Clinical presentations and long-term prognosis of childhood-onset polyarteritis nodosa in a single centre: a retrospective study

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Abstract

Background: Polyarteritis nodosa (PAN) is a systematic necrotizing vasculitis involving medium-sized arteries. Childhood-onset PAN ranges from mild to severe systematic disease causing damage and early mortality. As it is a rare disease in children, there is less study on clinical features, diagnosis and treatment than adults. And diagnosis occurs relatively late in most paediatric patients with polyarteritis nodosa. Therefore, this study aimed to investigate clinical manifestations, laboratory findings, treatment strategies, and long-term outcomes among patients with childhood-onset polyarteritis nodosa treated at a single-centre in Korea. We further aimed to evaluate the usefulness of the Birmingham Vasculitis Activity Score (BVAS) and Five-Factor Score (FFS) in paediatric patients.

Methods: We retrospectively analysed data collected from patients with childhood-onset PAN treated at our institution from March 2003 to February 2020.

Results: Nine patients (6 male and 3 female) were included in the study. The median ages at symptom onset and diagnosis were 7.6 (3–17.5) and 7.7 (3.5–17.6) years, respectively. The median follow-up duration was 7.0 (1.6–16.3) years. Eight patients were diagnosed with systemic PAN, while one was diagnosed with cutaneous PAN. All patients exhibited skin manifestations, while five exhibited Raynaud's phenomenon. Organ involvement was observed in one patient. Constitutional symptoms such as fever, arthralgia, myalgia, and weight loss were also observed. Antineutrophil cytoplasmic antibodies were absent in all patients. The median BVAS at diagnosis was 8 (range: 2–29), and one patient had an FFS of 1. Prednisolone was initially used for induction in all patients, and other drugs were added in cases refractory to prednisolone. All patients survived despite some complications such as intracranial haemorrhage or digital necrosis requiring amputation.

Conclusions: Early diagnosis and treatment may minimise sequelae in patients with childhood-onset PAN. Further multicentre studies are required to clarify the unique characteristics of childhood-onset PAN and establish treatment guidelines, early detection strategies, and biomarkers.

Trial registration: Retrospectively registered.

Background

Polyarteritis nodosa (PAN) is defined as a necrotising inflammation of medium- to small-sized arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and is not associated with antineutrophil cytoplasmic antibodies (ANCA) [1]. Although epidemiological data related to childhood-onset PAN are relatively scarce, the disease is known to be more common in adults than in children [2, 3]. Clinically, childhood-onset PAN presents as mild to severe inflammation, often leading to damage and early mortality [4]. A study from a major tertiary referral centre mainly following children with aggressive/advanced PAN reported a mortality rate of 1.1–10% [5]. Another large multicentre study from a tertiary referral centre, in which one third of patients exhibited cutaneous forms of PAN, reported a mortality rate of 1.1% [6]. Early diagnosis and appropriate treatment for childhood-onset PAN are important for minimising irreversible complications and improving prognosis [4]. Despite the presence of classification criteria, early diagnosis remains challenging because most patients with childhood-onset PAN visit the hospital due to non-specific constitutional symptoms. Myalgia and skin involvement are also significantly more frequent in patients with childhood-onset PAN than in those with adult-onset PAN [7], which may lead to further delays in diagnosis. Moreover, PAN is difficult to treat due to a lack of guidelines, and few evidence-based studies have investigated childhood-onset PAN.

There are vasculitis scoring for adult such as the Birmingham Vasculitis Activity Score (BVAS) and the Five-Factor Score (FFS). The BVAS is a clinical index of disease activity based on signs and symptoms, while the FFS is used for assessing prognosis and mortality. In previous studies, five-year mortality rates were 46% and 12% in patients with an FFS 2 and 0, respectively [8, 9]. Since vasculitis is rare in children, there is no scoring system for childhood-onset vasculitis.

The present study aimed to investigate the diagnosis, management, and outcomes of patients with childhood-onset PAN treated at a single tertiary centre in Korea over a period of approximately 17 years. We further aimed to assess the efficacy of the BVAS (version 3) and FFS in paediatric patients.

Methods

Patients

All patients with a diagnosis of PAN treated in our department, including those living outside our local catchment area, treated from March 2003 to February 2020 were eligible for this study. All patients were diagnosed prior to age 18 and satisfied both American College of Rheumatology criteria [2] and European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) criteria [10]. In accordance with these criteria, patients were diagnosed with PAN when they presented with a systemic illness characterised by either a biopsy showing necrotising vasculitis (i.e. granulocyte or mixed leukocyte infiltrates in the arterial wall) in small and medium-sized arteries or confirmed angiographic abnormalities (e.g., vascular aneurysms and occlusions). In addition, patients were required to exhibit at least one of the following five clinical items: skin signs, myalgia/muscle tenderness, peripheral neuropathy, hypertension, or renal vascular disease. Cutaneous PAN was classified as follows: necrotising vasculitis of medium-sized arteries within the skin, without

involvement of the internal organs, accompanied by fever, painful subcutaneous nodules, livedo reticularis, arthralgia, or myalgia [11, 12]. The present study was approved by the Institutional Review Board of Seoul National University Hospital in Korea (H-2004227-1119), who waived the requirement for informed consent because of the retrospective nature of the study.

Data collection at diagnosis

Each patient's medical records were reviewed in detail. From the time of diagnosis, the following data were retrieved: age; gender; the first clinical signs attributable to vasculitis; the time required to reach diagnosis (defined as the time from the first signs attributable to vasculitis until the date vasculitis was diagnosed via angiography or biopsy); signs of peripheral neuropathy; and manifestations of skin, central nervous system, genital, gastrointestinal, musculoskeletal, urologic, and renal involvement. We also collected data related to functional impairments such as fever (body temperature > 38.0°C); weight loss and malaise; laboratory findings including autoantibodies, viral serology, renal parameters (proteinuria, haematuria, and serum creatinine levels), and inflammation parameters (erythrocyte sedimentation rate [ESR] and high sensitivity C-reactive protein [hs-CRP] levels). We also reviewed initial treatments, responses to treatment, and histologic/radiologic findings.

Definition of disease activity and damage

At the time of diagnosis, disease activity was assessed using version 3 of the BVAS [13]. The BVAS is a clinical index of disease activity based on signs and symptoms in nine separate organ categories (systemic, skin, mucous membranes and eyes, ear–nose–throat, chest, heart and vessels, gastrointestinal, kidney, nervous system). The maximum possible BVAS score is 63. Prognosis was assessed using the FFS [9]. FFS assessments are based on the following five items: renal insufficiency, proteinuria (> 1 g/day), central nervous system involvement, cardiac involvement, severe gastrointestinal involvement (e.g., bleeding, infarction, and/or pancreatitis). Each item is assigned 1 point, and higher scores are considered indicative of increased mortality.

Data collection during follow-up

During follow-up, we collected treatment-related data and recorded the timing of symptoms at relapse. We also obtained photos reflecting changes in symptoms over time and re-assessed multi-system involvement (i.e., musculoskeletal, skin, cardiovascular, renal, gastrointestinal, peripheral vascular, neuropsychiatric). Comorbidities such as diabetes mellitus and other conditions such as haemorrhagic cystitis or proteinuria were also assessed. Relapse was defined as the reoccurrence of PAN manifestations in a patient whose disease had previously been in sustained remission and required the addition of or a change in immunosuppressive agents, reinstitution of corticosteroids, and/or an increase in dose.

Statistical analyses

Categorical variables are expressed as numbers (%), while continuous variables are expressed as medians (range: minimum–maximum) or the mean $\pm$ standard deviation (SD). All statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA).

Results

Clinical characteristics at diagnosis

Nine children (male: 6, female: 3) were included in the present study. The median age at initial signs or symptoms was 7.6 years (range: 3–17.5 years; mean: 9.1 ± 1.54 years), and the median age at diagnosis was 7.7 years (range: 3.5–17.6 years; mean: 9.3 ± 1.55 years). The median interval from onset of initial symptoms to diagnosis was 41 days (range: 30–249 days; mean: 90.0 ± 30.26 days). The median follow-up duration was 7.0 years (range: 1.6–16.3 years; mean: 7.8 ± 1.98 years). All patients were vaccinated against hepatitis B and had antibody levels expected to protect against the virus. No patients had a family history of rheumatic disease. Clinical manifestations and disease activity scores at diagnosis are summarised in Table 1. One patient was diagnosed with cutaneous PAN, while all others were diagnosed with systemic PAN. Skin signs were the most frequent initial manifestations of disease at diagnosis (purpura: 8, Raynaud's phenomenon: 5, skin infarct: 3, subcutaneous nodules: 3, livedo reticularis: 2), followed by musculoskeletal (arthralgia: 77.8%), systemic (fever: 66.7%), neurologic (headache, ptosis, stroke, and gait disturbance: 11.1%), and renal involvement (hypertension and serum creatinine elevation: 11.1%). No patients presented with mucous membrane, eye, ear, nose, throat, pulmonary, or cardiovascular symptoms. All patients were initially diagnosed with different diseases prior to the diagnosis of childhood-onset PAN. Five were diagnosed with joint problems such as reactive arthropathy, synovitis, psoriatic arthritis, or juvenile rheumatoid arthritis, three with unspecified vasculitis, and two with erythema nodosum. Thus, most patients ($n = 8$) had taken oral or high-dose intravascular corticosteroids prior to the diagnosis of childhood-onset PAN. One received intravenous immunoglobulin G (IVIG) prior to PAN diagnosis for the treatment of truncal ataxia, left ptosis, and gait disturbance, resulting in improvement of symptoms (ptosis and truncal ataxia).

Table 1
Clinical characteristics of nine patients at diagnosis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Sex	Male	Male	Male	Female	Male	Male	Male	Female	Female
Subtype	Systemic	Systemic	Systemic	Systemic	Systemic	Systemic	Systemic	Cutaneous	Systemic
Age at diagnosis, years	17.6	5.8	5.6	3.5	7.5	9.4	7.7	15.3	11.1
Diagnosis delay, days	30	30	62	192	31	89	41	249	32
Initial symptoms at diagnosis									
General	+	+	+	-	+	+	+	-	-
Fever ^a	+	-	-	-	-	-	-	-	-
Weight loss ^b	+	+	+	-	+	+	+	-	+
Arthralgia	-	-	-	-	-	-	+	-	+
Myalgia									
Skin	+	+	-	+	+	+	+	+	+
Purpura	+	-	+	-	-	-	-	-	+
Subcutaneous nodules	-	+	-	+	-	-	-	-	-
Livedo reticularis	-	-	-	-	+	+	+	-	-
Skin infarct									
Raynaud's phenomenon									
Nervous system	-	-	-	+	-	-	-	-	-
Ptosis	-	-	-	+	-	-	-	-	-
Gait disturbance	-	-	-	+	-	-	-	-	-
Headache									
Stroke									
Renal	-	-	-	+	-	-	-	-	-
Hypertension	-	-	-	+	-	-	-	-	-
Serum Cr ^{†c}									
Abdominal	-	-	-	+	-	-	-	-	-
Abdominal pain									
Initial diagnosis	EN Reactive arthropathy	Synovitis r/o JIA	Septic arthritis r/o vasculitis	Multiple sclerosis	Unspecified vasculitis	Unspecified vasculitis	Synovitis r/o JIA	EN	Psoriatic arthritis
Steroid Hx ^d	+	-	+	+	+	+	+	+	+
Diagnostic method	Skin biopsy	Skin biopsy	Skin biopsy	Angiography	Skin biopsy	Skin biopsy	Skin biopsy	Skin biopsy	Skin biopsy

EN: erythema nodosum; JIA: juvenile idiopathic arthritis; FFS: Five-Factor Score; BVAS: Birmingham Vasculitis Activity Score. ^aDocumented axillary temperature, raised threshold to 38.0°C; ^bLoss of dry body weight without dieting ≥ 2 kg; ^cIncrease in serum creatinine > 30%, from 0.4 to 0.6 mg/dl; ^dHistory, treated with prednisolone or methylprednisolone pulse therapy before prior to the diagnosis of childhood-onset PAN.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
FSS	0	0	0	2	0	0	0	0	0
BVAS	7	7	5	29	9	9	9	2	8

EN: erythema nodosum; JIA: juvenile idiopathic arthritis; FFS: Five-Factor Score; BVAS: Birmingham Vasculitis Activity Score. ^aDocumented axillary temperature, raised threshold to 38.0°C; ^bLoss of dry body weight without dieting ≥ 2 kg; ^cIncrease in serum creatinine $> 30\%$, from 0.4 to 0.6 mg/dl; ^dHistory, treated with prednisolone or methylprednisolone pulse therapy before prior to the diagnosis of childhood-onset PAN.

Five (55.6%) patients had leucocytosis (median: 14,740/uL, range: 6,960–31,290/uL), six (66.7%) patients had thrombocytosis (median: 463,000/uL, range: 230,000–706,000/uL), and three (33.3%) patients had anaemia (median: 12.1 g/dL, range: 9.7–14.1 g/dL). All patients exhibited ESR elevation (median: 48 mm/h, range: 9–125 mm/h), while seven (77.8%) exhibited increased hs-CRP (median: 8.13 mg/dL, range: 0.01–28.63 mg/dL). No ANCA were detected in any patient. Eight patients were diagnosed via skin biopsy. Perivascular lymphocytic infiltration was observed in seven patients (77.8%), neutrophilic infiltration was observed in three patients (33.3%), eosinophilic infiltration was observed in three patients, and fibrinoid necrosis (i.e., chronic PAN) was observed in one patient (11.1%) (Fig. 1a). Patient 4 was diagnosed via angiography because no inflammatory findings were observed in the skin, including adipose tissue and vessels. In this patient, cerebral angiography and abdominal aortography revealed multiple microaneurysms in the distal cerebral, renal, and splenic arteries, which resulted in ischemic damage in the brain (Fig. 1b) and kidneys (Fig. 1c).

The median BVAS at diagnosis was 8 (mean: 9.4 ± 2.56 ; range: 2–29). Only one patient (Patient 4) had an FFS of 2, while all others had FFS scores of zero.

Treatment modality

All patients were initially treated with prednisolone. Table 2 shows treatment modalities for all patients. In patients with mild organ involvement (i.e., peripheral neuropathy, cutaneous involvement without skin infarcts), medium- to low-dose steroids represented the treatment of choice, sometimes in combination with azathioprine. In patients with severe, life-threatening multi-system involvement (i.e., severe skin or brain infarcts, brain haemorrhage), the treatment of choice consisted of high-dose intravenous (IV) administration of 6-methylprednisolone (mPd) (10–30 mg/kg, once daily for 3 days), followed by oral prednisolone [2]. Patients who did not respond to high-dose IV mPd and those with severe skin infarcts or brain involvement were treated with high-dose IV cyclophosphamide (600 mg/m² body surface area) at 30-day intervals, oral cyclophosphamide (1–3 mg/kg/day), high-dose IV mPd again, and/or IV infliximab (Remicade®, anti-tumour necrosis factor alpha (TNF- α) inhibitor) at 5 mg/kg [14–16] depending on individual toxicity profiles or physician preference. IVIG was administered based on the patient's clinical status [17–19]. In six patients, other drugs were added for induction: cyclophosphamide in five patients (IV: 4, oral: 1), IVIG in two patients, and infliximab in one patient. Following treatment, patients were placed on maintenance therapy. Although azathioprine (1–2 mg/kg), methotrexate (10 mg/m² body surface area), or low-dose oral prednisolone represented the drug of choice in most patients, one patient was instead treated with cyclosporine due to the side effects of oral prednisolone. Four patients (Patients 5, 6, 7, and 9) presenting with Raynaud's phenomena were treated with vasodilators such as nifedipine and IV alprostadil (Eglandin®, prostaglandin E1).

Table 2
Major events during follow-up for nine patients

Patient	Follow-up, years	Initial treatment		1st relapse, days	Number of relapses	Symptoms at relapse	Operation	Remaining symptoms	Adverse drug reactions
		Induction	Maintenance						
1	2.5	IV high dose mPd	AZT, PD tapering	-	0	-	-	Hand tremor	Cushingoid face
2	1.6	PO PD	PD tapering	-	0	-	-	-	-
3	16.3	PO PD	PD tapering	112	4	Fever, oral ulcer, arthralgia, purpura, Raynaud phenomenon	-	Livedo reticularis	-
4 ^{a,b}	15.8	PO PD IV high dose CPM	PD tapering	155	6	Abdominal pain Headache, vomiting	-	Subcutaneous nodule Hemiplegia	Osteoporosis, Compression fracture of L1 Fatty liver
5 ^b	12.0	IV high dose mPd PO CPM IVIG	PD tapering	177	4	Fever, skin nodule, Raynaud phenomenon	Amputation	arthralgia	Osteochondritis, hypertension
6 ^{b,c}	9.9	IV high dose mPd IV high dose CPM → PO CPM	PD tapering, Cyclosporin	219	1	Raynaud's phenomenon	Amputation	-	Hypertension, seizure, cataract, gastritis pseudomembranous colitis
7 ^b	7.0	IV high dose mPd IV high dose CPM → PO CPM IVIG IV infliximab	AZT, MTX, PD tapering	117	3	Raynaud's phenomenon, Purpura	-	Subcutaneous nodule	Hypertension, Cushingoid face, Buffalo hump, haemorrhagic cystitis
8	3.0	PO PD	AZT	-	0	-	-	-	-
9 ^b	2.0	IV high dose mPd IV high dose CPM → PO CPM	AZT, PD tapering	147	1	Raynaud's phenomenon	-	Purpura	Cushingoid face

Major events during follow-up for nine patients. mPd, 6-methylprednisolone; AZT, azathioprine; PD, prednisolone; IVIG, intravenous immunoglobulin G; CPM, cyclophosphamide. ^aPatient 4 was treated with IVIG and several mPD pulse before diagnosis as PAN; ^btreated with nifedipine ointment and alprostadil for Raynaud's phenomenon; ^cOral cyclosporin A was used for maintenance and stopped because of hypertensive encephalopathy.

Clinical manifestations during follow-up

The clinical manifestations observed during follow-up are presented in Table 2. During follow-up (median: 7.0 years; range: 1.6–16.3 years), six patients (66.7%) experienced disease relapse. The median time to initial relapse was 151 days (range: 112–219 days, mean: 154.5 ± 16.3 days), and the median number of relapses was 1 (range: 0–6, mean: 2.1 ± 0.73). Relapses were mostly minor and predominantly involved the skin in all six patients. Five patients experienced multiple relapses during the follow-up period. The median time from the first maintenance treatment to relapse was 151 days (range: 46–219 days, mean: 143.5 ± 23.9 days). At the time of the first induction treatment, the median duration of administration was

53.5 days (range: 12–107 days, mean: 62.0 ± 13.3 days). After relapse, the median duration of induction treatment was 17 days (range: 0–29 days, mean: 15.8 ± 5.1 days). As such, the duration of hospitalisation was short during relapse. Skin necrosis was observed in the fingertips of three patients with relapse. Although two of these patients recovered completely, finger amputation was required in one patient. Patient 4 underwent surgery several times due to intracranial haemorrhage, which resulted in hemiparesis of the right side. No deaths were observed during the follow-up period (median: 7.0 years, range: 1.6–16.3 years).

Adverse drug reactions included hypertension in three patients taking prednisolone. Among them, one experienced a seizure and exhibited proven hypertensive encephalopathy. Other adverse drug reactions due to prednisolone included Cushing syndrome, gastritis, fatty liver, osteoporosis, compression fracture, and infection. One patient experienced haemorrhagic cystitis due to cyclophosphamide treatment, which improved followed discontinuation of the drug.

Disease status at the most recent follow-up

At the most recent follow-up, two patients (Patients 5 and 6) were in clinical remission without medication, while seven patients were in clinical remission with prednisolone for maintenance therapy. In Patient 4, who has experienced multiple relapses and multi-organ involvement thus far, the last relapse occurred in December 2013. She continues to take low dose prednisolone, methotrexate, and azathioprine and engage in rehabilitation therapy.

Discussion

To our knowledge, the present study is the first to report the clinical characteristics and long-term outcomes of childhood-onset PAN in Korea and analyse the utility of the FSS and BVAS in paediatric patients. Given the partial accordance of our findings with those of previous researchers, we believe that our study provides useful data related to the clinical manifestations of childhood-onset PAN.

Previous studies [6, 12, 20] have reported that skin involvement and arthralgia/arthritis are more common in children than in adults with PAN. In contrast, weight loss and renal, gastrointestinal, and neurologic involvement appear to be more common in adults with PAN. In the largest multicentre study to date, which included 110 paediatric patients with PAN (63 with systemic PAN) [6], 92% of patients exhibited cutaneous lesions, while 71.4%, 43%, 33.3%, 14%, and 11% exhibited myalgia, hypertension, central nervous system involvement, cardiac involvement, and pulmonary involvement, respectively. In another large paediatric series including 69 patients with systemic PAN [21], presenting features by organ system were as follows: skin involvement in 88%, myalgia in 83%, arthralgia/arthritis in 75%, weight loss in 64%, fever in 60%, renal involvement in 19%, severe gastrointestinal involvement in 10%, and central nervous system involvement in 10%. In accordance with previous findings, skin and joint symptoms were noted in most of our patients, although rates of myalgia were lower in our study. These findings suggest that cutaneous manifestations with nonspecific systemic symptoms in children necessitate referral to a specialist in paediatric rheumatology or dermatology to ensure prompt clinical diagnosis.

Laboratory features including serum creatinine, urinalysis, liver function tests, and muscle enzyme concentrations were largely non-specific and included elevated ESR and hs-CRP in most cases. However, these findings are neither sensitive nor specific for the diagnosis of PAN. That is, there are no laboratory findings that can be used to definitely diagnose either childhood- or adult-onset PAN. Evidence suggests that childhood-onset PAN affects girls more than boys, in contrast to adult-onset PAN [8, 20, 21]. Although we enrolled only a small number of patients, the prevalence of PAN appeared slightly higher in boys ($n = 6$) than in girls ($n = 3$). While previous studies have reported mortality rates ranging from 1–4% [6, 21], no deaths were observed during our study period.

We also evaluated BVAS and FFS in our patients. No patients exhibited involvement of the mucous membranes, eyes, ears, nose, throat, chest, or cardiovascular system (used for BVAS assessment). Skin manifestations, especially Raynaud's phenomenon with or without digital necrosis, were observed in six and five patients at diagnosis and at the first relapse, respectively. For the BVAS, Raynaud's phenomena are not considered, and the contribution of skin symptoms is relatively small. However, Raynaud's phenomena and skin symptoms greatly influenced the treatment strategies adopted for our patients. These findings suggest that more detailed subdivisions of skin manifestations are required to develop a new vasculitis scoring system for children. The highest FFS (2 points) was observed in Patient 2, who experienced hemiplegia due to cerebral bleeding and haematoma as well as several relapses. Fortunately, disease activity in Patient 2 has been well controlled with low-dose prednisolone, azathioprine, and methotrexate. Although this finding indicates that the FFS may be useful for predicting mortality in both childhood- and adult-onset PAN, our study was limited by the small number of included patients. As few patients exhibited multi-organ involvement, it was difficult to assess the utility of the FFS in paediatric patients.

The most appropriate treatments for PAN remain to be determined. Given the rarity of the disease, no treatment guidelines have been established, especially for children. In our study, four patients initially presented with Raynaud's phenomena in the fingers. Finger amputation was necessary in two of these patients due to delayed diagnosis (Fig. 2a). In contrast, two patients who had been diagnosed earlier recovered without the need for amputation (Fig. 2b). These findings suggest that early diagnosis and aggressive intervention can help to improve long-term outcomes. Initial treatment with corticosteroids is important achieving remission in patients with adult-onset PAN, and steroid monotherapy is currently recommended for patients with mild PAN [22, 23]. In addition, cyclophosphamide is considered to induce remission, and immunosuppressive agents such as azathioprine or methotrexate are recommended to maintain remission or as steroid-sparing agents [24]. For induction, all patients in the present

study were treated with high-dose corticosteroids or corticosteroid pulse therapy. The degree of multi-organ involvement and the response to initial treatment are the principal determinants for the addition of cyclophosphamide, IVIG, or infliximab. Given the lack of controlled studies, IVIG treatment for vasculitis has been restricted to patients exhibiting resistance to corticosteroids and immunosuppressive therapy [25]. Both steroids and cyclophosphamide are associated with several side effects when used in children, including growth problems, metabolic syndrome, adverse psychological effects, hypertension, infection, malignancy, and infertility [26–28]. In the present study, we also observed adverse drug reactions including Cushingoid face (n = 3), hypertension (n = 3), infection (n = 2), osteoporosis (n = 1), and haemorrhagic cystitis (n = 1). These complications are particularly worrisome for children with many years of life ahead of them. Although we did not detect late complications such as malignancy or infertility in our study, physicians should screen for signs of infertility and malignancy in patients exposed to cyclophosphamide.

Recent reports have highlighted the safety and efficacy of the anti-TNF- α inhibitor infliximab in patients with PAN [29, 30]. Indeed, treatment of skin necrosis with infliximab appeared effective in our study. Although not used in the current study, the interleukin-6 blocker tocilizumab has also shown promise for the treatment of vasculitis [31, 32]. Strategies that aim to reduce the treatment burden as much as possible should be a major goal for physicians when attempting to achieve remission. Furthermore, paediatricians should closely monitor growth, psychological status, and long-term outcomes in patients with childhood-onset PAN.

Multiple cases of systemic and cutaneous PAN have been identified in some Georgian Jewish or German families, consistent with an autosomal recessive inheritance-induced mutation in the adenosine deaminase 2 (*ADA2*)-encoding gene *CECR1* (cat-eye syndrome chromosome region candidate 1) [4]. The discovery of this association between *ADA2* and vasculitis has led to reconsideration in most cases of childhood-onset PAN. Hence, it remains critical to evaluate family history and identify *ADA2* mutations when considering a diagnosis of PAN, as anti-TNF- α agents and *ADA2* replacement therapy may be warranted in some cases [30].

This study has several strengths. First, all patients were managed by two expert physicians affiliated with Seoul National University Children's Hospital, helping to ensure homogenous referral and treatment patterns among patients. In addition, patients were followed up for a relatively long period of time, allowing us to better characterise disease status based on clinical and laboratory information. Despite these strengths, the study possesses some limitations of note, including its single-centre retrospective design, which prevented us from assessing correlations between various treatment strategies and final outcomes. Furthermore, we were unable to perform a comprehensive multivariate analysis including clinical manifestations, FFS, and BVAS due to the small number of included patients. Lastly, we cannot exclude the potential for bias due to the inclusion of patients with more severe disease, who may be more likely to consult at tertiary referral centres.

Conclusion

Childhood-onset PAN is a rare disease that can be associated with severe complications despite appropriate treatment. Patients exhibiting central nervous system involvement, either at onset or during the disease course due to treatment, tend to experience the worst outcomes. Therefore, early diagnosis and aggressive treatment for childhood-onset PAN are important for improving prognosis without sequelae. Although our study provides some insight, further multicentre studies are required to clarify the unique characteristics of childhood-onset PAN and establish treatment guidelines, early detection strategies, and biomarkers.

List Of Abbreviations

PAN: polyarteritis nodosa

ANCA: antineutrophil cytoplasmic antibodies

BVAS: Birmingham Vasculitis Activity Score

FFS: Five-Factor Score

EULAR/PRINTO/PRES: European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society

ESR: erythrocyte sedimentation rate

hs-CRP: high sensitivity C-reactive protein

SD: standard deviation

IVIG: intravenous immunoglobulin G

IV: intravenous

ADA2: adenosine deaminase 2

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of Seoul National University Hospital in Korea approved the research protocol (H-2004227-1119).

Consent for publication

The Institutional Review Board of Seoul National University Hospital in Korea, approving this study waived the requirement for informed consent because of the retrospective nature of the study

Availability of data and materials.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

This study was designed, directed, and coordinated by Soyoung Lee. Jeong-Seon Lee assembled and analysed clinical data and wrote the manuscript. Joong-Gon Kim contributed to the revision of the manuscript. All authors have read and approved the final version of the manuscript.

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Figures

Figure 1

Pathologic and radiologic findings. a Histological findings for skin tissue: Medium-sized vessels in the subcutis exhibiting lympho-histiocytic, some neutrophilic, and slight eosinophilic infiltration. b Brain arteriography showing small micro-aneurysms in the distal cerebral arteries and brain MRI showing brain infarction. c Ascending aortography showing multiple aneurysms and peripheral vascular luminal narrowing in the superior mesenteric artery, inferior mesenteric artery, and renal (bilateral), splenic, and right coronary arteries. Abdominal CT showing renal infarction and renal cortical thickening. MRI: magnetic resonance imaging; CT: computed tomography.

Figure 2

Treatment responses and final outcomes for patients with skin involvement. a This patient exhibited Raynaud's phenomenon in the 3rd, 4th, and 5th fingertips as well as skin necrosis in the 5th fingertip at diagnosis. Early diagnosis and aggressive treatment allowed for preservation of the 5th finger despite slight shortening. b This patient experienced finger pain at the initial visit and gangrene in the 3rd, 4th, and 5th fingers, which worsened at the time of transfer despite corticosteroid treatment. Despite aggressive treatment, amputation of the 4th and 5th fingertips was necessary.