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Polyarteritis nodosa as a multiorgan disease

Polyarteritis nodosa (PAN) also termed microscopic polyarteritis or formerly known as periarteritis nodosa is a systemic disease classified as a vascular collagenosis (12). The disease was first described by Kussmaul and Maier in 1866. On the basis of the localization and the macroscopic image they introduced the term of *periarteritis nodosa.* For many years it became common for most of the systemic forms of vasculitis (13). At the beginning of 1900 Ferrari and Dickson introduced the notion of polyarteritis nodosa (13) in order to emphasize the polyarterial character of the process as well as the localization of changes not only around arteries but also in every layer of the vascular walls. In 1948 Davson and his associates suggested the division of PAN into two groups depending on the presence of or the lack of glomerulonephritis. It allowed for the separation of the microscopic polyangiitis (mPA) and the classic form (cPA) (13).

mPA mainly applies to small vessels (arterioles, venules, capillary vessels) and is one of the most frequent causes of necrotizing glomerulonephritis. The serologic marker is autoantibodies against neutrophilic granulocytes and monocytes – ANCA (c-ANCA react with serine proteinase -3, in the intermediary immunofluorescence they produce scattered light in cytoplasm and p-ANCA – antibodies with perinuclear light, reacting with myeloperoxidase) (13).

The classic form of PAN (cPA), defined at the Chapel Hill Conference in 1994, is a medium and weak necrotizing arteritis, which does not affect the smallest vessels and is not the cause of glomerulonephritis (13).

Polyarteritis nodosa occurs in all the ethnic groups with the frequency of 6–7 cases per 100,000 people in a year. It may reveal itself at any age, also in newborns. However, the first symptoms occur between 35 and 55 years of age most often. Men become ill three times as often (3). The nature of PAN is the occurrence of infiltrative, necrotic and inflammatory changes. They spread over the small and medium muscle arteries, mostly in the place of bifurcations (12). Macroscopically, they are characterized by nodular thickenings occurring along the vessel routes, forming the image similar to the string of pearls (3). Microscopically, segmental thickening of all the vascular layers is confirmed. In the area of middle coat, where the inflammatory process begins, fibrinoid necrosis, pleomorphic inflammatory infiltrations from lymphocytes (especially CD4+), macrophages and granulocytes are visible. In some patients there occur immunologic complexes consisting of HBs antigen, anti-HBs antibodies, IgG, IgM immunoglobulins and C3 fraction of the complement (13).

In the course of the disease, due to the damage of vascular walls and the production of fibrous tissue, the proceeding stenosis or complete obliteration of vessels occur. It is connected with the occurrence of thrombuses, areas of infarction or hemorrhage, which lead to ischemia of the supplied tissues. The changes may be the cause of death if they are localized in life-important organs (6).

The cause of PAN is not fully known. In the pathomechanism, the deposition of immunological complexes in the vascular walls is likely to have an essential effect. Among the causal factors, viral

infections play a huge role, especially infections of hepatitis virus type B. In 30–70% of patients, permanent or temporary antigenemia HBs is confirmed. Presently, owing to common availability of the vaccine against WZW B, the number of new cases connected with HBV is estimated at less than 10% (13). The presence of antigen HBs is connected with the acute course of PAN and higher mortality in the first year of the disease (7). Vasculitis normally develops after about three–four months from the clinical hepatitis, whereas the degree of expanse and the advancement of hepatic lesions is often incommensurately mild compared with the intensification of vascular lesions (5). The causes of the disease might also be: parvovirus B19, streptococci of the group A, hepatitis virus C, cytomegalovirus and HIV virus (2). Among other causes there are hypersensitivity reactions to various chemical substances such as: arsenic, iodine, sulphonamides, barbiturates, thyouracil and some antibiotics (12). The familial occurrences of the disease, the coexistence with hairy cell leukemia and a case of polyarteritis nodosa as the first manifestation of gastric carcinoma have also been reported (6). In spite of numerous examinations, in 2/3 of the patients ill with polyarteritis nodosa it is impossible to determine the causes of the disease (3).

Polyarteritis nodosa is characterized by a rich and varied clinical image. The disease may affect every organ, have a limited form or have a systemic character. Most frequently the lesions are found in the vessels of the skin, the nervous system, the kidneys, the myoskeletal system, the cardiovascular system and the alimentary tract.

The changes in organs are normally preceded by general symptoms. They are atypical, shared by many diseases and may remain for weeks or even months. Most frequent symptoms are fever, weakness, easy fatigability, lack of appetite, weight loss, painful muscles and aching large joints (knees, elbows) (2). The joint lesions are migrating and temporary, they apply to about 50% of patients. In the case of arthritis, moderate leucocytosis with neutrophilic granulocytes prevailing is reported to appear in the intra-articular fluid (6, 13).

Skin changes are observed in about 40% of patients (3). They are not permanent and may be subject to self-restriction. Cutaneous polyarteritis nodosa (CPN), first described by Lindberg in 1931, is a benign disease. It often coexists with streptococci infections. It covers the area of buttocks and lower limbs, however, upper limbs and the trunk may also be affected. Limited to the skin and the subcutaneous tissue, CPN is often preceded by general symptoms. The changes in organs are less intense or do not occur at all. The disease is chronic and recurrent. The presence of inflammatory nodules, usually painful, with the diameter of 0.5–3 cm, is clinically proved. They are situated in the hypoderm along the vascular routes. They may disappear spontaneously or undergo ulceration. The skin changes also include livedo reticularis, purpura, extravasations of blood into the skin, swelling of lower limbs (14).

The cardiovascular system is affected in about 80% of patients (3). Most frequently observed symptoms are arterial hypertension and tachycardia. The consequence of the coronary vessels having been affected may be chronic cardiac insufficiency, angina pectoris and frequently silent myocardial infarction. Conductivity disorders and valvular insufficiency often occur. Pericarditis applies mainly to people with antigenemia HBs (7, 11).

Symptoms from the nervous system are confirmed in 40–50% patients with polyarteritis nodosa. They normally occur in the advanced stage of the disease (usually two–three years after the initial diagnosis). They may precede the occurrence of symptoms from other systems. Neurologically, mono- or polyneuropathies are confirmed, beginning with an asymmetric spread onto peripheral nerves. The cause of multifocal mononeuropathy, considered by some authors as the first manifestation of PAN, are inflammatory conditions in the area of nutrient vessels of the nerves (*vasa nervorum*). The neurological symptoms include headaches, epileptic seizures, ischemia and hemorrhage cerebral and medullary strokes, temporary losses of consciousness or sight disorders (10, 13).

The ocular changes apply to about 10–20% patients and are more often confirmed in the cases when the changes cover cerebral vessels. They assume the form of nongranulomatous ocular inflammatory disease, ulcerative keratitis, scleritis or retina vasculitis. The optic nerve may be affected. They may evoke symptoms of orbital pseudotumour. Known are the cases of the sudden, complete loss of sight as the first manifestation of the disease (6, 10, 13).

Renal disorders apply to 75% of patients with polyarteritis nodosa. In the classic form of PAN (c-PA), the changes in the area of intrarenal arteries, especially arched arteries, assume a mild form normally. In the mechanism of ischemia, as a result of clots and infarcts, stenosis or complete obliteration of vessels may occur. The emergence of aneurysms whose rupture may be the cause of massive hemorrhage is often observed (4). The consequence of the described ischemic changes is the development of angiorenal hypertension. The clinical involvement of the kidneys may be manifested by seizure-like lumbar pains. Moderate albuminuria occurs, rarely over 3.5 g/day, without any perceptible changes in the urinary sediment (4). In microscopic polyarteritis (mPA), the changes in the kidneys are observed in every case. They most often occur in the form of low immunological infection. It is caused by the presence of ANCA antibodies, especially p-ANCA. It is characterized by glomerulopathy with segmental fibronoid necrosis and the development of crescents with fibrin deposits. The changes in urine in the form of erythrocyturia and albuminuria, sometimes with nephrotic syndrome, is diagnosed in 90–95% of patients. For a long time they are very often the only manifestation of mPA. In 50% of the patients it is possible to observe rapidly progressing renal insufficiency and in 75% – passing renal insufficiency. Arterial hypertension seldom develops here (4).

In about 50% of patients, the vessels of the alimentary tract are affected. The very unspecific symptoms may cause diagnostic difficulties. Most frequently observed symptoms are stomach aches, nausea, vomiting, liver enlargement, duodenal ulcers, perforation of the stomach and the intestines (15). The cases of intrahepatic hemorrhages and the involvement of the pancreas in the development of pseudocyst (6) were also noted. The thrombosis of mesentery vessels with the sequential small intestine infarct is more often observed in patients with antigenemia HBs (7). The first symptom of the disease may be acute cholecystitis or appendicitis. In the case of cholecystitis, the clinical symptoms may only have the vascular background or coexist with calculosis (6, 13).

The clinical involvement of the respiratory system is especially typical of *microscopic polyangiitis* (13). In the autopsy they were confirmed in seven out of ten patients, which may indicate more frequent occurrences of pulmonary changes than it was formerly believed (9). Most frequently, these are inflammatory infiltrations from lymphocytes T and macrophages, nodules, cavities, hemorrhages. Interstitial fibrosis, diffuse alveolar damage and intravesicular hemorrhages occur. The whole lungs can be affected although the fibrosis is more severe in the inferior lobes (9). Clinically the changes assume the form of recurrent pneumonias, pleurisies or bronchial asthma (7). Positive correlation with antigenemia HBs is observed.

Polyarteritis nodosa may also be the cause of orchitis or ovaritis. The pathological involvement of the testicles is rather common in the systemic form of PAN (up to 85% of all the cases), however, it rarely is the first symptom of the disease. So far only eight cases of the isolated testicular form of polyarteritis have been documented. The clinical symptoms occur in a relatively small group of patients. They are atypical and similar to the isolated and systemic PAN. Most often these are pain, swelling, local mass, which may suggest the presence of a tumour, acute orchitis or the torsion of the testis (1). So far no cases of the spread onto women's reproductive organs in the generalized form of polyarteritis have been reported. The isolated form is most often detected accidentally during hysterectomy conducted on the basis of such indications as uterine myomas or menorrhagia. Generally, the changes affect the uterine cervix, much less frequently the uterus, ovaries or uterine tubes (1).

The diagnosis is established on the basis of the clinical image and additional examinations. The laboratory investigation confirm increased OB, leucocytosis, anemia, thrombocytemia, improper proportion of albumins to globulins, increased indicators of acute phase. The presence of antigen HBs as well as the discovery of ANCA antibodies in *microscopic polyangiitis* are of great importance. In the analysis of urine, in the case of the spread onto the kidneys, erythrocyturia and albuminuria are confirmed and in addition changes in the urine sediment in microscopic polyarteritis. They are a perfect expression of the activity of vascular inflammation.

Depending on the affected organs, lung function tests, joint x-rays, ECG, cardiac echo test, ultrasonography of abdominal cavity may be helpful (1, 2, 8). In the case of the spread onto the nervous system, apart from the neurological examination, EEG, CT of the head or MRI of the head or the spine also seem useful (10). In order to reveal the changes in the area of the sense organs, ophthalmologic and laryngologic examinations are indispensable. The diagnosis is confirmed by the evaluation of the myodermal segment, nerves or other tissues. In the case of mPA, it may be renal biopsy, while in the classic form of PAN arteriography seems more valuable than biopsy in revealing the vascular changes (1, 8).

According to the criteria of The American Rheumatologic Association from 1990, the confirmation of three of the ten following criteria allows to reveal polyarteritis nodosa with the 82.2% sensitivity and 86.6% specificity: 1) weight loss greater than or equal to 4 kg (not connected with any other factor), 2) livedo reticularis, 3) testicular pain in men or tenderness, 4) myalgias, 5) mono-or polyneuropathy, 6) diastolic blood pressure greater than 90 mmHg, 7) elevated blood urea nitrogen or serum creatine levels, 8) the presence of antigen HBs or antibodies anti-HBs in the serum, 9) arteriographic abnormality, 10) small and moderate morphological changes of arteries (muscle biopsy) (8).

Polyarteritis nodosa left untreated does not do any good. When treated, the chance to survive five more years increases from 10% to 80%. It is, however, connected with the risk of life-threatening drug-induced complications (1). Glycocorticosterides and immunoppressive drugs are used in the treatment. The initial dose of prednisolone is 60 mg/day. After six–eight weeks, the dose is decreased to 40 mg/day. After subsequent four weeks, the amount of the preparation is further decreased by 5 mg/week to 15 mg/day as a maintenance treatment.

Cyclophosphamide is administered in the dose of 500–1000 mg i.v. six times every two weeks. In case of improvement, the dosage is reduced to four doses every three weeks. In case of the mild form of the disease, cyclophosphamide can be administered orally in the dose of 100 mg/day ten days in a month for the minimum of six–twelve months. In case of no improvement, plasmapheresis, intravenous infusions of immunoglobulins, cyclosporine A, methotrexate are used. In the cases of polyarteritis nodosa connected with the presence of HBV antigen, short-term treatment with steroids, plasmapheresis and interferon-alpha (INF-alfa) is used. Successful short-term treatments with steroids, next with lamivudine (100 mg/day at efficient kidneys, up to six months) and plasmapheresis were also conducted (8, 13).

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SUMMARY

Polyarteritis nodosa (PAN) is an uncommon multiorgan disease. The nature of PAN is the occurrence of infiltrative, necrotic and inflammatory changes. They spread over the small and medium muscle arteries, mostly in the place of bifurcations. PAN is characterized by a rich and varied clinical image. The disease may affect every organ, have a limited form or have a systemic character. The diagnosis is confirmed by the evaluation of the myodermal segment, nerves or other tissues. Polyarteritis nodosa left untreated carries a grave prognosis. Glycocorticosterides and immunosuppressive drugs are used in the treatment.

Polyarteritis nodosa jako choroba wieloukładowa

Guzkowe zapalenie tętnic (*polyarteritis nodosa*, PAN) jest rzadką chorobą wieloukładową. Istotą choroby jest występowanie zmian o charakterze naciekowo-martwiczo-zapalnym w obrębie tętnic średniego i małego kalibru, najczęściej w miejscach ich rozwidlenia. PAN cechuje bogaty i różnorodny obraz kliniczny. Choroba może dotyczyć każdego narządu, mieć postać ograniczoną do jednego organu lub charakter ogólnoustrojowy. Rozpoznanie potwierdza ocena histopatologiczna wycinka skórno-mięśniowego, nerwów lub innych tkanek. Guzkowe zapalenie tętnic pozostawione bez leczenia rokuje bardzo źle. W leczeniu stosuje się preparaty steroidowe i leki immunosupresyjne.