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Vasculitis: What Have We Learned in the Last 50 Years?

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ABSTRACT. Realizing in the fall of 2021 that I had started medical school exactly 50 years ago, on September 7, 1971, I thought that it would be interesting for the 2022 Dunlop-Dottridge Lecture to briefly review what we knew about vasculitis prior to 1971 and then reflect on what we have learned since.

The History of Vasculitis Prior to 1971

The field of vasculitis is relatively young, as the first case of systemic vasculitis was reported only in 1866 by the famous German internist Adolf Kussmaul and his colleague, the pathologist Rudolf Maier.[1] Their patient, a 27-year-old man, presented with fever, severe myalgias, abdominal pain, and mononeuritis multiplex; he died 6 weeks after the onset of his symptoms. At the autopsy, he was found to have peculiar nodular thickening of the branches of the coronary arteries as well as of the arteries of his abdominal viscera and muscles. The authors named this new disease "periarteritis nodosa."[2]

As reported in a previous review, what would eventually be known as Henoch-Schönlein purpura had been described as early as 1801 by William Heberden.[3] In 1837, Schönlein described the association of arthralgia and arthritis with purpura; in 1874, his former student, Eduard Henoch, reported children with purpura, joint pain, abdominal pain, and bloody diarrhea, emphasizing that the disease could also affect internal organs.

Temporal arteritis was first recognized by Jonathan Hutchison in 1890 and he distinguished this disease from atherosclerosis. Years later, in 1932, Bayard Horton, who is credited for obtaining the first temporal artery biopsy (TAB) in a living patient, described the typical manifestations of the disease so well that, for many decades, giant cell arteritis (GCA) was called Horton disease.[3]

In 1908, the Japanese ophthalmologist Makito Takayasu reported the case of a young woman presenting with a peculiar retinopathy characterized by anastomosis of arterioles and veins in a wreath-like distribution.[4] There was no mention in his paper that his patient had pulseless disease and, as emphasized by Matteson in his review, there is a general consensus that Takayasu did not recognize the disease that was to be named after him by his colleagues in 1941 in recognition of his brilliant career.[3]

In 1931, Hans Klinger, a college roommate of Friedrich Wegener actually reported what would be known as Wegener granulomatosis (WG). To be fair to Wegener, Klinger thought that his patients had polyarteritis nodosa (PAN), whereas Wegener recognized the uniqueness of the cases that he reported in 1936, noting in particular the prominent nasal lesions, glomerulonephritis (GN), as well as the granulomatous inflammation and vasculitis seen on biopsy.[3]

While a number of authors had described cases of patients with PAN, asthma, and eosinophilia, Jacob Churg and Lotte Strauss reported in 1951 a series of 13 patients in which they carefully described the clinical and pathologic manifestations of the disease that would be named after them for a number of years.[5]

In my opinion, perhaps the most impressive of these giants is Tomisaku Kawasaki. Not only did he recognize in 1961 the first case of a peculiar new syndrome characterized by fever, lymphadenopathy, and mucocutaneous lesions in a child but he waited to report it until he carefully collected 50 similar cases over the following 6 years.[6] In 1974, Kawasaki and his colleagues described the full spectrum of the disease in the 6000 cases seen in Japan by then.[7]

The First Giant in the Vasculitis Field After 1971

By the early '70s, a little more than 250 cases of WG had been reported in the literature. The prognosis of the disease was abysmal, with the mean survival being less than 6 months. In 1973, Anthony Fauci and Sheldon Wolff reported on 18 patients with WG, 15 of whom were treated with cyclophosphamide (CYC).[8] Two died of their disease, one died of unrelated causes, and the other 12 went into remission for up to 5 years.[8] This dramatic response to CYC represented the first important advance in the management of this disease and eventually of other vasculitides.

In 1978, Fauci et al went on to write in the *Annals of Internal Medicine* a review that would be considered for many years as the classic paper on vasculitis.[9] In the classification that Fauci et al proposed, PAN and allergic granulomatosis (Churg-Strauss syndrome [CSS]) were considered part of the same spectrum. Cryoglobulinemic vasculitis (CV) was thought to be "essential" in the majority of instances, as the relationship of this condition with non-A, non-B hepatitis had not yet been recognized. Today, we know that 70–90% of CV cases are related to the hepatitis C virus and with the discovery in the past 20 years of direct antiviral agents capable of permanently eradicating the virus in > 90% of cases, CV is now becoming a much rarer condition.

In his paper, Fauci et al provided more details about the clinical manifestations of PAN.[9] The association back then with

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hepatitis B in up to 50% of cases was already well recognized. However, he reported that 30% of patients had GN, suggesting that these patients likely had microscopic polyangiitis (MPA), and that it was also likely coronary arteritis seen particularly in children may have been cases of Kawasaki disease.[9]

One would have to wait until 2010, when Christian Pagnoux and his French colleagues described the clinical features and outcomes of 348 patients with classic PAN and hepatitis B virus (HBV)-associated PAN seen between 1963 and 2005.[10] The originality of this paper lies in the fact that patients positive for antineutrophil cytoplasmic antibody (ANCA) were excluded, as were those with concomitant HIV, hepatitis C, cryoglobulinemia, or connective tissue diseases. Pagnoux et al also emphasized the steady decrease in the incidence of HBV-associated PAN after the late '90s, likely as a result of vaccination programs. Currently, HBV-associated PAN is responsible for < 5% of PAN cases.

The Discovery of ANCA and the Crucial Contributions From the Chapel Hill Group

In the '80s, many did not realize the importance of a letter submitted to *BMJ* in 1982 by Davies and his colleagues from Australia, in which they described 8 patients presenting with biopsy-proven necrotizing crescentic GN.[11] What was peculiar about these cases was that all the patients had in their serum a "factor that stained the cytoplasm of neutrophil leucocytes by indirect immunofluorescence," which had not been seen in > 5000 sera examined by the same investigators in the previous 5 years.[11] Three years later, nephrologists from Denmark and the Netherlands reported similar autoantibodies in 25 of 27 serum samples from patients with active WG and 4 of 32 samples from patients without active disease.[12] None were detected in 500 sera from healthy controls and various disease controls. In 1988, Falk and Jennette from Chapel Hill described 2 patterns on immunofluorescence: one was peripheral, which corresponded to reactivity to myeloperoxidase (MPO) on ELISA; and the other was cytoplasmic, with no reactivity to MPO on ELISA.[13] A year later, Niles and colleagues reported that a novel serine proteinase was the antigen responsible for the diffuse cytoplasmic pattern seen on immunofluorescence.[14] These new discoveries led Jennette et al to convene an International Consensus Conference in Chapel Hill in 1994, where participants would reach consensus on names for the most common vasculitic entities and provide a specific definition for each.[15] This nomenclature would eventually be refined in 2012, with eponyms for a number of the diseases being abandoned and replaced by more descriptive terms.[16]

Ever since the discovery of ANCA, an important question was whether these autoantibodies simply represented disease markers or if they had a pathogenic role. A number of very elegant studies conducted by Xiao and colleagues from Chapel Hill would provide very strong evidence that these antibodies are in fact pathogenic.[17,18,19]

The methodology was relatively simple. The investigators immunized mice lacking MPO ($MPO^{-/-}$) with purified mouse MPO or bovine serum albumin (BSA) and then administered suspensions of splenocytes from the immunized and control mice to $RAG2^{-/-}$ mice (which lack both B and T cells).

Within 2 weeks, they observed a dramatic rise in the blood urea nitrogen and creatinine in the mice who received the higher concentrations of splenocytes from the mice immunized with MPO but not in those immunized with BSA. On pathology, mice who received the higher concentrations of anti-MPO splenocytes developed severe necrotizing, crescentic GN, and many also had granulomatous inflammation and systemic necrotizing vasculitis in lymph nodes and lungs. Perhaps even more interesting is that injecting only MPO-ANCA rather than splenocytes (which contain B and T cells) led to similar results, demonstrating that these changes are independent of T cells and B cells.[17]

In a second paper, Xiao et al provided evidence that neutrophils are essential for MPO-ANCA to produce these changes, as mice pretreated with a neutrophil-depleting antibody did not develop GN.[18] In a third study, they demonstrated the crucial role of complement in the development of GN, as mice depleted of complement by prior treatment with Cobra venom factor did not develop GN when injected with MPO-ANCA.[19] In addition, using $C5^{-/-}$, $C4^{-/-}$, and factor $B^{-/-}$ mice, they observed that $C4^{-/-}$ mice developed the disease but not $C5^{-/-}$ nor factor $B^{-/-}$ mice, confirming the important role of C5a activated by the alternative complement pathway in the pathophysiology of the disease.

So, there it was: less than 20 years after the discovery of ANCA, we had solid evidence that ANCA, neutrophils, and complement products—and in particular, C5a—had a crucial role to play in the development of MPO-ANCA–associated vasculitis. What we are still struggling with to this day is to understand why some people develop ANCA and others do not, and why it is that some patients have ANCA in their circulation, sometimes in very high titers, without apparent clinical consequence.

A True Visionary

While the world was getting excited with the discovery of ANCA, a visionary, Prof. Loic Guillevin, was creating the French Vasculitis Study Group (FVSG) in 1980. Under his leadership, France became the first country in the world to conduct randomized multicenter controlled trials in patients with vasculitis.[20] The influence of Fauci's classification can be felt as the first trials done by the group assessed the role of plasma exchange in patients with PAN or CSS and concluded that it offered no advantage to standard therapy. In 1996, the group published the famous Five Factor Score (FFS), demonstrating that the prognosis of PAN and CSS varies very significantly depending on whether or not patients have cardiac, renal, gastrointestinal, or central nervous system involvement.[21] Using this prognostic tool, the group demonstrated later on that patients with PAN and CSS with a good prognosis (defined as having a FFS = 0) could be treated with corticosteroids alone in up to 40% and 60% of cases, respectively, with a good outcome.[20]

The Rest of Europe Wakes Up

In 1995, Niels Rasmussen from Denmark and David Jayne from the UK created the European Vasculitis Society (EUVAS). This

group was to publish a number of landmark studies, including CYCAZAREM, which demonstrated that maintenance therapy with azathioprine (AZA) in patients with ANCA-associated vasculitis (AAV) was as effective as CYC in maintaining disease remission.[22] This was a very important study, as until then, it was not uncommon for patients to be treated with CYC for years, with the consequence that many would develop serious side effects, including hemorrhagic cystitis and bladder cancer.[23] NORAM showed that methotrexate (MTX) was as effective as CYC in inducing remission in patients with granulomatosis with polyangiitis (GPA) without major organ involvement, but the rate of relapse was greater with MTX.[24,25] WEGENT, a study from the FVSG, demonstrated that MTX and AZA were equivalent in maintaining remission; however, that study dispelled the generally held belief that MTX may be safer than AZA as more patients in the MTX group had to stop the medication because of adverse events as compared to patients in the AZA group.[26] IMPROVE showed that mycophenolate mofetil was less effective than AZA for maintaining remission in patients with AAV.[27] CYCLOPS taught us that daily oral vs intravenous (IV) pulse CYC had similar efficacy in inducing remission, but patients treated with IV pulses had a higher rate of relapse, particularly if they were proteinase 3–positive.[28] REMAIN demonstrated that maintenance therapy for 4 years with AZA was associated with a significantly lower risk of both minor and major relapses than in patients treated only for 2 years.[29]

North America Joins the Party

In 2003, Peter Merkel, who at the time was at Boston University, led the creation of the Vasculitis Clinical Research Consortium (VCRC) with colleagues from the Mayo Clinic, Cleveland Clinic, and Johns Hopkins in the United States, and Mount Sinai Hospital in Canada. The VCRC studied large cohorts of patients with GPA, MPA, eosinophilic GPA (EGPA), PAN, GCA, and Takayasu arteritis followed longitudinally for years, and for any researcher interested in testing novel hypotheses in these diseases, the VCRC currently has a repository of serum, DNA, and tissue samples unequaled in the world.

Canada followed suit in 2010, with Christian Pagnoux creating the Canadian Vasculitis Research Network (CanVasc), whose goal is to bring together rheumatologists, nephrologists, respirologists, and neurologists interested in clinical research in vasculitis from each major city in Canada. Among the achievements of CanVasc is the publication of recommendations for the diagnosis and management of AAV[30], which were recently revised.[31]

One of the first effects of North America making its presence felt in the field of clinical trials in vasculitis was the publication of the RAVE trial in 2010.[32] That study, which was accompanied in the same issue of the *New England Journal of Medicine* by a smaller study from EUVAS limited to patients with ANCA-associated renal vasculitis,[33] confirmed the noninferiority of rituximab (RTX) vs CYC in patients with new-onset disease, but it showed its superiority in patients with relapsing disease.

In 2014, the FVSG published a study that would have a huge effect on how we treat our patients with GPA. Named the MAINRITSAN 1 trial, it demonstrated that maintenance with RTX is associated with a significantly lower relapse rate than AZA.[34] MAINRITSAN 3 demonstrated that stopping RTX after 2 years was associated with a higher risk of both minor and major relapses than continuing this treatment for 4 years.[35]

PEXIVAS was the largest study ever published in the field of vasculitis and it was led by a Canadian, Michael Walsh, from McMaster University.[36] It included 704 patients in 95 centers from 16 countries and demonstrated that plasma exchange did not reduce the incidence of end-stage renal disease or death in patients with severe AAV. It also showed that patients did as well with a reduced-dose corticosteroid regimen than a standard-dose regimen, with the advantage of the former being associated with a lower rate of infections.

The ADVOCATE trial showed that combining avacopan, a C5a receptor antagonist to RTX, resulted in the same degree of remission at 6 months than conventional therapy and a higher rate of remission at 1 year, but with significantly less corticosteroids.[37] However, a recent trial from Japan published after ADVOCATE compared a reduced-dose vs high-dose steroid regimen in combination with RTX and showed a similar rate of remission at 6 months between the 2 treatment groups.[38] When one compares that study with ADVOCATE, disease severity as measured by the Birmingham Vasculitis Activity Score at entry was similar, as was the rate of remission at 6 months with the same amount of steroids in both groups, suggesting that a trial needs to be done comparing avacopan vs a reduced-dose regimen of corticosteroids.

What About Large-vessel Vasculitides?

In my opinion, the most important advances in large-vessel vasculitides (LVV) in the past 50 years have been in the use of imaging modalities for their diagnosis and the understanding of the pathophysiology of these diseases.

The role of ultrasound (US) of the temporal and axillary arteries was popularized by Wolfgang Schmidt et al, who were first to describe the halo sign.[39] As reported in a previous systematic review, the halo sign has good sensitivity and specificity when using TAB as the gold standard to make the diagnosis of GCA, but the main limitation of that modality is that it is operator-dependent.[40] Interestingly, the creation of fast-track clinics where patients are seen within 24–48 hours of referral for clinical assessment and US of their temporal and axillary arteries has led to a reduction in the incidence of blindness from GCA.[41,42]

An alternative to US is magnetic resonance imaging (MRI) of the scalp arteries.[43] It may be more sensitive than US and equally specific, but it is more costly and not as available as the latter.[40]

^{18}F-fluorodeoxyglucose positron emission tomography, especially when combined with computed tomography or MRI, is another modality that has been shown to be very sensitive and specific, particularly in the diagnosis of large-vessel involvement.[44] However, in keeping with all imaging modalities used in these diseases, its role in following patients with LVV remains unclear.

Major advances to our understanding of the pathophysiology of GCA were made particularly by Cornelia Weyand who,

interestingly, is the only investigator who was invited twice to deliver the Dunlop-Dottridge lecture (1999 and 2009).[45] Thanks to her work and that of her colleagues, we have learned much about the role of both innate and adaptive immunity, as well as some of the signaling pathways and key mediators involved in the pathogenesis of the disease.[46,47]

However, despite this increased knowledge, glucocorticoids (GCs), to this day, remain the mainstay of treatment of GCA. Tocilizumab is currently the only drug that has been approved for the treatment of that disease after the GIACTA trial demonstrated its efficacy as a steroid-sparing agent.[48]

Where Do We Go From Here?

In the CanVasc consensus guideline, Mendel and colleagues proposed a number of interesting questions to address in the field of AAVs.[31]

At the industry level, there are major efforts to find more targeted therapies for both AAV[49] and GCA.[50] I believe that the need is more urgent for the latter, as there are numerous potential targets in GCA that have not yet been exploited and a number of trials are currently going on assessing some of those.[50]

In conclusion, we have seen huge advances in the past 50 years in our understanding of the pathophysiology of vasculitides, their diagnosis, and especially their management. Diseases such as PAN and CV have become rarer, thanks to better preventive methods and treatments. Others, such as AAV, which used to be considered lethal, are now treated very effectively and result in fewer side effects as new protocols to minimize GCs have been designed. The future looks much brighter for patients affected with these diseases in 2022 than it did in 1971.

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