobulinopathy (pathological protein fraction in blood proteinogram, Bence-Jones protein in the urine, increase in one class of immunoglobulins in the blood serum), presence of morphologically altered (dual core and others) and immature plasma cells (plasmablasts, plasmocytes) in the bone marrow. In patients with malignant tumors range of plasmatic cells of bone marrow is usually presented by mature plasmocytes. In addition, accumulations of atypical (tumor) cells may be found (though not necessarily) in bone marrow trephine biopsy or aspirate.

Osteal-articular-muscular PNS

The relationships between tumor and autoimmune processes are complex and depend on many factors: the course of allergic processes, developing on the background of some malignant tumors, additional sensitization, tumor antigens, violation of immunological tolerance to self-antigens, mutagenic effect of anticancer agents, ionizing radiation and the tumor itself for clones of immunocompetent cells producing pathologic antibodies responsible for development of secondary autoimmune syndrome [1].

PNS with such a pathogenesis include arthritis (rheumatoid-like syndrome), polymyalgia rheumatica, palmar fasciitis syndrome, migratory tenosynovitis, polymyositis (dermatomyositis), pseudosclerodermic syndrome, Sjogren’s syndrome.

Arthritis, emerging as PNS, is characterized by acute onset, asymmetrical lesions of the joints of the upper and lower extremities. The clinical picture can be similar to rheumatoid arthritis but there is no erosive process in joints, rheumatoid factor and rheumatoid nodules are not detected in the blood of. PNS is characterized by the discrepancy between a mild articular syndrome and, on the contrary, severe general state of patient. Arthritis as PNS often develop in elderly patients, rarely juvenile arthritis in tumors in children is described. Paraneoplastic arthritis may be associated with erythema nodosum, eosinophilia, polyserositis. Conventional therapy of arthritis is not effective.

The most common osteal-articular PNS is hypertrophic osteoarthropathy — thickening of the fingers like "drum sticks" with nail changes like "clock glasses". At

the heart of these changes there are phenomena of periostitis and neoplasms of bone structures. Radiographically, these changes appear in the form of layered periosteal overlays around the diaphysis. With the development of hypertrophic osteoarthropathy as PNS it manifests acutely, there is severe burning pain in the bones of the extremities, swelling and stiffness in the joints of the fingers, severe muscle weakness, swelling of the distal third of the extremities, local hyperemia and hyperthermia. The pathogenesis of hypertrophic osteoarthropathy is associated with osteoblasts-stimulating agents that are produced by tumor cells. In cancer of the digestive tract, such changes are rare (often upon bronchogenic carcinoma and mesothelioma) [3].

PNS in the form of polymyalgia rheumatica is manifested by pain in the proximal shoulder and pelvic girdle in the absence of joint damage. There is fever, greatly accelerated ESR.

Besides arthritis, PNS can manifest in the form of lesions of soft juxta-articular tissues and the ligamentous apparatus (polymyalgia, palmar fasciitis, tenosynovitis, and so on. D.).

Symptomatology of muscle lesions in the form of myalgia, myositis, myasthenia may precede the appearance of local evidence of tumor. A typical "rheumatology" PNS is polymyositis (myositis), the frequency of tumor myositis in adults is 15-20% of all cases, and in elderly patients is 50%. Polymyositis may develop in tumors of different localization, but this PNS is more common in patients with cancer of the digestive organs, lung cancer. Paraneoplastic polymyositis features are development after the age of 50, lack of skin lesions, less pronounced weakness of the hind neck muscles than in non-tumor dermatomyositis, mostly acute or subacute course, refractory to treatment with glucocorticoids and cytotoxic drugs. In view of the above-stated, each case of diagnosed polymyositis (myositis), especially in the elderly, requires the exclusion of cancer.

A combination of malignant tumors with rheumatoid arthritis, scleroderma, periarteritis nodosa, systemic lupus erythematosus, Hashimoto’s thyroiditis, Sjogren’s syndrome is described. In addition to combining with true autoimmune

diseases, tumors may manifest as PNS "imitating" these diseases. Thus, upon PNS joint damage may be combined with skin changes, serousitis, fever and so on. Lupus-like syndrome as PNS is characterized by the stability joint and muscular syndrome to treatment, rare visceral lesions, hypochromic character of anemia, thrombocytosis, leukocytosis. Pseudosclerodermic syndrome as PNS is also described, but it almost does not occur in tumors of the digestive system (can be found in ovarian, breast, lung cancer) [1, 3].

Other PNS variants

In gastric cancer (as well as lymphogranulomatosis, chronic lymphocytic leukemia, lymphoma and reticulosarcoma, lung cancer) in some cases there is a nephrotic syndrome, which is clinically manifested by peripheral edema, dropsy of the cavities, massive proteinuria, hypo- and dysproteinemia, hyperlipidemia. PNS severe form is an amyloidosis.

PNS in the form of damage to the nervous system occurs, according to different studies, in 2-18,5% of cancer patients. Psychosis and other mental disorders (more common in patients with pancreatic cancer) are marked out, as well as paraneoplastic neuropathy (encephalopathy and myelopathy).

Hyperuricemia with the blockade of renal convoluted tubules and severe nephropathy is described as PNS. You should keep in mind that intensive chemotherapy may contribute to these changes. Hypo- and hyperuricemia as PNS in cancer of the digestive organs do not develop (described at hematosarcoma, lymphogranulomatosis).

Not only the development of various PNS as manifestations of cancer of the digestive system is possible, but on the contrary, when the tumor is not localized in the digestive tract, the accompanying PNS are realized in the form of gastrointestinal disorders. Upon lymphogranulomatosis, perireticular deposition of amyloid masses in kidneys, liver, spleen, intestine is observed. PNS are also described, upon the development of which a violation of the immunological activity of the organism is important, as well as local changes associated with tumor growth. For example, cases

of sprue-like steatorrhea (celiac disease) occurring in patients with hepatosarcoma and manifested in "fatty" diarrhea and paroxysmal abdominal pain [1].

In cancer of the esophagus, besides the described above PNS, more rare variants of paraneoplastic lesions occur [5]:

1. "Cancer" coagulopathy (often on the background of thrombocytosis): a) Lian-Siguier-Welti syndrome — combination of diaphragmatic hernia and a tendency to recurrent phlebothrombosis of extremities; b) Trousseau syndrome — migratory thrombophlebitis, often indicating the running esophageal cancer; occurs in cancer of other localizations.
2. "Dermal" PNS: a) Bazex syndrome — spotty and itchy lesions of hyperkeratosis, appearing simultaneously with the development of the tumor, but sometimes before the onset of symptoms of esophageal cancer (even 1-2 years); b) Clark syndrome — palmoplantar hyperkeratosis and hyperhidrosis (sometimes with a bundle of nails); as PNS associated with cancer of the esophagus or lung; c) Gammel syndrome — paraneoplastic migratory erythematous-desquamative hyperkeratosis, paced a few months (but often at the same time) before signs of malignancy (including esophageal); g) Zinsser-Cole-Engeman syndrome — congenital dystrophy of the mucous membrane of the esophagus and skin: poikiloderma of the whole body, preferably the neck, chest and back, and also lobes of the ears, penis and skin of thighs, leukoplakia of oral cavity and mucous membrane of the esophagus, palmoplantar erythema with hyperhidrosis; e) Parnell-Johnson syndrome — palmoplantar hyperkeratosis.
3. Hormonally active Schwartz-Bartter syndrome — peculiar type lung or esophageal cancer course: hypersodiumureria, hyponatremia, edema, increased urinary excretion of 7-keto steroids and low — aldosterone, usually associated with the overproduction of antidiuretic hormone by tumor cells.

4. Denny-Brown’s syndrome —combination of myasthenia gravis with bronchocarcinoma or small cell cancer of the esophagus: the weakness of the proximal muscles, weakened tendon reflexes.

Many syndromes described as paraneoplastic are often prior to the symptoms of cancer (sometimes for years). The greatest time interval is marked for dermatological manifestations, neurological disorders, polymyositis, fever.

Paraneoplastic symptoms are non-specific tumor markers that should be considered and used in the early diagnostics of malignant tumors. In case if paraneoplasia develops simultaneously with tumor process, it often hinders detection of the tumor, masking its appearance (Fig. 5).

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Paraneoplastic syndromes in gastroenterology

E. Y. Cherevatskaya[1], N. B. Gubergrits[2]

[1]*Donetsk Regional Clinical Territorial Medical Union*

[2]*Donetsk National Medical University n. a. M. Gorky*

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Article presents the definition of “paraneoplastic syndrome”, variants of the pathogenesis of these syndromes. Peculiarities of dermal, endocrine, hematological, osteal-articular-muscular and other paraneoplastic syndromes are separately analyzed, localizations of tumors are indicated, upon which certain paraneoplastic syndromes are being formed. Article is aimed at the early detection of tumors and differential diagnostics if the patient has the relevant syndromes.

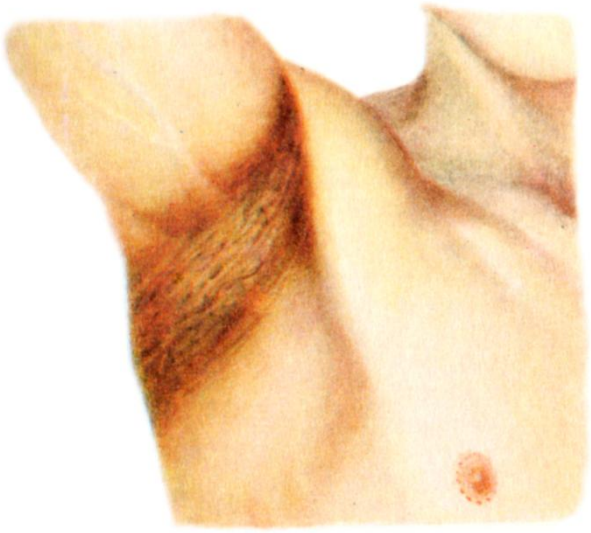


Fig. 1. Acanthosis nigricans (by M. A. Rosentool, 1974) [6].

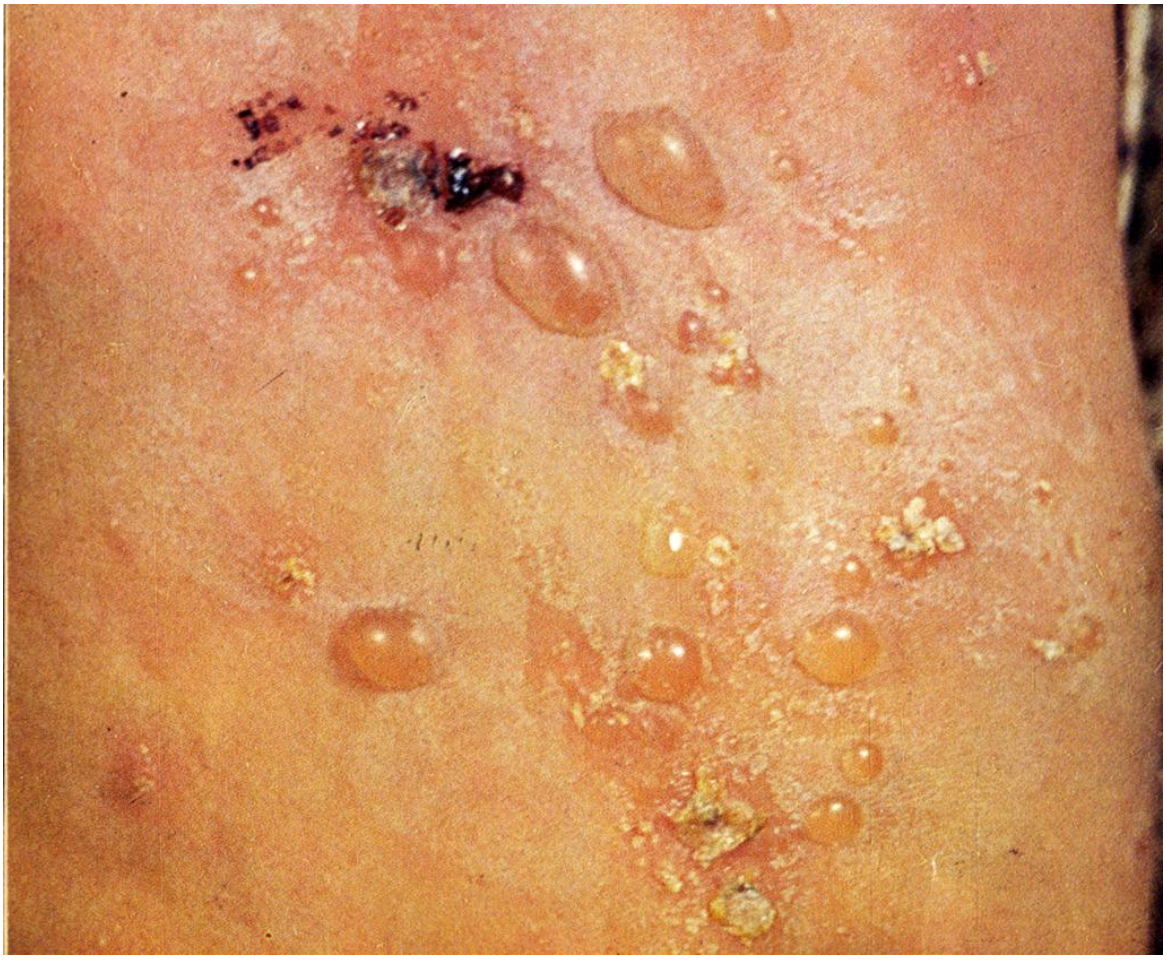


Fig. 2. Dermatitis herpetiformis Duhring (by V. V. Vladimirov et al., 1980) [2].

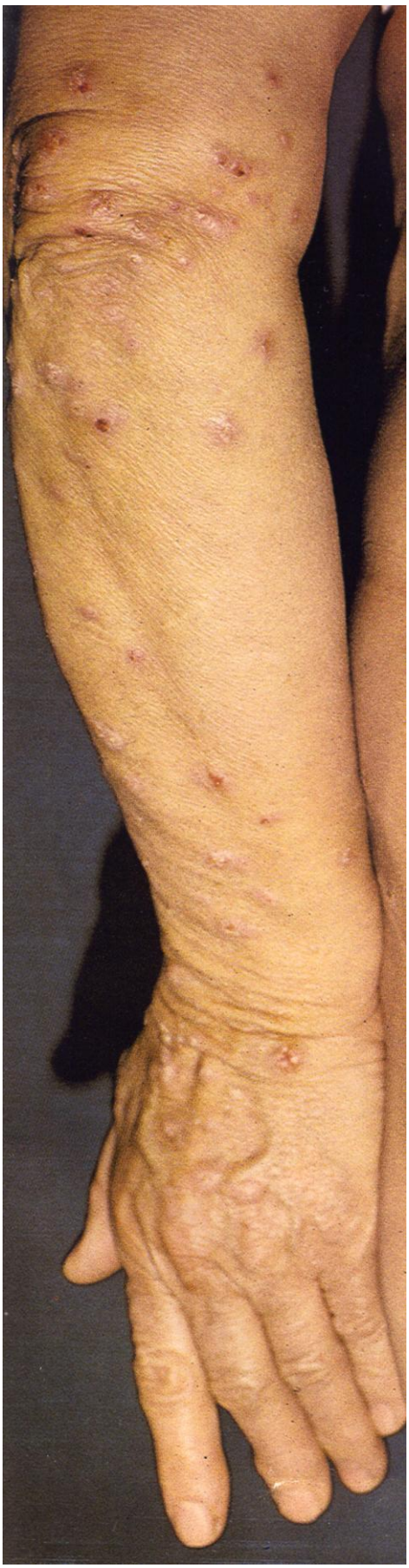


Fig. 3. Prurigo (by V. V. Vladimirov et al., 1980) [2].

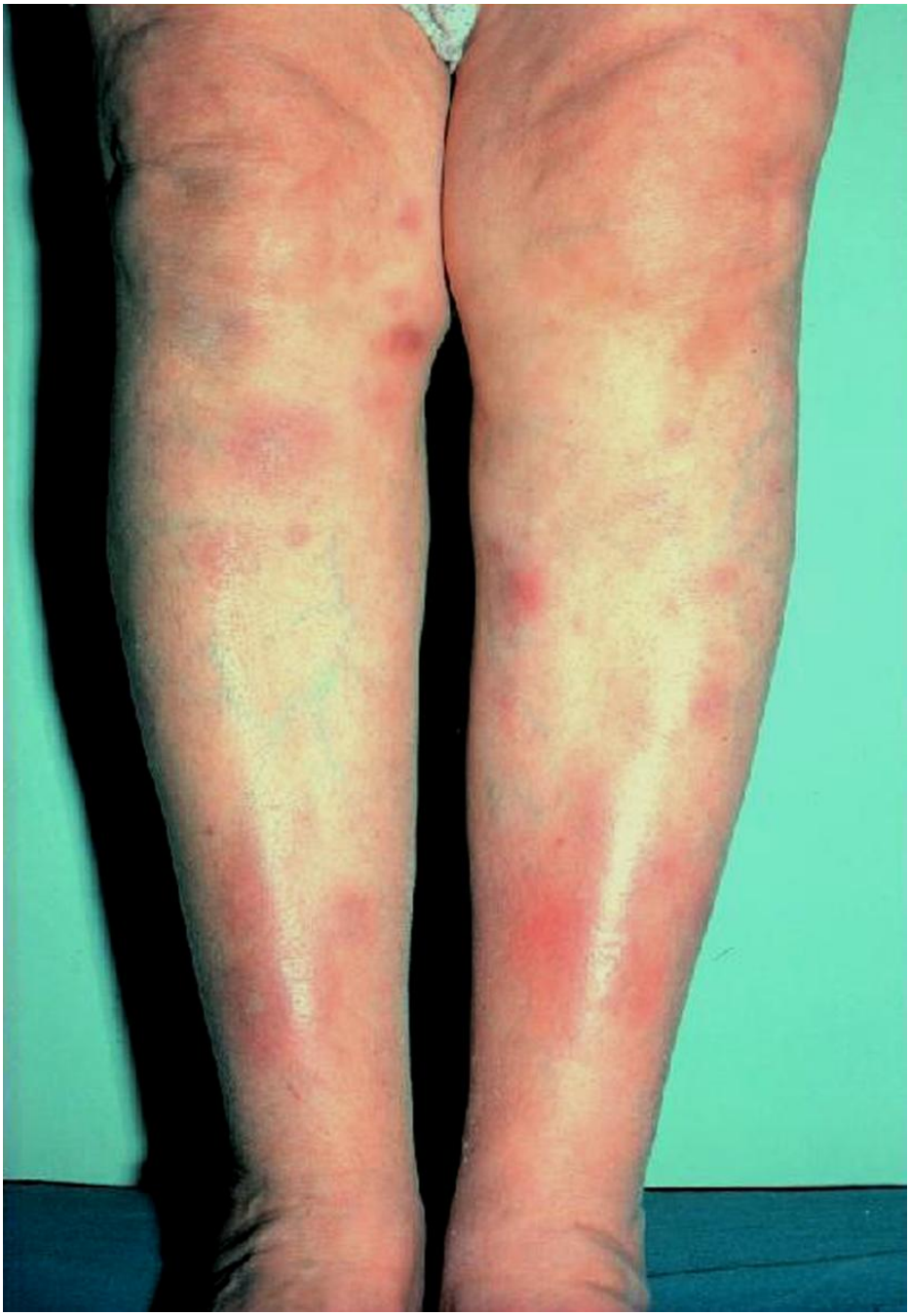
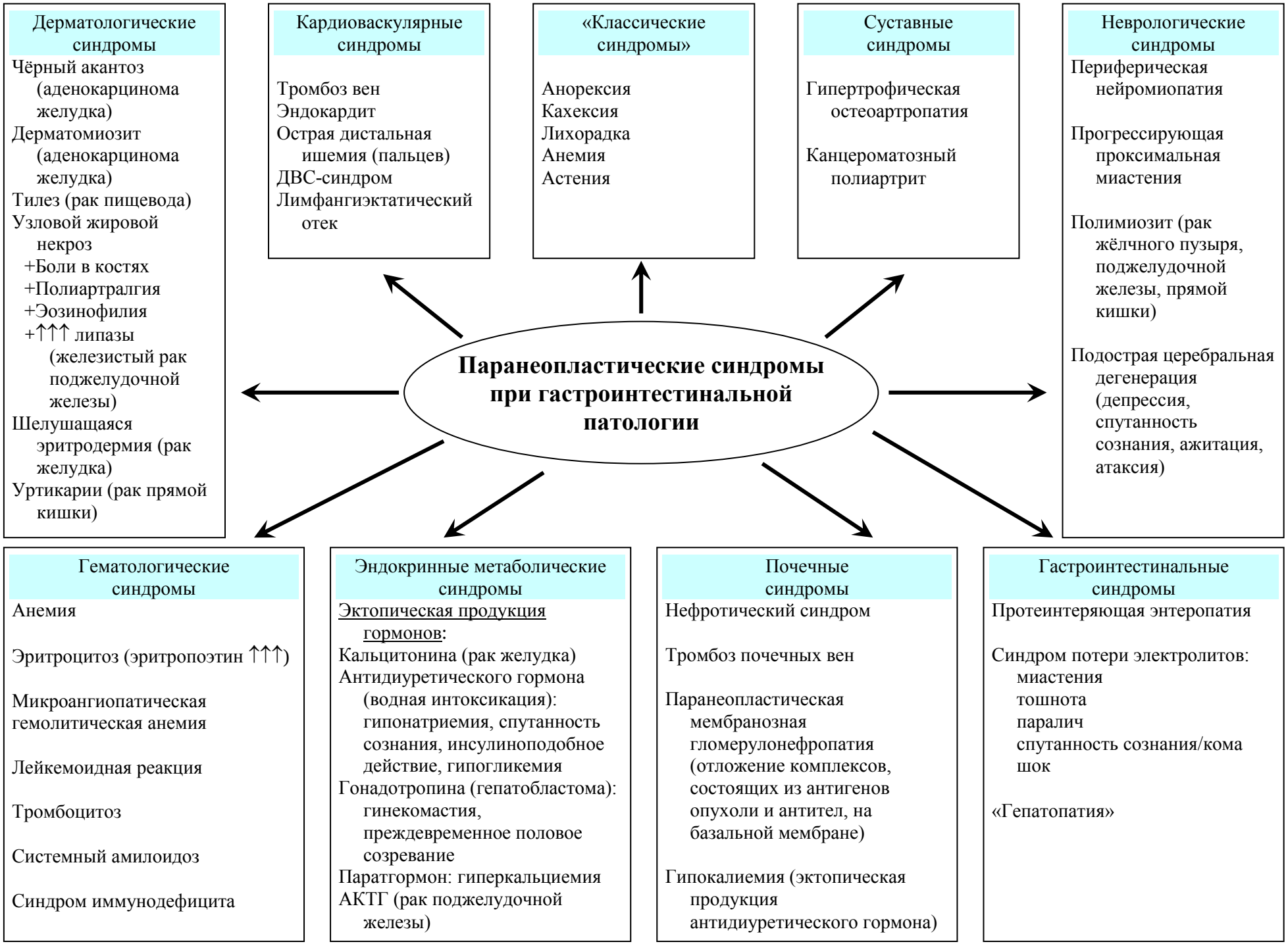


Fig. 4. Erythema nodosum.

Fig. 5. PNS upon gastrointestinal pathology.


Паранеопластические синдромы при гастроинтестинальной патологии
Дерматологические синдромы
Чёрный акантоз (аденокарцинома желудка)
Дерматомиозит (аденокарцинома желудка)
Тилез (рак пищевода)
Узловой жировой некроз
+Боли в костях
+Полиартралгия
+Эозинофилия
+↑↑↑ липазы (железистый рак поджелудочной железы)
Шелушащаяся эритродермия (рак желудка)
Уртикарии (рак прямой кишки)
Кардиоваскулярные синдромы
Тромбоз вен
Эндокардит
Острая дистальная ишемия (пальцев)
ДВС-синдром
Лимфангиэктатический отек
«Классические синдромы»
Анорексия
Кахексия
Лихорадка
Анемия
Астения
Суставные синдромы
Гипертрофическая остеоартропатия
Канцероматозный полиартрит
Неврологические синдромы
Периферическая нейромиопатия
Прогрессирующая проксимальная миастения
Полимиозит (рак жёлчного пузыря, поджелудочной железы, прямой кишки)
Подострая церебральная дегенерация (депрессия, спутанность сознания, ажитация, атаксия)
Гематологические синдромы
Анемия
Эритроцитоз (эритропоэтин ↑↑↑)
Микроангиопатическая гемолитическая анемия
Лейкемоидная реакция
Тромбоцитоз
Системный амилоидоз
Синдром иммунодефицита
Эндокринные метаболические синдромы
Эктопическая продукция гормонов:
Кальцитонина (рак желудка)
Антидиуретического гормона (водная интоксикация): гипонатриемия, спутанность сознания, инсулиноподобное действие, гипогликемия
Гонадотропина (гепатобластома): гинекомастия, преждевременное половое созревание
Паратгормон: гиперкальциемия
АКТГ (рак поджелудочной железы)
Почечные синдромы
Нефротический синдром
Тромбоз почечных вен
Паранеопластическая мембранозная гломерулонефропатия (отложение комплексов, состоящих из антигенов опухоли и антител, на базальной мембране)
Гипокалиемия (эктопическая продукция антидиуретического гормона)
Гастроинтестинальные синдромы
Протеинтеряющая энтеропатия
Синдром потери электролитов:
миастения
тошнота
паралич
спутанность сознания/кома
шок
«Гепатопатия»