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А.В. Ягода[1], А.В. Рыбас*[1], Е.Н. Данилова[2], Ю.В. Громова[2]

[1] — Кафедра госпитальной терапии ФГБОУ ВО «Ставропольский государственный медицинский университет» Минздрава России, Ставрополь, Россия
[2] — Государственное бюджетное учреждение здравоохранения Ставропольского края «Ставропольская краевая клиническая больница», Ставрополь, Россия

ПАРАНЕОПЛАСТИЧЕСКИЙ ВАСКУЛИТ У БОЛЬНОЙ С АСТРОЦИТОМОЙ ГОЛОВНОГО МОЗГА

A.V. Yagoda[1], A.V. Rybas*[1], E. N. Danilova[2], Yu. V. Gromova[2]

[1] — Department of Hospital Therapy of Stavropol State Medical University, Stavropol, Russia
[2] — Stavropol Regional Clinical Hospital, Stavropol, Russia

Paraneoplastic Vasculitis in a Patient with Astrocytoma of the Brain

Резюме

Представлено клиническое наблюдение паранеопластического васкулита на фоне астроцитомы головного мозга. Паранеопластический васкулит — редкая разновидность паранеопластического синдрома, частота его выявления у онкологических больных составляет 0,01-5%, причем в 70% случаев манифестация васкулита наблюдается задолго до клинических проявлений первичной опухоли. Васкулитом, как правило, сопровождаются медленно прогрессирующие опухоли, такие как рак молочной и предстательной желез. Васкулит развивается на фоне рака желудка, легкого, аденокарциномы почек, эпителиомы, саркомы, холангиокарциномы, других солидных опухолей, множественной миеломы, неходжскинской лимфомы. Из нозологических форм паранеопластических васкулитов (васкулопатий) указываются узелковый полиартериит, геморрагический васкулит, гранулематоз Вегенера, неспецифический аортоартериит, синдром идиопатической легочной гипертензии, тромбоваскулиты, протекающие под масками болезни Винивартера-Бюргера, синдрома Мошковиц, а также аллергический геморрагический васкулит, кожный васкулит, системный некротизирующий васкулит с повышением титра антител к антигенам цитоплазмы нейтрофилов (ANCA). В описанном наблюдении пациентка страдала паранеопластичеким васкулитом, морфологически напоминающим узелковый полиартериит, с развитием вторичного амилоидоза сосудов, тканей, вторичной артериальной гипертензии. Прогрессирование сосудистого процесса привело к поражению артерий мозга и сердца, к развитию ишемического инсульта и гемодинамически значимому стенозу коронарных артерий, развитию острого (повторного) инфаркта миокарда, осложнённого острой сердечной недостаточностью, послужившими причиной смерти. Клиническая значимость наблюдения заключается в описании не представленного в научной литературе паранеопластического васкулита, развившегося на фоне астроцитомы головного мозга с формированием вторичного амилоидоза.

Ключевые слова: *паранеопластический васкулит, паранеопластический синдром, астроцитома, острый инфаркт миокарда*

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*Контакты: Анна Викторовна Рыбас, e-mail: rybasdoc@mail.ru
*Contacts: Anna V. Rybas, e-mail: rybasdoc@mail.ru
ORCID ID: https://orcid.org/0000-0001-5360-0913

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Abstract

Clinical case of paraneoplastic vasculitis associated a brain tumor was presented. Paraneoplastic vasculitis is a rare type of paraneoplastic syndrome. The frequency of detection of paraneoplastic vasculitis in cancer patients is 0.01-5%. In 70% of cases, the manifestation of vasculitis is observed long before the clinical manifestations of the tumor. Most studies report so-called leukocytoclastic vasculitis (allergic) or allergic angiitis. Vasculitis is usually accompanied by slowly progressing tumors such as breast and prostate cancer. It also develops with of stomach cancer, lung cancer, kidney adenocarcinoma, epithelioma, sarcoma, cholangiocarcinoma, other solid tumors, multiple myeloma, non-Hodgkin's lymphoma. The nosological forms of paraneoplastic vasculitis include called polyarteritis nodosa, hemorrhagic vasculitis, Wegener's granulomatosis, non-specific aortoarteritis, idiopathic pulmonary hypertension syndrome, thrombovasculitis, allergic hemorrhagic vasculitis, cutaneous vasculitis, systemic necrotizing vasculitis with increased ANCA titer. The patient suffered from paraneoplastic vasculitis with the development of amyloidosis of vascular tissues and arterial hypertension. The progression of the vascular process led to damage of the arteries of the brain and heart, the development of ischemic stroke and hemodynamically significant stenosis of the coronary arteries, the development of acute myocardial infarction complicated by acute heart failure, which caused death. The clinical significance of the case lies in the fact that paraneoplastic vasculitis, which was developed due to a brain astrocytoma with the formation of amyloidosis was firstly described.

Key words: *paraneoplastic vasculitis, astrocytoma, acute myocardial infarction*

Conflict of interests

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ECG — electrocardiogram, MR — magnetic resonance, PNV — paraneoplastic vasculitis

Introduction

Paraneoplastic vasculitis (PNV) and vasculopathies are among the most challenging diseases for management in clinical practice. The paraneoplastic vascular lesion of the vasculitis type is a very rare phenomenon. According to different sources, the detection rate of PNV in cancer patients is 0.01–5%, while in 70% of cases, vasculitis manifests long before the clinical signs of the primary tumor; this fact should be considered when planning the examination for a patient with an "atypical" course of the vascular process.

Most studies report the so-called leukocytoclastic vasculitis (hypersensitive, allergic vasculitis, or allergic angiitis), which is often observed with secondary forms of lesions, including tumors — hairy cell leukemia, non-Hodgkin's lymphoma, lymphogranulomatosis, myeloma [1, 2].

Vasculitis is usually accompanied by slowly progressive tumors, such as breast and prostate cancer. PNV can also develop in patients with gastric, lung or renal adenocarcinoma, epithelioma, sarcoma, cholangiocarcinoma, other solid tumors, multiple myeloma, and non-Hodgkin's lymphoma [2, 3], with the predominance of blood tumors (hemoblastoses) in the etiology of PNV [1].

Nosological forms of paraneoplastic vasculitis and vasculopathies include the following: polyarteritis nodosa, hemorrhagic vasculitis, Wegener's granulomatosis, nonspecific aortoarteritis, idiopathic pulmonary arterial hypertension, thrombovasculites with the course simulating Vinivarter-Buerger disease or Moscowitz syndrome, allergic hemorrhagic vasculitis, cutaneous vasculitis, systemic necrotizing vasculitis, etc. The predominant clinical varieties of PNV include cutaneous forms of the purpura type, maculopapular, urticarial, petechial rash, and ulcers with different elements in one patient as one of the criteria for this type of vasculitis. The type of skin rashes is not related to the type of tumor or its localization [2–4].

Currently, there is no single theory of PNV pathogenesis. Most researchers discuss the autoimmune mechanism of development with the participation of cytokines and adhesion molecules with the deposition of immune complexes in the walls of blood vessels of various calibers and the subsequent development of inflammation and necrosis. The determination of a high titer of autoimmune antibodies (antineutrophilic cytoplasmic, antinuclear, antiphospholipid) in patients with PNV is evidence of the autoimmune nature of PNV [1].

Proponents of non-immune theories of PNV pathogenesis attribute inflammation in vessel walls to the exposure of the endothelial layer to mediators and substances produced by the tumor itself [1].

Tumor-associated vasculitis can occur in complicated forms, with a negative effect on the course of the tumor and the prognosis as a whole.

Case report

Patient P., 44 y.o., female, was hospitalized in the cardiology department of a regional clinical hospital. She was urgently transported for interventional treatment from the hospital, where she was examined and treated for ischemic heart disease (IHD) due to acute coronary syndrome (severe retrosternal pain and ST segment elevation on ECG in V_2–V_5) and clinical signs of nascent pulmonary edema.

Medical history revealed that the first symptoms of ischemic heart disease (retrosternal pain) appeared six years before hospitalization; stable exertional angina of functional class II was established. About six months ago, she suffered an acute cerebrovascular event (ischemic stroke). For more than six years, she noted increased blood pressure (BP), occasionally up to 200/110 mm Hg. Paroxysms of atrial fibrillation-flutter were registered, for which the patient regularly takes sotalol (80 mg). There is a family history of myocardial infarction (father).

Prior to hospitalization, the following results of outpatient and inpatient examinations of the patient were obtained.

Complete blood count: RBC — 3.95 × 10^{12}/l, hemoglobin — 118 g/l, hematocrit — 35.9%, WBC — 6.1 × 10^9/l (segmented neutrophils — 58%, stab neutrophils — 3%, lymphocytes — 28%, monocytes — 9%, eosinophils — 2%), platelets 183 × 10^9/l, erythrocyte sedimentation rate (ESR) — 22 mm/h. Common urinalysis: protein — 193 mg/dl, WBC — 15–20 per field of vision. Lipid profile: total cholesterol — 5.21 mmol/l, high density lipoproteins (HDL) — 1.71 mmol/l, low density lipoproteins (LDL) — 3.35 mmol/l, triglycerides (TG) — 1.20 mmol/l, atherogenic index (AI) — 2.0. Blood biochemistry: electrolytes within normal, aspartate aminotransferase — 13 U/l, alanine aminotransferase — 11 U/l, lactate dehydrogenase — 255 U/l, C-reactive protein — 4.8 mg/l, creatinine — 113 μmol/l, urea — 8.9 mmol/l. Total protein, bilirubin, blood glucose — without changes. Troponin T — 0.08 ng/ml, myoglobin — 54.72 ng/ml, creatine phosphokinase MB — 2.7 ng/ml. Hepatitis B surface antigen (HBsAg) and total antibodies to hepatitis C virus (anti-HCV) — not found. Coagulogram within normal. High level of brain natriuretic propeptide (NT-proBNP) — over 9000 pg/ml — is noteworthy.

Magnetic resonance (MR) imaging. Signs of ischemic stroke in the circulation zone of the right middle cerebral artery. Study over time — MR signs of poststroke cerebrospinal fluid cyst in the right frontal lobe.

Duplex imaging of brachiocephalic arteries. No structural changes or hemodynamically significant disorders of the blood flow in carotid arteries at the extracranial level were found. Deformed course of the third segment of both vertebral arteries with multifocal compensated stenosis up to 40%. Hypoplasia of the right vertebral artery. Asymmetric blood flow in vertebral arteries, 30–40% due to the relative decrease on the right.

Consultation with a neuro-ophthalmologist: retinal angiopathy of both eyes.

ECG: sinus rhythm with heart rate (HR) 90 per minute, QRS axis in horizontal position. Cicatricial changes in the anterior-septal-apical area of the left ventricle — LV (QS V_1–V_3, qV_4), signs of LV myocardial hypertrophy with hemodynamic overload.

24 hours Holter ECG monitoring: sinus rhythm with HR from 69 to 123 (mean 81, daytime — 92, nighttime — 74) per minute, single ventricular extrasystoles — VES (495), paired VES (6), ventricular extrasystole grade 5 (Lown), short unstable paroxysms (2) of ventricular tachycardia (duration up to 10 seconds), long QT syndrome, transient AV block grade 1. With increase in heart rate, downsloping ST segment depression and inverted T wave in leads II, III, aVF, V_5–V_6 were occasionally observed, accompanied by subjective feelings (heart pain, malaise, palpitations) with a total duration of 10 minutes 24 seconds.

Echocardiography with color flow mapping: left ventricle — end-diastolic dimension (EDD) 4.8 cm; end-systolic dimension (ESD) 3.3 cm; LV posterior wall in diastole (LVPWd) 1.1 cm; interventricular septum in diastole (IVSd) 1.3 cm, left ventricular myocardial mass index (LVMMI) 138 g/m^2, concentric hypertrophy, ejection fraction 60% (Teicholz). Systolic pressure in pulmonary artery — 35 mm Hg (normal up to 30 mm Hg). No evidence for myocardial motion disorders found. No separation of pericardial layers. Dilation of both atria, marginal thickening and fibrosis of the cusps of mitral and aortic valves, mitral and tricuspid regurgitation grade 1–2, pulmonary valve dysfunction. Additional chord in the cavity of the left ventricle.

Esophagogastroduodenoscopy: superficial gastritis.

Chest radiography: cardiac border expanded to the left.

On admission to the Regional Vascular Center: the general condition of the patient is severe; skin is pale, acrocyanosis, position — orthopnea. By auscultation — decreased vesicular breathing in the lower parts of lungs, large number of moist rales, respiratory rate — 22 per minute. Sinus rhythm with HR 100 per minute, heart tones are muffled. BP — 90/60 mm Hg. Abdomen is soft, non-tender. No swelling.

ECG at admission — sinus rhythm with HR 80 per minute, focal changes in anterior-septal-apical-lateral area of the left ventricle in the form of ST elevation.

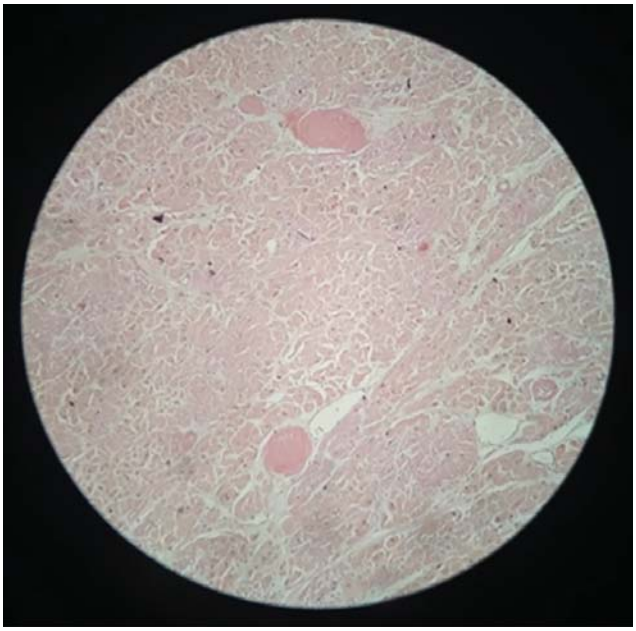

Figure 1. *Heart. Amyloid in a vessel wall. Complete obliteration of the lumen. Congo red stain, ×100*

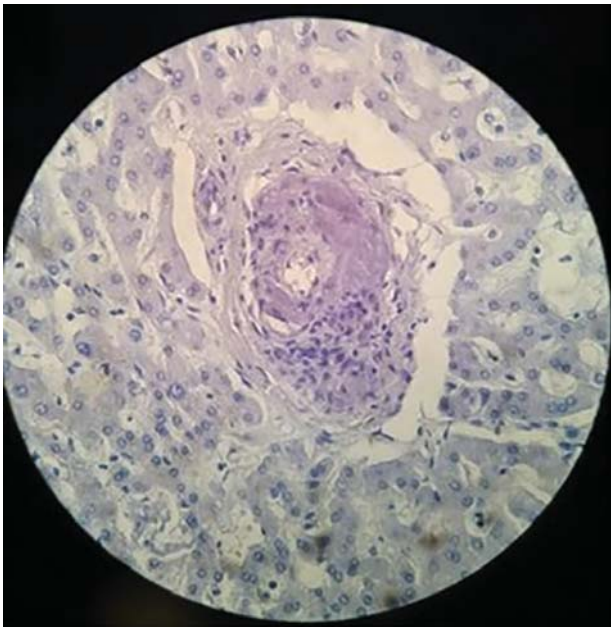

Figure 2. *Liver. Productive periarteritis. Hematoxylin stain, ×100*

The patient underwent emergency coronary angiography, with the following results: right-dominant circulation, coronary arteries normally positioned. Occlusion in the middle third of the anterior interventricular artery was found. Balloon angioplasty in the middle third of the anterior interventricular artery with a 2.5 × 25 mm balloon catheter was performed; TIMI 2 blood flow (contrast enhancement of the vessel with delayed filling of distal flow) along the entire length of the artery; there were no residual stenosis, dissections or extravasation.

After angioplasty, the patient's condition suddenly worsened, signs of respiratory and heart failure appeared, and cardiogenic shock developed. The patient received vasopressor and inotropic support and was transferred to mechanical ventilation. According to ECG — electromechanical dissociation of heart. Resuscitation measures had no effect. The patient died two hours after admission to the hospital.

Autopsy study: dense mottled myocardium with areas of yellowish and dark red color — in anterior and partially posterior-lateral walls throughout the whole thickness of the heart muscle. At the mouth of the left coronary artery — atherosclerotic plaque, 0.4 cm, flat. Arteries with dense whitish walls. LV cavity was enlarged. Histology: parenchymal myocardial dystrophy, foci of cardiosclerosis, zones of cardiac muscle necrosis of trasmural type in macroscopically described areas. Heart vessels along their entire length with significantly thickened sclerosed walls, with disorganization of all layers and deposits of amorphous lumpy eosinophilic masses, developing aneurysms in the form of nodules with significantly narrowed lumens, in some places — to complete narrowing, with lymphocytic infiltration — signs of periarteritis. Examination with Congo red stain and in polarized light revealed amyloid deposits in the walls of blood vessels, the stroma, and epicardium (Fig. 1).

Similar changes in the walls of arterial vessels are observed when examining lungs, kidneys, adrenal glands, spleen, uterus, its appendages, pancreas, and liver (Fig. 2).

On the basal surface of the brain, between pons and cerebral peduncles, there was a superficial dense rounded lesion, 1 cm in diameter, of grayish-white color, in the pia mater, the basilar artery was under this lesion. Histology revealed a nodular form of diffuse astrocytoma (Fig. 3).

Tumor nodules of fibrous white tissue, 3 and 4.5 cm in diameter, were found in the uterine body — interstitial-subserous leiomyoma.

Pathological diagnosis:

Main: Paraneoplastic vasculitis (polyarteritis nodosa) with predominant heart lesion, sclerotic phase in addition to diffuse astrocytoma of pons.

Complications: acute transmural myocardial infarction of the anterior-lateral wall of left ventricle. Acute heart failure: pulmonary edema. Cerebral edema. Symptomatic arterial hypertension (LV myocardial hypertrophy 1.6 cm). Secondary amyloidosis with predominant damage to the vessels of the heart, lungs, kidneys, liver, spleen. Acute heart failure: venous congestion and fibrosis of internal organs, right-sided hydrothorax (100 ml). Secondary pulmonary hypertension. Chronic cor pulmonale: RV myocardial hypertrophy 0.6 cm.

Comorbidity — interstitial-subserous leiomyoma of the uterine body.

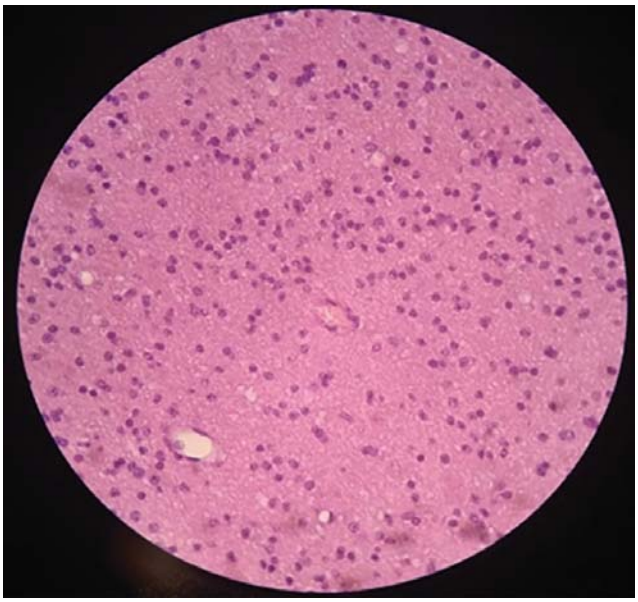

Figure 3. *Diffuse astrocytoma. Hematoxylin and eosin stain, ×400*

Discussion

Therefore, it was found (incidentally) that the patient had an astrocytoma (malignant glial tumor), which was not previously listed among the neoplasms that cause a systemic vascular lesion.

Coexistent vasculitis and tumors, the non-specificity of clinical findings and laboratory results, manifestation of vasculitis prior to the clinical manifestations of the brain tumor, and the generalized nature of the lesion suggest the paraneoplastic nature of the vascular process.

The patient suffered from paraneoplastic vasculitis with secondary vascular amyloidosis and secondary arterial hypertension. The progression of the vascular process led to damage to the brain and heart arteries, ischemic stroke and hemodynamically significant stenosis of coronary arteries, and acute (repeated) myocardial infarction, complicated by acute heart failure, which caused death. Despite a histological picture that resembles that of polyarteritis nodosa (aneurysms, nodules), we do not think this term can be used in this case, not only due to the incomplete range of morphological signs but also due to the lack of clinical criteria for this form of systemic vasculitis.

Amyloid deposits in tissues and in affected vessels do not contradict the theory of paraneoplastic vasculitis. In addition, systemic amyloidosis (Lubarsch-Pick syndrome) can be found — although quite rarely — as a paraneoplastic process: solid tumors make up about 7% of the causes of systemic amyloidosis [5].

The clinical significance of this observation lies in that it was the first described case of PNV that developed in association with brain astrocytoma with the development of secondary amyloidosis; it expands the range of causative tumors for this type of vasculitis and demonstrates new possibilities for its diagnosis in cases with simultaneous amyloidosis.

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А.В. Ягода: (ORCID: 0000-0002-5727-1640): разработка концепции, анализ и интерпретация данных, проверка содержания, окончательное утверждение рукописи для публикации

А.В. Рыбас: (ORCID: 0000-0001-5360-0913): анализ и интерпретация данных, разработка дизайна, оформление обзора, обоснование и написание рукописи

Е.Н. Данилова: сбор клинического материала, анализ, интерпретация данных

Ю.В. Громова: сбор и анализ гистологического материала, интерпретация данных

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

A.V. Yagoda: (ORCID: 0000-0002-5727-1640):): development of the concept, analysis and interpretation of data, validation of content, final approval of the article for publication

A.V. Rybas: (ORCID: 0000-0001-5360-0913): analysis and interpretation of data, research concept and design, design review, study and writing of the article

E.N. Danilova: data collection and processing, analysis, data interpretation

Yu.V. Gromova: collection and analysis of histological material, data interpretation

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