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Microscopic Polyangiitis is a "Masquerade Ball" in Modern Realities: A Literature Review

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Review Article

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Abstract

Microscopic polyangiitis (MPA) is an important new medical problem, as it shows increasing incidence and prevalence in the population, especially after the outbreak of coronavirus disease 2019 (COVID-19). MPA is a multisystemic destructive disease with a wide spectrum of heterogeneous clinical manifestations depending on the affected organs. The polymorphism of nonspecific clinical signs and the variability of the clinical picture, which differs from patient to patient, can cause a diagnostic delay and establish the correct diagnosis only in the late stages of the disease. That is why many patients consult and receive treatment from different doctors before verifying the diagnosis.

In the review article, an analysis of literary sources was made, which highlighted classic renal and/or pulmonary symptoms, skin, gastrointestinal, neurological and cardiovascular manifestations of MPA. It is important to note that the clinical manifestations of MPA can be very different from the usual recognized patterns and manifest as unusual manifestations of the disease with a hidden or atypical course, and therefore received the figurative name "the Great Masquerades". So MPA can often hide under the "mask" of other diseases, including COVID-19 itself, which significantly complicates its early diagnosis and treatment. That is why doctors should be better informed about the different variants of the clinical course of MPA and approaches to diagnosis, which will help eliminate delays in diagnosis. After all, the rapid diagnosis of MPA is important for the initiation of adequate immunosuppressive therapy, which can both save lives, preserve organs from damage, and improve the quality of life.

Keywords: ANCA-Associated Vasculitis; Microscopic Polyangiitis; Clinical Picture; Clinical Masks; COVID-19; New Coronavirus Infection SARS-Cov-2

Abbreviations: MPA: Microscopic Polyangiitis; ANCA: Antibody Associated Vasculitis; MPO: Myeloperoxidase; RF: Renal Failure; CHCC: Chapel Hill International Consensus Conference; PRES Posterior Reversible Encephalopathy Syndrome.

Introduction

Microscopic polyangiitis (MPA) is an important new public health concern as it shows increasing incidence and prevalence in the population, especially after the outbreak of coronavirus disease 2019 (COVID-19). MPA is a multiorgan destructive disease with multiple and variable clinical manifestations depending on the affected organs, which significantly complicates its diagnosis. Early diagnosis of MPA during the COVID-19 pandemic remains as challenging as it was before it, because these two multisystem diseases share common anatomic areas of involvement and pathogenetic mechanisms of development, as well as clinical manifestations that are causally related. Moreover, MPA is

a chameleon disease that can hide under the mask of other diseases, including COVID-19 itself, and cause a delay in diagnosis and adequate treatment, thereby worsening the consequences for the patient and the kidneys. That is why, in today's conditions, there is a demand for increasing the awareness and knowledge of practicing doctors about this problem.

MPA is an aggressive autoimmune necrotizing small-vessel vasculitis that belongs to a group of rare systemic diseases called antineutrophil cytoplasmic antibody-associated vasculitis (ANCA). (ANCA)-Associated Vasculitis (AAVs) has been officially defined as "a group of pauci-immune small-vessel vasculitides closely related to ANCA and specific for myeloperoxidase (MPO) or proteinase 3 (PR3), with inflammation and necrosis of the small vessel walls as the main manifestations." Among individuals with AAVs, more than 75% report renal involvement [1].

ANCA vasculitis has high morbidity and mortality [2] and is one of the most difficult types of vasculitis to treat. AAVs are a class of autoimmune diseases that can cause renal failure (RF) through infiltration of mononuclear cells and destruction of small and medium-sized blood vessels [3,4]. Renal involvement is usually characterized by mild immune-mediated necrotizing and crescentic glomerulonephritis with very rapid decline in renal function (rapidly progressive glomerulonephritis) [5] and is the most important predictor of mortality [6,7]. It is diagnosed in about 70% of patients with GPA and in almost 100% of patients with MPA [5,7-10]. If necrotizing and crescentic glomerulonephritis is not treated, it has an unfavorable course, which leads to the final stage of RF after a few weeks or months [5,11]. Patient survival and the risk of terminal RF are closely related to kidney function [11]. Therefore, early recognition and appropriate treatment of AAVs are mandatory for prevention or slowering the progression of RF to its end-stage [3].

It is generally accepted that the main clinical and pathological variants of AAVs are MPA, granulomatosis with polyangiitis (GPA, in the past - Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, in the past - Charg-Strauss syndrome) and single-organ AAV (for example, renal-limited AAV) [12,13]. This classification of vasculitis, which stratifies them according to the size of the vessel and the causes of their development, was first formulated in 2012 in the updated nomenclature of systemic vasculitis at the Chapel Hill International Consensus Conference (CHCC) [12,13].

It should be noted that the MPA was officially recognized at the first International Chapell Hill Consensus Conferencein 1994 which introduced the term MPA [14]. In the CHCC 2012 revised nomenclature of systemic vasculitis [12]. MPA is defined as necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Inflammation that is not centered on vessels, including granulomatous inflammation, is absent [12].

It is believed that the absence of granulomatous inflammation of the upper respiratory tract and the presence of pulmonary capillaritis distinguish MPA from GPA. In addition, MPA is associated with the presence of circulating ANCA, but a certain number of patients (10%) are ANCA-negative [6,8], which creates a diagnostic problem and a potential delay in adequate treatment, as well as worsens the outcome for such patients and their kidneys [9]. According to the data of various authors Geetha, et al. [6,8], the test for ANCA in MPA is positive in 84-90% of cases. Among these, perinuclear ANCA (p-ANCA) associated with myeloperoxidase (MPO-ANCA) are present in 58-60% of cases, while cytoplasmic ANCA (c-ANCA), which are associated with proteinase-3 ANCA (PR3-ANCA), present in 26-30% of cases. Taken together, there is compelling evidence that MPO-ANCA is directly associated with MPA pathogenesis [8].

Atypical ANCAs that are not directed against PR3 or MPO can be found in a number of non-vascular conditions (inflammatory bowel diseases, autoimmune diseases, and malignancies). PR3-ANCA or MPO-ANCA can also be detected in chronic infections (endocarditis, tuberculosis, HIV infection, hepatitis C, and bartonellosis). The presence of both anti-MPO and anti-PR3 antibodies in one patient is a very rare phenomenon and indicates drug-induced vasculitis [6].

Although ANCA-associated vasculitis is a rare autoimmune disease, the incidence and prevalence of AAVs in general and MPA in particular have increased over the past 20-30 years [2,6,8,9,15-18]. According to the 2020 Aladdin J Mohammad Epidemiology Update [19] for MPA, the mean pooled incidence rate per million was 5.04 in the 1990s, rising to 9.2 in the 2000s and continuing to rise. Moreover, these indicators vary greatly from one country to another. In particular, MPA is more common towards the equator, for example in Southern Europe, China and Japan [6,20,21] while GPA is more common in Northern Europe and Australia [9]. In general, the incidence of MPA is higher in southern than northern part of Europe. For example, if the incidence of MPA in Norway is 2.7 per million, in Germany - 2.6, and in Britain - 5.8, then in Spain it increases to 11.6 per million [8,19,21,22]. According to some medical sources [22], the incidence of MPA is estimated from 2.7 to 24 cases per 1 million.

The geographic distribution of AAV subtypes is partially explained by ambient UV radiation levels and latitude, but also implies genetic background heterogeneity [9,23]. Onset of AAV is often at age 65, and patients with renal involvement are on average 10 years older than those without [24]. Although AAV shows a slight overall male predominance, renal involvement is more often present in females, which may be explained by the female predominance of MPO-AAV and its higher incidence in glomerulonephritis [16]. PR3-AAV, on the other hand, is associated with male gender, younger age, and higher glomerular filtration rate [23]. However, male patients with MPO-AAV had a higher age of onset, shorter disease duration, and worse overall renal and patient survival outcomes compared with female patients [25].

Possible explanations for the increase in the incidence and prevalence of MPA may be the aging of the population [16], the true increase in incidence, the evolution of classification and definition criteria [9,16,19,20,26], the availability and wider use for diagnosis of primary immunological tests for PR3-ANCA and MPO-ANCA [16,26,27], without the categorical need for additional indirect immunofluorescence (IIF) [27], as well as increasing the awareness of physicians through their training [16,19,20,26]. The increase in the number of patients with MPA in recent years is confirmed by our own clinical experience both in the pre-war period [28] and during the COVID-19 pandemic [26].

In addition, a significant increase in the incidence of MPA has been observed since the outbreak of COVID-19. Despite the fact that COVID-19 has lost the status of a pandemic, the dangerous virus continues to negatively affect the lives and health of people around the world. According to real clinical practice, if before the COVID-19 pandemic in the regional center of nephrology and dialysis of the Communal Institution «Poltava Regional Clinical Hospital» isolated cases of the disease were detected per year [28], then only during 2022 8 new clinical cases of MPA among patients who suffered from COVID-19 were verified [26]. All patients were hospitalized at the regional center with the aim of finding out the cause and treating their azotemia against the background of various and heterogeneous clinical manifestations, often with multiple organ lesions [26,28]. It is important to note that elevated serum creatinine is associated with reduced survival in patients with MPA [6,29]. Therefore, the issue of early diagnosis and adequate treatment of MPA becomes urgent, which can slow down the progression of the disease and prevent organ damage in multisystem pathology.

It is appropriate to mention that in 2017 there was a paradigm shift in the diagnosis of ANCA. It is well known that ANCA are important laboratory markers used for the diagnosis of well-defined types of small vessel vasculitis, including GPA and MPA [30,31].

Previously, the standard method for ANCA detection was indirect immunofluorescence (IIF) as a screening test for ANCA, followed by an antigen-specific test for proteinase 3 (PR3) or myeloperoxidase (MPO) [32].

According to the revised 2017 international consensus guidelines [32], ANCA testing in small vessel vasculitis can be performed using PR3- and MPO-ANCA immunoassays without IIF [26,28,32,33]. Therefore, currently available tests for PR3-ANCA and MPO-ANCA are highly sensitive and specific for the diagnosis of MPA and GPA [30,31].

The coronavirus disease 2019 (COVID-19), which was caused by the SARS-CoV-2 coronavirus infection, has become a global problem since its outbreak in December 2019 and has fundamentally changed the world in which we live. Moreover, COVID-19 has significant implications for global public health. Since SARS-CoV-2 infection can break immune tolerance and cause autoimmune reactions, it can also cause the development of an autoimmune process [34].

In December 2021, the results of a systematic review of new systemic and rheumatic autoimmune diseases in patients with COVID-19 were published [35]. The authors found that the main registered diseases were vasculitis and arthritis [35]. In addition, the study of Mendes JL, et al. [36], who believe that the SARS-CoV-2 virus is associated with the development of rheumatic diseases, especially vasculitis of small vessels and arthritis, attracts attention. Usually, their onset occurs a few days or weeks after antigenic infection and in patients with a mild form of COVID-19 [36].

A large international study published by Liu Y, et al. [34] also highlights the existing relationship between COVID-19 and autoimmune diseases and the similarity of the immune response in both disease states. Similar to systemic autoimmune diseases, COVID-19 can be present with heterogeneous and systemic clinical manifestations. Both COVID-19 and autoimmune diseases manifest with many clinical symptoms affecting various organs and systems, such as blood, respiratory, cardiovascular, digestive, nervous, kidney, skin, pancreas, etc. Organ damage is caused by an uncontrolled immune response characterized by excessive production of cytokines and excessive activation of immune cells, as well as impaired immune tolerance, which leads to the production of autoantibodies. SARS-CoV-2 infection can cause cross-reactivity through molecular mimicry, leading to autoimmunity in patients with COVID-19 [34]. This study demonstrated by Liu Y, et al. that COVID-19 is similar to autoimmune diseases in terms of clinical manifestations, immune responses, and pathogenic mechanisms. Persistent immune responses are involved in the pathogenesis of both

diseases, and autoantibodies as a marker of autoimmune diseases can also be detected in patients with COVID-19 [34].

A British study by Liu Y, et al. [37] also emphasizes that COVID-19 and AAVs are multisystem diseases. It is interesting to note that these two diseases have a similar radiological picture of the chest, with minor differences: for example, both can lead to ground-glass opacities, but peripheral and inferior lesions tend to predominate in COVID-19 [38-40]. Other signs that may suggest the development of AAV in patients with recent COVID-19 include hemoptysis or the presence of cavitations, nodules, or pulmonary masses on chest radiographs [37,41].

A large number of works have been published that confirm that the 2019 coronavirus disease is a trigger for many immune-mediated conditions, such as ANCA-vasculitis [3,36,37,42-44].

According to literature sources, there is an increasing number of reports on the potential connection between SARS-CoV-2 infection and AAVs in children and adults [4,10,26,36,37,42-61], because: firstly, lung damage in COVID-19 can mimic the changes seen in patients with AAV [4,37,47,48]; secondly, two diseases can occur together; third, COVID-19 can cause AAV [4,48].

Based on the results of the analysis of literature sources in the PubMed, MEDLINE, EMBASE, CINAHL and EMCARE databases, British and Turkish scientists found that in 40-46% of cases, AAV was diagnosed one to six months after COVID-19, while in 50-60% these diseases were simultaneous [37,45].

Usually, most of the publications related to clinical reports of the occurrence of two serological types of AAVs associated with MPO-ANCA or PR3-ANCA without determining the clinical phenotype of the disease in patients who suffered from coronavirus disease. Only a small number of publications refer to new cases of MPA development in patients in the pre-clinical period [28,54,55] and after SARS-CoV-2 infection [10,26,42,44,56-59].

Since MPA is a systemic vasculitis, involvement of multiple organs and systems can result in a wide range of signs and symptoms [6,8,9,62-65]. However, most cases of MPA are associated with kidney and lung damage [8,10,21,37,62-64,66]. MPA can simultaneously or sequentially affect other organs, such as the nervous system, skin, musculoskeletal system, as well as the heart, eyes, intestines, etc [6,8,65].

However, more than 70% of patients with MPA have constitutional symptoms such as fever, arthralgia, myalgia, and weight loss at the time of diagnosis. Other initial manifestations include decreased appetite, urinary disturbances, cough with or without hemoptysis, skin manifestations (palpable purpura, livedo reticularis, nodules, urticaria, skin ulcers), mononeuritis multiplex, convulsions, other nonspecific neurological complaints, abdominal pain, gastrointestinal bleeding, chest pain, eye pain, sinusitis, testicular pain, etc. [8,10,21,54,63-65]. Otolaryngological manifestations are less frequent in patients with MPA [8,63].

The first joint consensus of the Austrian Societies of Nephrology and Rheumatology, «Diagnosis and treatment of granulomatosis with polyangiitis and microscopic polyangiitis - 2023: Consensus guidelines», which was published on September 20, 2023 [67], states that AAVs are rare, complex systemic diseases that are often difficult to treat diagnose due to nonspecific clinical symptoms during consultation. However, the clinical course can be very serious and even life-threatening, requiring immediate diagnosis and treatment. It is noted that patients with AAV usually have a variety of nonspecific symptoms, such as malaise (60%), fever (35%), joint pain (45%), indicating a systemic inflammatory process that often precedes the onset of the disease [67].

Individuals may have a latent onset of systemic symptoms such as fever, malaise, or weight loss. But more often the onset is acute in patients who complain of arthralgia and flu-like symptoms that last from days to weeks [8]. The disease may have an indolent course before a diagnosis is made. For example, nonspecific symptoms such as flu-like illness, arthralgias, malaise, anorexia, and weight loss may be observed for months to years before diagnosis without organ involvement [8,21]. Some patients may have an acute onset of fulminant disease with hemoptysis, hematuria, or even renal failure [8]. Moreover, the clinical features of MPA cause a diagnostic dilemma due to their non-specific and varied clinical manifestations [21,54].

It is quite obvious that it is difficult for a family doctor to recognize a real disease under the mask of respiratory infections, including the new coronavirus disease (especially during the «autumn-spring» epidemic period) or the mask of a paraneoplastic syndrome (fever, arthralgia, arthritis, weight loss, nephropathy). Rheumatic joint disease, myeloma nephropathy, systemic connective tissue diseases, other AAVs [68-70], systemic vasculitis, secondary forms of infections or drug-related diseases, as well as other diseases with a positive test, should also be considered and excluded. ANCA [67].

MPA is a systemic small vessel vasculitis that causes inflammation of the vessel walls, which can lead to necrosis and bleeding [8]. Kidneys and lungs are the most typical organs that are involved in the pathological process in

MPA [5-16,21-26,28,37,62-67]. In addition, MPA is the main cause of pulmonary-renal syndrome (PRS), which encompasses a group of diseases with distinct clinical and radiological manifestations, as well as different pathophysiological mechanisms. PRS can be caused by many systemic autoimmune diseases, in 70% of cases it is a consequence of ANCA-associated vasculitis affecting the alveoli and glomeruli [22,73]. In AAV, inflammation occurs due to neutrophilic infiltration of the vascular endothelium, which affects arterioles, venules, and capillaries, leading to destruction of the vessel wall and necrosis [22]. Necrosis can be fibrinoid or granulomatous [71].

PRS, in addition to MPA, includes GPA, Goodpasture syndrome (glomerular basement membrane disease (anti-GBM)), systemic lupus erythematosus, antiphospholipid syndrome, thrombotic thrombocytopenic purpura, ANCA-negative vasculitis, drug-induced vasculitis, etc [8,22]. LNS is a potentially life-threatening condition that requires prompt recognition, as progressive respiratory failure and/or terminal RF can rapidly occur and often require hospitalization in an intensive care unit for further treatment [22].

The term «pulmonary-renal syndrome» describes a clinical syndrome characterized by a combination of rapidly progressive glomerulonephritis (RPG) and diffuse alveolar hemorrhage (DAH) [22,71]. Simultaneous damage to the lungs and kidneys in these patients indicates a multisystem disease [54]. With recent advances in treatment, particularly the introduction of new immunosuppressive therapies, mortality rates have improved but remain high with some reports of mortality rates as high as 50% [22].

Clinical signs of PRS are nonspecific, so a high index of suspicion is necessary. PRS should be considered in patients with bilateral pulmonary infiltrates, low hemoglobin levels, and RF requiring hemodialysis [22,71]. It should also be considered in patients with unexplained sinusitis, mononeuritis multiplex, polyarthralgia, asthma, pericarditis, cerebral ischemia, purpura, and congestive heart failure [71]. In addition, the doctor should always remember that PRS at the first manifestation can not only imitate pneumonia, but in some cases can be provoked by pneumonia. Thus, treatment of all these patients should include extensive antibiotic use until further evaluation [71].

Manifestations of PRS vary depending on the underlying etiology. However, DAC and glomerulonephritis are unifying features.

Kidney damage is usually the most common manifestation of MPA, which according to various authors is observed in 80-100% of patients [5-16,21-26,28,37,62-67]. The most frequent manifestation is the «low-immune» form of rapidly progressing glomerulonephritis (RPGN). Clinical manifestations may vary from asymptomatic or microscopic hematuria, often with erythrocyte casts, subnephrotic proteinuria, increased serum creatinine from overt RF to end-stage RF requiring renal replacement therapy. In most patients, RPGN is manifested by loss of renal function with a marked decrease in GFR (up to ≥50%) over several days (weeks or months) to 3 months, sometimes accompanied by oliguria [5,9,10,62,63,65,72]. A kidney biopsy is indicated when kidney damage is suspected and especially in the presence of diagnostic uncertainties [67]. The renal biopsy finding is focal segmental necrotizing glomerulonephritis, which is seen in approximately 100% of patients. Glomerular crescents are also common, and may be present in approximately 90% of patients [21,67]. The most important prognostic feature in kidney biopsy histology is not the type and degree of glomerulonephritic damage, but rather the proportion of completely intact glomeruli [67].

Renal involvement in MPA is particularly important because it often leads to end-stage renal disease requiring renal replacement therapy and is associated with a poor prognosis and increased mortality [5,9,11,63,66,67]. It should also be noted that, according to literature data, with MPA, the prognosis was worse in patients with PRS [63]. In particular, the presence of impaired renal function and dependence on dialysis at the time of diagnosis increases the risk of death in patients with AAV [5-7,63].

Glomerulonephritis should be suspected in the presence of hematuria, proteinuria, and in the presence of erythrocyte casts in the urine («urine sediment») or the presence of blood in urine tests using test strips. Most importantly, hematuria may indicate significant renal pathology even when renal function is not impaired [67].

Therefore, initial and follow-up renal screening for overt renal dysfunction should include evaluation of proteinuria, urinalysis for erythrocyte casts, measurement of serum creatinine and estimated glomerular filtration rate (eGFR), with renal biopsy required to confirm the diagnosis of glomerulonephritis in ANCA-associated vasculitis. It can progress to the terminal stage of RF, requiring dialysis [22,71].

In recent decades, the recognition of MPA has become easier and faster since the introduction of ANCA testing in 1985. It is relevant to note that Uzzo M, et al. [72] performed a comparative analysis of clinical and histopathological characteristics at the time of diagnosis, assessed the risk of death, end-stage renal disease and recurrence rate in a large

cohort of patients diagnosed with MPA during 42 years of follow-up (between 1980 and 2022 years), grouping them into 2 periods: 1980-2001 and 2002-2022. The authors concluded that over the past decades, renal damage in MPA has become less severe with more active features on renal biopsy, leading to a lower risk of end-stage LV and a higher rate of recurrence, despite a comparable risk of death. However, the risk of death did not decrease. The risk of recurrence was numerically higher during the period 2002–2022 and had better renal function (eGFR) [72].

Patients with MPA have a high prevalence of lung involvement, ranging from 25% to 55% [8,21,73,74]. Usually, MPA is more often manifested by kidney damage and develops pulmonary manifestations at later stages [56]. According to Jin JJ, et al. [75] lung involvement was the initial manifestation in 28% of patients with MPA. Clinical manifestations were nonspecific, radiological findings included ground-glass attenuation, interstitial changes, infiltrates, and pleural effusion [21,75].

Features of lung lesions differ depending on the clinical and pathological variant and serological phenotype of ANCA-vasculitis. In EGPA, the main lung damage is bronchial asthma. The pulmonary manifestation of GPA is necrotizing granulomatous inflammation, including nodules, cavitary formations, airway stenosis, and DAH. It is also the most common pulmonary manifestation of MPA.

DAH is defined as the accumulation of erythrocytes in the alveolar space originating from alveolar capillaries or venules due to disruption of the alveolar-capillary interface [73,76]. Typically, DAH is observed in 30–50% of patients with MPA [22] and may be the initial manifestation of AAV [56,73]. In particular, severe alveolar hemorrhage is associated with a poor prognosis and requires rapid and more intensive treatment [67]. In addition, the prognosis in patients with DAH is worse than in patients with other manifestations of AAV [77].

In studies done in Europe and Japan, differences in ANCA frequency and serotype were observed in patients with AAV. Although the overall incidence of renal vasculitis was similar in Europe and Japan, PR3-ANCA-associated vasculitis (or GPA) appeared to be much less common in Japan [78].

A study by Japanese researchers Boyle N, et al. demonstrated that among AAV patients with DAH, the most common clinical diagnosis was MPA (52%), followed by GPA (41%) and EGPA (6%) [78]. At the same time, according to data from the European Respiratory Society, DAH is more common in GPA (42% of cases), compared to MPA (29%) and EGPA (3%) [22], which points to differences in the clinical manifestations of AAV on different continents.

It should be noted that interstitial lung disease (ILD) and DAH due to pulmonary capillaritis are two key pulmonary manifestations of MPA [64,73,78], which increase patient mortality [73,78]. MPA patients with pulmonary involvement present with dyspnea, cough, pleuritic chest pain, low-grade fever, and hemoptysis due to alveolar hemorrhage. Capillaritis with fibrinoid necrosis is a typical pathological feature in MPA patients with lung involvement [21,22,63].

According to many medical sources, capillaritis with alveolar hemorrhage is the most frequent manifestation of lung disease in MPA [21,64,73-80] At the same time, according to the data of a Chinese retrospective study, in a cohort of patients with MPA, ILD was 5 times more prevalent than DAH [80]. This study examined the clinical characteristics of pulmonary pathology in 181 patients with MPA who were hospitalized between 2002 and 2012. The authors found that 19 (10%) patients had DAH only, 96 (53%) had ILD only, 18 had DAH and ILD simultaneously, and 48 (26%) had no lung lesions. The median serum creatinine level in the DAH group was 449 μmol/L, which was significantly higher than that in the ILD group (123 μmol/L) and the DAH/ILD combination group (359 μmol/L). Patients in the ILD group were older than those in the DAH group (median: 69 years vs. 57 years) [80].

DAH is a potentially life-threatening clinical syndrome [76], early recognition of which is important for the patient. The criteria for DAH include: hemoptysis and/or pulmonary infiltrates and/or anemia (DAH triad) and hemorrhagic bronchoalveolar lavage (BAL) or siderophagic alveolitis [81]. Alexandre AT, et al. performed a comparative analysis of disease manifestations in 24 patients admitted with DAH, among which 11 had an immune cause (AAV, SLE) and 13 had a non-immune cause. The authors established that the triad of DAH was observed in 54% of patients, hemoptysis in 67%, anemia in 79%, and pulmonary infiltrates in all cases [81]. Also, patients with immune DAH more often had PRS, RF, shock and more often required hospitalization in the intensive care unit and blood transfusion. Patients with DAH due to immune causes were significantly younger, had more severe disease manifestations, and the worst outcomes [81].

A similar retrospective study of the clinical data of 39 patients with DAH (from December 2010 to December 2015) with a proven immunological origin was described by Quadrelli S, et al. [82]. The main causes of DAH were ANCA-associated vasculitis (74.3%), mainly GPA (n=14) and MPA (n=13). 30 patients (76.9%) had hemoptysis. All patients had a decrease in the level of hemoglobin from 1.0 to 3.0 g/dL. BAL fluid was macroscopically bloody in 43.6% of patients (n=17) and cytology revealed siderophagic alveolitis in 100%. The authors conclude that DAC can occur without hemoptysis and requires early bronchoscopy to confirm the

diagnosis [82]. Moreover, BAL with the release of bright red fluid is the best diagnostic clue, which also excludes infection and other causes of hemoptysis [76].

DAH is rarely asymptomatic in MPA. Most patients rapidly develop shortness of breath, obvious hemoptysis, anemia, or progressive respiratory failure. This is due to active rapid crescentic glomerulonephritis, which causes RF, leading to PRS [73,83,84]. Nevertheless, DAH can have a more indolent course with recurrent hemoptysis. In 25% of cases, symptoms may precede the diagnosis of DAH by more than a year [85]. Therefore, DAH should be suspected in patients with respiratory symptoms, decreased hematocrit, radiographic abnormalities, including diffuse pulmonary infiltrates and ground-glass opacification, as well as increased diffusing capacity [73]. The gold standard for confirming alveolar hemorrhage is BAL [66].

Therefore, hemoptysis is the most common clinical manifestation of DAH. However, 30–35% of patients may have DAH without signs of hemoptysis [22,81,82,86,87], which is confirmed by a number of retrospective studies [81,82].

Hemoptysis in DAH is usually mild, but can be large in volume [22]. Moreover, as noted by Lababidi, et al. [54], hemoptysis is sometimes absent due to the ability of the alveoli to absorb a significant amount of blood before it spreads into the large airways. Acute respiratory failure requiring intubation occurs in approximately 50% of cases [71].

The development of DAH in patients with MPA was confirmed in isolated reports prior to the emergence of the 2019 coronavirus disease [54,55,88] and in a significant number of clinical case reports of MPA with DAH during the COVID-19 pandemic [26,42,44,53,56-59,66,77]. According to Patel R, et al. [56] DAH as an initial symptom in MPA is rare. However, there are a large number of reports demonstrating the presence of DAH in patients with MPA at the onset of the disease [42,53,54,57,66,77,88]. It should also be noted that DAH can also occur at a late stage of the disease [44,55,56,58,59].

The results of chest imaging in patients with DAH show bilateral diffuse opacification of the air space [57]. However, there is a case report of unilateral DAH confirmed by BAL [57].

Although DAH is the most common and life-threatening pulmonary complication of MPA [22,44,53-58,74,75,77,78], there has been a recent increase in reports of interstitial lung disease (ILD) with MPA [73,74,78-80,89-104].

Usually, ILD occurs mainly in MPA (from 7% to 43% of patients), but in rare cases it is also seen in other types of AAV (in 23% in GPA, very rarely in EGPA). ILD is mainly associated with MPO-ANCA (46%–71%), while some cases (0%–29%) are positive for PR3-ANCA. In contrast, other pulmonary manifestations of AAV, such as nodules or pulmonary infiltrates, are equally associated with both MPO- and PR3-ANCA [73].

It is important to note that there were differences between studies in Europe and Japan regarding lung damage in AAV. Among patients with ANCA vasculitis, ILDs such as pulmonary fibrosis (PF) and interstitial pneumonitis have been found rarely (2–3%) in Europe but much more frequently in Japan (29–39%) [78]. The prevalence of AAV-related ILD in the Japanese population is higher than in Europeans, due to the higher prevalence of MPA and MPO-ANCA in Japan and the possible genetic predisposition of the Japanese to ILD. However, the prevalence of ILD in patients with MPA is similar worldwide [73].

In 2021, Kadura S, et al. [89] published the results of an analysis of publications over the past three decades reporting an association between ILD and ANCA or ANCA-associated vasculitis. The study demonstrated that the vast majority of cases of ILD occur in the background of positive anti-MPO antibodies and may be present in 45% of patients with MPA. However, cases of PR3-ANCA-associated ILD have been rarely reported. Pulmonary fibrosis and ANCA positivity can occur with or without systemic involvement. Pathogenetic mechanisms establishing the relationship between ANCA and the development of pulmonary fibrosis remain unclear. It has also been established that ILD on the background of AAV is associated with worse outcomes, so early detection and treatment of these patients is advisable. The authors of the publication recommend an ANCA antibody test as a baseline assessment in patients with idiopathic interstitial pneumonia [89]. In addition, several studies reported that pulmonary fibrosis was often the early and first manifestation of MPA [90-92] or co-occurred with AAV and had an adverse effect on the long-term prognosis of ANCA-vasculitis [92].

In 2012, Korean researchers Ahn JK, et al. reported that ILD was present at diagnosis in 23.6% of Korean MPA patients, with usual interstitial pneumonia (UIP) being the most frequent feature (84.6%) [93]. In other data (2023), overall ILD was the initial manifestation of MPA in 66.7% of patients seen at a South Korean medical center during a 6-year follow-up. 30.8% of patients were simultaneously diagnosed with MPA and ILD [94].

The main symptoms of ILD in MPA are usually nonspecific and include progressive dyspnea on exertion and/or a

nonproductive cough similar to symptoms of idiopathic pulmonary fibrosis. It should be noted that pulmonary symptoms may be masked by severe constitutional and extrapulmonary manifestations of vasculitis, which include fever, weight loss, arthralgia/myalgia, skin rash, or paresthesia [73].

Interestingly, MPA patients with ILD have less vasculitis activity, lower erythrocyte sedimentation rate, and less DAH, peripheral neuropathy, and glomerulonephritis than patients without ILD [74].

Attention is drawn to the research data of a group of Japanese scientists on behalf of the Japanese Research Group on Advanced Kidney Disease [78]. To clarify patient characteristics and prognosis according to lung lesions in AAV in Japan, the authors performed a retrospective and prospective multicenter cohort study where 1147 cases of AAV patients were analyzed. Moreover, alveolar hemorrhage was one of the predictors of 1- and 5-year mortality for the survival of patients with AAV, and ILD was added as one of the predictors of 5-year mortality. Thus, alveolar hemorrhage may be associated with short-term prognosis, and ILD with long-term prognosis in AAV [78]. In addition, iatrogenic causes (in particular infection) are also an important cause of death in these vulnerable MPA patients [64].

Although ILD is a rare manifestation in patients with MPA, it is associated with poor survival [91,92]. In the clinical course of patients with MPA-ILD, the most frequent pulmonary complication was pneumonia (23.1%), followed by acute exacerbation of ILD, DAH (17.9% each) and lung cancer (7.7%). An acute exacerbation of ILD was defined as worsening dyspnea within 30 days with new bilateral pulmonary infiltration that is not entirely attributable to heart failure or fluid overload and has no identifiable extraparenchymal cause (pneumothorax, pleural effusion, or embolism) [94].

In 2023, a group of Chinese scientists from Peking University [95] performed a retrospective analysis of ILD patterns and prognosis in a cohort of patients with ANCA vasculitis, which included 204 patients with AAV-ILD. Baseline computed tomography (CT) images were further classified as nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP), and unclassified ILD. According to CT, 152 patients had UIP (AAV-UIP), 39 had NSIP (AAV-NSIP), 3 had OP, and 10 had unclassified ILD. Microscopic polyangiitis was more prevalent in patients with UIP, while granulomatosis with polyangiitis was more common in the NSIP and OP groups, and eosinophilic granulomatosis with polyangiitis was more frequent in patients with unclassified ILD. Patients with UIP patterns had the worst prognosis, while those with NSIP patterns had the best long-term outcome. Specifically, patients with UIP patterns had an approximately 5-fold risk of death compared to those with NSIP. The authors found that BAL fluid neutrophilia was an independent predictor of mortality among patients with AAV-ILD, and therefore recommended considering the clinical utility of BAL in the diagnosis of AAV [95]. Similar results were obtained by Kim MJ, et al. who retrospectively analyzed the clinical data of 39 patients with MPA-ILD. Their results also suggest that older age and a higher number of neutrophils in BAL indicate a poor prognosis in patients with MPA-ILD [94].

According to Shao C, et al. [96] UIP, usual interstitial pneumonia, is the most common type of MPA associated with ILD, and patients may initially present with isolated pulmonary fibrosis, often leading to a misdiagnosis of idiopathic pulmonary fibrosis (IPF) [96].

A similar conclusion was formulated by Kim MJ and Shin K [73]. Although MPA is well known for its clinical manifestations of necrotizing glomerulonephritis and DAH, ILD is now believed to be a common and serious pulmonary complication of MPA, especially in patients with MPO-ANCA. ILD may initially present as isolated pulmonary fibrosis, preceding the diagnosis of MPA. It should be noted that its most common radiographic picture is UIP, similar to the characteristic picture observed in idiopathic pulmonary fibrosis. Therefore, all patients with isolated pulmonary fibrosis should be tested for ANCA at diagnosis and throughout the course of the disease, as ANCA may have a significant prognostic impact on both survival and risk of developing AAV, especially MPA [73].

As early as 2002, the American Thoracic Society/ European Respiratory Society (ATS/ERS) in the classification of idiopathic interstitial pneumonia (IIP) identified seven specific forms and provided them with standardized terminology and diagnostic criteria [97], which was supplemented and updated in 2012 [98]. The ATS/ERS International Multidisciplinary Classification of IIP showed that the most common radiographic picture was UIP (50%–57%), followed by nonspecific interstitial pneumonia (NSIP) (7%–31%) and desquamative interstitial pneumonia (14%) [98].

According to Zhang Y, et al. On chest CT, MPA-ILD predominantly has either usual interstitial pneumonia (UIP) or a UIP-like radiographic pattern followed by nonspecific interstitial pneumonia (NSIP), and the UIP pattern is associated with shortened survival compared to the NSIP pattern [99]. ILD significantly affects the quality of life and survival, while mortality increases 2-4 times, especially higher in patients with IPA with pulmonary fibrosis [100].

Lung involvement is usually symmetrical (50–100%) and mainly affects the periphery and lower lobes of the lungs. High-resolution CT (HRCT) findings of ILD in patients with MPA include ground-glass opacities (23%–94%), reticular opacities (41%–77%), septal thickening (41%–71%), induration (23%–78%), and cellular formation (23%–52%) [73]. In 32–55% of patients, respiratory tract disorders in the form of bronchiolitis, bronchial wall thickening, and bronchiectasis (BE) were also reported [73,101-102]. However, according to Yun Zhang, et al. Bronchiectasis is also the main subtype of MPA with lung involvement, accounting for 16–42% of IPA cases [99].

Moreover, Zhang Y, et al. [99] performed a retrospective study of 97 patients with a final diagnosis of MPA. Forty-seven of 97 (48.5%) patients had pulmonary involvement, including 37 patients with ILD, 12 patients with BE, and two patients with DAH. ILD and BE preceded MPA in 56.76% (21/37) and 75.0% (9/12) of patients, respectively. However, ILD and BE were detected simultaneously with the diagnosis of MPA in 40.54% (15/37) and 25.0% (3/12) of patients, respectively. The authors conclude that patients with MPA have a high prevalence of lung involvement, and ILD is the most common subtype of MPA. ILD and BE can be considered previous comorbidities or important complications of MPA. Elevated serum creatinine was associated with reduced patient survival in both the MPA with lung involvement and MPA-ILD groups. This current study showed that ILD and BE usually occur before MPA. These patients were diagnosed with MPA an average of 3.4 years and 5.0 years after confirmation of ILD and BE, respectively, and these results were in agreement with previous studies [99].

Another group of Chinese scientists Wu TT, et al. [103] published the results of a retrospective study of 28 patients with MPA associated with ILD (MPA-ILD). The authors studied the clinical signs, laboratory examination and imaging features of ILD associated with MPA and analyzed the survival rates of patients. Most patients (96.43%) were found to have ILD diagnosed before or concurrently with MPA, which is consistent with a number of published clinical reports [79,96]. In addition, patients with MPA-ILD had fewer symptoms of systemic vasculitis. The chest X-ray was predominantly usual interstitial pneumonia or UIP-like pneumonia, then nonspecific interstitial pneumonia. Elevated serum LDH was an independent risk factor for shortened survival in MPA-ILD, while elevated rheumatoid factor (RF) was a protective factor for prolonged survival in MPA patients [103]. It is appropriate to add that the presence of RF can be a predictor of the future development of MPA [73].

In another single-center retrospective study, Japanese researchers Takakuwa Y, et al. [104] analyzed clinical features, long-term survival, and prognostic factors for mortality among 76 patients with MPA, including ILD (MPA-ILD). ILD was classified as usual interstitial pneumonia or nonspecific interstitial pneumonia by computed tomography of the chest. The authors found that age ≥ 70 years and ILD of the UIP type were associated with high mortality due to susceptibility to infection and progression of ILD [104].

In most patients with AAV, ILD occurs simultaneously (36%–67%) with or before the onset of vasculitis (14%–85%) [73,99]. Rarely, the onset of AAV precedes the diagnosis of ILD (8%–21%). In particular, ILD may initially present as ANCA-positive idiopathic interstitial pneumonia (IPP), and months or years later, vasculitis may develop [73,92]. The prevalence of MPO-ANCA in patients with IIP ranges from 4% to 35%, whereas PR3-ANCA is rare (2%-4%) [73,99]. Patients with ANCA-positive IIP usually present with symptoms of dyspnea or cough, whereas hemoptysis and constitutional symptoms are less common.

Other manifestations of MPA include the following: cutaneous manifestations, cardiovascular, gastrointestinal, neurological manifestations, arthralgias (10-50%), testicular pain (2%), ocular manifestations (1%), sinusitis symptoms (1 %).

Skin lesions are observed in 30-60% of patients with MPA and are the initial symptom in 15-30% of patients [8,21,64]. Palpable purpura is the most common manifestation and occurs in 40% of patients [21]. Other cutaneous manifestations include live do reticularis, nodules, urticaria, and necrotizing skin ulcers. Dermatological manifestations in patients with MPA were usually associated with arthralgias [8,21]. MPA with urticarial erythema and Henoch-Schönlein purpura have been reported in two cases [105] and severe MPA limited to the skin [106].

The most common gastrointestinal symptom in MPA is abdominal pain [8,21,107], which may occur in 30–58% of patients [21]. While gastrointestinal bleeding occurs in 21–29% of patients [21], massive hemorrhage is rare [8,21]. According to Eriksson P, et al. [107] among 216 patients with MPA, diseases of the gastrointestinal tract were found in 6.5%. The most common symptoms were abdominal pain and gastrointestinal bleeding. Surgery was considered necessary only in cases of GI perforation or severe bleeding [107]. Other gastrointestinal manifestations have been reported, such as multiple GI ulcers in a patient with MPA [108], colonic ulcers [109], intestinal ischemia [110,111], extensive small bowel necrosis [112], and intestinal perforation [111]. However, they are probably less frequent in MPA compared to polyarteritis nodosa, as there are fewer reports of these manifestations in MPA patients in the published literature [21].

Liver damage in MPA is rare. Liver dysfunction may manifest as elevated liver enzymes, with alkaline phosphatase and γ-glutamyltransferase affected more than transaminases. These pathological findings may precede the development of glomerulonephritis or pulmonary hemorrhage, as reported in Japanese studies [113-115]. In addition, MPA associated with primary biliary cirrhosis has been reported [116,117].

In a retrospective analysis of the clinical data of 65 patients with MPA, in a medical center in South Korea, Kim MJ, et al. found that extrapulmonary involvement was found in 92.3% of patients, of which renal involvement was the most common and accounted for 83% of all extrapulmonary involvement lesions [94].

Neurological lesions in MPA are common and affect 37–72% of patients [21]. Peripheral neuropathy [64,118-120] occurs more often than lesions of the central nervous system (CNS).

A study by Bischof A, et al. [119], which included 218 MPA patients out of 955 AAV patients, found that vasculitic neuropathy was most often associated with skin, musculoskeletal, and cardiovascular manifestations. At the same time, patients with vasculitic neuropathy were less likely to have RF, damage of the eyes and the gastrointestinal tract. It is appropriate to add that vasculitic neuropathy is a consequence of the destruction of the vessel wall and blockage of the vessel lumen of small epineural arteries [121].

Predominant features of peripheral nervous system involvement include distal symmetrical polyneuropathy and mononeuritis multiplex. Biopsy of the sciatic nerve reveals necrotizing vasculitis in 80% of cases, and nerve conduction studies show acute axonopathy [8,21]. Rarely, patients may have posterior reversible encephalopathy syndrome (PRES) [8].

An unusual neurological complication has been reported in MPA [122]: partial loss of motor and sensory function of both lower extremities with sphincter dysfunction. This is the first reported case of epidural inflammation associated with MPA [122].

CNS pathology accounts for 17–30% of all neurological lesions in MPA [21]. CNS manifestations are diverse and may include cerebral hemorrhage [123-125], nonhemorrhagic cerebral infarctions [126], and pachymeningitis [8,127].

From literary sources it is known about atypical clinical manifestations in MPA. Tauseef A, et al. reported MPA as an incidental finding in a patient with stroke [120]. A 39-year-old woman is accidentally diagnosed with MPA, which had signs and symptoms of a stroke at a young age. It usually presents with fever, malaise, rash, weight loss, mononeuritis multiplex, and arthralgia/myalgia. Very rarely, it may involve the meninges, causing meningeal vasculitis, which may manifest as febrile convulsions [120]. In contrast to the previous case, the development of intracerebral hemorrhage in the short-term clinical picture of a patient with MPA without neurological symptoms at the time of diagnosis was reported [128].

Clinical cases of MPA accompanied by spinal intradural hemorrhage and intracerebral hemorrhage [129], acute spinal subdural hemorrhage [130], and selective involvement of the central and peripheral nervous system [131] have been reported.

Parra-Medina R, et al. report atypical manifestations of MPA with damage of the kidneys, lungs, skin, and central nervous system (hemorrhage in the brain) [124].

Cardiovascular manifestations include hypertension, signs of heart failure, myocardial infarction, and pericarditis [8]. From literary sources, it is known about an unusual picture of MPA associated with pleuropericarditis, pulmonary embolism and pulmonary bleeding as a complication of silicosis [88], ANCA-negative MPA with DAH masquerading as congestive heart failure [132], a case of MPA associated with aortic valve insufficiency [133] and aortic stenosis [134]. A rare case of complete heart block was reported in an elderly woman with MPA who presented with dyspnea on exertion and dizziness [135].

Eye examination may reveal retinal hemorrhage, scleritis, and uveitis [8].

Manifestations of symptoms from the ear, nose and throat (ENT organs) are not considered clinical signs of MPA, but according to Greco A, et al. in most described populations, ENT lesions were found in surprisingly high percentages [136].

In 2020, a group of French researchers Nguyen Y, et al. [137] published the results of a retrospective analysis of the clinical picture of 378 patients with MPA from the registry of the French Vasculitis Research Group. At diagnosis, the main clinical manifestations of MPA included renal dysfunction (74%), arthralgia (45%), skin manifestations (41%), lung lesions (40%), and mononeuritis (32%) and, less frequently, alveolar hemorrhage (16 %), cardiomyopathy (5%) and severe gastrointestinal symptoms (4%); the mean serum creatinine was 217 μmol/L [137].

An earlier study by Guillevin L, et al. also demonstrated that MPA is a multisystem disease [138]. The authors found

that the main clinical symptoms in 85 patients with MPA were renal manifestations (78.8%), weight loss (72.9%), skin lesions (62.4%), fever (55.3%), mononeuritis (57.6%), arthralgia (50.6%), myalgia (48.2%), hypertension (34.1%), lung damage (24.7%); alveolar hemorrhage (11.8%) and heart failure (17.6%) [138].

Therefore, MPA is a multisystemic disease, which is characterized by multiplicity of lesions, and at the same time polymorphism of clinical manifestations depending on the affected organs: renal symptoms are observed quite often, but the disease is also associated with general symptoms, arthritis, mononeuritis multiplex and other manifestations that are also observed in various other vasculitis [138]. That is why many patients before the diagnosis go to different doctors and are treated with different antibiotics due to increased inflammation parameters [67].

It is not for nothing that systemic necrotic vasculitis are great masks, and sometimes their manifestations can be very different from the usual recognized patterns, and therefore received the figurative name "the Great Masquerades" [139]. It is important to note that systemic necrotizing vasculitis can also present with unusual disease manifestations [88,139], which may vary from patient to patient.

According to medical sources, cases of an atypical pattern of MPA with extensive necrosis of the small intestine, DAH and RF [112], MPA associated with dermatomyositis [140], a case of MPA manifested by diffuse pulmonary symptoms without kidney damage [141], as well as hidden MPA , manifesting as fever of unknown origin [142] has been reported.

Călinoiu AL reported unusual clinical manifestations without kidney damage in MPA in his report [143]. A 48-year-old patient presented with diffuse myalgia, arthralgia of both hands and feet for 2 weeks before hospitalization. The patient had involuntary weight loss and a periodic increase in body temperature. Physical examination revealed microstomia and perioral radial furrows, slight thickening of the skin of the hands, and discrete cyanotic skin areas on the dorsum of both feet. Bilateral crepitant rales were heard in the lungs. The patient was initially suspected of having systemic scleroderma due to the appearance of microstomia and mild induration of the skin of the hands with diffuse arthralgia and myalgia, although with negative immune tests (anti-SCL70 and anti-centromere B antibodies) and normal nail fold capillaroscopy. Instead, a high titer of MPO-ANCA was detected. CT revealed early diffuse interstitial lung disease [143].

Clinical symptoms in MPA are quite diverse and may include unique manifestations: hearing and vision loss, dysphagia, and kidney dysfunction [144].

Cases of patients with ANCA-negative MPA have been described [132,145]. In addition, the variability of clinical symptoms may also be related to existing comorbidities. It is comorbid pathology from a clinical point of view that aggravates the course of the main disease, leads to changes in the usual clinical picture [26,28]. Moreover, the existing comorbidity can mislead the doctor and direct the diagnostic search in the wrong direction, which is clearly evidenced by the clinical case presented by us, which will be published in the near future.

In the report presented by us, there were significant difficulties in the early etiological verification of the disease in a patient with polyarticular lesions of the joints of the upper and lower extremities after suffering from COVID-19 with comorbid pathology of the urinary system in the form of CKD and often recurrent cystitis, who was treated on an outpatient basis for more than three years under the supervision of a urologist. Hyperuricemia (HUC), azotemia, and anemia revealed during the examination led to the erroneous interpretation of these data as CKD: gouty nephropathy, gouty arthritis, which for a long time masked the underlying disease. Moreover, gout itself is independently associated with both CKD and nephrolithiasis [146].

The complex of changes characteristic of gout (symmetrical polyarthritis, including involvement of the metatarsal-phalangeal joint of the 1st toe of the left foot, in combination with HUK, azotemia, and CKD in the anamnesis), dominating the patient's clinical picture, misled the doctors. Which directed the diagnostic search in the wrong way and caused a delay in the etiological verification of the diagnosis. For more than 9 months, doctors of many specialties managed the patient with this false diagnosis, which masked the main pathological process and complicated the diagnosis of MPA, which, unfortunately, like other clinical phenotypes of AAVs, is little known to a wide range of practicing doctors, as evidenced by the results of an online survey during of the COVID-19 pandemic among doctors in 21 countries of the world [147]. According to the research of Sreih A, et al. The average time to diagnosis of vasculitis is seven months in one cohort of patients in 2021 [148]. Patients with vasculitis have significant delays in establishing an accurate diagnosis. And 82% of patients reported that late diagnosis had negative consequences for their health [148].

That is why doctors should be better informed about the different variants of the clinical course of MPA and approaches to diagnosis, which will help eliminate delays in diagnosis. It is quite obvious that a quick diagnosis is important for the initiation of adequate immunosuppressive therapy, which can both save lives, preserve organs from

damage, and improve the quality of life for these patients.

Conflict of Interest

The authors declare no conflict of interest.

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