ARTHRITIS & RHEUMATISM
Vol. 65, No. 9, September 2013, pp 2476–2485
DOI 10.1002/art.38024

Systemic Polyarteritis Nodosa in the Young

A Single-Center Experience Over Thirty-Two Years

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Objective. **Polyarteritis nodosa (PAN) is a rare disease of childhood. The aims of this study were to describe the clinical features, treatment, and outcome of systemic childhood PAN and to identify predictors of relapse.**

Methods. **A single-center retrospective medical records review of children with PAN fulfilling the European League Against Rheumatism (EULAR)/Paediatric Rheumatology European Society (PRES)/Paediatric Rheumatology International Trials Organisation (PRINTO) classification criteria who were seen over a 32-year period was performed. Data on demographic and clinical features, treatments, relapses (recurrence of clinical signs/symptoms or occurrence of new symptoms after initial remission requiring escalation or resumption of immunosuppressive therapy), and deaths were recorded. A disease activity score was retrospectively assigned using the Paediatric Vasculitis Activity Score (PVAS) instrument. Cox regression analysis was used to identify significant predictors of relapse.**

Results. **Sixty-nine children with PAN were identified; 55% were male, and their median age was 8.5 years (range 0.9–15.8 years). Their clinical features at presentation were fever (87%), myalgia (83%), skin (88%), renal (19%), severe gastrointestinal (GI) (10%), and neurologic (10%) involvement. The PVAS at presentation was 9 of 63 (range 4–24). Histopathologic analysis of the skin showed necrotizing vasculitis in biopsy samples from 40 of 50 children. Results of selective visceral arteriography suggested the presence of PAN in 96% of patients. Treatment included cyclophosphamide and corticosteroids (83%), plasma exchange (9%), and biologic agents (after 2002; 13%). The relapse rate was 35%, and the mortality rate was 4%. Severe GI involvement was associated with increased risk of relapse ($P = 0.031$), while longer time to induce remission ($P = 0.022$) and increased cumulative dose of cyclophosphamide ($P = 0.005$) were associated with lower relapse risk.**

Conclusion. **Childhood PAN is a severe inflammatory disease of insidious onset and variable clinical presentation. Relapses occurred more frequently in those with severe GI involvement. A higher cumulative dose of cyclophosphamide was associated with a lower risk of relapse.**

Polyarteritis nodosa (PAN) was first described by Kussmaul and Maier in 1866 (1). The original and subsequent descriptions identified the pathologic features of necrotizing arteritis with nodules along the walls of medium and small muscular arteries, affecting multiple organ systems throughout the body (2). Despite some overlap with smaller vessel disease, PAN is a distinct entity and has an estimated annual incidence of 2.0–9.0/million in adults (3). The onset of the disease is typically between the ages of 25 and 50 years, but despite the lack of good epidemiologic data, it is becoming increasingly apparent that PAN occurs rather more frequently during childhood than the literature might suggest (2,4–6). Notably, the disease varies in its presentation from a relatively benign cutaneous form, which may resolve without treatment, to a severe systemic form

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Dr. Pilkington has received consulting fees from UCB (less than $10,000). Dr. Brogan has received consulting fees from Roche (less than $10,000).

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Submitted for publication November 29, 2012; accepted in revised form May 14, 2013.

(2,4–6). The etiology of PAN remains unclear, and it is likely that environmental triggers and host susceptibility play a key role (2).

System involvement in PAN varies, but the skin, the musculoskeletal system, the kidneys, and the gastrointestinal (GI) tract are most prominently affected, with cardiac, neurologic, and respiratory manifestations occurring less frequently (2,6,7). The characteristic histopathologic changes of PAN are fibrinoid necrosis of the walls of medium or small arteries, with a marked inflammatory response within or surrounding the vessel wall (2). The most valuable investigative procedure for the disease is selective visceral angiography (2,8). Arteriographic findings include aneurysms, segmental narrowing, and variations in the caliber of arteries, together with pruning of the peripheral vascular tree (8). Since many of the presenting features of PAN are nonspecific and mimic infectious or other, more common chronic inflammatory diseases of childhood, there is often considerable delay in diagnosis and a consequent delay in initiation of treatment, resulting in irreversible end-organ damage or death (2,4–6).

Documentation of large pediatric series of PAN is limited (9–11). The largest multicenter series was reported by Ozen et al (6) and described 110 children. This included children with either systemic (63 patients) or the milder cutaneous (33 patients) PAN, the latter generally having a more benign course (4,6,7,12), while the remaining children in that study had PAN associated with hepatitis B and microscopic polyangiitis. These previously published reports do not provide any basis for evaluating the prognostic significance of presenting signs and therapeutic approaches in the more severe systemic form of PAN. In addition, long-term outcomes with emphasis on disease and on treatment-related morbidity and mortality have not yet been explored in childhood PAN.

The aims of this study were to describe the presenting clinical, histopathologic, and arteriographic findings in children with systemic childhood PAN who presented to Great Ormond Street Hospital for Children NHS Foundation Trust, to describe the treatment given, to define the factors present at the time of diagnosis that were predictive of relapse, and to describe other longer-term complications of PAN and its treatment.

PATIENTS AND METHODS

Study population. Patients with a clinical diagnosis of PAN who were seen at the Great Ormond Street for Children NHS Foundation Trust between 1980 and 2012 and had been monitored for at least 12 months were identified from clinical and radiologic databases. Search terms used to look through the clinical database included polyarteritis nodosa, vasculitis, and PAN. Case notes were reviewed retrospectively, and patients fulfilling the European League Against Rheumatism (EULAR)/Paediatric Rheumatology European Society (PRES)/Paediatric Rheumatology International Trials Organisation (PRINTO) classification criteria for childhood PAN were included in the study (13,14). The classification criteria for childhood PAN are either histopathologic evidence of necrotizing vasculitis in medium or small arteries or angiographic abnormality (aneurysm, stenosis, or occlusion) as a mandatory criterion plus 1 of the following 5 features: skin involvement, myalgia or muscle tenderness, hypertension, peripheral neuropathy, and renal involvement (13). Patients with cutaneous PAN were excluded. Ethical approval was given by the Institute of Child Health/Great Ormond Street Research Ethics Committee for a retrospective review of case notes.

The demographic, clinical, and laboratory characteristics recorded at the time of diagnosis were sex, age, ethnicity (established via the information provided by patients or their parents to register with the hospital), organ involvement, the Paediatric Vasculitis Activity Score (PVAS) (15), the erythrocyte sedimentation rate (ESR), the serum C-reactive protein (CRP) level, platelet count, presence of proteinuria and/or hematuria, antineutrophil cytoplasmic antibody (ANCA) positivity (perinuclear or cytoplasmic), and histopathologic and arteriographic findings. The full glossary of terms used in the PVAS, as well as all variables of organ involvement assessed, have been published elsewhere (15). The glomerular filtration rate (GFR) was calculated retrospectively, based on the plasma creatinine concentration, using the Schwartz formula (16).

The time from diagnosis to first remission, the number of relapses, and the relapse symptoms were also recorded. In the case of deaths, information about the cause of the death and the contributing factors were documented. We reviewed the clinical charts for any clinical or laboratory signs of remission or relapse at every visit in order to record a global clinical evaluation in the database. Remission was defined as the absence of any clinical signs/symptoms of active vasculitis, as supported by laboratory evidence of normal CRP and ESR values and a PVAS of 0 of 63 (assigned retrospectively for every clinic visit), for 2 evaluations at least 1 month apart and with adherence to the prednisolone regimen. Relapse was defined as the recurrence of clinical signs/symptoms or the occurrence of new symptoms (PVAS >0) after an initial sustained remission of 3 months' duration, requiring the resumption of immunosuppressive therapy or the reinstitution of corticosteroids (dosage increased by $>50\%$ to >0.5 mg/kg/day).

Disease- and treatment-related morbidities, including infection and corticosteroid-related side effects, were also determined when the data were available. Osteopenia was identified if the Z score for bone density on dual x-ray absorptiometry (DXA) was >2 SD below the mean for the patient's age. DXA scans were performed on all children who had been receiving corticosteroids for >6 months and were repeated annually if children remained on steroid treatment. We compared the time to diagnosis, relapse rates, and deaths between the first and second 16-year study periods.

Statistical analysis. Continuous variables are summarized as the median and range except where indicated other-

wise. Categorical variables are presented as percentages and frequencies. To investigate the prognostic significance of each demographic, clinical, and laboratory characteristic, we computed the hazard ratio (HR) and 95% confidence intervals (95% CIs) for relapse in the study population as a whole, using Cox's regression analysis. Each variable was entered into a univariable analysis, and significant variables ($P < 0.1$) were then entered into a multivariable analysis. The proportional hazards assumption necessary for valid implementation of this model was assessed graphically after model fitting (17). For the analysis in which the first relapse was the outcome, patients were censored at the last followup or death. The proportion of patients surviving free of relapse was calculated using the Kaplan-Meier method and is presented graphically for the whole cohort. Kaplan-Meier curves were also plotted to assess between-group differences in relapse rates and were compared using log rank tests. All statistical analyses were performed using SPSS software, version 18.0. *P* values less than 0.05 (2-sided) were considered significant.

RESULTS

Demographic and clinical characteristics. Sixty-nine children who fulfilled the classification criteria for PAN were identified over a 32-year period from January 1980 to January 2012. Their mean age was 8.5 years (range 0.9–15.8 years), and 55% of them were male. The median duration of followup was 6 years (range 1.5–16 years). The majority of the patients were Caucasian (81%), 2 were Afro-Caribbean, and 11 were Asian. The median interval from onset of the first symptom to diagnosis was 1.2 months (range 0–20 months). The time to diagnosis was longer during the first 16 years of the study (median 1.1 months [range 0.4–20 months]) as compared to the second 16 years of the study period (median 0.6 months [range 0–15 months]; $P = 0.04$). The median PVAS at presentation was 9 of 63 (range 4–24).

The diagnosis of vasculitis was based on a combination of histopathologic evidence of necrotizing vasculitis in medium or small arteries and catheter digital subtraction arteriography (showing aneurysm, stenoses, and/or occlusion of a medium or small artery not due to fibromuscular dysplasia or other noninflammatory causes) in 43 of the 69 patients. In 22 of the 69 patients, arteriography alone was suggestive of medium-sized vessel vasculitis, and in 4 of the 69 patients, the diagnosis was based on histologic findings (skin biopsy samples revealed necrotizing vasculitis in medium-sized arteries), without arteriographic data.

The presenting clinical features are summarized in Table 1. Presenting features by organ system in the 69 study patients were as follows (descending order of frequency): skin involvement in 61 (88%), fever in 60 (87%), myalgia in 57 (83%), arthralgia/arthritis in 52 (75%), fatigue in 43 (62%), weight loss in 44 (64%), renal involvement in 13 (19%), hypertension in 11 (16%), severe GI involvement in 7 (10%), central nervous system involvement in 7 (10%), and peripheral neuropathy in 3 (4%). Additional categories and specific features are listed in Table 1. Skin nodules (16 patients

Table 1. Presenting clinical features in the 69 children with polyarteritis nodosa*

Presenting features	No. (%) of patients (n = 69)
Fever	60 (87)
Weight loss >5% of body weight	44 (64)
Fatigue	43 (62)
Myalgia or muscle tenderness	57 (83)
Arthralgia or arthritis	52 (75)
Skin involvement	
Livedo reticularis (purplish reticular pattern, usually irregularly distributed around subcutaneous fat lobules, often more prominent with cooling)	34 (49)
Skin nodules (tender subcutaneous nodules)	16 (23)
Purpura	28 (41)
Superficial skin infarctions (involving skin and superficial subcutaneous tissue) or other minor ischemic changes (nailbed infarctions, splinter hemorrhages, digital pulp necrosis)	3 (4)
Deep skin infarctions (involving deep subcutaneous tissue and underlying structures); necrosis/gangrene of digital phalanx or other peripheral tissue (nose and ear tips)	3 (4)
Other skin vasculitis (e.g., subcutaneous edema, RP)	16 (23)
Hypertension (systolic/diastolic blood above 95th percentile for height)	11 (16)
Renal involvement	
Proteinuria (>0.3 gm/24 hours or urinary albumin-to-creatinine ratio <30 mmoles/mg in a spot morning sample)	13 (19)
Hematuria (≥5 RBCs/hpf or RBC casts in the urinary sediment or ≥2+ on dipstick)	7 (10)
Impaired renal function (>10% increase in urinary creatinine or <25% decrease in creatinine clearance [GFR])	10 (15)
Neurologic involvement	
Motor mononeuritis multiplex	3 (4)
Sensory peripheral neuropathy	3 (4)
Meningitis/encephalitis	3 (4)
Cranial nerve palsy	4 (6)
Stroke	7 (10)
Testicular swelling/pain	4 (6)
Gastrointestinal involvement	
Abdominal pain	28 (41)
Peritonitis	3 (4)
Blood in the stool or bloody diarrhea	7 (10)
Bowel ischemia/perforation	3 (4)
Cardiac involvement	
Valvular heart disease	2 (3)
Pericarditis	1 (1)
Pulmonary involvement	
Pleural effusion	1 (1)
Infiltrate	1 (1)

* RP = Raynaud's phenomenon; RBCs = red blood cells; hpf = high-power field; GFR = glomerular filtration rate.

[23%]) and purpura (28 patients [41%]) were frequent, with livedo reticularis (34 patients [49%]) being the most common skin manifestation of the disease in the 69 study patients. Arthralgia that was not accompanied by joint deformity was present in 52 patients (75%). Myalgia was a prevalent clinical symptom reported in 57 cases (83%).

Abdominal pain was present in 28 patients (41%): 21 of these 28 patients had transient abdominal pain, which regressed spontaneously or in response to corticosteroid therapy and required no further investigation. The remaining 7 patients (10% of the study group) had more serious gastroenterologic pathology. In 7 patients, gastrointestinal hemorrhage (melena or hematemesis) was present. A laparotomy was performed in 3 of these patients. The most severe episodes of abdominal pain were due to peritonitis (3 patients), duodenal ulcer (1 patient), intestinal infarction (1 patient), and large bowel perforation (3 patients).

The urinary albumin-to-creatinine ratio was >30 mmoles/mg in 13 patients and was accompanied by hematuria (≥5 red blood cells/high-power field or the presence of red blood cell casts) in 7 patients. Significant renal involvement, as manifested by urinary creatinine levels elevated above the 95th percentile for age, was found in 10 of the 69 patients (15%), with a median GFR of 60 ml/minute/1.73 m^2 (range 41–80) in these 10 patients. Dialysis was necessary in 3 of the 69 patients (4%).

Peripheral neuropathy and mononeuritis multiplex were observed in some patients (3 patients each [4%]). Cranial nerve palsies involving cranial nerves III, IV, VI, and VII occurred in 4 patients. Strokes, which were defined as cerebrovascular accidents resulting in focal neurologic deficits, were documented in 7 patients and were associated with evidence of cortical or subcortical infarction.

All patients had elevated levels of acute-phase reactants at diagnosis, with a median ESR of 64 mm/hour (range 40–140), a median CRP of 56 mg/liter (range 35–120), and a median platelet count of 540 × 10^9/liter (range 250–750 × 10^9/liter). Testing for ANCA antibodies yielded positive results in 2 of the 69 patients (on immunofluorescence not confirmed on enzyme-linked immunosorbent assay, since that was not available at time of testing).

Histopathologic findings. Fifty-five patients underwent biopsy (10 renal and 60 nonrenal biopsies). Histopathologic assessment of the skin showed necrotizing vasculitis of small to medium-sized vessels was observed in 80% of the biopsy samples (40 of 50 biopsies), and 2 samples additionally revealed septal panniculitis. Nongranulomatous necrotizing vasculitis was found in 7 of the 10 biopsy samples from the GI tract. These intestinal biopsies were obtained via esophagogastroduodenoscopy, which was requested in view of the patients' reports of GI symptoms. Of the 10 renal biopsies performed, 2 were normal. Of the 8 abnormal renal biopsy samples, 2 showed focal segmental glomerulonephritis, 2 showed >10% crescent formation, and the remaining 4 showed membranoproliferative glomerulonephritis with necrotizing vasculitis, which was considered diagnostic of PAN. Fibrin deposition with vessel occlusion was noted in 3 of the 8 abnormal renal biopsy samples.

Table 2. Summary of the findings of catheter angiography in the 69 children with polyarteritis nodosa*

Arteriographic changes	No. (%) of studies
Aneurysms	32 (46)
Arterial cutoff	18 (26)
Arterial tapering stenosis	22 (32)
Beading of arteries or other caliber variations	54 (78)
Pruning of peripheral renal arterial tree	24 (35)
Perfusion defects on nephrography	20 (29)

* A total of 66 catheter angiographic studies showed changes supporting a diagnosis of polyarteritis nodosa in this cohort. See ref. 8 for a detailed description of each of the arteriographic signs.

Catheter digital subtraction arteriography and other vascular imaging. Arteriography revealed aneurysm formation or other changes consistent with vasculitis (arterial cutoff, arterial tapering, focal stenosis, beading of arteries or other caliber variations, pruning of the peripheral renal arterial tree, or perfusion defects on nephrography) in various mid-sized arteries in 94% of the patients (65 of 69 patients) (Table 2). Arteriographic changes were present in the renal, hepatic, mesenteric, and cerebral arteries in 62 of 66, 45 of 66, 22 of 66, and 7 of 35 patients, respectively. Five patients had normal findings on magnetic resonance angiography, while digital subtraction arteriography studies in the same 5 patients revealed the presence of arteriographic changes consistent with PAN. Echocardiography revealed involvement of the coronary arteries in 3 patients (4%).

Treatment. The treatments received by the study patients are summarized in Table 3. All patients achieved remission, with a median of 2 months (range 1–24 months) from diagnosis to remission (defined as PVAS of 0 of 63 plus normalization of acute-phase reactant levels).

Induction therapy. Fifty-seven patients (83%) received induction therapy with a combination of corticosteroids and cyclophosphamide. Of these 57 patients, 30

Table 3. Treatment in the 69 children with polyarteritis nodosa

Treatment	No. (%) of patients
Corticosteroids	69 (100)
Cyclophosphamide	
Oral	33 (48)
Intravenous	27 (39)
Azathioprine	54 (78)
Mycophenolate mofetil	9 (13)
Methotrexate	6 (9)
Infliximab	5 (7)
Rituximab	3 (4)
Cyclosporine	3 (4)
Colchicine	2 (3)
Intravenous immunoglobulin	2 (3)
Etanercept	1 (1)
Hydroxychloroquine	1 (1)
Mesalamine	1 (1)
Plasma exchange	6 (9)
Aspirin	39 (57)
Dipyridamole	24 (35)

received oral cyclophosphamide (first-line therapy from 1980 to 2002), 24 received intravenous (IV) cyclophosphamide (first-line therapy from 2002 onward), and 3 initially received IV cyclophosphamide and were then switched to oral cyclophosphamide early in the disease course. In general, a course of pulse cyclophosphamide consisted of monthly doses of IV cyclophosphamide at 500–750 mg/m^2 (maximum 1.2 gm) for a total of 6 doses, which was administered to 17 patients (regimen used from 1980 to 2006). For the remaining 10 patients given pulse cyclophosphamide, the regimen consisted of fortnightly doses of IV cyclophosphamide at 500–750 mg/m^2 for a total of 3 doses, followed by monthly treatments for another 2–4 doses (regimen used from 2006 onwards). The median cumulative dose of IV cyclophosphamide received was 110 mg/kg (range 90–120). A course of oral cyclophosphamide (1–2 mg/kg/day) was for 2–4 months (median cumulative dose 240 mg/kg [range 120–745]). All 69 patients received high-dose IV pulse corticosteroids at a dosage of 30 mg/kg/day for 3 consecutive days, followed by a tapering dose of oral steroids over 12–18 months. Eight patients (12%) received a combination of corticosteroids and azathioprine (2 mg/kg/day) for induction of remission, and 4 patients (6%) were treated with corticosteroids alone, based on the clinician's discretion.

Maintenance and adjunctive therapies. Patients achieving remission were maintained on a regimen of either azathioprine (2 mg/kg/day) or mycophenolate mofetil at a dosage of 600 mg/m^2 twice a day for 18–48 months. Sixty-three patients (91%) received aspirin or dipyridamole as an antithrombotic agent. Three patients (4%) received intravenous iloprost infusion for critical digital ischemia. Fourteen patients (20%) received trimethoprim/sulfamethoxazole, generally as *Pneumocystis jiroveci* pneumonia prophylaxis. Of note, prophylaxis with trimethoprim/sulfamethoxazole is currently used in all patients with PAN but was inconsistently used at our institution over the 32-year study period. Penicillin prophylaxis was added in 21 children (30%) in whom a streptococcal infection was believed to be the trigger of their disease presentation. Other adjunctive modalities used to induce remission and/or to treat recalcitrant vasculitis included plasma exchange (6 patients, 5 with glomerulonephritis and 1 with cerebral vasculitis; 2 volume exchanges per day over 7 cycles in all 6 patients), methotrexate (6 patients; 10–15 mg/m^2/week orally or subcutaneously), infliximab (5 patients; 6 mg/kg IV at 0, 2, 4 weeks and then every 6 weeks thereafter), cyclosporine (3 patients; 3–5 mg/kg orally twice a day), and rituximab (3 patients; 2 IV doses of 750 mg/m^2 given 14 days apart, with IV cyclophosphamide at 375 mg/m^2). Thirty-four (49%) children discontinued all treatment at a median of 36 months (range 25–60 months) from their initial diagnosis.

Relapse. A total of 24 patients (35%) experienced a relapse of their disease at a median of 12 months (range 7–48 months) and had a median of 2 episodes of relapse (range 1–4 episodes) (Figure 1A). Of these 24 patients, 22 were receiving maintenance therapy, and 2 had stopped therapy a median of 4 months (range 3–6 months) previously. Overall, in the univariable analysis, GI involvement (blood in the stool or bloody diarrhea, and/or peritonitis, and/or bowel ischemia) was associated with an increased risk of relapse (HR 3.980 [95% CI 1.142–13.868], $P = 0.031$). A longer time to achieving remission was associated with a lower risk of relapse (HR 0.369 [95% CI 0.157–0.865], $P = 0.022$) (Table 4), as was an increased cumulative cyclophosphamide dose (HR 0.995 [95% CI 0.795–0.995], $P = 0.005$). These parameters remained significantly associated with relapse risk in the multivariable model (increased risk for GI involvement HR 3.820 [95% CI 1.201–12.548], $P = 0.035$; lower risk with increased time to remission HR 0.340 [95% CI 0.160–0.986], $P = 0.03$; and lower risk with increased cumulative cyclophosphamide HR 0.895 [95% CI 0.795–0.998], $P = 0.003$). All patients with severe GI involvement experienced a relapse following the onset of GI manifestations. Male sex, age >5 years, PVAS at diagnosis, myalgia/arthralgia, skin, renal, and neurologic involvement, ESR >100 mm/hour, CRP >100 mg/liter, and platelet count were not significant on univariable analysis (Table 4). Relapse rates for all patients with PAN according to severe GI disease status

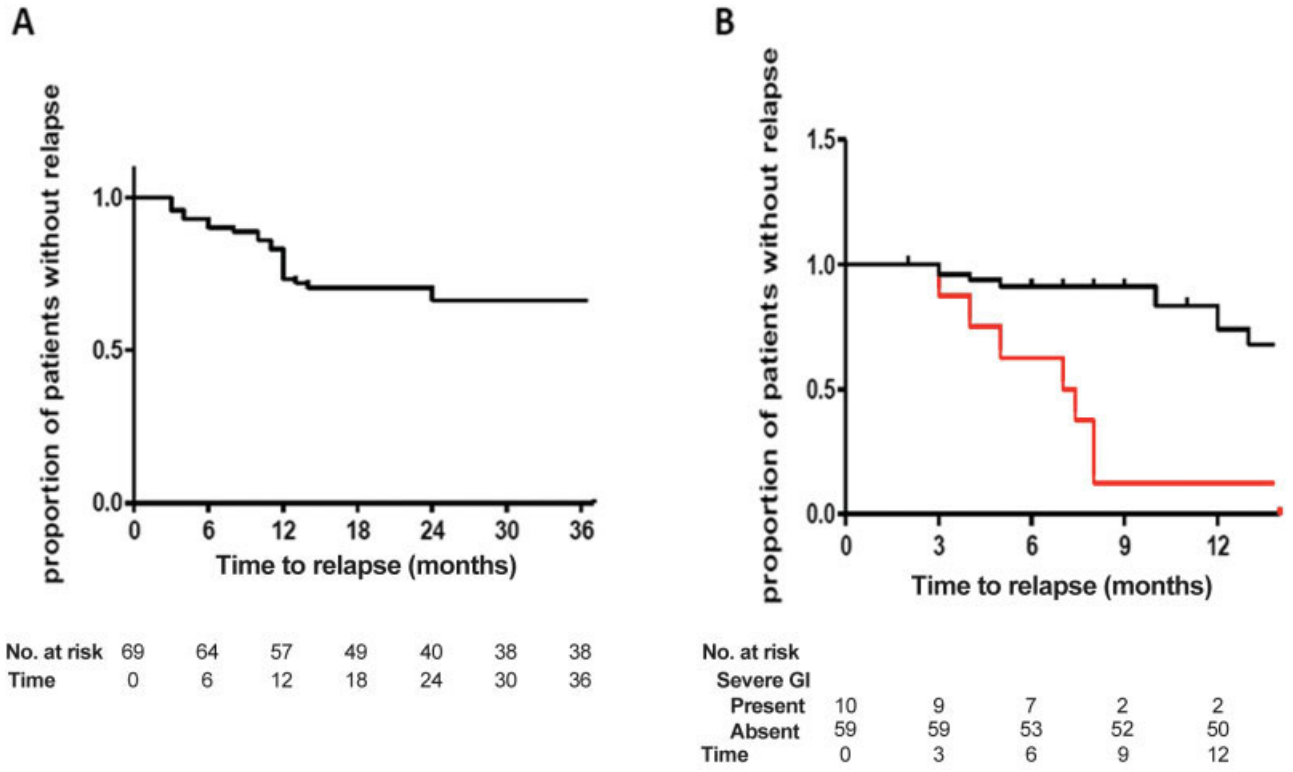


Figure 1. A, Relapse-free survival in 69 children with polyarteritis nodosa (PAN) over a 3-year period of followup. **B,** Relapse-free survival in 69 children with PAN over a 1-year period, according to the presence (red line) or absence (black line) of severe gastrointestinal (GI) disease. The rates differed significantly between patients with severe GI disease (blood in stools or bloody diarrhea, and/or peritonitis, and/or bowel ischemia) at any stage and those without severe GI disease (2-sided $P = 0.0006$, by log rank test).

are shown in Figure 1B. There was no significant difference in the relapse rate between the first 16 years of the study period and the second 16 years of the study period ($P = 0.671$).

Adverse events and deaths. Significant corticosteroid-induced side effects included Cushing's syndrome (22 of 69 patients [32%]) and osteopenia (18 of 69 patients [26%]). One child developed azoospermia secondary to testicular vasculitis. A total of 19 infections occurred in 17 patients. Two patients contracted shingles, 1 patient (4 years old with a background of duplex kidney) developed pyelonephritis requiring intravenous antibiotics and hospitalization, another patient (8 years old) developed cerebral abscesses complicating her acute presentation with bowel perforation due to her active PAN. Other infections in the 69 patients included paronychia in 2 patients, staphylococcal cellulitis in 1, chickenpox in 4, dental abscess in 1, pertussis infection in 1, urinary tract infections in 2, aspergillosis in 1, Epstein-Barr virus reactivation in 1, cytomegalovirus

Table 4. Association between the clinical and laboratory findings and the risk of relapse in 66 children with polyarteritis nodosa*

	Hazard ratio (95% CI)	*P*
Male sex	1.531 (0.443–5.285)	0.501
Age >5 years	1.012 (0.909–1.126)	0.828
PVAS at diagnosis	1.020 (0.939–1.108)	0.636
Myalgia/arthralgia	0.869 (0.358–2.112)	0.757
Skin involvement	1.345 (0.540–3.351)	0.524
Renal involvement	1.602 (0.606–4.237)	0.342
Neurologic involvement	1.234 (0.408–3.735)	0.710
Severe GI involvement	3.980 (1.142–13.868)	0.031
ESR >100 mm/hour at diagnosis	1.537 (0.625–3.780)	0.349
CRP >100 mg/liter at diagnosis	1.601 (0.875–3.560)	0.412
Time to remission, months	0.369 (0.157–0.865)	0.022
Cumulative CYC dose, mg/kg	0.895 (0.792–0.998)	0.005

* Three of the 69 children died during the study period. Hazard ratios and 95% confidence intervals (95% CIs) were determined by Cox regression analysis. Severe gastrointestinal (GI) involvement was defined as blood in the stool or bloody diarrhea, and/or peritonitis, and/or bowel ischemia. Time to remission was defined as the time from diagnosis to the time of remission (defined as a Paediatric Vasculitis Activity Score [PVAS] of 0 of 63). *P* values less than 0.05 (2-sided) were considered significant. ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CYC = cyclophosphamide.

infection in 1, and mycobacterial infection in 1 patient. No hepatitis B infections were noted.

A total of 3 deaths occurred during the observation period (all in the first 16 years of the study period), yielding a mortality rate of 4%. These 3 children died after a median followup of 3 weeks (range 4–8 weeks) and without ever achieving remission. One of the children was 2 years old and had presented with acute renal failure, livedo reticularis, arthralgia, myalgia, fever, weight loss, and left-sided hemiparesis. Arteriography showed small aneurysms in the renal and cerebral circulation. She received therapy with corticosteroids, IV cyclophosphamide, and plasma exchange, but died of staphylococcal septicemia 3 weeks after initial presentation. The second child was 12 years old and had presented with weight loss, fever, livedo reticularis, myalgia, and hypertension. Arteriography demonstrated small aneurysms in the hepatic and intrarenal arteries. He was treated with high doses of IV corticosteroids and IV cyclophosphamide but died of gram-negative bacterial septicemia 5 weeks following initial presentation. The third child was 12.5 years old and had presented with fever, myalgia, and arthritis. Arteriography revealed multiple small aneurysms in the intrarenal renal and hepatic arteries. He died of invasive aspergillosis and atypical mycobacterial infection 8 weeks following hospital admission. There was no documented infertility or malignancy during pediatric followup.

DISCUSSION

Our retrospective study describes the largest single-center cohort of pediatric patients with systemic PAN and adds to the available data from previously reported series. The clinical presentation was varied and broad, reflecting the multisystemic nature of childhood PAN. Tissue biopsy and visceral digital subtraction arteriography were important diagnostic tools in our patients. First-line treatment for induction of remission was a combination of high-dose corticosteroids and cyclophosphamide; plasma exchange and biologic agents were used for refractory cases. Azathioprine combined with low-dose corticosteroids was the most common maintenance therapy. The main clinical predictor of relapse was severe GI involvement. A longer time to achieving remission and an increased cumulative cyclophosphamide dose were associated with reduced risk of relapse. The mortality rate was 4%, which was an improvement over the 10% mortality rate for systemic PAN last reported at our institution in 2002 (18), possibly reflecting increased awareness of the disease, leading to prompt referral and advances in available therapies, particularly biologic agents (19), for recalcitrant systemic vasculitis. Despite this, treatment failure and disease- and therapy-related morbidity remain significant concerns for systemic PAN.

Most of our patients presented with nonspecific constitutional symptoms, such as fever, fatigue, weight loss, and myalgia. The other major systems involved were the skin (88%), the musculoskeletal system (75%), and less frequently, the renal system (19%). However, a significant percentage of patients had gastrointestinal (10%) and neurologic involvement (10%) as well. Notably, 2 patients demonstrated both typical mid-size and small artery involvement, manifesting aneurysms on renal arteriography in addition to glomerulonephritis confirmed on renal biopsy. This degree of polyangiitis overlap has been well described in the primary systemic vasculitides, and this highlights the limitations of the current classification systems that are based on the size of involved arteries (2,20).

The diagnosis of PAN was based on a combination of clinical criteria, characteristic histopathologic changes, and the presence of arteriographic changes compatible with medium-size vessel arteritis. Systemic PAN often presents insidiously, which may partly explain the delay in diagnosis (average of 1.2 months, considerably longer in some cases). The classic arteriographic finding of aneurysms of medium and small muscular arteries predominantly affecting the renal and mesenteric arteries has been well documented and accepted as largely diagnostic (although not pathognomonic) of PAN (2,8,21). Well recognized but less emphasized are the nonaneurysmal changes affecting the smaller order vessels (8). It has been shown that children with PAN manifest a spectrum of aneurysmal and nonaneurysmal angiographic changes that affect the renal, hepatic, and mesenteric vascular beds (8). Although larger aneurysms can be detected with computed tomographic angiography or even ultrasound, in our experience, these are uncommon in children, and such techniques cannot currently identify the subtle arterial abnormalities that are much more prevalent.

Induction therapy with oral and/or high-dose pulse IV corticosteroids, cyclophosphamide, and antiplatelet agents, followed by maintenance therapy with low-dose prednisolone and a steroid-sparing agent (most commonly azathioprine) was standard in our patients. The case for this approach is based largely on clinical trials in adults with PAN (22,23) or other forms of systemic vasculitis, particularly the ANCA-associated vasculitides (AAVs) (24), since there has never been a

randomized controlled trial in PAN. More-invasive therapies, such as plasma exchange, were reserved for those in whom remission was not achieved with standard therapy or those who presented with fulminant, acutely life-threatening vasculitis. Successful treatment with biologic agents, such as infliximab or rituximab, has been previously reported in children with systemic vasculitis unresponsive to conventional therapy or in cases where there are concerns relating to high cumulative doses of cyclophosphamide (19), and after 2002, biologic agents were used in a minority of our patients (9% receiving infliximab or etanercept and 4% receiving rituximab) (19). Since 2005, treatment of systemic PAN at our center has been standardized (16,25).

Notably, severe short-term complications, such as infections and corticosteroid-induced side effects, were observed, and these remain a concern for children with PAN receiving standard therapy. Furthermore, late complications associated with cyclophosphamide therapy include malignancy and infertility (26,27), which are particularly worrisome for children with many years of life ahead of them. Although we did not detect these complications in our retrospective review, this could be because of the relatively short followup in our cohort and the lack of systematic screening for infertility in pediatric patients exposed to cyclophosphamide who graduate to adult care. The importance of this is emphasized by a report of 8 children with AAV who were monitored for 11–30 years: 4 were infertile, 2 had skeletal complications, and 1 developed a malignancy (28). These worrying data, albeit limited and related to AAV, emphasize the need for long-term followup studies of children with systemic PAN and other systemic vasculitides who survive into adulthood (29). Thus, finding the most efficacious and least toxic therapeutic regimen remains an important priority for systemic PAN.

The relapse rate for systemic PAN in our series was 35%, somewhat higher than the relapse rate of 8.9% for systemic PAN previously reported in a retrospective multicenter cohort (6). This could suggest a referral bias, with more severe and relapsing cases being referred to our hospital since it is a specialist pediatric vasculitis center that accepts national and international referrals. Our observed relapse rate, however, was lower than the 50% relapse rate widely reported for adults with granulomatosis with polyangiitis (Wegener's) (30). Childhood PAN, therefore, appears to be a condition in which permanent remission can be achieved (2,4,6). Relapses do occur, but despite these, a real possibility of cure can be anticipated (2,4,6).

The finding that severe GI disease was associated with an increased risk of relapse of systemic PAN is a novel observation. We have previously reported on a series of children with systemic PAN presenting with indeterminate intestinal inflammation, and highlighted the diagnostic challenges and significant morbidity and mortality associated with GI involvement (31). Similarly, Guillevin et al have also demonstrated a poor outcome (increased mortality) for adult patients with PAN and intestinal disease (32). Of note however, the limited number of patients and the retrospective nature of this study did not allow us to explore in detail the factors contributing to the association of GI disease with increased relapse risk. Interestingly, longer time to achieve remission was associated with reduced relapse risk. This may have been due to higher cumulative cyclophosphamide doses used in those patients as shown herein and as also suggested by meta-analysis data from adults with AAV (30). Furthermore, the use of multiple sequential treatments (cyclophosphamide, plasmapheresis, and biologic agents) to obtain disease control in select cases may have resulted in a reduced relapse risk in these children.

We report a mortality rate of 4%, which is lower than that reported in previous series (11,18,33). We speculate that this could be due to increased disease awareness leading to prompt tertiary center referral, and/or improved treatments including introduction of biologic agents in 2002 for recalcitrant cases (7,18).

Our study is limited by all the confounding factors associated with any retrospective case series. As highlighted previously, there is a possibility that referral bias resulted in us receiving the most severe cases of systemic PAN. Additionally, we did not monitor our patients into adulthood and, hence, cannot fully assess long-term sequelae (including late relapses) of systemic PAN and its treatment. Late morbidity, such as premature atherosclerosis, and the aforementioned concerns regarding malignancy and infertility could occur many years after the onset of systemic PAN. Notably, a previous study in children with PAN demonstrated increased pulse wave velocity (a measure of arterial stiffness) and, hence, decreased arterial distensibility that was amplified during acute inflammatory exacerbations (34). Clinical trials in adults suggest that mycophenolate mofetil could be a less toxic alternative to cyclophosphamide, with comparable efficacy, in the treatment of systemic lupus erythematosus (35). A multicenter, open-label, randomized controlled trial (RCT) of mycophenolate mofetil versus cyclophosphamide for the induction of remission of childhood PAN (the

MYPAN trial) is thus currently being developed and is the first RCT of treatment in systemic PAN.

In summary, we report the largest single-center series of patients with childhood systemic PAN. Improving the safety of treatments while maintaining or improving efficacy needs to be the focus for the future. RCTs linked to prospective long-term followup studies are now urgently needed in order to provide the currently lacking evidence base for the treatment of children with PAN.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Eleftheriou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Eleftheriou, Dillon, Klein, Brogan.

Acquisition of data. Eleftheriou, Dillon, Tullus, Marks, Roebuck, Klein, Brogan.

Analysis and interpretation of data. Eleftheriou, Dillon, Marks, Pilkington, Klein, Brogan.

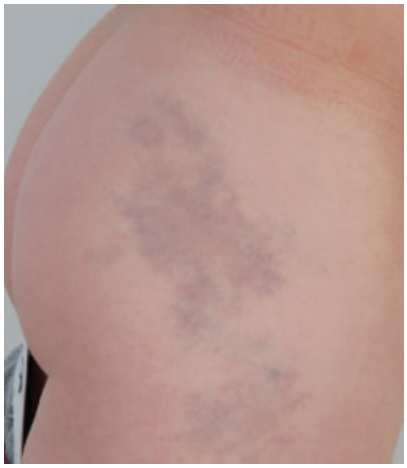
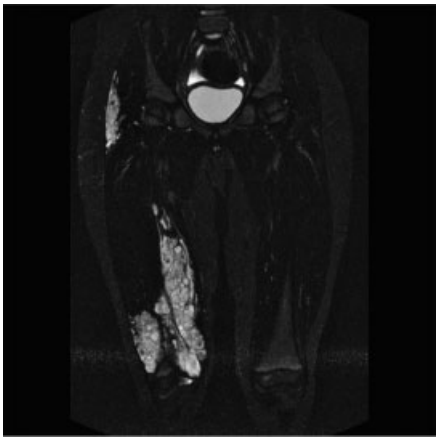
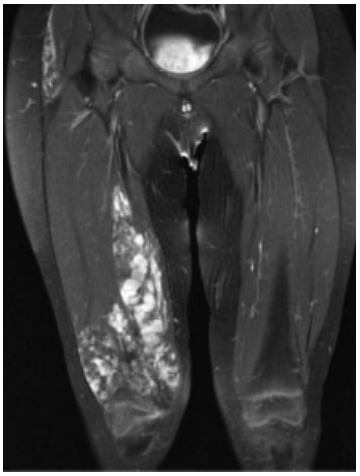
REFERENCES

1. Kussmaul A, Maier R. Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht. Dtsch Arch Klin Med 1866;1:484–518.
2. Dillon MJ, Eleftheriou D, Brogan PA. Medium-size-vessel vasculitis. Pediatr Nephrol 2010;25:1641–52.
3. Watts RA, Scott DG. Epidemiology of vasculitis. In: Ball GV, Bridges SL, editors. Vasculitis. 2nd ed. Oxford: Oxford University Press; 2008. p. 7–21.
4. Ettlinger RE, Nelson AM, Burke EC, Lie JT. Polyarteritis nodosa in childhood: a clinical pathologic study. Arthritis Rheum 1979;22: 820–5.
5. Besbas N, Ozen S, Saatci U, Topalog-clu R, Tinaztepe K, Bakkaloglu A. Renal involvement in polyarteritis nodosa: evaluation of 26 Turkish children. Pediatr Nephrol 2000;14:325–7.
6. Ozen S, Anton J, Arisoy N, Bakkaloglu A, Besbas N, Brogan P, et al. Juvenile polyarteritis: results of a multicenter survey of 110 children. J Pediatr 2004;145:517–22.
7. Ozen S, Besbas N, Saatci U, Bakkaloglu A. Diagnostic criteria for polyarteritis nodosa in childhood. J Pediatr 1992;120:206–9.
8. Brogan PA, Davies R, Gordon I, Dillon MJ. Renal angiography in children with polyarteritis nodosa. Pediatr Nephrol 2002;17: 277–83.
9. Dillon MJ. Classification and pathogenesis of arteritis in children. Toxicol Pathol 1989;17:214–8.
10. Dillon MJ. Vasculitic syndromes. In: Woo P, White PH, Ansell BM, editors. Paediatric rheumatology update. Oxford: Oxford University Press; 1990. p. 227–42.
11. Dillon MJ. Diagnosis and clinical management of childhood vasculitic disease. Vasc Med Rev 1993;4:133–43.
12. Kumar L, Thapa BR, Sarkar B, Walia BN. Benign cutaneous polyarteritis nodosa in children below 10 years of age—a clinical experience. Ann Rheum Dis 1995;54:134–6.
13. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al, for the Paediatric Rheumatology International Trials Organisation (PRINTO). EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis 2010;69: 798–806.
14. Ozen S, Ruperto N, Dillon MJ, Bagga A, Barron K, Davin JC, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. Ann Rheum Dis 2006;65:936–41.
15. Dolezalova P, Price-Kuehne FE, Ozen S, Benseler SM, Cabral DA, Anton J, et al. Disease activity assessment in childhood vasculitis: development and preliminary validation of the Paediatric Vasculitis Activity Score (PVAS). Ann Rheum Dis 2012. E-pub ahead of print.
16. Rees L, Brogan PA, Bockenhauer D, Webb NJ, editors. Paediatric nephrology. 2nd ed. Oxford: Oxford University Press; 2012.
17. Collett D. Modelling survival data in medical research. London: Chapman & Hall; 1994.
18. Brogan PA, Shah V, Dillon MJ. Polyarteritis nodosa in childhood [abstract]. Cleve Clin J Med 2002;69 (Suppl II):SII-179.
19. Eleftheriou D, Melo M, Marks SD, Tullus K, Sills J, Cleary G, et al. Biologic therapy in primary systemic vasculitis of the young. Rheumatology (Oxford) 2009;48:978–86.
20. Leavitt RY, Fauci AS. Polyangiitis overlap syndrome: classification and prospective clinical experience. Am J Med 1986;81:79–85.
21. Miller DL. Angiography in polyarteritis nodosa [letter]. AJR Am J Roentgenol 2000;175:1747–8.
22. Gayraud M, Guillevin L, Cohen P, Lhote F, Cacoub P, Deblois P, et al, and the French Cooperative Study Group for Vasculitides. Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. Br J Rheumatol 1997;36:1290–7.
23. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Genereau T, et al. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis: a prospective, randomized trial in sixty-two patients. Arthritis Rheum 1995;38:1638–45.
24. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310–7.
25. Foster H, Brogan PA, editors. Paediatric rheumatology. Oxford: Oxford University Press; 2012.
26. Feng PH, George CR, Evans RA, Murkin GE, Spicer E, Thomas BS, et al. Cyclophosphamide and infertility. Lancet 1972;1:840.
27. Travis LB, Curtis RE, Glimelius B, Holowaty EJ, Van Leeuwen FE, Lynch CF, et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. J Natl Cancer Inst 1995;87:524–30.
28. Arulkumaran N, Jawad S, Smith SW, Harper L, Brogan P, Pusey CD, et al. Long-term outcome of paediatric patients with ANCA vasculitis. Pediatr Rheumatol 2011;9:1–7.
29. Booth AD, Wallace S, McEniery CM, Brown J, Jayne DR, Wilkinson IB. Inflammation and arterial stiffness in systemic vasculitis: a model of vascular inflammation. Arthritis Rheum 2004;50:581–8.
30. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term followup. Ann Rheum Dis 2012;71:955–60.
31. Brogan PA, Malik M, Shah N, Kilday JP, Ramsay A, Shah V, et al. Systemic vasculitis: a cause of indeterminate intestinal inflammation. J Pediatr Gastroenterol Nutr 2006;42:405–15.
32. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome: a prospective study in 342 patients. Medicine (Baltimore) 1996;75:17–28.
33. Dillon MJ. Diagnosis and management of vasculitides in childhood. Br J Rheumatol 1994;33:187–92.
34. Cheung YF, Brogan PA, Pilla CB, Dillon MJ, Redington AN. Arterial distensibility in children and teenagers: normal evolution

and the effect of childhood vasculitis. Arch Dis Child 2002;87: 348–51.
35. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20:1103–12.

DOI 10.1002/art.38005

Clinical Images: Vascular malformation as a cause of limp in a child

The patient, a 4-year-old boy, presented with recurrent episodes of right knee pain and swelling associated with an antalgic gait of 2 years' duration. The episodes lasted for a few hours and as long as 2 days, without precipitating or relieving factors. Results of physical examination performed when the patient was asymptomatic were normal. Specifically, muscle atrophy was not found; however, a hemangioma over the upper lateral right thigh and buttock (left) was noted. Complete blood cell count, erythrocyte sedimentation rate, C-reactive protein levels, and antinuclear antibodies were normal or negative. The D-dimer level was 5.4 μg/ml (normal $<$0.51). Magnetic resonance imaging (MRI) (STIR image) of the right thigh showed a large lobulated, multiseptated, hyperintense soft tissue mass involving the quadriceps muscle, gluteus muscle, and suprapatellar joint space. There was no evidence of hemarthrosis or knee joint arthropathy (middle). Heterogeneous enhancement following intravenous injection of gadolinium was seen (right). These findings are compatible with a venous malformation. The patient had an excellent clinical response to intralesional sclerotherapy. Venous malformation is a congenital low-flow vascular malformation, consisting primarily of dilated and disorganized venous channels that communicate with normal veins. In the knee, it causes episodic hemarthroses, and recurrent hemarthroses can cause chronic changes similar to hemophilia. Thrombosis of the veins also may occur, which can lead to acute pain. Bluish cutaneous lesions of venous malformation or prominent superficial veins found on physical examination may provide a clue to the diagnosis, and in large venous malformations, hypofibrinogenemia and elevation of D-dimer levels may result from continuous formation of intralesional microthrombi (Tsai A, Chaudry G, Spencer S, Kasser JR, Alomari AI. Misdiagnosis of knee venous malformation as juvenile idiopathic arthritis. J Pediatr Orthop 2011;31:683–90). MRI plays a pivotal role in identifying the lesion (Dalmonte P, Granata C, Fulcheri E, Vercellino N, Gregorio S, Magnano G. Intra-articular venous malformations of the knee. J Pediatr Orthop 2012;32:394–8). Therapy should be tailored to each patient, and treatment options include sclerotherapy or synovectomy.

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