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A case of an ALS patient with an SQSTM1 mutation — implications for the p62/NF-κB/Nrf2/autophagy pathways in the selection of individualised therapeutic strategies: a preliminary report

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Abstract: Introduction: Amyotrophic lateral sclerosis (ALS) represents a heterogeneous group of neurodegenerative disorders sharing a common ALS phenotype but arising from diverse genetic and molecular mechanisms. Among the genes implicated in ALS, *SQSTM1*, encoding the multifunctional protein p62, plays a pivotal role in maintaining neuronal homeostasis through the regulation of autophagy and the crosstalk between NF-κB and Nrf2 pathways. Disruption of these mechanisms contributes to oxidative stress, neuroinflammation, and protein aggregation in motor neurons.
Material and Methods: A comprehensive genetic analysis, including next-generation sequencing (NGS), whole-exome sequencing (WES), and multiplex ligation-dependent probe amplification (MLPA), was performed in a patient clinically diagnosed with ALS. Literature data regarding the role of *SQSTM1*, NF-κB/Nrf2 signaling, and autophagy modulation in ALS pathogenesis were reviewed to contextualize the findings.
Case Presentation: We describe a 49-year-old woman with a 12-month history of progressive bulbar-onset ALS. Genetic testing revealed a heterozygous *SQSTM1* c.1175C>T (p.Pro392Leu) variant inherited from her father, classified as likely pathogenic. The patient received dimethyl fumarate (Nrf2 activator), celecoxib (NF-κB inhibitor), and rapamycin (mTOR pathway modulator) as part of an individualized treatment strategy.
Discussion: Mutations in *SQSTM1* contribute to ALS pathogenesis through dysregulation of autophagy, impaired protein clearance, and excessive neuroinflammation mediated by NF-κB activation. The interplay between NF-κB and Nrf2 signaling pathways suggests that targeted therapeutic modulation may attenuate neurodegeneration. The patient's case illustrates the clinical and molecular heterogeneity of ALS and supports the concept of pathway-specific, precision medicine approaches.
Conclusions: This case highlights the relevance of *SQSTM1*-related pathogenic mechanisms within the heterogeneous ALS spectrum and underscores the importance of advanced genetic testing for identifying candidates for personalized therapy.

Keywords: amyotrophic lateral sclerosis (ALS), *SQSTM1* mutation, p62, NF-κB, Nrf2, autophagy, precision medicine, neuroinflammation.

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Introduction

Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disorder characterised by progressive motor neuron degeneration. The pathogenesis of ALS is multifactorial, involving neuroinflammatory processes, oxidative stress, and autophagy dysregulation [1]. Notably, excessive activation of the NF-κB pathway has been recognized as a key mechanism contributing to neurodegeneration, particularly in the context of ALS associated genetic mutations, including *C9orf72*, *SOD1*, *TDP-43*, *FUS*, *SQSTM1*, *OPTN*, and *TBK1* [2–7].

The *p62/SQSTM1* protein plays a pivotal role in regulating autophagy and mediating the crosstalk between the NF-κB and Nrf2 pathways, thereby maintaining neuronal homeostasis. Mutations in *SQSTM1* have been implicated in disrupting these mechanisms, leading to chronic oxidative stress and exacerbated neuroinflammatory processes [8, 9].

In this study, we present a case of a patient with ALS harbouring a *SQSTM1* mutation (*c.1175C>T; p.Pro392Leu*), providing direct insights into the pathogenic mechanisms underlying the disease. Given that *SQSTM1* dysfunction may disturb the balance between NF-κB activation and Nrf2-mediated neuroprotection, this mutation could drive sustained neuroinflammation and impaired proteostasis. These findings highlight the potential therapeutic relevance of targeting NF-κB signalling and restoring autophagic homeostasis as part of a genetically informed, precision medicine approach in ALS.

Materials and Methods

Study design

This study presents a case report of a patient diagnosed with amyotrophic lateral sclerosis (ALS) harbouring a pathogenic variant in the *SQSTM1* gene, supplemented by a comprehensive genetic analysis and a review of the literature. The review focuses on the role of p62, the NF-κB pathway, and autophagy in ALS pathogenesis, with particular emphasis on the potential therapeutic implications of epigenetic modulation.

Genetic analysis

A genetic analysis was conducted to identify the *SQSTM1* (c.1175C>T; p.Pro392Leu) variant. Genomic DNA was extracted from the patient's peripheral blood. Initial screening was performed using next-generation sequencing (NGS) with an ALS/FTD gene panel, which did not reveal any pathogenic variants. Given the negative result of the primary screening, a comprehensive triple genomic analysis was undertaken, comprising:

- Whole-exome sequencing (WES) — to detect single-nucleotide variants and small insertions/deletions (indels).
- Repeat-primed PCR (RP-PCR) — specifically targeting *C9orf72* expansions, a well-established genetic contributor to ALS.
- Multiplex ligation-dependent probe amplification (MLPA) — employed to identify copy number variations (CNVs) in ALS-associated genes.

The extended genomic investigation confirmed the presence of a heterozygous *SQSTM1* mutation inherited from the patient's father. This variant has previously been reported as a risk factor for ALS and frontotemporal dementia-associated ALS (FTDALS3) (PMID: 24042580, 24899140).

Literature review

A literature review was conducted using *PubMed*, *Scopus*, and *Web of Science*, focusing on the following key areas:

- The role of p62 (*SQSTM1*) in ALS and other neurodegenerative diseases.
- The NF-κB and Nrf2 signalling pathways and their involvement in ALS-related neuroinflammation and autophagy dysregulation.
- Epigenetic mechanisms regulating gene expression in ALS, with particular reference to histone deacetylase (HDAC) inhibitors and resveratrol as potential therapeutic agents.
- Preclinical and clinical research on NF-κB and autophagy-targeted therapies in ALS.

The collected data enabled a contextualisation of the patient's case within a broader pathophysiological and therapeutic framework, providing insights into the potential for personalised therapeutic strategies in ALS management.

Case report

A 49-year-old female patient presented with initial symptoms of amyotrophic lateral sclerosis (ALS) approximately 12 months prior to diagnosis, manifesting as progressive speech disturbances. Neurological examination revealed tongue atrophy with fasciculations, exaggerated pharyngeal and palatal reflexes, and the presence of frontal release signs. Additionally, atrophy of the first dorsal interosseous muscle of the right hand was observed.

Electrophysiological studies demonstrated chronic neurogenic changes at the bulbar level and in the cervical spinal cord. A comprehensive differential diagnostic workup was conducted, including magnetic resonance imaging (MRI) of the brain and spinal cord, cerebrospinal fluid (CSF) analysis, and autoantibody screening, all of which failed to reveal alternative neurodegenerative or immune-mediated conditions. Based on the clinical presentation and supplementary investigations, a diagnosis of ALS was established based on Golden Coast criteria.

Genetic testing was conducted by CeGaT GmbH (Tübingen, Germany), including trio whole-exome sequencing and targeted panel analysis (BSCL2, GBE1, HEXA). The SQSTM1 variant c.1175C>T; p.Pro392Leu (ClinVar ID: 8108) was identified in a heterozygous state and classified as likely pathogenic according to ACMG/ACGS guidelines (PS3, PS4, PM2; cumulative score +7). The variant was paternally inherited. Laboratory confirmation was performed in accordance with CAP and ISO 15189:2014 standards. Use of this data complies with the German Genetic Diagnostics Legislation. This variant has previously been described as a risk factor for ALS and frontotemporal dementia-associated ALS (FTDALS3) (PMID: 24042580, 24899140).

The patient was initiated on treatment with dimethyl fumarate, which has potential neuroprotective properties via activation of the Nrf2 pathway. Additionally, nonsteroidal anti-inflammatory drugs (NSAIDs), celecoxib were introduced to modulate NF-κB activity. Rapamycin, an mTOR inhibitor with potential effects on autophagic processes in motor neurons, was also included in the treatment regimen.

Discussion

Mutations in the *SQSTM1* gene, encoding the p62 protein, have been implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTDALS3), exhibiting significant phenotypic heterogeneity [10]. p62 plays a crucial role in cellular homeostasis by regulating autophagy, proteostasis, and intracellular signalling, particularly through the NF-κB and Nrf2 pathways [11]. Dysfunction of p62 due to *SQSTM1* mutations leads to impaired degradation of misfolded proteins, contributing to the accumulation of TDP-43, SOD1, and FUS aggregates, which are hallmark features of ALS pathology [12]. Moreover, excessive NF-κB activation driven by p62 dysregulation exacerbates neuroinflammation, further accelerating motor neuron degeneration [10].

The clinical presentation of *SQSTM1*-associated ALS is highly variable, with some patients developing concomitant frontotemporal dementia or Paget disease of bone, highlighting the multisystemic impact of these mutations [13]. Studies have identified multiple missense mutations, including *P392L*, in ALS patients, with a frequency of 2–3% in both familial and sporadic cases [14]. Functional analyses suggest that these mutations disrupt selective autophagy, impair protein clearance, and alter oxidative stress responses [10]. Given the involvement of *SQSTM1* in multiple neurodegenerative processes, therapeutic strategies targeting NF-κB inhibition, autophagy enhancement, and Nrf2 activation have been proposed [11].

Further research is needed to elucidate the precise pathogenic mechanisms of *SQSTM1* mutations and their role in disease heterogeneity. Advanced molecular studies, including gene-editing models and autophagy-targeted therapies, may pave the way for personalised treatment approaches in ALS and related disorders [12].

Inflammation plays a crucial role in the pathogenesis of amyotrophic lateral sclerosis (ALS), as evidenced by numerous studies on microglial activation and pro-inflammatory signalling pathways. Rifai *et al.* (2023) identified two distinct neuroinflammatory profiles (NPS1 and NPS2), which differ in the degree of NF-κB activation and the expression of pro-inflammatory genes [15].

The NPS1 profile is characterised by excessive NF-κB activation and increased expression of pro-inflammatory genes, such as *TNF-α*, *IL-6*, and *CD163*. This phenotype is associated with heightened neuroinflammation, predominant microglial activation, and accelerated disease progression. In contrast, the NPS2 profile exhibits lower NF-κB activity and increased expression of genes related to axonal transport and synaptic function, which may correlate with a slower disease course [15].

Furthermore, the interaction between NRF2 and NF-κB suggests that oxidative stress and inflammation are closely interconnected in ALS. NRF2 is a key regulator of antioxidant defence mechanisms, while NF-κB governs inflammatory responses. Under physiological conditions, the balance between these pathways allows for the neutralisation of reactive oxygen species and neuronal protection. However, in ALS, excessive NF-κB activation suppresses NRF2, leading to increased oxidative stress, enhanced motor neuron degeneration, and the accumulation of pathological proteins such as TDP-43 and SOD1 [16].

Sulejczak *et al.* (2023) analysed the expression of NF-κB subunits (*p50* and *p65*) in spinal motor neurons of patients with sporadic ALS (sALS). Their findings revealed significantly reduced NF-κB expression in ALS motor neurons compared to healthy controls. Moreover, NF-κB localisation was altered — being predominantly present in the cytoplasm rather than the nucleus in ALS neurons, which limits its role in regulating protective gene expression. In contrast, NF-κB in glial cells exhibited excessive activation, highlighting the critical role of neuroinflammation in ALS pathogenesis [17].

These findings suggest that NF-κB dysregulation in ALS is multifaceted, involving both impaired neuroprotective NF-κB activity in motor neurons and its excessive activation in glial cells. Concurrent disruption of NRF2 interactions exacerbates oxidative stress, further driving neuronal degeneration. Therefore, targeted therapeutic strategies that simultaneously inhibit NF-κB in microglia while preserving its protective role in neurons could be pivotal in the personalised treatment of ALS [15–17].

The NF-κB signalling pathway is a key regulator of inflammatory and immune responses. It consists of a highly conserved family of transcription factors, including p50, p52, p65 (RelA), c-Rel, and RelB, which remain sequestered in the cytoplasm under resting conditions by IκB inhibitors. NF-κB activation occurs through two primary pathways:

- The canonical NF-κB pathway (rapid) — activated by p65, p50, and c-Rel in response to infections and pro-inflammatory cytokines, leading to the production of cytokines such as TNF-α and IL-6.
- The non-canonical NF-κB pathway (slower) — regulated by NIK and p100/p52, playing a role in long-term immune regulation and cellular differentiation [18].

NF-κB activation exerts distinct effects across different CNS cell types, including neurons, microglia, and astrocytes, contributing to ALS progression through cell-specific mechanisms.

NF-κB in Neurons

Under physiological conditions, NF-κB plays an essential role in synaptic plasticity, memory formation, and learning [19]. However, its chronic activation under pathological conditions promotes neurodegeneration.

- Increased NF-κB activity has been observed in the spinal cords of ALS patients, correlating with oxidative stress and neuronal loss [12].
- Studies in ALS mouse models (SOD1G93A, TDP-43) indicate that NF-κB inhibition improves motor and cognitive function and prolongs survival [20].
- NF-κB inhibition also reduces mutant SOD1 accumulation, suggesting a potential neuroprotective strategy [1].

NF-κB in Microglia

Microglia, as key mediators of CNS immunity, undergo chronic activation in ALS, shifting towards two distinct phenotypes:

- M1 (pro-inflammatory) — produces neurotoxic cytokines (e.g., TNF-α, IL-1β), which amplify neuronal degeneration.
- M2 (anti-inflammatory) — promotes neuroprotection and tissue repair.

In ALS, the M1 phenotype dominates, exacerbating disease progression [21].

- In *SOD1G93A* mice, sustained NF-κB activation in microglia accelerates axonal degeneration and motor neuron death [22].
- Blocking NF-κB in microglia enhances neuronal survival and delays disease onset [3].

NF-κB in Astrocytes

Astrocytes exhibit a dual role in ALS, initially providing neuroprotection but later transitioning to neurotoxic functions.

- They regulate glutamate clearance from synapses, a process governed by NF-κB [23].
- Under pathological conditions, NF-κB activation in astrocytes disrupts neuroprotective functions, leading to the secretion of pro-inflammatory and neurotoxic factors [24].
- Microglia and astrocytes mutually activate NF-κB, intensifying inflammatory cascades in ALS [25].
- ALS models indicate that NF-κB silencing in astrocytes alone is insufficient for therapeutic benefits, underscoring the necessity of simultaneous microglial modulation [26].

These findings suggest that NF-κB-targeted therapies in ALS should consider the dynamic interactions between neurons, microglia, and astrocytes, with treatment efficacy potentially depending on the timing of intervention and underlying pathological mechanisms driving disease progression.

Emerging evidence suggests that autoimmune inflammation plays a critical role in sporadic ALS (sALS), driving cytotoxic T-cell infiltration and chronic NF-κB activation. Persistent NF-κB activation induces the expression of pro-inflammatory cytokines, including IL-1β, IL-6, and IFN-γ, thereby exacerbating neurodegeneration. One of the mechanisms linking NF-κB to ALS pathology involves the cGAS-STING pathway, responsible for detecting cytoplasmic DNA abnormalities in neurons [27].

Dimethyl fumarate (DMF), a prodrug metabolised into monomethyl fumarate (MMF), activates the Nrf2 pathway while inhibiting NF-κB, reducing oxidative stress and inflammation. In ALS models, DMF has been shown to suppress NLRP3 inflammasome activation, improve motor function, and mitigate neuronal degeneration. Therapeutic doses equivalent to 480 mg/day demonstrated neuroprotective effects. However, despite its clear anti-inflammatory and antioxidant properties, the overall clinical benefit of DMF in ALS remains limited, and its efficacy appears to depend on disease-specific mechanisms, requiring further validation as a potential ALS treatment [28].

DMF, widely used in multiple sclerosis therapy, exhibits potent immunomodulatory and NF-κB-inhibitory effects, positioning it as a candidate for ALS treatment. Studies assessing DMF's impact on pro-inflammatory cytokine expression and NF-κB activity in ALS patients and cellular models applied doses equivalent to 480 mg/day, mirroring those used in multiple sclerosis. Findings revealed that DMF reduces IL-1β, IL-6, and IFN-γ levels while attenuating microglial and T-cell activation, suggesting its potential neuroprotective role [29].

A randomised, double-blind, phase 2 clinical trial assessed the safety and efficacy of DMF in ALS. 107 patients were divided into groups receiving DMF (480 mg/day) or placebo, with a 36-week observation period. The results demonstrated that DMF failed to slow ALS progression, showing no significant improvement in ALSFRS-R scores, respiratory function, or quality of life. Although a minor reduction in neurophysiological decline was observed, the effect was not statistically significant. DMF was well tolerated; however, its immunomodulatory effects proved insufficient in halting neurodegeneration in ALS [30].

These findings provide class I evidence confirming that DMF alone is not sufficient to alter ALS progression, highlighting the complexity of neuroinflammatory mechanisms in the disease [29]. While NF-κB modulation remains a promising therapeutic avenue, a more comprehensive, multi-targeted approach addressing oxidative stress, protein homeostasis, and neuroinflammation is required to achieve meaningful clinical benefits.

The mechanistic target of rapamycin (mTOR) pathway is a critical regulator of cellular metabolism, influencing synaptic plasticity, autophagy, and protein synthesis [31, 32]. In neurodegenerative

diseases, excessive mTORC1 activation disrupts autophagy, leading to the accumulation of toxic proteins, including β-amyloid, phosphorylated tau, and α-synuclein [31, 33].

Preclinical studies on ALS models suggest that mTOR inhibition via rapamycin may offer therapeutic benefits, enhancing protein degradation pathways and slowing disease progression [34–36]. However, the impact of rapamycin on neurodegenerative diseases is complex and context-dependent. Studies in SOD1^G93A mice have demonstrated that rapamycin at a dose of 2 mg/day, instead of exerting neuroprotective effects, accelerates motor neuron degeneration and shortens survival. Despite inducing autophagy, SOD1 aggregate degradation remained insufficient, indicating a failure of the autophagy process at the level of autophagosome clearance. Moreover, increased mitochondrial damage and apoptosis activation were observed, which may further contribute to neurodegeneration. These findings challenge the assumption that autophagy activation is inherently beneficial in ALS, underscoring the need for precise modulation of protein degradation pathways [37].

A phase 2 clinical trial of rapamycin in ALS, published in 2023, aimed to assess its safety, biological efficacy, and potential clinical effects. The study enrolled 63 patients, who received rapamycin at doses of 2 mg/m²/day, 1 mg/m²/day, or a placebo. While rapamycin demonstrated anti-inflammatory properties, reducing IL-18 expression, it failed to alter ALS progression or improve patient quality of life. The higher dose (2 mg/m²/day) showed greater effects on inflammatory biomarkers but was also associated with more frequent adverse events, including gastrointestinal disturbances and immunosuppression. Neurofilament levels remained stable, suggesting no measurable impact on neurodegeneration. Although the drug was well tolerated, its limited blood-brain barrier penetration may have contributed to its lack of clinical efficacy [38].

Recent studies using a zebrafish model with SQSTM1 knockdown have demonstrated that loss of SQSTM1 function leads to motor deficits and axonal shortening in motor neurons, closely mirroring the pathophysiology of ALS and frontotemporal lobar degeneration (FTLD). These findings were accompanied by hyperactivation of the mTOR pathway, suggesting that SQSTM1/p62 functions as a negative regulator of mTOR signalling. Rapamycin administration at 100 nM partially rescued motor deficits and promoted axonal elongation, indicating a beneficial effect of autophagy induction under SQSTM1-deficient conditions. However, ALS/FTLD-associated SQSTM1 mutations failed to restore normal phenotype, implying that disease pathogenesis is driven by a loss-of-function mechanism rather than a toxic gain-of-function effect of the mutant protein [39].

Ubiquitination plays a crucial role in regulating protein homeostasis and inflammatory processes in neurodegenerative diseases such as Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). In particular, linear ubiquitination (Met1-linked ubiquitination), catalyzed by the LUBAC (Linear Ubiquitin Chain Assembly Complex), influences NF-κB pathway activation, which may exacerbate neuroinflammatory processes contributing to disease pathogenesis. In ALS, TDP-43 aggregates contain both K48-linked ubiquitin chains (associated with proteasomal degradation) and K63/M1-linked chains (involved in autophagy and NF-κB signaling), suggesting a multifaceted role of ubiquitination in disease progression. Research on targeted ubiquitination modulation opens new avenues in neurodegenerative disease therapy by controlling protein aggregation and inflammatory responses [40].

An analysis of data from five large cohort studies involving over 780,000 participants found that the use of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, does not significantly affect the risk of developing ALS. These findings suggest that, despite previous hypotheses regarding the role of chronic inflammation in ALS pathogenesis, NSAIDs do not exhibit

a neuroprotective effect, highlighting the need for further research into neuroinflammatory mechanisms and potential therapeutic targets [41].

Chronic neuroinflammation plays a crucial role in ALS pathogenesis, leading to microglial activation and excessive production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, which contribute to motor neuron degeneration. Clinical studies on PrimeC (ciprofloxacin + celecoxib) have shown that celecoxib, a selective COX-2 inhibitor, may help reduce neuroinflammation in the CNS by lowering pathological TDP-43 levels and enhancing autophagy mechanisms. While previous studies on NSAIDs in ALS have not demonstrated clear efficacy, combination therapies targeting both inflammation and protein degradation may offer a more effective therapeutic approach. Further clinical research is necessary to determine the optimal strategies for modulating neuroinflammation in ALS and their potential impact on disease progression [42].

Conclusions

The presented data underscore the critical importance of advanced genetic diagnostics in identifying patients within the heterogeneous spectrum of diseases exhibiting an amyotrophic lateral sclerosis (ALS) phenotype. The complexity of the molecular mechanisms underlying ALS highlights the necessity of personalized therapeutic strategies, particularly in the context of rapid advancements in gene therapy.

A growing body of evidence suggests that the timing of therapeutic intervention is a crucial determinant of efficacy, with earlier administration significantly improving treatment outcomes. For instance, NF-κB inhibition should precede the transition of astrocytes from an anti-inflammatory to a pro-inflammatory state, thereby enhancing neuroprotective effects. Likewise, delayed administration of rapamycin has been associated with exacerbated muscle degeneration, underscoring the importance of precise therapeutic sequencing to maximize benefits while minimizing adverse effects.

While NF-κB modulation via dimethyl fumarate has demonstrated potential neuroprotective effects, current findings indicate that DMF alone is insufficient to halt ALS progression. This reinforces the necessity of comprehensive, multi-targeted treatment strategies, incorporating neuroinflammation modulation, autophagy regulation, and oxidative stress reduction to optimize clinical efficacy.

Autophagy modulation via mTOR inhibition remains a promising therapeutic avenue in ALS and FTLD, further emphasizing the pivotal role of SQSTM1 in neuronal homeostasis. However, merely inducing autophagy may be ineffective if degradation pathways are already compromised or if simultaneous activation of inflammatory and apoptotic cascades negates its potential benefits.

Beyond direct disease modification, timing also plays a critical role in sustaining patient survival long enough to allow for the development and implementation of precision-based genetic therapies. The future of ALS treatment will likely rely on highly individualized genetic interventions, such as gene silencing and neurotrophic gene implantation, which hold promise for targeted molecular correction and long-term disease stabilization. The growing success of therapies like tofersen further underscores the importance of therapeutic window optimization, reinforcing the concept that early and precisely timed interventions are essential for achieving meaningful clinical impact.

However, a major limitation in achieving effective therapeutic concentrations of drugs in the central nervous system is the restrictive nature of the blood-brain barrier (BBB). Given that ALS pathology occurs primarily within this immunologically privileged compartment, many promising neuroprotective agents face challenges in reaching their intended targets at sufficient

concentrations. Addressing BBB permeability through advanced drug delivery systems, such as nanoparticle-based transport, receptor-mediated transcytosis, or direct CNS administration, will be essential to fully harness the potential of emerging ALS therapies.

In conclusion, an effective ALS treatment paradigm must integrate a time-sensitive, multimodal approach, encompassing autophagy modulation, neuroinflammation control, oxidative stress attenuation, and personalized genetic therapies. Future research should focus on refining the precise sequencing and combination of these interventions, while also overcoming the pharmacokinetic limitations imposed by the BBB, aiming to extend survival, slow disease progression, and enhance the quality of life for ALS patients.

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Conflict of interest

None declared.

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Ethics and consent

Written informed consent was obtained from the patient for publication of this case report.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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