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Review

# Epidemiological, clinical and laboratory profiles of cutaneous polyarteritis nodosa patients: Report of 22 cases and literature review

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ABSTRACT

Cutaneous polyarteritis nodosa (CPAN) is a rare disease that affects small and middle caliber vessels of the deep dermis and subcutaneous tissue and its etiopathology remains yet to be understood. Methods: Retrospective review of twenty two cases diagnosed as CPAN and confirmed by skin biopsy over the last 11 years was evaluated in our department. Results: We found predominance in white woman, mean age of 39.4 years, showing no comorbidities in most of our sample. Mean follow-up time was 58 months. The most frequent cutaneous manifestations were ulcers, livedo racemosa, subcutaneous nodules, *atrophie blanche* lesions and purpuras; with lower limb involvement in all cases, however other areas were also involved. The main regional symptoms were pain and paresthesia, while systemic complaints were absent in the majority of cases. Mononeuritis multiplex was identified in a quarter of our sample. Most of the laboratory findings were non-specific. There was evidence for previous contact with *Mycobacterium tuberculosis* in 46.1% of cases which were tested for purified protein derivative (PPD) test. In our patients the disease course was benign and without complications, and systemic polyarteritis nodosa did not develop in any patient. Conclusions: An extensive work-up including autoimmune laboratory tests, thrombophilic factors and investigation of infectious diseases, specially previous contact with tuberculosis agent should be part of CPAN investigation.



**Contents**



## 1. Introduction

Classic polyarteritis nodosa (PAN) was the first systemic vasculitis described. In 1866, Kussmaul and Maier characterized this fatal condition, originally named "periarteritis nodosa". In 1903, Ferrari pointed out the transmural nature of the arterial inflammation involving medium caliber vessels, leading him to propose the term "polyarteritis

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nodosa". However, it was only in 1931 that Lindberg recognized the existence of a limited cutaneous form of PAN [1,2].

Multi-organ involvement in systemic PAN is pervasive, particularly in the kidneys, heart and liver; although in most cases cutaneous findings are the first evidence of the disease. On the other hand, the cutaneous polyarteritis nodosa (CPAN), which affects predominantly the skin, could also be associated with extracutaneous findings and includes fever, malaise, myalgias, arthralgias and neuropathy. The distinction between the systemic and the cutaneous form is essential. The clinical course of CPAN is chronic, varying the number of remissions and relapses [3–7]. Its true incidence is to be yet accurately identified, affecting subjects that could be placed in all ages, ranging from infants to elderly individuals and affects predominantly women [1,3,4,8].

The etiology involved in CPAN lingers in an uncertain ground, but current knowledge advocates that it is a disorder mediated by immune complexes. Direct immunofluorescence often shows IgM and C3 deposits within affected arterial walls [1,8,9]. Furthermore, a 77.8% prevalence of IgM antibodies against the phosphatidylserine–prothrombin complex among patients with CPAN helps to embed the theory that prothrombin bound for apoptotic endothelial cells induces an immune response. This process would, then, lead to the development of anti-phosphatidylserine–prothrombin complex antibodies, which, by its turn, presumably activates the classical complement pathway to cause CPAN [9].

A large number of infectious and non-infectious entities have been associated both to the beginning and the recurrence of CPAN. Among infectious agents, the one that plays the most frequent role is group A beta-hemolytic streptococcus, especially in children [10–12]. With its relation to hepatitis B and C, HIV, B19 parvovirus and *Mycobacterium tuberculosis* have been pointed out, among others [13–19].

In the context of non-infectious diseases, an association with autoimmune diseases has been pointed out, such as myasthenia gravis, Chron's disease, ulcerative retocolitis and auto-immune hepatitis [20–23]. Still, other categories are listed apart like neoplasms, vena cava thrombosis and immunization against diphtheria, tetanus and hepatitis B [24–27]. Drugs such as penicillin and tetracycline are also related to CPAN, minocyclin being the main one involved. In these cases, withdrawal of medication tends to be followed by improvement of the skin lesions [28–30].

Until present time, and to our knowledge, there are no studies concerning epidemiological data of CPAN in Brazil, making available in the literature only anecdotal case reports. Hence, our study aims to establish a database on epidemiological, clinical and laboratory information of CPAN patients admitted to the vasculitis clinics of our tertiary hospital.

## 2. Patients and methods

This is a cross-sectional, retrospective and descriptive study; with data collection from files comprehending the period between January of 2003 and December of 2014. All files with a clinical diagnosis of CPAN were selected from the vasculitis clinics of the Dermatology Department Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo (HCFMUSP), previously confirmed by histopathological study. A total of 22 cases were obtained.

The histopathological findings considered had to gather the criteria described ahead: necrosis of small-sized arteries at the dermo-subcutaneous junction, muscular arteries in the subcutis or arterioles in the deep dermis and/or fibrin thrombi in the vascular lumen; fibrinoid necrosis in the intima and infiltration of lymphocytes and neutrophils around the vessel walls, without leukocytoclasia. Cases that did not fulfill these criteria, or lacked clinical information, were excluded.

Information that originated from medical records included age onset of the disease, gender, clinical manifestations, relevant medical history, histopathologic diagnosis and laboratory test results either from our chronic ulcers or vasculitis protocol available at our institution then. These ancillary tests included complete blood count and general exams as biochemical and research for autoimmune conditions, prothrombotic states and infectious disease.

The epidemiological, clinical and laboratory data were registered in a structured form, originating a database featuring the characteristics of each patient individually. From that assembling of information an analysis was conducted by one of the authors as a fail-safe mechanism to avoid bias in data collection and registration.

Microsoft Excel® was used as the datasheet template, allowing analysis for descriptive statistics. Continuous data were represented as mean and standard deviation (mean ± SD), and categorical variables as percentages.

## 3. Results

### 3.1. Distribution by gender and age

The study group consisted of 17 female (77.3%) and 5 male (22.7%) patients. The male to female ratio was 1:3,4. Age ranged from 9 to 61 years, with a mean age at the time of diagnosis of 39.4 years (SD 15.2 years). Female mean age ± standard deviation was 41.7 ± 14.5 years, while male mean age ± standard deviation was 31.6 ± 16.6 years (Table 1).

### 3.2. Skin color

Patients were classified according to race/skin color. Sixteen patients were white (72.7%), 4 patients were mullato (18.2%) and 2 patients were black (9.1%).

### 3.3. Profession

The occupational attributions of the 5 male subjects were airplane pilot, carpenter, delivery motorcycle pilot, doorman and student. Among women, 6 were housemaids, 3 were nurse technicians, 3 were school teachers and the remainder were declared as a secretary, cook, student and accountant.

### 3.4. Follow-up beginning and duration

The patient that has been in regular follow-up for the longest time in our department had his admittance in 2003. From that point on, 2 new CPAN cases were identified in 2004, 1 other in 2006, 3 in 2008, 2 in 2009, 4 in 2010, 2 in 2011, 5 in 2013 and 2 in 2014. In a total of 22 patients, 18 of them remained associated to our institution and 4 dropped out. The timeframe concerning follow-up from admittance varied from 7 to 132 months, with mean disease duration of 58.36 months and SD 38.97 months.

**Table 1**
Distribution by gender and age.

| Age | Male | Female |
|---|---|---|
| 0–10 | 1 | 0 |
| 11–20 | 0 | 1 |
| 21–30 | 1 | 2 |
| 31–40 | 2 | 5 |
| 41–50 | 0 | 3 |
| >50 | 1 | 6 |
| Total | 5 | 17 |

Mean age ± standard deviation (SD) 39.4 ± 15.2 years.
Female's mean age ± standard deviation (SD) 41.7 ± 14.5 years.
Male's mean age ± standard deviation (SD) 31.6 ± 16.6 years.



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