Cureus
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Open Access Case Report

Canakinumab Response in an Undifferentiated Autoinflammatory Disease With a Tumor Necrosis Factor Receptor-Associated Periodic Syndrome Phenotype: A Case Report

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Review began 10/30/2026
Review ended 11/16/2026
Published 11/19/2026

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DOI: 10.7759/cureus.119937

Abstract

We present a 38-year-old African American woman with hereditary C1 esterase inhibitor deficiency, diabetes mellitus, and a hypercoagulable disorder who presented to rheumatology clinic with recurrent inflammatory episodes starting around nine years old. Flares lasted several days to weeks and included subjective fever, painful facial and truncal rash, myalgias, polyarthritis, gastrointestinal symptoms, headache, and weakness. Flares were accompanied by elevated inflammatory markers and neutrophil-predominant leukocytosis.

Infectious, autoimmune, and metabolic mimics were excluded, and autoinflammatory gene panel testing was never performed due to high costs to the patient. Several disease-modifying drugs were tried without benefit, while intermittent glucocorticoids were moderately effective. A tumor necrosis factor receptor-associated periodic syndrome (TRAPS)-like phenotype was suspected, and canakinumab, an anti-interleukin-1β (IL-1β) monoclonal antibody, was initiated at 150 milligrams (mg) every four weeks and eventually escalated to 150 mg every two weeks with symptom resolution. Undifferentiated autoinflammatory disease with a TRAPS-like phenotype is the presumed diagnosis as the patient fulfilled several clinical features of TRAPS and responded to IL-1β blockade. The disease has remained quiescent with no adverse events from canakinumab.

In a patient with a phenotype fulfilling clinical criteria for TRAPS but no accessible genetic testing, a sustained response to IL-1β blockade with reproducible flare on withdrawal was both therapeutic and supportive in diagnosis. This case illustrates how administrative barriers to testing contribute to diagnostic challenges in a rare disease, and it adds long-term outcome data for canakinumab in an unconfirmed TRAPS-like autoinflammatory disease.

Categories: Rheumatology
Keywords: autoinflammatory syndrome, canakinumab, hereditary periodic fever syndromes, interleukin-1 inhibition, tumor necrosis factor receptor-associated periodic syndrome (traps)

Introduction

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a rare, autosomal dominant autoinflammatory disease caused by gain-of-function variants in tumor necrosis factor receptor superfamily member 1A (TNFRSF1A), causing intracellular retention of misfolded tumor necrosis factor receptor 1 (TNFR1) and impaired autophagy, leading to excessive interleukin-1β (IL-1β) signaling [1-3]. Autoinflammatory diseases are characterized by a dysregulation of the innate immune system, leading to chronic inflammation, as opposed to autoimmune conditions that involve the adaptive immune system, triggering autoantibodies or T cells [2]. Attacks in TRAPS are prolonged and combine fever with myalgias and migratory rash usually over areas of muscular pain, serositis, abdominal pain, arthralgias, and arthritis. AA amyloidosis is a long-term complication [3,4]. Diagnosis is made through molecular testing. However, in the absence of pathogenic TNFRSF1A variants, the clinical criteria from the Eurofever/PRINTO (Paediatric Rheumatology International Trials Organisation) study include the presence of at least two of five features: flare duration longer than seven days, myalgia, migratory rash, periorbital edema, and suggestive family history, with a reported sensitivity of 95% and specificity of 99% [5,6].

IL-1 blockage is the treatment of choice, and canakinumab is the only IL-1 inhibitor that is approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for TRAPS [7,8]. The phase III CLUSTER (Canakinumab Pivotal Umbrella Study in Three Hereditary Periodic Fevers) trial enrolled only genetically confirmed patients and demonstrated complete response at week 16 in 45% of patients on canakinumab versus 8% on placebo, rising to 73% when patients who were up titrated to 300 mg every four weeks were included [1]. The open-label phase II study reported complete response in 19 of 20 patients (95%) with a median time to clinical remission of four days, universal relapse after withdrawal at a median of 91.5 days, and a recurrent response upon reintroduction [9]. Long-term extension data show more than 94% of patients with no or minimal disease activity at 72 weeks with no unexpected safety signals [10].

There is limited published data on patients with a TRAPS-like phenotype lacking molecular confirmation. A recent case report described a 40-year-old woman with a 20-year unclassified autoinflammatory syndrome carrying only a TNFRSF1A variant of uncertain significance, in whom multiple conventional and biologic agents failed, but canakinumab 300 mg every four weeks produced rapid and sustained remission [11]. We report a patient without a genetically proven TNFRSF1A variant whose phenotype satisfied published clinical criteria for TRAPS and has sustained remission of symptoms with IL-1β blockade. In addition to the clinical presentation discussed, the patient also has a history of hereditary C1 esterase inhibitor deficiency, a condition that involves recurrent episodes of angioedema without urticaria in the skin, gastrointestinal tract, and airway, which overlaps with her other episodic symptoms [12].

Case Presentation

Patient presentation

The patient is a 38-year-old African American woman with a history of hereditary C1 esterase inhibitor deficiency, insulin-dependent diabetes mellitus complicated by gastroparesis, previous tobacco use disorder, and a hypercoagulable disorder complicated by a port-associated left arm basilic vein thrombosis, internal jugular vein thrombosis, transient ischemic attack, and pulmonary emboli. She was briefly evaluated by rheumatology in 2015 for angioedema, atypical chest pain, and concern for an underlying autoimmune disease. Initial autoimmune evaluation was unrevealing, and she was subsequently lost to follow-up.

At the time of clinical evaluation in 2018, the patient reported recurrent inflammatory episodes beginning at approximately nine years old that had become more frequent and severe during adulthood and occasionally precipitated by alcohol exposure. The flares were described as lasting from days to one to two weeks and characterized by subjective fevers, headache, diffuse arthralgia and myalgias, abdominal pain, nausea, vomiting, diarrhea, pruritic facial rash, transient morbilliform eruptions involving the trunk, lower extremity dysesthesias, and weakness. The facial rash has appeared most consistently with the systemic flares and consists of painful, erythematous plaques with variable features including acneiform papules and hyperkeratotic scale, mostly affecting the forehead, nasolabial folds, and perioral region. It also previously presented as annular erythematous plaques around the sides of the face. Intermittent eruptions involving the trunk, chest, and back have been reported during flares but were less thoroughly documented. See Figure *1* for the evolution of the rash.

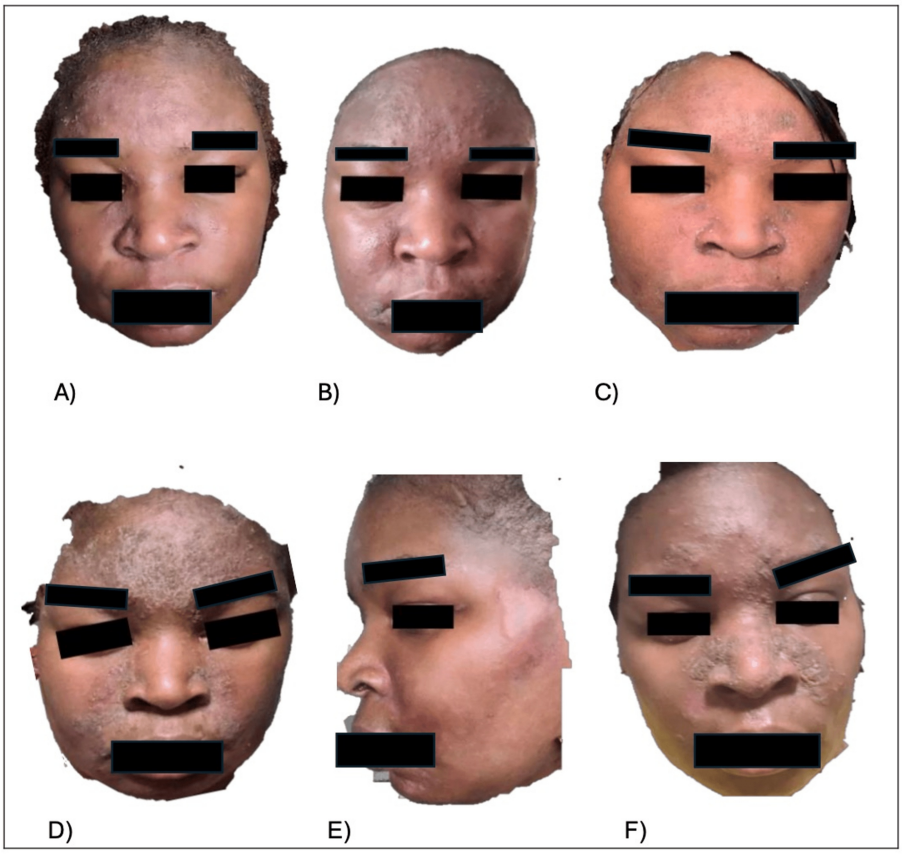


FIGURE 1: Evolution of facial rash throughout disease progression.

A: June 2021; B: October 2022; C: January 2023, flare requiring hospitalization; D: August 2023, flare requiring hospitalization; E: July 2025; F: June 2026, flare during missed dose of canakinumab.

On examination, she had chronic synovitis and symmetric inflammatory arthritis involving the hands, wrists, elbows, knees, and hips with progressive functional impairment including fixed contractures of the elbows and muscle weakness manifested as difficulty climbing stairs and inability to perform overhead activities. Radiographs over the duration of her disease demonstrated inflammatory arthritis with minimal osteoarthritic changes.

Family history is notable for a brother with similar symptoms and an unspecified autoimmune disease. There is no documented family history of periodic fever syndromes or AA amyloidosis. The disease has substantially impaired quality of life, and she is on medical disability due to the functional limitations of her condition. The pain has required chronic opioid therapy and prolonged corticosteroid use, subsequently leading to osteonecrosis of the left lateral femoral condyle and total arthroplasty.

Diagnostic assessment

Repeated investigations demonstrated chronic systemic inflammation despite persistently negative autoimmune serologies. These included anti-nuclear antibody (ANA), complement-3, complement-4, anti-double-stranded DNA, cyclic citrullinated peptide (CCP), anti-Sjogren's Syndrome A/B, anti-Smith, anti-Sm/RNP, anti-Scl-70, myeloperoxidase, proteinase-3, and tissue transglutaminase immunoglobulin A (IgA). Serum amyloid A and fibrinogen measurements were not performed.

Over time, the differential diagnosis included seronegative rheumatoid arthritis, systemic lupus erythematosus, drug-induced lupus, systemic vasculitis, acute intermittent porphyria, catecholamine-secreting tumor, and hereditary angioedema-related attacks. However, negative autoimmune serologies effectively ruled out conditions such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, scleroderma, and vasculitidies. Autoinflammatory gene panel testing, including TNFRSF1A, was not performed because of denied insurance coverage. Consequently, no pathogenic variant has been identified. By 2021, the combination of childhood-onset recurrent inflammatory events and episodic flares lasting days to weeks of fever, inflammatory polyarthritis, abdominal pain, and painful rash in the setting of negative infectious and autoimmune workup led to a diagnosis of an undifferentiated autoinflammatory syndrome most consistent with TRAPS. Table *1* outlines the chronological disease progression.

Year	Clinical Event	Laboratory Findings
Childhood	Recurrent febrile episodes with abdominal pain, rash, and inflammatory arthritis began.	None
2015	Initial rheumatology evaluation was started with unrevealing autoimmune workup.	IgE 15, IgA 392 (high), IgG 730, IgM 259 (high), CRP 9.4, ESR 26 (high)
2018	Methotrexate was initiated and patient had persistent seronegative inflammatory arthritis.	IgE 49.5, IgA 456 (high), IgG 892, IgM 236 (high), C3 157, C4 37, ANA 0.2, CCP Ab<15.6, SS-A/B Ab<0.2, DS-DNA Ab<12.3, CRP 33.2 (high), ESR 20 (high)
2019	The rash persisted and dapsone and chloroquine therapy were initiated.	CRP 22.9 (high), ESR 23 (high), CCP Ab<15.6, DS-DNA Ab<12.3
2021	The patient continued to have recurrent abdominal pain, headaches, tachycardia, rash, and polyarthritis. An undifferentiated autoinflammatory syndrome was suspected.	CRP 97 (high), ESR 22 (high), DS-DNA Ab < 1, SS-A/B Ab<1, Anit-Smith Ab<1, SCL-70 Ab<1, Sm/RNP Ab<1, ANA negative, myeloperoxidase Ab<1, proteinase-3 Ab<1
July 2021	Canakinumab 150 mg monthly was initiated.	CRP 16.5 (high), ESR 15
July 2022	Canakinumab dose was increased to 300 mg monthly (administered as 150 mg every two weeks) due to breakthrough fever and rash.	CRP 9.7, ESR 12
2025	The clinical diagnosis evolved to presumed TRAPS with sustained disease control on canakinumab 150 mg every 2 weeks.	CRP 4.4, ESR 4

TABLE 1: Timeline of significant clinical events.

ANA: Anti-nuclear antibody (reference range <1 U); Anti-smith Ab: anti-Smith antibody (reference range < 1 AI); CRP: C-reactive protein (reference range <10 mg/L); C3: complement 3 (reference range 83-193 mg/dL); C4: complement 4 (reference range 15-57 mg/dL); CCP Ab: cyclic citrullinated protein antibody (reference range <20 U/mL); DS-DNA Ab: double-stranded DNA antibody (reference range <30 IU/mL); ESR: erythrocyte sedimentation rate (reference range <20 mm/h); IgA: immunoglobulin A (reference range 87-352 mg/dL); IgE: immunoglobulin E (reference range <115 kU/L); IgG: immunoglobulin G (reference range 586-1602 mg/dL); IgM: immunoglobulin M (reference range 26-217 mg/dL); Myeloperoxidase Ab: myeloperoxidase antibody (reference range <1 AI); Proteinase-3 Ab: proteinase-3 antibody (reference range <1 AI); SCL-70 Ab: SCL-70 antibody (reference range <1 AI); Sm/RNP Ab: Smith/Ribonucleoprotein antibody (reference range <1 AI); SS-A/B Ab: Sjogren's Syndrome-related Antigen A/B antibody (reference range <1 U).

Management

Initial management consisted of empiric immunomodulatory therapy including: hydroxychloroquine 200 mg daily with limited benefit, chloroquine 250 mg daily which was discontinued due to gastrointestinal intolerance, dapsone 50 mg daily for rash with partial improvement, methotrexate 15 mg with partial improvement and discontinued due to gastrointestinal intolerance, recurrent courses of a prednisone 10 mg taper with consistent effectiveness, and occasional intra-articular corticosteroid injections with temporary improvement in symptoms. The limited benefit of these therapies further negated the likeilhood of an autoimmune condition like rheumatoid arthritis, systemic lupus erythematosus, Sjogren’s syndrome, or scleroderma.

Canakinumab was initiated in July 2021 at 150 mg subcutaneously every four weeks for presumed autoinflammatory syndrome. Clinical improvement was accompanied by progressive improvement in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leukocytosis, and the absolute neutrophil count (ANC), as shown in Table *2*. Due to breakthrough fever and rash, the dose was eventually increased to 150 mg every two weeks. There was no prior treatment with other IL-1 inhibitors or TNF inhibitors. By 2026, maintenance therapy consisted of canakinumab 150 mg subcutaneously every two weeks, intermittent prednisone for symptomatic control of inflammatory flares, triamcinolone 0.5% cream for affected skin areas, and C1 esterase inhibitor 1500 units weekly and icatibant 30 mg as needed for up to three doses weekly for hereditary angioedema.

Date	CRP (mg/L)	ESR (mm/h)	Absolute Neutrophil Count (k/mcL)	Notes
November 2018	33.2 (high)	20 (high)	20.8 (high)	None
September 2019	12.2 (high)	23 (high)	7.7	None
May 2020	96.3 (high)	35 (high)	11.2 (high)	None
June 2021	97 (high)	22 (high)	11.1 (high)	Shortly before canakinumab initiation
July 2021	16.5 (high)	15	10.8 (high)	Canakinumab 150 mg monthly initiated
August 2021	3	6	2.1	Shortly after canakinumab 150 mg monthly dose initiation
March 2022	2.1	4	4.9	None
July 2022	9.7	12	2.7	Canakinumab dose was increased to 300 mg monthly after breakthrough flare
December 2022	12.7 (high)	9	7.1	Hospital admission for chest pain and cough, found to be COVID-19 positive
December 2023	1.6	17	3.7	None
December 2024	5.7	26 (high)	8.2	None
February 2025	6.4	51 (high)	9.5 (high)	Flare after missing canakinumab dose
January 2026	1.7	24 (high)	6.4	None

TABLE 2: Laboratory markers of disease over time.

CRP: C-reactive protein (reference range <10 mg/L); ESR: erythrocyte sedimentation rate (reference range <20 mm/h); ANC: absolute neutrophil count (reference range 1.7-8.5 k/mcL).

Discussion

Canakinumab has produced clinical remission of the patient's autoinflammatory syndrome. Following initiation in 2021, the recurrent episodes of fever, arthritis, abdominal pain, and rash decreased in frequency and severity. Serial laboratory assessment also demonstrated improvement in inflammatory markers, and corticosteroid requirements decreased. At follow-up in May 2026, the presumed TRAPS syndrome was clinically quiescent while receiving canakinumab 150 mg every two weeks. Continued monitoring of clinical symptoms and laboratory testing for drug safety and infection surveillance has not revealed any significant adverse events attributable to canakinumab since initiation. Long-term therapy continues despite lack of confirmatory genotyping due to repeated insurance denials for autoinflammatory gene panel testing.

The limitations of this study include the absence of TNFRSF1A sequencing, precluding definitive diagnosis of TRAPS and leaving unexcluded the potential of low-penetrance variants or other genetic etiologies. In addition, not all of the patient's symptoms are consistent with TRAPS, as the rash appears more isolated rather than migratory over areas of myalgias, and it's possible that her hereditary angioedema symptoms may overlap and obscure the diagnosis. Further, IL-1 responsiveness is shared across several autoinflammatory conditions and other periodic fever syndromes, including familial Mediterranean fever, mevalonate kinase deficiency, and cryopyrin-associated periodic syndromes, and is therefore not specific to TRAPS. Lastly, serum amyloid A was never measured, omitting the marker most sensitive to subclinical inflammation and AA amyloidosis risk, although it has not yet been planned to be tested going forward.

Conclusions

This case demonstrates sustained response to IL-1β blockade in a patient with genetically unconfirmed TRAPS-like phenotype. The patient met several clinical features of TRAPS, including prolonged flares of

fever, myalgia, rash, and a sibling with reportedly similar symptoms. Canakinumab, the only FDA-approved treatment for TRAPS, produced remission with normalization of CRP, ESR, and ANC. The need for dose intensification after breakthrough symptoms parallels findings in prior trials in which response rose with up-titration.

Therapeutic interruptions have further supported treatment efficacy. After missing a dose of canakinumab due to backorder of the medication, she developed recurrence of her characteristic syndrome, including fever, rash, diffuse myalgias, and gastrointestinal upset. She continues to experience difficulty receiving refills of the medication related to a recurrent need for prior authorization and medication backorders, causing her to miss doses frequently. Overall, when a compatible phenotype, exclusion of mimics, and a reproducible response to IL-1 inhibition present, targeted therapy should not be withheld pending genetic confirmation. In this patient, delayed IL-1 treatment resulted in chronic pain, physical impairments, and reduced quality of life over the several years between symptom onset and effective therapy.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Morgan Agner

Acquisition, analysis, or interpretation of data: Morgan Agner, David Maxwell

Drafting of the manuscript: Morgan Agner

Critical review of the manuscript for important intellectual content: Morgan Agner, David Maxwell

Supervision: David Maxwell

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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