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Literature Review

The Role of Conceptual Views in the Diagnostics of Systemic Vasculitis and Granulomatosis with Polyangiitis

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Abstract

Renaming of Wegener's granulomatosis in granulomatous polyangitis (GPA) was caused by the urgent need to revise the existing classification of systemic vasculitis (SV) and to improve terminology that could most fully reflect the pathomorphological features of the disease. Diagnosis of GPA and SV, as well as of any other diseases is inherently associated with their clinical dynamics. That is, recognizing that we can change our minds, if we are obliged to do this by facts, is a feature of the diagnostic process. In turn, for the facts to make us change our minds, the facts themselves must exist. Thus, we must identify them and come to the opinion of what is the fact and what is not, in the context of this or that pathology. Checking the correctness of the established diagnosis is often a difficult process, and does not always prove that the diagnosis is accurate.

Keywords: *Granuloma; Wegener; Granulomatosis with Polyangitis; Primary Systemic Vasculitis; Proteinase-3; Giant Multinucleate Cells; ANCA-Associated Vasculitis*

Traditionally, the SV group includes diseases with similar pathogenesis, which are based on generalized damage to blood vessels (arteries and veins of various calibers) with secondary involvement of the corresponding organs and tissues in the pathological process. The clinical and morphological basis of SV is inflammation and necrosis of the vessel wall. A distinctive feature of CB is their integral content in many clinical "pictures", for example, fever of unknown etiology, heart attacks of internal organs, gastrointestinal bleeding, skin manifestations, an increase in acute phase parameters in patients in serious condition, etc. The spectrum of clinical manifestations, the course and prognosis of SV is determined by the type of vasculitis, type, size and localization of the vessels involved in the pathological process and the features of their lesions [1].

It is generally accepted to distinguish between primary and secondary SVs. Primary vasculitis are considered diseases that are independent. Vasculitis associated with other diseases, exposure to drugs or various toxic agents are considered secondary. These include vasculitis caused by bacterial and viral infectious agents (hepatitis B and C, infective endocarditis, sepsis, HIV, etc.); developing with systemic connective tissue diseases or malignant neoplasms. So, The list of etiological factors of SV is quite large (infectious diseases, foreign proteins, autoimmune and oncological diseases, cryoglobulinemia), but they cannot be identified in about 50% of patients.

The annual incidence of SV is 40 cases per 1 million population (in the rural population of Great Britain); the prevalence ranges from 0.4 to 14 or more per 100,000 population [2], i.e., SV is a rare disease. It is assumed that it can be provoked by a viral or bacterial infection, taking medications and with tumor diseases (biopsy often reveals their leukocytoclastic nature, that is, allergic or necrotizing angiitis characterized by purpura that rises above the level of the skin - "palpable purpura"). Histologically, perivascular infiltrates consisting

of neutrophils or their remnants are detected, i.e. vasculitis, granulomas, or both. Fibrinoid changes or necrosis are noted in the walls of the vessels. VS often presents with skin symptoms (≈50%); more often on the extremities in the form of papules, vesicles, ulcers, subcutaneous nodes (Figure 1 and 2).

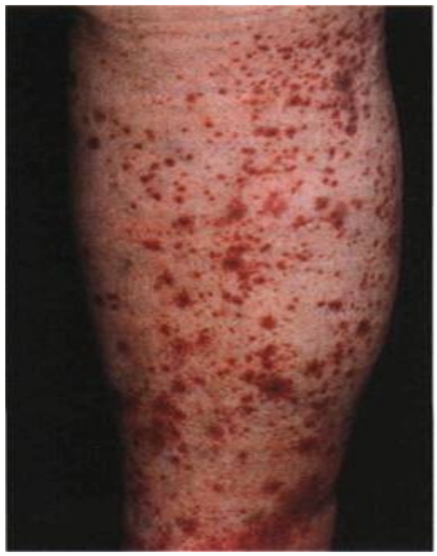


Figure 1: Hemorrhagic vasculitis: maculopapular hemorrhages.

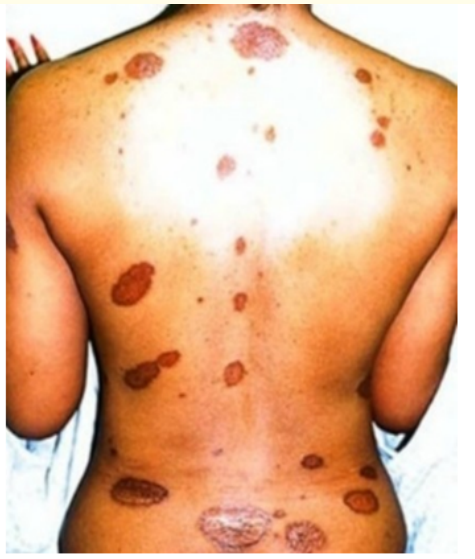


Figure 2

It should also be remembered that WS can be a component of another autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis) or develop primarily (granulomatous polyangiitis (GPA), Charge-Strauss syndrome and microscopic polyangiitis

(MPA), eosinophilic granulomatosis with polyangiitis (EGPA), which are ANCA-associated angiitis (AAV).The abbreviation ANCA (English) characterizes autoantibodies to proteins of cytoplasmic granules of neutrophils (granulocytes) and monocyte lysosomes, which are classified according to the type of luminescence in the reaction of indirect immunofluorescence (IRIF) [3].

Due to the ambiguity of the etiology, vasculitis is still classified according to morphological features, namely, the caliber of the affected vessels and the presence or absence of granulomas around the affected areas of the vessels. If the etiology of none of the many vasculitis is unknown, then one can only assume an infectious onset.

The mechanisms of pathogenesis, at least for GPA, have been studied to some extent. In other cases, pathogenesis can be considered by analogy.

So, according to the anatomical (morphological) classification, there are systemic vasculitis with lesions of large vessels: Takayasu's arteritis; giant cell arteritis; sarcoidosis; Cogan's syndrome; tropical aortitis and other rare species. During the process in the middle vessels, Kawasaki disease, polyarteritis nodosa, lepromatous arteritis, familial Mediterranean fever and others are isolated. Systemic damage to small and medium-sized vessels is manifested in Behcet's syndrome, OAB, Charge-Strauss syndrome, thromboangiitis obliterans and others. Inflammation of only small vessels causes cutaneous leukocytoclastic angiitis, pigmentary purpura Schamberg, Dego's disease, urticarial vasculitis, Shenlein-Henoch vasculitis (immunoglobulin A), monoclonal gammopathy, essential cryoglobulinemic vasculitis (special immune complexes - cryoglobulins, which, due to their size, can also clog small vessels, monoclonal gammopathy (nomenclature Arthritis Rheum, 1994 There is still a huge number of subtypes of vasculitis that affect individual organs. This group includes retinovasculitis, rheumatic vasculitis, etc. (Figure 3).

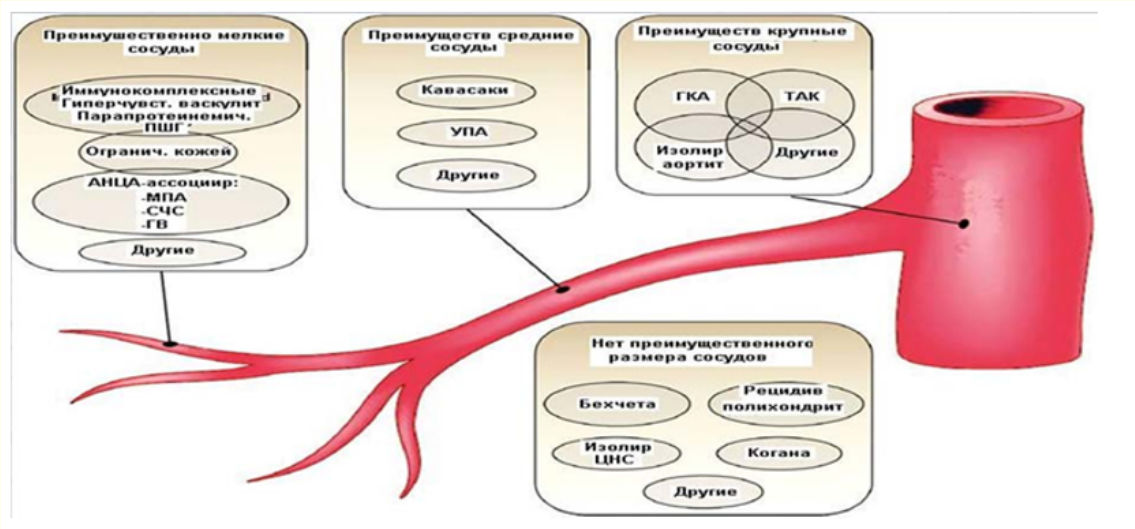


Figure 3

Formally, GPA is classified as a vasculitis affecting small vessels according to the Chapel Hill system (USA, 1992, 2012), although lesions can extend to both small and medium diameter blood vessels (capillaries, venules, arterioles, and arteries). Essentially, GPA is a combination of granulomatosis and angiitis.

In Schonlein-Genoch disease and cutaneous leukocytoclastic vasculitis (allergic cutaneous vasculitis, leukocytoclastic angiitis, dermal necrotizing vasculitis), small and medium-sized vessels are affected in the form of symmetrical hemorrhagic erythema, while superficial vessels of the skin suffer; whereas in polyarteritis nodosa and giant cell arteritis, the deep vessels of the muscular type, which are located in the subcutaneous fat, are affected. Most other forms of vasculitis, such as cryoglobulinemic and AAV, can affect both small, and large vessels. The diagnostic value of a skin biopsy depends on the depth of the biopsy. For accurate diagnosis of all vasculitis, with the exception of leukocytoclastic and Shenlein-Genoch disease, it is necessary to perform incisional (cutting) or excisional (cutting out a piece of tissue) biopsy of the subcutaneous fat (Figure 4).

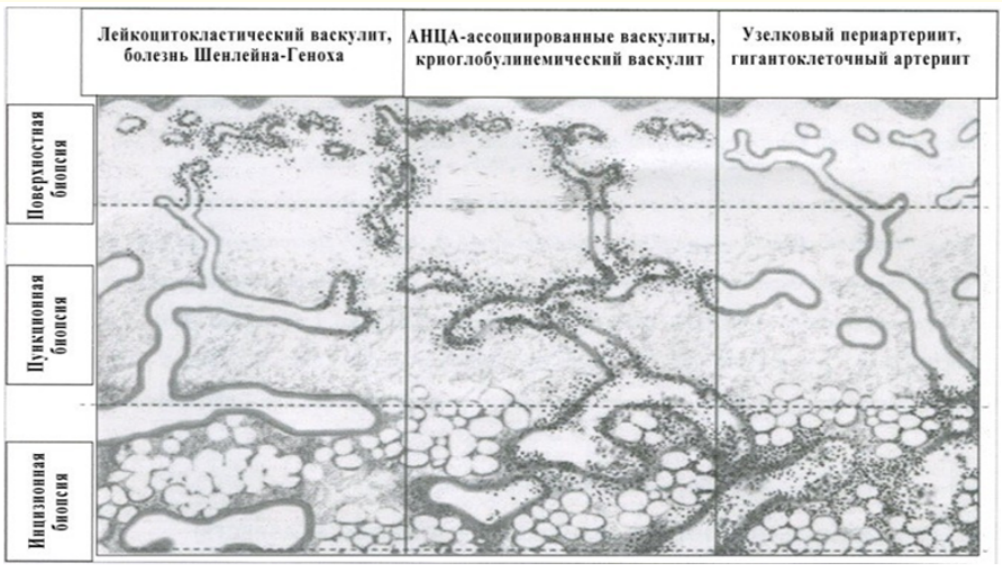


Figure 4: Histological classification of vasculitis with skin lesions (according to J.A. Carlson, 2010).

Systemic vasculitis is also classified into diseases with and without granuloma formation (Table 1).

Systemic vasculitis	
Granulomatous	Non-granulomatous
Temporal arteritis	Nodular periarteritis
Arteritis Takayasu	Kawasaki disease
Wegener's granulomatosis	Schönlein-Genoch purpura
Cherg-Strauss syndrome	Cutaneous cytoplastic vasculitis
	Cryoglobulinemic vasculitis
	SLE

Table 1: *Granulomatous and non-granulomatous systemic vasculitis.*

The most common primary systemic vasculitis is GPA, which is prevalent throughout the world. The incidence is 12.5 cases per 1 million population, while skin lesions occur in 50% of patients. True, with the cumulation of other diseases with skin vasculitis, GPA will no longer be the most common cause of their development.

According to other sources, the prevalence of GPA in the population is 25 - 60 cases per 1,000,000 population, the incidence is 3 - 12 cases per 1,000,000 people. According to the Vascular Foundation (Kansas City, USA), GPA/HB suffers from 1:20,000 to 1:30,000 people, that is, the disease is rare (in Europe - 2.1 - 14.4 per 1 million population per year) [4]. However, the incidence of GPA in European countries, according to some reports, has increased 4 times over the past 30 years. Men and women are equally affected. The disease can occur both in childhood and in old age, but in Mostly patients aged 30 to 50 years get sick. That is, it is statistically unusual that GPA can be contracted in childhood, although the diagnosis of this disease in the 70-80-year-old age group is not excluded. Also, GPA is not characterized by sexual selectivity, but a slight predominance of men is observed.

A distinctive pathomorphological feature of GPA is a granuloma, which is a focal growth of connective tissue cells that appear as small nodules. In itself, granulomatous inflammation is an inflammation in which nodules (granulomas) are formed, resulting from proliferation and transformation of cells capable of phagocytosis.

In turn, GPA is characterized by a specific type of inflammation and granulomatous injury to the blood vessels (vasculitis), which usually involves several organs, including the lungs, kidneys, and upper respiratory tract. That is, granulomatous inflammation occurs both in and around the blood vessels. A granuloma is one of several forms of localized nodular tissue inflammation. In short and simply, a granuloma is a type of inflammation of the tissues of the organ involved. Histological features include “geographical” basophilic necrosis on an inflammatory background with randomly distributed giant cells and the absence of sarcoidosis-like granulomas.

The understanding of GPA is expressed as a general characteristic that allows it to be attributed to a broader group of vasculitic diseases that have autoimmune aggression in the form of the production of circulating antibodies to neutrophils, called antineutrophil cytoplasmic antibodies (ANCA) in relation to small and medium-sized blood vessels. Normally, cytoplasmic ANCA (cANCA) reacts with proteinase-3, a serine proteinase found in the primary granules of neutrophils. In turn, proteinase-3 is directly related to the metabolism of alpha-1-antitrypsin. There are also ANCA-negative and ANCA-positive reactions with varying clinical prognosis.

As the name suggests, ANCAs target the non-nuclear cytoplasm of white blood cells. Their exact role in the disease process remains uncertain, but is of considerable diagnostic interest. ANCAs come in two main forms: 1) antineutrophil cANCA (cytoplasmic type of luminescence), these are antibodies to proteinase-3 (PR-3); 2) antineutrophil pANCA (perinuclear type of luminescence), that is, antibodies to myeloperoxidase (MPO), as well as aANCA, that is, a homogeneous type of luminescence, where there are atypical antibodies listed as unexplored. In addition, it has been proven that other enzymes that are contained in neutrophil granules also act as antigens: lactoferrin, elastase, bactericidal protein BPI and cathepsin G, in which specific ANCAs are formed, associated with a number of autoimmune diseases (Table 2) [5-8].

ANCA-associated diseases	Specific antibodies	Antigens
Wegener’s granulomatosis (GPA)	cANCA	PR-3
Microscopic polyangiitis (MPA)	pANCA	MPO
Chardja-Strossa syndrome (EGPA)	cANCA, pANCA	Rarely PR-3, MPO
Glomerulonephritis	cANCA, pANCA, anti-GBM	PR-3, MPO, GBM
Rheumatoid arthritis	pANCA, cANCA	Rare MPO, lactoferrin
Systemic lupus erythematosus	pANCA	Rare MPO, lactoferrin
Ulcerative colitis, Crohn’s disease	pANCA, cANCA	Cathepsin G, lactoferrin
Primary sclerosing cholangitis	pANCA, cANCA	Elastase, lysozyme
Primary biliary cirrhosis, autoimmune hepatitis	pANCA, cANCA	Cathepsin G, actin

Table 2

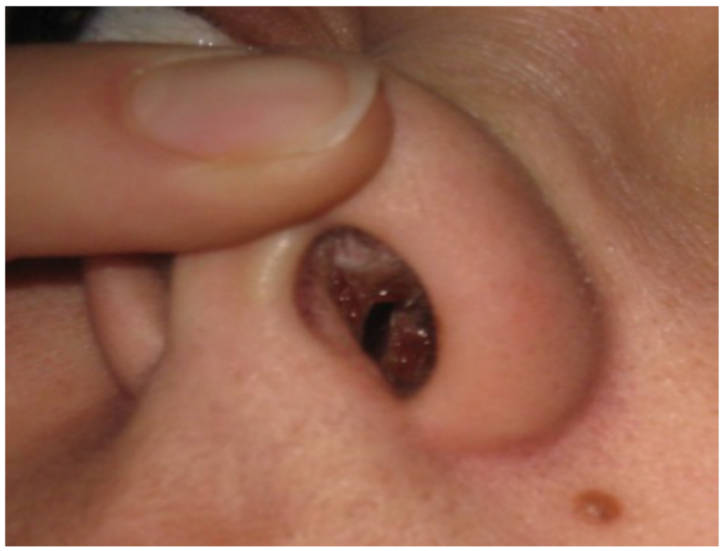
cANCA have a particularly strong association with OAB (up to 80% of patients and possibly more of those who are active). When cANCA is present in the blood of a patient whose symptoms or signs are suggestive of GPA, the likelihood of a diagnosis is greatly increased. However, in most cases it is still very important to biopsy the affected organ, that is, to verify the diagnosis.

The sensitivity and specificity of cANCA for diagnosing GPA is 30 - 90% and 98%, respectively. Such significant differences in sensitivity are explained by the fact that the presence of antibodies and their titer depend on the severity and activity of the disease.

Although antibodies to proteinase-3 in blood serum detected in cANCA patients are highly specific for GPA, they are also observed in other diseases that are characterized by systemic vasculitis, but the frequency of their detection varies significantly. So, with GPA, antibodies to proteinase-3 are found in 85%, with microscopic polyangiitis (MPA) - in 15 - 45%, with idiopathic crescentic glomerulonephritis - in 25%, with Churg-Strauss syndrome - in 10% and with nodular periarteritis - at 5%.

So, the distinguishing feature of vasculitis, in the diagnosis of which ANCA are of decisive importance, is primary systemic vasculitis, that is: GPA, microscopic polyangiitis (MPA) and Charge-Strauss syndrome (HR). All of them are small vessel vasculitis. They are characterized by a severe course, a high probability of death, frequent involvement of the lungs (cavitary granulomas), upper respiratory tract (ulcerations) and kidneys (glomerulonephritis). They are characterized by the absence of immune deposits and complement consumption, which gave rise to the term “poorly immune”, although this does not mean the absence of immunological disorders in the pathogenesis. When diagnosing, it is important to keep in mind that ANCA may not always be present in these diseases, and both cANCA and pANCA may be found in any of them.

One way or another, but GPA is a severe progressive disease, since without timely treatment it leads to death within 6 - 12 months. The clinical course is divided into two forms: local and generalized, which, according to some authors, are the stages of the disease. In the local form, the ENT organs are affected (90% of cases) (Figure 5-8) and the eyes (10%) with the development of rhinitis, nasopharyngitis, sinusitis, otitis, eustachitis, scleritis, episcleritis, and uveitis (Figure 9 and 10). Damage to the orbit and the eyeball can be secondary due to the spread of the disease from the sinuses or isolated [9,10].



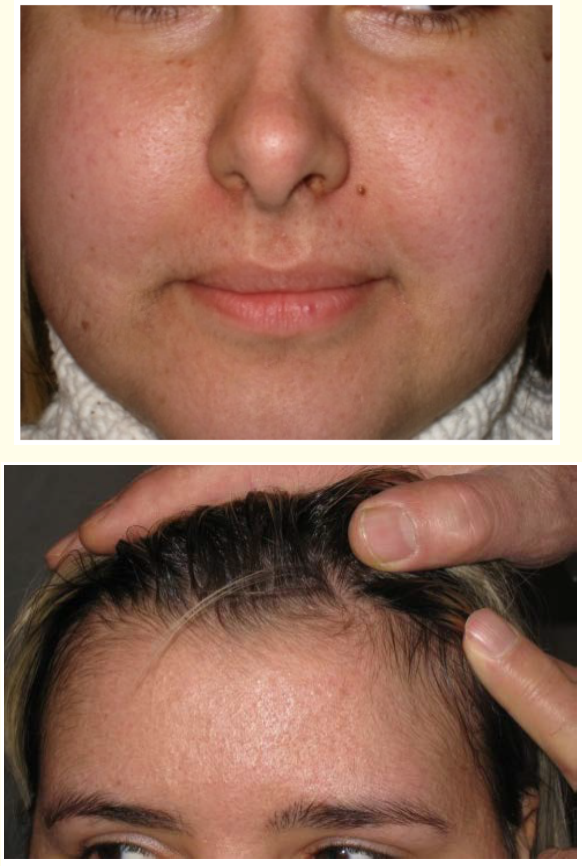


Figure 5: *Patient M. Multiple crusts on the septum of the nose (a), saddle-shaped deformation of the nose (b), nodular rash on the forehead skin (c).*

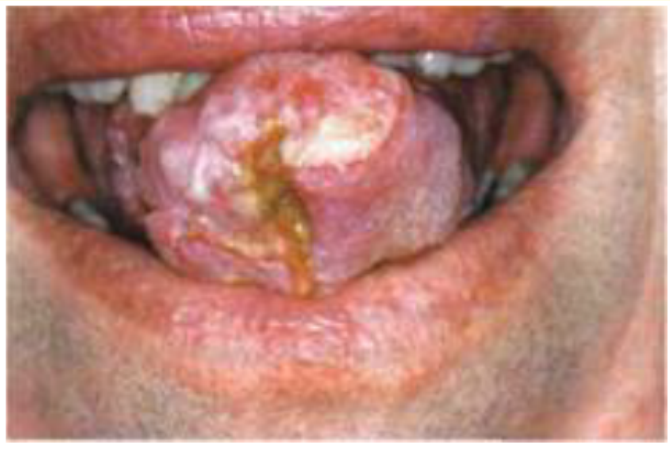


Figure 6: *Deforming ulcers of the tongue with granulomatous polyangiitis.*

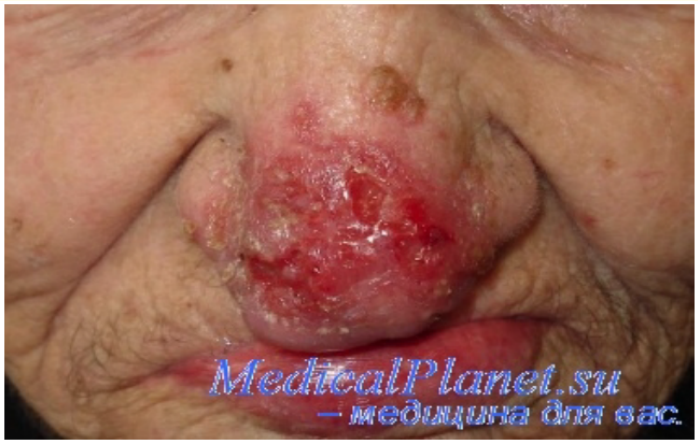


Figure 7: *Ulcerous-necrotic lesion of the nose with granulomatous polyangiitis.*

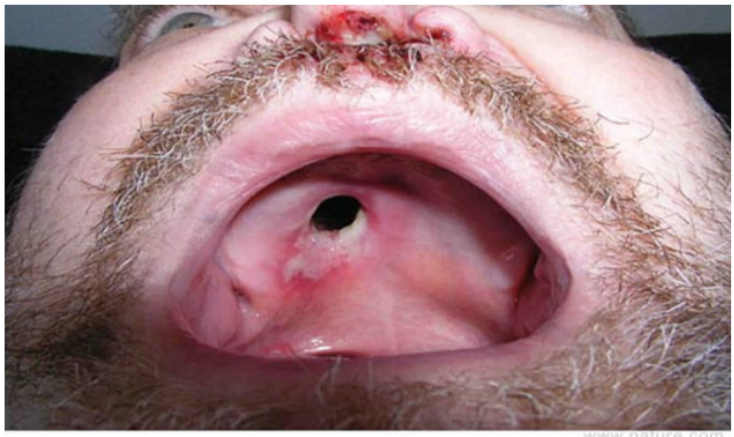


Figure 8: *Granulomatous necrotic lesion of the upper palate with granulomatous polyangiitis.*

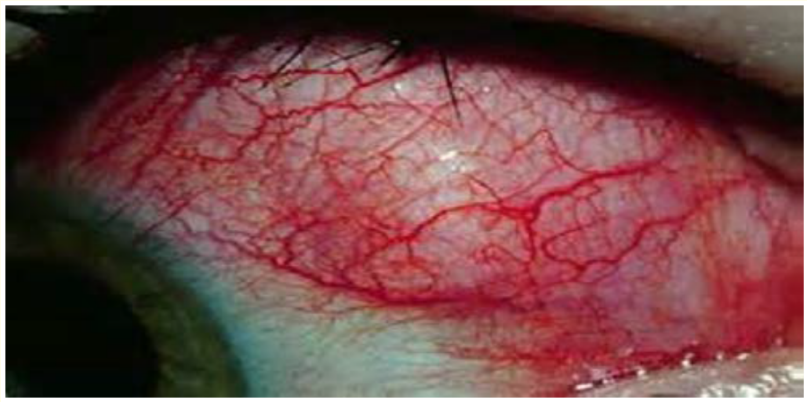


Figure 9: Scleritis with granulomatous polyangiitis.

Figure 10: *Granulomatous lesion of the orbit and eyeball with granulomatous polyangiitis.*

Sometimes the disease manifests itself only in the lower respiratory tract (trachea, bronchi, lungs), and this form of GPA is called "Wegener's headless granulomatosis" (Volchar J.). With a generalized form to the above lor- symptoms are accompanied by lung damage (80% of cases) in the form of pulmonary granulomatous vasculitis, usually resulting in the formation of pulmonary granulomas. Granulomas are prone to decay with the formation of cavities, which is often accompanied by pulmonary bleeding (Figure 11 and 12).

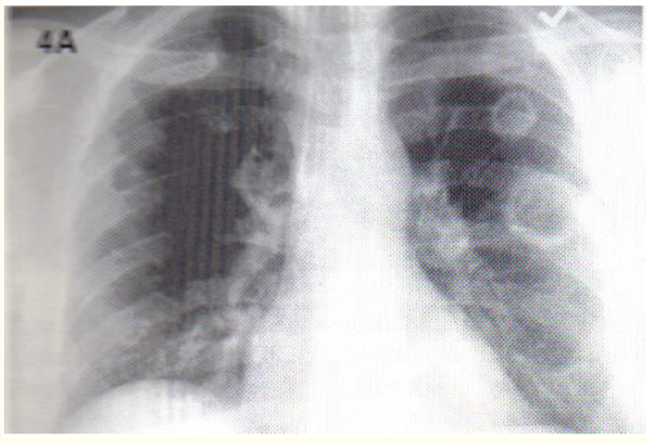


Figure 11: *Chest X-ray of the patient with granulomatous polyangiitis: in the upper and middle field of the left lung, two subpleural cavities with thick walls without exudate.*

Figure 12: *At a computer tomogram of the chest can be seen in both lungs nodular lesions of consolidation without a cavity and a cavity.*

So, in the clinical course, 4 stages are distinguished:

1) Stage of rhinogenic granulomatosis: Purulent-necrotic, ulcerative-necrotic rhinosinusitis, nasopharyngitis, laryngitis, destruction of the bone and cartilage of the nasal septum;
2) Pulmonary stage: Spread of the process to the lung tissue;
3) Stage of generalized lesion involving the respiratory tract, lungs, kidneys, cardiovascular system, gastrointestinal tract;
4) Terminal stage: Renal and pulmonary heart failure [11].

Kidney damage in the form of necrotizing and rapidly progressive glomerulonephritis is observed in 2/3 of patients. Given the frequent damage to the kidneys in GPA and SV in general, the European Association for the Study of Vasculitis (EUVAS) proposed a classification of vasculitis, taking into account the clinical course and laboratory parameters of renal failure, in which local vasculitis, early systemic vasculitis, generalized vasculitis, severe vasculitis and refractory to therapy for incurable vasculitis (Table 3) [12,13].

Category	Explanations
Local vasculitis	Localized systemic vasculitis that does not affect the function of vital organs. Diseases of the upper and/or lower respiratory tract without any other systemic or systemic symptoms. Creatinine <120 μmol/l (1.4 mg/dl)
Early systemic vasculitis	Other vasculitis without damage to vital organs and systems, not life-threatening. Creatinine <120 μmol/l (1.4 mg/dl)
Generalized vasculitis	Vasculitis with dysfunction of vital organs (life-threatening damage to the kidneys and/or other organs). Creatinine < 500 μmol/l (5.7 mg/dl)
Severe vasculitis	Damage to the kidneys and/or other organs with symptoms of multiple organ failure. Creatinine < 500 μmol/l (5.7 mg/dl)
Refractory incurable vasculitis	Progressive vasculitis that does not respond to glucocorticosteroids and cytostatics

Table 3: *EUVAS classification (2012).*

Quite often, GPA occurs with the development of cutaneous vasculitis (40% of patients) and lesions of the peripheral nervous system (15%) with the development of asymmetric polyneuropathy. Pericarditis is described in 5% of patients. The disease most often manifests itself with lesions of the upper respiratory tract and eyes. Damage to the internal organs usually occurs later.

Differential diagnosis with other vasculitis and non-vascular diseases (primarily infections) often presents significant difficulties. The clinical and pathogenetic similarity between MPA and GPA is such that extrarenal granulomatous inflammation may be the only feature that allows them to be distinguished. Granulomas may not be detected biopsy, since biopsy examination may be limited only to the kidneys, which leads to inadequate diagnosis of microscopic polyangiitis. The similarity of clinical manifestations is also reflected in the crossover results of the ANCA studies. For example, among a large group of patients with histologically proven microscopic polyangiitis, both antibodies to MPO and antibodies to proteinase (PR)-3 were detected.

So, the classic organs that are involved in the pathological process in GPA are the upper respiratory tract (sinuses, nose, ears and trachea), lungs and kidneys. However, GPA may affect other organs, but it is not as common and usually not as severe. Involvement of the upper respiratory tract, lungs, and kidneys forms a classic triad in which any combination of these three sites is possible, however, any organ involvement (vasculitis, granulomas, or both) is possible. GPA is often limited to granulomatous airway disease without evidence of systemic vasculitis.

From the point of view of the diagnosis of GPA, the localization of the process is important. For example, when the upper respiratory tract is affected, biopsy of these tissues is relatively non-invasive. But a biopsy from these tissues is quite low in information content, probably less than 50%. Therefore, sometimes interventional procedures are more necessary to make a correct diagnosis. Lung biopsy (open, thoracoscopic, transbronchial or transthoracic) is often the best way to diagnose HB. With these procedures, a sufficient amount of tissue can be obtained, which, as a rule, allows confirming the diagnosis. A kidney biopsy is also necessary, although the amount of tissue obtained is insignificant, which affects the verification of the corresponding pathological features. However, in the context of a patient's general symptoms, signs, and laboratory test results, it is often possible to formulate a correct diagnosis without biopsy material.

Experts don't know why GPA occurs. It is known that this is not an oncological process and not infectious, although the process itself can lead to infection. For example, granulomatous cavities of the lungs can become infected up to tuberculosis. Histologically, GPA is characterized by necrotizing vasculitis of small arteries and veins and the formation of granulomas both in the vessel wall and in surrounding tissues. Of course, GPA is different from periarteritis nodosa. In the vessels, the process goes through the same stages of edema and necrosis, but the formation of granulomas with a large number of giant multinucleated cells is specific.

Prior to the transition to the systemic phase, HPA can proceed as a subacute sluggish process of varying duration. Sometimes the systemic phase never occurs. Terrible signs, foreshadowing the development of an expanded pulmonary-renal syndrome, are rheumatic complaints, weakness, weight loss, fever, night sweats, damage to the eyes, ears, skin, peripheral and central nervous system.

It is believed that GPA is a life-threatening disease that requires long-term therapy. At the same time, some patients die due to the toxicity of therapy. With timely diagnosis and treatment, a patient with GPA can recover. But if left untreated, there is a risk of kidney failure and death.

Search, understanding, identification of internal patterns in some complex and unclear aspect of pathology is the main goal of diagnosis. For example, it is known that there is a certain genetic predisposition to GPA, that is, to a disease associated with the presence of histocompatibility antigens HLA B7, B8 and DR2, although the pathogenetic mechanisms for the development of GPA are unknown. Damage to the upper and lower respiratory tract suggests an allergic reaction to some antigen - exogenous or endogenous, characteristic of the respiratory tract. Moreover, in the pathogenesis of the disease, the hyperreactivity of the humoral link of immunity matters: an increase in serum and secretory IgA, IgG and IgE, RF, CEC, IgG autoantibodies are also detected.

Also, the pathogenetic role of any chronic focal infection (nasopharyngeal), prolonged use of antibiotics, and a viral infection are also not excluded. It has been reported that GPA recurrences are more likely to occur with carriage of *Staphylococcus aureus* in the nasopharynx. However, there is no clear evidence that this bacterium is involved in the development of the disease.

In some patients, immune complexes are detected in the blood and in the vascular wall, but their etiological role has not been finally proven. Granulomas with large the number of giant multinucleated cells, especially in the lungs, may be a manifestation of an allergic reaction of a delayed type or reaction to a foreign body, but there is currently no direct evidence.

The fluid obtained during bronchoalveolar lavage in patients with GPA contains a lot of neutrophils, while in other granulomatous lesions of the lungs, in particular with sarcoidosis, the number of lymphocytes is increased in it. The pathogenetic significance of this fact is also unclear.

Heart involvement occurs in 8% of cases and leads to pericarditis, coronary vasculitis, myocardial infarction, mitral and aortic valve disease, and AV block. The nervous system is involved in the process in 23% of GPA patients and includes cranial nerve neuropathy, multiple mononeuropathy, and occasionally cerebral vasculitis and cerebral granulomas.

Renal localization of granulomas was noted in 77% of patients with GPA, and usually their clinical picture prevails. Directly or indirectly, renal failure is the cause of death in most untreated HB patients. For a long time, the pathological process may be limited to mild glomerulonephritis with proteinuria, hematuria and erythrocyte casts, but as soon as renal failure appears, it progresses rapidly if treatment is not started.

So, the GPA classification criteria are distinguished:

1) Inflammation of the nose and oral cavity: ulcers in the oral cavity, purulent or bloody discharge from the nose;
2) Changes in the lungs during x-ray examination: nodules, infiltrates or cavities;
3) Urine changes: Microhematuria (> 5 erythrocytes per field of view) or accumulation of erythrocytes in the urine sediment;
4) Biopsy: Granulomatous inflammation in the wall of the artery or in the perivascular and extravascular space.

The presence of any two or more criteria in a patient makes it possible to diagnose GPA with a sensitivity of 88% and a specificity of 92%. An easy way to remember these criteria is the mnemonic abbreviation ROUGH (rough): R=Chest Radiograph; O = Oral ulcers (mouth ulcers); U=Urinary sediment (urine sediment); G=Granulomas (granulomas); H=Hemoptysis (hemoptysis). Hemoptysis during the period of illness is an additional fifth criterion. However, it should be noted that none of these features are specific to GPA. The prognosis of the untreated disease is poor. With treatment, remission can be achieved. The 5-year survival rate reaches 60%.

Discovery history: In June 1934, the pathologist Friedrich Wegener performed an autopsy on a 38-year-old man who died of kidney failure in the presence of prolonged febrile states. At the same time, the deceased had a saddle nose deformity, a ruptured nasal septum, and chronic rhinitis. Histologically, Wegener identified a special type of inflammation in the vessels of the kidneys and the nasal mucosa, that is, necrotic inflammation with granulomas. The first publications on this topic date back to 1936. and 1939 In a preliminary report "On generalized septic vascular diseases" ("Über generalisierte, septische Gefässerkrankungen"), F. Wegener described three patients (a man aged 38 and two women aged 33 and 36) with a 4 - 7-month history of fever, with an increased rate of sedimentation red blood cells, anemia, rhinitis at the onset of the disease and the subsequent development of stomatitis, laryngitis, pharyngitis and tracheitis. In the clinical picture of the disease, lesions of the nasal cavity prevailed, and in the histological picture in two patients was dominated by granulomatous changes with vasculitis of many vessels and organs, as well as diagnosed glomerulonephritis with the formation of periglomerular granulomas. Although the disease was accompanied by generalized arteritis, similar to that of periarteritis nodosa, Wegener in both of his works, he considered the cases cited by him as unique on the basis of the clinical course and differing in pathoanatomical changes.

In fairness, it should be said that the first case of systemic vasculitis, now known as GPA (Wegener), was described by a friend and roommate of F. Wegener during his studies in Munich, Heinz Klinger. Klinger observed a 70-year-old physician with nephritis, arthritis, and a history of chronic sinusitis with nasal discharge. Autopsy revealed invasion of a necrotic lesion at the base of the skull near the eyes, as well as ulceration of the trachea. On histological examination vasculitis and granuloma formation, including destruction of the nasal septum, were determined. H. Klinger described the second clinical case in a 51-year-old carpenter, who also had hemoptysis, polyarthralgia, glomerulonephritis, and profuse nasal discharge. Commenting on these two observations, Klinger had no doubt that the disease began in the oldest vessels or those areas that had suffered the most damage in the past. In particular, he considered the respiratory pathways that are directly exposed to exogenous irritant compounds. In both cases, the disease proceeded with exacerbations and remissions. Robert Rössle, director of the Institute of Pathology at the University of Berlin, where Klinger described his cases, cited observations of two more patients with vasculitis and necrosis of the mucous membrane of the nose and upper respiratory tract. Heinz Klinger first published his observations in 1931 and considered the clinical cases cited by him as a form of polyarteritis nodosa, and not as an independent nosological disease.

Of course, F. Wegener was familiar with the published observations of Heinz Klinger, which were interpreted by the author as a variant of polyarteritis nodosa and as an allergic hypersensitive process. But F. Wegener did not think that these cases could be explained in this way. He published his work in prestigious German journals, and in 1936 he gave a 10-minute report at a meeting of the German Society of Pathologists. F. Wegener himself described 7 cases of small vessel vasculitis with granulomatous inflammation.

So, F. Wegener interpreted vascular changes as one of the forms of periarteritis nodosa described by Kussmaul and Mayer. Although the disease was accompanied by generalized arteritis, similar to that of periarteritis nodosa. Wegener in both his works (1936 and 1939) considered the cases he cited as unique on the basis of the clinical course and differing anatomical changes. He was familiar with the recently published articles by Klinger and anatomical changes. He was familiar with the recently published articles by Klinger and Rössle describing observations of periarteritis nodosa, which interpreted the marked changes as rheumatic and considered the disease as an allergic-hypersensitive process. Wegener believed that his cases could not be explained in this way and could not be associated with an infectious agent. He denied that the disease is rheumatic in nature, since it did not find rheumatic changes either in the myocardium or in the endocardium and did not find any signs of Aschoff granuloma or other nodules in the examined joints and pulmonary lesions described by F. Klinge. Unlike Rössle, Wegener believed that the source of the pathological process is the internal regions of the nose. Granulomatous the disease usually lasted 4 to 7 months, began with cold symptoms, and subsequently progressed to necrotic lesions of the nose and throat with septic signs and progressive renal failure. The outcome was lethal.

In 1954, American doctors G.C. Godman and J. Churg described another 22 cases of this disease and proposed to name it Wegener's granulomatosis in honor of the first author who identified this disease as a separate nosological form based on typical histological changes and clinical features. This eponym has firmly entered world literature, although F. Wegener himself disappeared into obscurity after the war (for special reasons) until the 1980s, when he began to receive a lot of attention, until his death in 1990. After the publication of the article G.C. Godman and J. Churg, Wegener became an academic star, received the title of professor of pathology and taught at the Medical University in Lübeck (Germany). Judging by the reviews, his students admired him as a teacher. When he left the university in 1970 to resume private practice, students organized a torchlight procession in protest. F. Wegener died of a stroke in 1990 at the age of 83 in Lübeck.

Conclusion

In conclusion, it should be noted that the clinical and pathological descriptions made in 1934 and 1954 made it possible to better define the diagnostic criteria for GPA. And in 1966, a limited form of the disease was described, in which there is no damage to the renal glomeruli. Subsequently, the researchers demonstrated the effectiveness of cytotoxic therapy in GPA, which was an important milestone in the development of therapy, since it gave rise to the direction of using cytotoxic drugs and approaches used in oncology in non-tumor diseases.

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