UNIVERSITY OF MEDICINE AND PHARMACY
CRAIOVA

DOCTORAL SCHOOL

CLINICAL- EPIDEMIOLOGICAL CONSIDERATIONS ON SYSTEMIC VASCULITIS WITH PULMONARY DETERMINATIONS

SUMMARY

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Chapter I. Introduction.

1.1. Definitions. Motivation.

Systemic vasculitis is a condition characterized by inflammation and destruction of the vascular wall. Any type of vessel in any organ can be affected, generating a wide variety of signs and symptoms. Clinical manifestations may depend on both the affected vessel and the organs involved. Vasculitis may have a variety of clinical manifestations, from localized mild to severe life-threatening forms. Histopathologically it is characterized by the triad: leukocyte inflammation, thrombotic vascular occlusion and fibrinogen necrosis of the blood vessels. These are complicated diseases both in terms of diagnosis and treatment and long-term surveillance. Diagnosis is difficult due to multi-organ damage and the need for permanent collaboration between multiple specialties, and treatment is difficult from the point of view of the medication the patient receives, most often followed by severe adverse reactions, as well as the long period of administration.

The natural evolution of these diseases is marked by increased morbidity and mortality as well as frequent recurrences.

The treatment of vasculitis syndromes has undergone changes in the last decades by the introduction of corticosteroids and subsequently of cyclophosphamide, which has caused radical changes in their evolution and prognosis, transforming them from acute, life-threatening diseases into chronic diseases with undue evolution, with relapses and remissions. Therapy aims to induce remission, maintain it and prevent relapses, with side effects and minimal complications.

With the completion of this paper, we hope to build a National Vasculitis Program and Vasculitis Notebook.

Chapter II. Systemic vasculitis

2.1. General considerations. History.

Vasculitis are classified in primary and secondary. Primary vasculitis represents a group of diseases, of undetermined etiology, with different clinical manifestations depending on the type of vessel affected and the extent of the disease. Secondary vasculitis occurs in the context of other diseases that precede the diagnosis of vasculitis.

History

The first case of systemic vasculitis was described by Michaelis and Martani in 1755. The nomenclature was also changed in 2012 with the international conference for revision of the vasculitis nomenclature, CHCC 2012 [9].

2 .1.5 .The second International Conference for reviewing the vasculitis nomenclature

In 2012, at Chapel Hill, a new meeting aiming at reviewing the associated ANCA primary vasculitis nomenclature took place**.** It was desired to change the name of some of the vasculitis, largely to have a concordance of terms with the other two primary vasculitis [23]. The CHCC 2012 classification is not yet unanimously accepted.

2.2.3. Vasculitis of small vessels ANCA-associated.

2.2.3.1. Granulomatosis with polyangeitis / former Wegener granulomatosis - GPA.

GPA is characterized by necrotizing granulomas complicated in the lower and upper respiratory tract, focal glomerulonephritis and necrotizing vasculitis [130,131,132,133], changes that have been identified histopathologicaly from deceased patients with head and neck, kidney and lung involvment. GPA is characterized clinically by the triad of upper, lower respiratory tract and and renal impairment.

2.2.3.2. Microscopic polyangiiitis - MPA

Necrotizing vasculitis affecting capillaries, venules and arterioles of an organ or more (lungs, kidneys, skin, liver, spleen, heart, muscle system).

2.2.3.3. Eosinophilic granulomatosis with polyangitis – GEPA - former Churg-Strauss syndrome

GEPA is characterized by 3 clinical phases: allergic rhinitis and asthma, typical late-onset asthma, eosinophilic infiltration with both peripheral and tissue eosinophilia, the third phase of systemic vasculitis of small vessels with granulomatous inflammation.

Chapter III. Epidemiology and pathogenesis of systemic vasculitis with pulmonary involvement.

3.1. Incidence and prevalence of pulmonary systemic vasculitis with pulmonary involvement

Systemic vasculitis is rare, difficult to diagnose and treat. Over time there have been significant changes in vascular classifications and names.

With the advent of the algorithm uses criteria derived by consensus (ACR CHCCşi EM) epidemiological situation begins to take shape. Under these conditions, epidemiology should be taken as more informative until now.

3.2. Age and gender

Systemic vasculitis with pulmonary involvement are diseases with higher incidence in women than in males. The start of the disease seems to be around the age of 50 years [41,42,43,44]. There are diseases such as IgA-induced vasculitis that starts most often in childhood.

3.6. ANCA - Anti-neutrophil cytoplasmic antibody and cells involved in the pathogenesis of pulmonary systemic vasculitis

ANCA – Anti neutrophil cytoplasmic antibody, endothelial cells, complement system, lymphocytes T and B have very important role in the pathogenesis of pulmonary effects vaculitelor sistemicecu [158, 159, 160].

ANCA was first described in 1982 [62]. The cytoplasmic type, cANCA, is characterized by a diffuse coloration, granular cytoplasm in indirect immunoflorescence, and the perinuclear type is characterized by nucleation, perinuclear zone or both. Positive coloration that cannot be classified as perinuclear or cytoplasmic is defined as atypical. Cytoplasmic type is due to antiproteinase 3 antibodies (PR3), and the perinuclear type is due to of antimyeloperoxidase antibodies (MPO).

Chapter IV. Clinic, diagnostic, treatment, and prognostic evolution

4.1. Clinical and paraclinical manifestations of systemic vasculitis with pulmonary involvment

Systemic vasculitis with pulmonary determinations is a rare disease with a difficult diagnosis, both due to clinical manifestations that may overlap other pathologies, and to treatment followed by many adverse reactions and an incidence also rare. The complete and careful clinical examination associated with a detailed history is extremely important in the diagnosis of vasculitis, taking into account the multitude of signs and symptoms that can be encountered in various other pathologies.

4.1.2. Paraclinic exploration in pulmonary systemic vasculitis

Correct and complete anamnesis, careful physical examination and characteristic paraclinical explorations underlie the positive diagnosis of vasculitis. To support the diagnosis of vasculitis, it is necessary to exclude other diseases [143,157] and to have very high clinical suspicion. The first disease to diagnose differential is cancer. The final diagnosis is based on the histopathological examination [144.145.146].

Minimally invasive investigations are preferred by both patients and clinicians, but the histopathological examination remains a standard "gold" in vasculitis diagnosis. An important role in vasculitis diagnosis is pulmonary biopsy [163,164].

4.2. Diagnosis and treatment of pulmonary systemic vasculitis.

Collaboration of doctors of various specialties (pneumologists, rheumatologists, nephrologists, dermatologists, anatomo-pathologists) is the unanimous recommendation for patients diagnosed with vasculitis [89].

Medications used to treat these diseases, as corticotherapy and cytotoxic immunosuppressive medications have significant side reactions. Because of significant side effects have emerged scores and indexes necessary to quantifies the disease activity in order to prescribe the treatment as accurately.

4.3. Evolution and quality of life

ANCA associated vasculitis evolution is not fully known at this time no. There is no therapy to cure the disease, but it significantly influences mortality and quality of life. In the absence of treatment, mortality reaches 80% a year [116]. Combined treatments survived at 10 years and could reach 75% [44].

Current treatments improve survival, but the quality of life remains unsatisfactory. Common side effects, recurrences and progression to respiratory or renal failure lead to severe impairment of quality of life.

Part II

Special Part

Chapter V. Personal Contributions

5.1. Objective and purpose of the study

I started this study due to the constantly increasing number of patients with pulmonary, renal, cutaneous affection, the majority of young patients whose diagnosis is often delayed or aggravated with evolution towards respiratory failure, renal failure with temporary or definitive hemodialysis and diffuse pulmonary haemorrhage, whose treatment is accompanied by multiple side effects,.

Multidisciplinary collaboration for the correct and complete diagnosis of these diseases is the key to a favorable evolution, a diagnosis as quickly as possible and a longer survival.

5.1.1. Individual study:

In this paper is considered a prospective and retrospective study on patients diagnosed with systemic vasculitis with pulmonary determinations hospitalized or with ambulatory consultations at the Marius Nasta Institute in Bucharest, in the nephrology section of the Fundeni Clinical Institute, the rheumatology department of the Clinical Hospital CFR2 and the Department of nephrology of SUUB, between January 2006 and March 2017.

Patient evaluation is performed in accordance with current diagnostic, clinical, and biologic, radiological and histopathological diagnostic protocols.

The study will be based on data from clinical observation sheets as well as other medical records (discharge notes, analysis bulletins obtained from interdisciplinary consultations (rheumatology, nephrology, dermatology), necropsy and reports of computer tomography investigations.

5.1.2. Study hypothesis:

1. Optimizing the diagnosis and treatment of vasculitis with pulmonary determinations as a result of a critical view of the diagnosis.

2. Assessing the quality of life and survival of patients with systemic vasculitis with pulmonary determinations based on the time of diagnosis and treatment.

3. Selection criteria for lung transplantation candidates.

Patients were monitored by clinical, biological examination at the beginning of treatment, at 3 and 6 months during treatment or when needed, for 3 of the patients included in the study.

For patients in whom we used data from observation sheets and other medical records, the agreement for this study was obtained from the patient's physician, and for patients diagnosed, consulted and treated during this study, the agreement was obtained without the constraint of some kind of the patient. Patients agreed to all investigations, agreements signed in the services where these were performed. Investigations were required for diagnosis or monitoring, and they were not performed to contribute to the study. Patient personal data has not been made public.

5.1.4. Relevance of the project:

It is intended to promote a diagnostic and therapeutic approach in line with international standards. Appropriate therapy results from a correct diagnosis and correct, complete and fast treatment.

5.2. The Vasculitis Notebook

Even though the information system is rather poor on cases of pulmonary systemic vasculitis, most of the cases encountered in nephrology and rheumatology, we want to lay the foundations of a National Vasculite Program that would ensure a more careful follow up of these cases, as well making a Vascularity Notebook. The Vasculite notebook will be published after the completion of this paper.

5.4. Data obtained.

5.4.1. Characteristics of the study group.

Patients included in the study were diagnosed with systemic vasculitis with pulmonary determinations. Patients with uncertain diagnosis and patients who could not be evaluated as indicated were excluded from the study. Overall, 61 patients were included in this study.

5.4.1.1. Batch distribution of patients according to demographic data.

Of the 61 patients included in the study at the beginning of the study, 29 (47%) were women and 32 (53%) men, data not overlapping to the literature, where the distribution appears to be slightly higher in female sex [45, 117, 127].

In the studied group, men predominate over women by about 4% (Fig. 3).

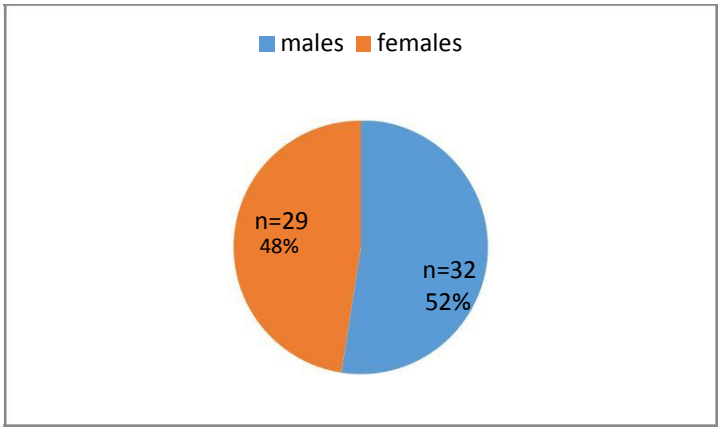

Figure 3. Patients distribution by gender (number of cases and percentage)

Age of patients at date of inclusion into the study:

This study included adult patients of both sexes who did not have psychiatric pathology proven in the past, were not pregnant or lactating women. Patients were aged between 19 and 79 years.

Of the 61 patients included in the study, patients over the age of 50 were

the majority, 37 patients (60.65%), as evidenced also by the literature, compared to 24 patients under the age of 50 years..

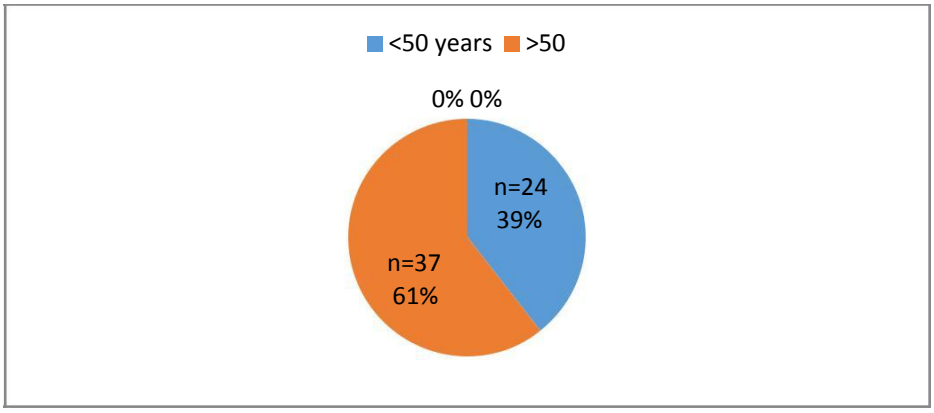

Figure 5. Distribution of patients under and over 50 years of age (number and percentage)

5.4.1.2. Distribution by year of systemic vasculitis cases with pulmonary determinations

As shown in the graph below, the annual mean of cases of pulmonary systemic vasculitis was 5.08 cases / year, confirming that systemic vasculitis is a rare disease with difficult diagnosis. All 12 years of study are after 2000, probably due to easier access to specific investigations, multidisciplinary collaboration, and last but not least due to the education and access to information of patients.

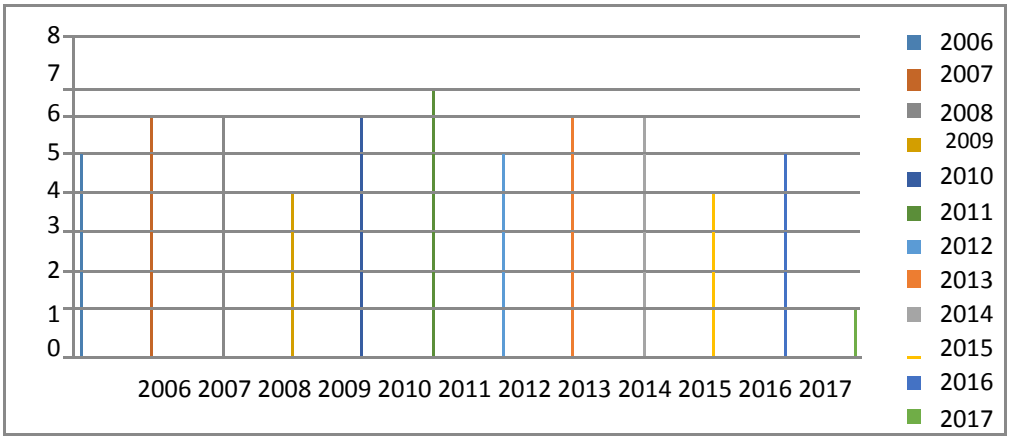

Figure 12. Annual distribution of cases with systemic vasculitis with pulmonary determinations

In the study group were included patients diagnosed with systemic vasculitis with pulmonary involvement as follows: 34(55.73%) patients with PMA, 12 (19.67%) patients with GPA, 8 (13.10%) patients with GEPA, 4 (6.55%), patients with systemic vasculitis associated with systemic diseases 3 (75%), patients with lupus vasculitis, 1 (1.63%) sarcoid vasculitis patient, 1 (1.63%) patient with systemic vasculitis with cryoblobulinemia and HCV, 1 (1.63%) patient with nodular polyarteritis, 1 (1.63%) patient with Henoch-Schonlein purple (IgA vasculitis).

5.4.1.3. Reasons for presentation in the clinic and symptomatology presented

All patients included in the study group were symptomatic at the time of diagnosis.

General symptomatology was present in all 61 patients with weight loss 42 (68.85%) of patients, physical asthenia all 61 (100%) patients, fever / low fever 19 (31.15%) patients, fatigue 4 (6.55%) patients.

Respiratory symptomatology was also present in all patients included in the study, considering that they were sent by the family doctor or the specialist doctor to the pneumology service.

5.4.1.4. Paraclinic investigations performed in patients from study group.
ANCA detection and vasculitis diagnosis.

c and p ANCA were performed in all of the 61 patients included in the study, although not positive in 100% of the vasculitis cases. ANCAs were identified by indirect immunofluorescence, only 6 of the patients performed ELISA testing. 42 (68.85%) of the patients were ANCA-positive from the first test, 3 (4.91%) patients were positive in the 2nd and 3rd tests and 16 (26.22%) patients remained negative on repeated testing.

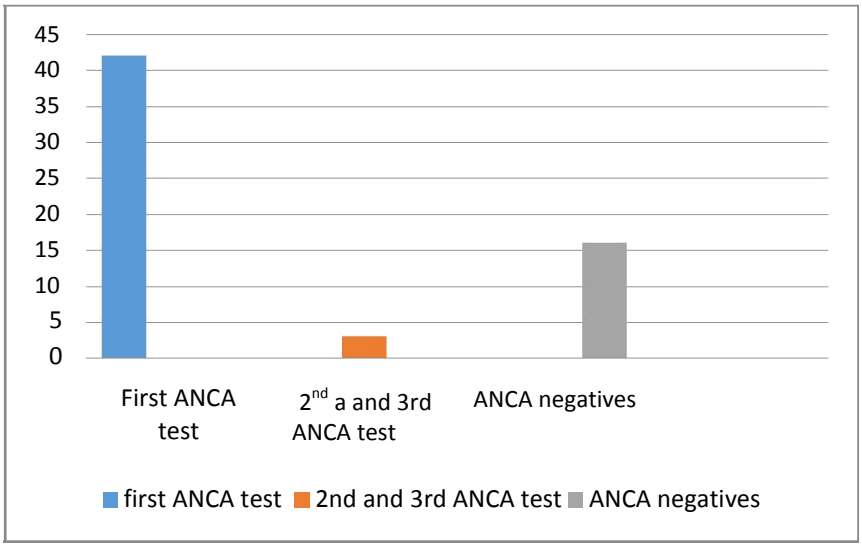

Figure 28. ANCA detection in patients included in the study

5.4.1.5. Treatment of systemic vasculitis with pulmonary determinations in the studied group

Patients in the study group received with all immunosuppressive medications, a simple or combination of cortisone and Cyclophosphamide. 5 (8%) of the patients in the study group received single oral cortisone therapy. The remaining patients, 56 (92%), benefited from combined oral cortisone therapy and Cyclophosphamide. All patients received pulse therapy with Cyclophosphamide.

5.4.1.6. Recurrences and deaths in study group

Of the 61 patients included in the study group, 12 patients have died, patients who had relapses during surveillance between 1 and 3. A single patient with two relapses survived.

Deaths occurred in the first 3 months of diagnosis in 4 of the patients, 1 patient died 5 months after diagnosis, 2 patients died at 12 months, 2 patients at 18 months, 2 patients at 36 months, 1 patient at 60 months.

5.4.1.7.1. ANCA testing and type of disease.

During the study, ANCA was tested by indirect immunofluorescence for all patients. Only 45 of them were found positive. c ANCA was positive in 17 patients (37.77%), and p ANCA was positive in 28 patients (62.23%). Positive p ANCAs were predominantly for c ANCA and negative ANCA patients.

Although the prognosis of patients diagnosed with systemic vasculitis has changed significantly since the year 2000, the death rate is still high. Out of the 12 deaths that occurred in the study group, 4 (33.33%) patients died within the first 3 months of diagnosis.

5.6. Discussions

In the study "Clinical - epidemiological considerations on pulmonary systemic vasculitis". I tried to bring new data on the epidemiology, clinical, diagnosis and treatment of these diseases and the need for interdisciplinary collaboration in such cases.

The study group consisted of 61 adult patients, being clinically, biologically, imagistically and functionally monitored.

Taking into account the relatively low global incidence of these diseases, the study group had a significant number of cases, with the mention of its development over a long period of time (12 years). The important number of cases is due to the fact that Marius Nasta Institute is the center of excellence for lung diseases, including systemic vasculitis, patients coming from both Bucharest and other parts of the country. At this time in the Marius Nasta Institute about 60% of the patients come from the other counties of the country.

The idea of this work started from the necessity of a quick and correct diagnosis of the inappropriate treatment established in most of the cases, as well as the necessity of setting up a National Vasculite Program and Vasculitis Notebook.

The annual average of cases of pulmonary systemic vasculitis was 5.08 cases / year, confirming that systemic vasculitis is a rare disease with difficult diagnosis,

with 7 cases in 2007. During the years of study the distribution was uniform.

Approximately 40% of the patients included in the study group were aged 50-59 years, vasculitis being considered in the literature, medically-onset disease [41, 42, 43, 45]. Patients with GPA and PMA are aged from all decades; GEPA patients are only young patients aged maximum 41 years and patients with vasculitis associated with systemic disease are patients over the age of 50 years. The small number of patients with Vasculitis with IgA and nodular polyarteritis cannot be statistically considered.

Although the gender distribution seems to be in favor of females [45, 117, 127], the 61 patients included in our study group were different, most of the cases being male (32 patients).

In the studied group, patients with PMA were approximately 56% (34 cases), 12 patients with GPA (approximately 20%), and 13% were patients diagnosed with GEPA, the rest of the patients were in too small number in order to bring statistically significant data.

Of the 61 patients included in the study group, 27 had the onset of symptoms in spring, 7 patients had the onset of disease in summer, 12 had the onset of symptomatology in the fall, and 15 had the onset of symptomatology in the winter. As it turns out, the onset of the disease is more common in the spring, data that do not overlap with the literature; there is no evidence of seasonal variation of vasculitis and the link with infectious factors.

All patients included in the study group were symptomatic at the time of diagnosis. The predominant general symptom was the physical asthenia present in all 61 patients**.** Patients with GPA had a higher prevalence of general symptoms than patients with PMA, but PMA patients had significantly greater specific symptomatology than GPA patients.

Respiratory symptoms were predominant in the study group, 58 (95.08) patients out of 61 had coughing, and renal symptomatology was present in 86% of patients.

Pulmonary radiography was one of the basic paraclinical investigations in diagnosing and monitoring the progression of patients with pulmonary systemic vasculitis. Radiological changes were seen in 89% of patients included in study.

c and p ANCA were performed in all of the 61 patients included in the study, although not positive in 100% of the vasculitis cases. 42 of the patients were ANCA-positive from the first test, 3 patients were positive at the 2 nd and 3 nd testing, and 16 patients remained negative for repeated testing. ANCA was identified in 17 out of 45 patients, p ANCA positive were identified in 28 of the 45 ANCA positive patients. p ANCAs have been identified in patients diagnosed with Churg-Strauss syndrome and microscopic poliangeitis, and c ANCAs have been identified more frequently in patients with granulomatosis with polyangeitis.

Systemic vasculitis is characterized by difficult diagnosis, multiple adverse reactions as well as multiple recurrences. Confirmation of the diagnosis of systemic vasculitis is histopathological confirmation. Diagnostic latency was in the study group between 6 weeks and 190 weeks, with an average of 28.2 ± 37.89 weeks.

Patients in the study group received all immunosuppressive medications such as cortisone or Cyclophosphamide. 5 of the patients in the study group received single oral cortisone therapy. The remaining patients, 56 (91.80%), benefited from combined oral cortisone therapy and Cyclophosphamide. All patients received pulse therapy with Cyclophosphamide.

Twelve patients died during the study and 13 relapses were recorded. The deaths were due to superior digestive haemorrhage, multiple organ failure, diffuse alveolar haemorrhage with respiratory failure and road accident. Patients had between 1 and 3 relapses, one patient with 2 relapses survived.

Deaths occurred in the first 3 months of diagnosis in 4 of the patients, 1 patient died 5 months after diagnosis, 2 patients died at 12 months, 2 patients at 18 months, 2 patients at 36 months, 1 patient at 60 months. 50% of deceased patients were diagnosed with PMA, statistically significant. Patients with PMA died within 3 years of diagnosis, but GPA patients died 8 years after diagnosis. The difference is statistically significant with $p = 0.06$ between the two types of disease.

Although the prognosis of patients diagnosed with systemic vasculitis has changed significantly since the year 2000, the death rate is still high.

Of the 61 patients included in the study group diagnosed with the pulmonary

involvement, 13 patients experienced 1-3 recurrences. 6 patients diagnosed with GPA, 3 patients diagnosed with PMA, 2 patients diagnosed with GEPA and 2 patients diagnosed with vasculitis in systemic illnesses had recurrences.

In recent years, the prognosis of pulmonary systemic vasculitis has changed with initiation of oral corticosteroid therapy and Cyclophosphamide, but side effects are not negligible. Reduced mortality and improved quality of life were achieved by adapting treatment to disease status and medication with low toxicity [117].

5.7. **Conclusions of the study**

Systemic vasculitis is a condition characterized by inflammation and destruction of the vascular wall. Any type of vessel can be affected, from any organ, causing an important variety of signs and symptoms. From a clinical point of view, the manifestations may be dependent on the affected vessel and the organs involved.

Vasculitis may have a variety of clinical manifestations, ranging from mildly located forms to life-threatening, severe forms. There are complicated diseases by diagnosis, treatment and long-term care. Diagnosis of vasculitis is difficult due to the multi-organic impairment and the need for permanent collaboration between multiple specialties, and treatment is difficult from the point of view of the medication the patient receives, most often followed by severe adverse reactions, as well as the long period of administration and relapses. Vasculitis are diseases that are difficult to diagnose and treat. Positive diagnosis may appear with the exclusion of cancers and infectious diseases. The diagnosis of certainty, the gold standard, remains the histopathological examination. Less invasive maneuvers are preferred by clinicians and patients, whenever possible.

Symptomatology is often unspecific, which is why the patient often presents to the doctor in advanced stages of the disease. The prognosis of patients diagnosed with vasculitis is found in the short time of diagnosis and therapy initiation. Easier access to the patient at consultation diagnosis and treatment in the last few years seems to be the basis for increasing the incidence of these diseases, as well as increasing patients access to information.

Respiratory manifestations are common, as was also the case in the study group. Patients may experience coughing with or without expectoration, low hemoptysis to massive life-threatening hemoptysis and respiratory failure. Kidney affection is often encountered, manifested by microscopic and macroscopic hematuria, oliguria to anuria, and acute kidney failure. ENT disorders can be manifested by epistaxis, rhinitis, sinusitis and throat. Blood externalization by hemoptysis, hematuria or epistaxis is often the time of the patient's appointment with the doctor.

From a biological point of view, patients with systemic vasculitis have moderate to severe anemia, significant inflammatory syndrome with maintaining values above the maximum limit even after initiation of therapy, nitrate retention syndrome, leukocytosis with neutrophilia and eosinophilia. ANCA determination can provide useful information in vasculitis diagnosis, even if not positive in 100% of cases. Patients may be positive at the first test, may become positive or may remain negative at repeated testing. In the study group, c ANCAs were identified in 17 (37.77%) of the 45 patients, p ANCA positive were identified in 28 (62.22%) of the 45 ANCA-positive patients.

Life expectancy increased with the introduction of combined treatments, cortisone and Cyclophosphamide, and survival at 10 years reached 75%, taking into account that in the absence of treatment mortality reached 80% at one year [44,116]. The multiple side effects of immunosuppressive therapy, as well as numerous cellular and molecular studies, can be the basis for the MMF and Rituximab new therapies. Rapid and accurate vasculitis treatment makes them become chronic diseases with prolonged progression in unlike the inevitable evolution to death in the absence of treatment. The immunosuppressant treatment, single or combined therapy, increase the survival but it is associated with multiple side effects and increased risk of cancer and infections.

The number of deaths remains high, approximately 20%, of all patients enrolled in the study. Deaths occurred within the first 3 months of diagnosis for 50% of patients. Increased mortality is present in patients with severe diagnosis, over 50 years of age, male, high-grade creatinine on diagnosis, ANCA-positive and with infections during treatment.

Multidisciplinary collaboration in the diagnosis, treatment and supervision of patients diagnosed with systemic vasculitis remains the gold standard for these patients.

In conclusion, the realization of a Vasculite National Program and Vasculitis Notebook can help clinicians by establishing diagnostic protocols, treatment and supervision, as well as helping patients through better knowledge of the disease.

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