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Title: Manifestations, clinical course and prognostic markers in cutaneous polyarteritis nodosa

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Summary

Background and objectives: Cutaneous polyarteritis nodosa (CPAN) is a comparatively rare form of vasculitis that affects small arteries and arterioles in the panniculus and dermo-subcutaneous junction. Limited information is available regarding its course in the European population. The aim of this study is to characterize the manifestations and prognostic markers of recurrence in CPAN.

Patients and methods: We report a retrospective study of patients with clinical and histopathologic evidence of CPAN, which was treated at two tertiary referral centers in Spain between 1989 and 2019.

Results: 31 patients were included. The most frequent manifestation was subcutaneous nodules (90.3 %); ulcers were frequent at diagnosis (35.5 %). Two thirds of the patients had at least one extracutaneous manifestation. Seventeen patients (54.8 %) experienced relapse. The strongest predictor of recurrence was ulceration in the initial episode (OR 18.6; 95 % CI 2.73–38; $p < 0.01$). The pre-treatment results of laboratory parameters associated with inflammation (such as C-reactive protein and neutrophil-to-lymphocyte ratio)

were significantly higher in the relapsing group. There were no disease-related deaths and none of the patients developed systemic PAN.

Conclusion: Although CPAN is a vasculitis limited to the skin, symptoms may involve adjacent skeletal muscle or peripheral nerves. While the condition is not life-threatening, the presence of ulceration and elevation of certain laboratory parameters predicts a worse prognosis.

Introduction

Polyarteritis nodosa (PAN) is a comparatively rare form of systemic vasculitis characterised by necrotising inflammation that predominantly affects small to medium-sized arteries and no association with antineutrophil cytoplasmic antibodies (ANCA).¹ Cutaneous symptoms are observed in 28% to 60% of patients with PAN, primarily purpura and livedo.^{2,3} H As purpura is a sign of small vessel vasculitis, its presence suggests that small vessels as well as medium vessels are involved in systemic PAN. However, a form of PAN restricted to the skin has also been recognized as a distinct subtype –cutaneous arteritis, also called cutaneous PAN (CPAN) – which affects arterioles and arteries in the dermis-subcutis junction and the subcutis itself and is characterized by the presence of subcutaneous nodules and a chronic, favorable course.³

Although CPAN is predominantly limited to the skin, patients may experience extracutaneous symptoms, particularly involving the muscles or nerves underlying affected skin.⁴ However, according to the diagnostic criteria for PAN defined by the American College of Rheumatology (ACR) in 1990,⁵ a patient with one cutaneous and one noncutaneous symptom and consistent histopathological findings could be diagnosed with PAN irrespective of the area involved. To reflect acceptance of these regional symptoms in the skin-limited form, a Japanese group proposed specific diagnostic criteria for CPAN,⁶ although these have not yet been validated.

While the prognosis of CPAN is usually favourable and progression to PAN is the exception,^{7,8} the chronic and sometimes relapsing course of the disease can present a therapeutic challenge and give rise to the need for

immunosuppressant therapy.^{9–12} Therefore, it would be highly desirable to identify specific prognostic markers for CPAN that would help to predict remission and relapse and the need for additional therapy. A recent Japanese study found that the presence of ulcers, as well as elevated C-reactive protein (CRP) levels and absolute neutrophil counts (ANC), could predict an increased risk of flares.¹³ However, some characteristics may be influenced by ethnicity and geography¹⁴ and to date the clinical course, frequency of systemic symptoms, and prognostic markers have not been fully determined in the European population.

The objective of this study was to characterise the features and long-term prognosis of CPAN and to identify potential predictors of relapse.

Methods

We retrospectively studied patients aged 18 or older who were diagnosed with CPAN at two hospitals. Patients fulfilling the following criteria were selected from those treated in the vasculitis clinics of the Dermatology and Rheumatology Departments: i) Clinical manifestations characterised as subcutaneous nodules, livedo, purpura and/or ulcers, ii) Histopathologic diagnosis of necrotising vasculitis of the small and medium arteries in the deep dermis or subcutis, iii) Exclusion of other vasculitis syndromes with similar manifestations, iv) Exclusion of systemic involvement, with the exception of extracutaneous symptoms limited to the area affected by the skin lesions, and v) a follow-up of at least 1 year.

The following data were collected: sex, age at diagnosis, cutaneous and systemic or extracutaneous manifestations, anatomical sites affected, pre-

treatment laboratory data at diagnosis, treatment, duration of follow-up, and number of relapses.

In this study, the definition of relapse was based on the European League Against Rheumatism (EULAR) recommendations for conducting clinical studies:¹⁵ the occurrence of new lesions requiring the use of prednisone at a dose of more than 20 mg/d and/or the additional use of immunosuppressants 6 months after attaining a stable remission. Systemic immune-inflammation index (SII) was calculated with the formula $SII = (\text{platelets} \times \text{neutrophils})/\text{leucocytes}$.

All data were recorded on a spreadsheet (Microsoft Excel 2019) and expressed as n (%) or as mean $\pm$ standard deviation (SD). To identify risk markers associated with relapse, we used the Mann-Whitney U test and Pearson χ^2 test to compare clinical and laboratory findings between the groups with and without relapse. A *P* value less than 0.05 was considered statistically significant. We also calculated the cumulative incidence of relapse, and compared the groups with erythrocyte sedimentation rate (ESR) values above and below 20 mm/h and ANC values above and below $6.5 \cdot 10^3/\mu\text{L}$ using the Kaplan-Meier method. Statistical analyses were performed using SPSS, version 25.

Results

Of the patients diagnosed between January 1989 and January 2019, 36 fulfilled the inclusion criteria. Five patients were excluded because of missing clinical information. Of the remaining 31 patients, 20 were women (64.5%) and 11 were men (35.5%); a female to male ratio of 1.9:1. The mean age was 47.5 years (range 18-76).

The clinical manifestations of the patients with CPAN are summarised in Table 1. The cutaneous lesions at diagnosis were mainly subcutaneous nodules (90.3%), livedo reticularis (45.2%), ulceration (35.5%), livedo racemosa (12.9%) and purpura (3.2%). Healing of ulcers resulted in an ivory-white stellate scarring (atrophie blanche) in 8 patients. All the patients presented skin lesions on the lower legs (below the knee), which were complemented in some cases by lesions on the thighs (41.9%), arms (32.3%) and trunk (19.4%).

Data on clinical comorbidities were also extracted (Table 2). The most frequent comorbid conditions were 7 cases (22.6%) of systemic hypertension, 5 (16.1%) of type 2 diabetes mellitus and 3 (9.7%) of autoimmune hypothyroidism. None of the patients had renovascular hypertension or visceral damage associated with systemic arterial hypertension.

All of the patients had been screened for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) and tuberculosis (PPD or IGRA test). HBV infection was detected in 1 patient, HCV in 2, and latent tuberculosis in 1. In 3 patients the development of CPAN coincided with the course of an infection: *Chlamydia trachomatis* in 1 patient, recurrent streptococcal pharyngitis in another, and *Rickettsia* in the third.

Of the 31 patients, 67.7% reported at least one extracutaneous manifestation, limited in all cases to the site of the skin lesions. Eighteen patients (58.1%) experienced myalgia, 14 (45.2%) paraesthesia, and 6 (19.4%) arthralgia without arthritis. Electroneuromyography was performed in 21 patients and mononeuritis multiplex was documented in 9 (29%). Asthenia (67.7%) and fever (9.68%) were also reported (Table 1).

Fourteen (45.2%) patients had a single episode of CPAN during follow-up, while 17 (54.8%) presented with a relapsing form of the disease (Table 3). The average number of relapses was 2.4 (± 1.9), and the number of episodes ranged from 2 to 8. When analysing clinical prognostic markers of CPAN relapse, a significant difference between the relapse and nonrelapse groups was detected only for ulceration (1 of 14 in the nonrelapse group vs 10 of 17 in the relapse group), which was the strongest predictor (OR 18.6; 95% CI 2.73-37.9). There were no differences between the relapsing and nonrelapsing groups in either local extracutaneous manifestations or systemic symptoms (Table 4).

The pre-treatment laboratory data was also recorded. ANCAs were negative in all patients, and liver, renal function and urine analysis were within normal limits or negative. Abnormalities in complete blood count were detected, and normochromic, normocytic anaemia was present in 12 (38.7%) patients; however, they were no different between groups. Changes in white blood cell count were frequent and patients in the relapsing group had significantly higher median (range) ANC quantification in the first pre-treatment blood test (8.6 [3-10.5] vs. 3.4 [2-8.1] $\times 10^3/\mu\text{L}$; $P = 0.001$). The index values derived from this measurement were also elevated: neutrophil-to-lymphocyte ratio -NLR- (3.2 [1.9-6.9] vs. 1.3 [0.7-3.4]; $P = 0.003$) and SII (770 [481.9-1888] vs. 319.2 [122.1-779.6]; $P = 0.006$) (Table 4). Significantly higher median (range) values were also found in the relapse group for ESR (28 [5-68] vs. 3 [1-32] mm/h; $P = 0.007$) and CRP (58 [2.5-170] vs. 3.2 [0.2-62]; $P = 0.007$). Patients with ESR levels ≥ 20 mm/h (Figure 1A) had a higher cumulative incidence of relapse (13 of 16 [81.3%] vs 4 of 15 [26.6%]) compared to the group of patients with values below

this threshold. The same occurred in the analysis of the groups with ANC above and below $6.5 \cdot 10^3/\mu\text{L}$ (14 of 15 [93.3%] vs 4 of 15 [18.8%]) (Figure 1B).

Initial treatments included prednisone in 25 patients (80.6%), intravenous pulse methylprednisolone in 2 (6.5%) and NSAIDs in 4 (12.9%). Over half of the patients required additional immunosuppressant therapy because of recalcitrant lesions and/or recurrence. These included methotrexate in 16 patients (51.6%), azathioprine in 2 (6.5%), mycophenolate sodium in 2 (6.5%), cyclophosphamide in 2 (6.5%), thalidomide in 1 (3.2%) and rituximab in 1 (3.2%). Median follow-up was 4.7 years (range 1-31.7). Interestingly, while 14 patients were followed for more than 5 years, none of the cases studied progressed to PAN. In this group of patients with CPAN, no disease-specific deaths were recorded. One patient did require below-knee amputation of one leg because of recalcitrant cutaneous ulceration that had progressed to gangrene.

Discussion

CPAN is a rare form of vasculitis. Although the true incidence is unknown, the estimated prevalence is 31 cases/million and it may account for approximately 4% of all cases of PAN.^{16,17} While CPAN occurs at all ages, from childhood¹⁸ to old age, it usually affects individuals in their fourth or fifth decade. Mean age at the time of diagnosis (47.5) in our study was similar to that observed by other authors. Female predominance was observed in our cohort, with a female to male ratio of 1.9:1, similar to that reported in previous case series.¹⁹

Although most often idiopathic, CPAN can be associated with an underlying disease, infection or drug. In our cohort, we found at least two

comorbidities that have been infrequently reported in the literature: adult Still's disease^{20,21} and ulcerative colitis.^{22,23} A relationship has been demonstrated between CPAN and infection with *Mycobacterium tuberculosis*, hepatitis B virus and hepatitis C virus.^{24,25} In our study, 1 patient had active hepatitis B infection, and we had 2 cases of hepatitis C and 1 of latent tuberculosis. One patient developed recurrent CPAN associated with *Streptococcus pyogenes* pharyngitis, which finally resolved after tonsillectomy; this resolution after surgical treatment has been well documented, in both children and adults.²⁶ Finally, two episodes were presumed to be linked with infections with *Rickettsia* and *Chlamydia* species, an association less reported to date.

The predominant size of the affected vessels explains the more frequent presentation of CPAN with subcutaneous nodules, with or without livedo, rather than purpura. Ulceration has been described in over 50% of CPAN cases in the literature.^{19,27} Concomitant ulcers on initial presentation was specifically documented in 35.5% of the patients in our series. Atrophic, ivory-white stellate scars with telangiectasias, known as atrophie blanche, were observed in 25.8% of patients at the end of the study period. This scarring, caused by segmental hyaline degeneration of the vessel wall and fibrin deposition, has also been previously reported in CPAN.²⁸ In this context, the term is merely descriptive and should not be confused with livedoid vasculopathy, which is a distinct entity.

Since CPAN was first described by Lindberg²⁹ in 1931, two aspects of the disease have been widely debated: its "limited" course and its "benign" prognosis.

Firstly, while CPAN is a predominately skin-limited (or skin-dominant) form of vasculitis, some patients do experience extracutaneous symptoms.

These systemic manifestations, limited to the areas affected by the skin lesions, have been well documented in over 50% of patients. They include myalgia (22%-63.7%), arthralgia (9.1%-67%) and paraesthesia (2%-42%).^{6,25,30,31} Two thirds of the patients in our study reported at least 1 local manifestation. The pathogenesis of these symptoms has not been determined; however, one school of thought is that they are secondary to the deep and intense skin damage. Constitutional symptoms, such as asthenia and fever, may also accompany the disease. We also identified mononeuritis multiplex in 29% of patients, a condition that has been documented in 22% to 57% of cases in the literature.^{25,30}

According to the diagnostic criteria established by the American College of Rheumatology (ACR), a patient with both cutaneous and at least 1 extracutaneous manifestation and appropriate histopathological findings could be diagnosed with systemic PAN.³² In order to better reflect the skin-predominant (but not limited) expression of CPAN, Nakamura et al.⁶ proposed specific diagnostic criteria, which are currently recognised by most dermatologists, although they have not been yet validated. They explicitly mention the possibility of peripheral neuropathy, arthralgia (arthritis) and myalgia (myositis) in CPAN. However, when any of those symptoms are observed outside of the area affected by the skin lesions, the systemic form should be considered.

Secondly, CPAN normally has a benign and non-life-threatening prognosis. However, the course of the disease more often tends to be chronic and relapsing than is the case with systemic PAN. A recent study found a rate of relapse of 45.2% for cutaneous arteritis, while in the systemic form

exacerbations occur in only 9.2% of patients.³¹ This recurrent clinical course and the development of recalcitrant lesions—mainly ulcerations and skin necrosis—requires the use of more intensive therapeutic agents. In our series, 17 patients (54.8%) experienced relapses. Kato et al.²⁰ recently explored potential risk factors for recurrence in a Japanese cohort of 22 patients. Despite the low statistical power of the population studied, their results indicated that ulceration was associated with relapse. Other predictive factors included the presence of CRP and ANC. Derived indexes, such as NLR^{33,34} and SII,³⁵ have previously been used as prognostic markers in other inflammatory and autoimmune conditions, and in the context of malignant disease, and were also associated with an increased risk of relapse. In our study population, ulceration at presentation was the strongest predictor of recurrence (OR 18.6), and elevated pre-treatment values of ESR, CPR, ANC, NLR and SII were also associated with a poor prognosis in terms of recurrence. Although we could not demonstrate an association between a relapsing course and neuropathy or other regional symptoms, other authors have hypothesised that these manifestations could indicate a more severe form of the disease and a worse prognosis.³⁰

In 1997, Daoud et al.¹⁹ reviewed 79 cases of CPAN, none of which progressed to PAN. More recent case series have not shown progression to systemic PAN. These observations have led several authors to suggest that CPAN is a distinct clinical entity. However, to date no appropriate clinical or serological diagnostic markers have been identified that distinguish CPAN from PAN. Moreover, rare cases of patients initially presenting with skin lesions and then progressing to systemic disease after a long period of follow-up makes

Careful long-term follow up is essential in patients with CPAN.⁸ Long-term follow-up is also justified because of the recurrent course of the disease and the risk of refractory ulceration, digital infarction and autoamputation. Because of the risk of relapse and a worse prognosis, it is important to identify markers that can predict a more severe course in these patients. Although limited data is available, our results in a cohort of Caucasian patients are similar to those reported in the Japanese series and point to some prognostic markers: mainly ulceration at first presentation and elevation of certain inflammatory parameters, such as ANC and ESR. These markers could help to predict a relapsing course and indicate the appropriate length of follow-up.

There is still considerable debate about whether the prognosis of CPAN is, in fact, limited and benign. In this context, the 2012 Revised Chapel Hill Consensus Conference (CHCC), which modified the previous CHCC published in 1994, added a new group of vasculitis, the single-organ vasculitis (SOV), which includes cutaneous arteritis.¹ However, it stressed the possibility of progression of the skin-limited variant to the systemic form. In February 2018, a consensus group published an Addendum to CHCC 2012 focusing on cutaneous vasculitis. This document clarified the differences between the cutaneous and systemic forms of PAN and specified the absence of postcapillary venule involvement in CPAN.³⁶

The ACR is currently in the process of drafting new evidence-based guidelines for the diagnosis, management and treatment of systemic vasculitis. However, cutaneous polyarteritis nodosa will not yet be treated as a separate entity. The participation of both dermatologists and rheumatologists is essential to properly define these forms of vasculitis that predominantly affect the skin but

are not always skin-limited. Future definitions and advances in the understanding of cutaneous vasculitis will help to improve the management of these diseases.

The present study is limited by its retrospective design and small sample size—a consequence of the low incidence of the disease.

Conclusions

CPAN is a vasculitis that predominately affects the skin. Unlike systemic PAN, it has a chronic course and is not life threatening. However, recurrence is frequent and at least half of all the patients affected will require additional immunosuppressants to prevent relapse. The presence of ulceration on initial presentation and elevated levels of inflammatory markers (primarily ESR, CRP and ANC) pre-treatment may help to predict relapse and consequently influence disease management, additional therapies and follow-up in patients with CPAN.

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Figure 2 Characteristic manifestations of cutaneous polyarteritis nodosa (CPAN): A sharply ulcerated subcutaneous nodule with a background of livedo racemosa (network pattern with incomplete and irregular rings), localized on the lower leg below the knee.

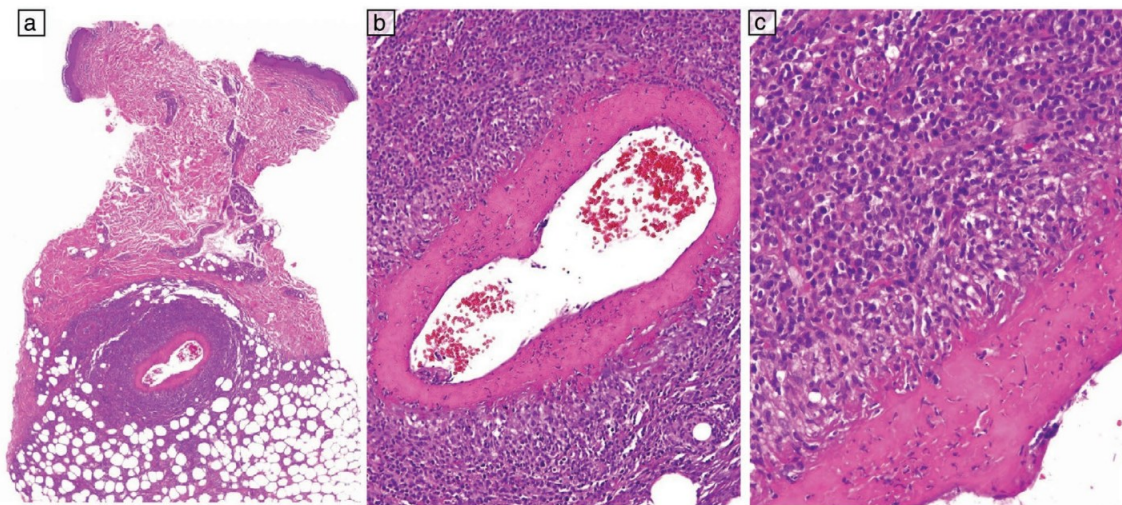


Figure 3 Necrotizing vasculitis of an artery of the deep dermis and subcutis. Marked thickening of the whole circumference of the vessel wall, resulting from edema and both fibrinous and cellular exudates (Hematoxylin-eosin staining, original magnification $\times 40$) (a). The infiltrate is composed predominantly of neutrophils (with some lymphocytes) and it is localized to the vessel and its immediate vicinity (Hematoxylin-eosin staining, original magnification $\times 200$) (b). Fibrinoid necrosis and neutrophilic debris are present (Hematoxylin-eosin staining, original magnification $\times 400$) (c).