Original Article

Metabolic Syndrome in Patients with Polyarteritis Nodosa: A Single-Center Case-Control Study

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Abstract

Background: **Metabolic syndrome (MetS) is highly prevalent in systemic autoimmune diseases and associated with increased cardiovascular risk. However, its occurrence in polyarteritis nodosa (PAN) remains unexplored.**

Objectives: **To assess the prevalence of MetS and identify associated factors in patients with PAN.**

Methods: **A single-center, case-control study included 21 consecutive patients with PAN who were matched by sex and age to 63 controls at a 1:3 ratio. MetS was defined according to National Cholesterol Education Program - Adult Treatment Panel III (NCEP ATP III) criteria. Clinical, anthropometric, laboratory, and lifestyle data were systematically collected.**

Results: **The median age at PAN diagnosis was 38.0 years (interquartile range 29.0–52.0), and current median age was 52.9 years (interquartile range 41.3–62.8); 61.9% were women. Patients with PAN showed significantly higher prevalence of MetS than controls (42.9% vs. 12.7%; p = 0.003), hypertension (71.4% vs. 28.6%; p < 0.001), diabetes mellitus (23.8% vs. 3.2%; p = 0.010), and family history of cardiovascular disease (23.8% vs. 4.8%; p = 0.021), as well as elevated low-density lipoprotein (LDL) cholesterol levels. In multivariable analysis, MetS (odds ratio [ORs] = 6.58; 95% confidence interval [CI] 1.53–23.71; p = 0.004) and family history of cardiovascular disease (ORs = 9.14; 95% CI 1.83–54.78; p = 0.015) were independently associated with PAN. Among patients with PAN, those with MetS were older (54.9 vs. 45.1 years; p = 0.048) and had higher triglyceride and LDL cholesterol levels.**

Conclusions: **Patients with PAN presented a higher prevalence of MetS compared with controls. These findings highlight the need for systematic cardiovascular risk assessment and early preventive strategies in PAN management.**

Keywords: **Cardiovascular Diseases; Polyarteritis Nodosa; Metabolic Syndrome; Systemic Vasculitis.**

Introduction

Polyarteritis nodosa (PAN) is a primary systemic vasculitis characterized by necrotizing inflammation of medium-sized arteries. It is defined by the absence of glomerulonephritis, the lack of involvement of arterioles, capillaries, and venules, and the absence of an association with antineutrophil cytoplasmic antibodies (ANCA). In addition to the systemic form, a cutaneous-limited variant exists, characterized by painful nodules, livedo reticularis, and ulcers (cutaneous PAN).[1]

Metabolic syndrome (MetS) is defined as a cluster of interrelated metabolic and clinical abnormalities that, when present simultaneously, substantially increase the risk of cardiovascular disease and type 2 diabetes mellitus. The diagnosis is established by the presence of at least three of the following criteria: central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol levels, systemic arterial hypertension, and fasting hyperglycemia.[2]

A high prevalence of MetS has been reported in several systemic vasculitides, suggesting that the interplay between chronic inflammation, immunometabolic pathways, and cardiometabolic risk factors contributes to disease outcomes. In ANCA-associated vasculitis, MetS has been associated with increased cardiovascular risk, worse prognosis, higher mortality, and higher relapse rates.[3] Similarly, in Takayasu arteritis, a high frequency of MetS has been described and linked to alterations in adipokines and pro-inflammatory cytokines, further supporting the relationship between metabolic dysfunction and vascular inflammation.[4] In addition, prolonged exposure to glucocorticoids, a cornerstone of vasculitis treatment, contributes to metabolic disturbances, including weight gain, hypertension, insulin resistance, and dyslipidemia.[5]

Despite this growing body of evidence, the prevalence and clinical relevance of MetS in PAN have not been previously investigated. Therefore, the primary objective of this study was to assess the prevalence of MetS in patients with PAN. As a secondary objective, we examined clinical, laboratory, and therapeutic factors associated with MetS in this population.

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Central Illustration: Metabolic Syndrome in Patients with Polyarteritis Nodosa: A Single-Center Case--Control Study

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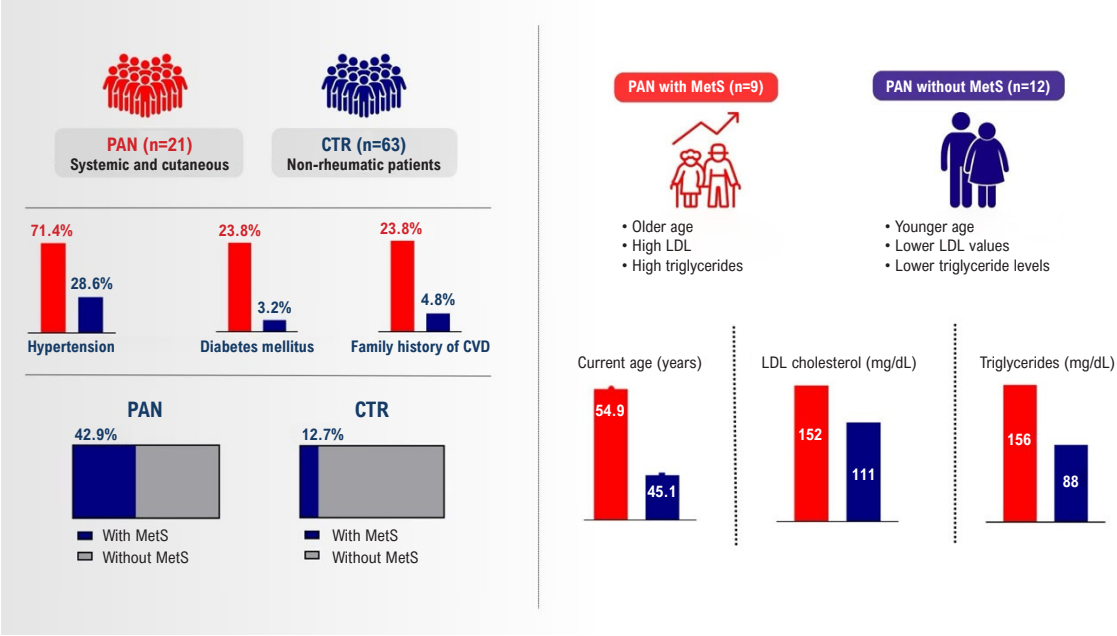

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CTR: control group; CVD: cardiovascular disease; LDL: low-density lipoprotein; MetS: metabolic syndrome; PAN: polyarteritis nodosa.

Although the prevalence and clinical relevance of MetS in PAN remain unknown, there are biologically plausible reasons to hypothesize an association. Recent literature on cardiovascular risk in vasculitis demonstrates that systemic vasculitides are associated with substantial cardiometabolic burden, driven by chronic vascular inflammation, endothelial dysfunction, and oxidative stress.[6] PAN is a chronic necrotizing vasculitis, and persistent vascular inflammation may promote endothelial dysfunction, oxidative stress, and metabolic imbalance. Additionally, modern imaging approaches have revealed that cardiac manifestations of systemic inflammatory diseases, including vasculitis, are more frequent than previously recognized, underscoring the importance of comprehensive cardiovascular assessment in these populations.[7] In addition, long-term glucocorticoid exposure may contribute to central adiposity, insulin resistance, hypertension, and dyslipidemia.

Recent studies have emphasized that systemic inflammation, endothelial dysfunction, and adipokine imbalance contribute to the cardiometabolic burden observed in systemic vasculitides and other autoimmune diseases, providing a biologically plausible rationale for evaluating MetS in PAN. Therefore, investigating MetS in PAN is relevant from both cardiovascular and immunometabolic perspectives.

Methods

This single-center study included adult patients with PAN who were under regular outpatient follow-up at our tertiary referral institution. The study protocol was approved by the local ethics committee.

Twenty-one patients were evaluated. Patients with PAN fulfilled the 1990 American College of Rheumatology (ACR) classification criteria.[8] Cutaneous PAN was diagnosed based on characteristic dermatologic findings, including painful nodules, livedo reticularis, or ulcers, in the absence of systemic involvement.[9]

Given the rarity of PAN, the sample was consecutive and convenience-based, and no formal sample size calculation was performed.

Participants were interviewed during routine clinic visits. The following data were collected:

- Demographic characteristics: age, sex, ethnicity.

- Clinical characteristics of PAN: symptom onset, clinical and laboratory manifestations, pharmacologic treatment, disease course, relapses, and complications.

- Cardiovascular history: prior cardiovascular events (stroke or myocardial infarction) and associated risk factors; family history of cardiovascular disease defined as acute myocardial infarction occurring before age 55 in the father and/or before age 65 in the mother.

- Anthropometric measurements included weight, height, body mass index, and body composition. Body composition was assessed using skinfold adipometry according to the Durnin and Womersley protocol.[10] All measurements were performed by a single trained

professional at the same time of day, prior to the outpatient consultation. Skinfold thicknesses were measured at the biceps, triceps, subscapular, and suprailiac sites on the right side of the body, with participants standing. Body density was estimated using age- and sex-specific equations,[11] and body fat percentage was calculated using the Siri formula.[12]

MetS was defined according to the NCEP ATP III criteria.[2] The following components were assessed: HDL cholesterol < 40 mg/dL (men) or < 50 mg/dL (women); triglycerides ≥ 150 mg/dL or use of lipid-lowering therapy; fasting glucose ≥ 100 mg/dL; abdominal circumference > 102 cm (men) or > 88 cm (women); and blood pressure ≥ 130/85 mmHg or use of antihypertensive medication. MetS was considered present when at least three criteria were met.

The control group included individuals without rheumatic diseases, who were matched by sex and age to patients with PAN at a 1:3 ratio.

All data were recorded and stored in the Research Electronic Data Capture (REDCap) database hosted at our institution. REDCap is a secure, web-based platform for clinical research data management, ensuring traceability, user access control, and audit capability. Data were anonymized with coded participant identifiers to maintain confidentiality and integrity.

Statistical analysis

Data distribution was assessed using the Shapiro–Wilk test. Continuous variables were expressed as median and interquartile range (25th–75th percentiles), and categorical variables as frequency (%). Group comparisons were performed using Student's t test, Mann–Whitney U test, chi-square test, or Fisher's exact test, as appropriate. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of associations between categorical variables. In addition to comparisons between patients with PAN and controls, a subgroup analysis was conducted among patients with PAN according to the presence or absence of MetS to evaluate clinical, laboratory, and therapeutic differences. A two-sided p value < 0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism, version 8.0.2 (San Diego, CA, USA).

Results

Between 2003 and 2025, 33 patients with PAN were identified, of whom 21 maintained regular outpatient follow-up and were included in the analysis, along with 63 sex- and age-matched controls (Table 1). The sex and age distribution was similar between the groups. Among the patients, 16 had systemic PAN and 5 had cutaneous PAN. Baseline anthropometric measures, including body mass index and abdominal circumference, as well as lipid profile, fasting blood glucose, and sedentary behavior, did not differ significantly between patients and controls (Central Illustration).

In contrast, the burden of traditional cardiovascular risk factors was higher in the PAN group. Compared with controls, patients with PAN had a higher prevalence of systemic arterial hypertension, diabetes mellitus, and family history of cardiovascular disease, as well as higher serum low-density lipoprotein (LDL) cholesterol levels and a substantially higher frequency of MetS (Table 1).

In the multivariate analysis, the presence of MetS remained independently associated with PAN, with an OR of 6.58 (95% CI 1.53–23.71; p = 0.004), indicating higher odds of PAN among individuals with MetS than among those without MetS. Family history of cardiovascular disease was also associated with the outcome, with an OR of 9.14 (95% CI 1.83–54.78; p = 0.015). In contrast, age (OR = 0.98; 95% CI 0.92–1.04; p = 0.465) and sex (OR = 0.81; 95% CI 0.26–2.53; p = 0.707) did not remain as independent predictors of the presence of PAN in the adjusted model (Table 1).

When comparing patients with and without MetS within the PAN cohort, MetS was associated with older age, higher triglyceride levels, and higher LDL cholesterol levels (Table 2, Central Illustration). In the logistic regression model specific to the presence of MetS among patients with PAN, age showed a trend toward association, with an OR of 1.09 per additional year (95% CI 0.99–1.18; p = 0.067), suggesting a progressive increase in the odds of MetS with aging, although without reaching significance at the 5% level. No significant differences were observed between the groups with and without MetS regarding sex, clinical phenotype, or other clinical and therapeutic variables evaluated.

Discussion

In this case-control study, patients with PAN presented a higher prevalence of MetS than controls, and within the PAN cohort, those with MetS were older and had higher triglyceride and LDL cholesterol levels (Central Illustration).

Recent contemporary cohorts suggest that PAN is a heterogeneous disease with substantial long-term morbidity, since relapse remains frequent and mortality is mainly driven by older age, severe gastrointestinal involvement, central nervous system involvement, acute kidney injury, and necrotic skin lesions.[13,14] A recent international study of 196 patients with PAN diagnosed since 2005 confirmed that clinical outcomes vary markedly across phenotypes and etiologic subgroups, with systemic involvement, renal disease, and neurologic manifestations being associated with worse prognosis.[15] These data reinforce the importance of systematic cardiometabolic risk assessment beyond vasculitis activity alone.

The main limitations of this study are the observational case-control design, which precludes temporal or causal inference; the single-center setting, which may limit generalizability; the small sample size and limited number of events, which reduce precision and increase the risk of unstable estimates; and the possibility of selection bias, given that only patients in regular outpatient follow-up were included. Additionally, the regression models may be prone to overfitting due to the small number of participants relative to the number of covariates analyzed. Information on cumulative glucocorticoid exposure, duration of therapy, and historical steroid use was not systematically available for all participants and therefore could not be included in the analyses.

Consistent with our findings, other systemic vasculitides are

also associated with a relevant cardiometabolic burden. In ANCA-associated vasculitis, MetS has been reported in approximately half of patients at diagnosis and remains frequent even among non-obese individuals, with multiple MetS components being independently associated with increased mortality.[3] Similarly, in Takayasu arteritis, a high prevalence of MetS has been described together with more frequent hypertension, dyslipidemia, and lower adiponectin levels. In our PAN cohort, MetS was present in 42.9% of patients and was more frequent among older individuals, indicating that cardiometabolic risk should be considered in the clinical evaluation of PAN.

Internal comparisons showed that MetS was associated with older age and elevated LDL cholesterol. In addition to age and LDL cholesterol, triglycerides were also significantly higher among PAN patients with MetS, reinforcing the adverse cardiometabolic profile observed in this subgroup. No differences were observed regarding sex, clinical phenotype, body composition, or medication use. These findings support the hypothesis that shared immunometabolic pathways may contribute to the development of MetS in PAN. Recent evidence demonstrates that MetS is associated with low-grade systemic inflammation mediated by adipokines and pro-inflammatory cytokines such as IL-6 and TNF-α, which are also central to vasculitic inflammation.[6] Additionally, chronic inflammation, endothelial dysfunction, visceral adiposity, and treatment-related metabolic effects may contribute to the development of MetS in PAN, although these mechanisms could not be directly tested in the present study. This interpretation is also consistent with recent epidemiologic data showing that PAN often involves multiple organ systems, including neurologic, gastrointestinal, renal, and cutaneous disease, and that clinical outcomes vary markedly across phenotypes and etiologic subgroups.[15] These findings provide novel insight into cardiometabolic risk in PAN.

Importantly, modern PAN cohorts indicate that the etiologic landscape has changed over time, with the emergence of secondary PAN and the recognition of mimickers such as Hepatitis B virus (HBV) associated disease, DADA2, FMF -associated vasculitis, and vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS), while idiopathic PAN still exists.[16] This evolving classification may influence the interpretation of metabolic and cardiovascular risk profiles in PAN cohorts, as secondary forms and mimickers may have distinct immunometabolic signatures compared to classical idiopathic PAN. Patients with PAN had an adverse cardiometabolic profile even in a stable outpatient setting. Chronic inflammation, potentially compounded by glucocorticoid exposure, may contribute to persistent metabolic imbalance beyond isolated control of vasculitis activity.

Although physical exercise may improve insulin resistance, lipid profile, blood pressure, and inflammatory markers in MetS, this study was not designed to evaluate structured exercise interventions. Therefore, physical activity was analyzed only as a baseline lifestyle variable.

The broader literature also shows that cutaneous involvement is the most frequent PAN manifestation, while relapse occurs in roughly one quarter to one third of patients, and mortality remains close to 13%, with substantial variability across adult, pediatric, systemic, cutaneous, and HBV-related subgroups.[15] In this context, MetS may represent an additional modifiable burden that deserves attention in routine follow-up.

These findings emphasize the need for comprehensive cardiovascular risk assessment in PAN, incorporating screening, prevention, and management of MetS alongside vasculitis control to optimize long-term outcomes. Taken together, these data support the inclusion of more recent literature on vasculitis-related cardiovascular risk and immunometabolic mechanisms in the interpretation of our findings.

Conclusions

Patients with PAN presented a higher prevalence of MetS than controls. Within the PAN cohort, MetS was associated with older age and higher triglyceride and LDL cholesterol levels. These findings support systematic cardiovascular risk screening in PAN and justify further longitudinal studies to clarify the underlying mechanisms and temporal relationships.

Author Contributions

Conception and design of the research, analysis and interpretation of the data, statistical analysis, writing of the manuscript and critical revision of the manuscript for intellectual content: Lima MAA, Figueredo ML, Santos AM, Shinjo SK; acquisition of data and obtaining financing: Lima MAA, Figueredo ML, Shinjo SK.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Hospital das Clínicas HCFMUSP under protocol number CAAE 41762820.1.0000.0068 on March 1, 2021. All procedures in this study were conducted in accordance with the ethical standards outlined in the 1975 Helsinki Declaration and its later amendments. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The data are available upon request for corresponding author.

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