Trends in Immunotherapy (2022) Volume 6 Issue 2
doi:10.24294/ti.v6.i2.1452

MINI-REVIEW

The concise review of etiology, pathology, and treatment strategy of polyarteritis nodosa

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ABSTRACT

Polyarteritis nodosa (PAN) is a necrotizing vasculitis that targets medium-sized muscular arteries and can involve small-sized arteries. The pathogenesis of classic PAN remains unclear, except for secondary PAN or vasculitis that is indistinguishable from PAN due to genetic abnormalities such as deficiency of adenosine deaminase 2. The histopathological characters of PAN change over time from the onset. The type of remission induction therapy to be adopted depends on the disease severity. When it results in remission, corticosteroid dose reduction will begin and will be shifted to remission maintenance therapy.

Keywords: Polyarteritis Nodosa; Deficiency of Adenosine Deaminase 2; Anti-Phosphatidylserine-Prothrombin Complex Antibodies

ARTICLE INFO

Received 2 April 2022
Accepted 6 April 2022
Available online 6 September 2022

1. History and etiology of PAN

Polyarteritis nodosa (PAN) is a necrotizing vasculitis that targets medium-sized muscular arteries and can involve small-sized muscular arteries, and form segmental lesions in damaged vessels. PAN frequently occurs in people in their fifties and sixties and is more prevalent in men. Although it has been pointed out that some PAN cases have been associated with viral infections such as hepatitis B virus in Western countries, it is rare in Japan. Classic PAN is a disease with an unknown etiology, partially because of changes in the disease concept of PAN.

The history of PAN began in 1866 when Kussmaul and Maier reported inflammatory arterial nodules as periarteritis nodosa. Later, it was revealed that the inflammation spread to the whole arterial wall rather than the periarterial area, and the name was changed to polyarteritis nodosa. Anti-neutrophil cytoplasmic antibodies (ANCA) were identified in cases of glomerulonephritis in 1982[1] and c-ANCA was reported to be positive in microscopic polyangiitis in 1985[2], and the pathogenicity of ANCA was proved. In response, a group in which ANCA was involved in the pathogenesis of vasculitis and in which vasculitis was unevenly distributed in small vessels, namely, microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis, became recognized as separate diseases from PAN. PAN is now defined as necrotizing arteritis of medium and small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with ANCA according to the

revised Chapel Hill Classification[3] published by the Chapel Hill Consensus Conference published in 2012, and it has become to be recognized as a rare disease.

Additionally, deficiency of adenosine deaminase 2 (DADA2) cases existed among the cases diagnosed with PAN. DADA2 is an autoinflammatory disorder characterized by immunodeficiency such as hypogammaglobulinemia due to the absence or low of class-switch memory B cells, hematological abnormalities such as cytopenia and necrotizing vasculitis of small and medium vessels pathologically indistinguishable from PAN. It can cause early onset lacunar infarction and skin symptoms such as livedo racemosa. Although the majority present in early childhood, adult-onset cases have also been reported. There are phenotypic differences such as age of onset and symptoms between and within families. DADA2 was reported as a group of cases showing autosomal recessive inheritance of adenosine deaminase 2 and loss-of-function mutations in the biallelic form, and 2 of 9 DADA2 cases had PAN[4]. Additionally, recessive loss-of-function mutations in adenosine deaminase 2 were found in Georgian and German families with familial childhood PAN[5]. In a cohort study of 60 cases of DADA2, dermatopathy was the most prevalent symptom, 74% had livedo racemosa and 57% had a history of cutaneous manifestations of PAN and nodules[6]. Nine of the 60 primary chronic pediatric vasculitis cases registered in the Pediatric Vasculitis Initiative international study had ADA2 variants, among which 5 of the 16 patients who had been diagnosed with PAN prior to testing had proven variants[7]. 2021 American College of Rheumatology/Vasculitis Foundation guidelines for managing PAN[8] has strongly recommended treatment with TNF-alpha inhibitors over corticosteroids alone in cases with clinical manifestations of DADA2.

The involvement of vascular damage during viral replication in PAN associated with hepatitis B virus infection and the involvement of genetic aberrations in DADA2 have been suggested, respectively, but the pathogenesis of classic PAN remains unclear including the involvement of immune complexes. However, there have been reports suggesting the involvement of anti-phosphatidylserine-prothrombin complex (PS/PT) antibodies and anti-moesin antibodies. It was reported that serum anti-PS/PT IgM antibodies were detected in 81.3% of cutaneous arteritis cases and their titers were significantly higher than systemic lupus erythematosus cases although they were not detected in healthy individuals[9]. It was also reported that the titer of anti-PS/PT antibodies in PAN cases with skin symptoms manifesting necrotizing vasculitis decreased significantly after treatments[10], indicating that anti-PS/PT antibodies serve as markers of PAN. Additionally, Kawakami *et al.* reported that serum anti-PS/PT IgM antibodies were higher in systemic vasculitis cases with skin involvements (3 cases of IgA vasculitis, 2 cases of eosinophilic granulomatosis with polyangiitis, 1 case of microscopic polyangiitis, and 1 case of granulomatosis with polyangiitis) and 1 case of cutaneous arteritis than healthy controls and cases of systemic vasculitis without skin involvements (2 cases of eosinophilic granulomatosis with polyangiitis, 2 cases of microscopic polyangiitis, 1 case of granulomatosis with polyangiitis, 1 case of rheumatoid vasculitis, and 1 case of PAN), but there was no significant difference in serum anti-PS/PT IgG antibody titers, suggesting that serum anti-PS/PT IgM antibodies were involved in the pathogenesis of cutaneous vasculitis[11]. Okano *et al.* reported the overexpression of moesin in affected skin vessels and that the titer of serum anti-moesin antibodies in PAN cases with skin involvements due to necrotizing vasculitis is positively correlated with the Birmingham Vasculitis Activity Score and the Vasculitis Damage Index[10].

2. Pathology of PAN

There is a certain correlation between the location of damaged blood vessels by vasculitis in the skin and the skin symptoms[12] (**Figure 1**). The small vessel vasculitis that affects superficial dermal vessels such as ANCA-associated vasculitis can cause palpable purpura and wheals, whereas PAN, which is one of medium vessel vasculitis, which affects small-sized arteries in deep dermis and subcutaneous tissue can show livedo reticularis, infiltrative erythema, and nodules (**Figures 2** and **3**), sometimes

with deep ulceration and necrosis.

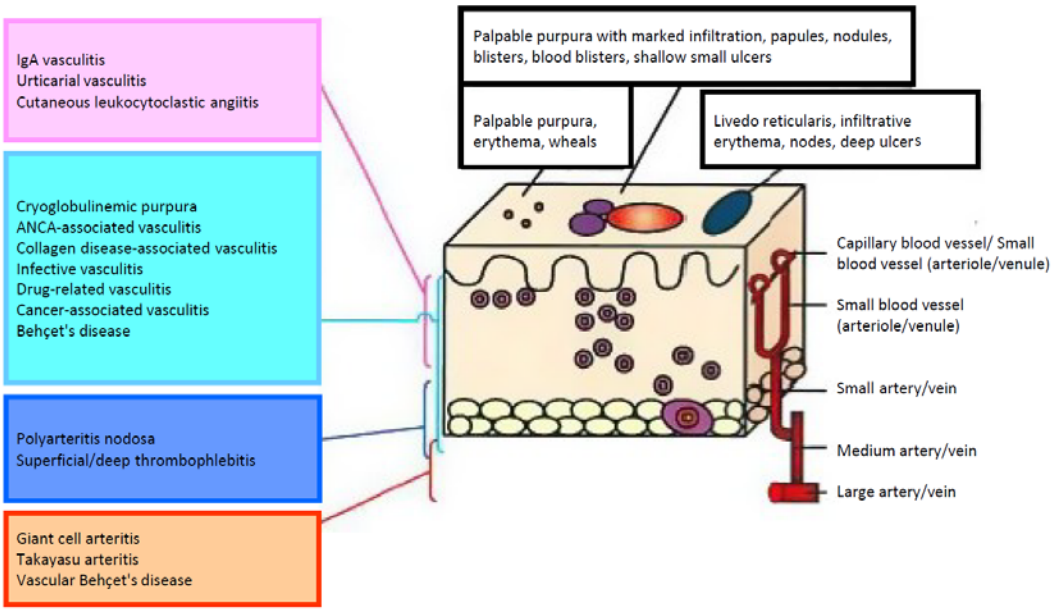


Figure 1. Correlation of skin symptoms and affected vascular levels[12].

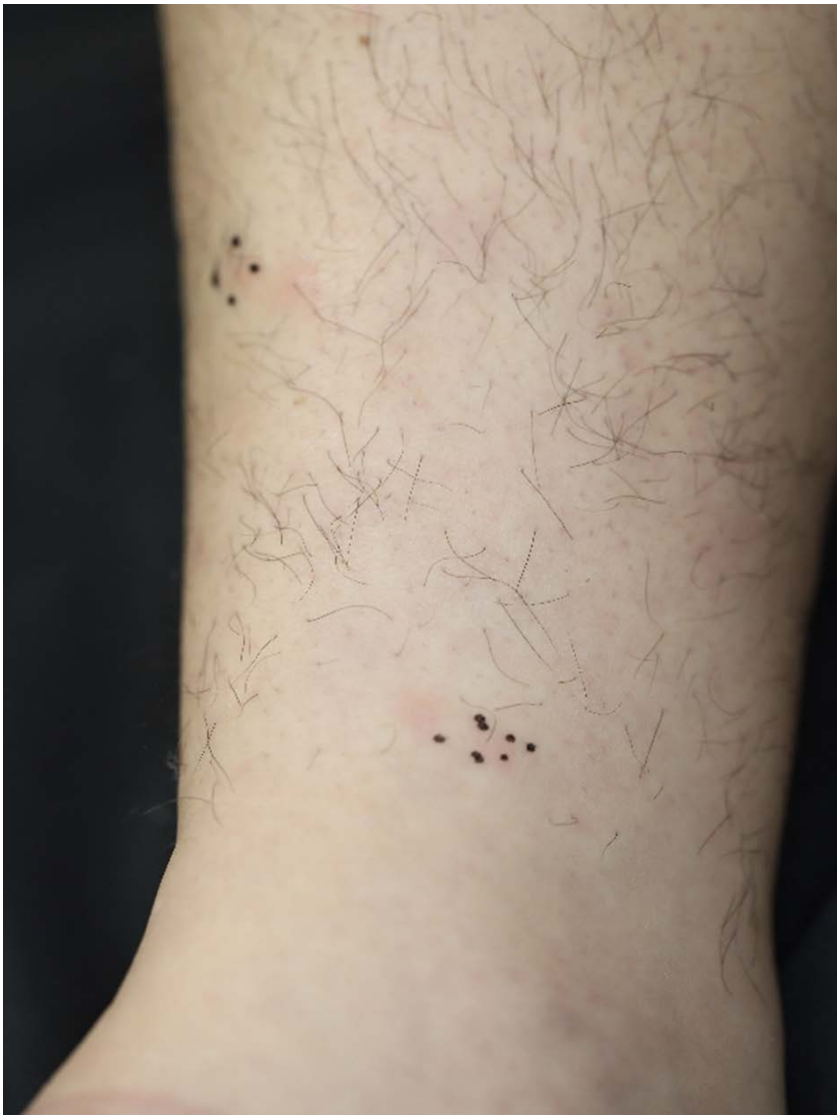


Figure 2. Subcutaneous nodules due to polyarteritis nodosa (medial lower leg).

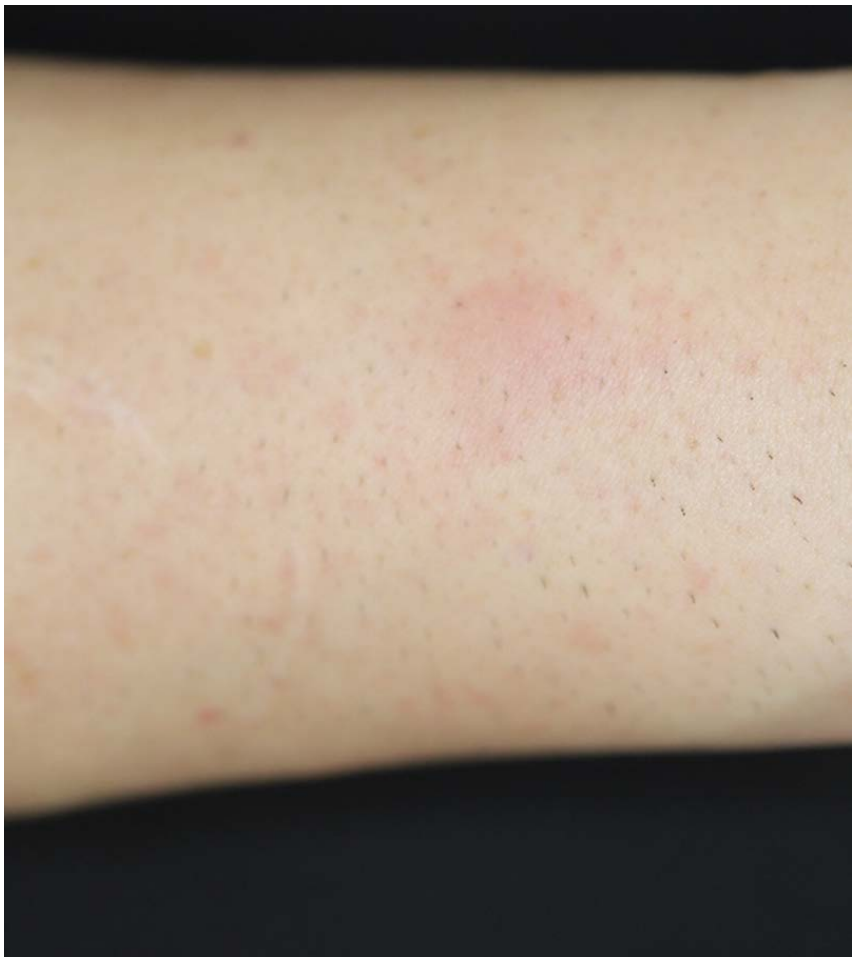


Figure 3a. Infiltrative erythema due to polyarteritis nodosa (forearm).

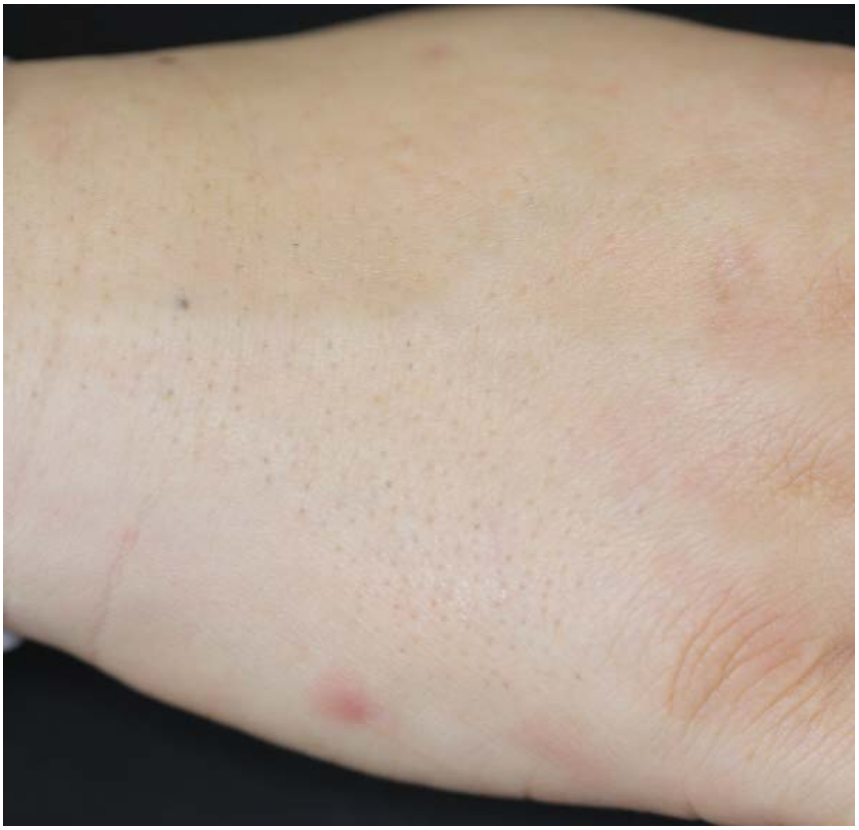
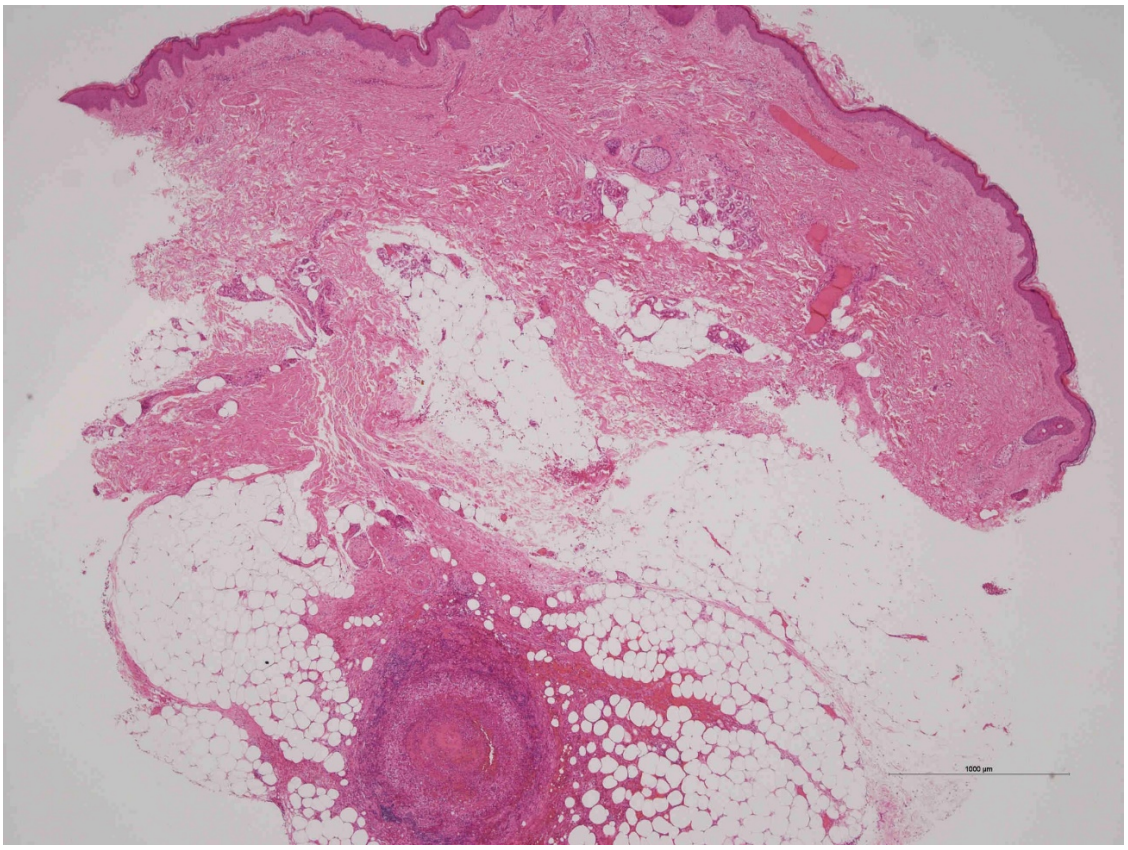
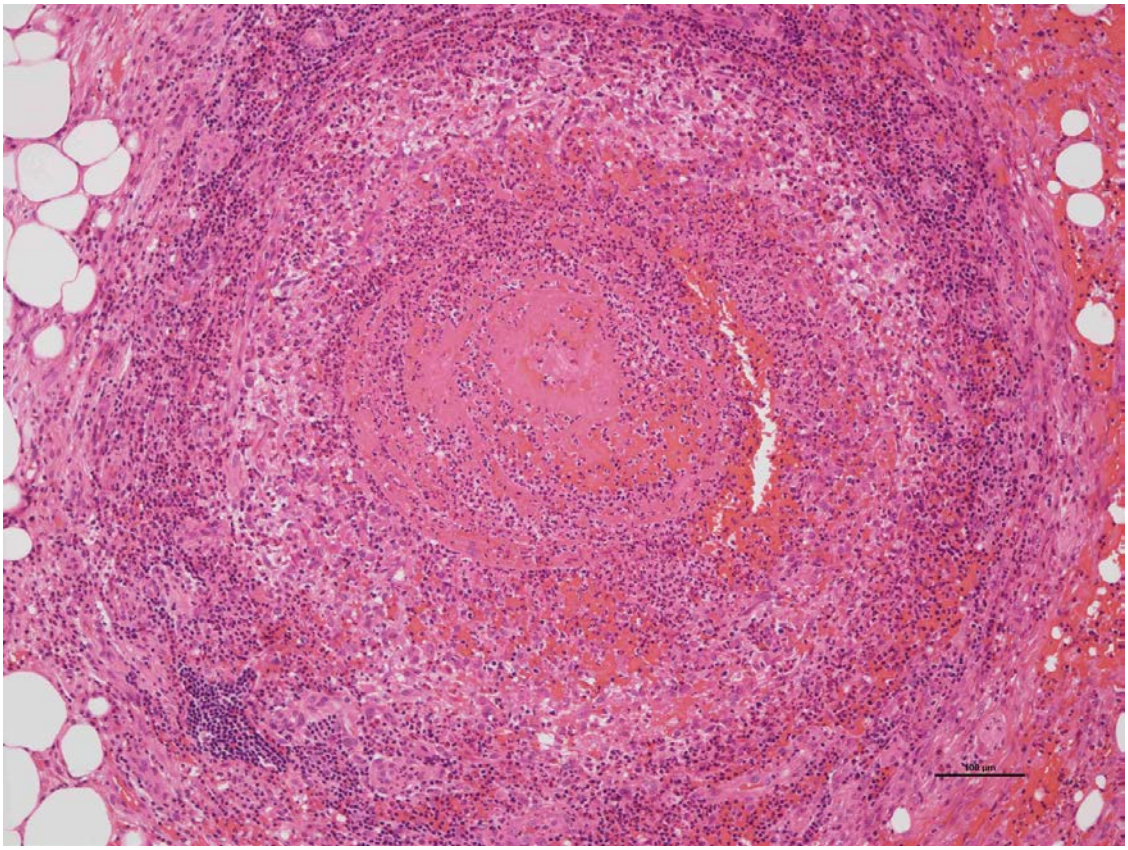


Figure 3b. Nodule with erythema due to polyarteritis nodosa (hand).



(a)



(b)

Figure 4. Dermatopathological image of polyarteritis nodosa. (**a**) High degree of inflammatory cell infiltration in and around the muscular artery in the subcutaneous adipose tissue is observed. (**b**) Fibrin-like material is deposited in the intima of b, and inflammatory cell infiltration mainly involving neutrophils appears to be centered on the arterial wall.

The histopathological characters of PAN change over time from the onset (**Figure 4**). The middle and inner membranes of the affected arteries undergo fibrinoid degeneration and infiltrating neutrophil-dominated cells cause inflammation. Later, infiltrating cells become lymphocyte-dominated, the intima become thickened, and the cavities become narrowed. Farther, the inner and outer elastic lamina rupture and granulation tissues are formed. Finally, aneurysms are formed with scarring of damaged blood vessels. Reflecting these pathological changes, the clinical manifestations of PAN include systemic symptoms caused by inflammation, such as fever and weight loss, and can cause ischemic symptoms of damaged organs such as myocardial and cerebral infarction.

3. PAN treatment strategy

The pathogenesis of classic PAN remains unclear, except for secondary PAN such as PAN related to hepatitis B virus infection or vasculitis that is indistinguishable from PAN due to genetic abnormalities such as DADA2. In any case, to date, classic PAN has been treated with the use of glucocorticoids and immunosuppressive agents, and it is fully considered that some immune abnormalities are involved.

Generally, remission induction therapy and remission maintenance therapy after entering remission are examined separately.

The type of remission induction therapy to be adopted depends on the disease severity. In the clinical practice guidance for PAN published in Japan in 2021, “severe disease” is defined as showing five factor score ≥1, or in American College of Rheumatology/Vasculitis Foundation guidelines in 2021[9], it refers to life- or organ-threatening conditions such as renal disease, mononeuritis multiplex, muscle disease, mesenteric ischemia, coronary involvement, and limb/digit ischemia. For severe cases, the treatment with glucocorticoids and cyclophosphamide has been proposed or conditionally has been recommended over glucocorticoids alone in both. For non-severe cases, the Japanese guidance has proposed the treatment with glucocorticoids alone over glucocorticoids and azathioprine because the results of systematic review in the guidance showed that the combination therapy leaded to more remission but increased the frequency of severe infections without significant differences. Additionally, the treatment with intravenous cyclophosphamide or azathioprine has been proposed to be added when the efficacy of the induction treatment with glucocorticoids alone has been inadequate. On the other hand, the American College of Rheumatology/Vasculitis Foundation’s guideline[9] has conditionally recommended the treatment with glucocorticoids and nonglucocorticoid immunosuppressive agents such as azathioprine and cyclophosphamide over glucocorticoids alone because the additional noncorticosteroid therapies were ultimately required in many cases even if treated with corticosteroid monotherapy and it might lead to minimize glucocorticoid use and toxicity.

Specific doses of the drugs have been recommended in guideline for management of vasculitis syndrome by Japanese Circulation Society in 2017[13]. For moderate-to-severe PAN with lesions in vital organs, prednisolone 1 mg/kg/day for 4 weeks with cyclophosphamide (adjusted for age and renal function, cyclophosphamide pulse therapy has been 10–15 mg/kg/dose 3–6 times every 3–4 weeks) and for PAN with extremely severe symptoms steroid pulse therapy (methylprednisolone 0.5–1 g for 3 consecutive days) simultaneously have been recommended to be performed. Furthermore, it has been recommended that for mild PAN without significant organ involvement administration of prednisolone alone at 0.5–1.0 mg/kg/day has been performed and cyclophosphamide or the like has been added if no improvement was obtained. If remission induction therapy results in remission, corticosteroid dose reduction will begin 3–4 weeks after the start of treatment and will be shifted to remission maintenance therapy. It has been suggested that prednisolone has been reduced and continued at 5–10 mg/day and cyclophosphamide has been changed by azathioprine at 1–2 mg/kg/day or methotrexate.

Many skin symptoms such as palpable purpura and infiltrative erythema caused by vasculitis can be treated with systemic administration of glucocorti-

coids or immunosuppressive agents according to the severity in other organs. However, some cutaneous symptoms such as vasculitis-induced skin ulcers should be treated not only with corticosteroids or immunosuppressants but also with vasodilators and antiplatelet agents, as well as with topical treatments according to wound conditions. There are no studies reporting superiority of the invasive treatments including skin grafts nor evidence of their usefulness over the conservative treatments, thus, the conservative treatments should be dedicated.

Diseases that cause vasculitis only affect vessels of specific sizes, and the skin symptoms caused by vasculitis correspond to the size of the cutaneous vessels damaged by the disease.

Conflict of interest

No conflict of interest was declared by the author.

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