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CLINICAL CASE

# Paniculitis as manifestation of prolonged febrile syndrome: Case report

## Paniculitis como manifestación de síndrome febril prolongado en pediatría. Caso clínico

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### Abstract

**Introduction:** Fever of unknown origin (FUO) is defined as fever over 7 to 10 days without a diagnosis despite a complete initial study. The most frequent causes are infections, autoimmune and tumors. Even though most cases are self-limited there is a minority that has an underlying etiology with an ominous forecast, encouraging a systematized study. **Objective:** To report a rare case of a boy who presented fever of unknown origin associated to panniculitis and was diagnosed of subcutaneous panniculitis-like-T cell lymphoma and to emphasis the importance of a sequential study of FUO, in order to reach a diagnosis in patients who need a timely intervention. **Clinical case:** A ten year old boy, previously healthy, presented subcutaneous nodular lesions of 2 month of evolution, located in abdominal region and extremities, given few symptoms, associated with prolonged fever. He was hospitalized for proper study, in first instance infectious and immune causes were discarded and through lesions biopsy the diagnose of subcutaneous panniculitis-like-T cell lymphoma was reached. **Conclusion:** When FUO is diagnosed, most prevalent causes must be discarded. Then, differential diagnosis, such as immune and neoplasic etiologies, have to be considered. If FUO is associated to elemental nodular lesions, biopsy must be indicated early, in order to find potential malignant cases, avoiding therapeutic delay.

**Keywords:**
Fever of unknown origin;
panniculitis;
panniculitis like T cell lymphoma;
children.

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## Introduction

In the 1960s, Petersdorf and Beeson conducted a prospective study at Yale University with a sample of 100 patients with body temperature above 38.3 ° C for more than 3 weeks without diagnosis, despite a week of etiological study hospitalized, coining the term "fever of unknown origin" (FOD)[1,2]; The FOD is equivalent to the concept of prolonged febrile syndrome (PFS), which in adults maintains the 3-week temporality criterion, but in pediatrics it is currently defined as a febrile episode of at least 7-10 days of evolution, without etiological diagnosis, despite an initial study consisting of anamnesis and complete physical examination together with basic laboratory tests[2-4].

As to the etiology of this syndrome, infectious, immunoreumatological, neoplastic and miscellaneous causes are distinguished[1-4]. After an exhaustive study, in 10-32% of cases, according to geographic location, no etiology is determined[2-9]. It should be mentioned that identifying the etiological diagnosis can be complex, due to atypical presentations of frequent clinical pictures[3-5].

The epidemiological situation of the pediatric PFS in Chile shows a great preponderance of infectious cause, being described in 68% of the cases, among which we find cat scratching, typhoid fever, urinary infection and infectious mononucleosis. Secondly, there are neoplastic and immunoreumatological etiologies, which are important in the differential diagnosis, with a prevalence of 4.8% for each[2,4]. Although the majority is progressing favorably, one out of ten patients has a final etiological diagnosis with ominous prognosis[2].

Hence the importance of close monitoring of the patient until the resolution of his symptoms.

Establishing that the PFS is a diagnostic challenge for the medical team, it is necessary to carry out a systematic study, following a logical order that allows optimizing resources and avoiding diagnostic delays, to the benefit of the patient[3,4,10].

It is relevant to carry out a thorough and complete anamnesis to parents or caregivers, emphasizing epidemiological antecedents and a thorough physical examination, evaluating the patient at least daily, especially during febrile increases, due to the possible appearance of new clinical signs that could guide to the diagnosis[3].

Panniculitis is described within the rare causes of PFS in pediatrics. This entity corresponds to an heterogeneous group of diseases that present with inflammation of the subcutaneous fat[11-13]. Childhood panniculitis exist, such as neonatal subcutaneous fat necrosis, neonatal scleroderma, post-steroidal panniculitis and cold panniculitis. In addition, cases of pediatric presentations of panniculitis described in adults, such as erythema nodosum, have been described[12,13].

The objective of this work is to present the clinical case of a schoolboy with SFP associated with panniculitis and to emphasize the importance of a sequential study of SFP to investigate patients requiring timely intervention.

## Clinical case

A 10 years old patient consulted for a period of two months of evolution characterized, initially, by isolated lesions such as subcutaneous nodules, without inflammatory signs, located in the epigastric region. After a month presenting these lesions, he presented a self-limiting picture of acute diarrhea without pathological elements, after alimentary transgression. He remained asymptomatic for 5 days, then he started with fever, with axillary temperatures of up to 40 °C, presenting a poor general condition and with acute body pain, mainly at the back of his legs. On the third day of symptoms, there were new palpable, sensitive nodular lesions, which appeared with local inflammatory signs with a violet color, more evident in relation to thermal elevations, mostly located at the back of the legs and forearms, but also in thighs, abdomen and arms (figure 1) . Physical examination showed no inflammatory joint signs, lymphadenopathy, rash or visceromegaly.

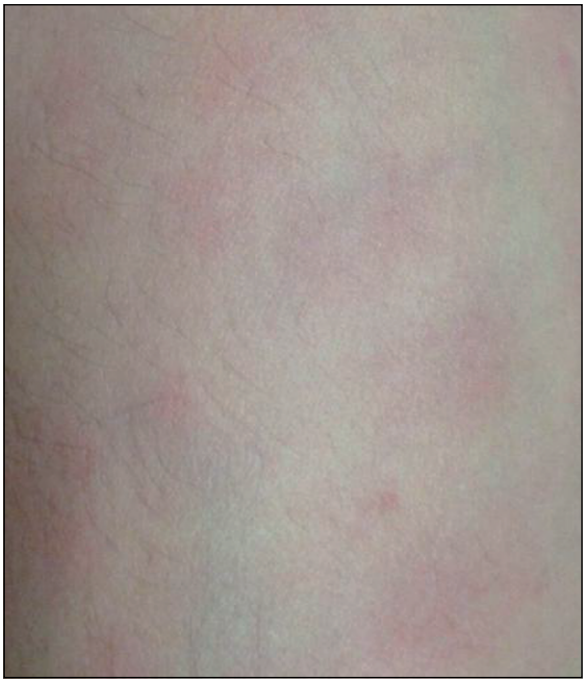

**Figure 1**. Erythematous zones are appreciated in the anterior aspect of the forearm above of nodular palpable lesions, without ulceration nor atrophy of the skin.

He had a background of current vaccination without administration of recent vaccines; A 3-year-old cat as a pet and presented an azithromycin intake of 250 mg/day for three days, which was self-medicated at the start of the fever and other mentioned symptoms.

He consulted a pediatrician on the seventh day of fever, who indicated hospitalization, with a diagnosis of SFP and panniculitis, also considering an observation of erythema nodosum. Among the results of laboratory tests performed were: normocytic-normochromic mild anemia, normal white and platelet series, ESR 39 mm/hr, normal PCR and procalcitonin, glycemia, calcemia, phosphemia, magnesemia, liver profile and albuminemia were normal; Negative microalbuminuria with normal renal function and complete urinalysis.

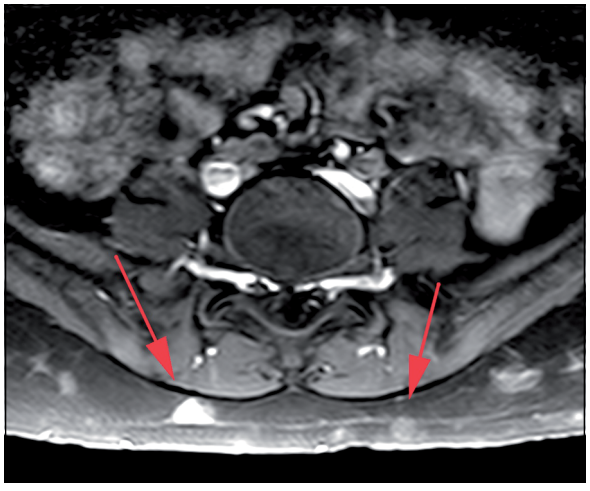

**Figure 2.** Lumbar spine MRI. Axial T1-weighted fat sat with Gd. Image showing subcutaneous nodules (red arrows).

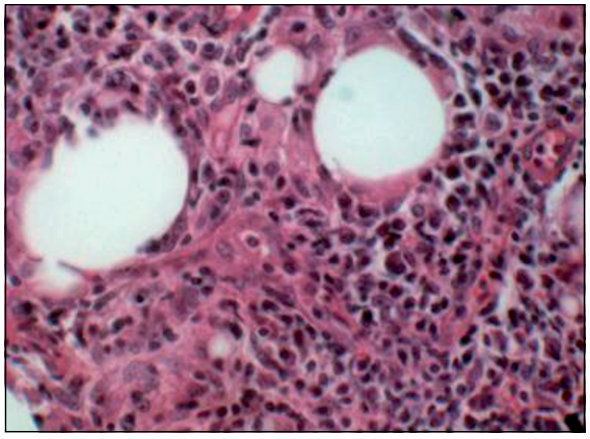

**Figure 3.** Mycro photografy 200x original magnification, showing atypical lymphocytes , of irregular nucleus, surrounding mature adipocytes. Hematoxylin-eosin stain.

Chest x-ray and abdominal ultrasound without pathological findings. Infectious study: Negative serology for Bartonella henselae, Mycoplasma pneumoniae, Epstein-Barr Virus, Cytomegalovirus, Parvovirus, Toxoplasma gondii, Brucella spp., HIV, quantiferon-TBC and antistreptolysin, blood cultures and coproculture were negative; The echocardiogram showed a normal cardiac structure, with minimal mitral insufficiency. Study with Autoantibodies (Anti-nuclear, Anti-DNA, Anti-neutrophil cytoplasm, Antibodies Extracts from the nucleus –ENA- and Rheumatoid Factor), negative.

The patient evolved with an overall conservation status, pallor of skin and mucosa, two daily febrile peaks up to 38 ° C, which yielded with intravenous metamizole and oral acetaminophen, associated with nocturnal sweating, without weight loss, discrete bimalleolar edema and with persistence of sensitive nodules and low back pain. Bone scintigraphy was reported as normal and magnetic resonance imaging (MRI) of the lumbar spine highlighted multiple nodular lesions in the deep subcutaneous (figure 2). On the third day of hospitalization, a dermatologist performed a skin and subcutaneous biopsy of the lesions for current study, immunofluorescence and PCR for Koch's bacillus. The report, which was received after progressing in the study, revealed histological and immunohistochemical findings (figure 3), which were consistent with panniculitis-type T-lymphoma, demonstrated by T lymphocyte clonality test, by means of gamma chain rearrangement in recipients. The patient was referred to a reference center for cancer pathology.

## Discussion

We initially faced a PFS with panniculitis in this clinical case, without a clear cause after a long background, physical examination and initial laboratory tests.

Referring to this particular case, initially a careful clinical evaluation was performed, followed by laboratory tests and basic imaging studies, ruling out probable infectious and autoimmune causes. Simultaneously, skin and subcutaneous cell biopsy were requested. Based on the pain in the lumbar region and due to suspicion of discitis, more complex examinations were indicated: bone scintigraphy and MRI of the back (lumbar region), evidencing the latter the presence of multiple nodules in the subcutaneous tissue of the dorsolumbar region, which confirmed that this finding was part of the patient's panniculitis.

Panniculitis are a very rare entity in pediatrics, which belong to a heterogeneous group of diseases that occur with inflammation of the subcutaneous fat[11-13].

Table 1 shows the classification of panniculitis ac-

cording to etiology. Childhood panniculitis are described, such as neonatal subcutaneous fat necrosis, neonatal scleroderma, post-steroidal panniculitis and cold panniculitis[12-16].

There are very infrequent reports on pediatric presentations of panniculitis that are well described in adults, being the most frequent, the erythema nodosum, a septal panniculitis without vasculitis, clinically characterized as the appearance of inflammatory and painful cutaneous nodules that mainly compromise the pretibial region of the lower limbs, which usually solve spontaneously in 1 to 6 weeks, without ulceration or cutaneous atrophy. It is a plurietiological syndrome that occurs frequently secondary to a hypersensitivity reaction associated with streptococcal, tuberculous or enteric disease in children and also to the use of beta-lactams and macrolides[12,13].

Panniculitis are presented clinically as deep plaques or nodules, regardless its origin or cause. Thus, it is necessary to complement its study with an histopathological study in order to approach to a correct diagnosis[11]. Even so, its histology is not simple to interpret, considering the limited ability of adipose tissue to react with different patterns[12,13]. The best diagnostic tool is the skin biopsy and it is the role of the physician to determine the appropriate time to perform it, being advisable to perform it in early stages to avoid evolution to lesions with less specific histological changes[13].

In order to identify the specific cause of panniculitis in the study, a trained dermatologist in the biopsy is fundamental as well as a good clinical pathological correlation. To reach a good diagnostic, it is essential to obtain a representative sample of subcutaneous tissue, so the biopsy must be excisional and deep[13].

In addition, panniculitis associated with malignant disease are described, which, although very rare, are important to consider when presenting atypical lesions or associated with constitutional symptoms[12].

In this clinical case, the diagnosis of Non-Hodgkin's lymphoma of T cells type panniculitis was reached through the biopsy. This represents less than 1% of non-Hodgkin's lymphomas[13,17], with cases reported in children only exceptionally, according to Vishal et al[18], who reported 26 cases. Any cases have been reported in Chile.

Subcutaneous panniculitis-like T-cell lymphoma is defined as the primary infiltration of subcutaneous cellular tissue by pleomorphic T cells of small, medium and large size. It is usually presented in young adults, with a mean of 36 years, and presenting a slight female tendency[19], as one or more subcutaneous nodules or plaques, usually not ulcerated, predominating in the legs. It could also compromise the trunk, upper limbs and face[17,18]. Up to half of the cases are associated with constitutional commitment with B symptoms (fever, nocturnal diaphoresis and weight loss) and possible hematological alterations[20,21]. Histologically, atypical lymphocytes are commonly seen forming a ring-like around necrotic adipocytes as a loop[13, 17-21]. In the immunohistochemistry, two subtypes are described: the alpha/beta with an indolent course and favorable prognosis and the gamma/delta, which has an aggressive course and a greater association with hematopagocytic syndrome. The estimated survival of the first is 80% and the second 10% to 5 years[21].

We reviewed 9 pediatric cases described in the literature[17-23], and we found some similar features with the present clinical case, as the presence of erythematous-violaceous non-ulcerated few sensitive nodules in the anterior abdominal wall, dorsum and extremities, nodules of insidious installation and evolution in outbreaks. In 6 of the 9 cases there was concomitance with PFS and 7 of them, kept their weight[17,18,22,23]. The absence of lymphadenopathy and visceromegaly were all described. Regarding to age, only 2 of the cases occurred in schoolchildren[18,23]. From the laboratory collected data, the presence of mild anemia and elevation of ESR was observed in 4 of the cases, right as it was presented in the current case[17,18,23]. The biopsy revealed the presence of panniculitis compatible with subcutaneous T-cell lymphoma, showing an association with hematophagocytosis in only one single patient, which did not occur in the present case[18].

**Table 1. Classification of the panniculitis of children**

| |
|---|
| *Specific panniculitis of children* |
| Subcutaneous fat necrosis of the newborn |
| Sclerema neonatorum |
| Cold panniculitis |
| Poststeroid paniculitis |
| *Adult-type panniculitis appearing in children* |
| Erythema nodosum |
| Enzymatic panniculitis |
| Pancreatic panniculitis |
| Infectious panniculitis |
| Bacterial Mycobacterial Fungal |
| Panniculitis in connective tissue disease |
| Lupus panniculitis , Dermatomyositis, Polyarteritis nodosa |
| Granulomatous panniculitis: |
| Sarcoidosis |
| Physical panniculitis |
| Facticial, Blunt trauma |
| Malignant paniculitis: |
| Subcutaneous panniculitic T-cell lymphoma |
| Histiocytic cytophagic panniculitis |
| Idiopathic panniculitides |

Adapted from Torrelo[3].

## Conclusion

Once the PFS is diagnosed, it is essential to follow some important steps as an organization during the study, first discarding infectious causes, then raising rheumatologic and neoplastic pathology. In case of PFS with elemental lesions, with no clear etiological diagnosis, biopsy of lesions should be carried out early in order not to delay the diagnosis and management of a potential malignant cause.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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## Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

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