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CASE REPORT

# Dupilumab-Induced Systemic Hypoperfusion in an Elderly Patient: A Case Report

Huishang Feng[1,2], Yao Liu[3], Xinglu Dong[4], Li Zhou[4]

[1]Department of Dermatology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, People's Republic of China; [2]Second Clinical Medical School, Beijing University of Chinese Medicine, Beijing, People's Republic of China; [3]Department of Hepatology, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, People's Republic of China; [4]Department of Neurology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, People's Republic of China

Correspondence: Xinglu Dong; Li Zhou, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, People's Republic of China, Email arthasdxl@163.com; zhouljk7211@163.com



**Background:** Dupilumab is generally considered safe and effective for treating bullous pemphigoid (BP). We report the first case of recurrent hypoperfusion-induced cerebral infarction temporally associated with dupilumab administration in an elderly patient.

**Case Presentation:** A 96-year-old male with BP, type 2 diabetes, and a history of stroke developed acute hypotension, depressed consciousness, and reduced oral intake within 24–72 hours after three separate dupilumab injections. Initial neuroimaging revealed watershed infarcts. Proactive volume expansion during one administration successfully averted new infarction, whereas lack of prophylactic hydration on another occasion precipitated a transient ischemic attack (TIA).

**Observations & Analysis:** A significant temporal association was documented. The Naranjo Adverse Drug Reaction Probability Scale score was 8, indicating a probable association. The patient's advanced age, compromised cerebrovascular reserve, and mandatory discontinuation of antithrombotics created a hypervulnerable substrate. The hypotensive mechanism is hypothesized to involve IL-4/IL-13 pathway blockade, potentially disrupting endothelial function and vascular tone regulation.

**Conclusion & Clinical Implications:** This case report describes a potential, albeit rare, serious adverse effect associated with dupilumab in an elderly individual at high risk. Based on this single experience, we suggest at least 72 hours of post-injection blood pressure monitoring for high-risk patients. Management could include administering prophylactic fluid replacement based on the patient's actual condition and critically reassessing concomitant antihypertensive regimens. This finding highlights the need for heightened clinical vigilance and suggests that the drug's safety profile in advanced-age patients may warrant further investigation.

**Keywords:** bullous pemphigoid, cerebral infarction, hypoperfusion, dupilumab, adverse drug reactions in elderly patients

## Introduction

Bullous pemphigoid is a chronic, subepidermal autoimmune blistering disorder, the pathogenesis involves autoantibodies targeting hemidesmosomal proteins BP180 and BP230, which are essential for dermal–epidermal adhesion.[1] Patients typically present with erythema, erosions, and tense subepidermal blisters, frequently accompanied by intense pruritus. Mucosal involvement may also occur, contributing to the heterogeneous clinical manifestations.[2] Its incidence is increasing with population aging, with the highest prevalence observed in individuals aged 60 years and older, particularly those over 80 years.[3]

Given the extended therapeutic duration of bullous pemphigoid, some patients opt for self-administered home injections, potentially delaying detection of mild adverse events. Herein, we present a case of recurrent hypoperfusion-induced cerebral infarction during dupilumab treatment in an elderly hospitalized patient. This represents the first documented case featuring comprehensive vital sign dynamics monitoring before and after multiple drug administrations. The findings offer critical clinical insights regarding medication safety in geriatric populations. The study was approved by the Ethics Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (Approval No: 2025DZMEC-461-01), and written informed consent obtained from both the patient and legal guardians.

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## Details of the Case

A 96-year-old male presented with pruritus and vesicular eruptions in early 2025. Following diagnostic confirmation of bullous pemphigoid at an external institution, initial therapy combining minocycline hydrochloride with antihistamines yielded suboptimal response, demonstrating progressive blister formation. Subsequent neurological consultation for hypersomnia and fatigue attributed these symptoms to antihistamine-induced somnolence. The patient had multiple comorbidities, including: type 2 diabetes mellitus (>40-year duration) managed with sitagliptin phosphate, acarbose, repaglinide, and insulin glargine; recurrent cerebral infarction (2013 and 2024, Figure 1A) resulting in persistent hypercoagulability (elevated D-dimer and fibrinogen); contraindication to antiplatelet/anticoagulant therapy due to hemorrhagic risk necessitating continuous defibrinogenation with lumbrokinase; and history of lower-extremity deep vein thrombosis (2017) requiring inferior vena cava filter placement. Multidisciplinary consensus deemed immunosuppressants and glucocorticoids contraindicated given advanced age and bleeding predisposition, recommending dupilumab for targeted therapeutic intervention.

On January 20, 2025, subcutaneous dupilumab therapy was initiated with a 600 mg loading dose. Minocycline hydrochloride was discontinued, while antihistamines were administered as needed for pruritus control. Two weeks post-initiation, blister formation ceased with marked pruritus improvement, prompting dose reduction to 300 mg biweekly. The injection interval was progressively extended to 4-week and 6-week cycles following disease stabilization. During treatment, caregivers documented recurrent post-dose adverse events including acute hypotension, altered consciousness (predominantly somnolence), and reduced oral intake. Diagnostic workup revealed one new-onset cerebral infarction and two transient ischemic attacks temporally associated with dupilumab administration (Figure 2).

Upon recognizing the potential association between these symptoms and dupilumab therapy, we implemented rigorous monitoring of peri-administration fluid balance (Figure 2A), blood pressure, and heart rate (Figure 2B). Analysis revealed recurrent post-dose manifestations including reduced oral intake, hypotension, depressed consciousness (somnolence), and motor weakness, correlating with repeated transient ischemic attacks (TIAs) and cerebral infarction. Neuroimaging confirmed ischemic cerebrovascular events (Figure 1B), with initial post-treatment MRI (January 22, 2025) demonstrating: DWI: Punctate hyperintensities in the left cerebellum, frontal lobe, periventricular regions, and bilateral occipitoparietal lobes (white arrowheads, Figure 1B–1). FLAIR: Increased signal intensity in bilateral frontoparietotemporooccipital cortices, centrum semiovale, periventricular zones, basal ganglia, and brainstem (blue arrowheads, Figure 1B–2).

Preventive hydration during dupilumab administration on March 17, 2025, effectively mitigated hypoperfusion-related symptoms and prevented new infarctions. Conversely, omission of preventive hydration during subsequent dosing at a nursing facility (April 17, 2025) precipitated recurrent TIA, with symptom resolution following emergent volume resuscitation. Follow-up MRI (April 24, 2025; Figure 1C) confirmed absence of new infarcts. Implementation of standardized preemptive hydration before each subsequent injection eliminated further hypoperfusion-related cerebrovascular events or associated symptoms during longitudinal follow-up.

## Discussion

Dupilumab has been widely adopted for bullous pemphigoid management, achieving significant improvement in cutaneous manifestations including vesicular eruptions and pruritus in this case. However, temporally patterned adverse events emerged post-administration: systemic hypotension (nadir within 24–72 hours), depressed consciousness (somnolence), and hypophagia. Notably, the initial loading dose was temporally associated with extensive acute hypoperfusion-induced cerebral infarction, with subsequent administrations associated with significant blood pressure fluctuations and transient ischemic attacks.

Crucially, the inpatient setting facilitated prompt multidisciplinary intervention by dermatological and neurological teams despite the primary admission diagnosis. This collaborative management proved vital given the patient's advanced age and complex comorbidity profile. Implementation of prophylactic volume expansion effectively mitigated cerebral hypoperfusion and prevented further ischemic events.

Using his detailed timeline and medication history, we completed the Naranjo Adverse Drug Reaction Probability Scale.[4] Supported by objective evidence, the Naranjo adverse drug reaction score is 8, indicating a probable causal

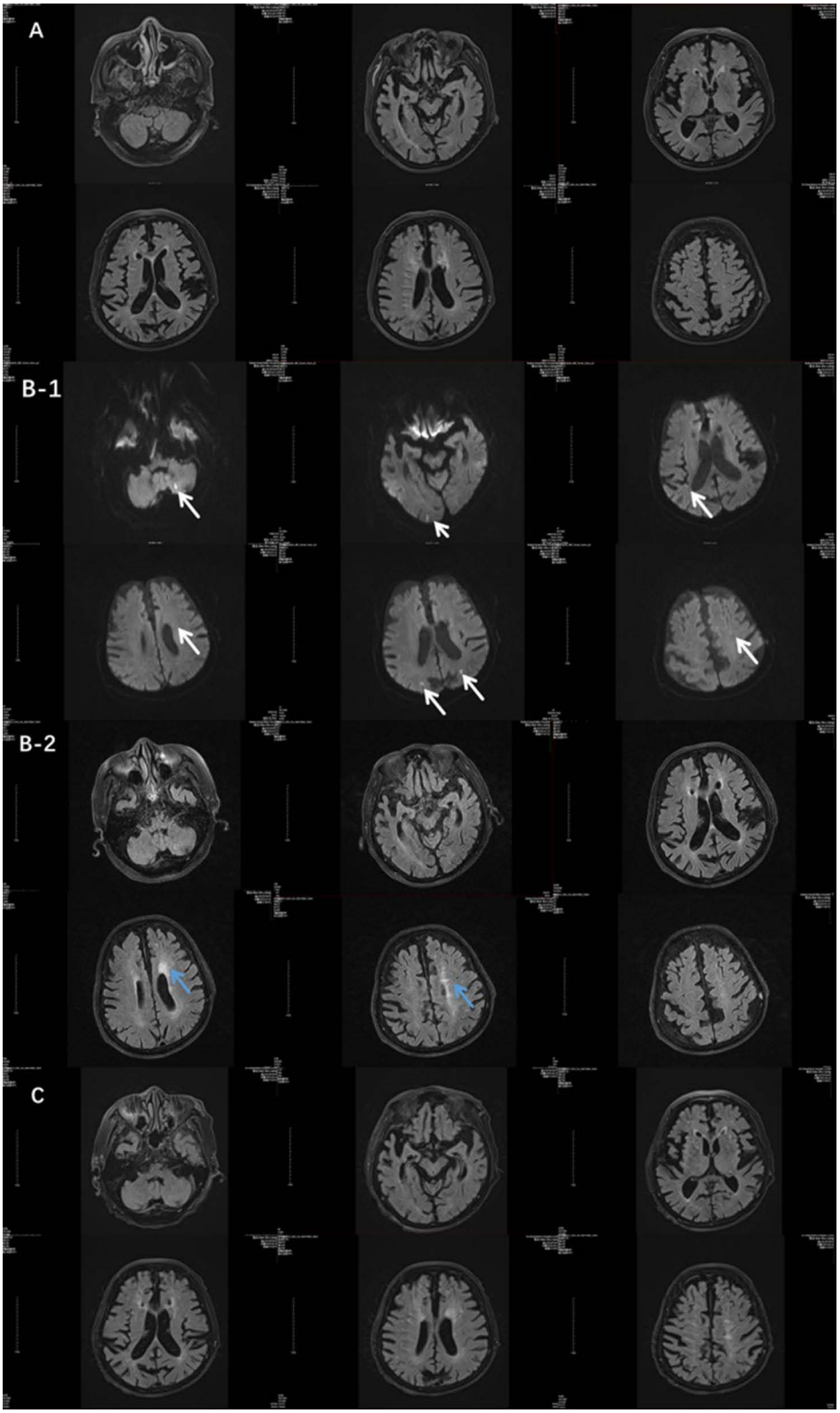


**Figure 1** Serial MRI imaging data of the patient (**A)** Brain MRI-FLAIR sequence of the patient on September 18, 2024, prior to pemphigus onset, showing scattered ischemic infarctions. No obvious infarcts were observed in the cerebellum, occipital lobe, or internal watershed areas; **(B)** Brain MRI findings two days after the first administration of dupilumab (January 22, 2025). White arrows indicate lesions on diffusion-weighted imaging (DWI) sequences; blue arrows indicate lesions on fluid-attenuated inversion recovery (FLAIR) sequences. (**B-1**) Cranial DWI sequence showing punctate hyperintense signals in the left cerebellum, frontal lobe, periventricular area, and bilateral parieto-occipital lobes. (**B-2**) Cranial FLAIR sequence showing hyperintense signals in the bilateral frontal, parietal, temporal, occipital lobes, semi-oval center, periventricular area, basal ganglia, and brainstem.**(C)** Cranial DWI and FLAIR sequences on April 24, 2025, showing no diffusion restriction (DWI) and findings generally consistent with prior imaging (FLAIR), 6 days after transient dysphagia occurred following the 5th administration of dupilumab on April 17, 2025.


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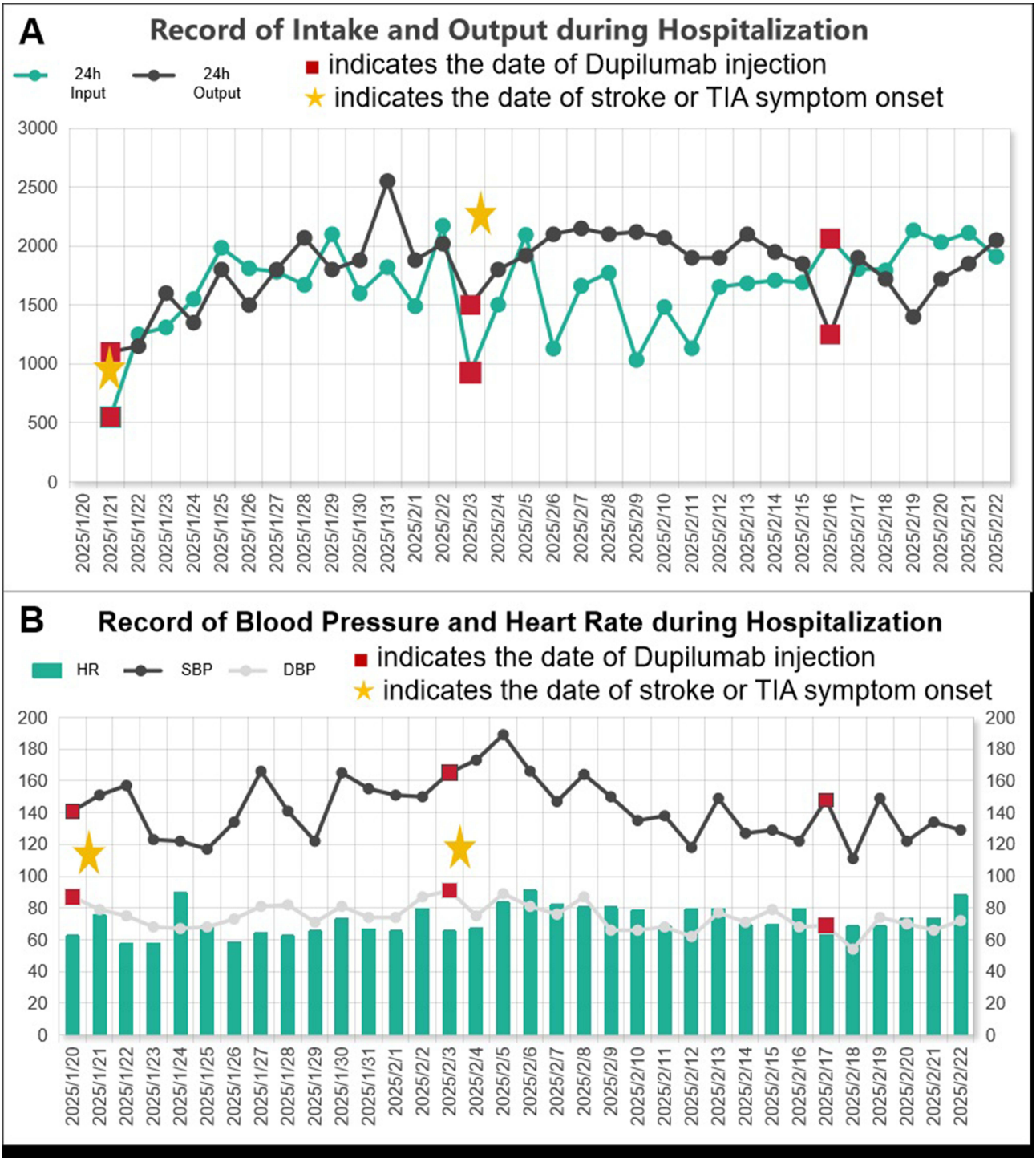


**Figure 2** Trends in the patient's daily intake-output, blood pressure, and heart rate **(A)** Record of Intake and Output during Hospitalization;**(B)** Record of Blood Pressure and Heart Rate during Hospitalization.

relationship between dupilumab therapy and hypoperfusion-related cerebral infarction. The case was immediately escalated to the institutional pharmacovigilance unit, with mandatory reporting to the China National Adverse Drug Reaction Monitoring System (CNARMS) per regulatory requirements.

A strong association exists between cerebrovascular disorders and bullous pemphigoid (BP) pathogenesis. BP180 antigen is expressed not only in the skin's basement membrane zone but also in neuronal cytoplasm, suggesting

a potential shared mechanism.[5–7] Epidemiological studies support a significant link between stroke and BP development.[8–10] Stroke—encompassing infarction, ischemia, and mixed subtypes—shows rising global incidence and ranks as the second leading cause of mortality worldwide.[11] While the exact immunopathological pathways remain unclear, this comorbidity adversely affects patients' quality of life and survival outcomes.

First-line BP management typically includes minocycline, glucocorticoids, or immunosuppressants (eg, cyclosporine). However, these options require cautious use in elderly patients with comorbidities due to risks such as hepatorenal toxicity, gastrointestinal bleeding, and infection susceptibility.[12] Consequently, dupilumab—with its favorable safety profile—has become increasingly utilized in geriatric BP patients, supported by emerging evidence of clinical efficacy.[13–15]

Dupilumab, a fully human monoclonal antibody, exerts therapeutic effects by binding to the interleukin-4 receptor alpha (IL-4Rα) subunit, thereby inhibiting signaling pathways of both IL-4 and IL-13. This mechanism confers significant clinical efficacy in type 2 inflammation-mediated diseases.[16] Currently approved indications include atopic dermatitis (AD), prurigo nodularis (PN), asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and eosinophilic esophagitis (EoE).[17–21] As bullous pemphigoid represents a type 2 inflammatory disorder, Phase III clinical trials have established dupilumab's therapeutic efficacy for this condition.[22] Owing to its consistent efficacy and favorable safety profile, dupilumab has been integrated into international treatment guidelines for BP, demonstrating excellent clinical outcomes across diverse populations including elderly patients.[23]

Comprehensive analysis of this case yields the following critical observations: ①Temporal Association: A significant chronological correlation exists between dupilumab administration (January 20, February 17, and April 17, 2025) and hypoperfusion events. Documented hemodynamic alterations - including hypotension and altered consciousness/appetite - consistently manifested within 1–3 days post-administration. ②Hemodynamic Profile: Marked blood pressure fluctuations (eg, 165/91 mmHg → 109/62 mmHg) demonstrated partial reversibility with volume expansion and antihypertensive cessation. This pattern suggests that dupilumab may disrupt vascular homeostasis, leading to relative hypovolemia or impaired vasomotor tone. The 2024 hypoperfusion-related cerebral infarction indicated severely compromised cerebrovascular autoregulatory reserve. ③Hypoperfusion-Induced Infarction: The neuroimaging characteristics of the initial post-treatment infarction (watershed distribution) were pathognomonic of hemodynamic failure. Subsequent transient ischemic attacks without radiographic infarction may reflect effective cerebral perfusion rescue through prompt hydration. ④High-Risk Substrate: Concomitant factors - advanced age, chronic diabetes mellitus, cerebral arteriosclerosis, prior hemodynamic infarction, and mandatory antithrombotic discontinuation - collectively established cerebrovascular hypervulnerability. Dupilumab likely functioned as a "second-hit" precipitant for severe hypoperfusion. ⑤Neurological Manifestations: Consciousness disturbances and hypophagia represented global cerebral hypoperfusion, exacerbating hypovolemia through reduced intake and establishing a self-perpetuating cycle. ⑥Pathophysiological Hypothesis: While dupilumab's hypotensive mechanism remains undefined, IL-4/IL-13 pathway blockade may drive M2 macrophage polarization, activate inflammatory cascades, and increase vascular endothelial permeability - ultimately disrupting endothelial function and vascular tone regulation in hemodynamically compromised elderly patients.[24,25] Emerging evidence implicates immunomodulatory IL-34 in vascular structural homeostasis and cerebrovascular dynamics,[26] suggesting novel investigative pathways for IL-4/IL-13 interactions in neurovascular unit maintenance via vascular-central nervous system macrophage crosstalk.

This study has several limitations that should be noted. First, being a single-case report, its generalizability is limited. The patient also had severe comorbidities that could have independently affected outcomes. Additionally, confounding factors such as advanced age, history of strokes, diabetes, and antithrombotic use were not controlled, making it difficult to establish a clear causal relationship between the drug and the adverse event. Furthermore, the exact mechanism remains unclear, and our findings only suggest a possible association rather than a proven causal pathway. Finally, the observed clinical progression might reflect the natural course of the underlying disease, rather than being solely attributable to the drug. Future studies with larger cohorts and mechanistic investigations are needed to confirm these observations.

## Conclusion

Any pharmacological agent may elicit adverse reactions beyond its intended therapeutic effects, with such events documented for dupilumab in the literature.[27–29] Hypoperfusion constitutes a critical pathological mechanism underlying cerebral ischemic events in the elderly. Notably, drug-induced hypoperfusion presents greater diagnostic stealth compared to alternative etiologies such as volume depletion, hemorrhage, or excessive diaphoresis. We suggest that for patients with a similar profile, particularly those with significant cerebrovascular burden or prior hypoperfusion-related infarction, enhanced post-administration vigilance may be prudent. This could include considerations for extended monitoring of blood pressure and consciousness status, attention to hydration, and careful review of concurrent antihypertensive regimens. Reporting of similar events and future registry data will be crucial to corroborate this potential association and clarify the underlying mechanisms.

## Abbreviations

BP, bullous pemphigoid; IL-4Rα, interleukin-4 receptor α; TIA, transient ischemic attack; CNARMS, China National Adverse Drug Reaction Monitoring System; AD, atopic dermatitis; PN, prurigo nodularis; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis.

## Data Sharing Statement

Authors agree to make data and materials supporting the results or analyses presented in this paper available upon reasonable request. Further inquiries can be directed to the corresponding authors.

## Statement of Ethics

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article. The Ethics Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine approved the study (No.: 2025DZMEC-461-01). The study complies with the Declaration of Helsinki.

## Author Contributions

Hui-shang Feng contributed to the conceptualization, formal analysis, investigation, methodology and writing original draft of the study. Yao Liu contributed to the data curation, validation and writing original draft of the study. Xing-lu Dong contributed to the resources, software, visualization, writing review and editing of the study. Li Zhou contributed to the funding acquisition, project administration, supervision, writing review and editing of the study. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors have no financial or ethical conflict of interest regarding the content of this paper.

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