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Adult-onset Still's disease masquerading as acute coronary syndrome: a case report and review of the literature

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Abstract

Introduction Adult-onset Still's disease is a rare systemic autoinflammatory disease. We present a case of a young man with a constellation of symptoms and myopericarditis as a complication of this disease.

Case A 36-year-old Hispanic man with no significant past medical history developed a quotidian fever pattern following an upper respiratory tract infection. He initially presented with chest pain concerning for myocardial infarction and underwent cardiac catheterization, which revealed non-obstructive coronary artery disease. He was found to have myopericarditis, significant neutrophilic leukocytosis, and hyperferritinemia. He improved on high-dose corticosteroids but developed steroid-induced psychosis, and 4 months from symptom onset, he finally received tocilizumab, which eventually induced remission without adverse reactions.

Discussion Adult-onset Still's disease should be considered in a patient with fevers of undetermined origin. Due to its multisystemic involvement, adult-onset Still's disease is often a diagnosis arrived at after an extensive cardiac, hematologic, malignant, and infectious workup. Imaging, laboratory testing, and bone marrow biopsy were necessary to rule out alternative etiologies of this patient's presentation. Steroids are the mainstay of treatment because they are easily affordable, although the high risk of adverse effects makes them less desirable. Interleukin-1 inhibitors (anakinra or canakinumab) and interleukin-6 inhibitor tocilizumab are the steroid-sparing biologic agents of choice but are cost-prohibitive.

Conclusion Adult-onset Still's disease should be considered in the differential diagnoses of fever of undetermined origin. Early identification and initiation of treatment are critical to faster recovery and prevention of progression to severe complications. Steroids remain the standard first-line therapy and should be followed by disease-modifying steroid sparing drugs. The social determinants of health may preclude their timely initiation and should alert providers of proactive ways to avoid further delays.

Keywords Adult-onset Still's disease, Fever of unknown origin, Hemophagocytic lymphohistiocytosis, Bone marrow biopsy

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Introduction

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disease with an incidence of 1 per million people. It was first reported in 1971 by Bywaters [1, 2]. The condition was first described in children as early as 1896 by British pediatrician Sir George Still and is commonly referred to as systemic juvenile idiopathic arthritis (SJIA) in that population [3, 4]. AOSD has similarities to the condition known as systemic juvenile idiopathic arthritis as well as rheumatoid arthritis (RA). However, AOSD does not entirely fit the clinical picture of RA, hence its establishment as a separate disorder. Recent data suggest that AOSD and SJIA are part of the same disease continuum, with different ages of onset [5].

The etiology of AOSD is not fully characterized in adults, with studies suggesting genetic and infectious triggers [1]. Major clinical manifestations, in about 75–95% of affected individuals, include quotidian or double-quotidian fever, evanescent salmon-colored rash, and polyarthralgia [1]. AOSD most commonly presents in young adults, with an average diagnostic age of 36 years [6].

The hospital course for AOSD remains challenging due to a lack of specific diagnostic testing and limited management guidelines. We present a case of adult-onset Still's disease, initially presenting as ST-elevation myocardial infarction (STEMI) leading to cardiac catheterization. Through the presentation of this case, we hope to aid in expanding the knowledge base of the rare condition. We further reviewed the literature on various presentations of AOSD and discussed medical management options.

Case

Clinical presentation and history

A 36-year-old Hispanic man without significant medical history presented to an outside facility in May 2023 for a 2-week history of cough, shortness of breath, and persistent pharyngitis. He was initially treated outpatient with azithromycin and prednisone for a presumed sinus infection. Initial workup included a negative strep test. He had subsequent onset of "spastic" back pain that radiated to his left lower extremity, which was alleviated by muscle relaxants. A few days later, he developed 8/10 chest pain that persisted and worsened for approximately 1 week before he developed shortness of breath with minimal exertion. He became febrile, between 38.9 °C and 40 °C for 2 days, then spiking daily high temperatures for several hours before resolving and returning to normal approximately 24 hours later. On the third day of fever, he presented to an outside hospital emergency room, where he deferred a lumbar puncture, and 2 days later, he returned due to abdominal pain, nausea, emesis, chest pain, and dyspnea at exertion and rest.

His workup showed significant neutrophilic leukocytosis of 44 K/uL (reference range: 4–10), C-reactive protein (CRP) of 41 (< 0.50) mg/dL, elevated troponin, and an electrocardiogram (EKG) concerning for an ST-segment elevation myocardial infarction (STEMI). He underwent a left and right heart cardiac catheterization showing clean coronary arteries. The procedure was complicated by severe hypotension thought to be related to the procedure, which led to hypotensive shock and ultimately required vasopressors. Parenteral antibiotics were administered for presumed septic shock secondary to pneumonia on the basis of bilateral lower lobe infiltrates on his chest computed tomography (CT), leukocytosis, fevers, and chills. He stayed in the intensive care unit (ICU) for monitoring and sedation for agitation. He was found to have myopericarditis and was treated with colchicine 0.6 mg daily and high doses of oral prednisolone 60 mg daily. He had a negative infectious workup, which included respiratory viral panel [which also tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza A/B, adenovirus, rhino/enterovirus, and respiratory syncytial virus, among others], human immunodeficiency virus (HIV), and cytomegalovirus (CMV). EBV was positive at 640 copies per milliliter. Urine and blood cultures were negative. Fungal antigens in blood and urine, including cryptococcus capsular polysaccharide, histoplasma antigen, galactomannan, and β-d-glucan, were not elevated. Syphilis screening was negative. His tick and mosquito-borne infectious workup, which included anaplasmosis, ehrlichiosis, babesiosis, and malaria, was also negative. Lyme serology (ELISA) immunogobulin G (IgG) titers were positive, but confirmatory western blot test was negative. Leptospira antibodies were negative. His cerebrospinal fluid (CSF) was negative for cryptococcal antigen; however, adequate CSF for further testing was not obtained during lumbar puncture. His lactate dehydrogenase was 1089 units/L (reference range: 135–250), ferritin greater than 15,000 ng/ml (reference range: 30–400), and direct Coombs test was negative. His lipid panel was unremarkable except for triglycerides greater than 354 mg/dL (< 150). He continued to be febrile. A magnetic resonance imaging (MRI) brain was done due to encephalopathy, which was negative for intracranial abnormality. Hepatitis panel and antinuclear antibody (ANA) test were pending by the time he transferred to our facility. He continued to have intermittent fevers, chest pain, and lethargy. He was transferred to our hospital on day 7 for further workup for continued evaluation and management.

Initial differential diagnoses and additional laboratory findings

Upon arrival, he was tachycardic to 120 beats per minute, normotensive, and saturating well on room air. Within 24 hours of admission, he was febrile to a maximum temperature of 40 °C. Our initial differential diagnoses included EBV as an etiology for myopericarditis, given that the patient's EBV was positive at 640 copies per milliliter, however, repeat serology at our hospital was negative. We also considered sepsis likely secondary to bacteremia or viral etiology. His congestion and shortness of breath were attributed to viral upper respiratory infection (URI) versus pneumonia, with radiologic evidence demonstrating bilateral infiltrates on his CT chest. The patient also experienced several episodes of hemoptysis during his first 1–2 days of admission.

Timeseries of labs and inflammatory biomarkers are provided in Fig. 1. His liver function tests worsened: alanine transaminase (ALT) of 233 units/L (reference range: 0–41), total bilirubin of 3.5 mg/dL (reference range < 1.2), alkaline phosphatase (ALP) of 328 unit/L, aspartate transaminase (AST) of 226 unit/L (reference range: 0–40), and gamma-glutamyltransferase (GGT) of 232 unit/L (reference range 8–61). Other inflammatory markers reached a maximum of 91 mm per hour (90 on discharge, reference range: 0–15) and 30 mg/dL (22 on discharge, reference < 0.5) for ESR and CRP, respectively. His triglyceride level was 385 mg/dL (< 150), raising suspicion for hemophagocytic lymphohistiocytosis (HLH), but he did not demonstrate findings of hepatosplenomegaly. His soluble interleukin-2 (IL-2) receptor (CD25) level was elevated to 5531 pg/mL (reference range: 175–858). His hepatitis B and C serologies were negative. Repeat EBV PCR at our hospital resulted at 108 copies per milliliter. Doppler of the hepatic veins was also negative for thrombosis.

Peripheral smear demonstrated normocytic, normochromic anemia, leukocytosis with absolute neutrophilia and lymphopenia, thrombocytopenia, and red blood cells with mild anisopoikilocytosis. There were no spherocytes or schistocytes, excluding autoimmune hemolytic anemia/hereditary spherocytosis or microangiopathic hemolytic anemia. No nucleated red cells were observed. Neutrophils predominated and exhibited mild left shift to the band forms with occasional cytoplasmic vacuoles. Lymphocytes were rare, small to medium, with rare reactive lymphocytes. No blasts were observed. Platelets were small to large with normal morphology.

He underwent CT-guided left posterior iliac bone marrow biopsy, which showed a hypercellular marrow with an increase in all three cell lines, more prominent in the megakaryocytic lineage, however, with normal megakaryocyte morphologies. The myeloid lineage was increased as well, but there was no evidence of increased blasts or Auer rods evident on flow cytometry or visual examination. There were no lymphoid aggregate, granuloma, or metastasis; no increase in lymphocytes, plasma cells, or blasts; and no hemophagocytosis observed. *JAK2 V617F* mutation polymerase chain reaction (PCR) testing was negative. NeoGenomics testing including fluorescence in situ hybridization (FISH) analysis of t(9;22) *BCR:ABL*, evaluation of mutations in FLT3, IDH1, IDH2, and NPM1 all returned negative. Overall there was no evidence of acute leukemia or lymphoma, which can be inciting causes of AOSD or HLH.

His H-score was calculated to be elevated to 182, +49 for a temperature above 102.9 °F, +50 for a ferritin greater than 6000 ng/mL, +64 for triglycerides greater than 354 mg/dL, and +19 for an AST greater than 30 unit/L. A score of 182 signifies a 70–80% likelihood of hemophagocytic syndrome, and while the bone marrow biopsy did not demonstrate findings of HLH, it cannot be ruled out.

His rheumatology workup demonstrated ANA positive (titer 1:320), but extractable nuclear antigen antibody panel including anti-double stranded DNA, anti-Smith, anti-ribonucleoprotein (RNP), anti–Sjögren's-syndrome-related antigen A (anti-SSA), anti–Sjögren's-syndrome-related antigen B (anti-SSB), anti-centromere, anti-scleroderma 70, anti-histone, and anti-JO1 antibodies were negative. His anti-mitochondrial antibody was negative. His complement levels were normal, with a C4 of 8 and a C3 of 73.

Imaging and diagnostic tests

CT chest showed bilateral trace pleural effusion and adjacent-dependent consolidations in both lower lobes, mostly consistent with atelectasis. His CT abdomen and pelvis showed no acute abnormalities. His transthoracic echocardiogram was normal and MRI of the brain was normal. The patient had multiple EKGs done, given several episodes of chest pain of varying severities accompanied by tachycardia throughout his hospital course. His EKGs from our facility consistently showed diffuse PR segment depression consistent with pericarditis (Supplementary figure).

Treatment

He was started on oral colchicine 0.6 mg daily and oral dexamethasone 10 mg twice daily at the outside hospital. Our cardiology team recommended ongoing treatment of his myopericarditis with colchicine. The hematology and rheumatology teams at our institution recommended continuing with the steroids. He was switched to parenteral methylprednisolone 60 mg twice daily and transitioned to oral prednisone 60 mg daily for 3 weeks then 40 mg daily until outpatient rheumatology follow-up.

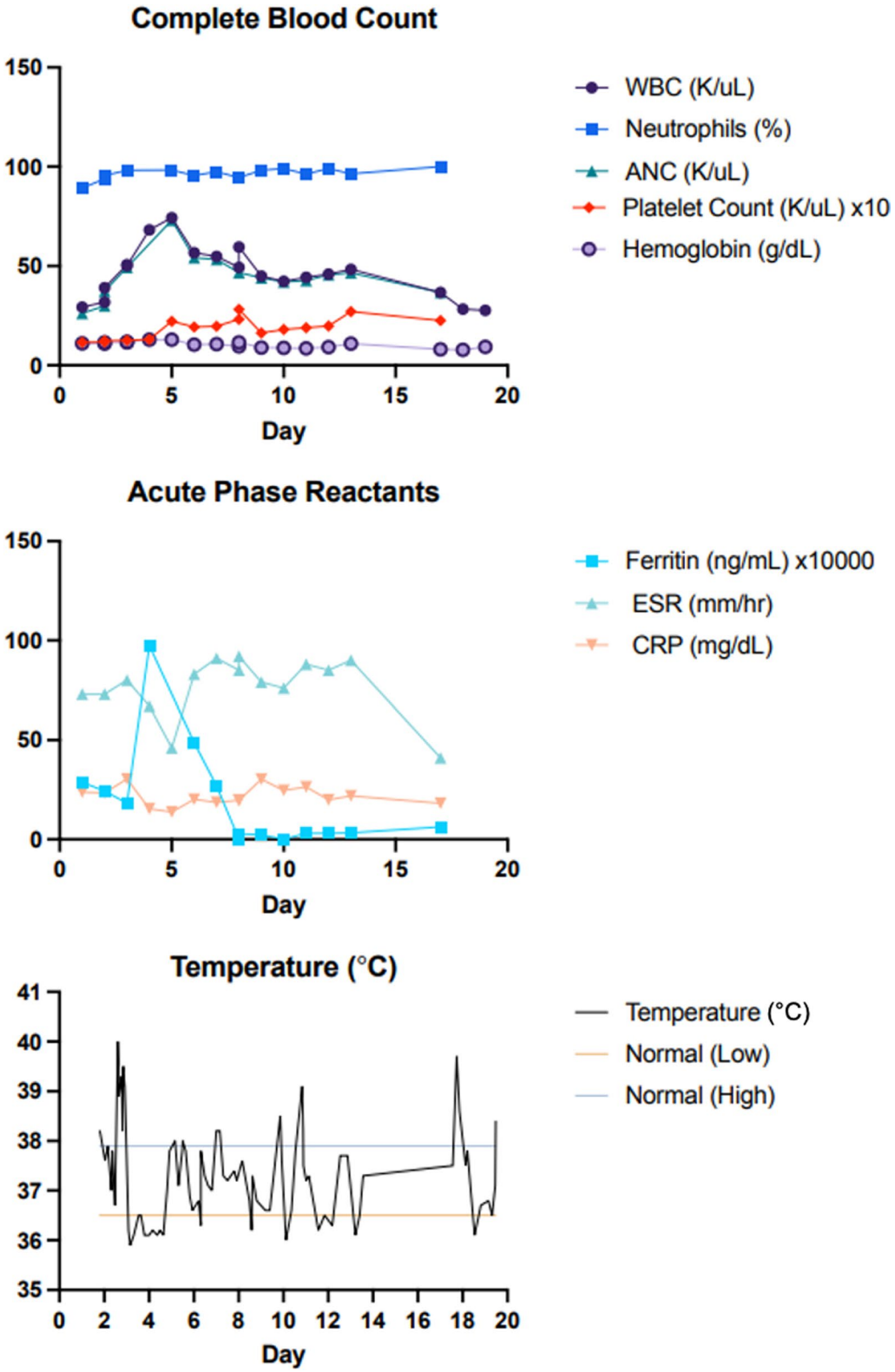

Fig. 1 Dynamic distribution of labs during hospitalization: complete blood count (top panel), acute phase reactants (middle panel), and temperature (bottom panel); note the quotidian fever pattern during hospitalization

Follow-up

The patient was discharged after 10 days but was readmitted 6 days later due to steroid-induced psychosis. His dose was subsequently reduced, and he continued to improve clinically. His inflammatory biomarkers also improved except for persistently elevated ferritin levels. We considered IL-1 inhibitor canakinumab or IL-6 inhibitor tocilizumab, but these were not approved at the time of readmission due to lack of insurance. He was discharged to continue with oral prednisone reduced to 40 mg daily while the rheumatology team worked on getting canakinumab as outpatient, a process that required care coordination among specialty pharmacy and prescription assistance teams. Canakinumab proved to be too prohibitive, while anakinra was deferred due to patient's preference to not get anxiety-provoking daily injections.

Four months post admission he started tocilizumab 160 mg subcutaneous every 2 weeks, which he tolerated, and which was associated with significant improvement of his symptoms. His steroids were tapered off after several weeks. He was seen again in clinic 2 months after starting tocilizumab. He was asymptomatic. He had no chest pains, arthralgia, rash and fevers. His inflammatory markers and labs were in excellent range. Blood pressure and heart rate were under good control.

Discussion

We present a rare case of adult-onset Still's disease, which acutely presented with quotidian fevers and a preceding upper respiratory infection leading to an extensive infectious and autoimmune disease workup. Although the patient was found to have non-obstructed coronary arteries, he was diagnosed with myopericarditis and benefited from colchicine. His symptoms responded to high doses of steroids, but resulted in steroid-induced anxiety and insomnia, which could have been mitigated by a sooner reduction in steroid dose and/or earlier initiation of steroid sparing interleukin-1 or interleukin-6 inhibitors. However, due to lack of insurance coverage, it took months before he started tocilizumab 160 mg subcutaneous every 2 weeks. He tolerated the medication and his clinical and laboratory markers improved significantly enabling steroid tapering and discontinuation.

The pathophysiology of AOSD has not been fully delineated. However, biomarkers and cytokine signalling pathways in the AOSD disease process have been hypothesized and described [7]. Significant overdrive of the innate immune system and excess production of proinflammatory cytokines IL-1, IL-6, and IL-18 are crucial in the pathophysiology [7]. Two current AOSD treatments are IL-1 antagonists and other management options being researched target inhibition of IL-6 and IL-18 [7–10]. The first step is the triggering of the innate danger signals, including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [7]. Danger signals can be prompted by bacterial and viral infections, which commonly precede AOSD [1, 7, 11, 12]. Macrophages and neutrophils detect these danger signals through Toll-like receptors, which lead to the activation of inflammasomes, then caspase activation, and as a result, excessive IL-1β production [13]. Ultimately, the innate immune system is driven into an overreactive state, leading to a cytokine storm [14]. One theory for the overproduction of cytokines is retrograde activation of macrophages and neutrophils by IL-1. [12, 14]. The role of genetics in AOSD remains unclear [7]. Currently, research is being conducted to see whether alleles that correlate strongly with systemic-onset juvenile idiopathic play a role in AOSD [15].

This case report highlights the need for clinicians to be vigilant in considering AOSD as a potential diagnosis earlier in the face of presenting fevers of undetermined origin associated with hyperferritinemia, usually > 4 times the upper limit levels. Currently, diagnostic testing for the condition is based on classification criteria. Two of the most utilized classification criteria for AOSD were developed by Yamaguchi in 1992 and Faurel in 2002 [11, 16, 17]. As outlined in Table 1, other cases of AOSD have been described after delayed diagnosis, up to 3 months after presentation, due to the clinical presentation being similar to that of severe pneumonia, malignancy, or other rheumatologic processes. A strength, in this case, is that resources at this tertiary care center were used to do a workup and rule out necessary diseases to narrow the differential to likely AOSD. Although his infectious workup, including blood cultures, was unrevealing, he was positive for EBV viremia of uncertain significance. It is difficult to know whether his upper respiratory infection that acted as the danger trigger for AOSD was caused by mononucleosis. Nevertheless, a sore throat is one of the minor criteria per Yamaguchi's diagnostic criteria.

The mainstay of treatment for AOSD is to suppress the immune system with either steroids and/or steroid-sparing biologics [5] in the acute setting, and to ensure that the patient has regular follow-up to monitor disease activity, recurrence, and response to medications.

Conclusion

Although considered rare, adult-onset Still's disease is not an uncommon cause of fever of undetermined origin. Early identification and initiation of steroid-sparing treatment are critical to faster recovery and prevention of side effects and progression to severe complications.

Table 1 Literature review of clinical presentation, treatment, and recovery of reported cases of AOSD

Case presentation	Publication year	Treatment	Follow-up
39-year-old woman presented with cough, chest pain, and fever for 1 week after 4 days of sore throat [18]	2011	–Methylprednisolone (1 mg/kg/d) –The dose of methylprednisolone was tapered and stopped at 6 months	–Symptoms improved markedly after 5 days of medication –Chest CT scan showed normal assessment in 6 days –All labs including serum ferritin levels normalized after 2 months of treatment – Symptoms and signs were stable during the 1-year follow-up period –She fully recovered and was off steroids
21-year-old man presented with fever, sore throat, and nonproductive cough for 10 days [18]	2011	–Methylprednisolone (80 mg/day) with a taper	–Symptoms improved markedly in 1 week –Subsequent chest CT scan showed normal results after 10 days of treatment –Patient recovered and no medication is currently prescribed
18-year-old woman presented with pain in the large joints of all extremities and pruritic and painless rash formation on the skin of the dorsum of the shoulders and both wrists and both sides of the thighs [19]	2021	–Symptomatic treatment, oral prednisone, and methotrexate	–Condition was stable without progression at 11-month follow-up
28 year-old woman presented with fevers, pain and swelling of multiple joints, recurrent sore throat, and rash for 2 years [20]	2020	–Prednisolone 40 mg per day –Weekly alendronate and ibuprofen –Prednisolone tapering was initiated after 1 month –15 mg per weekly methotrexate	–At 1 month of follow-up, her symptoms had improved with no fever, joint pain, and rash –Repeat labs at 2 months showed reduced ESR and leukocytosis

Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANA	Antinuclear antibodies
AOSD	Adult-onset Still's disease
AST	Aspartate transaminase
CMV	Cytomegalovirus
CRP	C-reactive protein
CT	Computed tomography
DAMPs	Damage-associated molecular patterns
EBV	Epstein–Barr virus
EKG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
FISH	Fluorescence in situ hybridization
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
ICU	Intensive care unit
IL	Interleukin
MAS	Macrophage activation syndrome
MRI	Magnetic resonance imaging
PAMPs	Pathogen-associated molecular patterns
PCR	Polymerase chain reaction
RA	Rheumatoid arthritis
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SJIA	Systemic juvenile idiopathic arthritis
STEMI	ST-elevation myocardial infarction:
URI	Upper respiratory infection

Supplementary Information

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Supplementary material 1

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IM, RK, and PS drafted the manuscript. IM prepared Fig. 1. WM, DE, AL, SAA, MAH, and CK reviewed subsequent drafts of the manuscript. All authors were directly involved in the clinical diagnosis-making process and the treatment of the patient. All authors read and approved the final manuscript.

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Consent for publication
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