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Churg-Strauss Syndrome: Clinical and Immunological Features

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1. Introduction

The vasculitides include a broad spectrum of disorders that span a clinical spectrum from benign, self-limited disease to fulminant conditions that are fatal in the absence of therapy. Whereas the large-vessel vasculitides consist of 2 principal disorders, giant cell arteritis and Takayasu arteritis, the medium- and small-vessel vasculitides are much more diverse, including multiple diseases that can affect nearly every organ system (Seo & Stone, 2007). This article is the second of a 2-part series that focuses on the challenges faced by clinicians who care for patients with vasculitis. The first article in this series discussed the large-vessel vasculitides. The problem of systemic autoimmune diseases such as systemic vasculitis with vascular lesions of medium and small vessels, including: Wegener granulomatosis, Churg-Strauss syndrome, microscopic poliangiitis, nodose poliarteriitis, attracts every year more attention of doctors, due to the worldwide relentless increase of patients with these diseases (Lhote & Guillevin, 2009; Tsukadaira, 2009). Recently, several reports have suggested that vasculitis is becoming more common.

Systemic vasculitis is a group of heterogeneous diseases (syndromes), characterized by inflammation and damage to blood vessels and which compromises or destroys the vessel wall leading to haemorrhagic and / or ischaemic events, giving impetus to the development of a wide spectrum of symptoms and signs. The forms of vasculitis may be varied: primary [idiopathic, e.g. cutaneous leukocytoclastic angiitis, Wegener's granulomatosis, Churg–Strauss syndrome and microscopic polyangiitis] and secondary [a manifestation of connective tissue disease, infection, adverse drug eruption, or a paraneoplastic phenomenon], local and generalized, transient, recurrent and chronic; included group of diseases in which vasculitis is a primary characteristic. They are general in nature, though sometimes a local clinic can manifest symptoms. General damage of blood vessels may occasionally appear and disappear, but in most cases there are long-term. Each new escalation leads to the increase of clinical symptoms. Clinical implications of SV course depend on a number of factors, including etiology, location, size and number of blood vessels, the extent and severity of disease, its activity and nature of treatment.

Systemic vasculitis as the existing disease was first described by A. Cussmaul and I. Maier, when they reported a case of necrotizing arteritis and called it nodose periarteriitis. There are over twenty different forms of Systemic vasculitis. One of the first classification was their classification by P. Zeek's, which included five categories of Systemic vasculitis: nodose

periarteriitis, hypersensitivity angiitis, allergic granulomatous angiitis, rheumatic angiitis, temporal arteritis. It was based on pathological data and damage and on their sizes. On the basis of etiologic and pathogenetic, clinical and pathomorphological criteria has been done many classifications of SV. But they are all flawed, because there are several factors that may affect the objectivity of classification opinions. They include: location and technology collection of fabrics, including various vascular pools, the possibility of angiography, variability in cellular composition depending on the morphogram stage, previous treatment options etc.

Primary systemic vasculitis has an incidence of more than 100 new cases per million. Currently, the most widely adopted vasculitis classification system is that of Chapel Hill Consensus Conference (CHCC), which is based on pathological criteria. The other widely used system is that of the American College of Rheumatology (ACR), which is based predominately on clinical findings.

The etiology of the systemic vasculitis is largely unknown, although they are widely believed to be autoimmune in origin, triggered by different environmental events. Epidemiologic studies have indicated factors, including silica exposure, infection, seasonal variation in occurrence, drugs, ultraviolet radiation and vitamin D, latitudinal gradient and etc.

Pathogenic mechanisms remain uncertain. In the modern literature widely discusses the pathogenic role in the development of systemic vasculitis of neutrophils, eosinophils, antineutrophil cytoplasmic antibodies, circulating immune complexes, lymphocytes, cytokines, total IgE and etc.

In general, systemic symptoms accompany all cutaneous vasculitic syndromes, and these symptoms include fever, malaise, weight loss, arthritis and/or arthralgias. In the majority of patients, vasculitic lesions will affect the lower extremities, mostly at dependent sites or underlying tight-fitting clothes. Upper extremity, trunk and head and neck involvement are infrequent and often signal the presence of more severe disease or coexisting systemic vasculitis. The subtlety and diversity of symptoms in the initial phase of vasculitis can be a real diagnostic problem, and thus early recognition of a vasculitic condition relies on the experience of a team of dedicated professionals from several different subspecialties, including laboratory medicine. The initial assessment will be to make a diagnosis, categorize disease severity and formulate a management plan. A structured approach, based on careful disease staging and evaluation, is the cornerstone of good disease management. Initial evaluation includes a comprehensive clinical assessment, serological tests, radiology and histology. The first step in the patients management is clinical history and examination, the second one of the initial investigations include full blood count, inflammatory markers [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)], renal function such as epidermal growth factor receptor (eGFR) and serology to include antiglomerular basement membrane antibodies. Inflammatory markers provide a non-specific tool for assessing inflammatory activity and monitoring treatment. Urinalysis detects proteinuria and haematuria.

Specific diadnostic is based on detection of specific markers: characteristic autoantibodies are formed towards enzymes and bactericidal proteins within the cytoplasmic granules of neutrophils and monocytes in a substantial proportion of patients with systemic vasculitis manifesting as Wegener's granulomatosis, microscopic polyangiitis and Churg–Strauss syndrome, as well as in patients with limited forms of these conditions. Histological examination of biopsy material is useful in confirming a diagnosis in the context of clinical findings and laboratory data. Also, skin biopsy is the gold standard for the diagnosis of

vasculitis type. For subsequent evaluations, it is effective and practical to measure clinical disease status for most patients with small and medium vessel vasculitis. Therapy is based on the pattern of vasculitis and on careful evaluation of the extent and activity of disease. The treatment of vasculitis comprises induction of remission followed by maintenance. Remission should be induced rapidly, balancing potential target organ damage against drug toxicity. Maintenance with immunosuppression should limit the amount of corticosteroid use and prevent relapse. Concomitant medication is used to treat or prevent adverse events from immunosuppressive treatment.

2. Connection between systemic vasculitis, bronchial asthma, eosinophilic syndrome and churg-strauss syndrome

The unreleased question of eiosinophilic background in patients with systemic vasculitis and its influence on the disease activity, is very actual today. The most important eosinophilic-associated systemic vasculitis between all vascular processes is Churg-Strauss syndrome, that occur with eosinophilia asdiagnostic criterion due to ACR,1990. Since its first description as allergic granulomatous angiitis in 1951 (Churg and Strauss, 1951), and subsequently its affiliation with the small-sized vessel systemic necrotizing vasculitides and, more specifically, the so-called subgroup of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides in the early 1990s, knowledge about the pathophysiological mechanisms of Churg-Strauss syndrome has greatly improved. Its natural clinical history and progression are better understood, but the syndrome's potential subsets are not yet totally elucidated. Major advances have also been made in the therapeutic management of affected patients, but much remains to be done because sustained off-treatment remissions are quite rare and patients often require a long-term low-dose corticosteroid therapy (Cohen et al., 2007; Ribi et al., 2008). International studies and workshops on vasculitis classification, immunology, genetics, and treatments are ongoing or planned. Here, we review the current known aspects of Churg-Strauss syndrome (Pagnoux, 2010). Churg-Strauss syndrome is a rare disease, with an annual incidence ranging between 0.5 and 6.8 per million inhabitants and a prevalence of 10.7-14 per million inhabitants (Pagnoux et al., 2007; Watts et al., 2005), with a mean age at onset around 50 years and no sex preponderance. No strong evidence of a differential geographical distribution pattern has been reported so far, nor a blatant change in its frequency over the past decades. However, some studies reported a slightly higher prevalence in northern, as opposed to southern, Europe, and in urban, as compared to rural, regions.

Several exogenous triggering factors for disease onset or flares have been identified or, more cautiously, suspected in some European or North American studies. They include vaccinations, desensitizations, and drugs, such as macrolides, carbamazepine, quinine, and also anti-asthma agents, like leukotriene-receptor antagonists and, more recently, omalizumab, a recombinant monoclonal anti-immunoglobulin E (IgE) antibody (Bibby et al., 2010; Pagnoux et al., 2007). These latter two often provide the opportunity for substantial tapering or withdrawal of corticosteroids in asthmatic patients, thereby unmasking an underlying 'forme fruste' of Churg-Strauss syndrome, which had so far been controlled by corticosteroids, but a direct triggering role of these agents cannot be excluded (Bibby et al., 2010). Whether or not "common" asthma represents a risk factor for Churg-Strauss syndrome *per se* has not been clearly determined, because both conditions share some underlying mechanisms. The earliest studies reported a higher annual incidence of Churg-

Strauss syndrome in asthmatic patients treated with non-leukotriene-modifying asthma drugs (64.4 per million asthmatics) or a leukotriene-receptor antagonist (about 60 per million asthmatics). A more recent study reported a somewhat lower Churg-Strauss syndrome incidence of 34.6 per million asthmatics per year (Harrold et al., 2005), which remains higher than in the general population; but other reported incidences varied from 0 to 67 according to disease definition. Whereas asthma often clusters in families, familial cases of Churg-Strauss syndrome are exceptional, diminishing the gene and environmental factor impact on the latter. However, results of several genetic studies suggested some predisposing hereditary factors, like the HLA-DRB1*04 and HLA-DRB1*07 alleles and the HLA-DRB4 gene, which are more frequent in Churg-Strauss syndrome patients than healthy controls, the interleukin IL10.2 haplotype, which is associated with enhanced IL-10 expression, and possibly the CD226 Gly307Ser polymorphism (Wieczorek et al., 2010).
Its most typical presentation consists of the appearance, in a patient with late-onset asthma, of vasculitic manifestations, like fever, cutaneous purpura and mononeuritis multiplex. In such a setting, the combination of blood eosinophilia and inflammatory syndrome is highly suggestive of the diagnosis, which can be further supported by the detection of antineutrophil cytoplasmic antibodies (ANCA), especially P-ANCA (perinuclear-ANCA) with anti-myeloperoxidase specificity and the presence of eosinophilic granulomas and/or necrotizing vasculitis in an affected-tissue biopsy. Asthma is the most common sign of Churg-Strauss syndrome, but Churg-Strauss syndrome can cause a variety of problems, ranging from hay fever, rash and gastrointestinal bleeding, to severe pain and numbness in your hands and feet. The wide range of symptoms — and their similarity to symptoms of other disorders — make Churg-Strauss syndrome challenging to diagnose. Biological phenotypes of interest for assessing severity of Churg-Strauss syndrome may be IgE level, ANCA, cytokines (IL-2, 4, 5, 10) and eosinophilia. Phenotypes other than usual Churg-Strauss syndrome need to be considered. Phenotypic heterogeneity may help to disentangle etiologic heterogeneity. Churg-Strauss syndrome, its verification and activity could be mediated by different pathogenetic mechanisms and realized mediators, such as ANCA, eosinophils, cytokines, total IgE etc. Severity of eosinophilia in patients with Churg-Strauss syndrome represents a clinical subphenotype of interest, and studying severe eosinophilia (extreme phenotype) may increase the power to detect linkage. It would be useful to define Churg-Strauss syndrome phenotypes unencumbered by the activity of disease, which may depend heavily on nongenetic factors, and free of gene-trigger interactions. Besides the activity, environmental factors and inadequate treatment can modify the severity of the Churg-Strauss syndrome phenotype. Consideration of treatment as a marker of severity implies that the relevant phenotype for etiological research is masked by the treatment.

Intermediate Phenotypes

Intermediate phenotypes are important with respect to pleiotropy and etiological heterogeneity. Bronchial hyperresponsiveness, total IgE, eosinophilia, ANCA-presence and vacular involvement are usually considered intermediate phenotypes for Churg-Strauss syndrome.

Refinement of Phenotypes

Considering environmental factors and potential interactions with genetic factors may increase our ability to detect genetic factors in multifactorial diseases such as Churg-Strauss syndrome.

There is increasing evidence that the associations of ANCAs, total IgE, and eosinophilia with environmental and clinical factors are different in patients with Churg-Strauss syndrome and different eosinophilia severity.

The most typical clinical presentation of Churg-Strauss syndrome is the appearance of vasculitic manifestations in a patient with known allergic rhinitis, nasal and sinus polyposis, and late-onset asthma (almost constant, and usually preexisting for 5-10 years). General symptoms (i.e., fever or weight loss), mononeuritis multiplex, and/or necrotic cutaneous purpura are the most frequent manifestations at disease onset, in combination with elevated blood eosinophilia and inflammatory syndrome. The detection of ANCA, especially P-ANCA (with perinuclear labeling pattern in indirect immunofluorescence) with anti-myeloperoxidase (antiMPO) specificity (in enzyme-linked immunosorbent assay), strongly supports the diagnosis, but they are present in only 35-40% of the patients (Sablé-Fourtassou et al., 2005; Sinico &Bottero, 2009). While Lanham et al. (1984) commendably described in the 1980s that Churg-Strauss disease most typically emerges through 3 successive phases (prodromic phase, with asthma and allergic manifestations; then, eosinophil infiltration into tissues, especially lung and/or myocardium; and eventually, systemic and vasculitic phase), not all patients experience this clear-cut stepwise progression and many have overlapping manifestations from these different phases.

In addition to almost constant asthma and airflow obstruction, lung manifestations include patchy and transient alveolar (eosinophilic) infiltrates and/or pleurisy, and, rarely, lung non-excavated nodules or alveolar hemorrhage. Allergic rhinitis, sinusitis, and/or nasal polyposis can be observed in 60-80% of the patients. Notably, Churg-Strauss syndrome patients must be evaluated for heart involvement, because it carries a poor prognosis, has therapeutic implications, and can be paucisymptomatic. In the earliest studies, heart involvement was reportedly occurring in up to 50-60% of the patients (Pagnoux, 2010) and represented the major cause of mortality, accounting for 48% of patient deaths (Pagnoux, 2010). In more recent reports, outcomes were better. For instance, Neumann et al. (2009) reported that there were “only” two deaths from severe endomyocarditis among the 22 patients with cardiac involvement, with recovery of nearly normal cardiac function in almost all of the survivors.

However, the reported cardiac manifestations and their frequencies are strongly dependent on which cardiac investigations were done. Cardiac magnetic resonance imaging might reveal clinically silent and echographically undisclosed myocardial involvement, whose clinical significance is uncertain today (Bhagirath et al., 2009; Neumann et al., 2009). Cardiac screening with magnetic resonance imaging can better delineate inflammatory pericardial involvement and reveal microvasculitis of the epi- and myocardial vessels, endo- and/or myocardial inflammation, and/or less reversible fibrosis. These are supposedly attributable to eosinophil infiltration and/or ischemic lesions due to coronary artery vasculitis, which, nonetheless, is rare in Churg-Strauss syndrome (Bhagirath et al., 2009). Intraventricular thrombi are other, but rare, possible cardiovascular abnormalities, usually also visible on echocardiography. Positron-emission tomography has also been used to evaluate cardiac involvement, with some interesting results.

The aim of this study was to analyze clinical, morphological and immunological features in patients with Churg-Strauss syndrome in comparison to the patients with bronchial asthma and systemic vasculitis with eosinophilia and to study eosinophils influence on vasculitis, especially Churg-Strauss, progression and complication.

The recognition of eosinophils as complex immunomodulatory cells has been increasing in recent years. Eosinophils are derived from hematopoietic stem cells that are committed

initially to the myeloid and subsequently to the basophil-eosinophil granulocyte lineage (Tefferi, 2005). The material in these granules includes cationic proteins major basic protein, eosinophilic cationic protein, eosinophil-derived neurotoxin, eosinophil peroxidase), cytokines (interleukins [ILs], tumor necrosis factor), and lipid mediators (leukotriene C4) (Rothenberg, 1998). Interleukin 5 is considered the major eosinophil growth and survival factor, whereas chemokines (eotaxin, platelet-activating factor, RANTES [regulated on activation, normal T expressed and secreted]) and endothelial adhesion molecules (integrins, vascular cell adhesion molecules) contribute to eosinophil trafficking (Elsner & Kapp, 2001; Tefferi, 2005). Major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin are the primary mediators of eosinophil-associated toxicity to microbes (parasites, protozoa, bacteria, viruses) and human tissue (myocarditis, pneumonitis, dermatitis, neuropathy, vasculitis) (Gleich, 2009). The lung and gastrointestinal systems constitute the main residence for eosinophils. Blood eosinophilia (absolute eosinophil count [AEC] ≥600 cells/μL) is the usual initial clue for the presence of an eosinophilic disorder. The degree of blood eosinophilia, in the absence of active treatment, can be categorized into mild (AEC 600-1500 cells/μL), moderate (AEC 1500-5000 cells/μL), or severe (AEC >5000 cells/μL) (Brito-Babapulle, 2003; Tefferi, 2005). Target organ damage is unusual with mild eosinophilia, but its occurrence in association with moderate to severe eosinophilia does not appear to depend on the specific cause of eosinophilia. The eosinophil has been perceived as a terminal effector cell in allergic airway diseases. However, recent work has shown that this multifunctional cell could be more involved in the initial stages of allergic disease development than was previously thought, particularly with regard to the ability of the eosinophil to modulate T-cell responses. In this review, we discuss recent advances that suggest that eosinophils can present antigen to naïve as well as to antigen experienced T cells, induce T helper 2 cell development, cytokine production or both, and affect T-cell migration to sites of inflammation. These findings are changing the way that eosinophil function in disease is perceived, and represent a shift in the dogma of allergic disease development (Walsh & August, 2010).

The pathogenesis of eosinophilia and tissue damage in Churg-Strauss syndrome is yet unclear, but an unknown allergen or environmental trigger is thought to provoke fatal consequences in pre-sensitized asthma patients. On a cellular level, a strong shift towards a Th2-like response with massive T-cell activation is evident (Walsh & August, 2010). *In vitro*, T-cell lines from Churg-Strauss syndrome patients produce significant amounts of IL-4 and -13 (Rothenberg, 1998). This is underlined by the fact that active CSS patients have usually high serum levels of IgE and IgE-containing immune complexes (Gleich, 2009). In tissue biopsies, granulomatous vasculitic lesions filled with eosinophils, macrophages and lymphocytes are observed (Elsner & Kapp, 2001). Local activation with degranulation of eosinophils and subsequent release of granule proteins such as eosinophil-derived neurotoxin (EDN) and major basic protein (MBP) is thought to contribute to vasculitic damage.

However, the molecules specifically contributing to eosinophilia and subsequent degranulation in Churg-Strauss syndrome are enigmatic. Recently, animal and human studies have revealed the role of a chemokine family ('eotaxins') involved in tissue eosinophilia and eosinophil maturation in allergic asthma and eosinophilic oesophagitis (EO) (Gleich, 2009). To date, three members of the eotaxin family have been described: eotaxin-1 (CCL11), eotaxin-2 (CCL24) and eotaxin-3 (CCL26). All eotaxins bind to and activate chemokine receptor 3 (CCR3) but have little homology and seem to possess different physiological properties. We hypothesized that these eotaxins might play a role in eosinophilia in Churg-Strauss syndrome and thus compared serum levels of eotaxin-1, -2 and -3 in active and inactive Churg-Strauss

syndrome patients with healthy controls (HC). Furthermore, we determined local expression of eotaxin-3 at sites of active disease in Churg-Strauss syndrome.

Skin biopsy is the gold standard for the diagnosis of cutaneous vasculitis, whose manifestations include urticaria, infiltrative erythema, petechiae, purpura, purpuric papules, haemorrhagic vesicles and bullae, nodules, livedo racemosa, deep (punched out) ulcers and digital gangrene. Skin biopsy, extending to subcutis and taken from the earliest, most symptomatic, reddish or purpuric lesion is crucial for obtaining a high-yielding diagnostic sample. Based on histology, vasculitis can be classified on the size of vessels affected and the dominant immune cell mediating the inflammation (e.g. neutrophilic granulomatous, lymphocytic, or eosinophilic).

Disruption of small vessels by inflammatory cells, deposition of fibrin within the lumen and / or vessel wall coupled with nuclear debris allows for the confident recognition of small vessel, mostly neutrophilic vasculitis (also known as leukocytoclastic vasculitis).

The main histopathological features in the cutaneous lesions of Churg-Strauss syndrome are dermal leukocytoclastic vasculitis with a variable eosinophilic infiltrate and non-vasculitic tissue eosinophilia with granuloma formation. This wide histopathological spectrum may account for the various skin manifestations of Churg-Strauss syndrome. However, the unique histopathological combination of dermal eosinophilic vasculitis and subcutaneous granulomatous phlebitis accompanied by bulla formation has not been previously described. We report an unusual Churg-Strauss syndrome case showing dermal necrotizing eosinophilic vasculitis and granulomatous phlebitis in purpuric lesions coupled with subepidermal blistering. The blisters showed dermal granulomatous dermatitis and eosinophilia without evidence of vasculitis. Dermal necrotizing eosinophilic vasculitis was characterized by fibrinoid alteration of the vessel wall, a prominent perivascular eosinophilic infiltrate, a few infiltrating histiocytes along the affected vessel wall, and the absence of neutrophilic infiltration. The underlying subcutaneous granulomatous phlebitis was characterized by an angiocentric histiocytic infiltrate surrounded by marked eosinophilic infiltrate. Deposition of cytotoxic proteins and radicals derived from eosinophils in the vessel walls and papillary dermis followed by a secondary granulomatous response may account for the unique clinical and histopathological features in this case (Gleich, 2009; Pagnoux, 2010).

3. Results of the research

We identified 30 unselected consecutive patients in whom Churg-Strauss syndrome (14 men and 16 women) aged from 19 to 78 years (40,35 ± 2,99 years) was diagnosed clinically at internal medicine departments (nephrology, clinical immunology and rheumatology, pulmonology, neurology, and others) in Lviv oblast clinical hospital and immunologicaly – at the department of clinical immunology and allegrology of Lviv national medical university and at West-Ukrainian medical center of clinical immunology and allergology in Ukraine between 2000 and 2010. There were observed 30 patients with bronchial asthma (15 men and 15 women) aged from 18 to 70 years (31,9 ± 4,4 years) and 19 patients with systemic vasculitis with eosinophilia (8 men and 11 women) aged from 19 to 78 years (37,6 ± 3,8 years) and consulted at the department of clinical immunology and allegrology of Lviv national medical university and at West-Ukrainian medical center of clinical immunology and allergology in Ukraine between 2000 and 2010. We examined the medical records of all these patients. Churg-Strauss syndrome was defined according to the Chapel Hill Consensus Conference nomenclature (Rothenberg, 1998). The classification criteria for

Churg-Strauss syndrome of the American College of Rheumatology (ACR) (Masi, 1990) as well as Lanham's (Hammersmith) criteria (Gleich, 2009) were retrospectively applied to the study population. All patients had direct (histologic) or indirect (using surrogate markers) evidence of vasculitis (Keogh, 2003). Systemic vasculitis with eosinophilia, bronchial asthma (according to Global Initiative for Asthma [GINA] guidelines) and eosinophilic syndrome (ES) were diagnosed according to approved medical diagnostic protocols too.

Sign	Patients with BA and eosinophilia (n = 30)		Patients with SV and eosinophilia (n = 19)		Patients with CSS (n = 30)		P 1-2	P 1-3	P 2-3
	1		2		3				
	Abs.	%	Abs.	%	Abs.	%			
1	2	3	4	5	6	7	8	9	10
Disease duration	9,6±2,9		8,3±2,1		7,0±2,3		NS	NS	NS
Complicated genetic (family) allergic anamnesis	19	63,3	10	52,6	23	76,7	NS	0,05	NS
Complicated ontogenetic allergic anamnesis	30	100	10	52,6	21	70	0,001	0,01	0,01
Polinosis	11	36,7	-	-	14	46,7	-	NS	-
Food allergy	4	13,3	-	-	6	20	-	NS	-
Insect allergy	14	46,7	-	-	2	6,7	-	0,001	-
Drug allergy	-	-	10	52,6	2	6,7	-	-	0,001
Allergic rhinitis	4	13,3		-	11	36,7	-	0,01	-
Allergic rhinitis and nasal poliposis	4	13,3		-	10	33,3	-	0,01	-
Bronchial asthma	30	100	-	-	26	86,7	0,001	NS	0,001
Bronchial asthma and nasal poliposis	-	-	-	-	7	23,3	-	0,001	0,001
Complicated genetic (family) autoimmune anamnesis	-	-	5	16,7	7	23,3	-	-	NS
Often pulmonary infection diseases: pharyngitis, laryngitis, bronchitis, pneumonia over the time of year	18	60,0	14	46,7	17	56,7	NS	NS	NS

Table 1. Main anamnesis features in patients with bronchial asthma with eosinophilia, systemic vasculitis with eosinophilia and with Churg-Strauss syndrome (M±m)

Clinical manifestations were usually confirmed by instrumental examinations as appropriate and/or tissue biopsy. One or more biopsy specimens from affected tissues were obtained when considered necessary by the clinicians. A biopsy specimen was considered consistent with a diagnosis of Churg-Strauss syndrome when eosinophilic tissue infiltration and/or vasculitis were found. Routine laboratory tests were performed in all cases at the time of diagnosis and at followup. The presence of ANCAs, IgE, CIC was determined in all patients at the time of diagnosis due to the necessity, using approved methods for each detection.

Statistical analysis. All analyses were performed using Stata statistical software, release 8.2 (Stata Corporation, College Station, TX). The differences between patients with Churg-Strauss syndrome and different eosinophilia severity in continuous variables were tested by the Mann-Whitney U test and in categorical variables by Fisher's exact test. All reported *P* values are 2-sided. *P* values less than 0.05 were considered significant.

In the result of this research it was observed some clinical features in patients with Churg-Strauss syndrome in the comparison with patients with bronchial asthma and systemic vasculitis with eosinophilia.

In patients with bronchial asthma and systemic vasculitis with eosinophilic syndrome, as well as Churg-Strauss syndrome have had a variety of anamnesis data(presented in the Table 1), severity of clinical symptoms (presented in the Table 2) and features of the course, activity and severity (presented in the Table 3).

The analysis of anamnesis data in the comparable groups of patients has showed in Table 1, which includes the following features as duration of the disease - we examined 30 patients with Churg-Strauss syndrome and it was fixed an average of 7,0 ± 2,3 years, and in 30 patients with bronchial asthma with eosinophilia - 9,6 ± 2,9 years and in 19 patients with systemic vasculitis with eosinophilia - 8,3±2,1 years.

NS- not significant

Ontogenetic history of allergy was loaded in 21 (70%) patients with Churg-Strauss syndrome, in 47,4% patients with SV with eosinophilia (p<0,01) and in 30% patients with bronchial asthma with eosinophilia (p<0,05). Pollen allergy, which manifested with pollinosis was found in 14 (46.7%) patients with Churg-Strauss syndrome, as compared with one (36,7%) patient with bronchial and eosinophilia (p< 0,05). Complicated genetic autoimmune anamnesis was found in 7 (23,3%) patients with Churg-Strauss syndrome and in 5 (16,7%) patients with systemic vasculitis with eosinohilia (P<0,05) and was not impeded in patients with bronchial asthma and eosinophilia.

Complicated immunodeficiency anamnesis (six or more respiratory diseases during the year) was established in 17 (56,7%) patients with Churg-Strauss syndrome, in 18 (60%) patients with bronchial asthma and eosinophilia and in 14 (73.6%) patients with systemic vasculitis with eosinophilia.

NS- not significant

In the Table 2, low level of productivity cough was recorded in 17 (56,7%) patients with Churg-Strauss syndrome and in 16 (53,3%) patients with bronchial asthma with eosinophilia (p<0,05). Complicated nasal breathing was found in 21 (70%) patients with Churg-Strauss syndrome and in 19 (63,3%) patients with bronchial asthma and eosinophilia (p<0,05). Typical night asthma attacks were noted in 5 (16,7%) patients with bronchial asthma with eosinophilia, in 14 (46,7%) patients with Churg-Strauss syndrome (p<0,01). Skin itching

were found in 17 (56,7%) patients with Churg-Strauss syndrome and in 8 (26,7%) patients with bronchial asthma with eosinophilia ($p<0,05$) and in patients with systemic vasculitis with eosinophilia ($p<0,05$). Erythematous rash noted in 7 (23,3%) patients with Churg-Strauss syndrome, in 4 (21%) patients with systemic vasculitis with eosinophilia ($p<0,05$); multiform erythema - in 6 (20%) patients with Churg-Strauss syndrome and in 5 (26,3%) patients with systemic vasculitis with eosinophilia ($p<0,05$). These skin manifestations was not typical for patients with bronchial asthma.

Sign	**Patients with BA and eosinophilia (n = 30)**		**Patients with SV and eosinophilia (n = 19)**		**Patients with CSS (n = 30)**		**P 1-2**	**P 1-3**	**P 2-3**
	1		2		3				
	Abs.	%	Abs.	%	Abs.	%			
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Complaints and clinical signs									
Underproductive cough	16	53,3	-	-	17	56,7	-	NS	-
Complicated nasal breathing	19	63,3	-	_	21	70	-	NS	-
Night attack of coughing	5	16,7	-	-	14	46,7	-	NS	-
Skin itching	8	26,6	11	31,6	17	56,7	NS	0,05	0,05
Erythematous rash	-	-	4	21,1	7	23,3	-	-	NS
Erythema multiforme	-	-	5	26,2	6	20	NS	NS	0,001
Non-palpable spot haemorrhagic rush		-	-	-	6	20,0	-	-	-
Palpable spot haemorrhagic rush	-	-	2	10,5	14	46,7	-	-	0,01
Haemorrhagic rash with confluence ability	-	-	1	5,3	18	60,0	-	-	0,001
Papular rash	3	10,0	4	21,1	14	46,7	NS	0,01	NS
Vesicular rash	-	-	6	31,6	19	63,3	NS	NS	0,01
Hyperpyrexia	-	-	8	42,1	17	56,7	-	-	0,05
Arthralgia	-	-	11	57,9	20	66,7	-	-	0,05
Arthritis	-	-	4	21,1	17	56,7	-	-	0,01
Myalgia	22	73,3	18	94,7	23	76,7	NS	NS	NS
Lymphadenopathy		-	-	-	8	26,7	-	-	-
Diarrhea	-	-	-	-	4	13,3	-	-	-
Polyneuropathy	-	-	-	-	14	46,7	-	-	-
Weakness	16	53,3	17	89,5	21	70,0	NS	NS	NS

Table 2. Main anamnesis features in patients with bronchial asthma with eosinophilia, systemic vasculitis witheosinophilia and with Churg-Strauss syndrome (M±m)

Sign		Patients with BA and eosinophilia (n = 30)		Patients with SV and eosinophilia (n = 19)		Patients with CSS (n = 30)		P 1-2	P 1-3	P 2-3
		1		2		3				
		Abs.	%	Abs.	%	Abs.	%			
1		2	3	4	5	6	7	1	2	3
Course character	exacerbation	-	-	5	26,3	10	33,3	-	-	0,05
	subacute	-	-	3	15,8	8	26,7	-	-	NS
	chronical	22	73,4	11	57,9	12	40	0,05	0,01	0,05
Disease activity	I degree	-	-	4	21,1	9	30	-	-	NS
	II degree	-	-	13	68,4	14	46,7	-	-	NS
	III degree	-	-	2	10,5	7	23,3	-	-	0,05
Severity stage	mild	8	26,7	4	21,1	3	10	0,05	0,05	NS
	intermittent / moderate	14	46,7	11	57,9	21	70	NS	0,05	0,05
	severe	8	26,7	4	21,1	6	20	0,05	NS	NS

Table 3. Trends of course, activity and severity of disease in patients with bronchial asthma with eosinophilia,, systemic vasculitis with eosinophilia and with Churg-Strauss syndrome (M±m)

In the same time, not-palpable hemorrhagic rash, was detected only in 6 (20%) patients with Churg-Strauss syndrome ($p<0,001$); palpating hemorrhagic spot rash - in 14 (46,7%) patients with Churg-Strauss syndrome, in 2 (10,5%) patients with systemic vasculitis with eosinophilia ($p<0,01$); hemorrhagic rash with a penchant of mergers - in 18 (60%) patients with Churg-Strauss syndrome, and only in one (5.3%) patient with systemic vasculitis with eosinophilia ($p<0,001$). Hemorrhagic eruption of different nature in patients with bronchial asthma and eosinophilia were not detected. Papular and vesicular rash were typical for patients with Churg-Strauss syndrome too. The common symptoms in examinated patients were distributed as follows: hyperthermia was found in 17 (56,7%) patients with Churg-Strauss syndrome and in 8 (42,1%) patients with systemic vasculitis and eosinophilia ($p<0,05$), arthralgic syndrome - in 20 (66,7%) patients with Churg-Strauss syndrome and in 11 (57,9%) patients with systemic vasculitis and eosinophoilia ($p<0,05$), arthritic syndrome - in 17 (56,7%) patients with Churg-Strauss syndrome and in four (21,1%) patients with systemic vasculitis and eosnophilia ($p<0,01$), mialgia - in 23 (76.7%) patients with Churg-Strauss syndrome, in 18 (94,7%) patients with systemic vasculitis ($p<0,05$) and in 22 (73,3%) patients with bronchial asthma and eosinophilia ($p<0,05$). Importantly, the lymphadenopathy was referred only in 8 (26,7%) patients with Churg-Strauss syndrome ($p<0,001$), diarrhea - in four (13.3%) patients with Churg-Strauss syndrome ($p<0,001$), polyneuropathy - in 14 (46 7%) patients with Churg-Strauss syndrome ($p<0,001$). These clinical signs were not identified in other groups of examined patients.

Weakness was recorded in 21 (70%) patients with Churg-Strauss syndrome and in 17 (89,7%) patients with systemic vasculitis with easinophilia ($p<0,05$) and in 16 (53,3%) patients with bronchial asthma and eosinophilia ($p<0,05$).

The most severe and active course of disease is more typical for patients with Churg-Strauss syndrome ($p<0,05$), that is presented in the Table 3.

Sign	Patients with CSS and mild eosinophilia (AEC 600-1500 cells/μL) (n=12)		Patients with CSS and moderate eosinophilia (AEC 1500-5000 cells/μL) (n = 13)		Patients with CSS and severe eosinophilia (AEC >5000 cells/μL) (n = 5)	
	1		2		3	
	Abs.	%	Abs.	%	Abs.	%
1	2	3	4	5	6	7
Polinosis	4	33,3	7	53,8	3	60,0
Allergic rhinitis	5	41,7	12	92,3	4	80,0
Allergic rhinitis and nasal poliposis	2	16,7	6	46,2	3	60,0
Bronchial asthma	9	75,0	12	92,3	5	100
Nasal poliposis						
Bronchial asthma and nasal poliposis	2	16,7	3	23,1	2	40,0
Underproductive cough	2	16,7	10	76,9	5	100
Complicated nasal breathing	4	33,3	12	92,3	5	100
Bronchial hyperreactivity	3	25,0	11	84,6	3	60,0
Skin itching	3	25	12	92,3	4	80,0
Erythematous rash	-	-	4	30,8	3	60,0
Erythema multiforme	-	-	3	23,1	3	60,0
Non-palpable spot haemorrhagic rush	4	33,3	2	15,4	-	-
Palpable spot haemorrhagic rush	6	50,0	4	30,8	4	80,0
haemorrhagic rash with confluence ability	2	16,7	11	84,6	5	100,0
Papular rash	8	66,7	5	38,5	1	20,0
Vesicular rash	3	25	12	92,3	4	80,0
Hyperpyrexia	6	50,0	7	53,8	4	80,0
Arthralgia	6	50,0	11	84,6	3	60,0
Arthritis	4	33,3	8	61,5	5	100,0
Myalgia	6	50,0	12	92,3	5	100,0
Lymphadenopathy	1	8,3	4	30,8	3	60,0
Diarrhea	1	8,3	1	8,3	2	40,0
Polyneuropathy	5	41,7	5	38,5	4	80,0
Weakness	4	33,3	13	92,3	4	80,0

Table 4. Main clinical signs in patients with Churg-Strauss syndrome depending of eosinophilia severity (M±m)

NS- not significant

There were found some clinical features, which were more typical for patients with Churg-Strauss syndrome and were more expressed in patients with Churg-Strauss syndrome: chronical disease course, III activity degree and moderate stage of severity are more typical for patients with Churg-Strauss syndrome compared with patients with bronchial asthma and systemic vasculitis with eosinophilia.

There were found some clinical signs in patients with Churg-Strausss syndrome depending of eosinophilia severity too, that is presented in the Table 4.

NS- not significant

For patients with Churg-Strauss syndrome and severe eosinophilia are more typical in anamnesis such signs as polinosis, allergic rhinitis, allergic rhinitis with nasal poliposis, bronchial asthma with nasal poliposis. Between clinical signs more typical for patients with severe eosinophilia are underproductive, complicated nasal breathing cough, erythematous rash, erythema multiforme, palpable spot haemorrhagic rush and haemorrhagic rash with confluence ability, hyperpyrexia, arthritis, lymphadenopathy, diarrhea and polyneuropathy.

There are many immunological peculiarities that play very important role in the opportunity of examined diseases development, activity, severity and complication. Some of such immunological peculiarities are presented in the Table 5.

Indexes		Patients with BA and eosinophilia (n = 30)	Patients with SV and eosinophilia (n = 19)	Patients with CSS (n = 30)	P_{1-2}	P_{1-3}	P_{2-3}
		1	2	3			
Lymphocytes	cells/μL)	1,70±0,23	1,86±0,19	1,89±0,12	NS	NS	NS
$CD3^+$	%	63,7±3,18	50,8±2,55	50,8±2,89	0,05	0,05	NS
	cells/μL)	1,08±0,12	1,11±0,27	0,96±0,13	NS	NS	NS
$CD4^+$	%	40,9±1,60	29,8±1,75	42,6±2,60	0,05	NS	0,05
	cells/μL)	0,43±0,04	0,31±0,03	0,41±0,10	0,05	NS	0,05
$CD8^+$	%	23,3±1,72	21,0±1,67	18,3±1,49	NS	NS	NS
	cells/μL)	0,24±0,03	0,24±0,09	0,18±0,04	NS	NS	NS
$CD16^+/56^+$	%	14,1±1,26	16,00±2,59	16,01±1,30	NS	NS	NS
	cells/μL)	0,25±0,05	0,30±0,07	0,30±0,05	NS	NS	NS
$CD19^+$	%	16,9±1,94	20,8±3,60	22,40±2,24	NS	0,05	NS
	cells/μL)	0,31±0,03	0,38±0,05	0,44±0,07	NS	0,05	NS
$CD25^+$	%	17,9±1,12	21,3±1,62	29,4±1,19	NS	0,01	0,05
	cells/μL)	0,34±0,02	0,40±0,05	0,56±0,05	NS	0,001	0,01
HLA DR^+	%	27,3±1,22	30,0±1,48	26,30±1,83	NS	NS	NS
	cells/μL)	0,48±0,02	0,53±0,02	0,50±0,07	NS	NS	NS
$CD95^+$	%	17,3±0,88	18,6±2,66	24,7±1,37	NS	0,05	0,05
	cells/μL)	0,29±0,05	0,35±0,03	0,47±0,05	NS	0,01	0,05

Table 5. Trends of lymphograme indexes and lymphocytes activity markers in patients with bronchial asthma, systemic vasculitis with eosinophilia and with Churg-Strauss syndrome (M±m)

NS- not significant

There were found some peculiarities of immunological parameters in patients with Churg-Strauss syndrome, such as significantly lower proportional level of CD3 +lymphocytes ($p<0,05$), higher proportional and absolute level of CD19 +-lymphocytes ($p<0,05$), intensively expressed proportional ($p<0,01$) and absolute ($p<0,001$) early count of lymphocyte activation marker (CD25 +) and significantly intensively proportional ($p<0,05$) and absolute ($p<0,01$) expression of CD95+ in patients with Churg-Struss syndrome compared with patients with bronchial asthma and eosinophilia. Compared with patients with systemic vasculitis with eosinophilia, patients with Churg-Strauss syndrome had a significantly higher proportional ($p<0,05$) and absolute ($p<0,05$) mean of CD4 +lymphocytes, intensively expressed proportional ($p<0,05$) and absolute ($p<0,01$) count of early lymphocyte activation marker (CD25 +) and significantly intensively proportional and absolute expression of CD95+ ($p<0,05$).

There were found some immunological signs in patients with Churg-Strausss syndrome depending of eosinophilia severity too, that is presented in the Table 6.

Indexes		**Patients with CSS and mild eosinophilia (AEC 600-1500 cells/μL) (n=12)**	**Patients with CSS and moderate eosinophilia (AEC 1500-5000 cells/μL) (n = 13)**	**Patients with CSS and severe eosinophilia (AEC >5000 cells/μL) (n = 5)**	**P_{1-2}**	**P_{1-3}**	**P_{2-3}**
		1	**2**	**3**			
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Eosinophils	**cells/μL)**	0,59±0,05	3,58±0,82	5,81±0,92	0,001	0,001	0,05
Lymphocytes	**cells/μL)**	1,61±0,15	2,24±0,47	3,01±0,15	NS	0,05	NS
$CD3^+$	%	56,7±1,66	48,53±2,26	46,50±1,18	0,05	0,05	NS
	cells/μL)	0,91±0,09	1,08±0,05	1,39±0,06	NS	0,05	NS
$CD4^+$	%	36,5±2,16	41,20±3,97	50,30±4,21	NS	0,05	0,05
	cells/μL)	0,33±0,06	0,44±0,08	0,70±0,09	NS	0,01	0,01
$CD8^+$	%	19,65±1,72	18,50±2,68	16,67±2,33	NS	NS	NS
	cells/μL)	0,18±0,03	0,20±0,07	0,23±0,07	NS	NS	NS
$CD16^+/56^+$	%	14,91±2,07	14,80±1,52	18,3±1,76	NS	NS	NS
	cells/μL)	0,24±0,03	0,33±0,05	0,55±0,08	NS	NS	NS
$CD19^+$	%	20,05±1,86	22,03±2,61	25,0±2,12	NS	0,05	NS
	cells/μL)	0,32±0,05	0,49±0,03	0,75±0,09	NS	0,05	0,001
$CD25^+$	%	28,33±2,73	29,82±1,89	30,4±1,58	NS	NS	NS
	cells/μL)	0,46±0,07	0,66±0,09	0,92±0,12	NS	0,01	0,05
HLA DR^+	%	20,05±1,68	26,50±1,46	31,9±2,48	NS	0,05	NS
	cells/μL)	0,32±0,05	0,59±0,06	0,96±0,11	NS	0,001	0,05
$CD95^+$	%	20,73±1,27	23,50±2,67	29,9±7,06	NS	NS	NS
	cells/μL)	0,33±0,03	0,52±0,05	0,89±0,1	NS	0,001	0,05

Table 6. Trends of lymphograme indexes and lymphocytes activity markers in patients with Churg-Strauss syndrome depending of eosinophilia severity (M±m).

NS- not significant

There were found some peculiarities of immunological markers in patients with Churg-Strauss syndrome and different eosinophilia severity, such as the highest eosinophils level in patients with Churg-Strauss syndrome and severe eosinophilia in comparison to the patients with mild eosinophilia ($p<0,001$) and moderate eosinophila ($p<0,05$), significantly lower absolute level of lymphocytes in patients with Churg-Strauss and severe eosinophilia $p<0,05$) in comparison to patients with mild eosinophilia; significantly lower proportional and absolute level of CD3 +lymphocytes ($p<0,05$), CD4 +lymphocytes ($p<0,05$), CD19 +lymphocytes ($p<0,05$), significantly intensively expressed early lymphocyte activation markers such as (CD25 +) ($p<0,01$), late lymphocyte activation markers such as (HLA DR +) ($p<0,001$) and significantly intensively expression of CD95+ ($p<0,001$) in patients with Churg-Struss syndrome and severe eosinophilia compared with patients with Churg-Strauss syndrome and mild eosinophilia. There were found some significantly lower proportional and absolute level of CD4 +lymphocytes ($p<0,05$), absolute level of CD19 +lymphocytes ($p<0,001$), significantly intensively expressed early lymphocyte activation markers such as (CD25 +) ($p<0,05$), late lymphocyte activation markers such as (HLA DR +) ($p<0,05$) and significantly intensively expression of CD95+ ($p<0,05$) in patients with Churg-Struss syndrome and severe eosinophilia compared with patients with Churg-Strauss syndrome and moderate eosinophilia.

No significant peculiarities were found in patients with Churg-Strauss syndrome and mild or moderate eosinophilia.

We have also analyzed the features of serum interleukins (IL-2, IL-4, IL-5, IL-10) in patients with Churg-Strauss syndrome and other examined groups, that is showed in the Table 7.

Interleukins		Patients with BA and eosinophilia (n = 30)	Patients with SV and eosinophilia (n = 19)	Patients with CSS (n = 30)	P_{1-2}	P_{1-3}	P_{2-3}
		1	2	3			
IL-2	pg/ml	3,79±0,98	6,31±0,75	8,78±0,26	0,05	0,05	0,01
IL-4	pg/ml	8,17±0,17	5,38±0,55	6,64±0,16	0,01	0,05	NS
IL-5	pg/ml	6,60±1,26	12,4±2,28	97,9±17,5	0,001	0,001	0,001
IL-10	pg/ml	2,88±0,19	3,27±0,29	2,12±0,14	NS	0,05	0,05

Table 7. Trends of pro-inflammatory (IL-2) and anti-inflammatory (IL-4, IL-5, IL-10) cytokines in patients with bronchial asthma, systemic vasculitis with eosinophilia and with Churg-Strauss syndrome (M±m)

NS- not significant

Comparing realizing possibility of pro- and anti-inflammatory mechanisms of cytokines such as IL-2, IL-4, IL-5 and IL-10 in patients with bronchial asthma with eosinophilia, systemic vasculitis with eosinophilia and Churg-Strauss syndrome it was found significant increase of IL-4 ($p<0,01$) and IL-5 ($p<0,001$) level in patients with bronchial asthma and eosinophilia, increase of IL-2 ($p<0,05$), IL-4 ($p<0,05$) and IL-5 ($p<0,05$) in patients with systemic vasculitis with eosinophilia, increase of IL-2 ($p<0,05$) and IL-5 ($p<0,001$) level and decrease of IL-10 ($p<0,05$) level in patients with Churg-Strauss syndrome.

There were found some cytokines production peculiarities in patients with Churg-Strausss syndrome depending of eosinophilia severity, that is presented in the Table 8.

Interleukins		Patients with CSS and mild eosinophilia (AEC 600-1500 cells/μL) (n=12)	Patients with CSS and moderate eosinophilia (AEC 1500-5000 cells/μL) (n = 13)	Patients with CSS and severe eosinophilia (AEC >5000 cells/μL) (n = 5)	P_{1-2}	P_{1-3}	P_{2-3}
		1	2	3			
IL-2	pg/ml	8,44±0,11	8,74±0,16	9,18±0,08	NS	0,05	NS
IL-4	pg/ml	5,7±0,13	6,8±0,11	7,42±0,09	NS	0,05	NS
IL-5	pg/ml	32,7±7,5	49,4±9,6	211,6±29,5	NS	0,001	0,001
IL-10	pg/ml	2,34±0,08	2,04±0,09	1,98±0,05	NS	0,05	NS

Table 8. Trends of pro-inflammatory (IL-2) and anti-inflammatory (IL-4, IL-5, IL-10) cytokines in patients with Churg-Strauss syndrome depending of eosinophilia severity (M±m)

NS- not significant

Analizing realizing possibility of pro- and anti-inflammatory cytokines such as IL-2, IL-4, IL-5 and IL-10 in patients with Churg-Strauss syndrome and different eosinophilia severity, it was fixed significant increase of IL-2 (9,18±0,08 pg/ml, $p<0,05$), IL-4 (7,42±0,09 pg/ml, $p<0,05$), and IL-5 (211,6±29,5 pg/ml, $p<0,001$) and decrease of IL-10 (1,98±0,05 pg/ml, $p<0,05$) level in patients with Churg-Strauss syndrome with severe eosinopilia compared with patients with Churg-Strauss syndrome and mild eosinophilia. Also, it was fixed significant higher IL-5 level in patients with Churg-Strauss syndrome and severe eosinophilia compared with patients with moderate eosnophilia ($p<0,001$) too.

The patients with systemic vasculitis and eosinophilia and with Churg-Strauss syndrome were divided in some subgroups depended on ANCA –presence.

In our series of patients, we found that ANCA positivity was correlated with renal involvement, especially with the histologic picture of necrotizing crescentic glomerulonephritis, and, to a lesser extent, with constitutional symptoms. Moreover, ANCA-positive patients had a significantly higher frequency of certain organ system clinical manifestations, such as pulmonary hemorrhage, purpura, and mononeuritis multiplex. In contrast, ANCA-negative patients had a higher frequency of heart and (less severe) lung disease.

Limited data have been reported on the correlation between ANCA positivity and the clinical features in CSS, even though it should be noted that most (if not all) reported cases of necrotizing crescentic glomerulonephritis in CSS involved ANCA-positive (usually MPO pANCA) patients, as in our cohort. Moreover, the results of studies of small series of patients have suggested that MPO ANCAs may be associated with the onset of glomerular disorder in CSS.

There were fixed some morphological peculiarities in patients with Churg-Strausss syndrome depending of eosinophilia severity, that is presented in pictures 1,2 and 3.

We have selected the three most informative results of skin-muscular samples biopsies patients with Churg-Strauss syndrome with different eosinophilia severity, that reflected in three figures.

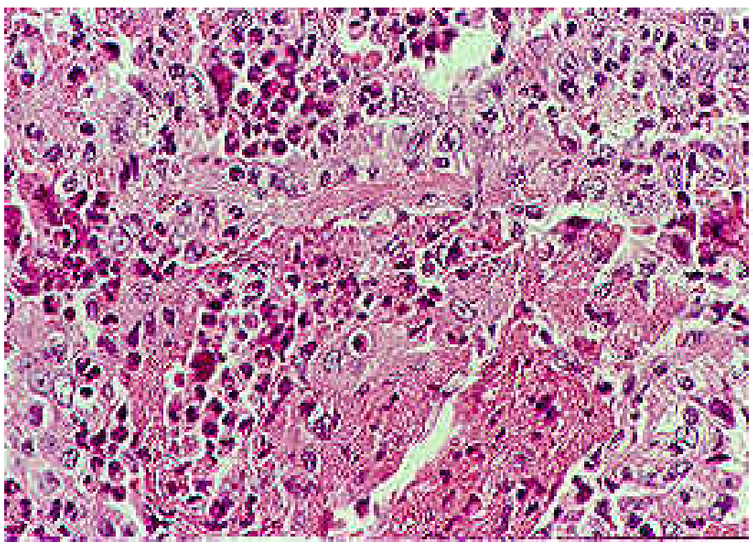

Fig. 1. Churg-Strauss syndrome: Tissue eosinophilia is a frequent finding in cutaneous lesions of Churg–Strauss syndrome. Hematoxylin, eosin × 300; clinical: light/mild eosinophilia

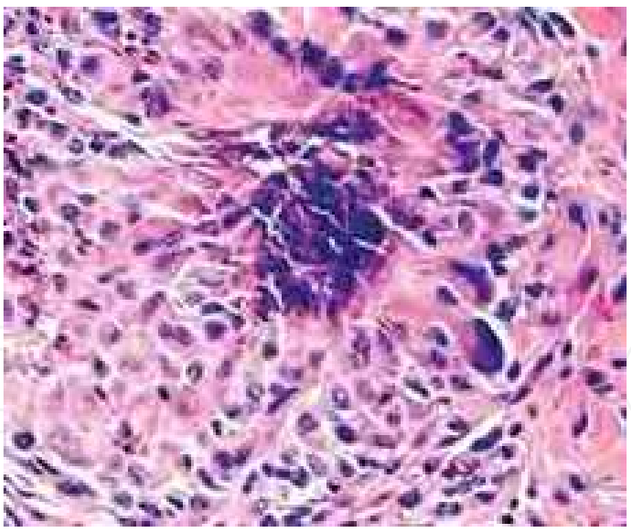

Fig. 2. Churg-Strauss syndrome: Skin biopsy which was indicative of small vessel vasculitis, showing the presence of an inflammatory infiltrate predominantly constituted by eosinophils and plasmocytes around blood vessels. Hematoxylin, eosin × 400; clinical: medium eosinophilia

The analysis of the founded morphological features, that were identified in patients with Churg-Strauss syndrome with different eosinophilia severity, shoved eosinophilc infiltration of the dermis in patients with Churg-Strauss syndrome and mild eosinophilia

(Fig.1); necrotizing changes in the center of granulomas, extensive infiltration of neutrophils, eosinophils of vessel wall until the formation of circular eosinophil infiltrates in the vessels of patients with Churg-Strauss syndrome and severe eosinophilia (Fig.3)

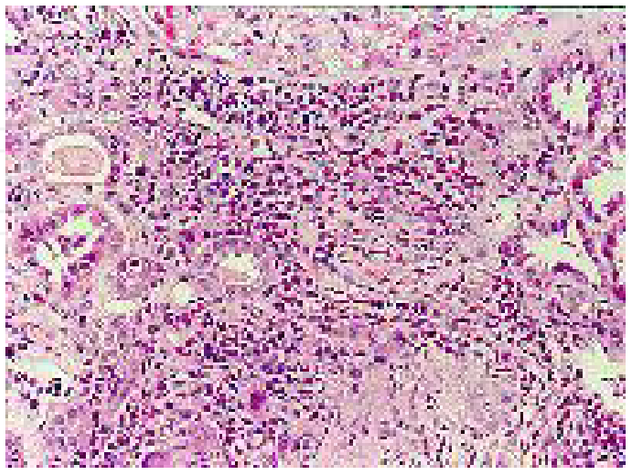

Fig. 3. Churg-Strauss syndrome: Skin-muscular biopsy which showing eosinophilic circular infiltration of the intermuscular arteriole. Hematoxylin, eosin × 400; clinical: severe eosinophilia

4. Conclusion

Substantial advances have been made in the understanding of immune mechanisms (especially eosinophils, circulating immune complexes, total IgE, antineutrophicytoplasmic antibodies, cytokines) implicated in Churg-Strauss syndrome and its management. While it definitively remains a systemic necrotizing small-sized vessel vasculitis, its membership in the ANCA-associated vasculitis group has become more controversial. More complex and numerous mechanisms are involved in Churg-Strauss syndrome (Hoffman and Langford, 2005; Pagnoux and Guillevin, 2010). Similarly, one of its earlier denominations, allergic granulomatous angiitis (Churg and Strauss, 1951), has become dated because not all patients have (eosinophilic) granulomas. Moreover, several disease subgroups have been identified, essentially based on clinical or biological findings (Walsh &August, 2010). There are a large number of works devoted to studying of the problem of rare disease – Churg-Strauss syndrome – especially its clinical and laboratory features, but it was firstly by us described clinical, immunological and morphological features of Churg-Strauss syndrome with different severity of eosinophilia in these patients.

It was fixed special clinical signs in patients with Churg-Strauss syndrome and severe eosinophilia such as: underproductive, complicated nasal breathing cough, erythematous rash, erythema multiforme, palpable spot haemorrhagic rush and haemorrhagic rash with confluence ability, hyperpyrexia, arthritis, lymphadenopathy, diarrhea and polyneuropathy. There were found some peculiarities of immunological markers in patients with Churg-Strauss syndrome and different eosinophilia severity, such as the highest eosinophils level in patients with Churg-Strauss syndrome and severe eosinophilia in comparison to the patients with mild eosinophilia ($p<0,001$) and moderate eosinophila ($p<0,05$), significantly lower absolute lymphocytes level in patients with Churg-Strauss and severe eosinophilia

(p<0,05) in comparison to patients with mild eosinophilia; significantly lower proportional and absolute level of CD3 +lymphocytes (p<0,05), CD4 +lymphocytes (p<0,05), CD19 +lymphocytes (p<0,05), significantly intensively expressed early lymphocyte activation markers such as (CD25 +) (p<0,01), late lymphocyte activation markers such as (HLA DR +) (p<0,001) and significantly intensively expression of CD95+ (p<0,001) in patients with Churg-Struss syndrome and severe eosinophilia compared with patients with Churg-Strauss syndrome and mild eosinophilia. Other subgroups may be brought forth in the future, relying on more subtle molecular and genetic characteristics (IL-4, IL-5, IL-5RA gene polymorphism).

Therapeutic strategies also require further improvement. Treatment should be adapted as closely as possible to each patient's characteristics. New treatments (monoclonal antibodies) are needed to lower the rate of frequent, low-dose but long-term, corticosteroid-dependence that represents a major issue and the lingering disappointment in current therapeutic strategies for Churg-Strauss syndrome.

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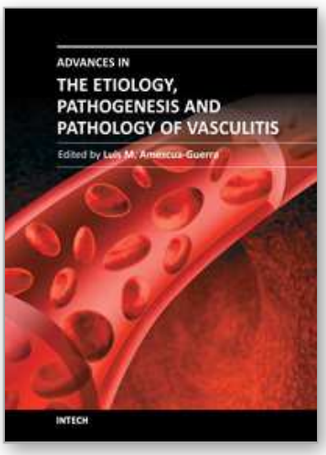

Advances in the Etiology, Pathogenesis and Pathology of Vasculitis

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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to devote their work to this book by keeping both the text and the accompanying figures and tables lucid and memorable. Here, you will find an amalgam between evidence-based medicine to one based on eminence, through an exciting combination of original contributions, structured reviews, overviews, state-of the-art articles, and even the proposal of novel pathogenetic models of disease. The book contains contributions on the etiology and pathology of vasculitis, the potential role of endothelial cells and cytokines in vascular damage and repair as well as summaries of the latest information on several primary and secondary vasculitis syndromes. It also covers selected topics such as organ-specific vasculitic involvement and quality of life issues in vasculitis. The editor and each of the authors invite you to share this journey through one of the most exciting fields of the medicine, the world of Vasculitis.

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