Review

Polyarteritis nodosa revisited: a review of historical approaches, subphenotypes and a research agenda

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ABSTRACT

Polyarteritis nodosa (PAN) is a rare form of primary systemic vasculitis with heterogeneous presentations, treatments and disease course. Historical approaches to classification and diagnostic terminology are reviewed. Since differentiation of PAN from microscopic polyangiitis (MPA) and other ANCA vasculitides by the Chapel Hill conference statements, and with hepatitis associated PAN defined as a secondary vasculitis, the phenotyping and subclassification of PAN has received little attention. Monogenic disorders similar to PAN have been described (familial Mediterranean fever, adenosine deaminase-2 deficiency), and cutaneous PAN and single organ vasculitis, discussed. The overlapping phenotypes between PAN and other primary vasculitic syndromes and subphenotypes within PAN are explored. This work will underpin development of newer treatment regimens and future genetic and related aetiologic studies.

Introduction

The term peri/polyarteritis nodosa has been used for more than 150 years as a diagnosis for patients with primary systemic vasculitis defined by the presence of a necrotising arteritis of muscular, 'medium sized' arteries with or without aneurysms. However, advances in clinical and laboratory phenotyping have led to specific syndromes, such as microscopic polyangiitis (MPA) being separated from an inclusive PAN categorisation. In parallel, there have been improvements in understanding of certain causes of PAN, with hepatitis B-related PAN defined as a 'Vasculitis Associated With Probable Etiology' (1), and the association of the monogenic disorder- Deficiency of Adenosine Deaminase 2 (DADA2) (2) with a PAN phenotype (Fig. 1).

However, the majority of PAN cases reflect a variety of phenotypes of unknown cause and lack a system of phenotypic subclassification. PAN can occur at any age with wide variability in organ involvement, although survival and recommended treatment strategies broadly reflect severity. We propose that subphenotypes within PAN having different clinical courses may be different diseases rather than a spectrum of the same disease. There is a need to better understand these subphenotypes to underpin further clinical and translational research and improve patient outcomes. This paper aims to assess the heterogeneity of the clinical spectrum of PAN and highlight differences between subphenotypes. After reviewing the historical evolution of the classification of PAN, approaches to diagnostic terminology, and the similarities and differences of subphenotypes will be considered. This will form the basis for a recommended research agenda, such as, further histopathological evaluation of specimens and autopsy materials and a genome wide association study in PAN.

Historical background

Rudolf Virchow proposed that vasculitis might occur in blood vessels and originate in the adventitia in a treatise on histopathology in 1847 (3, 4). In 1852, Rokitansky described mesenteric aneurysms in the branch points of arteries in an autopsy case of polyarteritis (5). Then Kussmaul and Maier introduced periarteritis to the literature with the autopsy report from a 27-year old tailor's journeyman (6).

"A peculiar mostly nodular thickening (periarteritis nodosa) of countless arteries and below the caliber of the liver artery and the major branches of the coronary arteries of the heart, principally in the bowel, stomach, kidneys,

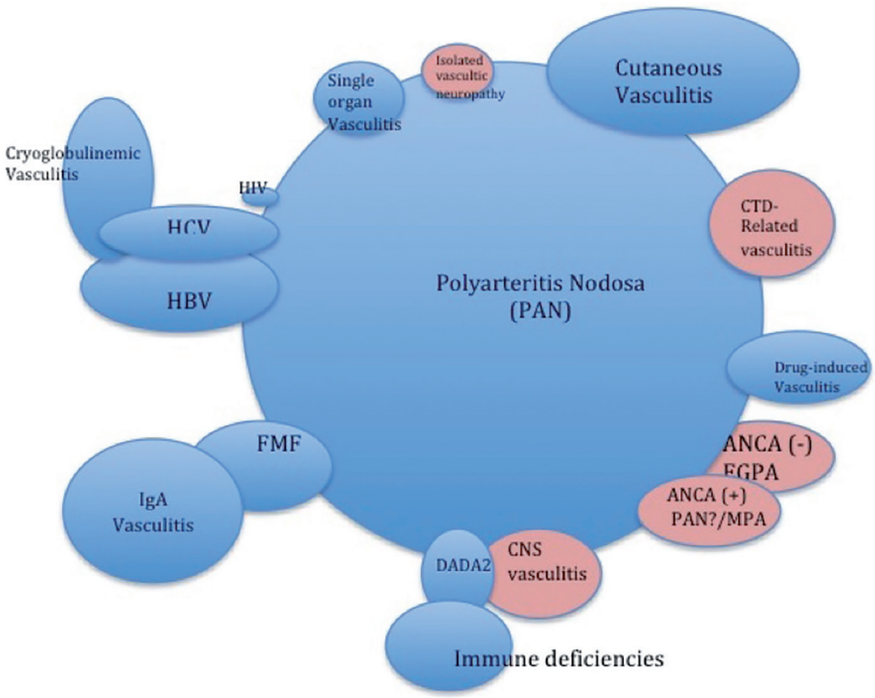

Fig. 1. Schema representing etiologic/genetic factors and subgroups of poliarteritis nodosa (PAN). Less studied/related subgroups are shown in purple.

spleen, heart and voluntary muscles, and, to a lesser extent, also in the liver, subcutaneous cell tissue, and in the bronchial and phrenic arteries."

Because inflammation was not confined to the adventitia, and primary changes were in the media, Dickson suggested the name, polyarteritis nodosa (PAN) (7). In the 1930s, approximately 150 cases of PAN were reported, 20 from the US and mostly from autopsies (8). They believed that any organ or combination of organs may be affected at any time in the course of the disease, and the resulting clinical manifestations may be bizarre in the extreme.

As the nosology and nomenclature of the systemic vasculitides became better defined, PAN became less frequently diagnosed. Many different forms of vasculitis were described. By the early 1950s, hypersensitivity vasculitis was distinguished from polyarteritis nodosa (9). Afterwards, necrotising vasculitis confined to the skin without systemic involvement – Cutaneous PAN – was described and distinguished from PAN in 1974. In the early 1970s, studies by several authors suggested chronic hepatitis B (HBV) infection could cause PAN (10).

In the 1980s immunoglobulin G (IgG) autoantibodies against extra-nuclear components of polymorphonuclear granulocytes were detected in serum samples from patients with Wegener's granulomatosis (now granulomatosis with polyangiitis) and called anti-neutrophil cytoplasm antibodies (ANCAs) (11). The association of ANCA with a pauci-immune vasculitis and evidence supporting the pathogenetic role of ANCA led to the definition of ANCA associated vasculitis as an aetiologic and phenotypically separate vasculitis subgroup.

Meetings and statements for classification/diagnostic criteria and nomenclature of vasculitides

The American College of Rheumatology (ACR) 1990 criteria for the classification of polyarteritis nodosa (12)

According to this classification system, patients with systemic vasculitis were classified as PAN if they had least three of 10 criteria: weight loss above 4kg, livedo reticularis, testicular pain/tenderness, myalgia, weakness or leg tenderness, mononeuropathy/polyneuropathy, diastolic blood pressure above 99 mmHg, elevated urea and creatinine, HBV, arteriographic abnormality, and biopsy of a small or medium-sized artery containing polymorphonuclear neutrophils.

This study described four PAN subsets according to clinical features at presentation:

- Positive arteriogram with abnormal AST or ALT;
- Positive arteriogram, male sex; normal AST and ALT;
- Positive artery biopsy and neuropathy; negative arteriogram;
- Neuropathy and weight loss >6.5 kg, negative arteriography and artery biopsy.

Because this classification system did not include a category for MPA, MPA cases would have been included in the PAN or hypersensitivity vasculitis cohorts.

Proposal of an international consensus conference on nomenclature of systemic vasculitides, Chapel Hill (CHCC) (13)

The name "polyarteritis nodosa-(PAN)," or alternatively, the name "classic PAN," is restricted to disease in which there is arteritis in medium-sized and small arteries without involvement of smaller or microscopic vessels.

The proposed distinguishing feature for PAN *versus* MPA, is the absence *versus* the presence of vasculitis in arterioles, venules, or capillaries. By this definition, involvement of "microscopic" vessels must be present in microscopic polyangiitis, although medium-sized or small arteries can also be involved. In contrast, PAN must have no involvement of "microscopic" vessels, including no glomerulonephritis. Additionally, mucocutaneous lymph node syndrome was mentioned as the defining feature that sets Kawasaki disease apart from PAN.

The European League Against Rheumatism (EULAR)/Paediatric Rheumatology European Society (PReS) endorsed consensus criteria for the classification of childhood vasculitides (14)

New updated classification scheme split the old term PAN into classical PAN, cutaneous PAN, MPA and HBV-related PAN.

To classify a child as having PAN required a biopsy showing a small and mid-size artery necrotising vasculitis or angiographic abnormalities (aneurysms or occlusions) in addition to at least two of the systemic features (skin involvement; systemic hypertension; mononeuropathy or polyneuropathy; abnormal urine analysis and/or impaired renal function, testicular pain or tenderness, signs or symptoms suggesting vasculitis of any other major organ system-gastrointestinal, cardiac, pulmonary, or central nervous system) are required. Magnetic resonance angiography (MRA) was an acceptable modality to assess angiographic abnormalities firstly. Conventional angiography is recommended when MRA is negative.

Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and PAN for epidemiological studies (15)

The underlying principles of this international study group (European Medicines Agency) were that each patient should be classified into a single category and that there should be a minimum number of unclassified patients. According to this algorithm a patient with symptoms and signs characteristics of PAN should be excluded from Wegener's granulomatosis, Churg-Strauss syndrome and MPA and have at least one of compatible findings with histologic proof of vasculitis or angiographic findings to diagnose as PAN for epidemiological studies. The presence of histologically proven small vessel vasculitis or glomerulonephritis differentiates MPA from PAN. ANCA was considered to be a feature of MPA and not PAN.

EULAR points to consider in the development of classification and diagnostic criteria in systemic vasculitis (16)

An expert consensus group evaluated the dissatisfaction with previous ACR and CHCC criteria/definition and outlined 17 statements to consider in the development of classification criteria and definitions in the systemic vasculitides. The percentage of committee dissatisfaction with the disease criteria or definition for PAN was 76% for ACR 1990 Criteria and 59% for CHCC definition. They mentioned the absence of ANCA has diagnostic value in suspected PAN.

They discussed the importance of abdominal angiography. Despite the absence of evidence, the risks of formal angiography encouraged increased use of digital subtraction angiography and MRA as alternatives (Fig. 2).

Due to the evidence to suggest that HBV and HCV viruses induce direct vessel damage via immune complex formation in PAN and cryoglobulinaemic vasculitis, they stated that the names of viruses should be reflected in their definitions and names.

They subcategorised vasculitis into primary and secondary forms. Primary entities could move into the secondary category if aetiologies were discovered. Secondary vasculitis included vasculitis due to infection, drugs, malignancy and connective tissue diseases.

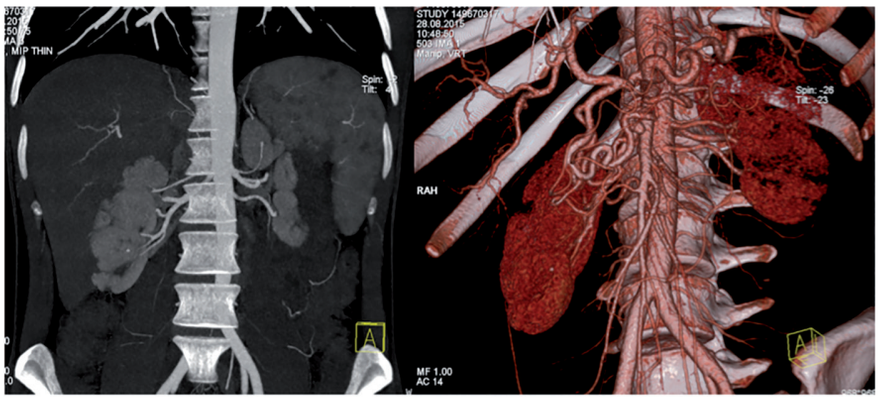

Fig. 2. MR Angiography of a patient with PAN (Courtesy of Hazirolan T, Professor in Hacettepe University Department of Radiology, Ankara-Turkey) (CT Coronal MIP image (**A**), volume rendered image (**B**). There is a microaneurysm at the lower parts of right kidney. And there are multiple cortical loss areas at both kidneys.

2012 revised International CHCC Nomenclature of Vasculitides (1)

PAN was defined as 'necrotising arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with ANCAs with a more clear dissociation from MPA with glomerulonephritis and ANCA positivity'. This nosology also brought new entities for vasculitides classification which can involve medium vessels, including single organ vasculitis, vasculitis associated with systemic disease, and vasculitis associated with probable aetiology.

Subgroups of PAN; subphenotypes or distinct diseases?

Virus-associated PAN

HBV, HCV, and Human immunodeficiency virus (HIV) have been associated with PAN (17-20). However, the prevalence of HBV-PAN has decreased as a result of increased HBV vaccination and improvements in blood banking. The coexistence of HCV and PAN-like vasculitis in medium-sized vessels has been highlighted in a few reports. HIV-associated PAN is thought to be the most common form of HIV-associated vasculitis (20).

In the comparison of 123 HBV-associated PAN with 225 non-HBV associated PAN, the HBV-associated group had higher disease activity, lower relapse risk, and had microaneurysms in mesenteric but not in renal arteries (18). Cutaneous manifestations seem to be more common in HCV-PAN and predominated in older females. In HIV-associated PAN, commonly involved organs were primarily skin with peripheral nerve, skeletal muscle, central nervous system, lung, gastrointestinal tract, and kidney involvement. (20).

There are major differences between viral-induced PAN. HBV-related PAN being the most severe and HIV-related PAN being the mildest form, relapses are most frequent in HCV-related and least frequent in HIV-related PAN. For

HCV-related PAN, the reported duration of the viral infection prior to PAN onset was approximately 20 years, but for HBV-related PAN it was usually less than a year. HIV- and HCV-related PAN do not bear a specific correlation to viral load.

The pathological course of HBV-related PAN is thought to be a 'type III' reaction where immune complexes precipitate and are trapped in vessel walls causing vascular injury (21). HBs Antigen and anti-HBs antibody immune complexes have been demonstrated in the vascular lesions. The presence of large masses of HbsAg immune complexes in recent vascular lesions, with lesser amounts in healing lesions and their absence in healed lesion points towards a primary role played by the immune complexes in the pathogenesis of the vascular lesions. When the virus is eliminated, this generally results in complete remission of the disease without occurrence of relapses and in prevention of long-term hepatic complications (17). Conversely, HBV vaccination might be a triggering factor for vasculitis in individuals with a genetic predisposition (22).

In the EULAR/PReS consensus document HBV-associated PAN and non-hepatitis PAN are considered as two completely separate conditions (14). If clinical features, prognosis and response to therapy differ, this decision seems logical (23). Similarly, ln the 2012 Chapel Hill nomenclature, HBV-related PAN was described as a separate entity 'vasculitis associated with probable cause', emphasising the role of infection (1). This dissociation could be done also for other HCV and HIV-related PAN. However, there is no clear answer to the question as to why only a small number of patients with these infections develop PAN.

Monogenic diseases and monogenic diseases-related PAN

Familial Mediterranean fever (FMF) is the most prevalent type of periodic fever. Among the vasculitic disorders reported to be associated with FMF, IgA vasculitis, and PAN are most frequent, possibly followed by protracted febrile myalgia (PFM) (24). Actually, the association of PAN with FMF was first noted in 1965, before the discovery of MEFV gene link of FMF in 1997 (25, 26).

Patients with PAN and FMF tend to be younger, compared to classic PAN patients (27). Peri-renal haematoma is a distinctive feature in FMF-PAN since about 50% of patients develop this manifestation prior to or at diagnosis. They frequently suffer from severe myalgia raising suspicion in PFM. Survival was better in FMF-PAN than expected for other classic PAN.

FMF may predispose to the development of vasculitis. Indeed, as suggested by some authors, IgA vasculitis and PAN associated with FMF may actually be features of this disease rather than separate entities (24, 27).

DADA2 is a recently identified autoinflammatory diseases (28, 29). It is due to autosomal recessive deleterious mutations in Cat Eye Syndrome Chromosome Region 1 (CECR1) gene, encoding for adenosine deaminase 2 (ADA2). DADA2 is mainly characterised by early-onset polyarteritis, haemorrhagic and ischaemic strokes and hypogammaglobulinaemia (2). Additionally, hepatosplenomegaly, and mild immunodeficiencies were seen in the disease course.

In many patients not only the clinical picture but also the histopathologic features are undistinguishable from those of PAN. Skin biopsy has revealed a non-granulomatous, necrotising vasculitis of small and medium-sized vessels, with the same histopathologic features of PAN. These patients meet classification and diagnostic criteria for both adult and childhood PAN. DADA2 is included in the medium-sized vessels vasculitis, even if it can affect arteries of any size. Association with DADA2 identifies the vasculitis as having a genetic basis, and it has been proposed to group this disease in the 'Vasculitis with a probable cause' according to the CHCC (2).

Vasculitis associated with systemic disease

Vasculitis associated with systemic disease generally have a prefix specifying the systemic disease (*e.g.*, rheumatoid vasculitis, lupus (SLE) vasculitis, etc.) (1). Rheumatoid vasculitis is now recognised to primarily affect small to medium-sized blood vessels, and is highly heterogeneous in its clinical presentation (30). Cutaneous vasculitis and vasculitic neuropathy remain the most common features followed by scleritis and pericarditis. Rheumatoid vasculitis shares many features with PAN, albeit without the development of microaneurysms. Histopathologic examination reveals mononuclear or neutrophilic infiltration of the vessel walls in association with features of vessel wall destruction (necrosis, leukocytoclasis and disruption of the elastic laminae). Necrotising vasculitis of medium-sized vessels resembling PAN can occur in Sjögren's syndrome, when patients develop a necrotising vasculitis of medium-sized arteries that resembles that found in PAN (31).

Even though, connective tissue disease related PAN is now in a different category of PAN following the 2012 CHCC statement, there can be difficulties in differentiating between two primary inflammatory processes occurring in the same patient. Indeed, arthritis and polymyalgia can be a presenting feature of arteritis. Small patient numbers have limited further differentiation of these subgroups. Thus this concept is colored as purple in the schema (Fig. 1).

Cutaneous PAN

Cutaneous polyarteritis nodosa (cPAN) is a variant of PAN that is limited primarily to the skin (Fig. 3). It may reflect underlying disease, infection, or medication use such as minocycline (32). A relationship of cPAN with inflammatory bowel disease is also described (33).

The extra-cutaneous manifestations of peripheral neuropathy and myalgia in CPAN occur only adjacent to the cutaneous lesions, while they are more widespread systemic PAN (32). While systemic PAN frequently is first evident with the cutaneous findings of cPAN, multi-organ involvement in systemic PAN is pervasive, particularly in the kidneys, heart, and liver. Progression from cPAN to systemic PAN appears to be rare. Only 1 of 41 patients with cPAN evolved into systemic PAN dur-

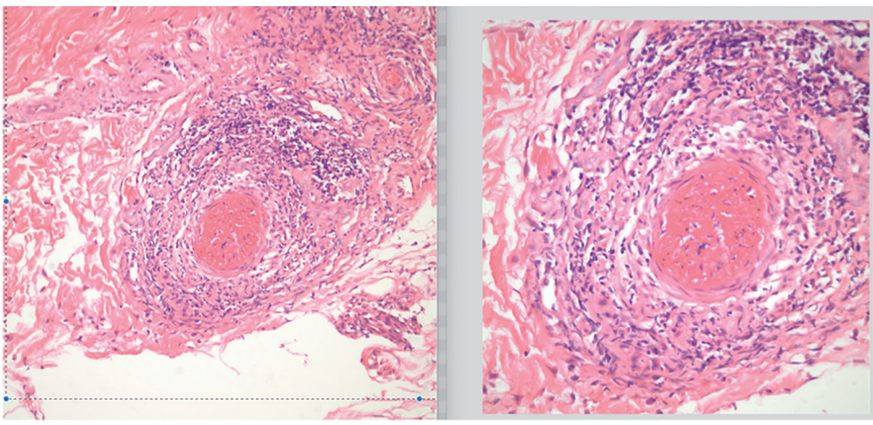

Fig. 3. Histopathology of a patient with cutaneous PAN (Courtesy of Arzu Saglam, Assoc Professor in Hacettepe University, Department of Pathology, Ankara-Turkey).
A: Low power microscopy showing fibrinoid necrosis and perivascular inflammatory reaction.
B: High power view where karyorrhexis can be discerned.

ing the disease course in Mayo Clinic cohort (34). Analogous findings have been reported by two other studies (2 of 20 and 0 of 79 patients, respectively) (33, 35).

To explore possible similarities and differences; a Japanese group compared skin biopsies from seven systemic PAN patients with three cPAN patients and three with superficial venous thrombosis (36). They showed elevated moesin mRNA levels in the skin of patients with systemic PAN, based on real time RT-PCR compared to control groups. Moesin is an intracellular protein that links the cell membrane and cytoskeleton. Furthermore, the moesin mRNA copy numbers were correlated with disease activity measured by the Birmingham Vasculitis Activity Score (BVAS).

Single-organ vasculitis (SOV) and medium vessel involvement

There are numerous reports of isolated PAN affecting a single organ such as the testis, appendix, and gall bladder with no systemic involvement (37-39). Most cases were discovered incidentally when an organ was surgically removed for unexplained symptoms or by misdiagnosis.

The natural history of isolated arteritis of a single organ is not known (39). Although histology of testicular PAN is similar in isolated and systemic forms, the existence of infarcts in the affected testis correlates more with systemic PAN (40).

Vasculitis limited to the gastro-intestinal tract can rarely be observed as a form of SOV (41, 42). Histopathologic and angiographic findings of necrotising vasculitis limited to the GI system cannot be distinguished from PAN. There are scarce data regarding vasculitis limited to the GI tract. In one report, 6 of 23 patients with isolated vasculitis of GI tract progressed to systemic PAN during follow-up (43). In another, there was no progression to PAN among the patients with GI vasculitis (34). PAN localised to the calf muscles with no other signs or symptoms of more widespread involvement is very rare but there are few case reports published (44).

A major dilemma is whether single organ PAN is really an isolated form of the disease or just the presenting symptom of a multisystem vasculitis, for which aggressive immunosuppressive treatment is indicated.

Organ specific (primary CNS, nerves)

Vasculitis restricted to the peripheral nervous system (PNS), referred to as non-systemic vasculitic neuropathy (NSVN), has been described in many reports since 1985. Classification is complicated by the occurrence of vasculitic neuropathies in many systemic vasculitides affecting small-to-medium-sized vessels and such clinical variants as non-systemic skin/nerve vasculitis and diabetic/non-diabetic lumbosacral radiculoplexus neuropathy (45).

NSVN is identical to but less severe than systemic vasculitis-associated neuropathies (SVNs). Without a specific clinical/laboratory marker, the condition depends on nerve biopsy for diagnosis. Biopsies showing necrotising vasculitis are about 50% sensitive, mandating reliance on "suspicious" changes in many patients. Vasculitic lesions predominate in smaller epineurial vessels and are milder than those in SVNs. The disorder is often accompanied by subclinical involvement of adjacent muscles and skin. Many nosologic, pathogenic, diagnostic, and therapeutic questions remain unanswered. ANCA is positive in some cases, without other organ features of an ANCA associated vasculitis, suggesting that this subgroup has the same underlying cause as the ANCA group.

Primary angiitis of central nervous system (PACNS)

Vasculitis of the central nervous system can be regarded as a SOV-primary CNS vasculitis when there are no features of a systemic vasculitis (1). A number of phenotypes have been described affecting different structures and vessel sizes within the brain, some with granulomatous and some with non-granulomatous pathology. As with other SOV, a diagnosis of primary CNS vasculitis requires determining that CNS vasculitis is not a component of a systemic vasculitis (*e.g.*, GCA, MPA, GPA, EGPA), caused by infection (*e.g.*, syphilis), or associated with a systemic disease (*e.g.*, lupus, sarcoidosis) or part of a malignant process, such as angiocentric lymphoma.

Drug-induced PAN

Clear evidence for an association with the development of drug-induced vasculitis has been shown for hydralazine, anti-tumour necrosis factor-α (TNF-α) agents, sulfasalazine, D-penicillamine and minocycline; with most evidence limited to case reports (46). The largest series for medium vessel vasculitis is with minocycline (47). Minocycline use was defined as medication use at the time of onset of first symptom. Nine patients were reported; four had isolated cutaneous disease, while five had systemic involvement including

renal artery microaneurysms, cholecystitis, mononeuritis multiplex, and mesenteric vasculitis. The median duration of minocycline use was two years. Cutaneous, as well as systemic, PAN-like vasculitis may occur in association with minocycline use. However, these patients had atypical ANCA serologies and negative hepatitis B testing (47).

Overlapping presentations with ANCA vasculitis: EGPA-PAN and MPA-PAN

Currently, ANCA testing for Proteinase 3-ANCA and Myeloperoxidase-ANCA is a key step in the differential diagnosis of patients with suspected vasculitis (48). However, patients with ANCA-negative AAV may have ANCA that cannot be detected with current methods or may have ANCA of as-yet-undiscovered specificity, or pathogenic mechanisms that do not involve ANCA at all may be occurring. Some patients with clinical and pathological features of ANCA-associated disease who were determined to be ANCA-negative using conventional clinical assays reacted with a specific MPO epitope when a highly sensitive epitope-excision method was used; this epitope was blocked from reacting with ANCA IgG in serum because of competitive binding by a fragment of ceruloplasmin, which is a natural inhibitor of MPO (49).

Although EGPA is characterised by eosinophilia and tissue eosinophil infiltration there are overlapping features with GPA and MPA particularly in the minority of EGPA patients who are ANCA positive. ANCA-negative EGPA may have features of medium sized artery involvement, indistinguishable from PAN. In fact several patients have been reported to manifest systemic vasculitis but have no features that put the disorder definitively into a single category or whose manifestations overlap several of the well-defined and distinct syndromes, *e.g*. PAN or EGPA or MPA (50, 51). Although the 1990 ACR Classification Criteria of PAN did not include the ANCA test, or MPA as a diagnostic category, subsets of PAN were noticed (12). A patient group with neuropathy and weight loss >6.5 kg, negative arteriography and artery biopsy is one of those groups and could be in the undifferentiated/overlapped MPA/EGPA/MPA group.

Histopathologically, PAN, MPA and EGPA manifest necrotising vasculitis with fibrinoid degeneration accompanied by infiltration of inflammatory cells through all layers of artery. In addition, smaller arteries less than 500microm in diameter are involved in EGPA and MPA. In clinical practice, sometimes accessing appropriate histologic specimens for diagnosis is difficult. The overlapping features of EGPA and PAN were proposed as a new syndrome in 1986 (51). So a phenotypic overlap between PAN and MPA and between PAN and EGPA should be kept in mind.

What to do next in PAN?

There are still many unanswered questions. Is there any impact of ethnicity and geographic area on PAN? Are there clusters of PAN defined by genetic or phenotypic features? Or are there distinctly different diseases? There is a need to better understand and identify such subgroups of PAN.

Even though PAN is rare, well-designed multicentre studies might identify the clinical characteristics defining possible subphenotypes. As a first step for this collaboration, we collated demographic and clinical features of PAN patients from the UK and Turkey and compared these parameters (52). Turkish PAN patients were younger by 10 years at disease onset and had more monogenic disease. In the Turkish cohort the presence of genetic factors that predispose to inflammation might have been effective in the younger onset due to the relevant genetic load (53). A network for next steps for identification of subgroups and genetics studies in PAN was established.

Using newer and different modalities might highlight the differences/similarities of subgroups. Histopathological evaluations could be useful not only for differential diagnosis but also therapeutic approach. Masuda *et al*. studied 19 patients who had undergone autopsy with a diagnosis of cutaneous PAN (54). The cutaneous PAN group showed high matrix metalloproteinase-1 and TNF-α expressions and decreased smoothelin expression in the vascular wall. On the other hand, since cPAN and macular lymphocytic arteritis share some clinico-pathologic features, the question is raised whether they are not two different entities (55).

Targeted biologic therapy with B cell depletion in ANCA vasculitis (56), IL6r blockade in giant cell arteritis (57) and IL5 blockade in EGPA (58) has shown proven value in clinical trials and is being translated to the clinic with direct benefit for patients. Although there have been anecdotal reports of success with biologics in PAN, there have been no randomised controlled trials, and patients are missing out on an opportunity for improved disease control and outcomes. Combining such studies with deep phenotyping could both define patient subsets by their clinical response and give insights into pathogenesis.

The genetic risk factors in the development of various vasculitides diseases have been increasingly discovered. The central role of autoimmunity in ANCA associated vasculitis has been confirmed by the association with HLA polymorphisms; interestingly, the three main AAV subtypes are associated with distinct HLA variants, *i.e.,* GPA with HLA-DP1, microscopic polyangiitis with HLA-DQ and EGPA with HLA-DRB4 (59). A genome wide association study of HCV and cryoglobulin-related vasculitis identified associations with cryoglobulin-related vasculitis identified by SNPs near NOTCH4 and MHC Class II genes (60). In Takayasu's arteritis, genetic susceptibility loci with a genome-wide level of significance in IL6 (rs2069837), and an intergenic locus on chromosome 21q22 (rs2836878) were identified (61). In genome-wide association studies (GWAS) of Kawasaki syndrome, novel susceptibility genes associated with coronary artery aneurism formation were identified (62). Study of the genetics of PAN is limited by its rarity, the small number of familial cases and the complexity of disease phenotypes. A multinational collaborative effort will be required to perform a GWAS study in PAN.

Conclusion

The terminology of peri/polyarteritis nodosa and the corresponding patient

groups has changed over the last two centuries. However, there is no uniform definition of PAN associated with a condition exhibiting protean and overlapping clinical manifestations, and no specific serologic diagnostic tests have been developed.

In contrast to a distinct vasculitis such as ANCA associated vasculitis, PAN might define the pathological state of a group of idiopathic (at least still unidentified) vasculitis disorders. Several subgroups have already been defined by their aetiologic association, including: HBV-related, FMF-related, connective tissue disease related and DADA2-related PAN. Further subgroups are likely to be identified. Overlaps between PAN, other vasculitides and other inflammatory conditions require further explanation. As seen in other vasculitides, it is time to concentrate on subphenotypes of PAN. Better identification of clusters along with histopathology and GWAS studies might result as splitting of PAN into different parts and more effective therapeutic choices.

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