Polyarteritis Nodosa and Microscopic Polyangiitis: Etiologic and Diagnostic Considerations

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Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis of medium-sized vessels with clinical manifestations resulting from ischemia and infarction of affected tissues and organs. Although the cause of most cases of PAN and the related disorder microscopic polyangiitis (MPA) remains largely unknown, there has been significant progress in understanding the pathogenesis of vascular inflammation. The diagnostic approach to PAN and MPA should be individualized and based on specific organ involvement. Because no test or clinical finding reliably indicates the presence or absence of PAN or MPA, diagnosis requires integration of clinical findings, angiography, and biopsy data.

Introduction

Polyarteritis nodosa (PAN) is the prototype of systemic vasculitis. The original description of PAN in 1866 by Kussmaul and Maier [1] was of necrotizing arteritis of medium-sized arteries resulting in aneurysm formation and organ infarction. Included in the original description were observations of glomerular lesions, representing a component of small vessel involvement. In 1950, Davson [2] coined the term microscopic PAN to distinguish those patients with PAN who developed segmental necrotizing glomerulonephritis as the dominant feature of their disease. This was in contrast to those with classic PAN in whom organ infarction due to medium-sized vessel involvement was the principal manifestation [3]. Initially, this distinction between classic and microscopic PAN was not universally accepted because of the similarities between the two diseases.

The precise classification of PAN remains controversial, as evidenced by the two classification systems of systemic vasculitis. The 1990 American College of Rheumatology (ACR) classification criteria for the major vasculitides [4••], based mainly on clinical criteria, does not make a distinction between PAN and microscopic PAN (Table 1). The 1994 Chapel Hill Consensus Conference (CHCC) definitions of systemic vasculitis [5••], based on pathologic criteria, made a clear distinction between classic PAN and microscopic polyarteritis, which they termed microscopic polyangiitis (MPA) to further distinguish the two. The CHCC narrowly defined classic PAN as a disease of medium- and small-sized arteries without glomerulonephritis or vasculitis in small vessels (*ie*, arterioles, capillaries, or venules). MPA was more broadly defined as vasculitis affecting small vessels (capillaries, venules, or arterioles), which may involve medium-sized arteries. MPA connotes pauci-immune (*ie*, few or no immune deposits) necrotizing vasculitis affecting small vessels. Cryoglobulinemic vasculitis, Henoch-Schönlein purpura, and other forms of immune complex-mediated small vessel vasculitis must be ruled out to make this diagnosis. Small vessel involvement is the definitive criterion for MPA but excludes the diagnosis of classic PAN, even if medium-sized artery involvement is seen.

The discrepancy between the two systems can largely be explained by the different goals of each group for devising their specific system. The ACR classification criteria were designed to compare groups of patients with one type of vasculitis with another group for therapeutic or epidemiologic studies, not for diagnosis of individual patients [6]. Although it was not intended for that use, the CHCC definition has been used widely for classification of patients because it includes the only definition/classification for MPA.

The effect of these two classification systems on the evaluation of the epidemiology of PAN and MPA was demonstrated by Watts *et al.* [7], who reported on an unselected cohort of 131 patients with systemic vasculitis in the UK from 1988 to 1994 [7]. The study found that eight of 131 patients met the ACR criteria for PAN; however, these same eight patients met the CHCC definition of MPA rather than classic PAN. In a recent 10-year epidemiologic study of vasculitis by the same group in the UK, a similar discrepancy existed, with 33 of 82 patients meeting the ACR criteria for PAN, but classified as having MPA by the CHCC definition [8•].

Table 1. 1990 ACR criteria for the classification of polyarteritis nodosa [4••]

Criterion	Definition
Weight loss > 4 kg	Loss of 4 kg or more of body weight since illness began, not due to dieting or other factors
Livedo reticularis	Mottled reticular pattern over the skin or portions of the extremities or torso
Testicular pain or tenderness	Pain or tenderness of the testicles, not due to infection, trauma, or other causes
Myalgias, weakness, or polyneuropathy	Diffuse myalgia (excluding shoulder and hip girdle) or weakness of muscles or tenderness of leg muscles
Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy
Diastolic BP > 90 mmHg	Development of hypertension with the diastolic BP > 90 mmHg
Elevated BUN or creatinine	Elevated BUN > 40 mg/dL (1.43 μmol/L) or creatinine > 1.5 mg/dL (132 μmol/L), not due to dehydration or obstruction
Hepatitis B virus	Presence of hepatitis B surface antigen or antibodies to it in serum
Arteriographic abnormality	Angiogram showing aneurysm or occlusion of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia, or noninflammatory causes
Biopsy of small or medium-sized artery containing PMNs	Histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall

For classification purposes, a patient with vasculitis shall be said to have polyarteritis nodosa (PAN) if at least three of these 10 criteria are present. The presence of any three or more criteria yields a sensitivity of 82.2% and a specificity of 86.6%.
ACR—American College of Rheumatology; BP—blood pressure; BUN—blood urea nitrogen; PMN—polymorphonuclear neutrophils.

Despite these differences in classification, PAN and MPA display major clinical differences beyond the size of the vessel involved. MPA is associated with glomerulonephritis; pulmonary capillaritis may be seen, although at a lower frequency than glomerulonephritis. Kidney involvement in PAN is a vascular nephropathy rather than glomerulonephritis, and pulmonary involvement does not occur in PAN [9••]. The hepatitis B virus (HBV) is an etiologic factor of PAN but not of MPA. MPA is associated with the presence of antineutrophil cytoplasmic antibodies (ANCA), especially perinuclear ANCA (pANCA), whereas ANCA positivity is rare in PAN.

Etiology and Pathogenesis of PAN

In most cases, the cause of PAN remains unclear. The association of HBV infection and classic PAN was first described in the early 1970s [10]. In this subset of PAN, immune complexes play a primary role with hepatitis B surface antigen (HbsAg) as the triggering antigen. Immune complexes deposited in vessel walls can cause vascular damage through several different mechanisms. Direct endothelial damage occurs through the C5b-9 membrane attack complex; chemotactic factors (C5a) recruit neutrophils and monocytes to the area and stimulate the kinin and clotting cascades, leading to vessel thrombosis. Immune complexes can directly activate inflammatory cells through binding of Fcγ receptors on neutrophils and monocytes [11].

Hepatitis C virus does not appear to be an etiologic agent for PAN [12]. Other viruses associated with PAN include HIV [13] and varicella zoster virus [14]. Parvovirus B-19 infection has been reported to play a role in PAN [15], but this is debatable [16]. PAN has been associated with hematologic malignancies, specifically hairy cell leukemia [17]. Although immune complexes play a primary role in HBV-related PAN, they are not found in the serum or active lesions of patients with PAN unassociated with HBV infection. It appears that T cells, cytokines, and leukocyte-endothelial interactions mediate the inflammatory process.

T-lymphocytes

CD4+ (helper) and CD8+ (cytotoxic) T-lymphocytes likely play a significant role in vascular inflammation. In muscle and nerve biopsy specimens from patients with PAN, cytotoxic T cells and macrophages are the dominant cells in the inflammatory infiltrates in the vessel walls [18,19]. Recruitment and activation of macrophages is likely mediated by cytokines secreted by CD4+ T-lymphocytes. Oligoclonal expansion (*ie*, large populations using a particular T-cell receptor V segment) of activated CD4+ T cells has been observed in the peripheral blood of patients with systemic vasculitis [20,21]. Analysis of peripheral T-cell expansions from patients with PAN or Wegener's granulomatosis (WG) revealed dominant sequence motifs in the normally diverse TCR β chain CDR3 regions [22]. This report suggests the existence of a common vasculitis-associated antigen, but larger studies are needed to confirm this.

Cytokines

Quantitative and qualitative abnormalities in cytokines have been described in vasculitis syndromes. Elevated serum levels of IL-1, IL-2, IL-6, and TNF have been found in patients with active disease. TNF and IL-1 are of particular importance in vasculitis because of their biologic effects, which include: 1) direct toxic effects on endothelial cells [23]; 2) up-regulation of expression of adhesion molecules on endothelial cells [24]; and 3) induction of the production of neutrophil-attracting chemokines in endo-

thelial cells [25]. The expression of adhesion molecules and production of chemokines in endothelial cells is regulated in part by activation of the transcription factor NFκB [26].

Adhesion molecules

Endothelial cell adhesion molecules bind to ligands on the surface of leukocytes, thereby directing adhesion and transmigration of inflammatory cells from the vasculature into tissues. Adhesion molecules expressed on endothelial cells important in inflammation are categorized into several groups based on their structure, and include the integrin, immunoglobulin, and selectin superfamilies [27]. Expression of members of the immunoglobulin superfamily, such as ICAM-1, VCAM-1, and PECAM-1, is increased by endothelial activation via inflammatory cytokines (TNF and IL-1) or lipopolysaccharide (LPS). The selectins, such as L-selectin on leukocytes and E-selectin on endothelial cells, are cell surface carbohydrate-binding proteins involved in early leukocyte endothelial interactions. L-selectin is important in the "rolling" of neutrophils along endothelium [28]. E-selectin is rapidly and transiently induced on endothelial cells in acute inflammation; it and other selectins bind to sialyl Lewis X glycoprotein on leukocytes [29].

The relevance of leukocyte-endothelial interactions via adhesion molecules has been increasingly recognized in the pathogenesis of inflammation [30], including inflammatory vasculitis [31]. Qualitative and quantitative changes in the expression of adhesion molecules on leukocytes and endothelial cells have been observed in systemic vasculitis. Elevated levels of circulating ICAM-1, VCAM-1, and selectins are found in patients with systemic vasculitis [32,33] including PAN [34]; the levels do not always correlate with disease activity.

Leukocytes express several adhesion molecules on their cell surface. The β1 and β2 integrins appear to be the most relevant in the pathogenesis of vasculitis [35]. The β2 integrins, CD11a/CD18 (LFA-1) and CD11b/CD18 (MAC-1), are constitutively expressed on neutrophils, monocytes, macrophages, and NK cells. Activation of these cells leads to increased expression and increased avidity of these molecules for their ligand (ICAM-1) on endothelial cells. VLA-4, a β1 integrin present on all leukocytes except neutrophils, is also involved in leukocyte interaction with its ligands VCAM-1, on endothelial cells, and fibronectin [36]. This binding is thought to play a role in the accumulation of T-lymphocytes in sites of inflammation [37].

A dynamic pattern of adhesion molecule expression, which varies according to the stage of the lesion, has been described in the vasculature of muscle and nerve biopsy specimens from patients with PAN [38]. Microvessels were observed within and surrounding the inflammatory lesions, but were not present in the uninvolved portion of the vessel. These microvessels displayed intense staining for endothelial adhesion molecules. The authors suggest that these microvessels result from angiogenesis related to inflammation, and that adhesion molecules in the microvascular are important mediators of the inflammatory process in PAN [38].

Antineutrophil cytoplasmic antibodies in vascular injury

Antineutrophil cytoplasmic antibodies have been implicated as an etiologic factor in MPA and other small vessel vasculitides. By indirect immunofluorescence, ANCA are identified as cytoplasmic (cANCA), characterized by coarse granular staining of cytoplasm; perinuclear (pANCA), with staining of the nucleus and perinuclear area; and atypical ANCA [39]. The antigens responsible for cANCA are usually proteinase 3 (PR3), whereas myeloperoxidase (MPO) often is the antigen for pANCA. Myeloperoxidase (MPO)-ANCA can occur in up to 70% of patients with MPA [40••].

Based largely on studies of WG, it is hypothesized that ANCA are of pathogenic importance in vasculitis, but this supposition has not been proven [41]. Two hypotheses have been advanced to elucidate the putative role of ANCA in vasculitis. The first proposes that the release of PR3 or MPO antigenic targets of ANCA from neutrophil primary granules or monocyte lysosomes results in binding of these antigens to blood vessel walls, with subsequent in situ immune complex formation; however, there are few immunoglobulin or complement deposits in ANCA-positive vasculitis. Perhaps this finding is due to clearance of such deposits in late stages of inflammation. The second hypothesis is that ANCA interact with primed neutrophils, which are then capable of injuring endothelial cells. In vitro studies have shown that ANCA can activate TNF-primed neutrophils and macrophages, which causes release of reactive oxygen species and secretion of pro-inflammatory cytokines [42]. It is thought that MPO or PR3 become available on the cell surface under the stimulus of TNFα and IL-8 [43], in contrast to "unprimed" neutrophils in which PR3 and MPO reside in the cytoplasm and presumably are inaccessible to extracellular antibodies [44]. TNF-primed neutrophils incubated with ANCA undergo accelerated apoptosis without the expression of surface phosphatidylserine, a necessary signal for phagocytosis; this is a potential mechanism contributing to necrosis and tissue damage [45].

Despite numerous in vitro observations of ANCA-induced vasculitis, in vivo studies argue against a primary role of ANCA in vasculitis. Mice immunized with human IgG ANCA generate high-titer murine ANCA, but do not display any evidence of vasculitis [46]. In addition, there are many patients with small vessel vasculitis, MPA, or WG who do not have ANCA. ANCA titers do not always correlate with disease activity.

Anti-endothelial cell antibodies in vasculitis

Antibodies against human endothelial cells (AECA) have been detected in up to 80% of patients with systemic vas-

culitis (including PAN [47]), and have been implicated in its pathogenesis [31]. Human IgG AECA are capable of causing activation of endothelial cells in vitro, with up-regulation of adhesion molecules and secretion of inflammatory cytokines [47]. It should be noted that AECA are present in diseases other than vasculitis [48], which reduces its usefulness as a diagnostic tool and impugns its importance in the pathogenesis of vasculitis. Additional studies of target autoantigens on endothelial cells are needed to elaborate whether AECA are of pathogenic significance.

Clinical Manifestations

The clinical manifestations of PAN have been described in several studies [49], and are reviewed by Guillevin [9••]; most of these studies did not make a distinction between PAN and MPA. Due to predominant kidney involvement in MPA, most of the initial clinical studies were from nephrologists [50–58]. In general, there are clear differences in clinical manifestations and patterns of disease activity in PAN and MPA. PAN usually has an acute, severe disease onset with few flares. MPA has a more protracted and indolent disease course with flares occurring in up to one-third of the patients.

General symptoms

Most patients with PAN and MPA present with constitutional symptoms, including fever, malaise, and weight loss. Myalgias and arthralgias are frequent and often severe.

Neurologic manifestations

Mononeuropathy multiplex is found in up to 70% of patients with PAN [59] and in 14% to 58% of patients with MPA [58]. Nerve involvement is usually peripheral, asymmetric, and localized to the lower extremity (*ie*, superficial peroneal or sural nerves). Less often, the neuropathy involves the upper extremity (cubital or median nerves). Motor deficits usually have an abrupt onset, whereas pain and paresthesias reflect sensory involvement. The degree of recovery from neurologic deficits is difficult to predict. Recovery is slow, frequently taking up to 18 months for maximal improvement. Physical rehabilitation is important to facilitate clinical improvement. Cranial nerve palsies have been found in 1% and 7% of patients with PAN [52] and MPA [40••], respectively. CNS involvement is rare in PAN and MPA and portends a poor prognosis.

Cutaneous involvement

Skin lesions can be present in PAN and MPA. Vascular purpura, the most frequently reported lesion, reflects small vessel involvement, and is more frequently found in MPA. Livedo reticularis is seen in both diseases but is more common in PAN; lower extremity ulcers and digital gangrene may occur. Subcutaneous nodules are less common, but they are a manifestation of medium vessel involvement, thus are helpful diagnostically.

Renal involvement

Polyarteritis nodosa-associated vascular nephropathy produces varying degrees of renal insufficiency. It is the consequence of renal infarcts and tends to develop rapidly and early in the disease course. Renin-dependent hypertension associated with vascular nephropathy can be severe or malignant. Angiotensin-converting enzyme (ACE) inhibitors are effective in treating PAN-related hypertension [60].

Microscopic polyangiitis is characterized by glomerulonephritis in most patients (82%) [40••]. Initial manifestations are microscopic hematuria and proteinuria. Renal impairment is typically mild at diagnosis but tends to deteriorate rapidly if untreated. Renal biopsy reveals glomerular lesions and glomerular scars. Ureteral stenoses can occur as a consequence of vasculitis of the ureteral wall or periureteral fat [61].

Gastrointestinal involvement

Gastrointestinal manifestations are common in MPA and PAN; the most common symptom is abdominal pain. Gastrointestinal vasculitis frequently involves the small bowel and can cause ischemia, infarction, bleeding, or perforation [62]. Of these, gastrointestinal bleeding and bowel perforation are the most severe manifestations of PAN. Other organs less frequently involved are the esophagus, stomach, liver, gallbladder, pancreas, appendix, and colon.

Cardiac involvement

Cardiac manifestations occur in similar proportions between patients with PAN and patients with MPA. The myocardium is primarily affected due to vasculitis of coronary arterioles, but occasionally heart disease is secondary to uncontrolled hypertension [63]. The main clinical feature of myocardial involvement is congestive heart failure. Refractory tachycardia is commonly an initial sign of cardiac involvement. In addition, minor EKG abnormalities are frequently noted [63]. Despite coronary artery involvement, angina is rare and coronary arteriograms are usually normal.

Pulmonary involvement

Lung involvement has been noted in 25% to 50% of patients with MPA, but it does not occur in PAN. The clinical manifestations range from minor hemoptysis to severe lung hemorrhage secondary to diffuse capillaritis [56]. In a retrospective study by Lauque *et al.* [64], 29 patients with MPA and alveolar hemorrhage were observed to characterize their disease presentation and overall prognosis. The onset of alveolar hemorrhage was rapid and progressive in the majority of patients, but in eight patients (28%) the symptoms preceded the diagnosis by ≥ 1 year. Glomerulonephritis was present in 93% of the patients, and ANCA present in 93% (pANCA in 52% and cANCA in 41%).

Broncheolar lavage fluid was hemorrhagic in 93% of the patients, and a severe anemia (mean hemoglobin 8.1 ± 1.8 g/dL) present in the majority. The overall mortality rate was 31%, with 17.2% of the deaths related to vasculitis. Complete recovery of pulmonary function occurred in 69% of the patients.

Other manifestations

Orchitis is a characteristic manifestation of PAN, especially HBV-related PAN [65]. Ocular manifestations occur in PAN and MPA [66], whereas ear, nose, and throat lesions are commonly seen in MPA alone. Bone [67], spleen [54], breast [68], and uterus [69] lesions have been reported in PAN.

Diagnostic Evaluation in PAN and MPA

There is no single diagnostic test for PAN or MPA, so the clinician must integrate clinical findings, angiography, and biopsy data. As discussed earlier, several clinical and serologic features allow the clinician to distinguish PAN from MPA. Mimickers of vasculitis should be considered in the differential diagnosis of patients with clinical findings suggestive of PAN or MPA [70•]. The diagnostic approach should be based on specific organ involvement. The more clinical evidence for involvement of a particular tissue or organ, the more likely a biopsy of that tissue or organ will provide useful diagnostic information [71]. Conversely, biopsies without laboratory or radiographic indications that specific organs are involved are seldom helpful. Although biopsies may reveal inflammation without specific diagnostic changes, histopathologic findings are often helpful in suggesting a specific type of vasculitis. Angiography or other imaging studies may be preferable to tissue biopsy when the risk of biopsy is great or when medium or large vasculitis is suspected.

Albert *et al.* [72•] used published data to calculate the sensitivity and specificity of visceral angiography and muscle, nerve, testicle, and kidney biopsy. They constructed and compared different test sequence strategies. The aggressive strategy consisted of repeated tests until there was a positive finding or until the available tests were exhausted. The conservative strategy was comprised of one biopsy procedure plus angiography. The conservative approach begins with biopsy of nerve or muscle if symptomatic, or with visceral angiography if there is no symptomatic nerve or muscle. The conservative approach was found to be optimal for most prior probabilities (degrees of suspicion) of PAN. The aggressive strategy was more costly and had a higher rate of morbidity than did the conservative strategy. Thus in most cases, the preferred diagnostic evaluation of patients with symptoms suggestive of PAN consists of angiography or other imaging studies, and a single biopsy procedure.

Laboratory data

Most patients with PAN and MPA have findings consistent with systemic inflammation, including an elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leukocytosis (occasionally with eosinophilia defined as ≥ $1500/mm^3$), and normochromic normocytic anemia. Patients with MPA and pulmonary hemorrhage typically have more severe anemia than those with PAN. Hepatitis B surface antigen (HbsAg) and ANCA should be obtained routinely in all patients suspected of having PAN or MPA. Although HBV-related PAN is becoming increasingly uncommon (a result of screening of blood donors and blood products, and the HBV vaccine), it usually occurs within the first 6 months after infection, so it can be the first sign of HBV infection [73]. Pharmacologic therapy of HBV-related PAN differs vastly from that of non–HBV-associated PAN, thus it is essential to exclude HBV infection before initiating conventional therapy for vasculitis.

Antineutrophil cytoplasmic antibodies are rarely found in PAN, but are present in the sera of approximately 75% of patients with MPA [40••]. Most ANCA are pANCA/anti–MPO, although cANCA/PR-3 can be seen. The specificity of anti–MPO-ANCA for MPA is not as high as that of anti–PR-3 ANCA for WG. Anti–MPO-ANCA can be detected in other systemic vasculitides (*eg*, Churg-Strauss syndrome) and occasionally in patients with rheumatoid arthritis, systemic lupus erythematosus (SLE), and inflammatory bowel disease [40••].

In early studies, renal abnormalities (elevated serum creatinine, microscopic hematuria, or nephrotic range proteinuria) were reported in virtually all patients with MPA [58]. In a more recent retrospective analysis of 85 patients with MPA seen in a rheumatology practice, the proportion of individuals with evidence of renal impairment was lower. Guillevin *et al.* [40••] found renal insufficiency in 70.1%, proteinuria in 80.6%, and hematuria in 67.2% of the patients. This discrepancy is most likely due to referral bias in the initial studies, which reported mostly patients seen by nephrologists. Histologic findings on renal biopsy from patients with MPA include focal, segmental, necrotizing, and thrombosing glomerulonephritis, whereas the classic biopsy finding in PAN is necrotizing arteritis of arcuate or interlobular arteries.

Angiography

Angiographic studies in patients with PAN commonly demonstrate microaneurysms (1–5 mm in diameter) and stenoses involving medium-sized vessels. These angiographic findings, although not pathognomonic for PAN, are rarely seen in patients with MPA. Vessels of the kidneys, mesentery, and liver are most commonly involved in PAN, but the coronary arteries may be affected. With treatment, these angiographic findings tend to regress [74].

Cross-sectional imaging

Conventional angiography remains the imaging technique of choice for PAN because of its superior ability to detect subtle areas of stenosis, occlusion, or dilation in small arteries [74]. However, in advanced disease, CT angiography and magnetic resonance angiography (MRA) can frequently detect arterial abnormalities such as large intrarenal and extrarenal aneurysms, stenosis, and occlusion of the main renal artery and its branches [75]. CT provides excellent visualization of the organ changes and complications accompanying necrotizing vasculitis, such as peripheral wedge-shaped areas of renal cortical ischemia/infarction.

Electrophysiologic studies

In patients with PAN and MPA and neuropathy, electrophysiologic studies typically reveal an axonal pattern of involvement. Nerve conduction velocities are normal or slightly decreased, whereas electromyography often shows changes of diffuse denervation [76]. Electrophysiologic abnormalities are not diagnostic of PAN or MPA, but provide useful information for determining an adequate site for biopsy [76].

Tissue analyses

Nerve and muscle are the most frequent sites for biopsy in the diagnostic evaluation of systemic vasculitis. To improve the diagnostic yield of the tissue biopsy, the biopsy site should be clinically and electrophysiologically abnormal. Tissue analysis should include whole nerve and muscle tissue. In PAN, histopathologic analysis of the nerve often reveals a necrotizing vasculitis of the main epineural artery or its branches, consistent with medium vessel involvement [77]. Skin biopsy in patients with PAN commonly reveals a leukocytoclastic vasculitis (*ie*, small vessel involvement), so caution must be used when using skin biopsy to diagnose a vasculitic syndrome.

Temporal artery biopsy is another potentially useful diagnostic procedure. In a small retrospective study from Norway, five patients with PAN underwent temporal artery biopsy [78]. All five patients had evidence of vasculitic changes without the presence of giant cells. The patients' clinical symptoms were consistent with PAN (fulfilling ACR criteria), whereas none of the patients had symptoms typical of giant cell arteritis (GCA). In a larger, prospective study, conducted by the French Vasculitis Study Group, two of 141 (1.4%) consecutive patients who underwent temporal artery biopsy were found to have systemic necrotizing vasculitis rather than GCA [79]. The authors retrospectively analyzed 27 cases of systemic necrotizing vasculitis diagnosed by temporal artery biopsy; most of the biopsies revealed fibrinoid necrosis and a polymorphonuclear infiltrate, which are rare in GCA. Important observations were that temporal artery involvement was often the first manifestation of the systemic vasculitis, and that the initial symptoms of the disease could mimic GCA.

Conclusions

The classification of PAN and MPA remains controversial. Although some etiologic factors have been identified in PAN, the cause of PAN or MPA remains unknown in most patients. Despite the limitations of the classification and definition of PAN and MPA, important observations have been made. PAN is usually acute and severe at onset, may be associated with HBV infection, and displays characteristic angiographic abnormalities. MPA has a more indolent and protracted course with frequent flares. It is characterized by glomerulonephritis and renal insufficiency in most cases; occasionally there is concomitant pulmonary capillaritis. Tests for ANCA (pANCA/anti-MPO) are often positive in MPA; angiograms are typically normal.

Although the cause of most cases of PAN and MPA remains unknown, significant advances in molecular and cellular immunology have provided important insights into the vascular inflammatory process. The significant role of inflammatory cytokines and adhesion molecules provide potential targets for modulating the inflammatory response and may translate into improved outcomes for patients with these often debilitating illnesses.

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Papers of particular interest, published recently, have been highlighted as:

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