Case Report

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An undiagnosed patient with skin rash, polyarthritis, and edema responding to low-dose colchicine: A case report

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Abstract

A 54-year-old man was referred to our hospital with painful rashes on the extremities. He also developed polyarthritis and pitting pedal edema. Blood tests showed no specific autoantibodies and were negative for human leukocyte antigens B51, B15, and B27. Lower extremity venous ultrasonography and computed tomography angiography showed no vascular disorders. Skin biopsy showed no evidence of thrombosis or vasculitis. Direct fluorescence antibody analysis showed no antibody or complement deposition. Joint ultrasonography showed mild synovial thickening and/or synovial effusion in the extremities. Non-steroidal anti-inflammatory drugs and topical steroids were administered, followed by oral steroids. However, the signs and symptoms did not improve. Oral steroids were discontinued, and colchicine (0.5 mg/day) was administered. Thereafter, the symptoms of arthritis improved, and no skin rash developed. In potentially inflammatory conditions with skin rash, edema, and polyarthritis that are difficult to diagnose, low-dose colchicine administration may be considered for prompt relief of symptoms.

Keywords

Arthralgia, arthritis, colchicine, steroid, unclassified disease, undetermined disease, undiagnosed disease, undifferentiated disease

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Introduction

Advances in medicine continue to decipher the etiology and pathophysiology of many previously unexplained diseases. However, in some patients, establishing a definitive diagnosis is difficult, even if necessary physical examination, blood tests, or imaging studies were adequately performed.[1,2] Approximately 7%−35% of patients with unknown fever cannot be precisely diagnosed, and treatment may be initiated before a definitive diagnosis is established.[3] In general outpatient clinics, 25%−75% of patients complain of medically unexplained physical symptoms,[4] some of which may be due to unknown diseases.[5]

Colchicine, an alkaloid originally extracted from the autumn crocus plant, is an inexpensive and potent anti-inflammatory drug for gout.[6,7] It is also prescribed in familial Mediterranean fever, Behçet's disease, and pericarditis. Colchicine is thought to act by preventing leukocyte adhesion, mobility, and cytokine production through inhibiting tubulin polymerization and microtubule generation, thereby exerting anti-inflammatory effects.[8,9]

Herein, we present an undiagnosed patient with multiple symptoms and findings, including skin rash, arthritis, pitting edema of the extremities, and inflammation that responded significantly to low-dose colchicine treatment, following ineffective treatment with steroids and non-steroidal anti-inflammatory drugs (NSAIDs).

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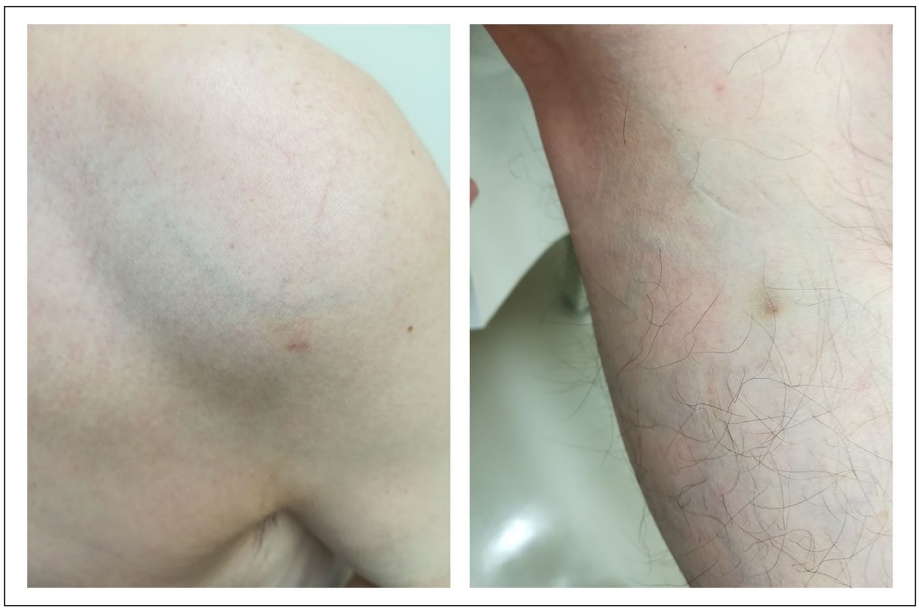

Figure 1. Skin rash in the patient. The rash started with erythema, followed by purpura and pigmentation. Non-palpable purpura and pigmentation on the patient's shoulder are shown (left). Non-palpable purpura and pigmentation on the superficial vein of the patient's lower leg are shown (right).

Case

A 54-year-old man with a history of alcoholic liver dysfunction and gout was referred to our hospital with rashes on his extremities (Figure 1). Five years ago, the patient had small and linear painful erythema on both lower limbs. Treatment was started with NSAIDs and topical steroids. However, the rash did not improve. Three years ago, a dermatologist suspected the patient to have erythema nodosum and/or thrombophlebitis. A year later, oral steroids were added at initial doses of 25 mg/day of prednisolone and continued at 5−20 mg/day as a maintenance dose according to symptoms. However, the symptoms did not improve. Skin rashes appeared solely along the superficial veins of the lower limbs over the sites touching footwear (boots), especially after standing in the afternoon. A year ago, similar skin rashes appeared on his upper limbs, along with pain, edema, and morning stiffness of both fingers, and he could not put on his ring. Subsequently, he began to experience pitting pedal edema and pain around the toes and heels (Figure 2).The symptoms of the affected joints were never in complete remission for more than a year without obvious joint swelling with erythema. He had no fever, weight loss, respiratory symptoms, impaired blood flow to the extremities, tophi, stomatitis, genital ulcers, folliculitis, or ocular symptoms.

Lower extremity venous ultrasonography showed no thrombus. Lower extremity computed tomography (CT) angiography showed no arterial occlusive lesions or arteriovenous shunting. Skin biopsy showed no evidence of thrombosis or vasculitis. Direct fluorescence antibody analysis showed no antibody or complement deposition. The disease's etiology remained unknown despite a detailed examination, and the patient was referred to our hospital.

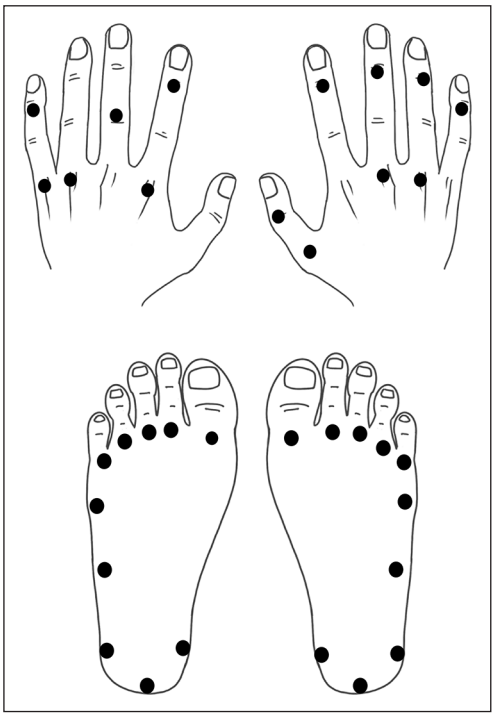

Figure 2. Area of point tenderness. Tender points on the patient's hands and feet are shown (black dots).

Dermatologists, gastroenterologists, rheumatologists, endocrinologists, and general practitioners participated in a multidisciplinary approach to the patient's diagnosis and treatment. At the first visit to our hospital (Table 1), blood tests showed mild abnormalities in C-reactive protein (CRP) levels and erythrocyte sedimentation rate, with alcoholic

Table 1. Hematological and biochemical investigations at the patient's first visit and during follow-up.

Parameters at the first visit	Results
White blood cell count (/μL)	6360
Neutrophil (%)	63
Lymphocyte (%)	31.6
Monocyte (%)	4.9
Eosinophil (%)	0.2
Basophil (%)	0.3
Red blood cell count ($\times 10^4$/μL)	312
Mean corpuscular volume (fl)	103.2
Mean corpuscular hemoglobin (pg)	33
Platelet (/μL)	186,000
Erythrocyte sedimentation rate (1 h/2 h) (mm)	51/86
Prothrombin time-international normalized ratio	0.88
Activated partial thromboplastin time (control) (s)	23.7 (28.1)
Lupus anticoagulant	Negative
Total protein (g/dL)	5.7
Albumin (g/dL)	2.9
Blood urea nitrogen (mg/dL)	16
Creatinine (mg/dL)	1
Sodium (mmol/L)	141
Potassium (mmol/L)	3.6
Chloride (mmol/L)	108
Calcium (mg/dL)	7.9
Inorganic phosphorus (mg/dL)	2.1
Uric acid (mg/dL)	6.4
Total cholesterol (mg/dL)	468
Triglyceride (mg/dL)	2038
Aspartate aminotransferase (U/L)	49
Alanine aminotransferase (U/L)	28
Alkaline phosphatase (U/L)	141
Lactate dehydrogenase (U/L)	222
Total bilirubin (mg/dL)	0.4
Gamma-glutamyl transferase (U/L)	337
C-reactive protein (mg/dL)	0.292
Cholinesterase (U/L)	280
Creatine phosphokinase (U/L)	43
Glucose (mg/dL)	95
Hemoglobin A1c (%)	5.1
IgG (mg/dL)	338
IgA (mg/dL)	105
IgM (mg/dL)	117
IgD (mg/dL)	1.5
C3 (mg/dL)	97
C4 (mg/dL)	30
CH50 (U/mL)	52
Thyroid stimulating hormone (μIU/mL)	2.01
Free triiodothyronine (pg/mL)	2.74
Free thyroxine (ng/dL)	0.74
Rapid plasma reagin test	Negative
Treponema pallidum latex agglutination automated test	Negative
Hepatitis B e antigen	Negative
Hepatitis B surface antigen	Negative
Hepatitis C Antibodies	Negative
Anti-streptokinase antibody	1280
Anti-streptolysin O antibody (IU/mL)	239
Proteinase-3-antineutrophil cytoplasmic antibody	Negative
Myeloperoxidase-antineutrophil cytoplasmic antibody	Negative
Rheumatoid factor (IU/mL)	27
Anti-cyclic citrullinated peptide antibody (U/mL)	<0.5
Anti-nuclear antibody	<40
Anti-double-stranded DNA antibody	Negative
Anti-Smith antibody	Negative
Anti-SSA/Ro antibody	Negative
Anti-SSB/La antibody	Negative
Anti-Scl-70 antibody	Negative
Anti-RNA polymerase III antibody	Negative
Anti-Jo1 antibody	Negative
Anti-cardiolipin antibody (U/mL)	<1
Anti-centromere antibody	Negative
Interferon-γ release assay	Negative
Parameters during follow-up	**Results**
Thyrotropin receptor antibodies (IU/L)	<0.8
Thyroglobulin (ng/mL)	14.8
Anti-thyroid peroxidase antibodies (U/mL)	<9
Anti-thyroglobulin antibody (IU/mL)	<10
Vitamin B1 (ng/mL)	32
Vitamin B2 (ng/mL)	76.2
Vitamin C (μg/mL)	9.7
Fibrin degradation products (μg/mL)	<2.5
D-dimer (μg/mL)	0.6
Antithrombin III (%)	90
Protein S (%)	125.3
Protein C (%)	134
Angiotensin-converting enzyme (U/L)	23.3

liver damage and hypoproteinemia. He had been administered febuxostat 10 mg/day for hyperuricemia for years, and his uric acid level was within the reference range. No specific autoantibodies were found. A chest radiograph showed no pulmonary hilar lymph node enlargement. Moreover, electrocardiogram and echocardiogram showed no cardiac abnormalities. Plain radiographs of the hands and feet showed no signs of joint space narrowing or erosions. Joint ultrasonography showed mild synovial thickening and/or synovial effusion (grade 1 in all affected joints) in bilateral fingers, wrist, elbow, shoulder, ankle, and toe. Hyperechoic spots in the synovium and double contour sign, which are gout characteristics, were not detected. Doppler ultrasonography showed mild blood flow signals only in the synovium of bilateral shoulder joints. Reexamination of the skin biopsy showed only hemorrhages and edema, with no specific findings. No human leukocyte antigen (HLA) specific to Behçet's

Table 2. Changes in CRP and ESR levels before and after taking colchicine.

Date	First visit (2019/3/11)	(2019/7/5)	(2019/10/15)	First day after colchicine administration (2019/10/23)	(2019/11/29)	(2020/3/5)	(2019/6/5)
CRP (mg/dl)	0.292	0.200	0.413	–	0.027	0.03	<0.02
ESR (1 h/2 h) (mm)	51/86	–	13/33	–	–	–	–

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

disease, such as B51, B15, and B27, was found. First, recommendations for abstaining from alcohol and improving diet were provided as alcoholic liver disorders treatment. The previously prescribed oral steroids were tapered off and discontinued, and colchicine 0.5 mg/day was initiated for the treatment of polyarthritis. After taking low-dose colchicine, the patient noticed a gradual improvement in pain in his extremities. No acute toxicity due to colchicine was observed. After approximately 1 month of colchicine treatment, the patients' subjective symptoms of arthritis improved such that the pain intensity decreased to nearly one-third of the pretreatment value. The patient could put on his ring without difficulty, and his weight decreased from 64 to 62 kg. In addition, no new-onset skin rash was observed. After 6 months of colchicine treatment, CRP levels were normalized (Table 2), and the joint pain nearly disappeared; the patient only reported mild stiffness in the hand for brief periods in the morning, so he was able to lead a normal life.

Discussion

This case report highlights two important issues. First, physicians need to treat symptoms appropriately, regardless of causes, even if these are medically unexplained symptoms.[10] In Japan, blood tests, ultrasonography, and biopsy are all covered by the Japanese national public health insurance. Some undiagnosed cases are referred to the Initiative on Rare and Undiagnosed Diseases led by the Japan Agency for Medical Research and Development for genetic analyses.[11] This facility is not easily available in all regions of Japan. In our patient, a multidisciplinary approach was used to diagnose possible diseases, such as chronic gout, thrombophlebitis, Behçet's disease, sarcoidosis, vasculitis, coagulopathy, nutritional disturbances, and substance abuse. Although treatment should ideally be started before establishing definitive diagnoses, physicians are often reluctant to begin it. It has been reported that symptomatic relief for even acute abdominal diseases does not delay in diagnosis.[12,13] Since definitive or effective treatment does not always exist, the goal of treatment should be to provide symptomatic relief and improve daily activities.[5]

Second, colchicine could be effective in undiagnosed disease patients complaining of skin rashes, polyarthritis, and edema, especially those with some features similar to autoinflammatory or autoimmune diseases. Colchicine is reported to be effective in many diseases, including recurrent polychondritis,[14] pyoderma gangrenosum,[15] adult-onset Still's disease,[16] interstitial pneumonia,[17] pericarditis, gout, and familial Mediterranean fever. Possible diagnoses of these diseases were ruled out in our case. The efficacy of low-dose colchicine in preventing cardiovascular events after myocardial infarction has also been reported,[6] and its anti-inflammatory effect on atherosclerosis is currently anticipated. Colchicine is not a common treatment choice for various inflammatory arthritis that is difficult to classify. For example, patients with early persistent undifferentiated inflammatory arthritis and evaluated as being at risk of persistent arthritis are recommended to receive disease-modifying antirheumatic drugs (DMARDs) as early as possible (ideally within three months). These treatments might be administered even if patients do not meet the inflammatory rheumatologic disease criteria, and colchicine is not considered a therapeutic option.[18] The guidelines for undifferentiated spondyloarthritis include DMARDs, NSAIDs, and steroids as treatment options, and colchicine is not considered a treatment choice.[19] Even in the absence of a definitive diagnosis, colchicine may improve symptoms and contribute to improving the quality of life in cases with suspected abnormalities in leukocyte function or cytokine production as the pathophysiology.

Conclusion

We presented an undiagnosed patient with main symptoms of skin rash, polyarthritis, and edema. In potentially inflammatory conditions that are difficult to classify, low-dose colchicine administration could be effective in symptomatic treatment.

Author contributions

H.M. conceived the idea and wrote the original draft of the manuscript. T.K. developed the theory and supervised the findings of this study. All authors discussed the case and commented on the manuscript. H.M., T.K., and T.A. revised and edited the manuscript. All authors gave final approval before submission of the manuscript.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from the patient for publication of this case.

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