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CASE REPORT

Eosinophilic Granulomatous Polyangiitis with Autoimmune Hemolytic Anemia: A Case Report and Review of the Literature

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Abstract: EGPA can affect multiple organ systems, typically presenting with respiratory symptoms as the initial manifestation. The absence of specific diagnostic biomarkers makes it prone to misdiagnosis. This article describes a 40-year-old female patient who presented with asthma-like symptoms, neurosensory impairment, anemia, peripheral blood eosinophilia, and pulmonary involvement. The patient was diagnosed with EGPA combined with AIHA. After ineffective treatment with glucocorticoids alone, the patients' symptoms were relieved by the addition of the immunosuppressant cyclophosphamide. Cyclophosphamide was discontinued after the total dose reached 7g and the patient relapsed. Subsequent treatment for the patients involved a combination of glucocorticoids and MMF, with no evidence of recurrence. This case is relatively rare in clinical practice, and fortunately the final treatment effect is satisfactory.

Keywords: asthma, eosinophilic granulomatosis with polyangiitis, autoimmune hemolytic anemia, recurrence

Introduction

Eosinophilic Granulomatosis with Polyangiitis (EGPA) is a rare, multisystem disorder encompassing eosinophilia and Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis. Histopathologically, EGPA is characterized by profound eosinophil infiltration, resulting in tissue inflammation, ischemia, and subsequent organ injury.[1] It has been reported that the pathophysiology of EGPA can be divided into two disease phenotypes based on ANCA positivity: an ANCA-positive vasculitis-driven condition and an ANCA-negative eosinophil-driven condition.[2] Complications of EGPA may arise across multiple organ systems, though the coexistence of Autoimmune Hemolytic Anemia (AIHA) is relatively uncommon, with the management of the original disease serving as the cornerstone of therapeutic intervention. Treatment for EGPA is guided by five-factor score (FFS), and in cases of recurrent disease, the use of glucocorticoids in conjunction with immunosuppressants is advised.[3] Given the variability in efficacy among immunosuppressants, tailored selection is of utmost importance. The use of biologic agents is becoming increasingly widespread. However, economic constraints may prevent it from being the initial treatment choice for the majority of patients. Here, we describe a case report involving a patient with EGPA and concurrent AIHA, who was effectively managed using a combination of glucocorticoids and the immunosuppressant mycophenolate mofetil, leading to sustained disease stability.

Case Report

The First Admission to Hospital

A 40-year-old female patient presented to the clinic on March 24, 2021, with a ten-day history of cough, sputum production, fever, and dyspnea. In reviewing past medical history, she has had asthma for 10 years, and previous

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pulmonary function tests indicate a positive bronchodilation test. She has suffered from epilepsy for over 30 years, maintains long-term therapy with sodium valproate at 0.6g daily, carbamazepine at 0.3g daily, and has experienced seizures two to three times annually. On admission for a physical examination, the patient's body temperature was 37.8 °C, heart rate 115 beats per minute, respiratory rate 25 breaths per minute, and blood pressure 116/96 mmHg. The patient exhibited erythematous skin, with visible confluent papules. Pulmonary examination revealed moist crackles and wheezes. The right upper limb demonstrated decreased pinprick sensation, and both lower limbs presented with moderate pitting edema. Mild cyanosis was observed in the extremity skin, with a slight decrease in the pulsation of the dorsalis pedis artery. No signs of superficial lymphadenopathy were noted.

Blood analysis on March 24, 2021: White blood cell count was 7.36×10^9/L, the absolute value of eosinophils was 3.28×10^9/L, the percentage of eosinophils was 44.5%, Hemoglobin was 136.0 g/L, high-sensitivity c-reactive protein was 25.51mg/L; Serum creatinine was 58.8umol/L; total cholesterol was 4.28 mmol/L, triglycerides was 1.48 mmol/L; erythrocyte sedimentation rate was 15 mm/h; lactic dehydrogenase 1143IU/L. Serum IgA, IgG, and IgM levels were not elevated. No abnormalities in rheumatoid factor were detected. Specific autoantibodies, including anti-nuclear (ANA), anti-cyclic citrullinated peptide (CCP), anti-ribosomal RNA-protein (rRNP), anti-nuclear ribonucleoprotein (nRNP), anti-Smith (SM), Anti-Sjögren's-syndrome-related antigen A (Anti-SSA), anti-Scl 70, anti-Jo-1, Anti-double-stranded (ds) DNA were negative. ANCA were negative, while IgG isotype anticardiolipin antibodies were positive. Acid-fast bacilli were not detected in sputum smears. Cranial CT imaging revealed bilateral ethmoid and maxillary sinusitis. Computed tomography (CT) of the chest, abdomen, and pelvis disclosed bilateral pulmonary inflammation with ground-glass opacities, multiple lymphadenopathies in both axillae and the mediastinum, splenomegaly, and lymphadenopathy in both inguinal regions. Electromyography demonstrated that sensory conduction in the bilateral superficial peroneal nerve was absent, and the amplitude of the left common peroneal motor nerve was reduced, indicating neurosensory impairment.

According to the patient's multi-system symptoms and examination findings: The diagnosis adheres to the criteria set forth by the American College of Rheumatology (ACR) in 1990: 1) Asthma; 2) Eosinophilia (>10% of the total white blood cell count); 3) Neuropathy; 4) Nonfixed pulmonary infiltrates; 5) Nasal sinusitis; 6) Extravascular eosinophils. Patients met five of them, so she was diagnosed as EGPA after admission. Methylprednisolone, administered at a dosage of 80 mg/day for five days, led to an improvement in symptoms of fever and edema. However, subsequent to treatment, the patient experienced epileptic seizures and an acute exacerbation of asthma. In light of the potential for epilepsy triggered by high-dose methylprednisolone, the administration of glucocorticoids was discontinued. Subsequently, gamma globulin was administered at a dose of 10g/day for three days, in conjunction with cyclophosphamide at 0.2g/day for seven days. Additionally, the dosage of methylprednisolone was decreased to 40mg/day for eleven days. The patient's cough, asthma, and edema symptoms were fully resolved. A follow-up lung CT revealed considerable absorption of ground-glass opacities and the regression of lymph node enlargement in the mediastinum and axilla, although splenomegaly remained unchanged. Following discharge, the patient was prescribed prednisone at a dose of 20 mg in the morning and 20 mg in the evening to sustain the remission, accompanied by instructions for outpatient follow-up to taper the dose progressively. Nevertheless, the patient subsequently discontinued the medication without medical advice.

The Second Admission to Hospital

The patient was admitted to the hospital again on April 10, 2022, with a two-day history of cough, sputum, and fever. Concurrently, she exhibited symptoms indicating a new presentation of abdominal pain, diarrhea, nausea, and vomiting, alongside jaundice and anemia. Physical examination on admission: Wet rales were heard in both lungs, and tenderness was noted under the xiphoid process and in the abdomen, with edema in both lower extremities. The patient's liver function has rapidly deteriorated, with alanine aminotransferase (ALT) at 149.3 U/L, aspartate aminotransferase (AST) at 399.5 U/L, total bilirubin at 157.17 μmol/L, indirect bilirubin at 61.08μmol/L, hemoglobin at 34 g/L, reticulocyte percentage at 21.88%, and absolute eosinophil count at 0.08 × 10^9/L. Autoimmune hepatitis and hemolytic anemia cannot be ruled out. Further comprehensive assessments revealed Direct antiglobulin test-positive (DAT-positive), indirect antiglobulin test-positive (IAT-positive), the complete set of autoantibodies, the full spectrum of vasculitis,

and the serum total IgE were all within the normal range. Serum ferritin level was 841.82 ng/mL. Peripheral blood smear: Neutrophil nuclei were shifted to the left, toxic granules were visible, and immature red and granulocytic cells were observed. Maturation red blood cells showed agglutination. The neutrophils exhibited 12% rods and 73% segmented nuclei, lymphocytes accounted for 7%, and monocytes for 12%. Abdominal Color Doppler Ultrasound: The left hepatic vein is dilated with partial tortuosity, gallbladder polyps, splenomegaly, and peritoneal effusion (deepest point 7.2 cm). The chest and abdomen/pelvic CT imaging demonstrated multifocal ground-glass opacities in the bilateral lungs (Figure 1A), along with partial thickening of interlobular septa and bronchial wall thickening, indicating eosinophilic infiltration; accompanied by splenomegaly, cholecystitis, gallbladder fossa effusion, abdominal and pelvic fluid accumulations, and periumbilical subcutaneous fat edema. Reviewing the medical history, liver function damage, ascites, and anemia were all new conditions diagnosed within the past year.

Upon admission, the patient's urine routine did not show red blood cells, and combined with jaundice, extravascular hemolysis was considered as a potential cause. Given the patient's clinical presentation of extravascular hemolytic anemia, characterized by anemia, jaundice, splenomegaly, along with elevated bilirubin levels, elevated lactate dehydrogenase, a reticulocyte count of 21.88% (greater than 4%), and a positive DAT, the diagnosis aligns with autoimmune hemolytic anemia (AIHA). The patient's hemoglobin level was 77g/l prior to admission, dropping to a minimum of 34g/l shortly thereafter, demonstrating a sharp decline over a short period. This prompted consideration of a relapse of EGPA complicated by AIHA. Concurrently, it was recommended that the patient undergo a bone marrow aspiration to clarify the presence of hematologic disorders; however, the patient refused the procedure.

Upon admission, the patient received a transfusion of two units of washed red blood cells and was initiating pulse therapy with methylprednisolone at 200mg and intravenous immunoglobulin at 20g daily for a three-day period. Following this, the dose of methylprednisolone was progressively reduced. On April 22, a 0.4g dose of intravenous cyclophosphamide was introduced. As a result, hemoglobin levels elevated slowly. Simultaneously, supportive therapies comprising anti-infection, hepatoprotection, anti-seizure medication, and diuretics were administered, leading to symptom improvement and the subsequent hospital discharge of the patient. Following discharge, two weeks later, the patient received cyclophosphamide 0.4g sequentially via intravenous infusion, while taking methylprednisolone tablets at a dose of 60mg per day orally. Subsequently, during the outpatient follow-up, the methylprednisolone was sequentially tapered down to a maintenance dose of 6mg per day, and cyclophosphamide was discontinued after accumulating a total dose of 7g.

The Third Admission to Hospital

On August 9, 2023, the patient was admitted to the hospital with anorexia that had persisted for over two months. She also reported chest tightness and asthma, but no nausea or vomiting. Bowel movements were normal, with no signs of melena or hematochezia. The outpatient blood routine indicated hemoglobin of 68.0 g/l, C-reactive protein of 46.43 mg/l,

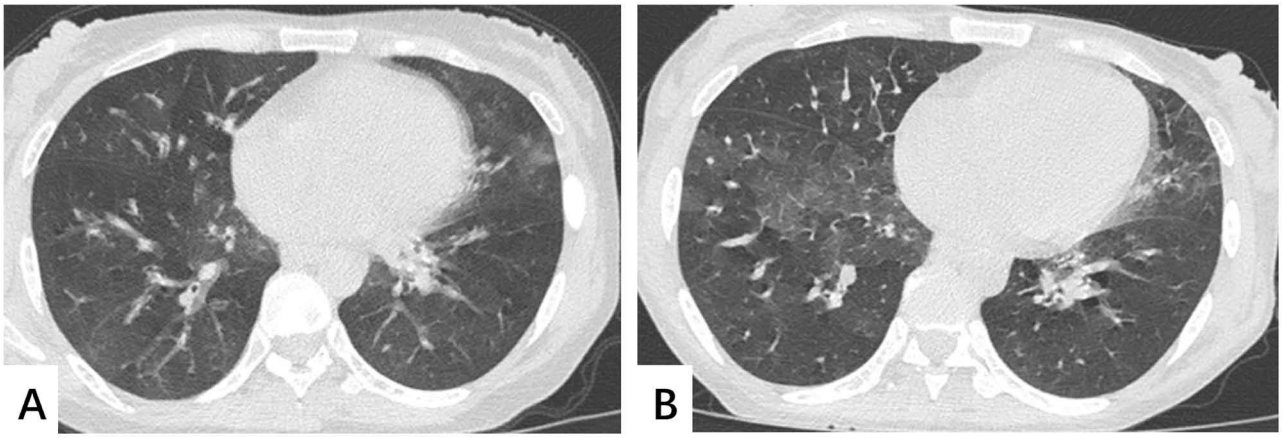

Figure 1 Lung computed tomography (CT) images. (**A**) Bilateral lungs show multiple ground-glass opacities, accompanied by partial thickening of the interlobular septa and bronchial wall thickening. (**B**) Bilateral lungs display multiple ground-glass opacities, with some interlobular septa thickening, showing progression compared to (**A**).

white blood cells of 4.25×10^9/l, eosinophils of 0.17×10^9/l, total bilirubin of 34.65 μmol/l, aspartate aminotransferase of 42 U/l, and alanine aminotransferase of 10 U/l. On admission, the physical examination revealed a body temperature of 36.5 °C, a heart rate of 68 beats per minute, a respiratory rate of 20 breaths per minute, and blood pressure of 98/63 mmHg. The patient appeared pale, with mild jaundice of the sclera, no petechiae or ecchymosis on the skin, and no edema in the lower extremities. On August 10, examination: hemoglobin 72.0 g/l, C-reactive protein 34.79 mg/l, erythrocyte sedimentation rate 2.0 mm/h; urine routine leukocytes, erythrocytes, bacteria are increased; complement, rheumatoid factor, autoantibodies, anti-CCP antibody, cardiolipin antibody showed no apparent abnormalities.

Treatment included intravenous administration of methylprednisolone at a dose of 20mg daily for a duration of 7 days. Following this regimen, the patient's body temperature escalated to 38.2°C. A subsequent review revealed a hemoglobin level of 41.0g/l, with a significant increase in total bilirubin levels and abnormalities in liver function. The anemia deteriorated progressively, yet there were no manifestations of active bleeding. Subsequent chest CT reevaluation demonstrated a progressive increase in bilateral ground-glass opacities compared to the prior scan (Figure 1B). Abdominal ultrasound imaging disclosed the presence of ascites and splenomegaly. Given that the patient had not been prescribed additional immunosuppressive agents to sustain remission following cessation of cyclophosphamide, a thorough clinical evaluation resulted in a diagnosis of EGPA complicated by AIHA recurrence.

The patient was treated with a second course of methylprednisolone at 200mg for 5 days combined with high-dose intravenous immunoglobulin 10g for 3 days, alongside the administration of two units of washed red blood cells. Subsequently, the methylprednisolone dose was tapered to 120mg/day for 5 days and then to 80 mg/day for 4 days, with the addition of mycophenolate mofetil (MMF) 1g/day. The patient's condition improved, leading to discharge from the hospital, with follow-up visits scheduled at two-week intervals. Following discharge, the patient was prescribed prednisone 60mg daily and MMF 0.5g twice daily. The patient remained asymptomatic with no recurrence of symptoms, and the ascites resolved gradually. Upon continued routine follow-up, the prednisone dose was tapered down to 10 mg daily, while the MMF regimen remained unchanged.

Discussion

EGPA is defined by eosinophil-rich, necrotizing granulomatous inflammation, predominantly affecting the respiratory tract, accompanied by necrotizing vasculitis involving small-to-medium vessels. It is strongly associated with bronchial asthma and peripheral blood eosinophilia.[4] In addition to distinguishing EGPA from bronchial asthma, the differential diagnosis should include chronic eosinophilic pneumonia (CEP), hypereosinophilic syndrome (HES), allergic bronchopulmonary aspergillosis (ABPA), granulomatous polyangiitis (GPA), among others. Cryptogenic organizing pneumonia (CEP) is a rare, idiopathic interstitial lung disease that primarily affects middle-aged women, presenting with symptoms such as cough, fever, dyspnea, fatigue, and malaise.[5] When systemic vasculitis manifestations occur, asthma and a slightly lower sensitivity to corticosteroids tend to favor the diagnosis of EGPA.[6] HES has been divided into multiple subgroups based upon clinical, laboratory, and molecular features. Major categories of HES include myeloproliferative HES (M-HES) and lymphocytic HES (L-HES), with some other well-defined clinical entities.[7] The most common systems involved in HES include hematologic, cutaneous, cardiovascular, pulmonary, and neurologic, among others, and it is most often misdiagnosed as EGPA. However, asthma is generally rare in the clinical manifestations of HES and generally does not involve the lungs, and the pathology is generally free of vasculitis and granulomatous changes, and there is no positive manifestation of ANCA.[8–11] ABPA is generally caused by Aspergillus fumigatus sensitization, belongs to the hypersensitivity reaction, in the respiratory system, the clinical manifestations are similar to EGPA, may be accompanied by bronchodilation, serum total IgE levels exceed 1000U/mL, skin test Aspergillus tachyphylaxis reaction is positive, serum Aspergillus specific IgG is elevated and/or precipitin positive.[12] ABPA infrequently involves systems other than the respiratory system, ANCA is often negative, and pathology is free of vasculitis and granulomas.[12–14]

Currently, no validated diagnostic biomarkers are available to reliably differentiate EGPA from other disorders. Approximately 75% of active EGPA patients have elevated IgG4 levels, which is associated with disease activity.[15] Serum eotaxin-3 levels are significantly elevated in patients with active EGPA, demonstrating a sensitivity of 87.5% and specificity of 98.6%, which positions it as a promising and reliable diagnostic biomarker for EGPA.[16] The primary driver

of disease in EGPA is the CD4 + T helper cell, in particular the type 2 (Th2) subtype. The tissue recruitment of Th2 cells is likely mediated by specific chemokines, such as CCL17, which is primarily produced by dendritic cells and shows a significant correlation with peripheral blood eosinophil counts.[11,17] Th2 cells primarily produce type 2 cytokines, specifically interleukin (IL)-4, IL-5, and IL-13.[18] IL-5 inhibition with mepolizumab has proven effective as a treatment for EGPA. Data-independent acquisition(DIA) combined with parallel reaction monitoring(PRM) mass spectrometry validated four new potential serum biomarkers, including SAA1, FGA, SAP, and CETP, that can be used to distinguish EGPA from severe asthma.[19] However, the diagnostic value of these potential biomarkers should be validated by other method.

EGPA can lead to multiorgan complications, with reported manifestations including heart failure, spontaneous splenic rupture, glomerulonephritis, diffuse alveolar hemorrhage, atopic dermatitis, optic perineuritis, and myasthenia gravis, among others.[20–26] Concurrent autoimmune hemolytic anemia (AIHA) is seldom reported in conjunction with EGPA. AIHA is characterized by the accelerated destruction of red blood cells, a process mediated by autoantibodies that target self-erythrocyte antigens. Approximately 80–90% of AIHA cases manifest as chronic extravascular hemolysis, marked by a stealthy onset, a higher prevalence in adult females, and classic symptoms including anemia, jaundice, and splenomegaly. Clinically, one-third of patients exhibit overt hemolysis with jaundice, over half present with mild-to-moderate splenomegaly, and one-third develop hepatomegaly. AIHA may develop secondary to immune or lymphoproliferative disorders, including chronic lymphocytic leukemia (CLL), systemic lupus erythematosus (SLE), and common variable immunodeficiency.[27] The patient's AIHA is presumably secondary to EGPA, considering the clinical association with this immune-mediated condition. Additionally, ascites was diagnosed during the second evaluation, having ruled out hepatic, cardiac, or neoplastic causes. The resolution of ascites post-therapy further supports the diagnosis of eosinophilic ascites.

The management of EGPA is guided by the assessment of disease severity using the Five-Factor Score (FFS), revised in 2011, to stratify patients and tailor treatment regimens. For patients with mild disease (FFS=0), glucocorticoid monotherapy is enough.[28] Glucocorticoid, especially prednisolone, is the first-line drug for EGPA, with an initial dose of 0.5~1 $mg \cdot kg^{-1} \cdot d^{-1}$.[29] In cases of multiple organ involvement or refractory disease, the administration of immunosuppressants, such as cyclophosphamide, methotrexate, and azathioprine, among others, is recommended.[29] Cyclophosphamide is most commonly used by oral administration of 2 $mg \cdot kg^{-1} \cdot d^{-1}$ or intravenous drip of 15 mg/kg every 2 weeks. Following three consecutive administrations of the intravenous route, the dosage may be reduced to once every three to four weeks. Following a 3- to 6-month period, the treatment can be transitioned to methotrexate or azathioprine for maintenance therapy.[29] The administration of glucocorticoids in combination with cyclophosphamide is recommended to induce remission in cases of new or recurrent EGPA accompanied by organ-threatening or life-threatening manifestations.[30] In refractory cases, adjunctive therapies such as intravenous immunoglobulin (IVIG) pulse therapy, tumor necrosis factor-α (TNF-α) inhibitors, and CD20 monoclonal antibodies may be utilized.[29] Mycophenolate mofetil is a widely used immunosuppressive drug. Mycophenolate mofetil appears to be well tolerated and effective in inducing disease remission among patients with newly diagnosed or relapsing EGPA.[31] Furthermore, the employment of biological agents such as Rituximab, Benralizumab, Mepolizumab, and Dupilumab has been extensively utilized. In the early 2000s, rituximab emerged as the first effective drug to replace cyclophosphamide. It has demonstrated particular efficacy in cases of recurrent diseases and has become increasingly selected as a first-line inducer. Its use has now expanded to encompass the longer-term prevention of recurrence.[32] The anti-interleukin 5 agent, mepolizumab, has been shown to reduce glucocorticoid usage, enhance remission rates, and decrease relapse rates in patients diagnosed with EGPA.[32] The study by Adrien et al demonstrated that benralizumab is an effective therapeutic agent for refractory asthma or ear-nose-throat (ENT) manifestations in EGPA, with a favorable safety profile.[33] However, its efficacy was notably reduced in patients who previously failed mepolizumab treatment or exhibited objective vasculitic features.[33] Dupilumab is relatively new to clinical practice with limited patient experience. The study by Berengere et al suggests that dupilumab may effectively treat uncontrolled asthma, ENT manifestations, or glucocorticoid-dependent symptoms in eosinophilic granulomatosis with polyangiitis (EGPA), while allowing for glucocorticoid dose reduction.[30] The patients in this article did not choose biological agents for economic reasons.

This patient had previously been diagnosed as having asthma. Ten years after initial presentation, the patient presented with persistent chest tightness and wheezing resistant to conventional therapy. Based on the presence of asthma symptoms, an elevated peripheral blood eosinophil count of >10%, pulmonary infiltrates non-fixed in the lungs, sinusitis, and neuritis, along with cutaneous lesions, the diagnosis of EGPA was confirmed. The patient had a rare complication of EGPA relapse complicated by AIHA at the second visit, which improved after glucocorticoid combined with gamma globulin pulse therapy and cyclophosphamide. Post-discharge, patients received low-dose hormone therapy in combination with maintenance cyclophosphamide. AIHA recurred following a year. Due to the recurrent EGPA accompanied by AIHA, the patient was treated anew with a combination of glucocorticoids and gamma globulin pulse therapy. Subsequently, therapy was revised to involve glucocorticoids in conjunction with mycophenolate mofetil sequential therapy. During subsequent outpatient follow-up visits, the patient's hemoglobin remained within the normal range without recurrence of symptoms indicative of anemia, ascites, or other systemic issues. Treatment outcomes met the anticipated goals.

Conclusion

Respiratory symptoms frequently serve as the initial presentation of EGPA and may be overlooked or inaccurately diagnosed due to the absence of diagnostic biomarkers. Clinicians should be cautious of patients with markedly elevated eosinophil levels in peripheral blood and should be more observant when assessing patients with a history of asthma and rhinitis for possible EGPA correlation. Concurrently, consideration must be given to other systemic symptoms that may arise after the diagnosis of EGPA. This is crucial, as it influences the selection of subsequent treatment strategies. Our report shows that the treatment of EGPA complicated by AIHA is still based on the treatment of the primary disease. Low-dose glucocorticoid and immunosuppressive maintenance therapy can effectively reduce recurrence in patients.

Abbreviations

EGPA, Eosinophilic granulomatosis with polyangiitis; ANCA, Antineutrophil cytoplasmic antibody; AIHA, Autoimmune hemolytic anemia; FFS, Five-factor score; MMF, Mycophenolate mofetil.

Ethical/Copyright Corrections

The manuscript has been approved by the institution (The Third Affiliated Hospital of Anhui Medical University) and can be published. The approval code is 202504101.

Informed Consent

Written informed consent was obtained from the patient to publish the details of the case.

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We thank the patient for granting permission to publish this information.

Disclosure

The authors report no conflicts of interest in this work.

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