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Case report

Successful treatment with mepolizumab for allergic bronchopulmonary mycosis complicated with bilateral septic arthritis of the knee joints caused by Methicillin-resistant *Staphylococcus aureus*

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ABSTRACT

We report the case of a 50-year-old man with allergic bronchopulmonary mycosis (ABPM) complicated with bilateral septic arthritis of the knees caused by Methicillin-resistant *Staphylococcus aureus* (MRSA). He had a background of bronchial asthma and end-stage renal failure on maintenance dialysis. He was treated with 30 mg/day of prednisolone for 14 days for ABPM. He developed bilateral septic arthritis of the knees, caused by MRSA during prednisolone treatment. He underwent bilateral arthroscopic washout with a 2-week course of intra-articular arbekacin, concomitantly treated with a 6-week course of intravenous teicoplanin and oral rifampicin, subsequently followed by oral linezolid treatment. However, he suffered exacerbation of ABPM during treatment of septic arthritis. Because of these serious infectious complications, he was treated with mepolizumab instead of corticosteroids for the ABPM, which resolved all symptoms and clinical features. This case highlights mepolizumab treatment as an alternative to corticosteroid therapy for treatment of ABPM in patients with comorbidities such as infection.

1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an eosinophilic pulmonary disease resulting from a hypersensitivity reaction to *Aspergillus* species colonizing the airways, predominantly in patients with asthma or cystic fibrosis [1,2]. Recently, it has been recognized that fungi other than *Aspergillus* species can cause the same symptoms, and collectively these diseases are called allergic bronchopulmonary mycosis (ABPM) [3]. Because ABPM is caused by a hypersensitivity reaction to bronchial colonization by some fungi, standard treatment comprises a combination of systemic corticosteroids and anti-fungal agents. Some patients with ABPM, however, do not respond or are intolerant of this standard therapy due to comorbidities. In this report, we describe a case of ABPM successfully treated with mepolizumab, a humanized anti-IL-5 antibody. This treatment was selected due to complications with bilateral septic arthritis of the knees caused by Methicillin-resistant *Staphylococcus aureus* (MRSA).

2. Case report

A 50-year-old man was admitted to Hamanomachi Hospital with a three-week history of painful bilateral knee joints. He claimed that his knee pain started after repeated jet-skiing. He underwent acupuncture treatment around both knee joints, but knee pain was exacerbated. His medical history includes end-stage renal failure due to focal glomerulosclerosis and maintenance dialysis for more than a year, and bronchial asthma over twenty years. He was treated with fluticasone furoate and vilanterol trifenatate. He did not smoke and had no history of dust exposure.

He complained of a persistent cough with sputum since one month before admission. Physical examination revealed rhonchi and crackles. His chest X-ray image showed newly emerging club-shaped masses in both lung fields (Fig. 1). Chest computed tomography (CT) showed central bronchiectasis, mucoid impaction, and tree-in-bud opacities (Fig. 2A). Densities of mucoid impactions were higher than those of paravertebral muscles (80–90 Hounsfield Unit [HU] vs. 40–60 HU,

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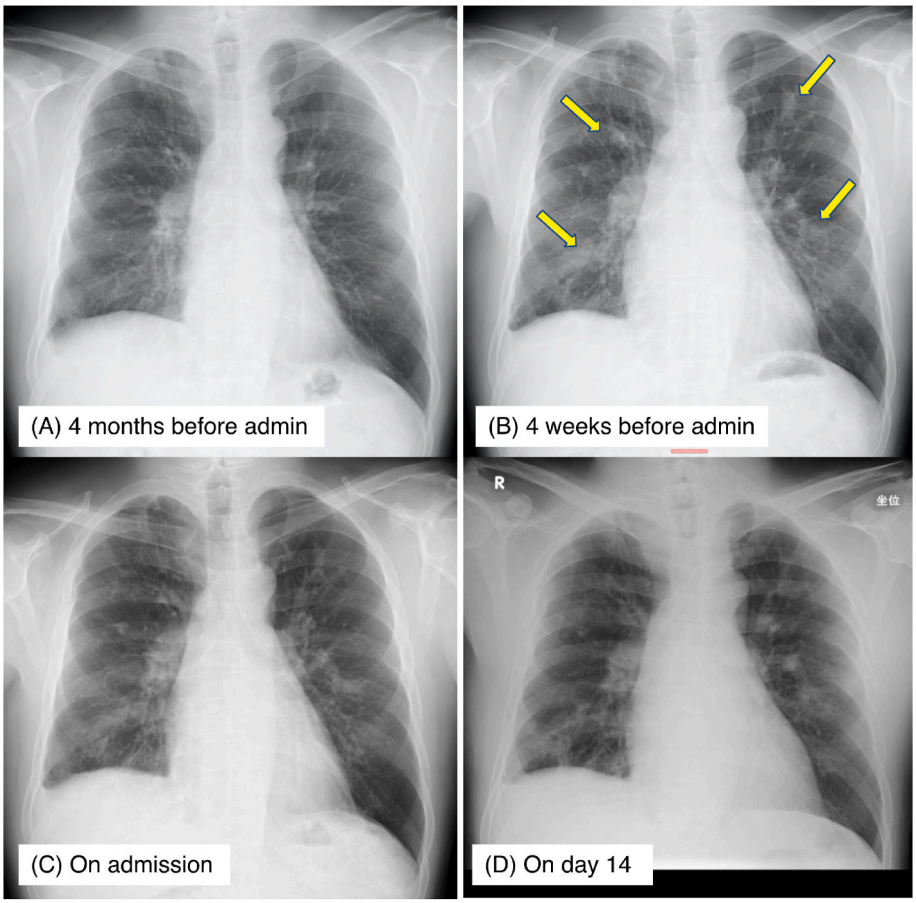

Fig. 1. Chest radiographic images of the patient. Chest X-ray images 4 months before admission (A), 4 weeks before admission (B), on admission (C), and admission on day 14 (D). Arrows indicate newly emerging club-shaped masses in both lungs. The image on day 14 was performed by bedside X-ray in the anteroposterior (AP) sitting position.

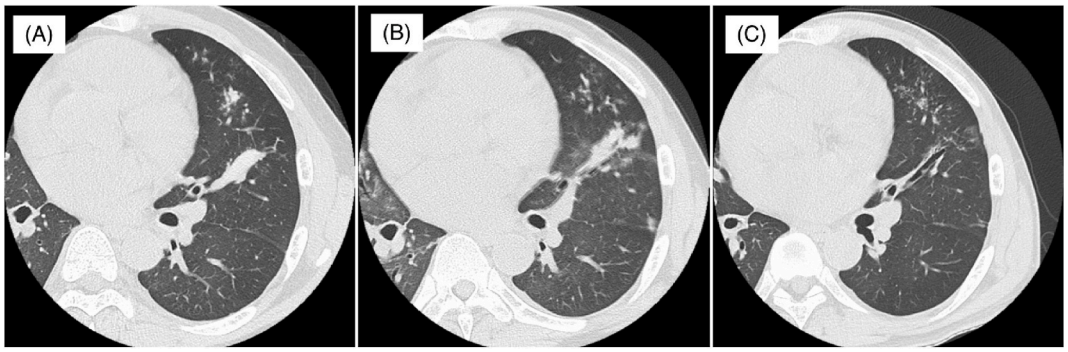

Fig. 2. Chest CT images of the patient. (A) Mucus plugging and tree-in-bud opacities were apparent before prednisolone treatment and (B) at the time of mepolizumab treatment. (C) Mucus plugging was resolved 43 days after mepolizumab treatment.

respectively). Laboratory examination showed peripheral blood eosinophilia (1906/μL) and an extremely elevated total serum IgE value of 6000 IU/mL. Specific IgE against *Aspergillus fumigatus* later proved positive (26.8 UA/mL). Pulmonary function testing was unavailable due to the global *Coronavirus* pandemic (COVID-19). He was clinically diagnosed with allergic bronchopulmonary aspergillosis/mycosis (ABPA/ABPM) (Table 1) and treatment was initiated with 30 mg/day of prednisolone 12 days before admission (Fig. 3). Mucus plugs were later confirmed by bronchoscopy after admission (Fig. 4), although fungal hyphae were not detected, presumably because of the effect of treatment. *Aspergillus fumigatus* was the most suspect allergen in this case, based on the specific IgE result, but we prefer to consider the condition as ABPM, because of the lack of a positive culture for *Aspergillus* species.

On admission, he had a temperature of 36.5 °C (afebrile, possibly because of prednisolone treatment), blood pressure of 138/77 mmHg, a heart rate of 86 beats per minute, oxygen saturation of 98% under room air. Chest auscultation revealed no murmur nor wheezes. Both of his knees were swollen and warm. He had difficulty in bearing weight on his knees and exhibited tenderness in both. Hip and ankle joints were normal. Laboratory examination revealed elevated inflammatory markers, with a white blood cell (WBC) count of 12.8 × 10^3/μL (Neutrophils 10.7 × 10^3/μL, Eosinophils 500/μL) and C-reactive protein (CRP) of 17.20 mg/dL. Although his chest X-ray showed persistent club-shaped masses in both lung fields (Fig. 1C), no abnormal respiratory

Table 1
Application of new clinical diagnostic criteria for allergic bronchopulmonary mycosis to this case. Diagnosis for ABPM: meet 6 or more of the criteria below, proposed by the Japan ABPM research program [4]. This case met 7 criteria.

	THIS CASE	CRITERIA
1	○	Current or previous history of asthma or asthmatic symptoms
2	○	Peripheral blood eosinophilia (≧ 500 cells/mm^3)
3	○	Elevated total serum immunoglobulin E levels (IgE ≧ 417 IU/mL)
4	○	Immediate cutaneous hypersensitivity or specific IgE for filamentous fungi
5		Presence of precipitins or specific IgG for filamentous fungi
6		Filamentous fungal growth in sputum cultures or bronchial lavage fluid
7		Presence of fungal hyphae in bronchial mucus plugs
8	○	Central bronchiectasis on computed tomography (CT)
9	○	Presence of mucus plugs in central bronchi, based on CT or mucus plug expectoration history
10	○	High attenuation mucus in the bronchi on CT

sounds with improved eosinophilia (Fig. 3) suggested the partial effect of prednisolone treatment for ABPM. An MRI of the right knee revealed a small amount of fluid retention in the knee joint and a hyperintense signal in soft tissues of the medial aspect of the lower leg by T2 weighted-image sequencing (Fig. 5A). There was also synovitis around the suprapatellar capsule. A needle aspiration from the right knee revealed thick, cloudy pus with Gram-positive cocci being phagocytosed by neutrophils (Fig. 5B). which proved to be MRSA. Blood cultures were also positive for MRSA. Empirical intravenous ceftriaxone and teicoplanin (TEIC) were administered, but ceftriaxone was discontinued on day 3, when the culture results proved positive for MRSA.

He was then given bilateral knee arthroscopies and washouts on day 3. Cultures from the left synovial fluid were also positive with MRSA. He was thus diagnosed with bilateral septic arthritis of the knees caused by MRSA. He underwent a 2-week course of intra-articular arbekacin with oral rifampicin. An echocardiogram revealed no vegetations, and subsequent blood cultures were negative.

He suffered shortness of breath with wheezing from day 9. Considering the exacerbation of ABPM, he was treated with 200 mg of

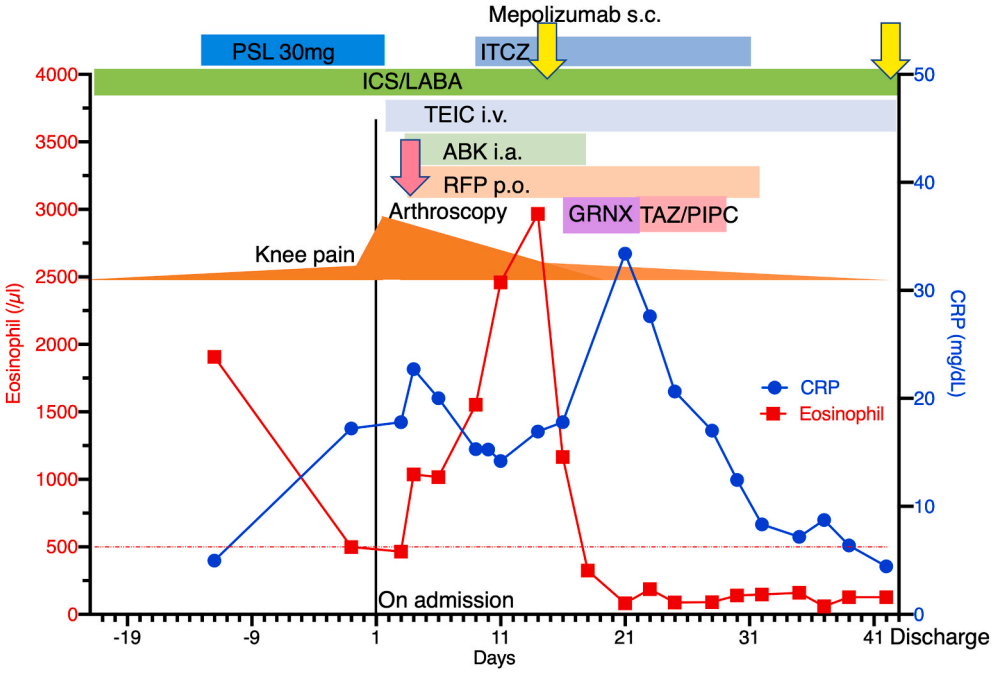

Fig. 3. Clinical course of the case. The patient was treated with 30 mg/day of prednisolone (PSL) for ABPM starting 12 days before admission. He developed bilateral septic arthritis of the knees caused by Methicillin-resistant *Staphylococcus aureus* (MRSA) during prednisolone treatment. He underwent bilateral arthroscopic washout with a 2-week course of intra-articular arbekacin (ABK), concomitantly treated with a 6-week course of intravenous teicoplanin (TEIC) and oral rifampicin (RFP). He suffered exacerbation of ABPM during treatment of the septic arthritis and was treated with mepolizumab on admission day 15. Garenoxacin (GRNX) followed by tazobactam/piperacillin (TAZ/PIPC) was transiently administered for the treatment of bronchopneumonia by *Pseudomonas aeruginosa* from day 16 to day 27. He was discharged on day 43.

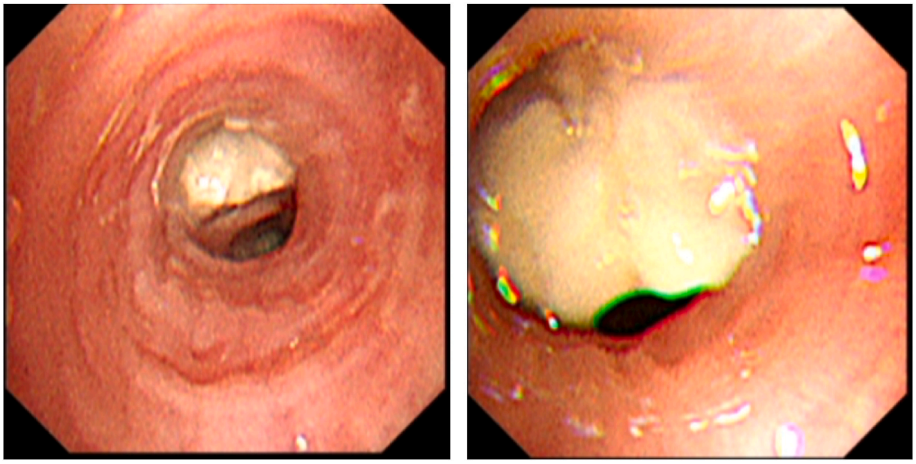

Fig. 4. Bronchoscopic findings showing a mucoid plug in the left lingular bronchus.

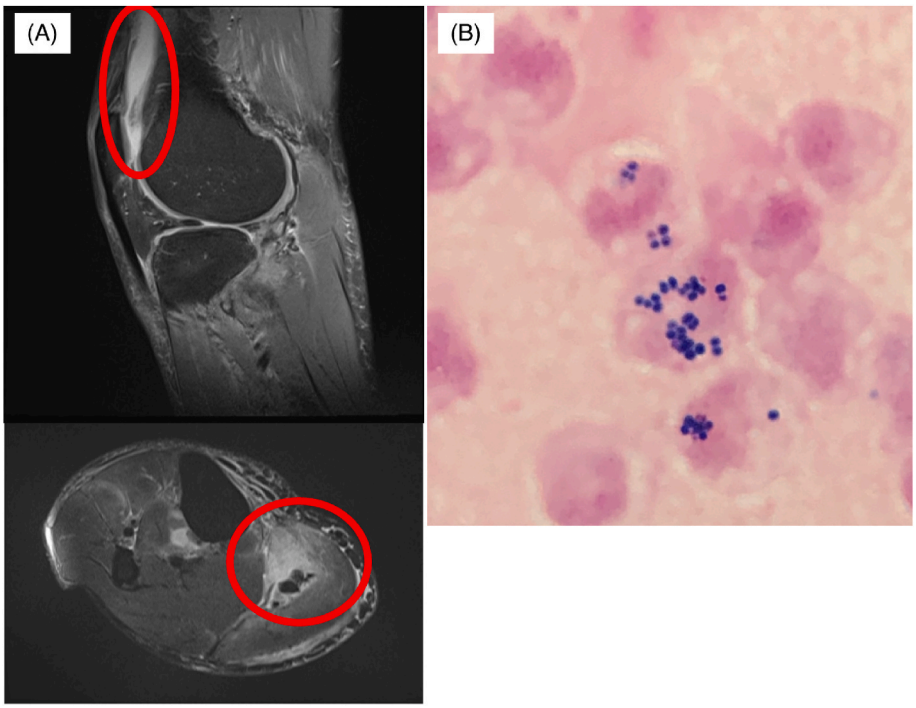

Fig. 5. Clinical features of septic arthritis of the knee. (A) An MRI of the right knee revealed a small amount of joint fluid retention in the knee and a hyperintense signal in the soft tissues of the medial aspect of the lower leg, based on T2 weighted-image sequencing. (B) Gram stain of knee synovial fluid showed Gram-positive cocci being phagocytosed by neutrophils.

itraconazole, which did not improve his symptoms. Eosinophil cell count rose linearly, reaching 2966/μL on day 14 (Fig. 3). Laboratory examination showed sustained elevation of CRP level (16.9 mg/dL). His oxygen saturation dropped below 90% in room air on day 14. His chest X-ray showed newly emerging lung infiltration in the right lower lung field compared to that on admission (Fig. 1D). Cultures from sputum on day 13 were positive with *Pseudomonas aeruginosa*. Causes of respiratory deterioration were clinically indistinguishable from exacerbation of ABPM and bronchopneumonia caused by *Pseudomonas aeruginosa*. We therefore decided to address both possible situations. One of the reasons for this was the difficulty in assessing the presence of respiratory infections serologically due to the complication of bilateral septic arthritis. We used mepolizumab instead of systemic corticosteroid for exacerbation of ABPM. Garenoxacin followed by tazobactam/piperacillin was transiently administered for treatment of *Pseudomonas aeruginosa* bronchopneumonia from day 15 to day 27 (Fig. 3). Eosinophil cell count dramatically decreased after mepolizumab administration. Accordingly, his respiratory symptoms and oxygen saturation gradually improved.

He showed a good recovery with a 6-week course of intravenous teicoplanin and oral rifampicin for his septic arthritis. He was discharged on day 43, replacing intravenous teicoplanin with oral linezolid. The IgE level tended to decrease at 5220 IU/mL, and mucus plugging was resolved 43 days after mepolizumab treatment (Fig. 2C). No relapse of septic arthritis nor exacerbation of ABPM was observed for two months after discharge.

3. Discussion

We report a case of ABPM, complicated with bilateral septic arthritis of the knee joints, that was successfully treated with mepolizumab. First, we employed new diagnostic criteria for ABPM proposed by the Japan ABPM research program [4]. The new criteria showed higher sensitivity and specificity for ABPM (94.4% and 96.0%, respectively), compared to the Rosenberg-Patterson criteria proposed in 1977, or the International Society for Human and Animal Mycology (ISHAM) criteria proposed in 2013 [4]. Moreover, the new criteria are practical for ABPM screening since they show improved AUC (= 0.95) for ROC curve analysis, compared to previous criteria, even in the absence of pathological examinations of mucus plugs [4]. Indeed, in this case we were able to diagnose ABPM without positive fungal hyphae in mucus plugs.

In general, systemic corticosteroids are considered the mainstay of treatment of acute ABPM, based on results of case series and studies [5–7]. Because of the serious infectious disease, however, it was difficult to use systemic corticosteroids for exacerbation of the ABPM. Since antifungal therapy is reportedly effective [2,7–9], we then chose itraconazole as a second choice for the exacerbated ABPM; however, it resulted in no improvement at all. Molecular targeted drugs have been used for refractory asthma, including omalizumab (anti-IgE), mepolizumab (anti-IL-5), and dupilumab (anti-IL-4R) [10]. These drugs have potential to improve ABPM, and several case reports found omalizumab, mepolizumab, or dupilumab efficacious for treatment of ABPM.

Omalizumab, a humanized anti-IgE monoclonal antibody, is reportedly beneficial in treatment of ABPM in cases of uncontrolled asthma [11,12]. Dosing of omalizumab follows a nomogram based on weight and total serum IgE levels. However, the nomogram may be difficult to apply to ABPM due to high levels of serum IgE. The level of serum IgE was over 6000 IU/mL (out of range) in this case, calling for doses above the nomogram-based upper limit. Indeed, some case reports describe an insufficient efficacy of omalizumab for ABPM [13]. We thus doubted the efficacy of omalizumab in this case and decided not to use it.

Mepolizumab, a humanized monoclonal antibody against IL-5, inhibits binding of IL-5 to its receptor, leading to suppression of eosinophil activation. Therefore, we expected mepolizumab to be efficacious for treatment of ABPM. Several cases of ABPM treated with mepolizumab have been reported so far [14–20]. All were controlled, and none of these patients experienced adverse events with mepolizumab. Activated eosinophils can reveal a non-apoptotic cell death pathway, named eosinophil extracellular trap cell death (EETosis) that mediates eosinophil cytolytic degranulation [21]. EETosis contributes to formation of mucoid impaction [21] and trapping of fungi. As Hirota et al. reported [14], inhibition of eosinophilic activation by mepolizumab might lead to

suppression of mucoid impaction, which resulted in improvement of ABPM.

Dupilumab, a humanized monoclonal antibody against IL-4 receptor, also has potential for treatment of ABPM [13,22]. We had no idea whether mepolizumab or dupilumab was preferable for this case from the perspective of biological effects. We chose mepolizumab just because of the longer treatment interval (mepolizumab every four weeks, dupilumab every two weeks). As with application of different biologics in severe asthma, there are problems related to selection criteria. Further study will be needed to determine the appropriate role and selection guidelines of biologics in ABPM.

In this case, the patient was on maintenance dialysis. Based on population pharmacokinetic analyses, mepolizumab clearance was similar between patients of hyper-eosinophilic syndrome with creatinine clearance values between 50 and 80 mL/min and patients with normal renal function [23]. Although there are no data available in subjects with creatinine clearance values less than 50 mL/min, renal impairment should not affect mepolizumab pharmacokinetics, as mepolizumab is not filtered by the kidney due to its high molecular weight, as with other biologics [24]. Mepolizumab is thought to be metabolized by ubiquitous proteolytic enzymes [24].

Septic arthritis is an infection in a joint, often destructive, and usually caused by bacteria. Predisposing factors include advanced age, pre-existing joint disease, skin or soft tissue infection, intravenous drug use, immunosuppression, and recent joint surgery or injection [25–28]. Although the knee is the most common joint involved in septic arthritis (>50%) [29], bilateral involvement is rare. In this case, the patient's background of end-stage renal failure on maintenance dialysis may have increased the chance of hematogenous seeding of MRSA from the skin, providing an immune-suppressed condition. Treatment with prednisolone further suppressed the immune system. Injury of the knees by repeated jet-skiing probably increased the chance of MRSA to adhere to synovial tissues. Acupuncture treatment around both knee joints may have seeded bacteria into the joint, as previously reported [30]. All of these conditions synergistically resulted in severe bilateral septic arthritis, which complicated therapy.

In conclusion, this case highlights biologic treatment such as mepolizumab as an alternative to corticosteroid therapy for treatment of ABPM in patients with infections.

Patient consent for publication

Written informed consent was obtained from the patient.

Declaration of competing interest

The authors declare no conflict of interest.

Conflicts of interest

All authors of the manuscript declare that there are no conflicts of interest.

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