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Case Report

Medical management and positive outcome after prolonged recumbency in a case of equine herpesvirus myeloencephalopathy

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ABSTRACT

A 17-year-old mare presenting with acute fever, weakness and bladder dysfunction was diagnosed with equine herpesvirus myeloencephalopathy (EHM). The mare become transiently recumbent, underwent parenteral fluid therapy, plasma infusion, steroidal/nonsteroidal anti-inflammatory drugs (SAID/NSAIDs) and bladder catheterization. After 10 days the mare was hospitalized. Neurological evaluation revealed ataxia and proprioceptive deficits mainly in the hind limbs. The mare was able to stand but unable to rise from recumbency or walk. Secondary complications included *Escherichia coli* cystitis, corneal ulcers and pressure sores. A full-body support sling was used for 21 days. Medical treatment included systemic antimicrobials, NSAIDs, gradual discontinuation of SAIDs, parenteral fluid therapy and bladder lavage. The mare tested positive for *Varicellovirus equidalpha* 1 (EHV-1) DNA in nasal swab and blood samples on day 13 and in urine samples on days 13 and 25 after the onset of fever. Neurological signs improved over a period of 34 days and the mare was discharged with mild hind limb weakness/ataxia. Secondary complications resolved within 2 weeks. At the eight-month follow-up, marked improvement in locomotory function had been achieved.

1. Introduction

Clinical manifestations of *Varicellovirus equidalpha* 1 (or *Equine herpesvirus* 1, EHV-1) infection include respiratory disease, late abortion, neonatal death, myeloencephalopathy and chorioretinopathy [1–3]. Equine herpesvirus myeloencephalopathy (EHM) is an uncommon clinical manifestation of EHV-1 infection, of importance due to its devastating impact in the equestrian industry [2,3]. Clinical signs of EHM range from ataxia to paralysis that may lead to recumbency, often involving the caudal spinal cord with resultant hind limb weakness, bladder dysfunction and perineal sensory deficit [2]. Less common are cortical, brainstem or vestibular lesions [2]. These clinical manifestations reflect viral cytotoxicity on the endothelium of the central nervous system (CNS) with inflammation, thrombosis, ischemia and tissue necrosis [2,4]. It is strongly suspected that the magnitude and duration of viremia are involved in the clinical presentation, despite the lack of scientific evidence [5].

To date, the main route of infection is direct contact through nasal discharge, but also through aborted fetuses and fetal membranes, semen and embryos [5–9]. Diagnosis of EHV-1 infection is currently based on clinical signs and viral DNA detection from nasal swabs and blood [10]. According to the literature, the virus is excreted by the respiratory route for approximately 14 days post-infection (PI) and viremia can be observed for 21 days PI [5], with EHV-1 DNA detection in nasal secretions and blood samples up to 21 and 30 days PI, respectively [10].

Therapy for EHM is largely empirical and supportive. The most commonly used drugs are non-steroidal anti-inflammatory drugs (NSAIDs), steroidal anti-inflammatory drugs (SAIDs) and antivirals [2]. To note, a recent systematic review on pharmacological interventions for the treatment of EHV-1 reports minimal or no benefit, either as a prophylactic or post-exposure treatment, for any of the reviewed interventions, including valacyclovir [11], *Parapoxvirus ovis*-based immunomodulator [12], human interferon alpha [13], herbal supplement [14], cytosine analogue [15] and heparin [16], in mitigating EHV-1-associated disease outcome [17]. A key aspect is the management of signs and their consequences, such as trauma, bladder akinesia, respiratory tract infections and gastrointestinal complications [10].

The literature reports a poor prognosis in cases of severe

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manifestations of EHM, especially if recumbency persists for >3 days as there is little chance of complete recovery of neurological function [18, 19]. To the authors' knowledge, there are no reports in terms of time to complete recovery from severe EHM or long-term follow-up.

The present case reports the diagnosis, medical management, clinical course of neurological signs and complications in a horse severely affected by EHM with a positive outcome after a prolonged recumbency.

2. Case description

The owner provided informed consent, as part of the hospital consent form, for the use of the horse's data in the study.

Fig. 1 shows a graphic outline of the main events, clinical findings and diagnostic testing during the course of the disease.

2.1. History

On December 4th, 2022 a 17-year-old Italian Saddlebred mare trained for show-jumping acutely manifested inappetence and hyperthermia (40°C). The mare had been in the same stable in north-eastern Italy for the past 5 years with a few resident horses; 2 weeks before the onset of signs the mare had participated in a national competition with about 500 horses. The mare was unvaccinated for EHVs. The mare was initially treated with benzylpenicillin-dihydrostreptomycin and NSAIDs. Three days later, neurological signs such as hind limb weakness/ataxia, neck stiffness (inability to bend to the right) and flaccid tail carried to the left, and non-specific signs such as bruxism appeared. Shortly, the mare became unable to stand and void, and became transiently recumbent. Appetite and fecal output were maintained. On the third day after the onset of fever (T0), serum sample and buffy coat (BC) obtained from EDTA blood sample were tested in a diagnostic laboratory (LABOKLIN, Bad Kissingen, Germany) for West Nile virus RNA (*end-point* RT-PCR), IgM and IgG (ELISA test), Tick-borne encephalitis virus IgM and IgG (ELISA test), *Orthobornavirus* RNA (*end-point* RT-PCR) and EHV-1 and 4 DNA (*end-point* PCR), testing positive for EHV-1 DNA only. The treatment plan was changed to intravenous fluid therapy, intravenous hyperimmune plasma (12 L of commercial plasma were administered empirically over 10 days by the treating veterinarian), SAIDs, DMSO and continued NSAID. The mare was managed in recumbency and turned manually for 10 days; while bladder catheterization was performed twice daily.

2.2. Hospital admission

On December 17th, appetite and thirst increased, the mare was lifted manually, was able to keep standing for up to 10 hours and urinated spontaneously for the first time. At this stage, the mare was transported in a veterinary ambulance equipped with a sling to the Veterinary Teaching Hospital of the University of Bologna, Italy, for hospitalization. The mare was in moderate (5/9) body condition score (BCS) and slightly lethargic. The rectal temperature was 37.7°C, heart rate was 58 bpm and respiratory rate was 16 breaths/min. Ataxia and weakness of the hind limbs and proprioceptive deficits were severe, the neurologic exam was otherwise unremarkable. The mare ate and drank spontaneously, had normal stools and was able to urinate, albeit there was dysuria with pollakiuria and stranguria. Bilateral eyelid lesions, conjunctival hyperemia and chemosis were present. The right eye had lower eyelid entropion and a superficial avascular corneal ulcer about 1.5 cm in diameter (Fig. 2), and the left eye had a smaller superficial ulcer with circumferential corneal edema. The mare had multiple injuries on her body, including pressure sores and traumatic abrasions on her head and at the level of the bony prominences.

At the initial clinical examination, the following list of diagnoses was assessed: (i) EHM; (ii) suspected urinary tract infection, more likely secondary bacterial, (iii) bilateral corneal ulceration and skin lesions, likely due to recumbency and trauma.

A complete blood count (CBC) showed a slight neutrophilia, while serum biochemistry showed slightly elevated bile acids and aspartate aminotransferase (AST) and creatine kinase (CK) enzymes, and was otherwise unremarkable. Inflammatory markers were within normal limits. CBC, serum biochemistry, blood gas analysis and fibrinogen concentration on admission are reported in Appendix A: Supplementary material.

Urinalysis, including assessment of urine specific gravity (USG),

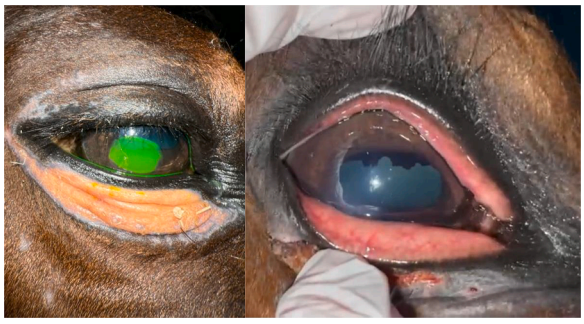

Fig. 2. Clinical course of the corneal ulcer of the right eye. Left, positive fluorescein test on day 13, at the time of hospital admission. Right, resolution of the corneal ulcer on day 25, after 3 days from a single corneal cross-linking treatment with riboflavin/UV-A.

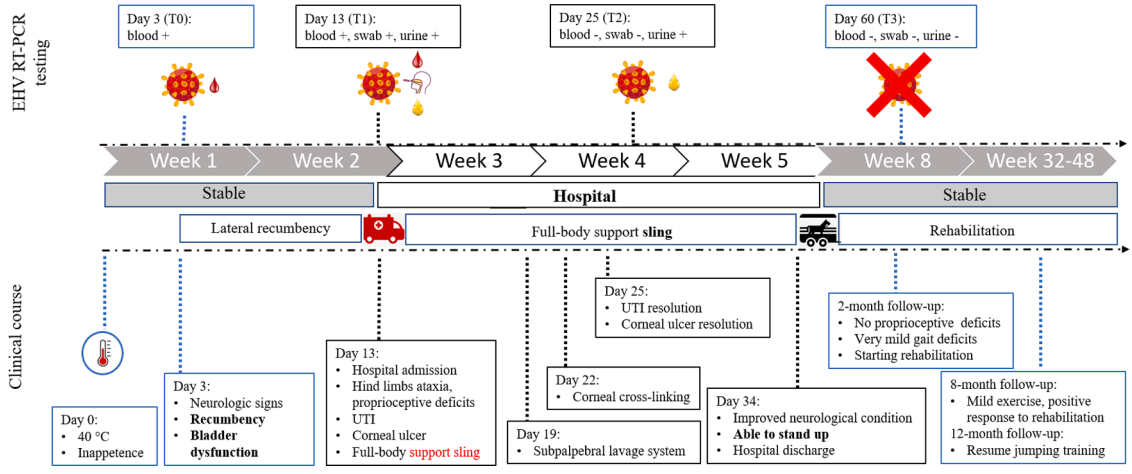

Fig. 1. Time line that graphically represents the main events, clinical findings and diagnostic testing during the course of the disease. UTI = urinary tract infection.

dipstick evaluation and microscopic sediment examination, showed brown colored and turbid urine, with USG 1034 and pH 8. Leukocytes (5 to 10 leukocytes/field at a magnification of 40x) and numerous rod-shape bacteria were also present. A bacterial culture and sensitivity test of urine yielded a multi-resistant *Escherichia coli*. A corneal and conjunctival swab tested positive for *Staphylococcus aureus*. An ultrasound examination of the chest and abdomen to rule out major complications due to prolonged recumbency was unremarkable.

2.3. Clinical course and medical management

After a few hours of hospitalization, the mare fell down and was unable to stand up. A full-body support sling was applied and maintained for the next 21 days.

Medical treatment included systemic antimicrobials based on susceptibility test to treat the bacterial urinary tract infection (ceftiofur, 2.2 mg kg^{-1} iv BID for 11 days); tapering dose of SAIDs (dexamethasone, 0.04 mg kg^{-1} iv SID for 2 days, then 0.02 mg Kg^{-1} iv every other day (EOD) for 3 times); NSAIDs (flunixin meglumine 1.1 mg kg^{-1} iv BID for the first 12 days, then switched to firocoxib 0.3 mg kg^{-1} po SID for 24h then 0.1 mg kg^{-1} po SID and paracetamol 20 mg kg^{-1} po SID for 6 days) and gastric protection (sucralfate (Carafate), 15 mg kg^{-1} po TID). Vitamin E (1.4 IU/kg iv SID) and selenium (0.02 mg kg^{-1} iv SID), and vitamin B (2.0 mg kg^{-1} iv SID) and vitamin C (30 mg kg^{-1} iv SID) were also administered. Parenteral fluid therapy was administered (Lactated Ringer's solution 10 L twice a day) to increase bladder wash-out. Bladder lavages were performed EOD for 3 times (2 L of Lactated Ringer's solution and 1 L of 10% DMSO). Topical ophthalmic therapy included antimicrobials based on susceptibility test (tobramycin, two drops, QID), autologous serum (two drops, QID) and artificial tears, bilaterally. Skin lesions received topical treatment twice a day, including cleaning and application of calendula cream.

The mare remained systemically stable throughout the 22 days of hospitalization. Neurological signs were evaluated daily; hindlimbs coordination and weakness progressively improved, albeit the mare was not able to stand up independently. Bacterial cystitis and dysuria showed significant clinical improvement after about ten days of treatment, and urinary sediment examination showed no bacteria. A control urine culture yielded very low UFC/mL of *Enterococcus caselliflavus*. In light of the clinical resolution, it was decided to discontinue systemic antimicrobials and bladder lavages. The left eye ulcer healed after 2 days of treatment, the right one was poorly responsive to treatment. On day 6 from admission, due to the mare's aggressive behaviour, a subpalpebral lavage (SPL) system was placed on the right upper eyelid to continue medication. After 3 days a purulent blepharitis developed and the SPL was removed. At this stage (10 days from admission; day 22), a single corneal cross-linking treatment with riboflavin/UV-A was performed in standing position, as previously described [20]. The procedure allowed the frequency of tobramycin eye drops to be reduced to twice daily and other eye treatments to be discontinued. After three days (13 days from admission; day 25), the ulcer had healed but with mild residual photophobia and blepharospasm, so therapy with firocoxib and paracetamol was continued for further 6 days.

On day 21 of hospitalization (34 days from the onset of fever), the mare was able to stand up without any support and the sling was removed. On day 22 of hospitalization, the mare was discharged with mild residual weakness/ataxia of the hind limbs. The owner was informed that the prognosis for life was positive, but that the sports prognosis was guarded to poor.

At the 2-month follow-up, a full-response to rehabilitation and an outstanding improvement in locomotory function were achieved; at the 8-month follow-up, the mare showed an almost complete recovery of gait and coordination to the point that was gradually resumed to training exercise; at the 12-month follow-up, the mare started training in saddleless jumping with excellent results.

2.4. EHV-1 DNA qPCR detection

After initial diagnosis, follow-up nasal swab (NS), whole blood and urine samples were tested for EHV-1 DNA by quantitative *real-time* PCR (qPCR). Samples were collected during and after hospitalization at three different time points: T1 at the 13th day after onset of fever, T2 at the 25th day after onset of fever, and T3 at the 60th day after onset of fever. Samples were stored at -20°C until analysis to avoid degradation of nucleic acids.

Genomic DNA was extracted from biological samples using a commercially available kit (NucleoSpin Tissue Kit; Macherey-Nagel, Germany) according to the manufacturer's protocol. Before extraction, the NS were resuspended in 250 µl of phosphate-buffered saline (PBS). Extracted DNA was stored at -20°C until use. The EHV-1 DNA detection was carried out using a TaqMan qPCR validated at the UK World Organisation for Animal Health (WOAH) Reference Laboratory according to the ISO 17025 quality system [21]. The assay, targeting a fragment of the glycoprotein B (gB) gene, was carried out using the TaqMan Fast Advanced Master Mix Kit (Life Technologies, USA) according to the manufacturer's protocol and the StepOnePlus Real-Time PCR System (Thermo Fisher Scientific, Life Technologies, USA). Serial 10-fold dilutions of a plasmid (pCR4 plasmid; Invitrogen, Life Technologies, USA) containing one copy of the gB gene target sequence (88 nucleotides in length, from nucleotide 61,952 to 62,039 of EHV-1 reference strain Hertfordshire/150/2016, GenBank ID: KY852346) was used as an external standard for the construction of the assay standard curve. The limit of detection (LOD) of the assay was assessed by testing serial 10-fold dilutions of the recombinant plasmid and was found to be one copy/µL. The DNA samples and known DNA standards were repeated within each run in duplicate. Positive and negative controls were also included on each run as reported in the WOAH Terrestrial Manual [21]. Results are reported in Table 1.

3. Discussion

The authors report the clinical course of a severe case of EHM, its medical management and complications, and positive outcome despite prolonged recumbency. In addition, the dynamics of EHV-1 DNA detection from nasal swab, blood and urine are described, showing a longer lasting positivity in urine than in other samples.

The literature reports a good prognosis both for life and for sports for EHM-affected horses with mild neurological signs, and a worse prognosis for horses with severe neurological signs and secondary complications [1,2]. The presented case is interesting because the mare suffered prolonged recumbency for >10 days and was then managed with a full-body support sling for another 21 days due to the severe deficits, with subsequent resolution of neurological signs and substantial recovery of motor skills in eight months after discharge. To note, the general physical condition remained good throughout the duration of the illness and the mare experienced relatively few complications due to neurologic deficits: bacterial cystitis, corneal ulceration and skin lesions.

Table 1
EHV-1 DNA detection in nasal swabs, whole blood and urine samples tested during the course of the disease. EHV-1 DNA detection was carried out by end-point PCR assay in T0 and by TaqMan real-time qPCR in T1, T2 and T3. The quantity of viral DNA detected by qPCR was expressed as copies of EHV-1 glycoprotein B (gB) gene per microliter of extracted DNA (copies/µL). "Pos" = positive, "Neg" = negative, "NA" = not available.

	EHV-1 DNA detection		
	Nasal swab	Whole blood	Urine
T0: Day 3 from onset of fever	NA	Pos	NA
T1: Day 13	2.8 copies/µL	1.0 copy/µL	13.5 copies/µL
T2: Day 25	Neg	Neg	7.2 copies/µL
T3: Day 60	Neg	Neg	Neg

In this regard, a point can be made about the intensive medical and supportive care received early in the stable, even before hospitalization.

The main purpose of treating EHV-1 infections is to manage clinical signs, reduce CNS inflammation and prevent thromboembolic sequelae [2]. Recommended therapy is based on blocking pathogenic mechanisms and improving tissue repair: the use of SAID/NSAIDs and antiviral drugs is most commonly suggested [2]. The use of anti-inflammatory drugs, including dexamethasone, flunixin meglumine and firocoxib, is supported by preliminary studies demonstrating their in vitro ability to reduce spread and replication of EHV-1 from infected peripheral polymorphonuclear cells to endothelial cells [22]. In the present case, the mare received early NSAIDs and SAIDs at the onset of fever and neurologic signs, respectively. On admission, the use of antiviral drugs was not considered because of the advanced course of the disease, and similarly dexamethasone was tapered to discontinuation. In fact, the action of these agents is greater with early signs of EHM [2]. Despite their uncertain efficacy in the advanced stage of infection, the administration of NSAIDs was necessary in this case for the anti-inflammatory and analgesic effects for bacterial cystitis and corneal ulcers, and to a lesser extent for multiple body wounds. Prolonged treatment with NSAIDs carries a risk of toxicity [23], so gastrointestinal and renal function was closely monitored, and to reduce this risk, flunixin was replaced with COX-2 selective NSAIDs (firocoxib) [23].

It is also crucial to provide supportive care and manage complications secondary to EHM. Bacterial urinary tract infections are often reported as a possible complication of bladder dysfunction [24] and continuous bladder catheterization for bladder akinesia [2]. Easther and colleagues described a case of suspected idiopathic hemorrhagic cystitis in a horse in which EHV-1 was detected by immunohistochemistry in the bladder wall; they suggested a possible role of the virus in the pathogenesis of cystitis, as observed in herpetic infections in other species such as humans, cats and ungulates [25]. There is no evidence for a pathogenetic role of EHV-1 in secondary cystitis in EHM cases.

The reported treatment of cystitis should begin by treating/removing (if possible) the predisposing causes of cystitis [26] and treating the infection if it is significant (>104 UFC/mL) [24]. The problem of multi-drug resistant bacteria, such as *E. coli* detected in this case, is becoming increasingly relevant [27]; therefore, their treatment becomes complicated. It is essential to perform an antimicrobial susceptibility test and select a molecule that reaches the urinary tract well (penicillin, cephalosporins and TMPS) [26,28]; in addition, it should be considered whether its action can be supplemented by other treatments, such as fluid overload and bladder irrigation. Bladder irrigation is reported in the literature mainly for saboulous cystitis [29], and at least anecdotally it is used with or without antiseptic solutions (e.g., iodopovidone, DMSO, Tris-EDTA) for refractory infections, but its efficacy needs to be investigated. In the face of resolution of clinical signs, and in agreement with the literature [26], the growth of a few *E. caselliflavus* colonies in urine was considered of little significance and further antimicrobial treatment was not considered indicated at that time. Nevertheless, given the high-risk of recurrent urinary infections by opportunistic bacteria in these cases, regular clinical monitoring is recommended.

Corneal cross-linking (CXL) phototherapy is a minimally invasive technique already introduced as a treatment of corneal ulcers in horses [20,30,31]. Due to the failure of SPL system in the present case CXL was performed to treat the right corneal ulcer once lesions of viral etiology were excluded (negative Rose Bengal test) [2]. Indeed, CXL phototherapy has been shown to be ineffective and even contraindicated in some cases of viral infectious keratitis in humans [32]. The use of CXL allowed a faster healing process and a reduction in the frequency of topical medication, facilitating the management of the untreatable mare. CXL might be a promising treatment in the management of traumatic corneal ulcers with bacterial superinfection [20,30,31]; these are a common complication in neurological patients, which can often be at the same time difficult to manage intensively.

Another factor to consider in the intensive management of this case is the large amount of commercial hyperimmune plasma (a total of 12 L in 10 days) administered by the referring veterinarian to the patient during the acute phase of the disease. In equine medicine, its use is reported mainly for failure of passive transfer of immunity in foals, sepsis conditions as an anti-endotoxic agent, coagulopathies, and to sustain osmotic colloidal pressure [33]. To the authors' knowledge, the administration of relatively high volumes of hyperimmune plasma in acute manifestations of viral infections has no specific references in the equine literature, should be considered empirical, and therefore its use cannot be supported; furthermore, in this case, there were no specific clinicopathological indications suggesting its use. While considering the risks of plasma administration [33], and pointing out the lack of scientific evidence of its use in this case, the authors cannot exclude and raise a question about the possibility that the amount of plasma provided immune, anti-inflammatory, oncotic and metabolic support [34] to the mare at the most critical stage of the disease. Furthermore, the plasma may have contributed to maintaining good general physical condition and limiting the development of complications, such as skin lesions and pressure sores, and secondary infections.

The mare tested positive for EHV-1 DNA in nasal swab and blood samples on day 13 after the onset of fever, consistent with data reported in the literature [10,18]. Interestingly, EHV-1 DNA was detected in urine samples also on day 25 after the onset of clinical signs. Recently, the detection of EHV-1 DNA in the urine of EHM-affected horses was reported during two outbreaks in Spain in 2021 and 2023, in which 2 out of 21 horses were positive for viral DNA in urine samples up to 22 days after the onset of fever [35]. Therefore, in this report, EHV-1 DNA in urine appears to persist longer than in nasal and blood samples conventionally used for diagnosis, and further studies with daily testing are needed to determine the timing of EHV-1 DNA disappearance. Furthermore, the qPCR assay used in this study for the detection of EHV-1 DNA did not include exogenous or endogenous controls, so it cannot be ruled out that the negative results obtained at time points T2 and T3 were due to potential inhibition of the reaction.

In this study, as in that of Velloso Alvarez and colleagues [35], the viability of EHV-1 in urine was not investigated by viral isolation. The presence of infectious virions in urine could represent a serious epidemiological risk, and the study by Dayaram and colleagues [36] on EHV-1 infections in equids suggests significant stability of the virus in aqueous substrates and under alkaline pH conditions often encountered in cystitis [36]. Notwithstanding, the viral DNA copy number reported in most urine samples in the study by Velloso Alvarez and colleagues [35] and in the presented case is rather low, making an epidemiological role unlikely. Further investigation is needed to understand whether the stage of infection or the type of storage may influence the results of qPCR on urine samples and whether urine may be a useful non-invasive diagnostic tool to detect EHV-1 DNA in horses, as suggested previously [35].

In conclusion, horses severely affected by EHM without multi-organ dysfunction and major complications after prolonged recumbency may fully recover from neurological dysfunction and resume physical activity. Intensive medical and supportive treatments may play a key role in the positive outcome, although scientific evidence for medical therapy is scarce and alternative or complementary treatments may be evaluated. For diagnostic purposes, further studies are needed to evaluate whether urine may be a useful non-invasive specimen, even in the later stages of EHV-1 infection. The possible presence of infectious virions in urine and the potential epidemiologic role require further investigation.

Ethical Statement

The owner provided informed consent, as part of the hospital consent form, for the use of the horse's data in the study.

Supplementary data associated with this article can be found, in the online version, at doi: …

CRediT authorship contribution statement

A. Mannini: Writing – original draft, Investigation, Data curation, Conceptualization. **N. Ellero:** Writing – original draft, Investigation, Data curation, Conceptualization. **L. Urbani:** Writing – original draft, Investigation, Data curation. **A. Balboni:** Writing – original draft, Data curation. **I. Imposimato:** Writing – original draft, Visualization, Data curation. **M. Battilani:** Visualization, Supervision, Resources. **R. Gialletti:** Visualization, Supervision, Resources. **F. Freccero:** Writing – original draft, Supervision, Resources, Data curation, Conceptualization.

Declaration of competing interest

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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We declare that this case was presented at the SISVET 2023 National Congress in Italy as a poster.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jevs.2024.105063.

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