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ORIGINAL ARTICLE

Panniculitis in pediatric rheumatology practice: experience of a pediatric referral center

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Abstract

Introduction and Objectives: Panniculitis is a group of disorders characterized by inflammation of the subcutaneous adipose tissue. We aim to characterize patients with panniculitis monitored in a Pediatric Rheumatology Unit. **Methods:** Descriptive, cross-sectional, retrospective study, from January 2004 to December 2020. Demography, clinical characteristics, laboratory tests, skin biopsy and treatment were evaluated. Patients were divided into two groups: erythema nodosum (EN) and non-erythema nodosum (non-EN). Non-EN panniculitis was confirmed by histology. Exclusion criteria: atypical EN without a biopsy. Laboratory and clinical characteristics were compared. **Results:** Twenty-seven patients were enrolled (girls: 70%; median age of onset: 11 years). The main etiologies of EN (n = 19) were undetermined (37%), streptococcal infection (32%) and Crohn's disease (11%). All patients with EN reported pain, 26% fever and 11% weight loss; 100% were treated with non-steroidal anti-inflammatory drugs (first-line therapy). Eight cases of non-EN panniculitis were included: lipoatrophic panniculitis (n = 3), lupus panniculitis (n = 2), cytophagic histiocytic panniculitis (n = 1 [CHP]), subcutaneous panniculitis-like T-cell lymphoma (n = 1; SPTCL), cutaneous polyarteritis nodosa (n = 1); 38% presented with nodules, 38% had fever and 38% had painful skin lesions. Seven non-EN panniculitis patients were initially treated with corticosteroids. The patients with CHP and SPTCL went into remission after immunosuppressive treatment and chemotherapy, respectively. The remaining patients were given immunomodulatory therapy. Patients with EN had more painful nodules and arthralgia/arthritis compared to non-EN patients. **Discussion:** New-onset constitutional symptoms during EN follow-up should prompt further investigation. Indurated and discolored nodules/plaques should evoke panniculitis. Histopathology can be helpful in non-EN panniculitis as it can guide towards specific diagnosis and appropriate treatment.

Keywords: Panniculitis. Erythema nodosum. Pediatrics. Rheumatology. Subcutaneous adipose tissue.

Paniculites na prática de reumatologia pediátrica: experiência de um centro de referência pediátrica

Resumo

Introdução e Objetivos: As paniculites são caracterizadas por inflamação do tecido celular subcutâneo. Objetivo de estudo: caracterizar os doentes com paniculite observados numa Unidade de Reumatologia Pediátrica. **Métodos:** Estudo descritivo, transversal, retrospetivo, de janeiro de 2004 a dezembro de 2020. Foram estudados dados demográficos, clínica, exames laboratoriais, biópsia de pele e tratamento de dois grupos: eritema nodoso (EN) e não eritema nodoso (Não-EN). As paniculi-

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tes Não-EN foram confirmadas por histologia. Critérios de exclusão: EN atípico sem histologia. Foram comparadas características laboratoriais e clínicas. **Resultados:** Foram incluídos 27 doentes (raparigas: 80%; idade mediana de início: 11 anos). As principais doenças associadas ao EN (n = 19) foram: indeterminada (37%), infeção estreptocócica (32%) e doença de Crohn (11%). Todos doentes com EN relataram dor, 26% febre e 11% perda de peso; todos foram medicados com anti-inflamatórios não-esteroides. Oito paniculites Não-EN foram incluídas: paniculite lipoatrófica (n = 3), paniculite lúpica (n = 2), paniculite histiocítica citofágica (n = 1; PHC), linfoma subcutâneo de células T tipo paniculite (n = 1; LSCTP) e poliarterite nodosa cutânea (n = 1); 38% apresentou-se com nódulos, 38% tinham febre e 38% dor. Sete paniculites Não-EN foram inicialmente tratadas com corticóides. Os doentes com PHC e LSCTP entraram em remissão após imunossupressão e quimioterapia, respetivamente; os restantes mantém-se sob terapêutica imunomoduladora. Os doentes com EN tiveram mais nódulos dolorosos e artralgia/artrite relativamente aos Não-EN. **Discussão:** Sintomas constitucionais de novo em doentes com EN devem motivar investigação de segunda linha. Nódulos ou placas endurecidas e com alteração da cor devem evocar paniculite. A histopatologia pode ser importante na paniculite Non-EN, orientando para diagnóstico específico e tratamento adequado.

Palavas-chave: Paniculites. Eritema nodoso. Pediatria. Reumatologia. Tecido adiposo subcutâneo.

Keypoints

What is known
- Panniculitis is characterized by inflammation of the subcutaneous adipose tissue, presenting with nodules or plaques. Many of these conditions are rare in pediatric age, leading to a paucity of published case series.
- Erythema nodosum is the most common panniculitis. Infection is its most frequent etiology and in most cases the course of disease is benign. First-line therapy is non-steroidal anti-inflammatory drugs and bed rest.
- Other type of panniculitis, such as conditions associated with autoimmune disease or malignant diseases are rare and potentially severe. They can have a similar presentation (nodules or plaques), making differential diagnosis challenging.

What is added
- We present a case series of 27 patients with panniculitis, evaluated by a Pediatric Rheumatology Unit over a seventeen-year span.
- Histopathology, following first-line assessment, is a powerful tool for diagnosis and timely treatment of non-EN panniculitis.
- When possible, early and specific treatment should be offered, as some forms of panniculitis can be disfiguring or may be a sign of severe disease.

Introduction

Panniculitis is a group of disorders that is rare in children, characterized by inflammation of the subcutaneous adipose tissue. Clinically, they present with solitary or multiple inflammatory subcutaneous nodules and/or infiltrated plaques. They occur mostly in the legs, thighs, buttocks or cheeks, and can be tender and accompanied by systemic symptoms (such as fever, arthralgia, malaise and weight loss)[1].

Etiologies vary, sometimes related to previous or concomitant infection, autoimmune disorders (such as connective tissue diseases or inflammatory bowel disease [IBD]), autoinflammatory disorders (such as familial Mediterranean fever) and even physical factors like trauma or cold weather[1]. There are some well-known pediatric-specific forms of panniculitis, such as subcutaneous fat necrosis of the newborn, cold panniculitis and post-steroid panniculitis and others that can present at any age, such as erythema nodosum (EN)[2]. Other types of panniculitis are rarer, particularly in pediatrics, leading to a paucity of case series in this age group[1].

Despite different etiologies, the initial clinical appearance can be similar, therefore associated symptoms and laboratory examinations can guide initial testing. Even so, ruling out typical EN and subcutaneous fat necrosis of the newborn, a definite diagnosis will only be possible after histological evaluation. Histologically, panniculitis is classified as lobular, septal or mixed, depending on where the inflammatory infiltrate is mainly located[1,3].

The aim of this study is to characterize the patients with panniculitis who were evaluated in a Pediatric Rheumatology Unit over the course of seventeen years.

Methods

This is a descriptive and retrospective study from January 2004 to December 2020, carried out in a tertiary referral hospital. We included all patients with a confirmed diagnosis of panniculitis evaluated by the Rheumatology team. We divided the patients into two

groups: EN and non-erythema nodosum panniculitis (non-EN).

The diagnosis of EN was based on clinical characteristics: acute multiple nodular (> 1 cm), erythematous violaceous and tender lesions localized in the lower legs (pre-tibial area), with scarless spontaneous resolution up to eight weeks[4]. Patients with an absence of pre-tibial lesions, unilateral and/or ulcerated nodules and lasting longer than 8 weeks, without a histological evaluation, were excluded. The diagnosis of non-EN was based on histological testing.

We evaluated the medical records and included demographic data (age at onset of the disease, sex, disease and follow-up duration); epidemiologic context; clinical characteristics at presentation (fever, weight loss, anorexia, arthralgia, arthritis, oral aphthous ulcers and diarrhea); characteristics of the subcutaneous nodules and/or plaques; treatment and outcome. We reviewed relevant laboratory data: blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tuberculin skin test (TST), interferon gamma release assay test (IGRA), serum immunoglobulins, throat culture, antistreptolysin O titer (ASLO), anti-DNAse B titer, viral serologies, serum angiotensin-converting enzyme (SACE), antinuclear antibodies (ANA) and microbiological cultures (throat and stool). Imaging exams as well as histopathological evaluation of biopsied lesions were also reviewed.

Previous streptococcal infection was defined by a positive rapid antigen detection test (RADT) for Group A *Streptococcus* (GAS) in the four weeks prior to clinical presentation or an elevated ASLO (> 500 U/ml) or Anti-DNAse B titer (> 500 U/ml)[5] with subsequent declining levels. Behcet's disease was diagnosed using the 2015 Pediatric Behçet's Disease Group criteria[6]. Anemia was defined as hemoglobin < -2 standard deviation for age and sex[7] and ESR was considered elevated if > 20 mm/hour.

We compared the clinical and laboratory characteristics of the two groups using SPSS® Statistics 22. A Mann–Whitney U test was used for the continuous variables and Fisher's exact test for the categorical variables. We considered $p < 0.05$ as statistically significant.

Results

Twenty-seven patients were enrolled, 70% (n = 19) were girls, with a female: male ratio of 2.5:1. The median age at symptom onset was 11 (min. 0.5; max. 17) years. Twenty-three (85%) patients presented with tender, erythematous or violaceous, subcutaneous nodules and six with an area of erythema that progressed to atrophic plaques (Fig. 1). Nineteen patients (70%) had EN and eight (30%) had non-EN panniculitis. Two (7%) were discharged in the first consultation. The remaining patients had a median follow-up duration of 10 (min. 1; max. 120) months.

Erythema nodosum (n = 19)

The median age for presentation was 12 (min. 3; max. 17) years and 68% (n = 13) were girls (eight girls under 12 years of age). The most common associated disease was streptococcal infection (32%). Two had active pharyngitis (RADT positive), two had odynophagia four weeks earlier and two had no history of respiratory symptoms. These last four patients had ASLO and ADNase B titers compatible with previous GAS infection and no evidence of other concurrent etiology. Crohn's disease (CD) was the second most frequent etiology (12%), with EN as the initial manifestation. In 37% of the patients, no underlying etiology was diagnosed. EN was the first sign of CD. Associated diseases, as well as clinical and relevant laboratory examinations, are summarized in table 1.

Eighteen patients (95%) had pre-tibial nodules, two of whom also had lesions on the extensor surface of the arms. One (5%) had nodules only on the posterior surface of the legs. All patients reported pain and had local erythema and heat.

The main reported symptoms were arthralgia in 37%, fever in 26%, asthenia in 21%, arthritis in 16%, odynophagia in 16%, abdominal pain in 16%, weight loss in 11%, ocular disease (uveitis and episcleritis) in 11%, diarrhea in 11% and oral aphthous ulcers in 5%.

Anemia was present in 11% of patients and a CRP level ≥ 6 mg/dl was also found in 11% of cases. Skin biopsies, performed in two patients (11%), showed septal panniculitis without vasculitis.

All patients were treated with non-steroidal anti-inflammatory drugs (NSAIDs) and, when diagnosed, due to its etiology, oral prednisolone (PDN, 1-2 mg/Kg/day) was associated in 16% of patients. Five (26%) were treated with antibiotics at the first observation, two with amoxicillin for GAS pharyngitis (after RADT) and three with flucloxacillin for suspected cellulitis. There was more than one episode in 37%.

Two (with streptococcal associated disease) were discharged in the first Rheumatology consultation and the remaining patients had a median follow-up duration of four (min. 1; max. 84) months. Patients with IBD were followed up in a gastroenterology consultation.

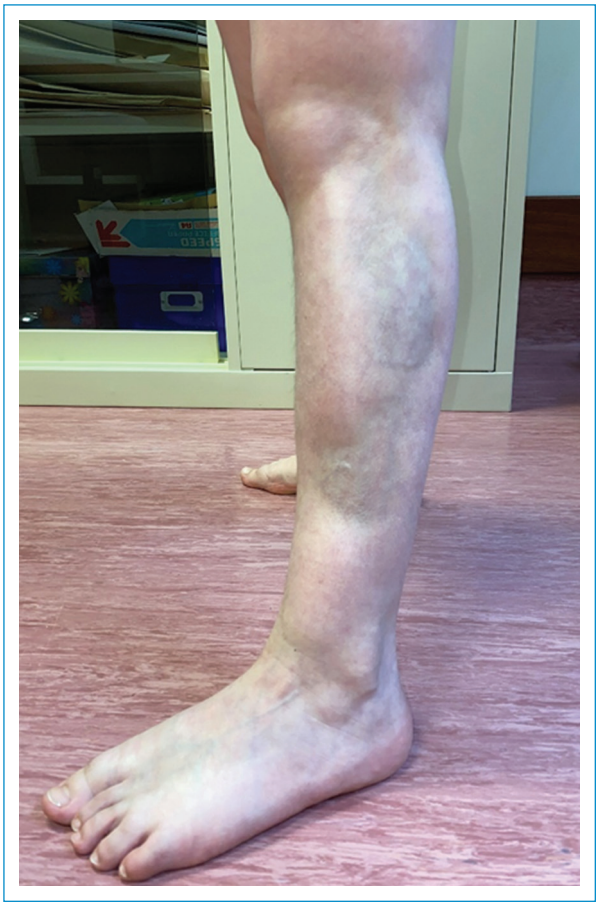

Figure 1. Atrophic plaque in a patient (patient 5 [Table 2]) with lipoatrophic panniculitis.

Non-erythema nodosum panniculitis (n = 8)

The median age at presentation was 10.5 (min. 0.5; max. 16) years, the median time until diagnosis was nine (min. 0.5; max. 72) months and the median time of follow-up was 4.5 (min. 0.25; max. 10) years.

The most common diagnosis was lipoatrophic panniculitis (n = 3 [38%]) followed by lupus panniculitis (n = 2 [25%]). Table 2 summarizes the demographic characteristics, clinical manifestations, laboratory, treatment and clinical course of this group.

Three patients (38%) presented with tender nodules and five (62%) with inflammatory plaques. In the latter group, four evolved to atrophic, depressed and hyperpigmented lesions and one, with subcutaneous panniculitis-like T-cell lymphoma (SPTCL, patient 7 [Table 2]), developed multiple subcutaneous nodules two months after presentation.

Reported symptoms were fever in 38%, pain in 38%, asthenia in 25%, weight loss in 25%, oral aphthous ulcers in 13%, diarrhea in 13% and acrocyanosis in 13%.

There was no evidence of infection when systemic symptoms were present, despite extensive laboratory investigations. A skin biopsy was performed in all non-EN panniculitis patients (Table 2). Two patients (25%) had anemia (patients 1 and 7 [Table 2]) and two (26%) had leukopenia (patients 6 and 7 [Table 2]) at presentation. ANA were positive in 38% (patients 1, 2 and 4 [Table 2]).

Patient 6 (Table 2), with cytophagic histiocytic panniculitis (CHP), had a myelogram which showed "very rare histiocytes with hemophagocytosis", a normal lymphocyte subpopulation and burst test.

Patient 8 (Table 2), with cutaneous polyarteritis nodosa (cPAN), presented with persistent cutaneous nodules that resembled EN as well as acrocyanosis. After six months, a skin biopsy was performed and histology showed "septal panniculitis with medium-sized artery vasculitis". ANCA antibodies were negative and adenosine deaminase 2 (ADA2) levels, as well as the urinalysis and electromyography, were normal. The only case with recurrent relapses was in this group.

Both CHP and SPTCL patients are in remission after immunosuppressive therapy and chemotherapy, respectively. The latter was followed up by the Pediatric Oncology team. Patient 1 evolved to systemic lupus erythematous and transitioned to adult care seven years after the initial presentation.

Statistical analysis

We found no statistically significant difference between the two groups regarding ESR (U = 35.000; $p = 0.09$) and CRP (U = 46.000; $p = 0.50$). There was no association between the two groups in the context of anemia ($X^2_{(1)} = 0.02$; $p = 1$), leukopenia ($X^2_{(1)} = 2.214$; $p = 0.32$), fever ($X^2_{(1)} = 0.25$; $p = 0.66$), weight loss ($X^2_{(1)} = 0.82$; $p = 0.56$), asthenia ($X^2_{(1)} = 0.79$; $p = 0.63$), aphthous ulcers ($X^2_{(1)} = 0,43$; $p = 0.51$) and abdominal pain ($X^2_{(1)} = 1,42$; $p = 0.53$). There was an association between EN and painful nodules ($X^2_{(1)} = 6.68$; $p = 0.20$) and arthralgia/arthritis ($X^2_{(1)} = 6.68$; $p = 0.20$).

Discussion

We describe a sample of pediatric patients with panniculitis observed by the Rheumatology Unit over a seventeen-year span, composed of EN and non-EN patients. Some of the non-EN cases are secondary to very rare disorders.

Table 1. Etiologies or associated disease, clinical and laboratory data on the patients with EN

Diagnosis	n = 19 (%)	Age (years) (median [range])	Associated symptoms (n)	Leukocyte count (uL) (median [range])	CRP (mg/dl) (median [range])	ESR (mm/1st h) (median [range])	Other relevant laboratory results (n)	Treatment (n)	Recurrences (n)
Streptococcal infection	6 (32%)	13 (5-17)	P (6), A (2), Ar (2), O (2)	11070 (6610-16200)	0.9 (0.17-2.7)	24 (10-48)	Positive RADT (2), ↑ASLO*(4), ↑Anti-DNAse B †(3)	NSAIDs (6), amoxicillin (2), flucloxacillin (2)	0 (4), 1 (1), 2 (1)
Crohn's disease	2 (11%)	11 (10-12)	P (2), A (2), F (1), Art (1), AP (2), WL (2), D (1)	10680 (8560-12800)	4.8-6.6	74.5 (74-75)	Anemia (2), Calprotectin - 7760 ug/mg (1)	NSAIDs (2), PDN (1)	0 (1), > 4 (1)
Probable reactive arthritis	2 (11%)	7.5 (3-12)	P (2), AP (1), Art (2), E (1), F (1), D (2)	11595 (9800-13390)	7.5 (6.7-8.3)	77 (64-90)	Negative stool culture	NSAIDs (2), PDN (1)	1 (1), > 4 (1)
Abscess secondary to *Staphylococcus aureus* cervical lymphadenitis	1 (5%)	5	p	13700	4.1	103	Normal IgG, lymphocyte subpopulation and burst test	NSAIDs	0
Behcet disease	1 (5%)	10	P, U, AU	10320	0.7	17	Negative ANA	NSAIDs	0
Idiopathic	7 (37%)	12 (7-17)	P (7), F (3), Ar (5), O (1)	9540 (6280-15300)	6 (1.18-7.8) N = 5	42 (17-95) N = 6	Positive ANA (1)	NSAIDs (7), PDN (1), flucloxacillin (1)	0 (5), 1 (1), > 4 (1)

*Elevation of initial ASLO titer with subsequent declining levels: 2 with > 1000 U/ml and 2 with 600-1000 U/ml.
†Elevation of initial Anti-DNAse B titer (> 600 U/L) with subsequent declining levels: 2 with > 1000 U/ml and 2 with 600-1000 U/ml
A: asthenia; ANA: anti-nuclear antibodies; AP: abdominal pain; Ar: arthralgia; Art: arthritis; ASLO: anti-streptolysin; AU: aphthous ulcers; D: diarrhea; E: episcleritis; F: fever; NSAIDs: non-steroidal anti-inflammatory drugs; O: odynophagia; P: pain; PDN: prednisolone; RADT: positive rapid antigen detection test for Group A *Streptococcus*; U: uveitis; WL: weight loss.

Table 2. Clinical details and disease course of non-EN panniculitis

Patient	Sex	Diagnosis	Age of onset (years)	Initial lesion	Evolution	Associated symptoms	ESR (mm/1st h)	CRP (mg/dl)	Histology	Initial treatment	MT	Outcome
1	F	Lupus Pn	11	RT: 5 x 3 cm, hyperpigmented, linear plaque	RT (initial lesion): 20 x 9 cm brown, indurated, depressed, linear plaque. Developed two similar plaques in the RUA (3 x 3 cm).	P, AU, F, C	90	8.5	LP + lymphoid follicles with germinative center	PDN	PDN + AZA	SLE stable
2	F	Lupus Pn	10	RT: 3 x 5 cm, indurated depressed plaque	Developed three similar plaques. LT: 1.5 x 1.3 cm; RUA: 2 x 1 cm; LUA: 0.5 x 0.5 cm.	Ø	8	Ø	LP + SP + lymphoid and plasma cells	PDN	HC	Stable
3	F	Lipoatrophic Pn	2	LL: 4 sc nodules, < 1 cm	LL (nodules converged): indurated, depressed plaque. Developed two plaques in the RL and LFA.	F, A	20	0.3	LP + SP + histiocytic cells	PDN	MTX	Stable
4	F	Lipoatrophic Pn	1	LL: 1 cm erythematous plaque	LL (initial lesion): 13 x 4 cm, hyperpigmentation, atrophy. Developed three similar plaques: LT: 4 x 4 cm; LF: 3 x 2 cm.	Ø	15	0.04	LP + predominant plasmocytic cells	PDN + MTX	MTX	Stable
5	F	Lipoatrophic Pn	9	LL: 8 x 6 cm, erythematous warmth plaque	Initial lesion: deep sc atrophy.	Ø	18	0.26	LP + polymorphous infiltrate	PDN + LFN	LFN	Stable
6	M	SPTCL	16	RT: painful, warm and indurated plaque	Multiple sc nodules in the right hip and thigh, thorax (anterior surface) and back.	F, P, A, WL	22	1.3	LP + atypical lymphocytes + necrosis	AB	Chemotherapy (oncology)	Remission
7	M	CHP	0.5	10 – 15 sc tender nodules, with < 1 cm in LUA, LL, back and abdomen.		F, P, A, WL, D	100	15	LP + SP + histiocytic cells + macrophages in cytophagocytosis	MPDN (high dose)	CS	Remission
8	F	cPAN	11	Bilateral multiple nodules with purple coloring (legs and feet).		P Acrocyanosis	29	2.37	SP + vasculitis (ANCA negative)	PDN + LFN	PDN + AZA + HCQ + nifedipine	Recurrence

A: asthenia; Ant: anterior; AU: aphthous ulcers; AZA: azathioprine; C: cough; CHP: cytophagic histiocytic panniculitis; cPAN: cutaneous polyarteritis nodosa; CS: cyclosporin; CT: corticosteroid; D: diarrhea; ESR: erythrocyte sedimentation rate; F: fever; HCQ: hydroxychloroquine; LF: left foot; LFA: left forearm; LFN: leflunomide; LL: left leg; LP: lobular panniculitis; LT: left thigh; LUA: left upper arm; MPDN: methylprednisolone; MT: maintenance treatment; MTX: methotrexate; N: (described) normal; AU: aphthous ulcers; P: pain; PDN: prednisolone; Pn: panniculitis; RL: right leg; RT: right thigh; RUA: right upper arm; sc: subcutaneous; SLE: systemic lupus erythematosus; SP: septal panniculitis; SPTCL: subcutaneous panniculitis-like T-cell lymphoma; WL: weight loss.

EN is the most common type of panniculitis in all ages and the incidence peaks between the second and fourth decades of life. Among children, it is less frequent in prepubertal children and rare below two years of age[4-8], which is corroborated by our study, as our youngest patient was three years of age. There is a female predominance in adults, but in children, there is generally no difference regarding sex[4-8]. In our sample, we still had a female predominance under 12 years of age (67%).

In our series, EN accounts for 70% of cases, one third secondary to streptococcal infection, the most common disease implicated in EN etiology[4-8]. The frequency of undetermined etiology varies between series, ranging from 13.5-43%[9-12] and in this study 37% were classified as idiopathic (Table 1).

Skin biopsies were performed in one patient with idiopathic typical EN, before being referred to our unit, and one with atypical presentation (nodules on the posterior surface of the legs), later diagnosed as CD.

EN is a known cutaneous manifestation of IBD and occurs in 4-15% of patients with CD and 3-10% of patients with ulcerative colitis[4-8]. During follow-up, both patients developed abdominal pain, weight loss and arthralgias that motivated screening and referral to gastroenterology (Table 1). Diarrhea appeared four months after the diagnosis of EN in both cases. Ileum histopathology confirmed CD.

In our series, we had two patients with probable reactive arthritis. Both had previous diarrhea treated with antibiotics (with a negative stool culture). One had episcleritis and oligoarthritis (knee and elbow), and was treated with prednisolone after ruling out infection and went into remission after more than four recurrences.

Our patient with Behçet disease had EN, uveitis and recurrent aphthous ulcers, fulfilling criteria for this vasculitis[6]. The laboratory evaluation was innocent, and ANA were negative.

We had no evidence of EN secondary to drug intake, one of the multiple causes of EN[4], but we believe that in the patient with staphylococcal abscess, previous antibiotic intake could also have played a role in its etiology. He had been empirically treated with amoxicillin plus clavulanic acid before a course of flucloxacillin.

All our EN patients were under symptomatic treatment, the first-line therapy[4-8], with NSAIDs and bed rest, most of whom had a favorable outcome. In three patients, with more recurrences, oral PDN was associated after ruling out infectious diseases.

One third of our sample had more than one episode. One patient with CD (before achieving remission) had frequent EN recurrences temporally related to bowel flares.

Two patients with streptococcal infection-associated EN were discharged after the first observation by the Rheumatology team as they were already asymptomatic, with declining ASLO and DNAse titers.

We report a 30% prevalence of non-EN panniculitis. In 2010, Moraes et al.[9] reported 17% non-EN panniculitis cases (diagnosed previously as cases of Weber-Christian disease).

In the non-EN group, systemic symptoms such as fever, asthenia and weight loss were present in two patients, one with SPTCL and one with CHP, reflecting systemic involvement. They can be present in other types of panniculitis and in our series, one girl with lipoatrophic panniculitis had fever and asthenia in the prodromic phase.

Lipoatrophic panniculitis is a rare entity, occurring mainly in children[14], and it has an inflammatory phase that can resemble EN (such as patient 3 [Table 2]). Lesions are typically located in the legs and ankles and can progress to permanent lipoatrophy. Some reported cases are related to autoimmune disorders[14]. We present three patients with lipoatrophic panniculitis with a typical presentation.

Lupus panniculitis is a rare cutaneous form of lupus erythematosus and has rarely been reported in children[1]. In a multicentric study in 2019, only six out of 847 (0.7%) child-onset systemic lupus erythematosus (SLE) patients had lupus panniculitis[15]. It can be a chronic cutaneous disease or a preceding manifestation of SLE. We have two patients with lupus panniculitis, both with positive ANA antibodies.

Patient 1 (Table 2) was sent to our unit for suspected SLE. She had a previous history of recurrent oral ulcers and a histological diagnosis of lupus panniculitis treated with 0.1% tacrolimus ointment. Two months before referral there was clinical worsening, with anorexia, fever, anemia and an increase in the panniculitis size and atrophy (Table 1). An SLE diagnosis was confirmed, as she fulfilled Systemic Lupus International Collaborating Clinics (SLICC)[16]: lupus panniculitis, oral ulcers, significant proteinuria (501 mg/24 hours), positive ANA (titer 1:320) and positive lupus anticoagulant. She was treated with oral PDN, improving quickly, and clinical stability was achieved with low-dose PDN plus azathioprine. At 18 years of age, she transitioned to adult care. Patient 2 (Table 2) had an exclusively cutaneous disease. Diagnosis was based on clinical, histological and laboratory (low C3 and positive ANA) findings. She was treated with hydroxychloroquine

for two years and, to date, has not fulfilled SLICC criteria[16].

CHP is a disorder consisting of lobular panniculitis with infiltration of cytophagic hystiocytes. It can be an isolated skin disease or it can be associated with triggering infections or malignant disease, such as SPTCL. SPTCL is a rare primary cutaneous lymphoma, and its T-cell clonal proliferation is frequently associated with an autoimmune disease[17]. Both entities, very rare in pediatric age, can be associated with secondary hemophagocytic lymphohistiocytosis, a severe systemic inflammatory syndrome that courses with fever, splenomegaly, cytopenias, hypertriglyceridemia and high ferritin, and may be lethal if untreated[18].

The patient with CHP (patient 7 [Table 2]) presented at six months of age with fever and diarrhea and initially was treated with intravenous ceftriaxone for suspected sepsis. He also had anemia (9.1 g/dl) and leukopenia (3700 uL) with neutropenia (600 uL). Even so, fever persisted, anemia worsened (minimum 8.2 g/dl), ferritin rose (maximum 528 ng/ml) and there was evidence of hemophagocytosis in bone marrow histology. He was successfully treated with cyclosporine A after methylprednisolone pulses. Given the initial symptoms, we believe that a preceding infection may have contributed to the development of CHP, even though there was no microbiological evidence in stools, urine or blood. Immunodeficiency screening was negative.

Before histological diagnosis, the initial clinical findings of the patient with SPTCL (patient 6 [Table 2]) resembled cellulitis and he was treated unsuccessfully with flucloxacillin. Initial laboratory evaluation revealed low ESR and CRP but showed leucopenia (2620 uL). The persistence of fever, weight loss and severe pain led to further investigation.

PAN is a necrotizing vasculitis of small and medium-sized arteries and is the third most common vasculitis in childhood[19]. Exclusive cutaneous involvement is more common in pediatric age. Differential diagnoses include deficiency of ADA2[20], a monogenic disorder, that was ruled out in our patient. Our patient (patient 8 [Table 2]), with a previous diagnosis of systemic juvenile idiopathic arthritis, was under PDN and leflunomide when cutaneous nodules appeared. EN was ruled out after histology results and the PDN dose was raised (maximum 0.25 mg/kg) with temporary improvement. She is currently under PDN, hydroxychloroquine, azathioprine and nifedipine and continues to suffer relapses of cutaneous vasculitis. The diagnosis for systemic PAN includes other criteria that the patient does not have, such as musculoskeletal pain, hypertension, peripheral neuropathy and renal involvement[21].

All EN panniculitis patients had favorable outcomes. The non-EN panniculitis cases had varying degrees of scarring.

We did not find a statistically significant difference between most clinical and laboratory characteristics. The small size of the non-ED group likely reduces the strength of the statistical study. The association of painful nodules and arthralgias in the EN group is expected, since the first of these is one of the diagnostic criteria and the second is a common symptom.

In conclusion, streptococcal infection is still the most common cause of EN, and although in the vast majority of cases the course is benign, in some patients it can be the first sign of severe disease. Follow-up of cases with an unknown etiology allows observation of eventual disease progression and early intervention. New-onset asthenia and anorexia, abdominal pain and arthralgia should prompt second-line EN investigation.

In the other hand, indurated, discolored or atrophic nodules or plaques should raise the suspicion of panniculitis other than EN. Different etiologies need to be considered, some of which are life-threatening and require prompt treatment. Histopathological assessment and an adequate clinical-pathological correlation can guide specific diagnosis and appropriate management.

Authors' contribution

L. Silva: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. F. Cardoso: Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. L. Ramos: Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. P. Estanqueiro: Conception and design of the study, report, review or other type of work or paper; Analysis or interpretation of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. J. Nascimento: Conception and design of the study, report, review or other

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Conflicts of interest

None.

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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