Delirium during COVID-19: A report of eight cases and a review of the literature

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Abstract. Delirium is an acute confusional state, often associated with long-term hospitalization, oxygen supplementation, the male sex and an older age. Since the start of the coronavirus disease 2019 (COVID-19) pandemic, there was an abrupt increase in intensive care unit (ICU) admissions and hospitalization in general, as well as in the need for oxygen therapy and enforced isolation due to the contagion risk. This caused a sudden increase in the episodes of delirium. The diagnosis of delirium, however, remains a difficult task, as it can often be misdiagnosed or confused with underlying dementia, particularly among the elderly. The present study describes present eight cases of patients admitted to hospital due to severe acute respiratory syndrome coronavirus 2 infection, who manifested delirium. Notably, only one of the patients had psychiatric comorbidities prior to hospitalization. The most prevalent sex was the male (7:1) one, the mean age of the patients was 81.7±4 years, and the mean duration of hospitalization was 23.6±6 days. In total, 3 patients had a virological recovery and were discharged, 3 had a clinical recovery and were transferred to a lower intensity COVID-19 facility and 2 patients did not survive. In the eight cases described herein, the mortality rate was 25%. Delirium was found to be commonly associated with a higher mortality rate and a longer hospitalization period. Therefore, it is imperative to develop protocols and tools with which to rapidly assess delirium and treat it accordingly. In addition, it is fundamental to improve the quality of life of hospitalized patients, supporting behavioral therapy and the environmental factors that can affect patients, to prevent delirium as well.

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Introduction

Delirium is an acute confusional state, also defined as acute brain failure or dysfunction. The pathophysiological mechanism behind delirium is not yet well understood. It is frequently observed in elderly individuals and in hospital settings (1,2).

Delirium is provoked by the transient disruption of regular neuronal activity and is associated with a slower recovery, increased mortality and morbidity, and a decreased quality of life (3).

According to the criteria of Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (4), the diagnosis of delirium requires a disturbance in attention, which develops acutely, is not explained by pre-existing dementia, and does not occur in the context of a reduced level of arousal, with one additional disturbance in cognition and evidence of an underlying organic disorder. Patients may experience hallucinations and manifest abnormal psychomotor behavior and a sleep-wake cycle (4).

Delirium can be described as hyperactive, hypoactive or a combination of both. Hyperactive delirium includes restlessness (for example, pacing), agitation, rapid mood changes or hallucinations and is more easily recognizable, while hypoactive, which includes a reduced motor activity, sluggishness and abnormal drowsiness, can pass unrecognized, despite being the most frequent among elderly patients, who usually manifest it with lethargy and a general slowness (5).

Delirium occurs in 85% of cases in palliative care settings, in up to 25% of patients post-surgery and in 50% of patients following major surgery (6). Beyond an older age and long-term hospitalization, other risk factors associated with the development of delirium are the male sex, underlying undiagnosed dementia, alcohol abuse, impairment in vision and/or hearing and depression (6,7).

Previous studies have suggested cerebral desaturation as a risk factor for the development of delirium (8-10), and it has been observed that the frequency of delirium is increased in intensive care units (ICUs) (11).

The appearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) abruptly led to a pandemic, particularly due to its transmission mode (12) and the onset of numerous variants (13,14). This rapidly led to an increase in the number of hospitalizations. The respiratory syndrome

consequent to coronavirus disease 2019 (COVID-19) (15), similar to the one caused by the first SARS-CoV, led to a sudden need in oxygen therapy, ventilation and admission to ICUs.

A number of complications, such as electrolytic impairment or macular rash, have been linked to SARS-CoV-2 infection (16-22). Neurological and psychiatric complications due to COVID-19 have also been described, such as obsessive-compulsive disorder or motor dysfunction (23,24). Researchers have already proven an increase in the number of episodes of delirium during the COVID-19 pandemic, mostly related to ICU admissions, long-term hospitalization and hypoxemia (25). Other aspects that have been found to be associated with an increased risk of developing delirium are the use of benzodiazepines, opioids, vasopressors, fever, smoking, a history of cardiovascular diseases, dialysis and thromboembolic illnesses (26). In some cases, the very same strategies and treatments for COVID-19, such as the use of the prone position can contribute to the development of delirium (27). Another important issue that has come to light with the COVID-19 pandemic is the isolation of positive patients, who have been unable to visit or come into contact with their families during the hospitalization period. All these factors have contributed to the development of delirium, particularly considering the more frail members of the population, such as the elderly (28-40).

Even though it is certainly more frequent among elderly patients, delirium concomitant to SARS-CoV-2 has been also observed in younger age groups (41) and even in pediatric cases (42-44). Moreover, it has been observed in some specific categories of patients who are considered to be more frail, such as pregnant women and immunocompromised individuals; thus, this should be considered in the concept of delirium (45-47). In some cases, it has been indicated that delirium may be the primary and sometimes, the only presenting symptom of COVID-19 (48-51).

Since the first cases of COVID-19, different manifestations of neuropathology secondary to the infection, such as anosmia and ageusia have been observed. There are a number of hypotheses regarding the pathophysiology of delirium in COVID-19, including the ability of SARS-CoV-2 to directly invade the central nervous system via the olfactory bulb, and it has been suggested that it may preferentially target the frontal lobes (52), or indirectly via the oxidative stress caused by the release of pro-inflammatory cytokines (53,54) microvascular damage (55), metabolic and/or endocrine dysfunctions and organ insufficiency (56,57).

In the study by Cuperlovic-Cul *et al* (58), a difference was noted in polyamines in patients with delirium and an association between the SARS-CoV-2 spike protein and monoamine oxidase was postulated. Therefore, it can be hypothesized that the development of delirium is a result of both environmental and organic factors (59).

The study by Batra *et al* (60) demonstrated that persistent viral shedding in patients was associated with in-hospital delirium episodes and a higher mortality rate. Notably, in the study by Dias *et al* (61), delirium was not found to have a higher prevalence in the COVID-19 group compared with the non-COVID-19, while it appeared to manifest in a more severe form in the COVID-19 group.

Delirium has been shown to be associated with a higher mortality rate in patients hospitalized for SARS-CoV-2 infection (62-66), prolongation in hospital stay (67), an impairment in physical functions (68) and cognitive impairment even after physical recovery from infection (69).

Despite being so widely diffused, delirium remains a challenging diagnosis and it is of utmost importance to develop tools to help physicians recognize this condition. A consistent barrier in recognizing delirium is the underlying dementia, particularly considering that the patients with a major risk of developing delirium are the elderly, who may already have cognitive impairment. This poses the difficulty of a juxtaposition of both neurocognitive impairment and it usually leads to a misdiagnosis or the non-recognition of delirium. Two valid instruments for the diagnosis of delirium are the Confusion Assessment Method-ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC), both developed for delirium screening in non-verbal patients in ICUs (70). Another tool with a high sensitivity and moderate specificity is the 4AT score (71).

A critical aspect of the neuropsychiatric consequences due to COVID-19 is the issue of the 'forgotten ones', namely all the individuals dismissed from hospital following recovery from COVID-19. It is known that SARS-COV-2 infection may lead to long-term alterations, which have been commonly defined as 'long covid' (72). Even though it often manifests with mild symptoms, in some cases, severe complications may occur post-COVID-19, as in the case described in the study by Hara *et al* (73); in that study, a patient developed post-COVID-19 encephalitis presenting with delirium as a first manifestation. Unrelated to the hospitalization, yet still an important consequence of the COVID-19 pandemic, is the effect of the lockdowns on elderly individuals, who are more susceptible to developing delirium in response to the amount of stress and anxiety, brought on by the feelings of isolation (74).

The aim of the present study was to evaluate the psychiatric risks related to hospitalization and to acute viral infections, such as COVID-19. It is of utmost importance to take into account the possibilities of developing delirium, particularly in elderly patients. An acute episode could not only lead to adverse consequences for health workers and the patients themselves, as in the case of the hyperactive form, but can also compromise the prognosis and the rehabilitation of hospitalized individuals.

Case report

Between March, 2020 and May, 2022, in the Infectious Diseases Unit of the 'Gaetano Martino' University Hospital in Messina, 8 patients hospitalized for SARS-CoV-2 infection presented delirium. The male sex was the most prevalent one, with a 7:1 ratio (Fig. 1). The mean age of the patients was 81.7±4 years (Fig. 2). The characteristics of the 8 patients are presented in Table I. In total, 5 patients (cases 2, 3, 4, 5 and 8) presented the feature of mild age-related dementia.

A total of 2 patients had at least two shots of the SARS-CoV-2 vaccine, while 6 patients were not vaccinated. In addition, 2 patients had a history of type II diabetes, cardiovascular diseases and chronic obstructive pulmonary disease, 1 patient had type II diabetes and cardiovascular disease,

Table I. Characteristics of the 8 patients in the present study.

Case no.	Age, years	Sex	Comorbidities	SARS-CoV-2 vaccination	Hospitalization days	Need for O^2 DH	COVID-19 therapy	Days between admission and delirium	Outcome
1	80	M		No	25	Yes	Casirivimab/ imdevimab	2	CR
2	90	M	DM, CV diseases; COPD	No	30	Yes		14	VR
3	90	M		No	12	No		36	CR
4	86	M	DM, CV diseases; COPD	Yes	15	Yes		1	Deceased
5	87	M	DM, CV disease, psychosis	Yes	56	Yes		38	Deceased
6	58	M	PD	No	16	No	Azithromycin, hydroxychloroquine	8	VR
7	70	F	Cancer	No	22	Yes		2	VR
8	93	M		No	13	Yes		9	CR

DH, during hospitalization; DM, diabetes mellitus; CV, cardiovascular; COPD, chronic obstructive pulmonary disease; PD, Parkinson's disease; CR, clinical recovery; VR, virological recovery.

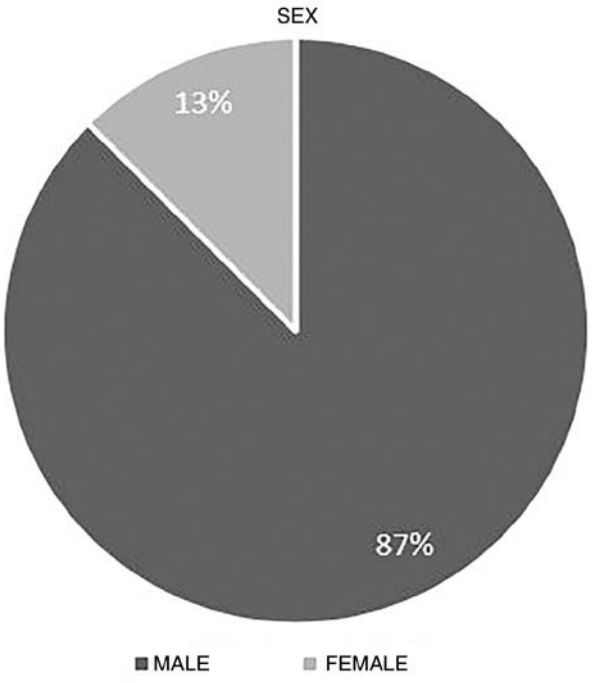

Figure 1. Percentages of males and females of among the 8 patients in the present study.

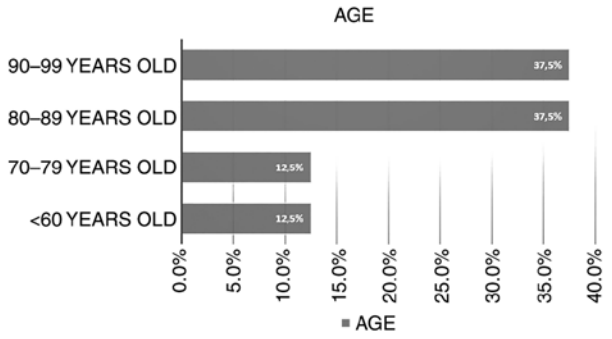

Figure 2. Percentages of the age ranges of the 8 patients in the present study.

1 patient had a history of cancer, and 1 patient had Parkinson's disease. Only 1 patient had a psychiatric comorbidity prior to hospitalization, as he was diagnosed with an unspecified psychosis and received chronic therapy with lorazepam, promazine and tiapride.

In total, 6 patients out of the 8 patients required oxygen implementation, 2 patients did not need it and were maintained in room air, and no patient required mechanical ventilation. The mean duration of hospitalization was 23.6±6 days, with the longest time being 56 days and the shortest time being 12 days (Table I).

As regards COVID-19 therapy, low molecular weight heparin (LMWH) was administered to all patients. In addition, 1 patient was treated with azithromycin and hydroxychloroquine for thromboembolic prophylaxis, and 1 patient received monoclonal antibody therapy with casirivimab/imdevimab (Table I).

In total, 6 patients (cases 1, 2, 4, 5, 7 and 8) received corticosteroids for respiratory impairment, 4 patients (1, 2, 4 and 7) received dexamethasone and 2 (5 and 8) patients received methylprednisolone. These patients were also treated with omeprazole for the duration of the corticosteroid therapy.

Table II. Chronic therapies used in the patients.

Medication	Patients (case nos.)
Cardioaspirin	6 (2, 3, 4, 6, 7 and 8)
Atorvastatin	5 (2, 4, 5, 6 and 8)
Bisoprolol	4 (1, 4, 5 and 8)
Nebivolol	4 (1, 2, 4 and 7)
Furosemide	4 (1, 4, 5 and 6)
Fondaparinux	2 (2 and 4)
Canrenone	2 (6 and 7)
Lorazepam/delorazepam/clonazepam	2 (5 and 8)
Finasteride	1 (7)
Nifedipine	1 (7)
Allopurinol	1 (1)
Pramipexole	1 (5)
Safinamide	1 (5)
Vortioxetine	1 (5)
Pregabalin	1 (1)
Promazine	1 (8)
Tiapride	1 (7)

Medication refers to the medication chronically taken by the patients; patients refers to the number of patients who took that medication; the case numbers which received each medication are indicated in parentheses.

Insulin therapy was administered to 3 patients who were diabetic.

Moreover, 5 patients (cases 1, 2, 3, 7 and 8) were treated with antibiotics for infections which occurred during hospitalization; the antibiotics used were meropenem, cefepime, amoxicillin/clavulanate and trimethoprim/sulfamethoxazole. The chronic therapies administered are listed in Table II.

During hospitalization blood analyses were performed routinely. In total, 2 patients (cases 4 and 5) exhibited alterations in glycaemia (251 and 337 mg/dl) upon admission and maintained a slightly altered level of hematic glucose during the whole period of hospitalization. Furthermore, patient 1 exhibited an abnormal renal function, with creatinine levels of 2,8 mg/dl and azotemia levels of 123 mg/dl upon admission, which improved during hospitalization. In another case (case 8), a worsening of renal function was observed during hospitalization. An increase in procalcitonin levels (max 10 ng/ml) was observed in cases 1, 2, 3, 7 and 8, who developed infection during hospitalization. C reactive protein levels were found to be altered in 6 patients (cases 1, 2, 3, 4, 7 and 8), with a minimum level of 1,50 mg/dl and a maximum level of 10,5 mg/dl. Of note, in case 6, a decrease in hemoglobin (8,9 g/dl) levels was observed in the blood analyses performed the day after the delirium episode. No significant alterations were found in the levels of other laboratory markers performed during hospitalization, such as transaminases, cholestasis indices, coagulation factors and a urine analysis.

In total, 4 patients (cases 2, 3, 6 and 7) were discharged with a negative nasopharyngeal swab (RT-PCR) for SARS-CoV-2: the mean time of viral shedding was 26.5±2 days, with the longest time being 35 days and the shortest time being 18 days. The mean number of days between the admission and the occurrence of delirium was 13.7±3, with the longest being 38 days, and the shortest being 1 day.

A delirium episode began with an abrupt manifestation of aggressiveness and violence: The patients, who were previously compliant, suddenly removed vascular accesses, oxygen masks and exhibited verbal aggressiveness, thus insulting health workers; 7 patients (cases 1, 2, 3, 4, 5, 7 and 8) used vulgar language, which had never been used by them before, as also confirmed by the families of the patients. In 3 cases (1, 3 and 5), the patients destroyed the room furniture and every other object they could reach. In all the cases, delirium manifested with a strong refusal to receive medical examination, or therapies and food. A total of 3 patients (cases 3, 6 and 7) experienced hallucinations referring to the presence of other individuals in the room and objects that were not effectively present, and 2 patients (3 and 7) also referred to hearing voices of other individuals. In addition, 1 patient (case 8) manifested self-harm and started beating and scratching himself and patient 5 presented persecutory delusions and suicidal ideation.

In all cases, delirium presented as hyperactive. Although, it should be mentioned that 1 patient (case 6) manifested a general slowness and became unresponsive immediately following a hyperactive delirium episode.

According to standard clinical practice, non-pharmacological interventions, such as verbal reassurance and orientation, were used at first. When it was deemed safe for health workers to intervene, as a first line pharmacologic treatment and according to psychiatric consultation, intramuscular tiapride (100 mg) was administered alone in 3 cases (patients 1, 3 and 4) and in association with haloperidol (1 mg) in case 7, promazine (25 mg) was administered alone in case 8, in association with valproate sodium at 300 mg in case 5 and with aripiprazole in another case (patient 2), and in case 6, aripiprazole alone was administered at increasing doses.

A complete resolution of delirium with no other recurrences was obtained in 3 cases (patients 3, 4 and 6). In 5 cases (1, 2, 5, 7 and 8), the patients had a recurrence of delirium. As second-line therapy, valproate sodium, promazine and tiapride were administered. In addition, 2 patients out of the 8 patients had a clinical recovery and were discharged to a COVID-19 low intensity cure facility, 4 patients had a virological recovery and 2 patients did not survive.

Discussion

With a mean age of 81.7±4 years and a huge prevalence of the male sex, the cases described in the present study appear to follow the evidence in the literature, which report a greater risk of developing delirium in males and among the elderly, a well as among patients hospitalized for COVID-19 (75-79).

Even though individuals with pre-existing psychiatric disorders appear to have a major risk of developing delirium (80), among the patients described herein, 1 patient had a history of psychiatric disorders. Age-related dementia was present in the majority of patients in the present study. Thus, it is considered that dementia and other types of neurocognitive age-related impairment are precipitating factors for delirium (6).

Table III. Treatment recommendations for delirium during the COVID-19 pandemic, as recommended by the Italian Society of Psychiatry.

Delirium therapy in COVID-19
Dexmetodimin (for patients in the ICU): Alpha-2 agonist, sedative anxiolytic-analgesic that does not cause respiratory depression
Tiapride: Useful if the patient is agitated (hyperkinetic delirium) and receiving therapy with lopinavir/ritonavir.
Promazine via intramuscular (if not contraindicated for coagulation problems)
Aripiprazole: Useful for hypokinetic delirium
Haloperidol: Low risk of respiratory depression
Avoid benzodiazepines unless delirium tremens is suspected

In the patients described in the present study, COVID-19 was the dominant cause capable of triggering delirium, since the other conditions either alone, or in combination, would probably have not been sufficient to cause this; i.e., in a population of patients of the same age and comorbidities, the prevalence of delirium would have been significantly lower.

Moreover, the presence of comorbidities found during viral infections can facilitate the onset of an acute confusional state (28,81,82). In a previous Chinese case study (83), the prevalence of some comorbidities was hypertension (16.9%), other cardiovascular diseases (53.7%) cerebrovascular diseases (1.9%), diabetes (8.2%), hepatitis B infections (1.8%), chronic obstructive pulmonary disease (1.5%), chronic kidney diseases (1.3%), tumors (11.1%) and immunodeficiency (0.2%). Those individuals who require ICU-level care, are the ones who can easily develop delirium.

The majority of the patients in the present study required oxygen supplementation, in some cases limited to a low-flow nasal cannula; however, in some cases, oxygenation had to be implemented at a high flow due to severe desaturation. This may support the hypothesis that cerebral desaturation may trigger delirium and that the need for oxygen supplementation is also related to delirium (8-10,25).

Considering the therapies administered for COVID-19, all the patients described herein were treated with LMWH for thromboembolic prophylaxis. In the study by D'Ardes *et al* (84), a protective role of LMWH in the development of delirium was suggested. Notably, in the present study, it did not play a protective role in preventing delirium.

Other than drugs, the time of hospitalization has been one of the main factors associated with the development of delirium in hospital settings. As aforementioned, long-term hospitalization is strongly associated with the development of delirium (6,7); however, in the present study, it is interesting to observe that the median time passed between admission and the episode of delirium was 13 days, and in in 3 cases, delirium occurred after 1 or 2 days after admission. This suggests that, while long-term hospitalization plays a critical role, pre-existing features may lead to the onset of delirium, despite the time in hospital.

There does not appear to be a prevalence of hyperactive vs. hypoactive delirium, although it also appears that there is a higher frequency of hypoactive delirium in the elderly population. Nevertheless, both forms were observed in hospital settings during the COVID-19 pandemic (85,86). Of note, all the patients described herein manifested a hyperactive form of delirium, exhibiting verbal and physical aggressiveness towards the health workers. Verbal and physical aggressiveness towards health workers can be considered, in psychopathological terms, a form of hetero-aggressiveness or heterodirect aggressiveness, which is a feature of hyperactive delirium, that is characterized itself by an aggressive behavior, according to DSM-5 (87-90). However, it is possible that some cases of hypoactive delirium have passed undiagnosed and have been resolved without the use of medications.

The treatment for delirium is controversial, particularly considering that some primary medications may be contraindicated due to the concomitant SARS-CoV-2 infection, with particular attention to the antivirals, even though no notable interactions have been reported (91). Specifically, haloperidol, risperidone and quetiapine may expose the patients to certain adverse effects of antivirals, due to their increased concentration (71). Given the high distress of patients admitted to hospital and in a enforced isolation, behavioral therapy should be the first-line treatment for the prevention of delirium. As regards pharmacological therapy, the Italian Society of Psychiatry suggested a number of therapeutic options for delirium during COVID-19 (92), as presented in Table III.

The treatment options suggested in previous studies include melatonin, in order to regulate the wake-sleep cycle, valproic acid or trazodone and dopamine agonist (93). In a letter by Khosravi (94), quetiapine was proposed as a safe therapy for delirium in the ICU.

The management of psychiatric drugs, their possible interactions with COVID-19 therapeutics and the concomitant necessity for psychological treatment are the main issues in treating delirium, particularly in ICU settings (95-97). Thus, the assessment and treatment of delirium in hospitalized patients with COVID-19 requires a multidisciplinary effort and collaboration (98).

The drugs most frequently used in the cases described herein were promazine, haloperidol and tiapride. It is noteworthy to observe that only 3 patients had a complete resolution of delirium, while the majority experienced a recurrence, despite therapies. The recurrence of delirium may be caused by the environmental factors that still pose a huge font of distress to hospitalized individuals, including isolation, the lack of communication, the limitations in motility and the treatments for underlying illnesses and COVID-19 itself. Therefore, the implementation of the quality of life, as a multidisciplinary effort, of patients hospitalized for COVID-19 is necessary

to achieve a resolution or, at least, avoid the repercussions of delirium (98).

In the cases described in the present study, the mortality rate was 25%, which is a critical indicator of how delirium can play a role in the mortality of hospitalized patients, as demonstrated by other studies (62-66).

It is imperative to create protocols and take action in order to prevent delirium. While some aspects are not modifiable, such as patient comorbidities or visiting restrictions, an improvement could be made regarding the wake-sleep cycle of the patients, considering the use of melatonin in treatment. The food intake also is a critical variable and a more balanced diet may play a positive role during the hospital stay of patients. The psychological aspect is probably the most crucial one; engaging the patients in conversations or implementing the use of psychologists and/or the digital system to maintain communications with families while in COVID-19 wards may improve the quality of life and the mental status of hospitalized patients (99-101).

In conclusion, in this period when SARS-CoV-2 has imposed enforced isolation, hospitalization and the need for oxygen, it is of primary importance to develop tools to diagnose delirium more effectively, including the less evident forms, and to take measures to improve the environmental factors that may contribute to delirium, with particular attention to behavioral therapy.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YR, EVR, CM, GN, VC and CPS conceptualized the study. YR, CM and VC were involved in the writing of the original draft and in manuscript preparation. EVR, CM, VC and GN were involved in the writing, reviewing and editing of the manuscript. VC was involved in visualization/impagination. GN supervised the study. YR and GN confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Written informed consent has been obtained from the patients described in the present case report. In the 2 cases which were then deceased, written consent was obtained from the patients prior to their death.

Patient consent for publication

Written informed consent has been obtained from the patients for the publication of their data. In the 2 cases which were then deceased, written consent was obtained from the patients prior to their death.

Competing interests

The authors declare that they have no competing interests.

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