

## Cutaneous polyarteritis nodosa in a 7-year-old boy: difficulties in diagnosis

Izabela Dybowska-Gotota<sup>1</sup>, Magdalena Krajewska-Włodarczyk<sup>2,3</sup>, Zbigniew Żuber<sup>4,5</sup>

<sup>1</sup>4<sup>th</sup> Department of Pediatric Rheumatology and Endocrinology, Regional Specialized Children's Hospital in Olsztyn, Poland

<sup>2</sup>Department of Internal Medicine, School of Medicine, *Collegium Medicum*, University of Warmia and Mazury, Olsztyn, Poland

<sup>3</sup>Department of Rheumatology, Municipal Hospital Complex, Olsztyn, Poland

<sup>4</sup>Department of Pediatrics, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Poland

<sup>5</sup>Ward for Older Children with Neurology and Rheumatology Subdivision, St. Louis Regional Specialized Children's Hospital in Krakow, Poland

### Abstract

Vasculitides are a diverse group of diseases. The potential diversity of their clinical symptoms requires the exclusion of other systemic connective tissue diseases, infectious diseases or malignancies. Due to similar clinical manifestations, comprehensive differential diagnosis is needed. This paper presents the case of a boy in whom polyarteritis nodosa, early stage of Behçet's disease or autoimmune/autoinflammatory syndrome induced by adjuvants was suspected following initial diagnostics. He was ultimately diagnosed with cutaneous polyarteritis nodosa.

**Key words:** juvenile polyarteritis nodosa, cutaneous polyarteritis nodosa, Behçet's disease, autoimmune/autoinflammatory syndrome induced by adjuvants, diagnostics.

### Introduction

Vasculitides are a heterogeneous group of diseases characterized by inflammatory infiltrates of the vascular wall. Systemic vasculitis (SV) is typically classified based on the size of blood vessels involved in the inflammatory process and includes large, medium and small vessels. Inflammation results in the narrowing and occlusion of the vascular lumen, which leads to ischemia and necrosis of tissues and organs [1–3]. Its etiology is unknown and pathogenesis is only partly understood. In some types of vasculitides, inflammatory extravascular granulomas are formed. Some are associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA).

Virtually all SV initially produce general symptoms, such as fatigue, fever, anorexia and weight loss, which hinders diagnosis at early stages of the disease. Most patients present with skin lesions which are often similar in different disease entities. It is not until new symptoms develop, which may involve nearly any system or

organ, and laboratory test results are available that a final diagnosis may be made [3].

Although most types of vasculitides affect both children and adults, there are some important differences in etiology, clinical manifestations, disease progression and prognosis. Systemic vasculitis is less frequent in children and is self-limiting with a good prognosis [4, 5]. In most cases, SV in growing children is ANCA-negative. Henoch-Schönlein purpura (HSP) followed by Kawasaki disease is most common in this age group. Symptoms of vasculitis are more often preceded by infection in children compared with adults. In adults, vasculitides are primarily idiopathic, but may also accompany tumors or occur following infection, medication use and exposure to toxic chemical agents [5].

There are also some differences in the clinical manifestations of particular SV. Polyarteritis nodosa (PAN) is very rare in children and is referred to by some authors as “juvenile PAN” [5, 6]. Peak incidence occurs at ages

---

### Address for correspondence:

Izabela Dybowska-Gotota, 4<sup>th</sup> Department of Pediatric Rheumatology and Endocrinology, Regional Specialized Children's Hospital in Olsztyn, 18 Żołnierska St., 10-561 Olsztyn, Poland, e-mail: [izabelago@vp.pl](mailto:izabelago@vp.pl)

Submitted: 9.07.2019; Accepted: 17.09.2019

9–11 with no gender specificity, while the disease affects male adults more often.

The risk of recurrence is three times greater in children than in adults, which should always be taken into account when planning the end of treatment. Children are affected primarily by the limited form of the disease, cutaneous polyarteritis nodosa (cPAN). Less than 100 cases of cPAN in children have been reported in the literature, while prevalence in adults is estimated at 31 cases/million [5–7]. Juvenile cutaneous PAN is typically associated with streptococcal infection, viral diseases and vaccination. In adults, the disease is associated with hepatitis B, HIV, Epstein-Barr virus, parvovirus B19 and HTLV-1 infection [6, 7].

In children, disease onset is less often characterized by purpura and muscle pain, while tender subcutaneous nodules are more common. Distal necrosis of the fingers is a potential complication which is more prevalent in children [3, 6]. The cutaneous form rarely transforms into the systemic form, prognosis is good, the disease may even resolve spontaneously, but often recurs [3, 6]. The recurrence rate is comparable in both age groups [5, 6].

## Case report

A boy aged 7 years and 6 months was admitted to hospital with fever and pain in the extremities. The boy had been diagnosed with stomatitis one week prior but showed no response to treatment on an outpatient basis. At 3 days, he initially developed mild pyrexia, followed by fever above 38°C and increased pain in the left lower extremity and upper extremities.

Past medical history showed no chronic diseases. The boy had previously suffered from occasional upper respiratory tract infections and reported toothache three weeks prior to hospitalization which subsided without dentist intervention. He had been vaccinated with a second dose of hepatitis B vaccine five months prior. His parents denied recent lack of appetite, weight loss, hyperhidrosis, abdominal pain, headache or testicular pain.

On admission to hospital the boy's condition was moderately severe; he was pyrexial and suffering. Pain in the extremities impeded normal movement; both active and passive movements were accompanied by very strong pain in the knee, ankle, wrist and left hip joints. During physical examination the boy complained of severe pain in the form of whole-body hyperesthesia.

Physical examination revealed palpable soft, tender subcutaneous nodules about 2 cm in diameter in the sternal area, subcutaneous edema around the knee, ankle and wrist joints, as well as ecchymosis near the left anterior iliac spine. Muscle force was weakened, especially on the left side. Reduced left hip abduction was ob-

served. Moreover, the tongue was tender, with a whitish coating, the tonsils were enlarged and erosions were observed in the mucosa and tonsils. Arterial pressure was normal, below the 90th percentile, and the remaining vital signs, such as pulse and breathing, were normal for the boy's age.

The conducted tests revealed high inflammatory marker activity with normal procalcitonin levels, anemia, thrombocythemia and leukocytosis with a predominance of neutrophils on peripheral blood smear, and a high tetrazolium reduction test result (82%, with a normal value of up to 12%). The activity of aminotransferases, lactic dehydrogenase, creatine kinase and aldolase, kidney function tests, and the levels of complement components C3c and C4 were normal.

Anti-CMV IgM and anti-parvovirus B19 IgM antibodies were detected. In contrast, no HbsAg or antibodies against Epstein-Barr virus, hepatitis C virus, *Borrelia*, *Chlamydia trachomatis* or *Mycoplasma pneumoniae* were detected. The  $\gamma$ -interferon release assay was negative. Similarly, anti-cyclic citrullinated peptide autoantibodies (ACPA), rheumatoid factor (RF), anti-nuclear antibodies (ANA), myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA), proteinase-3 anti-neutrophil cytoplasmic antibodies (PR3-ANCA), anticardiolipin antibodies (ACA), the Venereal Diseases Research Laboratory (VDRL) test and anti-vascular endothelial cell antibodies (AECA) levels were all negative.

Bone marrow features excluded neoplasm. Multiple blood and urine cultures were sterile, and swabs and cultures of the upper respiratory tract and stool material were normal. Ultrasound imaging revealed splenic enlargement and an effusion in the left hip joint. Electromyography (EMG) showed chronic nerve conduction impairment consistent with multifocal mononeuropathy.

No pathological changes were detected in imaging and function tests, including chest radiographs, echocardiography, electrocardiography, ultrasound imaging of the remaining peripheral joints, magnetic resonance imaging (MRI) of the head and the thoracic and lumbosacral spine, and capillaroscopy. No abnormalities were found in the cerebrospinal fluid.

A consulting neurologist found increased muscle tone and muscle weakness in the boy's upper extremities, enhanced left patellar reflex and left ankle clonus.

Dental assessment revealed several gangrenous teeth, while an ophthalmological examination failed to detect any abnormalities.

The boy's condition remained moderately severe; he was feverish and suffering. In the following days, cyanotic, tender, soft subcutaneous nodules emerged and quickly expanded (up to 3 cm) within the chest and thorax, the auricles, above the left knee joint and on the fin-

gers of the right hand. Ultrasound imaging revealed that these were dilated subcutaneous vessels with thickened walls and impaired flow, as well as a subcutaneous perivascular inflammatory infiltrate.

The clinical manifestations were inconclusive and suggested SV; given the clinical manifestations and disease course, as well as the conducted diagnostic tests, PAN, Behçet's disease (BD) and autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA) were included for differential diagnosis.

Due to the child's severe condition and clinical manifestations suggestive of SV, systemic steroid therapy was first implemented with methylprednisolone IV at 300 mg/day for three consecutive days and subsequently prednisone orally at 1 mg/kg body weight. Additionally, broad-spectrum antibiotics, nystatin, naproxen and acetylsalicylic acid were administered. Dental procedures were carried out.

As a result of treatment, the fever, pain and hyperesthesia, subcutaneous edema, nodular skin lesions and oral mucosal lesions resolved. Laboratory test results gradually returned to normal, while physical examination revealed persistent left-side muscle weakness. At four weeks from admission, the boy was discharged home with a recommendation to continue treatment with oral methylprednisolone at 16 mg/day and undergo follow-up at an outpatient rheumatology clinic.

One week after discharge, the patient was once again admitted to hospital due to renewed subcutaneous nodule formation and mild pyrexia of up to 37.5°C. On admission, the boy's condition was moderate. Small (up to 5 mm), tender subcutaneous nodules were observed in bilateral forearms and the left hand, his tongue had a white coating, he complained of whole-body hyperesthesia and lower limb paresthesia, and muscle weakness was observed in bilateral upper extremities and the left lower extremity.

Laboratory tests revealed increased activity of inflammation markers, platelet (PLT) count and percentage of neutrophils on peripheral blood smear, as well as enhanced anemia compared with previous test results.

The electromyography (EMG) showed myogenic changes with no evidence of polyneuropathy. Muscle enzyme activity and liver and kidney function tests remained normal. Sections of the skin and subcutaneous tissue were collected from a nodule on the wrist (a) and from the calf muscle (b) for histopathological assessment. These were described as follows:

a) increase in small vessels, surrounding infiltration made up primarily of CD4+ lymphocytes; aggregates of CD3+ and CD4+ lymphocytes, neutrophils (CD15+) and histiocytes (CD68+) between adipose tissue lobules in the subcutaneous tissue,

b) increase in vessels in the adipose tissue between muscle fibers, surrounded by aggregates of B lymphocytes (CD20+) and T lymphocytes (CD3+, CD4+, CD8+), granulocytes (CD15+), individual plasma cells (CD138+) and histiocytes (CD68+).

Based on the clinical manifestations and test results, the patient was ultimately diagnosed with cPAN. The patient once again received intravenous methylprednisolone at 300 mg, followed by intravenous immunoglobulin (IVIg) at 1 g/kg body weight and methotrexate (MTX) at 7.5 mg/week.

As a result of the implemented treatment, the fever, subcutaneous nodules, hyperesthesia and paresthesia resolved, muscle strength improved and test results gradually returned to normal: leukocyte and PLT count, percentage of neutrophils and activity of acute phase markers. At three weeks from admission, the boy was discharged home in overall good condition, with a recommendation to continue MTX treatment at 15 mg/week (15.5 mg/m<sup>2</sup>) and methylprednisolone at 16 mg/day.

During follow-up, no recurrence of symptoms was observed, the patient reported no complaints, left lower limb muscle weakness subsided completely, and laboratory test results returned to normal, including hemoglobin concentration, leukocyte and PLT count, acute phase marker levels, and EMG results.

Full clinical remission was observed within seven months of diagnosis and implementation of treatment. Treatment was later continued with a gradual decrease in the dosage of corticosteroids (CS), which were ultimately discontinued after 17 months of treatment.

During the following 2 months, the patient was given the dose of the hepatitis B vaccine that had been scheduled for earlier and no adverse effects or disease recurrence was observed. The boy is currently receiving MTX and is feeling well; laboratory test results are normal (Table I).

## Discussion

In the case that we present here, the symptoms and laboratory test results, once infection and neoplasm were excluded, were indicative of systemic small-vessel or medium-vessel vasculitis. The ANCA negativity allowed the initial exclusion of anti-neutrophil cytoplasmic antibody-associated vasculitis, while the lack of evidence of involvement of the kidneys or lungs and the negative test results for HBV and HCV infection excluded immune complex small-vessel vasculitis. Diagnosis of PAN, BD and, due to the recent vaccination in the patient's medical history, ASIA seemed most likely in the differential diagnosis. Each of the proposed diagnoses was equally plausible.

**Table I.** Laboratory test results

Hospitalization	Date	HGB g/dl (11.0–14.6)	PLT × 10 <sup>3</sup> /μl (140–440)	WBC × 10 <sup>3</sup> /μl (4.5–13.5)	Neutrophils % (40–60)	ESR mm/h (< 15)	CRP mg/dl (0.0–0.50)	Fibrinogen g/l (2.00–4.00)
First hospitalization	20.03.2017	11.3	656	23.3	80	47	6.3	5.14
	27.03.2017	9.2	1125	42.9	82.5	60	10.7	5.54
	12.04.2017	10	1025	22.9	66.9	45	4.4	5.01
Second hospitalization	20.04.2017	8.3	996	35.1	84.4	56	9.7	6.04
	9.05.2017	9.9	791	15.6	47.7	28	1.9	3.47
Follow-up	26.05.2017	10.3	580	13	75	12	0.5	2.46
	5.10.2017	10.7	528	7.4	41	2	0.1	–
	10.05.2018	11.8	411	10.4	42	2	0.1	–
	12.11.2018	13.2	405	7.1	35	2	0.2	–
	7.02.2019	12.7	426	7	40.6	4	0.3	–

HGB – hemoglobin, PLT – platelets, WBC – white blood cells, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein

In addition to the general symptoms, the diagnosis of PAN was supported by the occurrence of tender subcutaneous nodules which were described in the ultrasound examination as dilated vessels with a surrounding inflammatory infiltration, tender muscles and mononeuropathy of the peroneal nerve confirmed by EMG.

However, a firm diagnosis required histopathological confirmation using the sections collected and the result of this analysis was inconclusive, demonstrating an increase in vessels with a surrounding inflammatory infiltration but lacking the typical features, i.e. necrotizing vasculitis of small and medium arteries, fibrinoid necrosis and microaneurysms. These might have been present in sections from other locations as lesions in PAN are segmental in nature [4, 6, 8–10].

What was important was that no internal organs were affected. The clinical manifestations were thus fully consistent with the limited cutaneous form of PAN, where general symptoms are accompanied only by skin lesions (typically tender subcutaneous nodules), myalgia and peripheral neuropathy, most often multifocal mononeuropathy of the lower extremities [3, 7, 10].

Another considered diagnosis was BD, which was highly plausible given the presence of typical lesions in the oral mucosa, as well as the skin lesions and neurological symptoms. A firm diagnosis requires lesions in the oral mucosa and/or genitals to occur at least 3 times during a year [11–15]. Of course, at the time of diagnosis and making therapeutic decisions, we did not know whether this would indeed be the case.

Autoimmune/autoinflammatory syndrome induced by adjuvants was suggested due to the vaccination prior to the disease and the occurrence of the abovementioned clinical symptoms, which are included in the diagnostic criteria for the syndrome. However, the authors themselves suggest that with the current criteria, ASIA

may be diagnosed too easily and therefore further tests are required [16–18].

Due to the inconclusive manifestations, the final diagnosis was not certain. Individual patients are diagnosed using diagnostic criteria, which, being highly sensitive, allow one to make a diagnosis that is certain or at least possible. Unfortunately, international diagnostic criteria have been defined for only a few types of vasculitides. The similar clinical manifestations of particular disease entities make it very hard to specify diagnostic criteria in a conclusive manner. However, the classification criteria for most types of SV have been established. Classification criteria are used in the case of groups of patients with established diagnoses, so that clinical and experimental data may be compared by unifying the nomenclature, but these are not established for diagnostic purposes. Still, the existing classification systems help to distinguish one type of vasculitis from another in patients diagnosed with vasculitis [5, 19]. The current criteria, especially in the case of PAN, have been criticized for several years and attempts at updating these have been reported. The very low sensitivity of the 1990 American College of Rheumatology classification criteria results from the fact that these include a cohort of patients with PAN and microscopic polyangiitis (MPA). The 1994 Chapel Hill Consensus defined MPA and distinguished it from PAN. Later on, ANCA negativity in PAN was highlighted and updated 2012 Chapel Hill Consensus criteria were established [9, 20].

Moreover, it is of note that the clinical manifestations of vasculitides in children differ from those observed in adult patients and therefore the established criteria are not designed for children. To address this, attempts were subsequently made by EULAR/PRINTO/PRES to define the criteria for vasculitides in children. Classification criteria are currently available for chil-

dren with Takayasu arteritis, PAN, granulomatosis with polyangiitis (GPA), HSP and BD. No classification criteria have been established for the cutaneous form of PAN in children. The disease is diagnosed based on the clinical manifestations and biopsy results, i.e. the existence of inflammatory/necrotic lesions in vascular walls [4, 5, 7].

In the case of our patient, treatment was initiated before the final diagnosis due to the boy's severe and worsening condition, which was reflected by the evolving results of laboratory tests, the emergence of new, tender subcutaneous nodules, peroneal nerve palsy and its potential complications, and, in the case of PAN, also a potential threat to life.

## Conclusions

The case presented here exemplifies the possible difficulties in diagnosing vasculitis due to inconclusive clinical manifestations, which is especially true for rare disease entities, such as PAN in children [7, 21, 22]. In the case of our patient, the symptoms and laboratory test results were indicative of several disease entities. The nature of the skin and oral mucosal lesions, as well as the neurological symptoms, were important. Laboratory test results turned out to be critical: ANCA negativity, ultrasound features of the nodular skin lesions, histopathological results, EMG results, and imaging of the nervous system.

According to the international classification criteria for BD in children (2015), the diagnosis requires mucosal inflammation to occur at least three times in one year, which was not observed during follow-up of our patient, perhaps due to the implemented treatment.

With regard to ASIA, the vaccination was with a booster dose. No disturbing symptoms had been observed after the primary dose. Following remission, the boy received another dose of the vaccine and no features suggesting disease recurrence have been observed to date.

We suspected PAN, but the histopathological results were inconclusive. The fact that no internal organs were affected was also important.

In light of the observed disease course and response to treatment, cPAN seems to be the most plausible diagnosis in this case.

*The authors declare no conflict of interest.*

## References

- Maj J, Reich A, Baran E. Primary systemic vasculitis. *Post Dermatol Alergol* 2004; 21: 247-254.
- Woźniacka A, Jurowski P, Omulecki A, et al. Behçet's disease leaves the silk road. *Postepy Dermatol Alergol* 2014; 31: 417-420.
- Turska M, Parada-Turska J. Cutaneous polyarteritis nodosa. *Wiad Lek* 2018; 71: 73-77.
- Iudici M, Puéchal X, Pagnoux C, et al. Brief Report: Childhood-Onset Systemic Necrotizing Vasculitides: Long-Term Data From the French Vasculitis Study Group Registry. *Arthritis Rheumatol* 2015; 67: 1959-1965.
- Lakdawala N, Fedeles F. Vasculitis: Kids are not just little people. *Clin Dermatol* 2017; 35: 530-540.
- Iudici M, Quartier P, Pagnoux C, et al. Childhood- versus Adult-Onset Polyarteritis Nodosa Results from the French Vasculitis Study Group Registry. *Autoimmun Rev* 2018; 17: 984-989.
- He Q, Shu J, Chen F, Zhen FX. Analysis of the clinical characteristics and follow-up study of children with cutaneous polyarteritis nodosa. *Curr Neurovasc Res* 2019; doi: 10.2174/1567202616666190618112705 [Epub ahead of print].
- Colmegna I, Maldonado-Cocco AJ. Polyarteritis nodosa revisited. *Curr Rheumatol Rep* 2005; 7: 288-296.
- Hernández-Rodríguez J, Alba MA, Prieto-González S, Cid MC. Diagnosis and classification of polyarteritis nodosa. *J Autoimmun* 2014; 48-49: 84-89.
- Levy-Lahad E, Elkan-Navon P, Segel R, et al. OR13-002 Recessive mutations in CECR1, encoding adenosine deaminase 2 (ADA2), cause systemic and cutaneous polyarteritis nodosa (PAN). *Pediatr Rheumatol Online J* 2013; 11 (Suppl 1): A264.
- Koné-Paut I, Shahram F, Darce-Bello M, et al. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. *Ann Rheum Dis* 2016; 75: 958-964.
- Kanecki K, Nitsch-Osuch A, Goryński P, et al. Behçet disease: a rare systemic vasculitis in Poland. *Pol Arch Intern Med* 2017; 127: 652-656.
- Kotulska A, Kucharz EJ, Kopeć M. Behçet's disease in Poland. *Clin Rheumatol* 2005; 24: 667-668.
- Woźniacka A, Sysa-Jędrzejowska A, Jurowski P, et al. Morbus Behçet – a rare disease in Central Europe. *Arch Med Sci* 2015; 11: 1189-1196.
- Turowska-Heydel D, Żuber Z, Sobczyk M, Pilch B. Trudności diagnostyczne i terapeutyczne w młodzieńczej chorobie Behçeta – opis dwóch przypadków. *Reumatologia* 2010; 48: 276-281.
- Maślińska M, Perricone C, Shoenfeld Y. Autoimmune/inflammatory syndrome induced by adjuvants – a new diagnostic problem or the solution of a diagnostic riddle. *Reumatologia* 2013; 51: 437-444.
- Stolarczyk J, Kubiś M, Brzosko M. Autoimmunologiczny zespół indukowany przez adiuwanty (ASIA). *Pomeranian J Life Sci* 2016; 62: 35-39.
- Shoenfeld Y, Agmon-Levin N. ASIA Autoimmune/autoinflammatory syndrome induced by adjuvants. *J Autoimmun* 2001; 36: 4-8.
- Patarroyo PAM, Restepo JF, Rojas SA, et al. Are classification criteria for vasculitis useful in clinical practice? Observations and lessons from Colombia. *J Autoimmune Dis* 2009; 6: 1.
- Seeliger B, Sznajd J, Robson JC, et al. Are the 1990 American College of Rheumatology vasculitis classification criteria still valid? *Rheumatology (Oxford)* 2017; 56: 1154-1161.
- Kizawa T, Yoto Y, Mizukami M, et al. A case report of cutaneous polyarteritis nodosa in siblings. *Mod Rheumatol* 2018; 28: 1049-1052.
- Matteoda MA, Stefano PC, Bocián M, et al. Cutaneous polyarteritis nodosa. *An Bras Dermatol* 2015; 90 (3 Suppl 1): 188-190.