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Case Report

Clozapine-induced cholinergic urticaria: a case report

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***Abstract*:** Clozapine, renowned for its efficacy in treatment-resistant schizophrenia, is associated with rare yet potentially severe side effects, including hematological disorders, myocarditis, seizures and gastrointestinal obstruction. Dermatological adverse effects, though less serious, can profoundly impact patients' quality of life. We present the first reported case of cholinergic urticaria induced by clozapine, in a 25-year-old male with treatment-resistant schizophrenia. Four months into clozapine therapy, the patient developed intensely pruritic erythematous lesions triggered by sweating, significantly impairing his daily activities. Despite attempts at management, including dose reduction and antihistamine therapy, the urticaria persisted. However, a favorable outcome was achieved upon switching to quetiapine. This case underscores the importance of recognizing and managing treatment-related adverse effects, even when they arise late in treatment, and highlights the need for individualized therapeutic approaches. We discuss potential mechanisms underlying clozapine-induced cholinergic urticaria and emphasize the significance of patient-centered care in optimizing treatment outcomes in schizophrenia.

Plain language summary

Itchy rash from sweating with clozapine

Despite its undisputed efficacy, clozapine has attracted a great deal of attention for its rare but potentially serious side effects, such as hematological disorders (in particular, low white blood cell counts), seizures and inflammation of the heart muscle. Other effects, notably cutaneous, have also been reported, and although they are not serious, they can have a considerable impact on the patient's quality of life. Such is the case of our patient who became allergic to his own sweat while taking clozapine. To our knowledge, this is the first case described in the literature.

The patient was a 25-year-old man suffering from resistant schizophrenia, i.e. who had failed to respond to successive use of two different antipsychotics. Four months after starting treatment with clozapine, he developed a generalized cutaneous eruption characterized by intensely pruritic erythematous punctiform lesions which appeared with each episode of perspiration. The lesions considerably disrupted the patient's daily activities, making it necessary to refrain from physical effort and avoid exposure to heat. Despite attempts to manage symptoms, by treatment with antihistamines and clozapine dose reduction, the urticaria persisted. However, a favorable and durable outcome was observed after switching to quetiapine rather than olanzapine.

This case highlights the importance of recognizing and managing treatment-related undesirable side effects, even if they appear late in the course of treatment, and of not neglecting their impact on the patient's daily life. In this report, we have also tried to outline the hypothetical mechanisms that could explain this unusual side effect.

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This case encourages clinicians to always seek the optimal antipsychotic for their patients, even after several therapeutic failures and/or episodes of intolerance. Trial and error can lead to more effective, personalized treatment.

Keywords: case report, cholinergic urticarial, clozapine

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Introduction

Clozapine has been recognized as the gold-standard medication for treatment-resistant schizophrenia since the pivotal study of Kane et al.[1] Its superior efficacy, favorable tolerability profile compared with first-generation antipsychotics, and the observed reduction in mortality among treated patients[2] have earned it this distinction.[3,4] In 1975, however, 17 out of 2660 (0.7%) patients in Finland who had been treated with clozapine developed agranulocytosis (defined as an absolute neutrophil count $<500/mm^3$). Eight of these (47%) subsequently died from secondary infections. As a result, clozapine was withdrawn from the market by the manufacturer.[5] Nevertheless, due to increasing appreciation of resistance to other typical antipsychotics, as well as their potentially debilitating side effects,[6] interest in clozapine soon resurfaced. In 1989, clozapine was approved for treatment-resistant schizophrenia by the United States, and subsequently by drug licensing agencies in other countries.[1]

Despite the unique and well-documented effectiveness of clozapine, its use remains limited due to the potential for serious and potentially life-threatening side effects such as agranulocytosis, myocarditis, seizures, and gastrointestinal obstruction,[7] as well as the requirements for strict monitoring throughout the treatment period. Approximately 17% of patients who take clozapine discontinue their treatment due to adverse effects.[8]

Dermatological adverse effects attributable to clozapine are very rare. According to the manufacturers, adverse skin reactions occur in less than 1 in 10,000 patients.[9] They include pruritus, exanthematous reactions, urticaria, photosensitivity, drug-induced pigmentation, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrosis, DRESS syndrome, and drug hypersensitivity vasculitis.[10,11]

Cholinergic urticaria (CU) is a rare condition characterized clinically by pinpoint-sized papules with an erythematous halo that is highly pruritic. Although the symptoms are transient and usually resolve within an hour, CU can significantly impair the patient's quality of life, especially regarding everyday physical activity, including sexual activity.[12] The condition was first described by Duke in 1924[13] but despite this relatively long history, its pathogenesis has not been fully elucidated.

In this study, we report a case of severe and disabling clozapine-induced CU and a sustainable favorable outcome after switching to quetiapine rather than olanzapine.

To our knowledge, thus far in the literature, there are no case reports of clozapine-induced CU.

Case study

We present the case of a 25-year-old North African male, who was diagnosed with schizophrenia according to DSM-5 criteria. Relevant medical history included a 2-year history of polysubstance abuse (cannabis, benzodiazepines, and pregabalin) prior to his first hospitalization. On his paternal side, he had a significant family history of mental illness, including depression and psychosis. No notable somatic history was identified.

The patient was admitted to a psychiatric ward for the first time in December 2021 following a significant worsening of his symptoms, which had been gradually developing since 2019. At admission, his Positive and Negative Syndrome Scale score was 166, indicating severe schizophrenia psychopathology with prominent psychotic symptoms, including delusional ideation, persecutory ideas, auditory and visual hallucinations, severe conceptual disorganization, tangentiality, incoherent speech, loose associations, bizarre behavior,

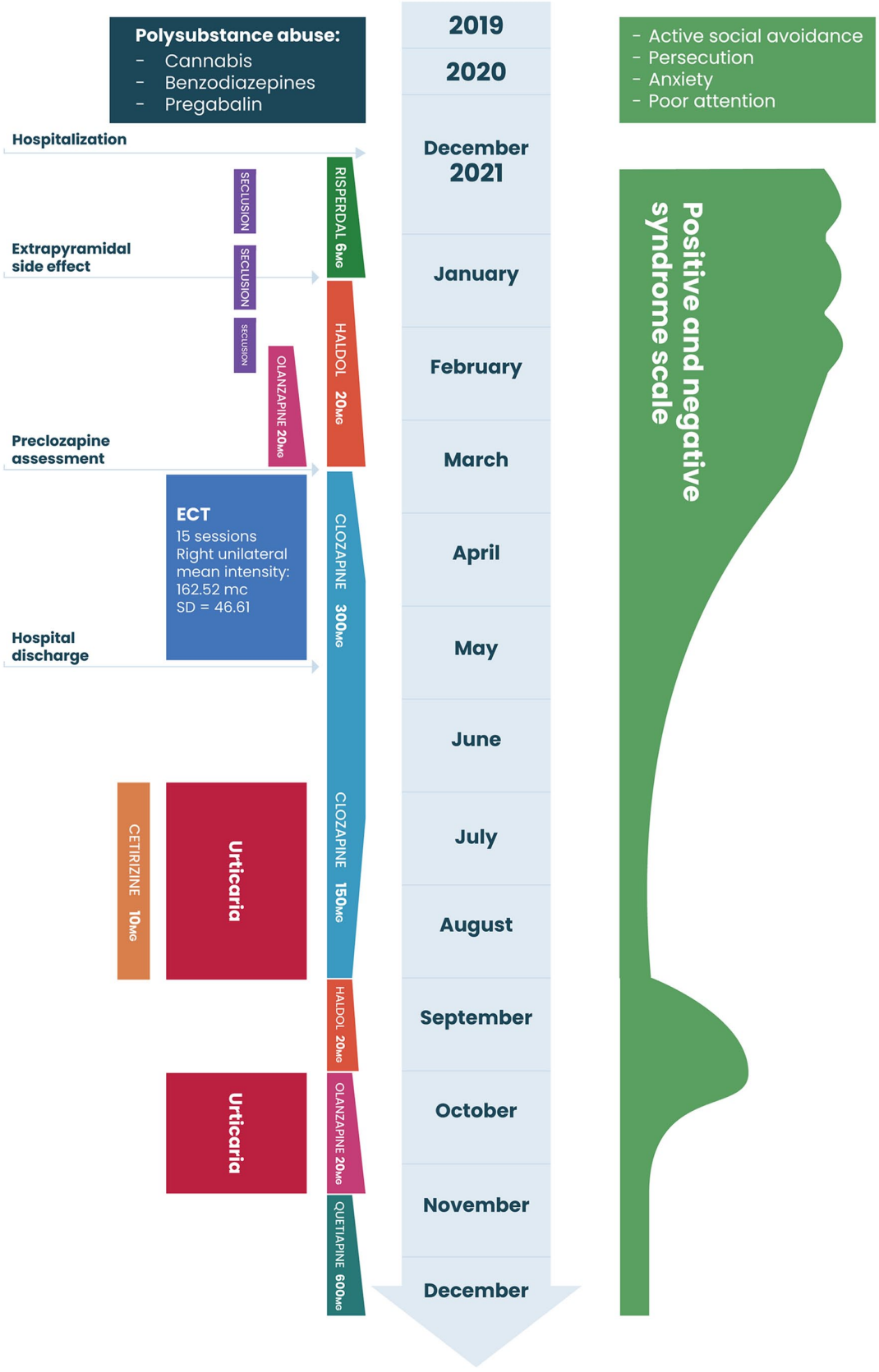

Figure 1. Timeline of interventions and outcomes.
NB: the switches between antipsychotics are not detailed in the figure.

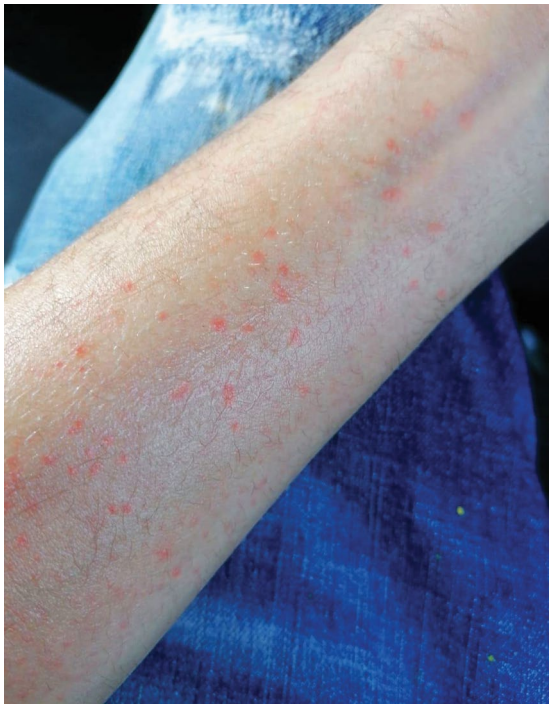

Figure 2. Typical appearance of cholinergic urticaria in our patient: pinpoint-sized, highly pruritic red wheals occur after sweating.

and a lack of insight. Other symptoms (i.e. high irritability and aggression) relating to a strong adherence to delusions were also present, leading to multiple episodes of agitation (Figure 1).

His severe and threatening condition necessitated three separate uses of seclusion, with an average duration of 12 days each, and a 48-h period of mechanical restraint.

The patient had been treated with several lines of antipsychotics without success: 6 mg of risperidone for 4 weeks with poor neurological tolerance followed by 20 mg of haloperidol for 4 weeks, and a combination of haloperidol at the same dose and 20 mg of olanzapine for 2 weeks, leading to a diagnosis of treatment-resistant schizophrenia.[14]

In March 2022, a switch to clozapine took place, along with concurrent electroconvulsive therapy (ECT) sessions. Prior to starting clozapine, the patient underwent a pre-clozapine assessment, including a complete blood count, serum electrolyte analysis, and an electrocardiogram, all of which showed no abnormalities. The initial complete blood count revealed a leukocyte count of 9110/mm^3 and eosinophils at 0/mm^3.

Clinical improvement was rapid and sustained after 15 sessions of right unilateral ECT (mean intensity 162.52 mc; SD 46.61) combined with 300 mg clozapine, resulting in a significant reduction in delusions and hallucinations and improved insight. He was discharged in May 2022, maintaining the same clozapine dose, with weekly hematological monitoring, followed by monthly monitoring.

Initially, clozapine was well tolerated by the patient, as indicated by a score of 17 on the clozapine-specific side-effects scale (GASS-C).[15]

Resuming a normal lifestyle, after 4 months of clozapine initiation, the patient developed a generalized skin rash characterized by erythematous punctiform lesions that were intensely pruritic and occurred following any episode of heat or exercise-induced sweating (Figure 2). These lesions were transient, and they rapidly resolved when the patient was at rest or not exposed to heat. However, they significantly impaired the patient's daily activities, necessitating the cessation of physical exertion and avoidance of heat exposure. The patient was not taking any other prescribed medications, nor was he self-medicating, and environmental causes were excluded based on the patient's account. Initially, photosensitivity was considered, but the lesions appeared even in the absence of sunlight exposure, including during evening hours and within the hospital setting, such as during follow-up appointments after climbing stairs.

No improvement was observed following treatment with antihistamines (10 mg of cetirizine per day). Consequently, a reduction in clozapine dose was attempted, but the lesions continued to reappear even at a dose of 150 mg, prompting a switch to haloperidol.

The switch to haloperidol was well tolerated, with a complete resolution of the cutaneous reactions. However, from a psychiatric perspective, the response was unsatisfactory, and the patient began to show early signs of a psychotic relapse. Therefore, it was decided that a different treatment was necessary, and due to the prior urticaria not being life-threatening, another molecule from the 'pine' family, namely olanzapine, was considered. One month of treatment with 20 mg of olanzapine per day resulted in a rapid and complete remission of psychotic symptoms, but also in a recurrence of the same cutaneous reaction as had been observed previously with clozapine.

In our comprehensive evaluation, conducted jointly by a dermatologist and an immunologist, of the patient's clinical presentation, several differential diagnoses were meticulously considered and systematically ruled out. CU was diagnosed, with symptoms manifesting post-heat or exercise-induced sweating, aligning with the distinct rash pattern characteristic of CU, implicating both olanzapine and clozapine as causative agents.

Since heat and exercise were the main triggers, we could always perform a provocation test to confirm the appearance of skin lesions, but the anamnesis was sufficient.

Distinct differentiation criteria exist between CU and other inducible urticarias or anaphylactic conditions. Notably, CU differs from exercise-induced anaphylaxis (EIA) and heat urticaria primarily based on triggering stimuli. While the strenuous activity may incite both EIA and CU, passive warming singularly induces CU, distinguishing it from EIA, which often exhibits larger and more variable wheal sizes.[16] The heat urticaria, a rare inducible urticaria variant, presents erythematous wheals restricted only to the heated area.[17] In addition, CU was clinically differentiated from aquagenic urticaria, provoked by water contact, and adrenergic urticaria, induced by stress or trauma. Adrenergic urticaria is typified by wheals surrounded by a vasoconstrictive white halo,[18] a presentation not observed in our patient.

Throughout the patient's follow-up, no biological abnormalities were detected, except for an elevated total immunoglobulin E (IgE) level of 382 KU/L (reference range < 114) while taking olanzapine. Unfortunately, this measurement was not performed during clozapine treatment for comparison.

The patient was severely affected by the situation. He was forced to stay indoors avoiding any physical activity, heat, and sun exposure. He tried reducing the olanzapine dosage to 5 mg/day on his own, but it had no effect on CU symptoms.

Through a progressive switch to 600 mg of quetiapine, a dramatic improvement was observed in the immuno-cutaneous reactions. Within just 3 weeks, the patient regained the ability to attend consultations under sunlight, resume physical activities, and even explore manual labor opportunities. The switch was well-tolerated, maintaining remission from schizophrenia while significantly reducing anxiety and depression resulting from the previous situation.

From the patient's perspective, this latest change has enabled him to 'have a life' and reintegrate into society. After months of seclusion due to the CU, he was 'finally' able to go out, look for a job, and even 'find love'.

Discussion

Clozapine, like many other antipsychotic medications, can cause skin rashes that manifest in various forms and levels of severity. These reactions are often described as rare in the literature, and most of them are benign.[5] However, to our knowledge, this is the first reported case of clozapine-induced CU.

CU remains a notably rare condition that, to date, lacks comprehensive elucidation. Based on its possible pathogenesis, only direct acetylcholinomimetics, such as bethanechol, pilocarpine, or nicotine, are postulated to induce this condition. However, the literature surprisingly lacks reported cases of such inductions. To the best of our knowledge, only one case of drug-induced CU has been documented thus far. The implicated molecule was carvedilol, a beta-blocker.[19]

CU is generally triggered by stimuli such as exercise or heat which increase the core body temperature and promote sweating.

Clinical and experimental observations have suggested a type I hypersensitivity mediated by IgE to either sweat itself or to a protein present in sweat.[20] Given that acetylcholine is known to induce both sweating and papules when injected intradermally,[21] another well-known hypothesis suggests that the etiology of CU involves a cholinergic stimulus, with acetylcholine being the primary mediator.[17,22]

Our observations and literature reviews have led us to propose two main hypotheses to elucidate the onset of CU in our patient under clozapine treatment.

Drawing from recent findings that shed light on clozapine's detection in sweat,[23,24] we hypothesize that clozapine or certain clozapine metabolites, when excreted in sweat, could serve as antigens, prompting an IgE-mediated hypersensitivity reaction.[17] The concomitant elevation of IgE levels in

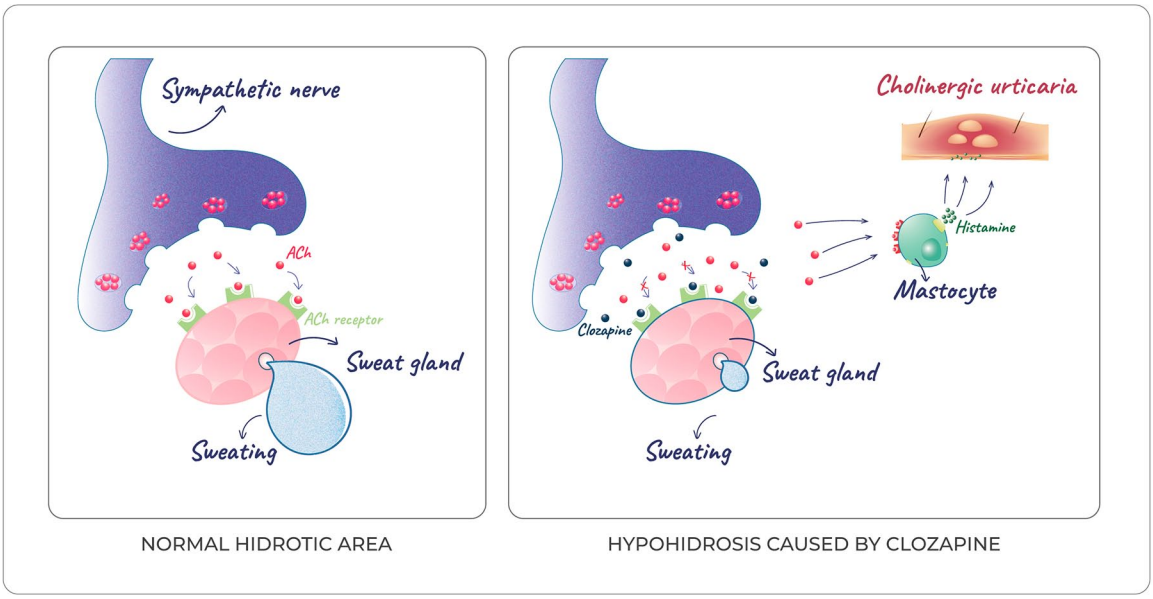

Figure 3. Hypothetical underlying mechanism of the induction of the CU with hypohidrosis induced by clozapine.
In the normal hidrotic area, acetylcholine (ACh) released from nerves upon exercise or heat exposure is completely trapped by acetylcholine receptors of the eccrine glands, which normally induces sweating. In the hypohidrotic area, acetylcholine released from nerves upon exercise cannot be completely trapped by the acetylcholine receptors (ACh receptor) of eccrine glands which are already saturated by clozapine and overflow to the adjacent mast cells. Subsequently, degranulation of the mast cells creates wheals and induces CU pain.
CU, cholinergic urticarial.

our patient, even if it lacks specificity, may point toward a potential immune-mediated pathway. As with any allergy, type 1 hypersensitivities can occur at any point in life, which may explain the 4-month interval between the introduction of clozapine and the onset of CU in our patient.

Within the context of this hypothesis, we speculate a distinct immunological profile in our patient, which may elucidate why our patient exhibited this specific reaction to clozapine, contrasting with others on the same treatment.[25] Nevertheless, it cannot be ruled out that this immunological profile is itself induced by the immunomodulatory properties of clozapine.[26]

However, it is essential to underscore that the exact relationship between clozapine treatment, the observed cutaneous reactions, and the elevated IgE levels is complex and warrants further investigation. Thus, we have ventured into another hypothesis to decipher this CU; paradoxically, the potent anticholinergic properties of clozapine, according to our second hypothesis, might be directly implicated in the onset of CU, by inducing a state of hypohidrosis, a known trigger of CU.[27] Due to the high affinity of clozapine to peripheral muscarinic receptors M3,[28] we may hypothesize that ACh released from nerves cannot be completely trapped by cholinergic receptors of eccrine glands already saturated by clozapine, and thus it overflows to the adjacent mast cells, leading to wheals (Figure 3).

We acknowledge that our assessment of hypohidrosis, based on clinical observations and the patient's subjective experience, without histochemical evidence, may present a limitation to this hypothesis.

It is important to note that while clozapine, olanzapine, and quetiapine possess different therapeutic profiles, they do exhibit overlapping receptor affinities. This shared neurobiological basis might lead to overlapping clinical manifestations or side effects.[29–31]

Given clozapine's pronounced anticholinergic properties, we switched to quetiapine, prioritizing its milder anticholinergic profile. We intended to harness the therapeutic advantages of the 'pine' family of antipsychotics while curtailing potential

anticholinergic repercussions. Paradoxically, we speculate that the lesser anticholinergic profile of quetiapine might mitigate the risk of CU onset.[32]

The hypotheses described in this report are only speculative. Nevertheless, this report suggests two important conclusions:

The first is that the side effect profile of antipsychotics within the 'pine' family differs and switching between agents within this family may allow a side effect to resolve. In this case, a switch from clozapine to quetiapine resulted in the resolution of CU, whereas this was not seen with an earlier switch from clozapine to olanzapine.

The second is to encourage clinicians to find the optimal antipsychotic for their patients, even after several therapeutic failures and/or intolerance episodes. Trial and error can indeed lead to more effective, personalized treatment.

Declarations

Ethics approval and consent to participate

Our study did not require ethical board approval because it did not contain human or animal experiments. The anonymity of the patient was completely preserved.

Consent for publication

The patient granted written consent for the publication of his case and accompanying photos.

Author contributions

Nadia El Ouni Amami: Conceptualization; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft.

Husen Ali-Diabacte: Writing – review & editing.

Sarra Ateb: Supervision; Writing – review & editing.

Hammadi Ben Rejeb: Writing – review & editing.

Avicenne Bellis: Writing – review & editing.

Reza Bellis: Investigation; Writing – review & editing.

Dominique Januel: Supervision; Validation; Writing – review & editing.

Noomane Bouaziz: Methodology; Supervision; Validation; Visualization; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

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