# 16
# Polyarteritis Nodosa

José Hernández-Rodríguez and Maria C. Cid

**Abstract** Polyarteritis nodosa (PAN) is a primary systemic necrotizing vasculitis that preferentially involves medium-sized arteries. The etiology of PAN is unknown. Several viral infections, such as hepatitis B virus infection, may be associated with blood vessel inflammation, clinically and histologically indistinguishable from PAN. Clinical manifestations of PAN are heterogeneous and multisystemic. Peripheral nerve and skin are frequently involved. Other organs including gastrointestinal tract, kidney, heart, and central nervous system can be targeted, conveying a poorer prognosis. Laboratory markers reflecting a prominent acute-phase response are common but not specific. When histologic confirmation cannot be obtained, angiography of involved territories, preferentially abdominal, may disclose multiple aneurysm formation supporting the diagnosis of PAN. Current treatment policy includes high-dose corticosteroids, which are combined with immunosuppressive agents when critical organ involvement or life-threatening complications occur. IV pulse cyclophosphamide in the remission induction phase, later switched to a safer immunosuppressant for remission maintenance, is a frequently used therapeutic scheme. A recent consensus algorithm for the classification of PAN has attempted to address some of the shortenings of previous classification criteria and has also confirmed the low prevalence of PAN compared with other necrotizing systemic vasculitides.

**Keywords** Polyarteritis nodosa · vasculitis · classification · treatment

Polyarteritis nodosa (PAN) is a primary systemic necrotizing vasculitis characteristically involving medium-sized arteries. PAN usually targets muscular arteries ranging from 300 μm to 1 cm in diameter (1, 2). Small vessels, including arterioles, capillaries, and postcapillary venules, are not affected (1).

## Epidemiology

PAN can be considered a rare disease, with an annual incidence that ranges from 0 to 1.6 cases per million inhabitants in European countries (3, 4, 5). Two different studies from Sweden and France [the latter including 7/23 patients with a concomitant hepatitis B virus (HBV) infection] have recently found a prevalence of up to 31 cases per million (6, 7). PAN affects patients with no clear sex or race predilection and can occur at all ages. The peak incidence appears to be in the fifth to sixth decades (3, 4, 5, 6, 7). Before vaccination against HBV was available, more than one-third of vasculitis patients with features suggestive of PAN were infected by HBV. Currently, less than 10% of patients with PAN lesions are HBV-infected in developed countries (8).

## Pathogenesis

PAN-like lesions have been reported in chronic viral infections, particularly in association with HBV. Infection by other pathogens, including HCV, HIV, cytomegalovirus, parvovirus B19, and human T-lymphotropic virus type I, has also been found in association with similar vasculitic lesions. Vascular inflammation associated with viral infections has been thought to be triggered by immune complexes (8). However, classic PAN is not usually associated with immune-complex deposition (1). The presence of dendritic cells and the abundance of $CD4^+$ lymphocytes in vascular inflammatory infiltrates suggests that antigen-specific T-cell-mediated immune responses may also play a role in the pathogenesis of vascular inflammation in PAN (9).

## Clinical Manifestations

PAN has a wide spectrum of clinical presentations and may run an indolent, subclinical course. Consequently, the diagnosis of PAN is often delayed. In other instances,

From: Y. Shoenfeld et al. (eds.): *Diagnostic Criteria in Autoimmune Diseases*, DOI: 10.1007/978-1-60327-285-8_16,

PAN may present as an acute, life-threatening disease. The occlusion or rupture of the inflamed vessels in PAN can damage any organ or territory throughout the body by producing tissue ischemia or hemorrhage. This leads to a high variety of clinical manifestations that are listed in Table 16.1. Clinical features in PAN include nonspecific constitutional manifestations such as malaise, weight loss, fever, arthralgia, and myalgia, present in a high percentage of patients (2, 8), and symptoms derived from dysfunction or damage of the targeted organs.

The most frequent focal manifestations are derived from the involvement of vessels supplying peripheral nerves and the skin (8). Peripheral nervous system involvement usually presents as mononeuritis multiplex although symmetrical peripheral neuropathy can also be observed. Cutaneous features include purpura, livedo reticularis, subcutaneous nodules, Raynaud phenomenon, and distal digital ischemia (8). Gastrointestinal tract and kidneys are also frequently affected (8). Gastrointestinal manifestations of PAN are frequently associated with a remarkable morbidity and mortality (10). Contrarily to microscopic polyangiitis (MPA), kidney involvement in PAN does not include necrotizing glomerulonephritis. Renal involvement in PAN consists of tissue infarction or hematomas (8). The latter are usually produced by rupture of renal microaneurysms. In some patients, multiple renal infarcts may lead to an acute renal failure, whereas, in others, kidney infarcts may be clinically silent from months to years (4, 8). Hypertension secondary to intrarenal artery involvement is common (4, 8).

TABLE 16.1. Principal manifestations in patients with polyarteritis nodosa (PAN) (8, 10).

| Clinical manifestations | Prevalence (%) |
|---|---|
| Systemic features | |
| Fever | 31–69 |
| Weight loss | 16–66 |
| Myalgia | 30–54 |
| Arthralgia | 44–58 |
| Cutaneous | 28–58 |
| Neurological | 40–75 |
| Mononeuritis multiplex | 38–72 |
| Central nervous system | 2–28 |
| Cranial nerve palsy | <2 |
| Gastrointestinal tract | 14–44 |
| Abdominal pain[a] | 37/38 (97) |
| Nausea/vomiting[a] | 12/38 (32) |
| Diarrhea[a] | 6/38 (16) |
| Hematochezia/melena[a] | 2/38 (5) |
| Hematemesis[a] | 3/38 (8) |
| Esophageal ulcerations[a] | 5/38 (13) |
| Gastroduodenal ulcerations[a] | 12/38 (32) |
| Colorectal ulcerations[a] | 2/38 (5) |
| Surgical abdomen/peritonitis[a] | 12/38 (32) |
| Renal | 8–66 |
| Cardiac | 4–30 |
| Hypertension | 10–63 |
| Eye – retinal vasculitis, retinal detachment, cotton-wool spots | 3–44 |
| Respiratory – pleural effusion | 5 |
| Testicles – orchitis/epididymitis | 2–18 |

[a] Abdominal manifestations from a series of 38 patients with PAN (10).

## Laboratory Features

There are no laboratory abnormalities specific for PAN. Erythrocyte sedimentation rate and C-reactive protein are commonly elevated. Chronic anemia and leukocytosis are frequently present (2, 8). Hypereosinophilia may be occasionally seen but, when present, clinical features of Churg–Strauss syndrome must be investigated and ruled out. Serologies for HBV, HCV, and other chronic viral infections are useful to diagnose viral-associated vasculitis (8). Given the unusual association of PAN with antineutrophil cytoplasmic antibodies (ANCAs), a positive ANCA test strongly supports the diagnosis of other systemic necrotizing vasculitis usually associated with the presence of ANCA, such as MPA, Wegener's granulomatosis, or Churg–Strauss syndrome (5, 11).

## Histologic Diagnosis

Biopsies should be performed on symptomatic or clinically abnormal sites (e.g., muscle, sural nerve, skin, bowel, or testicle). In carefully selected individuals in whom PAN is strongly suspected, muscular biopsies from clinically affected muscles and nerves may reveal vasculitis in about 70% of patients (12). In cases in which biopsies of muscle and nerve are blindly performed, vasculitis can be seen in up to one-third of patients (2, 8, 12). Testicular biopsy was advised in the past based on that testicles are frequently involved in necropsy studies of individuals with PAN. However, testicular biopsies do not have a suitable diagnostic yield (2) and should be performed only when testicles are clinically involved and biopsies from other symptomatic territories have been negative (12). During the workup of PAN, blind renal and liver biopsies should be avoided because of the potential presence of microaneurysms and their consequent hemorrhagic complications (2, 12). PAN or other necrotizing vasculitis can also be unexpectedly diagnosed in temporal biopsies from patients with clinical suspicion of giant-cell arteritis (13). Although the main temporal arteries may be affected, involvement of the surrounding branches is more commonly seen. Necrotizing vasculitis must be always ruled out when inflammation of the temporal artery branches with a spared temporal artery is observed in a temporal artery biopsy (13).

Vascular lesions are characteristically patchy and segmental (2). PAN inflammatory infiltrates are composed

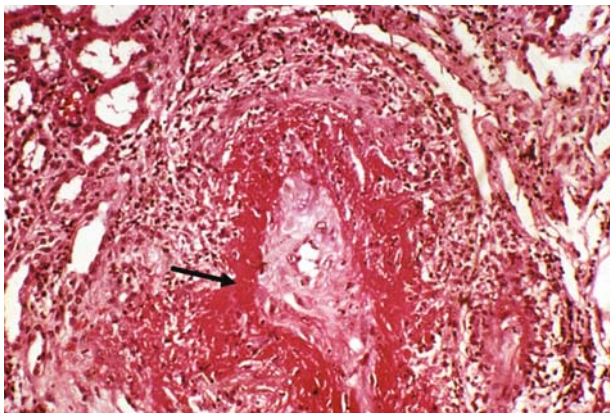

FIGURE 16.1. Typical histopathologic findings in polyarteritis nodosa: muscular artery with mixed inflammatory infiltrates and fibrinoid necrosis (arrow).

of lymphocytes, macrophages, and variable numbers of neutrophils and eosinophils (2, 9). Granulomas and giant cells are usually absent. Fibrinoid necrosis is frequently seen in active lesions (2, 9), and neutrophils are more frequently present in vessels with fibrinoid necrosis (9) (Figure 16.1). At later stages, lymphocyte and macrophage infiltration usually predominates and neoangiogenesis becomes apparent (9). In advanced lesions, vascular remodeling and healing lead to the development of intimal hyperplasia and diffuse fibrotic changes within the vessel wall (2). Severe vessel wall injury may result in the typical formation of microaneurysms (2). In PAN, vessels or vessel fragments with acute necrotizing lesions typically coexist with others with fibrotic or healing changes, representing different stages of the same inflammatory process (2, 9).

## Imaging Findings

Visceral angiography may be performed in situations in which PAN is highly suspected and: (a) histologic diagnosis of vasculitis cannot be achieved, or (b) in patients predominantly experiencing symptoms suggestive of abdominal, renal, or cardiac involvement. In these patients, visceral angiography may have higher diagnostic yield than blinded muscle or peripheral nerve biopsies (12). Typical arteriographic lesions in PAN are arterial saccular or fusiform microaneurysms (1–5 mm in diameter), which can occur concomitantly with stenotic lesions, predominantly in the renal, mesenteric and hepatic artery branches. When characteristic angiographic changes are detected by an experienced radiologist, in the appropriate clinical context, the diagnosis of PAN can be established, even in absence of histologic confirmation (5, 8, 12). It must be kept in mind that conditions other than PAN may lead to multiple aneurysm formation (14).

## Definition and Classification Criteria

In 1990, the American College of Rheumatology (ACR) classification criteria for PAN were established incorporating clinical, laboratory (including detection of HBV), angiographic, and histologic features (15). It is important to remark that the ACR criteria did not consider MPA as a clinicopathologic entity different from PAN. In 1994, in the Chapel Hill Consensus Conference, classical PAN was defined as a noninfectious vasculitis with distinct histopathologic features (1). PAN was also differentiated from MPA, which was considered as a systemic small- to medium-sized vessel vasculitis typically presenting with necrotizing glomerulonephritis and pulmonary capillaritis (1). The absence of pulmonary and glomerular capillary involvement in PAN has been useful in distinguishing this entity from other necrotizing vasculitides, involving small-sized vessels and frequently associated with the presence of ANCA. Both classification and nomenclature criteria are listed in Table 16.2.

TABLE 16.2. ACR criteria (15) and Chapel Hill definition (1) of polyarteritis nodosa.

| 1990 Criteria for the Classification of Polyarteritis Nodosa |
|---|
| 1. Weight loss >4 kg<br>Loss of 4 kg or more of body weight since illness began, not due to dieting or other factors |
| 2. Livedo reticularis<br>Mottled reticular pattern over the skin or portions of the extremities or torso |
| 3. Testicular pain or tenderness<br>Pain or tenderness of the testicles, not due to infection, trauma, or other causes |
| 4. Myalgias, weakness, or leg tenderness<br>Diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness of leg muscles |
| 5. Mononeuropathy or polyneuropathy<br>Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy |
| 6. Diastolic blood pressure >90 mmHg<br>Development of hypertension with diastolic blood pressure higher than 90 mmHg |
| 7. Elevated blood urea nitrogen or creatinine<br>Elevation of blood urea nitrogen >40 mg/dl or creatinine >1.5 mg/dl, not due to dehydration or obstruction |
| 8. Hepatitis B virus<br>Presence of hepatitis B surface antigen or antibody in serum |
| 9. Arteriographic abnormality<br>Arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia, or other noninflammatory causes |
| 10. Biopsy of small- or medium-sized artery containing polymorphonuclear neutrophils<br>Histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall |
| Patients were classified as PAN if at least 3 of the 10 criteria were present. The presence of any 3 or more criteria yielded a sensitivity of 82.2% and a specificity of 86.6%. |
| Definition of Polyarteritis nodosa (PAN) adopted by the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis |
| Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. |

After these categorization systems were established, several studies have demonstrated that most patients, who met ACR classification criteria for PAN, after being reevaluated, did not meet the definition of PAN according to the Chapel Hill Consensus Conference (3, 4, 5). Therefore, the incidence of PAN has been overestimated in studies performed before the establishment of the Chapel Hill definition. Reasons for re-definition have been subsequent histologic demonstration of glomerulonephritis or small vessel involvement, ANCA positivity, or detection of HBV, HCV, or other infectious agents known to be associated with vasculitis. Consequently, many patients previously diagnosed with PAN were later re-categorized as having MPA or infection-related vasculitis.

Recently, a consensus algorithm for the classification of PAN and other necrotizing vasculitides has been proposed by combining ACR and Chapel Hill criteria, and ANCA testing and surrogate markers of vascular inflammation, including clinical, laboratory, neurophysiologic, and imaging tests (Figure 16.2) (5). This classificatory scheme has

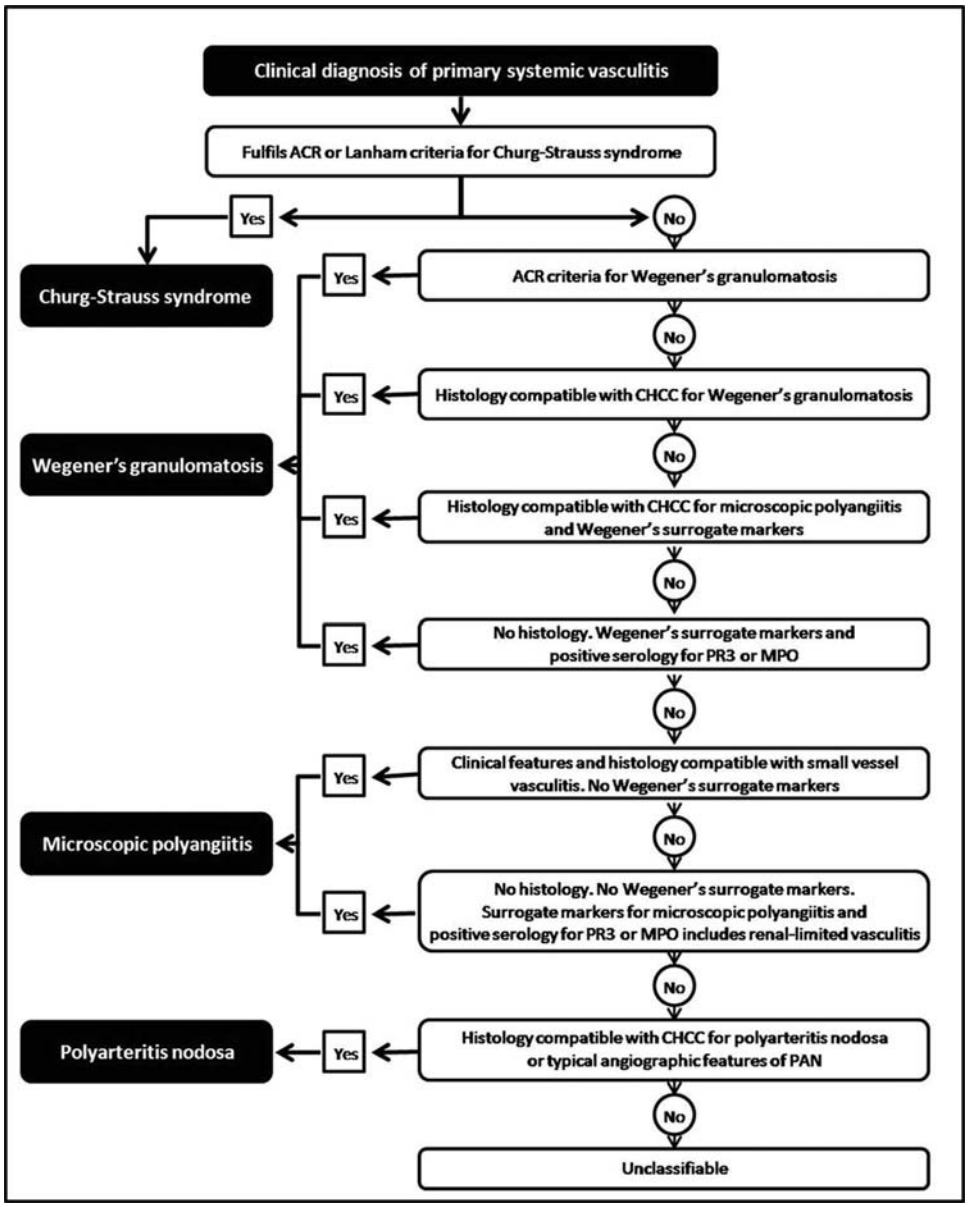


FIGURE 16.2. Consensus algorithm proposed by Watts et al. for the classification of Churg–Strauss syndrome, Wegener's granulomatosis, microscopic polyangiitis, and polyarteritis nodosa (reproduced with permission from ref 5.). ACR, American College of Rheumatology; CHCC, Chapel Hill Consensus Conference; MPO, myeloperoxidase; PR3, proteinase 3.
Note: The Lanham criteria for Churg-Strauss and the surrogate markers for Wegener's granulomatosis and microscopic polyangiitis are explained in detail in reference 5.

been already used in a large epidemiologic study analyzing different vasculitides and has definitively confirmed the low prevalence of PAN (7).

## Necrotizing Arteritis Confined to Single-Organs or Systems

Patients with necrotizing vasculitis localized within a specific organ or territory with no apparent systemic involvement have been repeatedly reported (16). Although the term *PAN* defines a systemic disease (1, 15), *isolated PAN* is the term most profusely used to define these cases of localized vasculitis. Several systems can be diffusely involved by necrotizing vasculitis; these include the central nervous system, peripheral nerves, and skin. Such entities, although isolated, cannot be treated by excision, and systemic therapy is required. Necrotizing vasculitis involving single organs has been reported in the appendix, intestines, gallbladder, pancreas, breast, male and female genital organs, and urinary structures. These forms of isolated vasculitis are usually found incidentally in organs excised because of focal symptoms or local abnormalities, and can be cured by resection of the involved tissues, and systemic treatment is not usually required (16). Clinical and laboratory markers of systemic inflammatory response are weaker in patients with single-organ vasculitis than in patients with widespread systemic involvement (16). Patients with single-organ vasculitis may be carefully evaluated to exclude systemic extent at diagnosis and subjected to a tight surveillance with regard to the appearance of systemic features during follow-up because patients with apparently isolated vasculitis at presentation and later evolving to a systemic disease have been reported (16).

## Disease Course and Prognosis

Contrarily to MPA and Wegener's granulomatosis, which are typically multi-relapsing diseases, PAN has been classically considered a monophasic disease with a relapse rate lesser than 10%. Nevertheless, a recent study of 10 PAN patients defined according to the Chapel Hill nomenclature criteria has shown a relapse rate higher than previously reported and similar to that seen in patients with MPA (4).

The prognosis of PAN depends on the organs involved. The French Vasculitis Study Group (FVSG) proposed the Five Factor Score (FFS), a prognosis index considering the following items: presence of severe gastrointestinal tract disease (defined as bleeding, perforation, infarction, or pancreatitis), renal involvement consisting of serum creatinine $\geq$1.58 mg/dl or proteinuria ($\geq$1 g/day), cardiac disease (infarction or heart failure), and central nervous system involvement. When present, each of those is given a score of 1 (17). The FVSG has reported a 5-year mortality of 12% for PAN patients with FFS = 0, 26% for those with FFS = 1, and 46% when FFS is $\geq$2. The overall 7-year survival for PAN is 79% (17).

## Treatment

It is important to keep in mind that the level of evidence supporting therapeutic decisions in PAN is low. As mentioned, grounds on which patients with necrotizing vasculitis have been classified as PAN patients have evolved over the years. The existing randomized clinical trials have been performed on mixed cohorts of patients with PAN and Churg–Strauss syndrome or MPA (17). The distribution of the involved organs and disease progression are the two principal determinants for treating patients with PAN. Current therapeutic approaches consider treating mild forms of primary PAN (with FFS = 0) with corticosteroids only: typically prednisone or prednisolone at doses of 1 mg/kg/day with subsequent tapering when remission is achieved (17). When prednisone cannot be tapered below 15–20 mg/day without recurrence, the addition of a second immunosuppressive agent is considered. In life-threatening situations or rapidly progressive disease, experts advise initiation of therapy with IV methylprednisolone pulses (1000 mg/day for 3 days). In the presence of critical organ involvement indicated by an FFS $\geq$1, immunosuppressants are given in addition to prednisone. Cyclophosphamide is used at doses of 2 mg/kg/day orally or as monthly intravenous doses of 0.6 g/m$^2$ for 6–12 months (18). According to the FVSG, monthly pulse intravenous administration is preferred to daily oral cyclophosphamide. Currently, as an extrapolation from the evidence obtained from trials performed with patients with MPA and Wegener's granulomatosis, cyclophosphamide is recommended to induce remission and a safer immunosuppressive agent such as azathioprine or methotrexate is advised to maintain remission (18). Cyclophosphamide treatment beyond 12 months is not recommended. Angiographic abnormalities can regress after treatment (10). Surgery may be required for some disease complications, such as perforation/rupture, ischemia, or hemorrhage of the gastrointestinal organs or kidneys (10).

Although biologic therapies have been used in other vasculitides with variable results (18), experience in treating patients with PAN, refractory to conventional therapies, with TNF-blocking agents remains anecdotal (19).

In patients with HBV-associated vasculitis, combination of short corticosteroid treatment with plasma exchanges and antiviral therapy (vidarabine, interferon-$\alpha$2a, or lamivudine) may be effective in controlling disease activity and in facilitating viral seroconversion. The control of the

viremia also helps in preventing the development of long-term hepatic complications of HBV infection (18). Relapses are rare in HBV vasculitis and never occur when viral replication has ceased and seroconversion has been achieved (10). In single-organ necrotizing vasculitis, a complete excision of the involved tissue may be curative in most cases (16).

*Acknowledgment*. The authors were supported by Ministerio de Educación y Ciencia (SAF 05-06250), Marató TV3 (05/0710), and Generalitat de Catalunya (SGR 0300/2005). José Hernández-Rodríguez was a research award recipient from Hospital Clínic (Barcelona, Spain) and from the RJ Fasenmyer Center for Clinical Immunology at the Cleveland Clinic Foundation (Cleveland, OH, USA).

## References

1. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37(2): 187–92.
2. Lie JT. Systemic and isolated vasculitis. A rational approach to classification and pathologic diagnosis. *Pathol Annu* 1989; 24(Pt 1): 25–114.
3. González-Gay MA, García-Porrúa C, Guerrero J, Rodríguez-Ledo P, Llorca J. The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. *Arthritis Rheum* 2003; 49(3): 388–93.
4. Selga D, Mohammad A, Sturfelt G, Segelmark M. Polyarteritis nodosa when applying the chapel hill nomenclature – a descriptive study on ten patients. *Rheumatology (Oxford)* 2006; 45(10): 1276–81.
5. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 2007; 66(2): 222–7.
6. Mahr A, Guillevin L, Poissonnet M, Ayme S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a french urban multiethnic population in. *Arthritis Rheum* 2004; 2000(1): 92–9.
7. Mohammad AJ, Jacobsson LT, Mahr AD, Sturfelt G, Segelmark M. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg Strauss syndrome within a defined population in southern Sweden. *Rheumatology (Oxford)* 2007; 46(8): 1329–37.
8. Lhote F, Cohen P, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome. *Lupus* 1998; 7(4): 238–58.
9. Cid MC, Grau JM, Casademont J, Campo E, Coll-Vinent B, López-Soto A et al. Immunohistochemical characterization of inflammatory cells and immunologic activation markers in muscle and nerve biopsy specimens from patients with systemic polyarteritis nodosa. *Arthritis Rheum* 1994; 37(7): 1055–61.
10. Pagnoux C, Mahr A, Cohen P, Guillevin L. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. *Medicine (Baltimore)* 2005; 84(2): 115–28.
11. Guillevin L, Lhote F, Amouroux J, Gherardi R, Callard P, Casassus P. Antineutrophil cytoplasmic antibodies, abnormal angiograms and pathological findings in polyarteritis nodosa and Churg-Strauss syndrome: indications for the classification of vasculitides of the polyarteritis nodosa group. *Br J Rheumatol* 1996; 35(10): 958–64.
12. Albert DA, Rimon D, Silverstein MD. The diagnosis of polyarteritis nodosa. I. A literature-based decision analysis approach. *Arthritis Rheum* 1988; 31(9): 1117–27.
13. Esteban MJ, Font C, Hernández-Rodríguez J, Valls-Solé J, Sanmartí R, Cardellach F, et al. Small-vessel vasculitis surrounding a spared temporal artery: clinical and pathological findings in a series of twenty-eight patients. *Arthritis Rheum* 2001; 44(6): 1387–95.
14. Molloy ES, Langford CA. Vasculitis mimics. *Curr Opin Rheumatol* 2008; 20(1): 29–34.
15. Lightfoot RW Jr, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990; 33(8): 1088–93.
16. Hernández-Rodríguez J, Molloy ES, Hoffman GS. Single-organ vasculitis. *Curr Opin Rheumatol* 2008; 20(1): 40–46.
17. Bourgarit A, Le Toumelin P, Pagnoux C, Cohen P, Mahr A, Le Guern V, et al. Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: A retrospective analysis of causes and factors predictive of mortality based on 595 patients. *Medicine (Baltimore)* 2005; 84(5): 323–30.
18. Guillevin L, Pagnoux C. Therapeutic strategies for systemic necrotizing vasculitides. *Allergol Int* 2007; 56(2): 105–11.
19. Al-Bishri J, le Riche N, Pope JE. Refractory polyarteritis nodosa successfully treated with infliximab. *J Rheumatol* 2005; 32(7): 1371–3.