Adverse skin reactions secondary to sintilimab for advanced gastric adenocarcinoma: A case report and literature review

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Abstract. Immune checkpoint inhibitors, a class of anticancer drugs, which act via enhancing T cell responses against tumor cells, are associated with immune-related adverse events. The skin is one of the most commonly affected organs. In the present study, a case of a 78-year-old man, who developed systemic eczema dermatitis due to neoadjuvant treatment of locally advanced gastric adenocarcinoma with sintilimab combined with Tigio plus oxaliplatin regimen, was reported. The eczema dermatitis completely subsided after treatment with methylprednisolone. The patient and his family strongly requested surgical intervention. Postoperative pathology revealed a pathological complete response.

Introduction

In the past few decades, cancer treatment has advanced into the era of immunotherapy. Immune checkpoint inhibitors (ICIs) are increasingly used against particular types of cancer and have achieved significant therapeutic effects (1). Sintilimab, a humanized monoclonal immunoglobulin G4 antibody, acts as a programmed cell death protein-1 (PD-1) antagonist. Therefore, it blocks the interaction between PD-1 and its ligands, namely programmed cell death ligand 1 (PD-L1) and PD-L2, thus alleviating immunosuppressive effects and activating T cell functions (2). For advanced gastric adenocarcinoma, the combination of sintilimab and chemotherapy as first-line treatment could notably improve patient survival rates (3). Currently, the combination of sintilimab and chemotherapy as neoadjuvant therapy for gastric cancer displays significant safety and promising efficacy (4). However, severe skin toxicity cannot only impair the quality of life of patients, but also limit the effectiveness of cancer treatments (5). Although the incidence of immune-related adverse skin reactions in patients treated with sintilimab alone or in combination is rare, the associated mortality rate is notably high (6). In the present study, a case of a patient who experienced severe immune-related cutaneous adverse reactions during neoadjuvant therapy was reported. Following surgery, the aforementioned immune-related adverse event (irAE) reached a pathological complete response (pCR).

Case presentation

A 78-year-old man was admitted to the Nanjing Jiangning Hospital of Traditional Chinese Medicine (Nanjing, China); afterwards, the patient underwent a computed tomography (CT) examination, which revealed locally advanced gastric adenocarcinoma. The tumor had invaded the lower end of the esophagus and surrounding lymph nodes (Fig. 1A and B). Upon admission on February 5, 2024, gastroscopy confirmed the diagnosis of gastric adenocarcinoma (Fig. 1C and D). After dehydration, biopsy samples taken via gastroscopy were embedded in paraffin, sectioned, and subjected to pathological diagnosis and immunohistochemical analysis. The tissue sections were 4 μm thick. The primary antibody was a ready-to-use reagent purchased from Fuzhou Maixin Biotech Co., Ltd., incubated at 37˚C for 32 min. The secondary antibody, also a ready-to-use reagent from Roche Diagnostics, was incubated at 37˚C for 32 min. Microscopic images were captured using a light microscope with an objective lens at a x40 magnification.

Pathology results were consistent with adenocarcinoma (Fig. 1E) and immunohistochemistry revealed CKpan (+), CK8/18 (+), CK5/6 (-), P40 (-), Ki-67 (+; rate, 90%), Her-2 (1+), MLH (+), PMS2 (+), MSH2 (+), MSH6 (+). The PD-L1 combined positive score was 60 % (Fig. 1E). According with

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Abbreviations: ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; SOX, oxaliplatin and Tigio; PD-1, programmed death protein-1; PD-L1, programmed cell death ligand 1; S-1, Tigio; pCR, pathological complete response

Key words: sintilimab, eczema dermatitis, neoadjuvant treatment, postoperative pathology, pCR

the 8th edition of the American Joint Committee on Cancer staging system for gastric cancer and considering CT and endoscopy results, the patient was diagnosed with TNM stage of cT3-4aN2-3M0, Stage III (7). He was then treated with three cycles of neoadjuvant therapy with sintilimab (200 mg on day 1), oxaliplatin (150 mg on day 1) and Tigio (S-1; 40 mg in the morning, 60 mg in the evening on days 1-14). After the third cycle, the patient complained of sporadic rash with pruritus on the front chest, back and both lower limbs (Fig. 1F-H). The male patient was finally diagnosed with eczema dermatitis at the outpatient clinic of the Institute of Dermatology of the Chinese Academy of Medical Sciences. However, the homemade medication containing Triamcinolone Acetonide Cream (40 g), Allantoin Cream (40 g) and Vitamin E Cream (40 g) provided by the hospital had no effect and therefore the eczema dermatitis became more severe, gradually spreading from the lower limbs to the knees (Fig. 1I and J). The skin on both lower limbs was red, swollen and itchy (Fig. 1H).

On April 10, 2024, the patient was admitted again to the Nanjing Jiangning Hospital of Traditional Chinese Medicine. Upon hospital admission, the patient underwent comprehensive blood tests. The results revealed high-sensitivity C-reactive protein (CRP) levels of 5.52 mg/l, white blood cell (WBC) count of $3.66x10^9$/l, elevated monocyte rate of 15.4%, eosinophil rate of 10.2% and basophil rate of 1.3%. Additionally, hemoglobin (HGB) levels of 121 g/l and platelet count (PLT) of $129x10^9$/l were recorded. Coagulation tests revealed D-dimer and fibrin degradation product (FDP) levels of 3.56 mg/l and 7.36 μg/ml, respectively. Routine urinalysis, stool analysis, liver and kidney function tests, blood lipid, electrolyte, troponin I, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), carbohydrate antigen (CA) 19-9, CA24-2, CA50 and CA724 levels, and thyroid function and immune system parameters were all within normal ranges. The patient reported unbearable itching and could not stop scratching repeatedly. A dermatology consultation was requested. The patient had no history of any skin diseases and he was ultimately diagnosed with eczema dermatitis, which was likely caused by the medication. The dermatologist recommended oral desloratadine citrate disodium tablets and topical halometasone ointment. The patient also received intravenous infusion of 40 mg methylprednisolone daily for five consecutive days. After five days, he switched to 20 mg methylprednisolone for two days, followed by administration of 25 mg prednisone for one week. After treatment, eczema dermatitis significantly improved (Fig. 2A and B), while the follow-up CT scan revealed that the mass of the soft tissue at the fundus of the stomach was significantly reduced, while the surrounding lymph nodes were smaller (Fig. 2C and D).

On April 25, 2024, the patient was re-admitted to the Nanjing Jiangning Hospital of Traditional Chinese Medicine to evaluate the indications for surgery, since he and his family strongly requested surgical treatment. Therefore, on April 26 gastroscopy was performed, which revealed inflammation at the cardia and chronic gastritis with hyperplastic-like protrusions (Fig. 2E and F). Preoperative blood tests revealed: High-sensitivity CRP levels of 2.78 mg/l, WBC count of $8.92x10^9$/l, lymphocyte percentage of 17.8%, and elevated neutrophil and monocyte counts of $6.55x10^9$/l and $0.67x10^9$/l, respectively. HGB was 142 g/l, while PLT count was reduced to $100x10^9$/l. Furthermore, coagulation tests revealed increased D-dimer (1.11 mg/l) and FDP (5.13 μg/ml) levels. Lipid profile displayed enhanced triglyceride (2.08 mmol/l) and total cholesterol (6.50 mmol/l). Finally, routine urinalysis, stool analysis, liver and kidney function tests, electrolyte, CEA, AFP, CA19-9, CA24-2, CA50 and CA724 levels and the infectious disease panel results were all within normal limits.

On April 27, 2024, the patient underwent total gastrectomy, esophagojejunal Roux-en-Y anastomosis and abdominal lymph node dissection at the Gastrointestinal Surgery Department of the Nanjing Jiangning Hospital of Traditional Chinese Medicine. The postoperative pathology indicated chronic inflammation of the cardiac mucosa, while no residual cancer tissue was found on the upper and lower resection margins. No cancer metastasis was detected in the lymph nodes around the cardia (0/13; Fig. 2G and H). Based on the pathological results, the patient's response evaluation suggested pCR (Fig. 3).

On June 3, 2024, follow-up chest and abdominal CT scans revealed no signs of tumor recurrence or lymph node enlargement, indicative of malignancy. Tumor marker levels, including those of CEA, AFP, CA199, CA24-2, CA50 and CA724, were all within normal ranges. The patient is currently undergoing regular follow-up examinations and has not received any further antitumor therapy.

Discussion

A literature review identified 33 cases of adverse reactions associated with sintilimab, including eight cases involving skin-related complications (Table I). Among the aforementioned eight cases, three cases of toxic epidermal necrolysis, one case of lichenoid mucocutaneous reactions, one of lichenoid dermatitis, one of refractory pruritus, one of bullous pemphigoid and one of eczema dermatitis, were recorded. All eight patients demonstrated improvement after treatment.

Gastric cancer remains one of the most common types of cancer and still exhibits the 3rd highest mortality rate among all cancers (16). Due to its molecular and phenotypic diversity, the main treatment approach for early-stage gastric cancer is endoscopic resection. However, since the majority of patients with gastric cancer are diagnosed in the middle or late stages of the disease, non-early operable gastric cancer is commonly treated with surgery. Emerging evidence has suggested that perioperative and adjuvant therapies can improve the survival rate of patients with gastric cancer (17,18). In China, immunotherapy combined with chemotherapy has been approved as a first-line treatment strategy for advanced gastric cancer (19). A previous study demonstrated that the adoption of the S-1 plus oxaliplatin and Tigio (SOX) regimen combined with a PD-1 inhibitor could improve the pathological response rate in patients with locally advanced gastric cancer (20). Sintilimab, an immune drug independently developed in China, has demonstrated significant efficacy in treating several types of malignant tumors (21). However, while immunotherapy has notably improved patient prognosis, it has also been associated with immune-related adverse events (irAEs).

Skin toxicities are the most commonly reported irAEs associated with ICIs (22). A wide range of dermatological manifestations, varying in severity, can occur in patients treated with ICIs, including vitiligo, lichenoid dermatitis, psoriasis,

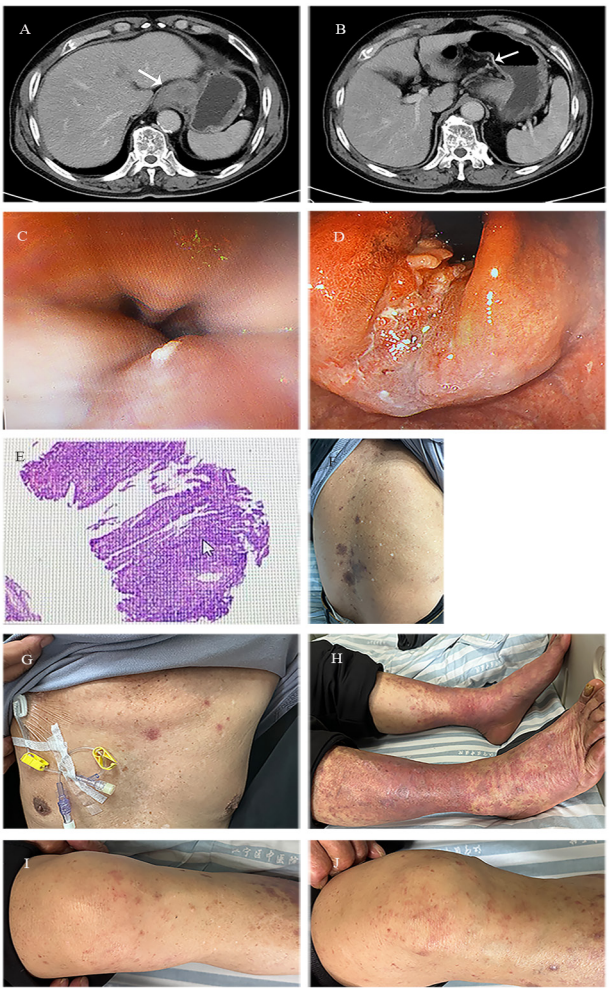

Figure 1. Radiological, endoscopic, pathological findings of gastric cardia adenocarcinoma and patient's skin before and after therapy. (A) Computed tomography scan revealed a mass of soft tissue in the fundus of the stomach, with uneven and moderate enhancement, with more pronounced enhancement in the edges, and an irregular serosal surface. (B) Multiple mildly enhanced and slightly enlarged lymph nodes were detected around the fundus of the stomach. (C) Gastroscopy revealed cardia stenosis, thus making it difficult for the gastroscope to pass through. (D) The gastroscopic findings indicated that the cardia extended to the lower esophagus and the fundus of the stomach, with a large irregular bulge, surface erosion, white coating and unclear boundaries. The biopsy was brittle and easily bleeding. (E) The pathological diagnosis was cardiac adenocarcinoma. (F-J) Prior therapy, the patient developed a widespread rash all over the body.

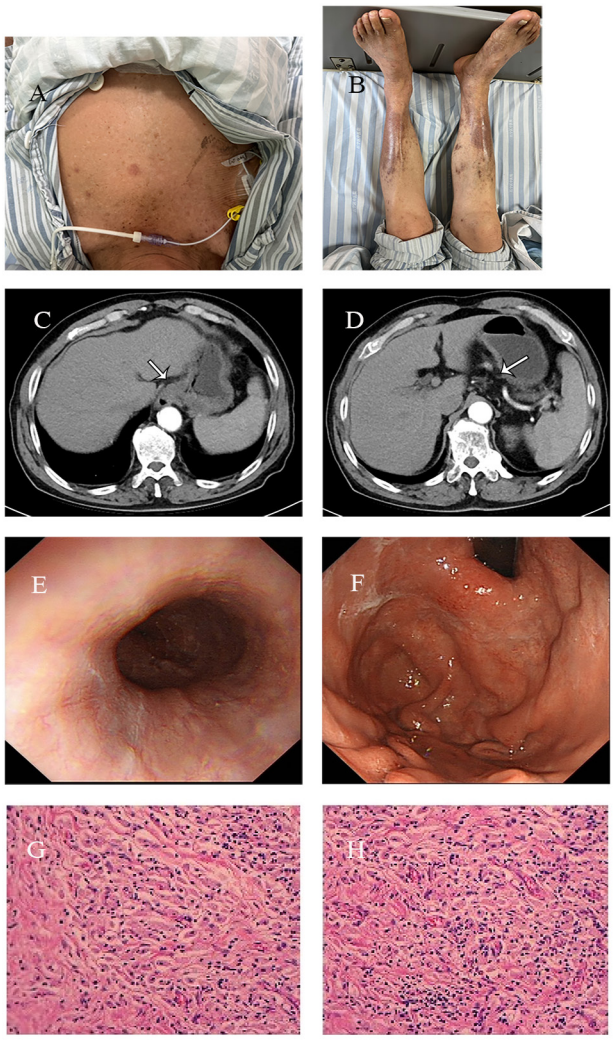

Figure 2. Radiological, endoscopic, pathological findings of gastric cardia adenocarcinoma and patient's skin before and after therapy. (A and B) The patient's skin was smooth, while no rash was observed after therapy. (C) The mass at the fundus of the stomach was reduced in size, the cardiac wall was thickened, with slight enhancement after contrast administration. (D) The lymph nodes around the fundus of the stomach were significantly smaller compared with those prior therapy. (E) Cardia and (F) gastric fundus mucosa were smooth. (G and H) The pathological examination revealed chronic inflammation of the cardia mucosa, with a large number of foam-like cells and few multinucleated giant cells in the submucosal and muscular layers. These two images are different fields of view captured from the same sample.

bullous pemphigoid, granulomatous diseases, drug rash with eosinophilia and systemic symptoms, and Stevens-Johnson and Sweet syndromes (23,24). Sintilimab-induced severe adverse skin reactions are rare. However, they are associated with high mortality rates (25). Skin-related adverse reactions to immunotherapy, such as rashes or dermatitis, typically occur during the first or second cycle of treatment. In the present case report, however, the rash appeared after the third cycle of sintilimab and subsequently spread throughout the body. The patient experienced difficulty in breathing when the rash occurred. The male patient had no prior history of skin-related conditions and the gastric cancer itself could not have caused a severe rash. Additionally, no adverse skin reactions were observed when the patient was previously treated with SOX. The multiple rashes on the patient's body subsided completely after treatment with corticosteroids. Based on the aforementioned findings, the physician suggested that the rashes in this case were directly associated with the use of sintilimab.

According to the 'Management of Immunotherapy-Related Toxicities Version 1.2022, National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology' published by the NCCN (26), the treatment approaches for immune-related skin toxicity include both systemic and topical therapy. For grade I adverse skin reactions, immunotherapy can be continued, while topical emollient and moderate potency steroids can be applied to the affected areas. Oral antihistamines can be used to treat itching, while a medium-potency topical steroid can be applied to the rash area. For grade II adverse skin reactions, in addition to the aforementioned treatments, if the patient does not respond to

Table I. Case analysis of literature on adverse skin reaction caused by sintilimab.

Number	Sex	Age	Cancer	Immunotherapy regimen	Occurrence time	Dermatological diagnosis	Treatment	Stop/ continue sintilimab	Outcome of the adverse event
1 (8)	Male	67	Advanced lung squamous carcinoma	Sintilimab combined with paclitaxel and cisplatin	33 days after first cycle	Eczema dermatitis	Hormones traditional Chinese medicine	Stop	Skin symptoms disappeared
2 (9)	Male	59	Centrally located squamous cell lung carcinoma and pulmonary tuberculosis	Sintilimab combined with paclitaxel and cisplatin	10 days after the post-oprerative adjuvant therapy	TEN	Intravenous methylprednisolone and oral prednisone	Stop	Relieved
3 (10)	Male	65	Lymphoma	Sintilimab, gemcitabine oxaliplatin	11 days after first cycle	TEN	Oral cetirizine methylprednisolone immunoglobulin pipracillin sodium/tazobactam and parenteral nutrition	Stop	Relieved
4 (11)	Male	72	Gallbladder carcinoma	Sintilimab, anlotinib	2 weeks after receiving 1 dose of sintimab	TEN	Methylprednisolone immunoglobulin albumin encapsulation tapering of glucocortico and oral nystatin	Stop	Relieved
5 (12)	Male	38	Non-small lung adenocarcinoma	Sintilimab	After the fourth cycle	Lichenoid mucocutaneous reactions	Gargling with a dexamethasone sodium phosphate solution	Continue	Oral mucosa lesions reap peared regularly but the skin lesions did not
6 (13)	Male	71	Advanced Non-small lung adenocarcinoma	Sintilimab	1 week later after the fifth cycle	Lichenoid dermatitis	Traditional chinse medine	Patient asked stop	Relieved
7 (14)	Male	70	Colorectal cancer	Sintilimab, fruquintinib	After 5 months	Bullous pemphigoid	Oral methylprednisolone	Patient asked continue	Relieved
8 (15)	Male	55	Gallbladder neuroendocrine carcinoma	Sintilimab, etoposide and cisplatin	39 days after the second cycle	Refractory pruritus	Naloxone	Not mentioned	Relieved

TEM, toxic epidermal necrolysis.

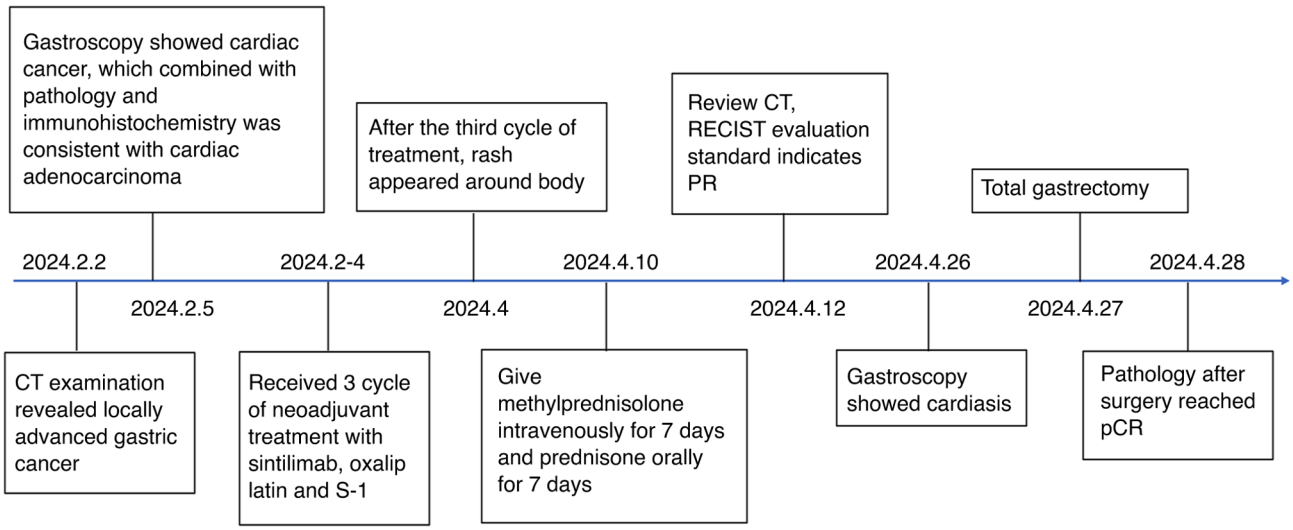

Figure 3 Timeline for diagnosis, neoadjuvant treatment and follow-up of patient. CT, computed tomography; S-1, Tigio; RECIST, response evaluation criteria in solid tumors; PR, partial response; pCR, pathological complete response.

a topical emollient within one week of application, treatment with 0.5 mg/kg/day prednisone and dermatologist consultation should be considered. When the patient's skin adverse reactions reach grade III or IV, treatment of the affected areas with high potency topical steroids and prednisone/IV methylprednisolone (0.5-1 mg/kg/day; increase dose up to 2 mg/kg/day if no improvement), urgent dermatology consultation and possible inpatient care should be considered. In the present case report, the patient's adverse skin reactions reached grade III and he was therefore treated with intravenous methylprednisolone, topical steroids and oral antihistamines. Immunotherapy with ICIs should be held, and treatment should be discontinued (27). Therefore, the patient discontinued sintilimab treatment, according to the NCCN and American Society of Clinical Oncology guidelines (27).

For patients needing long-term steroids, especially the elderly, diabetic or immunocompromised, it is vital to implement proactive strategies to manage toxicity. Immunotherapy should only be resumed once the toxicity has been reduced to a mild level. Patients must also be informed of the risk of recurring immune-related toxicities. For patients who have clearly benefited from immunotherapy, it may be unnecessary to continue, as the toxicity risks could outweigh the benefits (26-28).

In the present case, the patient experienced skin adverse reactions without any accompanying organ toxicity. A literature review similarly revealed no reports of organ toxicity in cases involving adverse skin reactions. However, in clinical practice, it is common to encounter patients with immune-related multi-organ toxicities. For instance, there was a case (Chen *et al*, unpublished data) of immune-related hepatitis, colitis, pneumonitis, and hypothyroidism occurring together, but without any skin side reaction involvement. Furthermore, a recent case report highlights cases of multi-organ toxicities induced by immunotherapy (29).

In the present case study, the patient's eczema dermatitis completely subsided after hormone therapy and the patient achieved pCR after surgery. This is a rare finding compared with the previous reported cases. Based on the aforementioned finding it was hypothesized that the patients who experienced irAEs could achieve improved outcomes. However, this finding warrants further investigation.

The early diagnosis and reasonable management of patients with irAEs are very crucial. Therefore, early detection, active intervention and dynamic follow-up are of great importance. The early identification and timely treatment of these adverse events could serve a significant role in improving prognosis and response to immunotherapy.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

YB contributed to manuscript writing, literature search and acquisition of data. HC undertook the treatment and monitoring of the patient, while he was also involved in study conception and design. YD, HS, HF and YY contributed to manuscript drafting, aggregation of materials and data analysis. YB was involved in manuscript revision and reviewing for intellectual content, and interpretation of data. YB and HC confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present case report was performed according to the guidelines of the Declaration of Helsinki and approved (approval no. JNZ-2024-N18, 16 May 2024) by the Institutional Ethics Committee of the Nanjing Jiangning Hospital of Traditional Chinese Medicine (Nanjing, China).

Patient consent for publication

The patient himself and his son Written informed consent for the publication of this case report and accompanying images was provided by the patient and his son.

Competing interests

The authors declare that they have no competing interests.

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