Parvovirus B19 infection presenting as polyarthritis: a nationwide clinical and epidemiological study

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ABSTRACT

Viral arthritis accounts for approximately 1% of acute arthritis cases and may be caused by several viruses, particularly parvovirus B19 (B19V). Diagnosis relies on clinical presentation, B19V immunoglobulin M (IgM) and/or immunoglobulin G (IgG) seropositivity, and the exclusion of other infectious and non-infectious etiologies.

Following a European outbreak of B19V between March and May 2024, we conducted a multicenter retrospective study. The primary outcomes were the clinical and laboratory manifestations of B19V-associated arthritis; secondary outcomes included progression to chronic inflammatory disease and the need for escalation to disease-modifying antirheumatic drugs (DMARDs).

A total of 28 patients (25 women and 3 men) were included, with a mean age of 44 ± 11.4 years; 16 patients (57.1%) reported epidemiological risk factors. Acute, additive, symmetrical inflammatory polyarthralgia was the predominant clinical feature (26 patients, 92.9%), while axial inflammatory pain was reported by four patients (14.3%). Laboratory evaluation revealed positivity for antinuclear antibody (ANA) in 32.1%, rheumatoid factor (RF) in 19.7%, and HLA-B27 in 7.1% of patients. Anti–double-stranded DNA (dsDNA) and anti–cyclic citrullinated peptide antibodies (ACPA) were negative in all cases. Complement consumption was observed in a minority of patients, with low C3 levels in four (14.3%) and low C4 levels in three patients (10.7%).

Regarding treatment, 39.3% of patients received nonsteroidal anti-inflammatory drugs (NSAIDs), while 60.7% were treated with systemic corticosteroids (prednisolone 10–40 mg/day); one patient required intravenous methylprednisolone (125 mg). Clinical remission was achieved in 24 patients (85.7%) after a mean duration of 34 ± 47.0 days. However, four patients experienced relapse during corticosteroid tapering, suggesting potential progression to a chronic inflammatory condition. Among these, one patient achieved adequate symptom control with intermittent courses of NSAID alone, whereas the remaining three required initiation of DMARD therapy.

This study provides one of the most comprehensive characterizations of B19V–associated arthritis in immunocompetent adults. Our findings emphasizes B19V infection as a significant viral mimic of early inflammatory rheumatic diseases and suggests considering it in the differential diagnosis of acute polyarthritis. Moreover, our study highlights the uncommon but notable potential of B19V infection to induce persistent inflammatory responses requiring immunosuppressive therapy.

Keywords: DMARDs; Infectious and arthritis; Viruses; Reactive arthritis; Corticosteroids; NSAIDs

INTRODUCTION

Viral arthritis accounts for approximately 1% of cases of acute arthritis and may either trigger the development of a systemic rheumatic disease (SRD) or closely mimic SRD-related arthritis[1]. Several viruses have been implicated in the etiology of this condition, most notably parvovirus B19 (B19V), Epstein–Barr virus, and hepatitis B and C viruses[2]. B19V, a member of the *Parvoviridae* family, is primarily transmitted through the respiratory tract[3]. During the initial phase of infection, the virus predominantly targets erythroid progenitor cells, potentially causing transient aplastic anemia. The following phase involves immune complex deposition, leading to an erythematous rash in children and acute arthritis in adults[3]. This arthritic presentation is more common in women of reproductive age[4].

Diagnosis relies on clinical features, B19V IgM and/or IgG positivity, and exclusion of other infectious or non-infectious causes. Some authors suggest that detecting viral DNA in the synovium of the affected joints is enough for diagnosis[4], but conflicting evidence shows that this test can also be positive in healthy individuals [2]. Based on these findings and the virus's tendency to affect multiple joints simultaneously, arthrocentesis is only performed when there is still diagnostic uncertainty.

B19V-related arthritis is usually self-limited, resolving spontaneously within two weeks[4], and typically only requires non-steroidal anti-inflammatory drugs (NSAIDs) or low dose corticosteroids. However, in approximately 17% of cases, chronic disease may develop due to mechanisms like cross-reactivity with the VP1 IgG B19 epitope, immune complex deposition, and viral persistence in tissues - particularly the synovium[4,5]. In these patients, treatment with intravenous immunoglobulin and conventional disease-modifying anti-rheumatic drugs (DMARDs) has shown positive results[4,5].

B19V is responsible for endemic outbreaks, especially in spring[3]. In the period between March and May 2024, multiple European countries reported a rise in B19V cases[6]. With the increase in global tourism and the use of immunosuppressive therapies such as chemotherapy, the risk of new outbreaks remains high[7]. Due to limited information on the management of B19V arthritis and the understanding of this condition, we conducted a multicenter study to investigate the clinical presentation and outcomes of B19V-related polyarthritis.

MATERIALS AND METHODS

Study design and population

This multicenter retrospective study was initiated in January 2025 following a national call for participation. The study aimed to include patients who presented with acute-onset arthritis and either a positive parvovirus B19 IgM test and/or relevant epidemiological risk factors identified between March and May 2024. Patients with a pre-existing diagnosis of SRD were excluded. Eight healthcare centers in Portugal participated in the study.

Data Collection and Definitions

Data were collected from electronic medical records, including demographic information, number and type of affected joints, disease duration, and presence of connective tissue symptoms. Laboratory tests included complete blood count, liver enzymes, inflammatory markers, and autoantibodies (rheumatoid factor [RF], anti-citrullinated peptide antibodies [ACPA], antinuclear antibodies [ANA], and anti-double-stranded DNA [dsDNA]). IgM/IgG anti-parvovirus B19 levels were also assessed. Treatment approaches and outcomes were recorded. The chronic stage was defined as disease persistence for more than six weeks without the possibility of treatment tapering, following criteria commonly used for other SRD, such as rheumatoid arthritis (RA). Statistical analysis was performed using SPSS software version 27. The study was approved by the ethics committee of NOVA Medical School - Faculdade de Ciências Médicas (reference 039/2025/CEFCM).

Outcomes

The main outcomes were the clinical and laboratory manifestations of B19V-induced arthritis, including symptom resolution, serological characteristics, and inflammatory markers (such as C-reactive protein and erythrocyte sedimentation rate). Secondary outcomes included the progression of the disease to a chronic inflammatory state and the need for escalation to DMARDs.

RESULTS

The demographic and clinical characteristics of the patients are summarized in Table I. Twenty-eight patients presenting with arthritis due to B19V infection were included. The majority of the study population was composed of female patients (25 women, 3 men) with a mean age of 44±11.4 years. Sixteen patients (57.1%) had epidemiological risk factors, specifically having sick offspring (50%) or working in childcare (7.1%).

In terms of clinical presentation, 26 patients (92.9%) exhibited acute, additive, symmetrical inflammatory polyarthralgia that worsened over a week (average duration of 7.5±6.6 days). The remaining two patients presented with oligoarthralgia. Physical examination revealed arthritis in small joints (wrists, hands, and feet) in 27 patients (96.4%) and in large joints (knees, ankles, elbows) in 15 patients (53.6%). All patients had upper limb involvement, with 71.4% also experiencing lower limb involvement. Axial inflammatory pain was reported in four patients, with two showing cervical involvement and two showing lumbosacral involvement, based on clinical symptoms without confirmatory imaging findings. Fever was present in 10 patients (35.7%), and 11 patients (39.3%) developed a rash. Additional symptoms (14.3%) included odynophagia (n=2), hand pitting edema (n=1), and cryoglobulinemic vasculitis (n=1).

Baseline laboratory findings included hematologic, hepatic, and inflammatory parameters (Table II). Anemia was present in 28.6% of the cohort, with hemoglobin levels ranging from 9.9 to 11.8 g/dL. Regarding liver enzyme analysis, aspartate aminotransferase (AST) was mildly elevated in 7.1% of patients (50–67 U/L), while alanine aminotransferase (ALT) levels were increased in 25% of patients (35–131 U/L). Gamma-glutamyl transferase (GGT) and alkaline phosphatase levels were within normal limits. Inflammatory markers were elevated in 60.7% of the patients, with variability across the cohort: C-reactive protein (CRP) ranged from 0.23 to 8.15 mg/dL, and erythrocyte sedimentation rate (ESR) ranged from 15 to 83 mm/h.

Immunological testing showed positive ANA in 32.1% of patients, with titers ranging from 1:160 to 1:1280. Anti-dsDNA was negative in all tested patients. C3 consumption was observed in 4 patients (14.3%), with values ranging from 64.5 to 82.3 mg/dL. Normal C3 levels were reported in 7 patients (25.0%), while data was unavailable for 17 patients (60.7%). C4 complement consumption was documented in 3 patients (10.7%), with values ranging from 7.0 to 9.0 mg/dL. Normal C4 levels were noted in 8 patients (28.6%), with data missing for 17 patients (60.7%).

Rheumatoid factor was positive in 3 patients (19.7%), with two of them presenting low titers (25 U/L and 28.3 U/L) and one with high titers (217 U/L). All ACPA tests were negative. HLA-B27 was positive in 2 patients and negative in 8; this analysis was not performed in 18 patients.

Regarding axial involvement, one out of four patients tested positive for HLA-B27, but did not progress to chronic disease.

B19V serology (IgM and/or IgG) was positive in 89.3% of patients, with IgM and IgG positivity not always overlapping. Diagnosis in IgM negative cases relied on clinical and epidemiological data, such as close contact with individuals with confirmed B19V infection. A thorough workup excluded other potential infectious and non-infectious causes with appropriate IgM/IgG serology or PCR testing.

Regarding treatment, 39.3% of patients were managed exclusively with NSAIDs. The remaining 60.7% were treated with systemic corticosteroids (prednisolone 10-40 mg/day), and one patient required intravenous methylprednisolone (125 mg) for severe polyarthritis. One patient initially treated with NSAIDs required subsequent escalation to prednisolone. In the subgroup with axial involvement, only one patient required NSAID treatment, while the remaining three did not need specific therapy for this manifestation. Remission was achieved in 24 patients (85.7%) after an average duration of 34±47.0 days, enabling corticosteroid tapering. Follow-up duration data were available for 19 patients, with a mean of 6±5 months.

Four patients experienced relapse during corticosteroid tapering, and progression to a chronic inflammatory state was considered after six weeks of persistent symptoms. In this subgroup, all patients tested negative for RF and ACPA antibodies. One patient had a positive ANA (titer 1:320) but showed no additional clinical or laboratory features of a SRD. No other immunological risk factors were identified in the remaining three patients.

In this subgroup, one patient achieved symptom control with intermittent NSAID use, while the other three required cDMARD therapy. One patient started sulfasalazine at 3 g/day but switched to oral methotrexate (15 mg/week) due to treatment failure. The other two patients initiated therapy with subcutaneous methotrexate at 15 mg/week. One patient switched to sulfasalazine (2 g/day) and low-dose prednisolone (5 mg/day) due to pregnancy planning, while the other switched to leflunomide (20 mg/day) due to adverse effects. Despite these changes, the latter

patient needed adalimumab 40 mg subcutaneously every two weeks due to persistent disease activity.

DISCUSSION

This national multicenter retrospective study provides a comprehensive characterization of the clinical and laboratory spectrum of B19V associated arthritis in adults. The results reinforce that B19V infection represents an important viral cause of acute arthritis in immunocompetent individuals, often resembling early-onset inflammatory rheumatic diseases such as RA[2,8].

The demographic profile of this cohort - predominantly middle-aged women - is in line with previous studies indicating a higher susceptibility among females[9]. A significant number of patients reported epidemiological risk factors, consistent with the known transmission dynamics of B19V through respiratory secretions and exposure to infected individuals, especially in household or childcare settings[3].

Clinically, most patients presented with acute, additive, and symmetrical polyarthritis primarily affecting small joints in the hands and wrists, consistent with previous reports from other outbreaks[5]. However, a study conducted in Milan by D'Onofrio et al. during the 2024 outbreak reported a higher frequency of oligoarthritis (67% of patients) compared to polyarthritis (30%)[6]. Further research is needed to understand the reasons for this variability across different regions, such as variations in viral strains, regional host factors, or other unidentified factors.

Although less common, the presence of axial inflammatory pain in a small subset of patients suggests that B19V infection may cause a wider range of musculoskeletal manifestations, as seen in other studies[10,11].
Cryoglobulinemic vasculitis, previously reported in the literature[12], was found in one patient. Another patient exhibited hand pitting edema, similar to a case reported by Pernadones *et al.* (2005)[13].

Laboratory findings were mostly nonspecific, with common occurrences of anemia, transient hepatic enzyme elevations, and mild to moderate increases in inflammatory markers. Immunological analysis revealed ANA positivity in about one-third of patients, with low to moderate titers, and RF positivity in three patients, without evidence of systemic autoimmune disease. The absence of ACPA highlights it as useful in distinguishing B19V arthritis from RA. Our

findings align with previous studies[4,5,8] but differ from the Milan study of 2024[6] that reported higher ANA positivity and one case of detectable ACPA.

Complement consumption was mild and inconsistently observed, suggesting limited and reversible immune complex formation, as reported by D'Onofrio *et al.* (2024)[6].

B19V serology was positive in most cases, supporting the diagnostic value of combined IgM and IgG testing in the right clinical context[2]. However, some patients were IgM negative, requiring diagnosis based on clinical and epidemiological findings.

Therapeutically, treatment decisions were based on the clinical judgment of the treating physicians. Patients with more severe clinical presentations, particularly those with extensive polyarthritis, generally received higher doses of corticosteroids. Most patients achieved remission with symptomatic management as typically observed in B19V-induced arthritis. Nevertheless, four patients in our cohort experienced relapses during corticosteroid tapering, leading to sustained synovitis beyond six weeks, suggesting a chronic inflammatory course. Among this subgroup, three patients required conventional DMARDs, with one needing tumor necrosis factor inhibitor (iTNF) therapy. While rare, these cases suggest that B19V infection may occasionally trigger persistent arthritis due to immune dysregulation. This is consistent with the findings of Colmegna et al. (2009), who reported that less than 17% of B19V arthritis cases progress to chronicity[4]. The absence of other clinical or immunological findings supports their classification as B19V-related.

Interestingly, among patients with axial involvement, only one was HLA-B27 positive and did not develop a chronic course. This observation raises the question of whether HLA-B27 positivity alone influences disease persistence or axial involvement in the context of B19V infection.

LIMITATIONS: This multicenter study has standardized case identification and focuses on a single outbreak, but its retrospective design limited additional assessments, such as axial magnetic resonance imaging. Missing laboratory data, lack of long-term follow-up, and inconsistent serological testing across centers may have affected the completeness and consistency of the findings. Additionally, some sites were unable to contribute data, resulting in a smaller sample size than the actual number of cases during the outbreak.

CONCLUSION

This national multicenter retrospective study, the largest ever conducted in Portugal, provides one of the most comprehensive characterizations of parvovirus B19–associated arthritis in immunocompetent adults. The findings confirm that B19V infection is an important viral mimic of early inflammatory rheumatic diseases, particularly RA. The predominant clinical presentation - an acute, symmetric polyarthritis involving small joints of the hands and wrists in middle-aged women - aligns with previous international reports. Additionally, a subset of patients exhibited axial involvement, a feature rarely associated with B19V infection.

Laboratory findings were nonspecific, reflecting transient systemic inflammation and mild autoantibody positivity without evidence of autoimmune disease. These results emphasize the diagnostic value of ACPA negativity in distinguishing B19V arthritis from early RA. While most patients achieved full remission with symptomatic therapy, a small subset developed persistent arthritis, suggesting that B19V infection may trigger prolonged inflammatory responses in predisposed individuals, leading to the need for immunosuppressive therapy.

This study highlights the importance of considering B19V infection in the differential diagnosis of acute polyarthritis, especially during outbreaks or in patients with transient autoantibody positivity. Early recognition can prevent unnecessary long-term immunosuppressive treatment in most cases. Prospective studies with extended follow-up are warranted to further elucidate the mechanisms underlying chronicity and to define optimal management strategies.

Tables and Figures

Table I. Clinical and demographic characteristics of patients.

Variable	Mean (±SD) / n (%)		Missings (n)
Total of patients, n (%)	28	(100)	
Women, n (%)	25	(89,3)	0
Age, mean (±SD)	44,0	(± 11,4)	0
Epidemiology			3
Infection in a household contact, n (%)	13	(46,4)	
High-risk occupation, n (%)	3	(19,7)	
No risk factors, n (%)	9	(32,1)	
Clinical presentation			
Fever, n (%)	10	(35,7)	0
Rash, n (%)	11	(39,3)	0
Polyarthritis, n (%)	26	(92,9)	0
Oligoarthritis, n (%)	2	(7,1)	0
Odynophagia, n (%)	2	(7,1)	0
Axial involvement, n (%)	4	(14,3)	0
Hand pitting edema, n (%)	1	(3,6)	0
Cryoglobulinemic vasculitis, n (%)	1	(3,6)	0
Clinical course			
Time to full clinical presentation in days, mean (±SD)	7,5	(±6,6)	0
Complete resolution, n (%)	24	(85,7)	0
Time to clinical resolution in days, mean (±SD)	34	(±47,0)	0

Table II. Baseline laboratory findings.

Variable	n (%)	Missings (n)
General laboratory findings		
Anemia [rv < 12.0 g/dL]	8 (28,6)	1
Raised AST [rv > 33 U/L]	8 (28,6)	5
Raised ALT [rv > 32 U/L]	9 (32,1)	5
Elevated CRP [rv > 0.5 mg/dL]	17 (60,7)	1
Elevated ESR [rv > 20 mm/h]	17 (60,7)	2
Immunology		
Positive Parvovirus IgM [rv ≥1.1 UI/mL]	25 (89,3)	0
Positive Parvovirus IgG [rv > 2.5 UI/mL]	25 (89,3)	3
IgM and IgG positive	22 (78,6)	3
Positive ANA	9 (32,1)	3
ANA 1/160	5 (17,6)	3
ANA 1/320	2 (7,1)	3
ANA 1/640	1 (3,6)	3
ANA 1/1280	1 (3,6)	3
Low C3 levels [rv <80 mg/dL]	4 (14,3)	17
Low C4 levels [rv < 10 mg/dL]	3 (10,7)	17
Positive dsDNA [rv > 15 IU/mL]	0 (0)	15
Positive ACPA [rv > 5 AU/mL]	0 (0)	6
Positive RF [rv > 15 IU/mL], n (%)	3 (19,7)	5
Positive HLA-B27	2 (7,1)	18

ANA - antinuclear antibody. ACPA - Anti–citrullinated protein antibody. CRP - C-reactive protein. ALT - alanine transaminase. AST - aspartate transaminase. ESR - erythrocyte sedimentation rate. Ig G - Immunoglobulin G. HLA-B27 - Human Leukocyte Antigen B27. IgM - Immunoglobulin M. n - number of patients. RF - rheumatoid factor. rv – reference value. SD – standard deviation.

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