

Challenges in Managing Disorganized Schizophrenia with Comorbid Treatment Non-Adherence: A Case Study from Indonesia

Muhammad Suro Madani¹, Hafid Algristian², Dian Setyorini³

¹²Universitas Nahdlatul Ulama Surabaya, East Java, Indonesia, ³Rumah Sakit Radjiman Wediodiningrat Lawang, Malang, Indonesia

Correspondence: dr.hafid@unusa.ac.id²

Abstract

Schizophrenia is a severe and chronic psychiatric disorder in which long-term adherence to antipsychotic medication is essential for relapse prevention, yet non-adherence remains highly prevalent, particularly in resource-limited settings such as Indonesia where families serve as primary caregivers. We report the case of an adult male with disorganized-type schizophrenia who experienced repeated relapses precipitated by persistent non-adherence driven by profound anosognosia and treatment fatigue. Upon admission, he presented with prominent persecutory, grandiose, and nihilistic delusions, marked disorganization, and complete lack of insight. This case illustrates a critical clinical paradox: the core symptom of schizophrenia—anosognosia—directly undermines its primary treatment modality when delivered in oral form. The case also reflects cultural and systemic challenges unique to Indonesian mental healthcare, including high caregiver burden and limited continuity of community-based services. Drawing from current global and regional evidence, we propose an integrated management model that positions long-acting injectable (LAI) antipsychotics as the pharmacological foundation to bypass daily adherence barriers, enabling more effective implementation of culturally adapted psychosocial interventions such as family psychoeducation and motivational interviewing. The novelty of this report lies in demonstrating how the interplay between neurobiological deficits, treatment fatigue, and sociocultural dynamics contributes to non-adherence, while highlighting how an LAI-based, culturally responsive, and system-aware strategy can disrupt the cycle of relapse and rehospitalization. This case underscores the importance of incorporating LAIs earlier in treatment planning and strengthening family-centered care within Indonesia's mental health system.

KEYWORDS

schizophrenia; non-adherence; anosognosia; long-acting injectables; cultural adaptation; family psychoeducation; Indonesia.

Introduction

Schizophrenia is a severe, chronic, and disabling psychiatric disorder that affects approximately 24 million people worldwide and remains one of the leading causes of years lived with disability among mental disorders (World Health Organization, 2021). Characterized by profound disturbances in perception, thought processes, emotional regulation, and social functioning, schizophrenia often follows a relapsing course that imposes substantial burdens on patients, families, and healthcare systems (Kane et al., 2019). Despite major advances in antipsychotic pharmacotherapy and psychosocial interventions, relapse continues to represent a central clinical challenge, with treatment non-adherence consistently identified as the most significant modifiable risk factor for symptom recurrence and rehospitalization (Haddad et al., 2014; Samalin et al., 2016).

In low- and middle-income countries (LMICs), including Indonesia, the management of schizophrenia is further complicated by structural limitations within mental health systems, such as restricted access to specialized services, shortages of trained mental

health professionals, and fragmented continuity of care following hospital discharge health professionals, and fragmented continuity of care following hospital discharge (Hartini & others, 2018; World Health Organization, 2021). Epidemiological studies indicate that the prevalence of psychotic disorders in Indonesia remains substantial, with many patients experiencing delayed diagnosis, intermittent treatment engagement, and recurrent relapse over the course of illness (Hartini & others, 2018). These challenges are compounded by sociocultural dynamics in which families assume the role of primary caregivers, often without adequate psychoeducation or professional support (Keliat & others, 2020).

Contemporary diagnostic frameworks, including the DSM-5-TR and ICD-11, conceptualize schizophrenia as a heterogeneous disorder involving positive symptoms, negative symptoms, cognitive impairment, and substantial variation in clinical course (American Psychiatric Association, 2022; Gaebel et al., 2020). Among these dimensions, impaired insight—commonly referred to as anosognosia—has emerged as a particularly influential determinant of treatment adherence and long-term outcomes (Bora & Murray, 2014; Lincoln & others, 2018). Anosognosia is not merely a psychological defense mechanism or a product of denial, but a neurobiologically grounded deficit in self-awareness that affects up to half of individuals with schizophrenia (Amador & David, 2020).

Neuroimaging and neuropsychological studies suggest that impaired insight is associated with dysfunction in frontal and parietal networks involved in self-monitoring and error awareness, rendering patients unable to recognize their illness or the need for ongoing treatment (Amador & David, 2020; Bora & Murray, 2014). The clinical implications of anosognosia are profound. Patients who lack insight are significantly more likely to discontinue antipsychotic medication, disengage from outpatient services, and experience repeated relapses requiring hospitalization (Haddad et al., 2014; Ochoa & others, 2020).

Importantly, symptomatic improvement during inpatient treatment does not necessarily translate into sustained adherence after discharge, as insight often remains impaired even when positive symptoms are partially controlled (Amador & David, 2020). This creates a paradoxical situation in which the core pathology of schizophrenia directly undermines its primary treatment modality, particularly when pharmacotherapy relies on daily oral medication that requires patient cooperation and insight (Velligan & others, 2017).

Global evidence consistently demonstrates that non-adherence to antipsychotic medication is associated with increased relapse rates, longer hospital stays, higher healthcare costs, and poorer functional outcomes (Kane et al., 2019, 2025; Samalin et al., 2016). Real-world studies estimate that up to 40–60% of patients with schizophrenia exhibit partial or complete non-adherence within the first year of treatment (Haddad et al., 2014). In LMIC settings, these figures may be even higher due to limited access to medications, inconsistent follow-up, and sociocultural factors influencing illness beliefs (Caqueo-Úrizar et al., 2020).

Long-acting injectable antipsychotics (LAIs) have been developed to address adherence-related challenges by eliminating the need for daily medication intake. Evidence from Asian populations also suggests that LAIs can provide comparable efficacy and safety to oral antipsychotics while improving treatment continuity and reducing relapse or hospitalization in selected patients (Ma et al., 2023). LAIs provide sustained therapeutic plasma levels over extended periods, thereby reducing the risk of abrupt discontinuation and covert non-adherence (Kishimoto & others, 2013). Meta-analyses and real-world studies demonstrate that LAIs are associated with lower relapse rates, reduced hospitalization,

and improved treatment continuity compared with oral antipsychotics, particularly among patients with a history of non-adherence (Correll et al., 2021; Kishi et al., 2021).

Despite these benefits, LAIs remain underutilized in many Asian countries due to clinician hesitancy, stigma, and systemic barriers related to access and service organization (Chang et al., 2020; Ma et al., 2023). In Indonesia, uneven distribution of psychiatric services and limited integration between inpatient and community-based care further restrict LAI implementation (Hartini & others, 2018; World Health Organization, 2021).

Beyond individual outcomes, relapse in schizophrenia carries substantial societal and economic consequences. Each relapse episode is associated with accelerated functional decline, reduced likelihood of employment, and cumulative cognitive impairment, contributing to long-term disability and increased healthcare utilization (Kane et al., 2019, 2025; Patel & others, 2023). From a policy perspective, relapse prevention represents a critical target for reducing the overall burden of schizophrenia in resource-limited settings.

Within the Indonesian context, these challenges intersect with cultural norms emphasizing family responsibility and respect for patient autonomy. Families may hesitate to enforce medication adherence when patients deny illness, particularly in the absence of clear clinical guidance (Chan & Yu, 2021; Keliat & others, 2020). Gaps in community mental health services further delay early intervention when relapse emerges (World Health Organization, 2021).

Despite these realities, empirical literature from Indonesia remains limited regarding integrated strategies to address severe non-adherence driven by anosognosia. Consequently, clinically grounded case-based evidence is needed to illustrate how pharmacological and psychosocial interventions can be adapted to local healthcare structures and cultural expectations.

By presenting a detailed case of chronic schizophrenia complicated by profound anosognosia and treatment fatigue, this report aims to address this gap and highlight how early adoption of LAIs combined with culturally attuned family psychoeducation may interrupt the cycle of relapse and rehospitalization.

Methods

Study Design and Case Report Approach

This study employed a descriptive case report design to describe the clinical characteristics, treatment non-adherence, clinical management, and treatment response of an adult male with disorganized schizophrenia complicated by profound impairment of insight (anosognosia). The case was selected because of the recurrent relationship between treatment non-adherence, impaired insight, treatment fatigue, and repeated relapse requiring hospitalization. The report was prepared with reference to the CARE (CASE REport) guideline to support transparent reporting of the patient's clinical history, clinical findings, diagnostic assessment, therapeutic interventions, clinical course, and outcomes.

Data Collection

Clinical information was obtained from the patient's psychiatric assessment, mental status examination, collateral interviews with family members, and review of previous hospitalization records. Information regarding the patient's psychiatric history, treatment adherence, previous relapses, medication discontinuation, family involvement, and clinical course was derived from available clinical documentation and information provided by the patient's family. Laboratory investigations and neuroimaging results were also reviewed to identify potential organic conditions that could contribute to the patient's psychiatric presentation.

Clinical Assessment

The clinical assessment focused on the patient's psychiatric history, psychotic symptoms, behavioral manifestations, treatment adherence, insight, and family-related factors affecting continuity of care. Mental status examination was performed to document the characteristics and severity of psychotic symptoms, including disorganized speech, delusional content, psychomotor agitation, behavioral abnormalities, and insight. At admission, the patient's insight was clinically assessed as absent (Grade 0). Diagnostic assessment was based on the clinical presentation, psychiatric history, mental status examination, collateral information, and available medical records. Laboratory investigations and neuroimaging were reviewed to exclude significant organic abnormalities.

Therapeutic Intervention and Follow-up

Management consisted of acute pharmacological stabilization followed by maintenance pharmacotherapy and psychosocial intervention. During the acute phase of hospitalization, intramuscular haloperidol and lorazepam were administered to manage severe psychomotor agitation. Following clinical stabilization, a long-acting injectable (LAI) antipsychotic was selected as the maintenance treatment because of the patient's history of repeated relapse associated with discontinuation of oral antipsychotic medication and persistent lack of insight. Paliperidone palmitate LAI was subsequently initiated after treatment options were discussed with the family. Treatment tolerability was monitored during initiation and titration.

Psychosocial management included structured family psychoeducation addressing the nature of schizophrenia, anosognosia, recognition of psychotic symptoms and early warning signs, the importance of treatment continuity, and the role of caregivers in supporting treatment and follow-up. Before discharge, a relapse-prevention plan was established that included scheduled LAI administration, caregiver-based monitoring, recognition of early warning signs, and regular outpatient psychiatric follow-up.

Outcome Assessment

Clinical outcomes were evaluated descriptively based on changes in psychomotor agitation, behavioral organization, intensity of psychotic symptoms, medication acceptance, insight, treatment tolerability, and the establishment of a relapse-prevention plan. Changes in the patient's clinical condition during hospitalization were assessed through repeated clinical observation and psychiatric evaluation. Because this report describes a single patient, no inferential statistical analysis was performed. Long-term functional outcomes beyond the observed stabilization period were not systematically assessed.

Result and Discussion

Clinical Characteristics and Initial Assessment

The patient was a 28-year-old unmarried male living with his nuclear family in an urban area of Indonesia. He had a seven-year history of schizophrenia, predominantly characterized by disorganization, with multiple relapses and recurrent hospitalizations. His illness began in late adolescence and was initially characterized by social withdrawal, disorganized thinking, and frequent episodes of inappropriate laughter. Over the subsequent course of illness, his symptoms progressed to severe disorganization, marked incoherence, and persistent delusional themes, including persecutory, grandiose, and nihilistic delusions.

The patient had no reported history of substance use, neurological disorders, or significant medical comorbidities.

Before the current admission, he had discontinued oral antipsychotic medication for approximately four months despite attempts by his family to supervise medication intake. The discontinuation was associated with profound anosognosia, reflected in his persistent belief that he was not ill and therefore did not require treatment. Treatment fatigue was also evident, as the patient reported that medication made him feel "slow" and interfered with his sense of autonomy.

At presentation to the emergency department, the patient exhibited severe disorganization, including loose associations, derailment, neologisms, and incoherent speech. He demonstrated marked psychomotor agitation, occasional muttering, and inappropriate laughter. His delusional content included beliefs that neighbors were plotting to kill him and that he possessed supernatural abilities. Insight was absent and clinically documented as Grade 0. The patient refused oral medication during the initial assessment.

A comprehensive psychiatric evaluation was conducted, including mental status examination, collateral interviews with family members, and review of previous hospitalization records. Laboratory investigations and neuroimaging did not reveal significant abnormalities. Based on the severity of the psychotic symptoms, level of agitation, and complete lack of insight, the patient was admitted for inpatient stabilization.

Acute Treatment and Clinical Stabilization

During the initial days of hospitalization, the patient remained markedly disorganized, with incoherent speech, loose associations, and persistent persecutory and grandiose delusions. Insight remained completely absent, and he continued to refuse oral medication. Considering the severity of his agitation and the need for acute behavioral stabilization, intramuscular haloperidol and lorazepam were administered.

Following a reduction in acute agitation, the treatment team evaluated options for long-term maintenance treatment. Given the patient's history of repeated relapse directly associated with abrupt discontinuation of oral antipsychotic medication, persistent lack of insight, and difficulty maintaining medication adherence, a long-acting injectable (LAI) antipsychotic was selected as the primary maintenance strategy.

After discussion of treatment options with the family, paliperidone palmitate LAI was initiated. The patient was monitored for treatment tolerability, and no significant adverse effects were reported during the initiation and titration period.

Clinical Course Following Maintenance Treatment

Following acute pharmacological stabilization and initiation of paliperidone palmitate LAI treatment, the patient's clinical condition gradually improved during hospitalization. The severity of disorganization and intensity of delusional symptoms decreased, and his behavior became more structured and manageable compared with his initial presentation.

Despite improvement in behavioral organization and psychotic symptom intensity, insight into his illness remained minimal. Thus, symptomatic improvement was not accompanied by complete restoration of illness awareness. Persistent impairment of insight remained an important clinical feature of the case.

Prior to discharge, the treatment team established a relapse-prevention plan focused on maintaining treatment continuity. The plan included scheduled LAI administration, caregiver-based monitoring, recognition of early warning signs, and regular outpatient psychiatric follow-up. The family agreed to coordinate with the outpatient clinic to facilitate timely administration of subsequent injections and to monitor the patient's clinical condition after discharge.

Family Involvement and Psychosocial Intervention

Collateral interviews identified substantial caregiver burden and limited family understanding of anosognosia. The family

had previously attempted to supervise oral medication intake but experienced difficulty maintaining treatment continuity because the patient denied having a mental illness and resisted medication.

Structured family psychoeducation was therefore provided during hospitalization. The intervention focused on the nature of schizophrenia, the neurobiological basis of impaired insight, recognition of psychotic symptoms and early warning signs, the importance of treatment continuity, and the role of the family in supporting ongoing treatment and follow-up.

Following the psychoeducation, the family agreed to participate actively in the patient's treatment and relapse-prevention plan. Family involvement was incorporated into post-discharge care through coordination of scheduled LAI administration, monitoring for early warning signs, and support for regular outpatient follow-up.

Overall Clinical Outcome

The overall clinical course demonstrated improvement in acute psychomotor agitation, behavioral organization, and intensity of psychotic symptoms following inpatient stabilization and initiation of maintenance treatment with paliperidone palmitate LAI. Treatment was tolerated without significant adverse effects during the reported initiation period.

However, impaired insight persisted despite symptomatic improvement. The management approach therefore shifted from reliance on daily oral medication adherence toward a maintenance strategy supported by LAI administration, family psychoeducation, caregiver involvement, and structured outpatient follow-up.

Because this was a single case report, outcomes were evaluated descriptively based on the documented clinical course. No inferential statistical analysis was performed. Long-term functional outcomes and the sustained effect of the intervention beyond the observed stabilization period were not systematically assessed.

This case illustrates the complex interplay of neurobiological, behavioral, familial, and systemic factors underlying persistent treatment non-adherence in schizophrenia. Despite repeated symptomatic improvement during inpatient treatment, the patient experienced multiple relapses following discharge, reflecting a well-documented pattern in which stabilization is undermined by poor long-term adherence (Haddad et al., 2014; Ochoa & others, 2020). This trajectory underscores that relapse in schizophrenia is not solely a consequence of inadequate pharmacological efficacy but is frequently driven by structural vulnerabilities embedded within the illness itself.

Anosognosia emerged as the central determinant of non-adherence in this case. Extensive evidence indicates that impaired insight is among the strongest predictors of medication discontinuation, service disengagement, and rehospitalization in schizophrenia (Amador & David, 2020; Bora & Murray, 2014). Importantly, anosognosia is not a psychological defense or a motivational deficit but a neurocognitive impairment associated with dysfunction in frontal and parietal networks responsible for self-referential processing and illness awareness (Bora, 2019). Consequently, treatment models that rely on sustained insight as a prerequisite for adherence are inherently fragile in patients with persistent insight deficits.

Treatment fatigue further compounded the risk of non-adherence. Long-term oral antipsychotic use is frequently associated with subjective burdens, including emotional blunting, reduced perceived autonomy, and interference with daily functioning, all of which are associated with treatment discontinuation (Samalin et al., 2016; Velligan & others, 2017). When combined with anosognosia, treatment fatigue

creates a high-risk profile in which daily medication adherence becomes unsustainable regardless of prior relapse-related consequences. This dynamic reinforces contemporary conceptualizations of non-adherence as a predictable outcome of neurobiological dysfunction rather than a voluntary behavioral choice (Haddad et al., 2014; Ochoa & others, 2020).

From a longitudinal perspective, repeated relapse carries implications beyond symptom recurrence. Growing evidence supports a neuroprogressive model of schizophrenia, in which recurrent psychotic episodes are associated with cognitive decline, structural brain changes, and progressive functional impairment (Andreasen et al., 2013; Vita et al., 2021). In this context, relapse prevention is not merely a symptomatic goal but a critical strategy for preserving long-term psychosocial functioning. The relapse pattern observed in this case therefore highlights the urgency of implementing adherence strategies that are resilient to insight failure.

Within this framework, long-acting injectable antipsychotics should be understood not merely as alternative drug formulations but as structural interventions designed to compensate for illness-related adherence vulnerabilities. By decoupling medication delivery from daily patient decision-making, LAIs reduce reliance on sustained insight, motivation, and executive functioning (Correll et al., 2021; Kishimoto & others, 2013). Meta-analytic and real-world evidence consistently demonstrate that LAIs are associated with lower relapse rates and reduced hospitalization compared with oral antipsychotics, particularly among patients with a history of non-adherence (Kishi et al., 2021).

The timing of LAI initiation represents a critical determinant of outcome. Historically, LAIs have been reserved for later stages of illness following multiple treatment failures. However, emerging evidence suggests that earlier introduction—particularly in patients with recurrent relapse, marked anosognosia, or high caregiver burden—may prevent cumulative functional deterioration and reduce relapse-related neuroprogression (Kane et al., 2019, 2025; Yasuma & others, 2021). In the present case, prolonged reliance on oral antipsychotics allowed repeated relapse cycles to occur, supporting a shift toward proactive, risk-based LAI utilization rather than a reactive model contingent on repeated failure.

Family dynamics played a pivotal role in shaping treatment continuity. In collectivist societies such as Indonesia, families often function as primary caregivers and informal care coordinators, influencing treatment acceptance, monitoring, and follow-up (Chan & Yu, 2021; Keliat & others, 2020). However, limited understanding of anosognosia may lead families to misinterpret non-adherence as intentional refusal or oppositional behavior, inadvertently escalating interpersonal conflict and increasing expressed emotion—both of which are associated with relapse risk (Degan et al., 2018).

The family psychoeducation provided in this case functioned as a critical mediating intervention. By reframing non-adherence as a symptom-driven consequence of neurobiological impairment rather than a moral failure, psychoeducation reduced caregiver blame and facilitated collaborative decision-making. Evidence suggests that such interventions are associated with reductions in caregiver burden, improved adherence, and enhanced clinical stability (Caqueo-Úrizar et al., 2020; Keliat & others, 2020; Rodolico et al., 2022). In this case, improved family understanding played a central role in acceptance of LAI treatment and continuity of outpatient follow-up.

Sociocultural and structural factors further contextualize the relevance of this intervention. In LMIC settings, including Indonesia, mental health service delivery is often constrained by limited workforce capacity, inconsistent follow-up, transportation barriers, and stigma (Hartini & others, 2018; World Health Organization, 2021). Under such conditions, reliance on daily oral medication imposes a disproportionate

burden on patients and families. LAIs may partially mitigate these vulnerabilities by reducing visit frequency, minimizing the consequences of missed doses, and enhancing predictability of care (Patel & others, 2023).

Ethical considerations surrounding LAI use in patients with impaired insight warrant careful examination. Concerns regarding autonomy, coercion, and informed consent are frequently raised in relation to injectable treatments. However, ethical analysis must also account for the foreseeable harms associated with repeated relapse, including social marginalization, occupational decline, stigma, and increased healthcare utilization (Amador & David, 2020). Contemporary bioethical frameworks emphasize relational autonomy, recognizing that decision-making capacity is embedded within social and clinical contexts rather than existing in isolation (Jeste et al., 2018). When implemented transparently, with family involvement and clinical oversight, LAIs may enhance patient dignity by promoting stability and reducing crisis-driven interventions (Velligan & Maples, 2021).

From a recovery-oriented perspective, sustained symptom control achieved through LAIs may enable gradual engagement in psychosocial rehabilitation, vocational activities, and community participation. Functional recovery in schizophrenia is strongly contingent on relapse prevention, and repeated relapse has been identified as a major barrier to long-term social reintegration (Kane et al., 2019; Renwick & others, 2023; Vita et al., 2021). In this regard, LAIs may indirectly facilitate recovery trajectories that extend beyond symptom remission, particularly when integrated with family-centered and community-based supports.

At the policy level, this case contributes to ongoing debates regarding equitable access to long-acting antipsychotics in LMICs. Despite robust evidence supporting their effectiveness, LAIs remain underutilized due to cost concerns, limited clinician familiarity, and restrictive reimbursement policies (Chang et al., 2020; World Health Organization, 2021). Case-based evidence from LMIC contexts is therefore essential to inform locally relevant guidelines and challenge assumptions that LAIs are suitable only for high-resource settings.

The present case is also consistent with evidence that family-based interventions can complement pharmacological relapse prevention. A large network meta-analysis found that most family intervention models reduced relapse compared with treatment as usual, with family psychoeducation showing clinically meaningful benefit even when delivered as a relatively simple intervention (Rodolico et al., 2022). This supports the integrated approach used in the present case, in which LAI treatment was paired with family psychoeducation rather than treated as a stand-alone solution. In addition, evidence from Asian settings indicates that implementation of LAIs must be interpreted within local healthcare systems, patient attitudes, caregiver roles, and service-access constraints (Ma et al., 2023).

Several limitations should be acknowledged. As a single case report, generalizability is limited, and causal inferences cannot be established. Long-term functional outcomes beyond the stabilization period were not systematically assessed. Nevertheless, case reports remain valuable for elucidating mechanisms and contextual factors that are often obscured in large-scale studies, particularly in underrepresented settings (Gagnier & others, 2013).

In summary, this case reinforces the conclusion that effective relapse prevention in schizophrenia requires a shift away from insight-dependent treatment models toward structurally adaptive and culturally responsive strategies. The integration of long-acting injectable antipsychotics with family-

centered psychoeducation and system-aware planning offers a clinically sound, ethically defensible, and contextually appropriate approach to addressing persistent non-adherence, particularly in LMIC settings such as Indonesia.

Conclusion

This case highlights the critical interplay between neurobiological deficits, behavioral patterns, and sociocultural factors in shaping long-term treatment adherence among patients with schizophrenia. The patient's persistent anosognosia, compounded by treatment fatigue and limited continuity of care, created a cyclical pattern of relapse that oral antipsychotics alone were unable to interrupt. The introduction of a long-acting injectable antipsychotic provided a practical and effective strategy to overcome adherence barriers while enabling the delivery of structured psychosocial interventions.

The novelty of this report lies in demonstrating how adherence challenges emerge not from a single factor but from the convergence of impaired insight, family caregiving dynamics, and systemic constraints within the Indonesian mental health context. By integrating pharmacological stabilization with culturally aligned family psychoeducation, this case illustrates a comprehensive approach that can be adapted for similar settings where resources are limited and family involvement is central.

The clinical implication is that long-acting injectables should be considered earlier in the management of patients with chronic non-adherence driven by impaired insight, rather than being reserved as a last-line option. Strengthening family-focused care and improving continuity of community-based follow-up may further enhance outcomes. Future research should explore how integrative treatment models combining LAIs with culturally tailored psychosocial interventions can be implemented more broadly, and how such models may inform national strategies for relapse prevention in schizophrenia.

Author contributions

Muhammad Suro Madani, conceptualized the study, developed the research design, and led the overall coordination of the manuscript preparation, collected clinical data, contributed to the interpretation of the patient's clinical course, and drafted the initial sections of the Case Presentation and Clinical Management. Dian Setyorini performed the literature review, contributed to the synthesis of evidence in the Introduction and Discussion, and participated in revising the manuscript for intellectual content. Hafid Algristian supervised the methodological framework, ensured compliance with the CARE case report guidelines, and provided critical revisions to the final manuscript. All authors reviewed the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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