ARTÍCULO DE REVISIÓN

Small vessel vasculitis

History, classification, etiology, histopathology, clinic, diagnosis and treatment

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Summary

Small-vessel vasculitis is a convenient descriptor for a wide range of diseases characterized by vascular inflammation of the venules, capillaries, and/or arterioles with pleomorphic clinical manifestations. The classical clinical phenotype is leukocytoclastic vasculitis with palpable purpura, but manifestations vary widely depending upon the organs involved. Histopathologic examination in leukocytoclastic vasculitis reveals angiocentric segmental inflammation, fibrinoid necrosis, and a neutrophilic infiltrate around the blood vessel walls with erythrocyte extravasation. The etiology of small-vessel vasculitis is unknown in many cases, but in others, drugs, post viral syndromes, malignancy, primary vasculitis such as microscopic polyarteritis, and connective tissue disorders are associated. The diagnosis of small-vessel vasculitis relies on a thorough history and physical examination, as well as relevant antibody testing including antinuclear antibody and antineutrophil cytoplasmic antibody, hepatitis B and C serologies, assessment of complement, immunoglobulins, blood count, serum creatinine, liver function tests, urinalysis, radiographic imaging, and biopsy. The treatment is based primarily on corticosteroid and immunosuppressive agents.

Key words: vasculitis, small vessel vasculitis, leukocytoclastic vasculitis, linphomonocitic vasculitis, ANCA associated vasculitis.

Resumen

El término vasculitis de pequeños vasos describe a un grupo de enfermedades caracterizadas por inflamación de vénulas, capilares y/o arteriolas con manifestaciones clínicas pleomórficas. El fenotipo clínico clásico es la vasculitis leucocitoclástica con púrpura palpable, pero con manifestaciones que varían ampliamente dependiendo del órgano comprometido. La histología en la vasculitis leucocitoclástica revela una inflamación segmentaria angiocéntrica, necrosis fibrinoide e infiltrado neutrofílico alrededor de los vasos sanguíneos, con extravasación de eritrocitos. La etiología de las vasculitis de pequeños vasos es desconocida, en muchos casos, pero en otros se ha asociado con drogas, síndromes post virales, neoplasias, vasculitis primarias como la poliarteritis microscópica, y enfermedades del tejido conjuntivo. El diagnóstico de las vasculitis de pequeños vasos se basa en la historia clínica y el examen físico, así como con estudio de anticuerpos como los anticuerpos antinucleares y los anticuerpos contra el citoplasma de los neutrófilos, serología de hepatitis B y C, determinación de inmunoglobulinas, complemento, creatinina sérica, función renal, urianálisis, estudios de imágenes y biopsia. El tratamiento se basa primariamente en el uso de corticosteroides e inmunosupresores.

Palabras clave: vasculitis, vasculitis de pequeños vasos, vasculitis leucocitoclástica, vasculitis linfomonocítica, vasculitis asociada a ANCA.

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Introduction

The systemic inflammatory vascular diseases are a heterogeneous group of conditions whose common feature is that of vessel inflammation. This vasculitis is characterized by fibrinoid necrosis, thrombosis, and sometimes a granulomatous reaction[1]. Vascular damage may occur in venules, capillaries, and arterioles, causing local and systemic clinical manifestations, depending on the organs involved. Vessels of any type in any organ can be affected, a fact that result in a wide variety of sign and symptoms. The clinical picture of small vessel vasculitis is also dependent on the extent of vascular bed involvement, delay in diagnosis, and treatment[1]. These heterogeneous clinical manifestations, combined with the etiologic non specificity of the histologic lesions, complicate the diagnosis of specific form of vasculitis.

Recognition of these features of vasculitis and evaluation with selected laboratory and other clinical tests and histologic evaluation of biopsy specimens generally permits a specific diagnosis, which directs the evaluation of activity, extent, and damage, and guides treatment. However, signs and symptoms of various forms of vasculitis are overlapping, and diagnostic precision is often hampered by the lack of diagnosis-specific histologic findings. This creates a clinical dilemma, because the treatment and prognosis of specific forms of vasculitis varies. For example, a patient with cutaneous leukocytoclastic vasculitis with abdominal and renal involvement may have disease due to classic polyarteritis nodosa (PAN) or to microscopic polyangiitis, or Henoch-Schönlein purpura. Indeed, there are few clinical conditions which cause as much confusion and consternation among clinicians and patients alike as do the protean presentations and management of vasculitis[1,2].

The gold standard for a diagnosis of vasculitis is histologic confirmation on biopsy, as few forms of vasculitis have a pathognomonic laboratory or imaging finding. Interpretation of the biopsy sample is dependent on a number of variables, including the interest and experience of the pathologist, tissue selection and quantity, and the amount of time which has occurred between diseases onset and ob-

taining the sample. These variables affect and aid verification of the diagnosis. A positive biopsy supports the diagnosis, while a negative one does not necessarily exclude it. This may be the case, for example, when vasculitis affects an organ or appendage which is poorly amenable to biopsy or biopsy of apparently involved tissue demonstrates a non-inflammatory vasculopathy[1,2].

Small vessel vasculitis with cutaneous involvement does not constitute a subgroup of either primary or secondary vasculitis. Rather, it can be associated with a number of comorbidities, further complicating diagnosis and, hence, treatment decisions. As an example, patients with small vessel disease may have hepatitis B or C, with or without cryoglobulinemia.

The discovery that autoantibodies against cytoplasmic antigens of neutrophils (anti-neutrophil cytoplasmic antibodies (ANCA)) are closely associated with vasculitic disorders has improved diagnosis of patients with clinically suspected vasculitis and/or glomerulonephritis (GN). Like the introduction of ANA serology for systemic lupus erytematosus, introduction of ANCA testing for vasculitis has revealed myriad clinicopathological presentations beyond the previously recognized patterns of systemic disease[3]. As a clinicopathological process, vasculitis occurs both as a primary process or idiopathic vasculitis and as a secondary feature of other diseases secondary vasculitis such as collagen vascular diseases, infectious disorders, malignancy and adverse drugs reaction.

The vasculitic syndromes share a common histopathological substrate inflammation within blood vessels resulting in vascular obstruction with tissue ischemia and infarction. Focal necrotizing lesions are the common vascular pathology that characterizes the ANCA-associated disorders: Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS). These lesions can affect many types of vessel and lead to a variety of symptoms and signs. Immunohistology shows little deposition of immune reactants, a feature which distinguishes lesions due to ANCA-associated vasculitis (AAV) from those of antiglomerular basement membrane disease, IgA nephropathy, and lupus nephritis[3].

ANCA were first described in 1982 by Davies and his associates as a cause of diffuse granular cytoplasmic inmuno-fluorescence staining (C-ANCA) on ethanol-fixed neutrophils in association with glomerulonephritis, vasculitis and Wegener's granulomatosis[4]. Two years later, Hall et al. confirmed this observation in four patients with small-vessel vasculitis[5]. Van der Woude et al.[6] in 1985 generated substantial interest by suggesting that detection of ANCA was a useful diagnostic and prognostic marker for Wegener´s granulomatosis. Subsequent work by Van der Woude et al. Falk et al. and others demonstrated that ANCA are closely associated with three major categories of small-vessel vasculitis: Wegener´s granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome[6-15]. These forms of vasculitis have subsequently been grouped together and are referred to as ANCA associated vasculitis[14].

The basis for the appearance of ANCA is not understood. One favored hypothesis is that environmental factors such infectious pathogen is required to activate the pre-existing potential autoimmune cellular repertoire. The proposed mechanisms by which infections break self tolerance can include bystander damage, unveiling of hidden self epitope, molecular mimicry and determinant molecular spreading. There is evidence that certain types of environmental exposure, to silica, for example, or to infectious pathogens, are associated with AAV[3, 16-19]. These mechanisms likely play a role in other forms of vasculitis as well.

Historical background

The first historical accounts of vasculitis are of small vessel vasculitis, especially forms associated with purpura. The Latin term vasculitis may have derived from the Greek porphyra, describing the color produced by a mollusk (purpura lapillus)[20]. By the XVI century, the word purpura had begun to refer to infectious diseases with fever, such as typhoid fever, but was also being used to describe other conditions often referred to as "purpura sine fever", "petechia sine fever," and the term palpable purpura carne into use[20]. The English dermatologist Willan classified purpura as simple, hemorrhagic, urticarial, and contagious[20, 21]. The concept of hemorrhagic fever he introduced in 1808 was expanded on by Bauer in 1824[21, 22]. A unifying concept of purpura and its relationship to leukocytoclastic vasculitis was put forward by Zeek et al. in 1948 and 1952, who called this form of vasculitis with small vessel involvement hypersensitivity angitis[23, 24]. Davson et al. and Godman et al. referred to it as microscopic polyangiitis, a concept adopted by the Chapel Hill international consensus conference in 1994, at which time several forms of small vessel vasculitis were more clearly defined[15, 25, 26].

This progress was the direct result of William's early work. He clearly distinguished purpura caused by systemic febrile infections from non infectious purpura[20, 21, 27]. Drawing on the earlier work of Riverius and Werlhof, Willan assigned to the ancient term purpura the meaning it retains to this day[20, 21, 27]. He considered the condition at length in this masterwork on cutaneous diseases (1808), and cases of palpable purpura consistent with Henoch-Schônlein syndrome can be recognized in both the text and the plates of his book[27]. Willan noted that non infectious purpura had a predilection for the lower extremities, was characterized by recurrent groups of lesions, and could be associated with different systemic disease. Schonlein, Henoch, and later Osler and others elucidated a broad spectrum of signs and symptoms that were associated with purpura and small-vessel vasculitis, including arthritis, peripheral neuropathy, abdominal pain, pulmonary hemorrhage, epistaxis and nephritis[28-32]. Osler recognized that these clinical manifestations were caused by necrotizing inflammation in small vessels[26, 27]. Other early descriptions were provided by Heberden, the describer of rheumatoid arthritis, in 1801 in his work "*Commentarii de morborum historia et curatione*"[33].

In October, 1893, Amy, age 6 years, was admitted to the Victoria Hospital for Sick children (London). She exhibited firm, tender, sharply defined, pale purplish-red nodules on the hands, elbows, knees, and buttocks. The patient was examined by Henry Radcliffe-Crocker (1845-1909), who was England's Mr. Dermatology at the time, as well as Jonathan Hutchinson (1828-1913), who pointed out the similarity to a case reported earlier by Judson Bury[27]. Radcliffe-Crocker named the condition erythema elevatum diutinum[34]. He failed, however, to identify the condition as a form of vasculitis, perhaps because

the lesions chosen for biopsy were too mature. Characteristic leukocytoclasia is ordinary prominent only in the early stages of the disease[27, 34]. In 1929, Fred Weidman and John Besancon of the University of Pennsylvania described the vasculitis of this condition[35]. This disease is considered to be a strictly cutaneous leukocytoclastic vasculitis, and is not mentioned in the classic classifications of vasculitis, although we consider that it likely represents a primary form of vasculitis, at least in its initial stages...

The classic description of vasculitis is that of Adolf Kussmaul and Rudolf Maier in 1866. They reported on a 27 year old patient who suffered a fulminant disease characterized by fever, productive cough, malaise, weight loss, myalgias, paresthesias and polyneuropathy, proteinuria and abdominal pain. They called the condition periarteritis nodosa, which later evolved into the more pathologically correct name polyarteritis nodosa[20-36]. For more than 50 years thereafter, and unfortunately even today in some settings, any patient with necrotizing arteritis was given a diagnosis of polyarteritis nodosa.

The first description of microscopic polyangiitis was by Friedrich Wohlwill in Germany in 1923[37-40]. Wohlwill effectively distinguished microscopic polyangiitis from polyarteritis nodosa, and Davson used the presence or absence of glomerulonephritis to separate classic polyarteritis nodosa, in which glomerulonephritis is absent, from polyarteritis nodosa[24], an observation adopted in the Chapel Hill vasculitis nomenclature[25]. The Chapel Hill authors preferred the term "microscopic polyangiitis: to "microscopic polyarteritis" to more accurately describe the small vessel involvement of arterials, venules, and capillaries[25, 26].

Another form of vasculitis associated with but not confined to small vessel inflammation is Wegener's granulomatosis, a systemic inflammatory disease with a broad clinical spectrum. The disease was first described in 1931 by a medical student at the Charité in Berlin, Heinz Klinger, who mistakenly believed it to be an atypical form of polyarteritis nodosa[41, 42].

At the 29th Meeting of the German Society of Pathology in Breslau, Friedrich Wegener, a good friend of Klinger's, reported on the post-mortem findings in three of his patients[41]. He reported 11 patients in detail in 1939 as an assistant at the Pathology Institute of the University of Breslau[27, 43]. Initial symptoms included sniffles and progressed to destructive lesions of the nose and throat, respiratory tract, spleen, and kidneys. Wegener had no difficulty in identifying the underlying pathologic changes as a mixture of vasculitis and granuloma formation. He believed the condition to be related to polyarteritis nodosa, but set apart from it in some way by its distinctive clinical picture. Recent developments in immunologic research support his position. The condition resists anti-eponymic attempts to assign a formal name and continues to be known everywhere as Wegener's granulomatosis[27, 41-43].

In 1949 Jacob Churg and Lotte Straus, pathologists at Mount Sinai Hospital in New York, gathered and studied 13 cases of patients who exhibited a fatal combination of severe asthma, fever, eosinophilia, necrotizing glomerulonephritis, cutaneous and subcutaneous nodular lesion, and symptoms of vascular compromise in other organ systems[27,44]. They suggested that the findings of granulomatous lesions within vessel walls as well as in connective tissues throughout the body set this entity apart from classical polyarteritis nodosa[27, 44]. This combination of signs, symptoms, and pathologic changes, which is usually designated as allergic angitis and granulomatosis, is also often called the Churg-Strauss syndrome[27, 44].

In 1954, Godman and Churg reported on their evaluation of the clinical and histopathologic aspects of their cases and compared them to typical Wegener's granulomatosis[15]. They viewed these as a spectrum of related conditions, a concept supported by the association of these diseases and microscopic polyangiitis with ANCA[15, 27, 44, 45].

Classification

One of the great challenges in medicine is the classification of vasculitis in the absence of an etiology, nonspecific signs and symptoms and few specific laboratory and imaging abnormalities. There have been a number of attempts to classify vascular disease including vascular inflammation since the mid 19th century. In 1952, Zeek put forward the classification scheme which has served as the basis for current understanding based upon vessel size and

histopathology[23, 24, 46]. With respect to small vessel vasculitis, the designation hypersensitivity vasculitis, as used by Zeek, originally referred to disseminated necrotizing vasculitis of small arteries with frequent involvement of glomeruli, but introduced confusion in the nomenclature of small vessel inflammatory disease[46].

The groundwork for many contemporary nosologica schemes was presented at the university of Texas Southwestern Medical Center by Gilliam and Smiley in 1976[47]. They proposed a revision of this classification scheme by subdividing Zeek´s existing categories. Thereafter, a number of alternative classification systems were been proposed, necessitating the formation of consensus groups to clarify the confusing terminology[47-50].

Unfortunately, defining the vasculitis small-vessel is complicated by their chameleon-like nature, overlapping symptomatology and historical appellations[51]. Large vessel vasculitis denotes involvement of the aorta and its primary branches. Medium vessel vasculitis includes those involving vessels of both medium and small caliber including the veins, while small vessel disease affects the arterioles, venules, and capillaries. Of all the vasculitides, cutaneous leukocytoclastic vasculitis is the most difficult to classify. The terms hypersensitivity vasculitis, microscopic polyangiitis necrotizing vasculitis and cutaneous small vessel vasculitis have a11 been used in description of leukocytoclastic vasculitis related entities[51].

The classification criteria currently most commonly employed are those of the American College of Rheumatology (ACR) from 1990 based upon clinical, laboratory, and histologic criteria, and those of the Chapel Hill Consensus Conferences based mainly upon histologic criteria[52, 53]. The 1990 ACR classification defined hypersensitivity vasculitis, whereby the sensitivity and specificity for hypersensitivity vasculitis was lowest among the vasculitides at 71% and 83.9% by traditional criteria. Palpable purpura and a maculopapular rash are undoubtedly important, though not ubiquitous features of this entity. An age range is arbitrary, histologic findings vary with disease vary with disease evolution, and an identified causative drug may or may not precipitate the disease. The histopathology of leukocytoclastic angiitis varied with time, progressing from a neutrophilic infiltrate to a monocytic infiltrate and back again[54, 55]. Clinically the lesions are often polymorphic, and at some stage the classic lesions become purpuric and palpable.

However, as we and others demonstrated, these classification schemes are insufficient for classifying some cases of vasculitis, particularly those involving small vessels. Further, the ACR and Chapel Hill criteria differ in numerous ways with regard to small vessel involvement in PAN, microscopic polyangiitis, Churg-Strauss syndrome, and Wegener's granulomatosis[53]. Another example of uncertainty in the Chapel Hill classification scheme is that of the medium vessel vasculitis, which, according to this scheme, should not involve small vessels, although the small vessel vasculitis may involve medium sized vessels[26, 53, 56]. The Chapel Hill consensus conference on the nomenclature of systemic vasculitis does not use the term hypersensitivity by vasculitis. Instead, the disease is classified as cutaneous leukocytoclastic angitis. Indeed, the majority of classification schemes including these entities have systemic disease with little cutaneous involvement. Some conditions such as hypersensitivity vasculitis, Henoch-Schonlein purpura, and polyarteritis nodosa are not universally recognized[25, 57-59].

Development of a classification that is clinically relevant, that is useable by various specialists, and that addresses clinical features, laboratory findings, and the underlying causes of vasculitis is a goal that remains elusive. An attempt to present a working classification was has been previously presented by Jorizzo in 1993 and others[60, 61]. From a practical standpoint, they suggested that vasculitis be classified as either a small-vessel cutaneous vasculitis or as a large-vessel necrotizing vasculitis. The small-vessel category may be subdivided into some of the following: idiopathic hypersensitivity vasculitis, Henoch-Schônlein purpura, essential mixed cryoglobulinemia, Waldenstrôm's macroglobulinemia, urticarial vasculitis, vasculitis associated with collagen vascular diseases such as lupus erythematosus or rheumatoid arthritis, and erythema elevatum diutinum. Thus, the patient who presents with palpable purpura and a biopsy that confirms leukocytoclastic vasculitis would be diagnosed with small vessel vasculitis.

Etiologic classification

In the following, we enumerate various causes of small vessel vasculitis (Table 1). Our aim is to provide a more practical clinical approach to the diagnosis of small vessel vasculitis rather than develop yet another novel classification scheme[51, 62, 63].

Histopathology

Small vessel vasculitis refers to inflammation in the walls of small vessels. Traditionally, these are cutaneous blood vessels. The classic phenotypic manifestation of small vessel vasculitis is palpable purpura; however, this is often not present. The histopathologic features of the vessel wall inflammation are important in defining the nature of the vasculitis.

Perhaps, currently, more important than the cellular characterization is the size of vessel involved. Until better histopathologic tools are developed, the anatomy of the lesion will continue to have primacy for the diagnosis of small vessel vasculitis. Involvement of arterioles, meta-arterioles, venules, and capillaries lead to many symptoms and signs, which are nonspecific with regard to pathogenesis or histopathologic subsumed in the finding "leukocytoclastic vasculitis"[60, 67, 68, 74, 76, 77].

The hallmark histopathologic pattern of small vessel vasculitis is leukocytoclastic vasculitis. A lymphocytic form (in which lymphocytes predominate) has also been described. There is still not enough evidence, however, to prove that the lymphocyte pattern is truly etiologically or clinically relevant. Old lesions of small vessel vasculitis may no longer demonstrate leukocytoclastic vasculitis and may contain mainly lymphocytes around blood vessels[67, 68, 78-80]. This latter consideration stresses the importance of timing when taking a biopsy in a dynamic process such as the vasculitic one. In the initial phase of disease we have observed that the predominant infiltrate is with monocytes and plasmocytes, without fibrinoid necrosis or the nuclear fragments characteristic of leukocytoclastic vasculitis[81].

Leukocytoclastic vasculitis is characterized by angiocentric segmental inflammation, endothelial cell swelling, fibrinoid necrosis of blood vessel walls (postcapillary venules), and a cellular infiltrate around and within dermal blood vessel walls composed largely of neutrophils showing fragmentation of nuclei (karyorrhexis or leukocytoclasia). Erythrocyte extravasation is another key feature[61, 65, 77, 82]. (Figures 1, 2) .

Epidemiology

The primary vasculitides are not common diseases, nor are they particularly rare. The incidence rates vary by reporting region and country. For
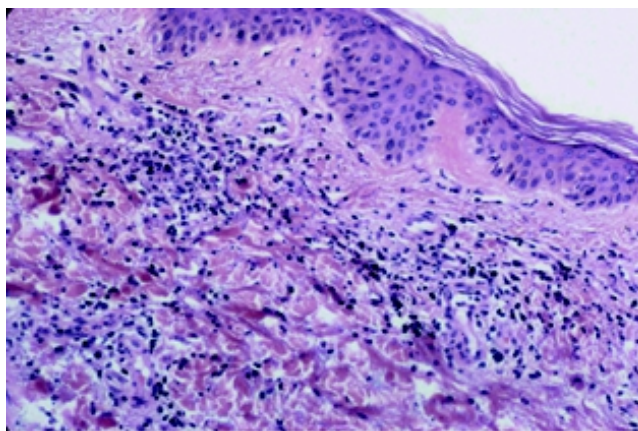

Figure 1. Small-vessel vasculitis. Inflammatory mononuclear and granulocyte cell infiltrates. Hematoxilin-eosin 20X.
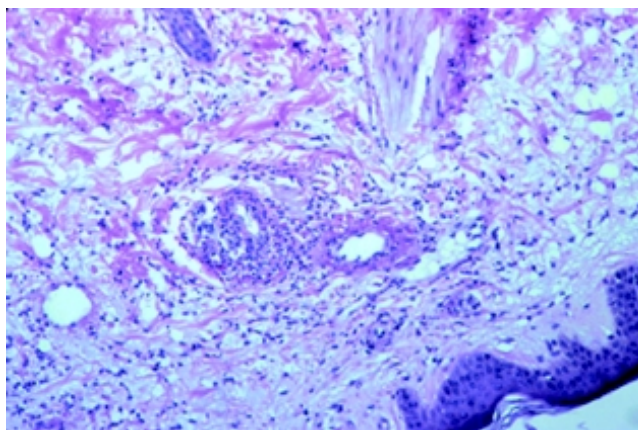

Figure 2. Small-vessel vasculitis. Fibrinoid necrosis of vessel wall with associated inflammatory cell infiltrate and organization (hematoxylin and eosin, 20X).

Table 1. Causes of small vessel vasculitis.

I. Vasculitis limited to capillaries and post-capillary venules

These vasculitides are characterized by leukocytoclastic vasculitis, especially of the skin, with few symptoms and virtually always without systemic involvement. Precipitating factors include chemical substances, foods, medications, and infectious processes. These subsume the category of hypersensitivity vasculitis[1].

II. Vasculitis associated with chemical compounds and medications

These are true vasculitides caused by idiosyncratic hypersensitivity, affecting small arteries, arterioles, capillaries, and venules. Histology reveals leukocytoplasia or lymphomonocytosis, and eosinophils may be noted in some specimens. Manifestations may include constitutional symptoms such as fever and peripheral white blood cell eosinophilia of about 5 percent[57-64].

III. Vasculitis of small arteries, especially arterioles and postcapillary venules

These include LCV with damage of the vascular wall and microthrombosis. Several subgroups may be identified, and most are associated with systemic complications[57-68].

    1. Small vessel vasculitis with systemic involvement

    2. Associated with connective tissue diseases such as systemic lupus erythematosus (SLE), primary Sjögren's syndrome, and rheumatoid arthritis

    3. Chronic infections

      a. Bacterial

        Leprosy (mycobacterium leprosa-Luzios's phenomenon)

        Staphylococcus aureus

        Streptococcus B

        Mycobacterium tuberculosa

      b. Viral

        Cytomegalovirus

        Herpes simplex

        Mononucleosis

      c. Fungal

        Candida albicans

        Histoplasmosis

      d. Parasitic

        Plasmodium malaria

        Schistosoma hematobium

        Schistosoma mansoni

    4. Neoplasia

      Myelogenous leukemia

      Chronic lymphocytic leukemia

      Histiocytic lymphoma

      Mycosis fungoides

      Hodgkin's disease

      Lymphosarcoma

      Multiple myeloma

      Solid tumors

        Colon

        Prostate

        Renal

IV. Small vessel vasculitis with acute and chronic systemic component or a manifestation of systemic disease[57-59, 64].

    Granuloma annulare

    Erythema elevatum diutinum

    Henoch-Schönlein purpura

    Drugs

    Foods

    Chemicals

    Urticarial vasculitis

    Cryoglobulinemia

    Microscopic polyangiitis

    Churg Strauss syndrome

    Wegener's granulomatosis

V. Primary vasculitides associated with small vessel vasculitis

    Microscopic polyangiitis

    Churg-Strauss syndrome

    Wegener's granulomatosis

VI. Urticarial vasculitis (normo- and hypocomplementemia)

    1. Associated with multiple antigens, foods, medications, chemicals (5-10%) of all cases of chronic urticaria[69, 70, 75].

    2. A. New syndrome combination (Hypocomplementemic urticarial vasculitis syndrome, Jaccoud´s Syndrome, valvulopathy[71].

    3. Associated with SLE (20% of all cases)[69].

    4. Associated with Primary Sjögren's syndrome (32% of cases)[69].

    5. Associated with Schnitzler's syndrome (IgM monoclonal gammopathy, urticarial vasculitis, fever, arthralgias, bone pain, acromegaly, and hepatomegaly, hyperostosis[57, 59, 64].

    6. Hypocomplementemic urticarial vasculitis with anti C1q precipitin.

      Features include iritis, uveitis, episcleritis, urticarial vasculitis, chronic obstructive pulmonary disease. 100% of patients with primary disease have C1q antibodies, as do 30-35% of patients with SLE.[72, 73].

    7. Associated with Muckle-Wells syndrome (deafness, glomerulonephritis, urticarial vasculitis[57, 59, 64].

VII. Vasculitis associated with IgA deposition in vascular walls (except for Henoch-Schönlein purpura)

    1. Dermatitis herpetiformis

    2. Ankylosing spondylitis (occasionally)

    3. Paraprotein IgA

    4. Inflammatory bowel disease

VIII. Miscellaneous conditions which may be associated with LCV

    1. Waldenström's disease

    2. Behçet's disease

    3. Sarcoidosis with LCV

    4. Relapsing polychondritis

    5. Primary biliary cirrhosis

    6. Ulcerative colitis

    7. Short bowel syndrome

    8. Chronic active hepatitis

IX. Noncutaneous, isolated small vessel vasculitis (for example: SMV of the uterine cervix[76].

example, rates in Europe have been detected to be between 115 and 435 per million adult populations, while secondary vasculitis occurs in about 1 per 26.5 million populations. In England, the annual incidence rate of systemic vasculitis has been reported to be 19.8 cases per million, with a prevalence of 144.5 cases per million[83]. In Europe, W. G. appears to be common at high latitudes, whereas PAM show the reverse pattern[84].

Henoch-Schönlein purpura (HSP) is more common in children; a recent study from Spain reported an incidence of 10.5 per 100,000 children younger than 14 years of age[84, 85]. HSP was more common in girls, with a mean age of onset of 5.5 years, and onset was more common in autumn and winter. In 36 of cases, an upper respiratory tract infection occurred before the onset of vasculitis[84, 85].

Studies of the incidence of small vessel vasculitis sui generous are complicated by the variable presentation, attribution, and lack of collaboration between physicians of different disciplines working in the field. Leukocytoclastic vasculitis comprised about 9 percent of vasculitis cases seen by rheumatologists in a study of vasculitis classification[56].

Small vessel vasculitis may affect persons of any age, with a mean of about 45 years. Men and women are affected equally. LCV is the most common form of small vessel vasculitis among Caucasians in North American and Spain[56, 86, 87].

One problem with using ANCA-specificity rather than the syndrome to characterize patients is that some patients with pauci-immune small vessel vasculitis are ANCA-negative, and the relationship between ANCA-specificity and clinical manifestations may be different between ethnic populations[88]. For example, Chen et al.[89] used the Chapel Hill nomenclature system definitions and ACR classification criteria to identify 89 patients with Wegener´s granulomatosis among 500 Chinese patients with ANCA –associated vasculitis. Of these 89 patients, 61% were myelopiroxidase –ANCA positive and 38% were proteinase 3 –ANCA positive. Thus in China, patients with Wegener granulomatosis more often have myeloperoxidase ANCA than proteinase – ANCA, which is the reverse of finding in North America and Europe. Another recent epide-

miological study by Gibson et al.[90] in a Southern Hemisphere region, demonstrates that patients of European lineage living in New Zeland have clinical and serological profiles for Wegener´s granulomatosis and microscopic polyangiitis that are very similar to Caucasian patients in Europe. That is why we set that vasculitis of small vessels can have different cutaneous and systemic phenotypic expressions and that the geographic area, race and environment contribute to the clinic heterogeneousity of the different primary vasculitis.

Etiology

Of all systemic vasculitides, vasculitis of small vessels is the form for which etiologies are best defined. Bacterial antigens may be noted in the wall of the small vessels, as may hepatitis B antigen[65, 87]. Still, as in all forms of vasculitis, most cases of small vessel vasculitis are idiopathic (45-54%), due to medications (10-45%), infections (10-36%), including hepatitis B (5%)[65, 87, 91, 92].

Medications most commonly associated with small vessel vasculitis are antibiotics (especially â-lactams) and diuretics. Upper respiratory tract infections were the most common (20%) infectious cause of small vessel vasculitis in one series from Spain[87].

Autoimmune diseases associated with secondary small vessel vasculitis include rheumatoid arthritis and systemic lupus erythematosus[65, 87, 91, 92].

Phenotypic manifestations of cutaneous lesions due to small vessel vasculitis

The various entities associated with small vessel vasculitis cause similar cutaneous lesions such as palpable purpura. Central necrosis may be seen, which is indistinguishable from septic vasculitis with immune complex deposition due, for example, to gonococcal infection of that of PLEVA syndrome. Other histologic features include secondary hemorrhage, secondary microvascular thrombosis or other vasculopathy. Phenotypically, these lesions may manifest as pruritic urticarial papules, palpable purpura with central necrosis, small cutaneous nodules, rash and ulcers (Figures 3, 4). The first step is diagnosis is to recognize that small-vessel vasculitis is present, and the second more difficult step is to

determine the specific type of the disease. The signs and symptoms of small-vessel vasculitis are extremely varied, and many are shared by all vessel vasculitis.

Clinical features

Cutaneous necrotizing vasculitis (small vessel vasculitis) is manifested clinically by a spectrum of cutaneous lesions, although palpable purpura is its clinical hallmark. At onset, the lesions might not be palpable, but almost all patients have purpura[82]. As the process continues, the lesions, which range in size from pinpoint to several centimeters, may become papulonodular, vesicular, bulbous, pustular, or ulcerated as superficial infarctions occur[82]. Occasionally, subcutaneous edema in the area of the vascular lesions can be observed. Lesions, usually at the same stage, occur in crops, and they appear first and predominate on the legs and ankles[82]. Other dependent areas under local pressure are also affected. Lesions may also occur on the other areas, but they are uncommon on the face, palms, soles, and mucous membranes. Lesions may be mildly pruritic or painful and subside within 3 or 4 weeks, leaving residual hyperpigmentation or an atrophic scar. The disease may be self-limiting, but can recur or become chronic and intermittent, with new crops of lesions appearing for months or years[61, 82, 93].

Every episode of eruptive cutaneous vascular lesions may be associated with fever, malaise, arthralgia, and/or myalgia. Unusual manifestations of small vessel vasculitis may occur on dependent areas of the body or areas under local pressure or otherwise traumatized (Koebner phenomenon)[52, 61, 82, 93]. Clinicopathological lesions may also occur in internal organs, presumably due to circulating immune-complex-mediated vessel damage at those sites. Small-vessel vasculitis involving the nervous system may be clinically manifested by focal or diffuse, central, or peripheral neurologic involvement. Similarly, the following effects may occur: small vessel involvement of glomeruli (proteinuria or hematuria), the synovia (polyarthritis), gastrointestinal tract (abdominal pain or gastrointestinal bleeding), the pleura (pleuritis), and pericardium (symptoms of pericardial effusion). Brief mention will be made here of other types of necrotizing vasculitis[54, 61, 82, 93, 94].

Urticarial vasculitis is characterized by wheals that persist for more than 24 hours, burn more than itch, and often leave residual purpura as they resolve[82, 95] (Figure 5). Erythema elevatum diutinum is characterized by erytematosus plaques distributed symmetrically on extensor surfaces. Septic vasculitis tends to occur acrally and lesions may occasionally be wedge shaped and or papulo-pustular[35, 96].

Some morphologic subtypes are considered bland. Noninflammatory cutaneous hemorrhagic microthrombosis is seen in the antiphospholipid syndrome, cold injury, cryoglobulinemia, and cryofibrinogenemia, as well as vasculopathy associated myelodysplasia, causing platelet aggregation and microthrombosis. The same findings may be seen in heparin or coumadin induced necrosis, disseminated intravascular coagulopathy, purpura fulminans, and some cases of cholesterol embolization[97, 99]. From an inflammatory stand point, these vasculopathic conditions are bland, due to microvascular occlusion and, in general, are not initially characterized by erythema of the cutaneous lesion. Reticular cutaneous lesions may also be associated with small vessel vasculitis. Both livedo and livedo reticularis are seen in cutaneous vasculitis due to IgA and livedoid vasculopathy. Reticular lesions may also be seen in Wegener's granulomatosis and in some cases of mixed cryoglobulinemia. These lesions are almost always erythematous at disease outset. They may be palpable and may become confluent, cause cutaneous ulcerations, and, occasionally, scarring[97-99].

Cutaneous lymphocytic vasculitis

This form of vasculitis is characterized by lymphomonocytic cell infiltration as a primary response to various antigens such as medications or antigens found in connective tissue diseases such as lupus erythematosus, primary Sjögren's syndrome. These inflammatory cells are present in the involved vessel wall, while fibrinoid necrosis and leukocytoclasis is absent. Activated lymphocytes elaborate cytokines, thereby damaging the vessel wall, either by direct action of the cytokine or promotion of apoptosis. This form of vasculitis is infrequent but poorly studied[57-60].

A particular form of vasculopathy associated with lymphocytic infiltrates, erythrocyte extravasation,

and presence of siderophagic cells without clear evidence of vascular wall damage may be found in purpuric eruptions and lesions, Schamberg's disease, purpura of Gougerot and Blum, lupus pernio and perniosis[57-59, 64, 92, 100].

Drug-induced vasculitis

Drug-Induced vasculitis should be considered in any patient with small-vessel vasculitis and will be substantiated most often in patients with vasculitis confined to the skin. Drug cause approximately 10 percent of vasculitic skin lesions. Drug-Induced vasculitis usually develops within 7 to 21 days after treatment begins[26, 101].

Acute and chronic forms of leukocytoclastic vasculitis

Erythema elevatum diutinum (EED) is characterized by papules appearing in a symmetric fashion on the extensor surface of the joints of the elbows, hands, knees, and, occasionally, the buttocks. These papular lesions often progress to larger anular lesions. Biopsy of early lesions reveals angiocentric neutrophil lymphocytoclasis. Rare deposits of fibrin may be present in the superficial and deep dermis. In addition, extravascular infiltrates with neutrophils, lymphocytes, plasmocytes, and histiocytes are present in the subdermal fatty tissues (so called cholesterolosis) or more generalized in the dermis (pandermic)[57-59, 64].

Chronic stages of this lesion reveal nodular angiocentric lesions with fibrosis, eosinophilia, and capillary proliferation. It is difficult to diagnose EED in this stage, in which there may be activation of factor XIII at the level of dermal dendrocytes. Streptococcal antigens such as streptokinase and streptodornase have been implicated as causative in EED[57-59, 64]. Other conditions associated with EED are myelodysplastic syndromes, IgA multiple myeloma, acute myeloid leukemia, inflammatory bowel diseases, relapsing polychondritis, and rheumatoid arthritis.

Small vessel vasculitis with systemic manifestations

Henoch-Schönlein Purpura (HSP) is the most common form of systemic vasculitis in children. IgA immune complexes are present in the walls of the arterioles, venules, and capillaries. The peak incidence in children is at about five years of age. It often follows an upper respiratory tract infection. Principle manifestations of HSP are palpable purpura, arthralgias, and abdominal pain. Up to one-half of patients develop hematuria and proteinuria, while only about 10 to 20 percent of patients present with pulmonary disease and neuropathy[1].

HSP can affect persons of any age. In adults, it most commonly occurs in about the third decade of life, with no gender predilection (Figure 6). Often, a precipitating antigen can be identified, such as infections or insect bites. In adults, however, the incidence of HSP and the severity of its clinical manifestations appear not to be the same as in children. Pillebout et al.[102] demonstrated that clinical presentation of HSP in adults is severe and its outcome relatively poor, worse than in children. Identification of clinical and histologic prognostic factors may permit the design of appropriate therapeutic prospective studies.

Secondary forms of small vessel vasculitis may simulate HSP. ANCA associated vasculitis may present with abdominal pain, palpable purpura, nephritis, and pneumonitis. These include microscopic polyangiitis, Wegener's granulomatosis (Figure 7), Churg-Strauss disease, and medication related ANCA-positive syndromes. The disease course may be severe, and high dose glucocorticosteroid therapy and immunosuppressive agents may be required[1].

Paraneoplastic syndromes

Small vessel vasculitis may appear as a manifestation of neoplastic disease. Symptoms and signs of neoplastic disease may also simulate vasculitis. Myeloproliferative disorders and B- and T-cell lymphomas may cause lymphomonocytic or lymphocytoclastic perivasculitic infiltrates simulating vasculitis. Such cases are often difficult to correctly diagnose and are refractory to treatment[1].

Diagnosis

The diagnosis and classification of patients with small vessel is based on clinical criteria, serologic as well as hispathologic; but the spectrum of small vessel vasculitis is very wide and this fact requires the

Figure 3. Small vessel vasculitis. Necrotic and blister lesions.

Figure 4. Small vessel vasculitis. Bilateral palpable purpura and necrotic lesions.

Figure 5. Small vessel vasculitic. Urticarial papules.

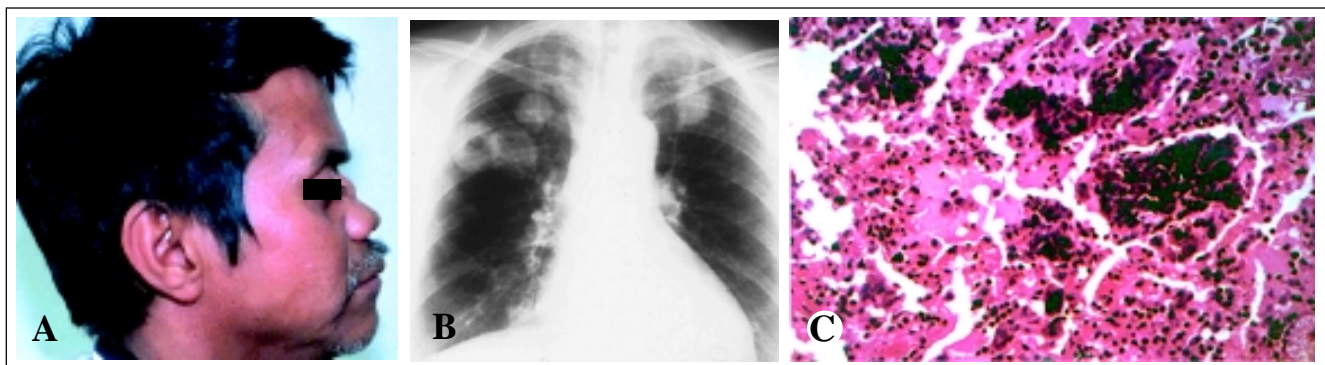**Figure 6.** Henoch-Schönlein purpura in an adult.

Figure 7. Wegener´s granulomatosis. **A.** Saddle nose. **B.** Nodules in the Lung. **C.** Pulmonary capillaritis in lung-kidney syndrome.

doctor to pay attention to the case, it is to have in mind the fact that it may exist some limitations in the search for etiologic agents and the specificity and sensitivity of some biologic markers as P and C-ANCA, which we consider here next. In most of leucocitoclastic vasculitis, we do not have a biologic marker to classify its etiology.

The diagnosis of ANCA-associated vasculitis is made on the basis of the clinical findings, by biopsy of a relevant involved organ (typically kidney, nasal mucosa, or occasionally lung) and the presence of ANCA. Testing for ANCA using both indirect inmu-nofluorescence and antigen-specific enzyme linked inmunosorbent assay is recommended and provides a high sensitivity (approximately 99%) and good specificity (approximately 70%)[3-14, 16, 18, 19].

How do these in vitro effects of ANCA correlate it disease activity, particularly in comparison with titles of ANCA Changes in various in vitro effects of PR3-ANCA have been suggested to follow changes in disease activity more accurately than changes in ANCA titles alone[18], but this suggestion is based on observations of small numbers of patients only and so far remains to be proven. Further elucidation of

the different epitopes on PR3 and MPO recognized by ANCA and their relation to disease activity may be one of the clues to this question[103-107].

Evaluation of vessels in patients with Wegener´s granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome revealed only a paucity of immunoglobulin deposits. This group of pauci-immune small vessel vasculitis was found to be closely associated with ANCA by serology. However, some patients have ANCA-negative. ANCA associate vasculitis[103-107]. Also, not all patients with ANCA-positive vasculitis have pauci-immune disease. As discussed by Hogan et al.[109-110] and by Hoffman and Langford[111] for some purpose it might be more appropriate to use the broad category of ANCA-associated vasculitis and to try to give a more specific syndromatic diagnosis (ie. Wegener´s granulomatosis, microscopic polyangiitis, or Churg-Strauss syndrome) to classify patient management, PR3 ANCAs and MPO ANCAS are sensitive and specific markers for the idiopathic paucimmune small-vessel vasculitides and are each associated with particular clinical and histopathology[112].

Is the pathogenesis of CSS different in patients who are persistently negative for ANCAs. The data from the study by Sinico et al.[113] suggest that small-vessel vasculitis is generally absent in these ANCA-negative patients and that tissue infiltration by eosinophils is more prominent.

Serological and radiological test lack the sensitivity and specificity to be employed in isolation for disease assessment[103] for this reason the current standard for disease assessment are clinical tools which integrate a large amount of information[103].

Laboratory findings

Laboratory screening tests are always required in patients with small vessel vasculitis, (cutaneous necrotizing vasculitis) both to confirm the diagnosis and to determine the extent of systemic vasculitis, or the existence of underlying associated diseases. The necessary laboratory evaluations include histopathologic and occasionally immunofluorescent and imunophenotypical microscopic studies, blood tests, and urinalysis. The next step should be the evaluation of the systemic involvement of the patient. Complete history,

physical examination, and laboratory screening are mandatory. Moreover, the identification of possible causative agents is a relevant part of patient evaluation. Three categories of etiologic factors should be considered: drugs, infectious agents, or diseases associated with increased levels of circulating immune-complexes[65, 97, 99].

Examples of implicated drugs induce vasculitis are aspirin, penicillin, thiazides, and sulfonamides Examples of infective agents more often associated with necrotizing venulitis are hepatitis B, streptococcal agents, and mycobacterium tuberculosis. Diseases associated with immune-complex formation include malignancies, connective tissue diseases, inflammatory bowel disease, and chronic active hepatitis[65, 97]. The patient should also be evaluated for cryoglobulinemia and macroglobulinemia, collagen vascular disease, Sjogren's syndrome, lymphoma, multiple myeloma, leukemias, and solid tumors. One should realize, however, that absolute proof of etiology for a given agent is usually difficult. A large number of the above-mentioned conditions have been implicated as causes of necrotizing venulitis by temporal association, but only a few have been supported by direct evidence (ie, antigen demonstration in circulating immune complexes and in dermal (blood vessels)[65, 97, 99].

Anti-neutrophil cytoplasmic antibodies (ANCA) are a heterogeneous group of autoantibodies with a broad spectrum of clinically associated diseases. ANCA testing has been established as a useful tool for the diagnosis of small vessel vasculitides, especially of 'ANCA-associated vasculitides' (AAV), such as Wegener's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome, in which circulating ANCA are commonly found. Within the last 20 years these antibodies were subject of intensive studies and a growing body of evidence arose for a distinct role of ANCA in the pathogenesis of the AAV. Our current concept of whether ANCA directly or indirectly contribute to vascular damage (ANCA-cytokine-sequence-theory) was mainly developed from in vitro studies and is supported by data from clinical investigations as well as animal models. Recently a direct causal link between ANCA and the development of glomerulonephritis and vasculitis has been demonstrated. We now know that a

passive transfer of ANCA is sufficient to induce disease, but it remains to be discovered how the autoantibodies to neutrophil antigens might triggered[3-14, 16, 18, 19, 103-111].

The ANCA can add to it a value to the specificity to the criteria diagnoses and when combining them with the clinic and histopathologic criteria, can establish a specific diagnose in agreement to the criteria of Chapel Hill of 1994. When analyzing and observing the clinical phantom of the of small vessels vasculitis not associated to ANCA, almost they do not jeopardize the kidneys and the lungs. On the contrary, the ones associated to ANCA and the systemic vasculitis related to hepatitis C, jeopardize the kidneys and the lungs. When discriminating if the antibodies are P and C - ANCA, the prevalence of these antibodies jeopardize the kidneys at the beginning, during the course and evolution of the disease, or in the relapses of those patients with both anti-PR3 and anti-MPO positives with vasculitis, when studying them globally, the prevalence oscillates between 75% to 90% according to the study of Franssen and cols.[114, 115]; but if the involvement is in the respiratory tree,, anti-PR3 are detected more frequent than anti-MPO, according to the studies of Falk et al.[116] and Franssen et al.[114, 115]. But if the skin and nervous system are involvement, anti-MPO are more frequent than anti-PR3.

One of the most interesting questions when studying this group of patients, it is to analyze the utility to follow up patients with ANCA associated vasculitis. One of the first studies was made by Tervaert et al.[117] in 1989 when studying the relationship between active Wegener´s granulomatosis and the titles of anti PR3. The authors observed that titles related to activity and the power to "forecast" relapses on the population studied. One year later, the same authors began to treat patients with Wegener´s granulomatosis based on the elevation of anti-PR3 and thus "prevent relapse"[118].

Predictors of relapse

Relapses in the vasculitis of small vessels are observed specially in AAV and complement-related vasculitis.

Differences in the pathomechanism may explain some of the variation in diseases characteristics. Are there specific features in that organ that are critical to the relapse, or are they simply organs where sub-clinical disease can evolve into clinically overt manifestations at an earlier stage into recognizable symptoms, signs, or serological evidence of active diseases. For example, it is easier to detect a recurrence of skin vasculitis, manifesting as a rash, than the presence of glomerulonephritis, which may only be found by careful testing of urine, assessment of renal function, and regular monitoring of blood pressure. Alternatively, some organs might be prone to flares due to a higher likelihood of infection such us nasal colonization with *Saureus*[105]. The pattern of organ involvement in a number of vasculitis is quite specific, even though in theory all vascular beds could be affected. Disease relapse occurred in 42% of patients who achieve a remission, which was within the range of previously reported relapse rated of 11% to 57%. A European study previously reported that patients with Wegener's granulomatosis were more likely to relapse than patients with microscopic polyangiitis[105]. Hogan et al.[109, 110] demonstrate the risk for relapse was increased in the presence of anti- PR3 antibodies and lung or upper airway involvement, whereas specific disease diagnosis (W.G vs P.A.M) did not independently predict relapse. Concluded that this difference in the predictive values of specific disease diagnosis possibly reflected differences in the relative frequency of the two diseases between Europe and the southeastern United States. An association between lung involvement and relapse was informed by Kyndt et al.[119] in 1999 and by Koldingsnes and Nossent[120] in 2003. Previous reports did not specifically identify upper respiratory tract diseases as a risk factor for relapse; however, upper airway colonization with Saureus was associated with a higher relapse rate in patients with W.G, according to the studies of Stegeman et al.[121] and Popa et al.[122]. According to conclusions of Hogan et al. study[109, 110] female, black patients, or those with severe kidney disease, may be resistant to initial treatment more often than other patients with AAV. In a study related to outcome and prognostic factors during the course of primary Small-vessel vasculitis (P.S V.V) by Pavone et al.[123] in Parma (Italy) about 75 patients, 36 with

Wegener´s granulomatosis (GW), 23 with Churg-Strauss syndrome (CSS), and 16 with microscopic polyangiitis (MPA), the authors conclude that Gastrointestinal (GI) involvement was associated with an increased risk of relapse, mainly in the patient with CSS, whereas renal disease and peri-nuclear antineutrophyl cytoplasmic antibody positivity were correlated with a lower risk of re-lapse. The presence of nasal *Staphylococcus aureus* tended to increase the risk of relapse in CSS , but to decrease it in WG[123]. Older age, renal and hepatic involvement, erythrocyte sedimentation rate > 100 mm /h, and serum creatinine level > 1.5 mg/ dl were all related to higher risk of death in univariate analy-sis; however, only cerebral, hepatic involvement and serum creatinine level > 1.5 mg / dl were independ-ently correlated with an unfavorable prognosis for survival[123]. The risk of death associated with each of these indicators did not depend on the form of PSVV. The Pavone study suggests that in CSS, patient have an increased risk of relapse if there is gastrointestinal involvement, supporting the con-cept that some clinical feature can predict out-come[123-125].

Finally, relapse is an important outcome measure in patients with AAV. Although relapses are com-mon in these diseases, it remains unclear why these occur and whether they are influenced by exogenous or endogenous factor[111] a key to minimizing the con-sequences of relapse is early recognition through monitoring[111, 124, 125]. This is particularly essential to detect glomerulonephiritis that is often asymptomatic and can be rapidly progressive. It would be impor-tant in the future to identify factors that may distin-guish patients at risk of relapse or markers that reliably predicts the occurrence of relapse prior to organ injury[111, 124, 125].

Treatment

Therapy of cutaneous vasculitis depends on whether or not there is clinical and laboratory evi-dence of internal involvement, the severity of cuta-neous and systemic disease. The treatment of small vessel vasculitis, can be divided in three: Vasculitis non associated to ANCA that constitutes most of the cases in the spectrum of small vessels vasculitis; ANCA associated vasculitis and the systemic

vasculitis related to the hepatitis C virus. In this pa-per we are going to reviews only the treatment of vasculitis associated and not associated to ANCA.

Vasculitis non- associated to ANCA

When we are facing this kind of small vessels vasculitis, we must do the identification of the an-tigens that induces the diseases. When the anti-gen is eliminated the vasculitis can be cured; for this reason, the list mentioned above must be in-vestigated, such as medicaments, agents that simu-late hemotopoiesis, vaccines, food, and leucotrieno inhibitors, modifiers of biologic response, it is not to forget that some medicaments can induce ANCA, such as herbicides, insecticides and other petroleum derives[52, 56, 97].

Patients with acute cutaneous vasculitis in whom there is an identifiable cause, such as a drug, are treated symptomatically in addition to removing the presumed causative agent. Similarly, patients with Henoch-Schönlein purpura usually have self-limiting disease and are often not given specific treatment. Sympto-matic measures include rest, elevation, gradient sup-port stockings, and antihistamines. Glucocorticoides (GS) have been used in patients with renal insuffi-ciency, specially the elderly. GS have been used in patients with severe gastrointestinal manifestations, such as abdominal pain; however, their use in the treat-ment of abdominal due to HSP is still controversial[126]. The management of HSP nephritis is also highly con-troversial. Patients with severe nephritis have been treated in many ways, including oral glucocorticoids or pulse therapy, alone or in combination with immu-nosuppressive agents such as cyclophosphamide, aza-thioprine, or cyclosporine[126].

The challenge is to treat the patient who has chronic cutaneous vasculitis in whom there is no easily identified cause and who does not have sig-nificant systemic involvement. There is often a ques-tion regarding the need for therapy, since these patients do not have life-threatening disease. How-ever, many of the patients have disease that alters their ability to function normally. Patients may de-velop small ulcerations that can become secondar-ily infected or may be painful. Patients may not leave their homes because of psychic distress that the presence of purpura causes. Last, patients with urti-

carial vasculitis complain of itching and burning of their lesions that may result in sleep disturbance.

Antihistamines have often been suggested as a first line of therapy, based on the observation that histamine may enhance the deposition of immune complexes in the vessel walls. Patients with palpable purpura rarely benefit from these agents. However, they are the corner stone of therapy for patients with urticarial vasculitis. Also, non-sedating agents may be used in the morning such as loratadine combined with a sedating antihistaminic prior to go to bed such as hydroxizine or doxepin.

For mild cutaneous involvement, 0,6 mg of colchicine two or three times daily may be helpful. Azathioprine 100-200 mg a day may be used alone or as a glucocorticoid sparing agent[65] other immunosuppressive agents, including methotrexate, 10-25 mg weekly, and cyclosporine, 3-5 mg/kg per day, may be given in acute progressive disease or systemic involvement, or as steroid sparing agents[65]. In severe disease, either extensive cutaneous involvement or severe systemic involvement, oral prednisone 60 mg q.d. with cyclophosphamide 100 mg. q.d is effective. A gradual taper of the prednisone should be undertaken to avoid disease rebound[65].

Dapsone

4,4' Diaminodiphenylsufone (DOS) is an interesting therapeutic choice for several forms of vasculitis, such as leukocytoclastic vasculitis and the urticarial vasculitis syndrome. The anti-inflammatory action of dapsone is linked to its strong quenching effect and the significant inhibition of the leukocyte respiratory burst pathway by direct suppression of the generation of toxic oxygen intermediates. It seems established that besides selectively inhibiting polymorphonuclear cytotoxicity and chemotaxis, dapsone can also inhibit mitogen-stimulated lymphocyte transformation and improve immune complex-mediated diseases[127]. The therapeutic potential of dapsone in vasculitis has been investigated as a monotherapy, and in combination with prednisone to allow the administration of lower doses of both drugs, thus minimizing side effects and the risk of relapse after treatment discontinuation. A daily dosage of 50 a 100 mg seems to provide a good anti-inflammatory effects. Dapsone 100 mg daily is

effective in many patients with involvement restricted to the skin, and in erythema elevatum diutinum[65].

Antimalarial drugs

The most widely used antimalarial drugs in dermatology include chloroquine and hydroxychloroquine. They are 4-aminoquinolones, synthetic derivatives of quinine, a naturally occurring alkaloid extracted from the bark of the South American cinchona tree. The effectiveness of antimalarials in small-vessel cutaneous vasculitis is controversial and reports are anecdotal. A larger controlled study should be performed to assess the successful indications of antimalarial therapy in cutaneous vasculitis[65, 127].

Corticosteroids

Corticosteroids (CS) are the most widely used drugs for vasculitis. They can be administered alone or in combination with cytotoxic agents depending on the severity of the disease. Corticosteroids are very active as both anti-inflammatory and immunosuppressive agents. Relevant side effects can derive from long-term therapy, so combined use of CS-sparing drugs can be useful in disorders characterized by a chronic course. Corticosteroids have variable effects on cutaneous vasculitis[128]. They are able to improve the symptoms related to inflammation, including pain and swelling. Prednisone is usually given at the starting dose of 30 to 60 mg/ day, which is maintained until symptom relief occurs[128]. On the basis of clinical response and side effects the daily dosage can be reduced weekly until a lower maintenance dose is able to control the symptoms. Suspension of the treatment is possible, but relapses are frequent[128].

ANCA associated vasculitis

Steroids and immunosuppressants are indicated to treat small vessel vasculitis. However, the therapeutic strategy is different from one disease to another. Treatment choice should be adapted to the predictable outcome, severity, pathogenic mechanisms and patient's general condition. In WG, Churg Strauss syndrome, and microscopic polyangiitis we have demonstrated that immunosuppressants should not be systematically prescribed. Immunosuppressants should be only prescribed in the most severe patients, when factors of poor prognosis are present. In Wegener's

granulomatosis, immunosuppressants should be sys-tematically prescribed together with steroids. The optimal treatment duration is usually of 12 months, or more for microscopic polyangeitis, and Churg-Strauss syndrome. A more prolonged treatment is mandatory in Wegener's granulomatosis, at least 18 months[128-134]. The new therapeutic strategies comprise also new immunosuppressants and new immuno-modulating agents which could replace or be associ-ated to the "older drugs"[129, 131, 134].

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