IJD Case Report

Clinical manifestation and management of Remdesivir infiltration: a case series

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Remdesivir is the first approved antiviral against severe acute respiratory syndrome coronavirus 2 (SARSCoV2) with a promising effect both on in-patient and out-patient settings. Regarding the acceleration program for the development of COVID-19 therapies and emergency use authorization, reporting new adverse events other than those mentioned in the first package inserts and beyond clinical trials is expected. Medication infiltration is one of the post-marketing reported remdesivir adverse events. The present study reported four new cases of remdesivir infiltration, their clinical courses, management, and outcomes. Moreover, all other reported cases were collected to identify event risk factors and provide recommendations for reducing the condition burden. All patients received non-pharmacological interventions and conservative therapy, which included aspiration, catheter removal, limb immobilization, non-occlusive dressing, and warm compresses. Intralesional triamcinolone acetonide was also administered for three cases. The remdesivir infusion continued through another intravenous line, and the event did not reoccur for the same patient. All patients recovered without sequels. The present study attempted to address all the factors that affect remdesivir infiltration and provide clinical recommendations to reduce the incidence and event burden. The principal step in prevention and successful management is staff education. After establishing staff instructions, event severity was significantly reduced in the studied center. Furthermore, non-pharmacological intervention and intralesional corticosteroid administration could prevent local reaction extension and could probably accelerate the healing process.

Keywords: SARS-CoV-2, COVID-19, remdesivir, extravasation, infiltration, Adrenal Cortex Hormones

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INTRODUCTION

Based on the World Health Organization (WHO) Coronavirus 2019 (COVID-19) Dashboard, more than 618 million confirmed COVID-19 cases and 6.5 million deaths have been reported until October 2022 [1]. Due to the enormous burden of the pandemic, there have been numerous initiatives to develop new medication for the management of

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COVID-19. As a result, the United States Food and Drug Administration (FDA) has established an emergency program entitled "Coronavirus Treatment Acceleration Program" (CTAP) to provide approved therapies as soon as possible. Accordingly, in October 2020, the FDA approved remdesivir as the first antiviral medication for COVID-19 management [2]. The active metabolite of remdesivir is a nucleotide triphosphate derivative with a broad in-vitro spectrum of activity against RNA viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. Regarding the acceleration program for the development of COVID-19 therapies and emergency use authorization, reporting new adverse events other than those mentioned in the first package inserts was expected [4]. Remdesivir infiltration was first reported as a post-marketing adverse event by Kumar *et al.*, in February 2021 for the first time [5].

Remdesivir is now considered as a non-vesicant medication. However, inadvertent extra-venous leakage of any non-vesicant solution into the surrounding tissue (infiltration) was reported in up to 6 % of adult patients [6]. These iatrogenic injuries have a direct influence on morbidity, duration of hospitalization, healthcare costs, and patient safety [7]. Infiltration of non-cytotoxic medications can initiate local tissue damage due to extreme osmolarity or pH, as well as vasoconstriction. The key point in managing these lesions is to document events and do serial examination, to determine tissue injury mechanisms, general supportive care, and drug-specific antidotes. Conservative measures are as follows: discontinuing the infusion, disconnecting the tube from the catheter, aspirating the residual drug, elevating the limb, avoiding manual pressure, immobilizing the limb, and applying cold or warm compress depending on the infiltrated medication [6,8]. Applying a warm compress was also recommended by Merendonk [9].

To the best of our knowledge, there have been few reports of remdesivir infiltration [5,9,10]. However, the present study reported four new cases and their management, as well as reviewed previously reported cases, to clarify these adverse event risk factors, course of disease, prevention, and management.

CASE PRESENTATION

Case 1

An 82-year-old man was admitted to the emergency department due to dyspnea. His symptoms initiated five days before his admission and included nonproductive coughs, myalgia, malaise, and fever. His reverse transcription polymerase chain reaction (rRT-PCR) test result for COVID-19 was positive. Besides, his lung spiral high-resolution computed tomography (HRCT) was suggestive of COVID-19 pneumonia. His past medical history was positive for hypertension, ischemic heart disease, and Alzheimer's. As the laboratory data was prepared, the loading dose of remdesivir (200 mg) was initiated. Therefore, 200 mg concentrated solution formulation of remdesivir (*Remdesivir-Ronak®, Iran*) was diluted in 500 mL of sodium chloride 0.9% solution and was infused through a peripheral 20-gauge catheter located in the dorsal surface of the right hand (Superficial venous palmar arch). After administering 200 mL of solution (80 mg remdesivir) for 15 minutes, nursing staff noticed bulging of skin adjacent to the catheter, in favor of solution infiltration. Cessation of infusion, aspiration of the infiltrated solution, removal of the catheter, application of cold compresses, and insertion of mechanical compression of the limb from the elbow to the injection site for fluid removal from the cannula insertion site were made by untrained nursing staff. After an hour and consultation with the pharmacotherapist, to avoid mechanical compression, the limb was elevated, immobilized, and treated with warm compress (cold compresses were used initially but then were switched to warm compresses after 2 hours), the extent of skin involvement was marked, and serial examinations of the limb were performed. After four hours, the erythema of extravasation injury extended through the dorsal surface of the forearm and 5 cm around the elbow joint (Figure 1A). The lesion was warm and purple, with no edema except near the IV line. There was also a skin laceration in the IV line site due to aspiration and deep compression to the superficial layer. The patient had moderate pain and a burning sensation at the lesion site. The results of the patient's blood tests showed no severe coagulopathy (PT = 13, PTT = 39, INR = 1, platelets = 115000) at the time of the event. The lesion was warm (without circulatory deficiency), and the veins were palpable at the time of the event till the end of the follow-up. Other clinical data are summarized in Table 1.

Thirty hours following event initiation,

Table 1. Patient characteristics, clinical manifestations, and interventions

	Author/ year	Age/ Sex	Comorbidities	Concurrent medication	Catheter site and gauge	Infiltrated Dose and Day of Event	Time until observation of infiltration	Rate of infusion	Volume and concentration of the infiltrated solution	Clinical manifestation	Management	Outcome
1.	Kumar [5] /2021	64/M	NM	NM	A peripheral catheter (20 gauge) in the left hand	Maintenance dose; Day 2	During administration; After 25 min h	100 mg/h	NM	Mild pain and a burning Sensation at the initiation of infiltration, then localized erythema and edema over the dorsum of the hand 6-7 hours the following event, eventually formation of blisters on a hemorrhagic background and lesion extension to the fingers with associated severe burning pain.	Limb elevation, immobilization, analgesics, and a non-occlusive dressing. Prednisolone 1mg/kg	The edema subsided by 50–60% and the blisters disappeared after 72 hours
2.	Merendonk [9] /2021	91/F	COPD Hypothyroidism Dementia HTN Arthrosis	dexamethasone	A peripheral catheter (20 gauge) in dorsal metacarpal vein	Maintenance dose; Day 4	1.5 h after administration of the full dosage	200 mL/h during 30 minutes	100 mg Remdesivir diluted with 0.9 sodium chloride solution up to 100 mL fully leaked.	3×3 cm injection site enlargement, redness, and local hypothermia. No pain or burning sensation was reported.	General Care Warm compress, hyaluronidase (255 unit) subcutaneously or intradermally	After seven days, the swelling and hematoma were decreased. Recovery takes more than six weeks.
3.	Merendonk [9] /2021	72/M	HTN DM	dexamethasone	A peripheral catheter (20 gauge) in the cephalic vein	Maintenance dose; Day 2	During administration; infusion discontinued	200 mL/h during 30 minutes	100 mg Remdesivir diluted with 0.9 sodium chloride solution up to 100 mL. The volume of infiltrated solution was not defined by the nursing staff.	Swelling, pain, and small hematoma	No general care; hyaluronidase subcutaneously or intradermally	After seven days, the swelling and hematoma were decreased. Recovery takes four weeks.

Table 1. Continued

	Author/ year	Age/ Sex	Comorbidities	Concurrent medication	Catheter site and gauge	Infiltrated Dose and Day of Event	Time until observation of infiltration	Rate of infusion	Volume and concentration of the infiltrated solution	Clinical manifestation	Management	Outcome
4.	Merendonk [9] /2021	67/F	Asthma Migraine	dexamethasone	A peripheral catheter (20 gauge) in basilica vein	Maintenance dose; Day 2	5 hours after administration of the full dosage	200 mL/h during 30 minutes	100 mg Remdesivir diluted with 0.9 sodium chloride solution up to 100 mL fully leaked.	tenderness on her right wrist dorsoradial surface and erythematous swelling about 3×2 cm	Aspiration of the leaked solution, general care interventions	Most of the signs were relieved after two days. Recovery takes four weeks.
5.	Conde-Estévez [10] /2022	68-f	NM	dexamethasone	A peripheral catheter radial vein at the left wrist	Maintenance dose; Day 4	During administration; 105 minutes after infusion initiation	100 mg/h; during 120 minutes	100 mg Remdesivir diluted with 0.9 sodium chloride solution up to 250 mL; the volume of the infiltrated solution was not defined.	4×6 cm swollen area without erythema; moderate pain around the site of injection	Aspiration, warm compress, limb elevation, and immobilization	after two days, the patient recovered without complications. After ten days of follow-up, no sequel was observed.
6.	The present study, Case [1]	82/M	HTN IHD Alzheimer's disease Parkinsonism	Dexamethasone (8 mg/day) Aspirin (80 mg/day) Atorvastatin (40 mg/day) Heparin (5000 unit/8h) Levofloxacin Ceftriaxone Losartan Montelukast	A peripheral catheter (20 gauge) in the right hand Doral venous arch	Loading dose; day 1	During administration; 15 minutes after infusion initiation	400 mg/h During 30 minutes	200 mg of Remdesivir diluted with 0.9 sodium chloride solution up to 500 mL; 200 mL of solution (equal to 80 mg of remdesivir) leaked.	Bulging and edema near the IV line, warm and purple-colored skin painless lesions. Laceration in the site of the IV line.	Aspiration, cold compress, and then Limb immobilization, non-occlusive dressing, limb elevation, warm compress. triamcinolone acetonide subcutaneously or intradermally	The color and extent of the lesion decreased by about 50% after two weeks and disappeared after his fourth week of follow-up.
7.	The present study, Case [2]	70/M	HTN IHD DM Stroke	Methylprednisolone (120 mg/ day), Heparin meropenem, vancomycin, famotidine, captopril, Aspirin Atorvastatin valsartan Insulin regular	A peripheral catheter (22 gauge) in the right limb Tributary of cephalic vein	Loading dose; day 1	During administration; 15 minutes after infusion initiation	100 mg/h; during 120 minutes	200 mg Remdesivir diluted with 0.9 sodium chloride solution up to 250 mL; 50 mL of solution (equal to 40 mg of remdesivir) leaked.	10*10 cm bulging near the IV line without erythema, ecchymosis, or pain	warm compress, limb elevation, immobilization, and the non-occlusive bandage; triamcinolone acetonide subcutaneously or intradermally	The bulging disappeared after 72 hours.

Table 1. Continued

	Author/ year	Age/ Sex	Comorbidities	Concurrent medication	Catheter site and gauge	Infiltrated Dose and Day of Event	Time until observation of infiltration	Rate of infusion	Volume and concentration of the infiltrated solution	Clinical manifestation	Management	Outcome
8.	The present study, Case [3]	51/M	Down syndrome	Dexamethasone (16 mg/day), pantoprazole Heparin	A peripheral catheter (20 gauge) in the left limb cephalic vein	Loading dose; day 1	During administration; 15 minutes after infusion initiation	100 mg/h; during 120 minutes	200 mg Remdesivir diluted with 0.9 sodium chloride solution up to 250 mL; 30 mL of solution (equal to 24 mg of remdesivir) leaked.	Bulging near the IV line with mild erythema	warm compress, limb elevation, immobilization, and the non-occlusive bandage	The erythema subsided after 48 hours
9.	The present study, Case [4]	37/M	Bipolar mood disorder	Methylprednisolone (180 mg/day)	A peripheral catheter (20 gauge) in the right limb cephalic vein	Maintenance dose; Day 2	During administration; 25 minutes after infusion initiation	100 mg/h; during 120 minutes	100 mg Remdesivir diluted with 0.9 sodium chloride solution up to 250 mL; 30 mL of solution (equal to 12 mg of remdesivir) leaked.	2+ edema, ecchymosis, and erythema	warm compress, limb elevation, immobilization, and the non-occlusive bandage; triamcinolone acetonide subcutaneously or intradermally	The edema subsided by 50–60% after four days and erythema disappeared after six days.

F: female; M: male; NM: not mentioned; COPD: Chronic obstructive pulmonary disease; HTN: hypertension; DM: diabetes mellitus; IHD: ischemic heart disease.

Figure 1. Skin lesions after remdesivir infiltration. a) Four hours after infiltration in case 1; b) Bulging the skin in the second reported case immediately after figuring out extravasation. c) Skin erythema in the third case one hour after infiltration. d) Extravasation site after administration of triamcinolone acetonide in the fourth case.

a dermatology consultation was conducted. Hyaluronidase enzyme was not available in our center. The intralesional injection of triamcinolone acetonide was performed as follows: 0.2 mL of 40 mg/mL triamcinolone acetonide (Hexal®; Germany) was diluted with 0.6 mL of sodium chloride 0.9% solution to achieve 10mg/mL concentration. Then, each site was injected with 0.02 mL of prepared solution at 1 cm intervals. Additionally, warm compresses and non-occlusive dressing were applied every 8 hours. The laceration was also filled with foam and was bandaged with hydrocolloid dressing. The burning sensation decreased after the initial measures (12 hours after the event); nonetheless, the pain persisted up to 40 hours after the complication (10 hours after the intralesional injection). After three days, the foam and dressing were replaced with new ones for the next three days. The color and extent of the lesion diminished by about 50% after two weeks and disappeared after the fourth week of follow-up (Figure 2).

Case 2

A 70-year-old man was admitted with dyspnea, productive cough, sore throat, anorexia, and fatigue. He had a history of diabetes mellitus, hypertension, ischemic heart disease, and a stroke one month before admission. Following a positive COVID-19 rRT-PCR test and primary para-clinical workups, a 200 mg loading dose of remdesivir concentrated

Figure 2. Case no.1 clinical course of skin lesions following remdesivir infiltration. a) Day 0, four hours after infiltration; b) day +2; c) day +5; d) day +8; e) day +11; f) day +13; g) day = 20; h) day +27.

solution (Remdesivir-Ronak®, Iran) was diluted in 250 mL of sodium chloride 0.9% solution and infused through an IV line at the rate of 125 mL/h. After about 20 minutes, the nursing staff figured out a 10×10 cm bulging of skin adjacent to the IV line without erythema, cyanosis, itching, or ecchymosis (Figure 1B).

The patient complained of local mild pain and a burning sensation. The medication infusion was stopped, and warm compresses, limb elevation, immobilization, and non-occlusive dressing were applied. Triamcinolone acetonide suspension for injection was intralesionally administered by the dermatologist as described in the first case. Pain and burning sensation subsided 6 hours following injections. The lesion did not progress over other parts till the next three days. Unfortunately, the disease developed into acute respiratory distress syndrome (ARDS), and the patient passed away four days following the adverse medication event.

Case 3

A 51-year-old man with Down syndrome presented to the emergency department with a cough, fever and chills, dyspnea, diarrhea, and anorexia. After clinical suspicion of COVID-19 and biochemical blood work, 200 mg of remdesivir concentrated solution (Remdesivir-Ronak®, Iran) was diluted in 250 mL of sodium chloride 0.9% solution and administered through an IV line at the rate of 125 mL/h. Based on the provided instructions, the nurse visited the patients and inspected the injection site every 15 minutes during remdesivir infusion and evaluated any evidence of extravasations. After

about 15 minutes, the nurse noticed infiltration of about 20 mL of diluted remdesivir and ceased the infusion and followed conservative therapies as instructed. The bulging area around the IV line showed mild erythema. However, no ecchymosis, pain, burning sensation, or tenderness was reported (Figure 1C), and the affected area did not worsen. The rest of the loading and subsequent daily doses of remdesivir were administered via another IV line. Without any intralesional drug administration, the erythema was resolved dramatically the next day. His laboratory results showed no coagulopathies or thrombocytopenia. Unfortunately, the patient died four days later, as his respiratory condition deteriorated. There was no trace of infiltration when the patient died.

Case 4

A 37-year-old man with a history of bipolar mood disorder and symptoms of dyspnea, cough, sore throat, and myalgia was admitted and diagnosed with COVID-19 pneumonia. 200 mg of remdesivir concentrated solution (Remdesivir-Ronak®, Iran) was diluted in 250 mL sodium chloride 0.9% solution and was infused through a cephalic IV line at the rate of 125 mL/h as the loading dose with no complications or local symptoms. However, during the infusion of the next dose (initial maintenance dose), the nursing staff figured out the bulging of the skin near the IV line after about 25 minutes. The infiltrated volume was about 30 mL. The infusion was stopped, and all the non-pharmacological recommendations were applied. Mild erythema, mild pain, and a burning sensation were reported. As reported in the first case, seven hours later, the dermatologist administered triamcinolone acetonide suspension for injection intralesionally (Figure 1 D), 24 hours following triamcinolone administration. Local pain and burning sensation subsided 9 hours following triamcinolone injections. The remaining daily doses of remdesivir were administered using another IV line. Seven days following drug infiltration, there was no sign of a lesion.

DISCUSSION

The present study reported four cases of remdesivir infiltration, including their clinical course, management, and outcomes. An overview of clinical data regarding the present and previously reported cases is summarized in Table 1. Figures 1 and 2 show the clinical presentation of adverse drug events on the first day, as well as the clinical course of the most severe case. As demonstrated in Figure 2, the course of the disease could last more than four weeks. Nevertheless, it could be resolved without any sequels. Post-extravasation cellulitis can develop months after the event [8]; thus, long-term patient follow-up is recommended. The present study attempted to address the factors that influence remdesivir infiltration and provide clinical recommendations to reduce the incidence and event burden. The influencing factors were discussed in three ways: (a) medication dependent (b), patient dependent, and (c) administration dependent factors. Furthermore, instructions for the prevention and management of remdesivir infiltration were provided. Besides, related questions were proposed to be addressed by future surveys.

Remdesivir infiltration risk factors

(a) Medication dependent factors

Remdesivir is known as a non-vesicant, small-molecule prodrug that is metabolically converted to GS-443902 [11]. The osmolality of remdesivir, 100 mg concentrated solution (5 mg/mL) and diluted solution in 250 mL sodium chloride 0.9% solution (0.4 mg/mL), was 1200 mOsm/Kg and 330 mosm/Kg, respectively. The osmolality of remdesivir, 100 mg lyophilized powder after reconstitution with sterile water for injection, was 498 mosm/Kg, and the osmolality of diluted solution in 250 mL sodium chloride 0.9% solution (0.4 mg/mL) was 301 mosm/Kg (i.e., the concentration of sulfobutylether β-cyclodextrin sodium (SBECD) in remdesivir was 6 g per 100 mg concentrated solution and 3 g per 100 mg remdesivir lyophilized powder). As the Osmolality of the final diluted solution was not more than 500-600 mosm/Kg, it could not be the underlying cause of tissue irritation after infiltration. The type of remdesivir formulation (concentrated solution vs. lyophilized dosage form) was not defined by researchers in previous reports, which could be an important variable [5,9,10]. Other pharmaceutical excipients in remdesivir formulations included hydrochloric acid and/or sodium hydroxide, which adjusted the formulation to a final pH of 3.0 to 4.0 in a concentrated solution or reconstituted one.

The final pH after dilution was not defined [12]. As previously mentioned, the first case (the most severe one) received remdesivir 200 mg diluted in 500 mL of sodium chloride 0.9% solution, which was twice the concentration specified in the manufacturer's instructions [13]. Accordingly, the molarity of acid content was reduced, and pH was adjusted to a more physiologic state. It seemed that high pH was not the cause of tissue damage in these cases.

To summarize, the main cause of tissue damage following remdesivir infiltration might be due to the drug nature, rather than the solution pH or osmolality. Based on the reported cases, possibly, it is time to consider remdesivir or other pharmaceutical excipients in formulations, such as SBECD, as an irritant or even vesicant medication. According to the literature [11], vesicant medication might cause blisters and irreversible tissue damage. Kumar *et al.* defined blister formation in their report [5]. Moreover, previous studies by Mechineni *et al.* and Conde-Estévez *et al.* reported that irritant medications cause inflammation and irritation at the extravasation site [3,10], as well as in the cases presented in this study. However, none of the patients presented in this study complained of pain or burning sensation in the affected area. Additionally, none of the nine reported cases had any sequels (Table 1).

(b) Patient dependent factors

Extreme age is a known risk factor for medication infiltration. Fragile veins in elderly patients are one of the potential causes. Six out of nine (66.6%) reported cases were 65 or older (Table 1). Excessive patient movement around the venous access site is another risk factor [7]. In a previous study, most of the extravasations occurred when the patient moved to the toilet [11], which indicated that the patient's compliance was an important factor in these adverse events. Psychologic and neurologic conditions could also affect the patient's adherence to medical advice during infusion. All of the cases presented in this study had a neurologic/psychologic condition, such as mental retardation, Parkinson's disease, stroke, Alzheimer's, or bipolar mood disorder, which might have contributed to the occurrence of this complication. Based on our experience, it was prudent to administer remdesivir infusion to such patients. However, more attention should be paid, and the vascular pathway should be monitored at short intervals. Patients were informed about limb immobilization. However, due to the underlying disease, non-compliance with this instruction was expected.

(c) Administration dependent factors

Cannulation Tanique plays a key role in infiltration risk. Multiple venous access attempts proximal to the venous access site can increase the probability of medication leakage. Hence, experienced staff who can perform cannulation with a single puncture can help reduce the risk of infiltration. Moreover, avoiding infusion through a vein after multiple venous access attempts can prevent the event. Teflon-type catheters, which were used in our center, had a medium infiltration risk. Polyurethane catheters were preferable in this situation [7]. The catheter location is also important. Based on our experience and other reported cases, the dorsum of the hand was associated with the incident and severity of remdesivir extravasation [5,9,10]. This area could be more severely damaged by extravasation [6]. Infusion duration and medication volume were also defined as extravasation risk factors. Large infiltrated volumes could pressure surrounding tissue and cause mechanical damage [9]. However, the thinner solution has lower osmolarity and higher physiologic PH. Thus, the optimal volume, concentration, and duration should be chosen. 250 mL volume of 100 mg medication plus diluent seemed logical. This volume provided acceptable PH and osmolarity. Accordingly, the loading dose could be diluted to a total volume of 500 mL. On the other hand, increasing volume was a risk factor for increasing the infiltrated volume and extending the affected area. Overall, a 250 mL volume of 100-200 mg medication plus diluent appeared reasonable. The present study recommended 120 minutes as the optimal duration. It could prevent infusion reaction following accelerated infusion and could also provide proper time to inspect the infusion site in 10-minute intervals. Infusion of 250 mL solution during 120 minutes with a 15-minute interval could cause a maximum of 20 mL infiltration of a more physiologic solution, as it occurred in cases 2-4 of the present study, which could be managed more efficiently.

Preventive measures

The most effective measures for preventing

remdesivir infiltration included proper cannulation technique, medication preparation for administration based on manufacturer instructions, and regular IV-line inspection. The primary stage is to educate the staff. They should be prepared for prompt action after encountering remdesivir extravasation. As described in case one management course and the same process in previous reports, untrained or unfamiliar staff were unable to quickly diagnose and manage the complication properly. Preparation for administration, infusion technique, and infiltration handling in an emergent situation should all be taught step by step. In the first case, the untrained staff applied mechanical pressure and cold compression. Besides, they noticed the complication later than in other cases (due to a lack of injection site inspection). Therefore, more volume of solution was infiltrated, and the extent of the lesion was more extended than in other cases. After establishing staff education and implantation of instructions, event severity was significantly reduced (case 1 vs. cases 2-4).

Management

(a) Conservative therapies

Merendonk defined non-pharmacological interventions [9]. These conservative interventions included discontinuing the infusion, disconnecting the tube from the catheter, residual drug aspiration, limb elevation, avoiding manual pressure, limb immobilization, dry warm compresses (for 15 minutes, every 8 hours, for 48 hours) [10], and a non-occlusive dressing. In the first case, the nursing staff did a cold compress before the consultation. The more bruising and worse course of condition might be attributed to this action to some extent. However, after staff training, warm compresses were applied for the remaining cases (3 out of four).

(b) Intralesional injections

Besides non-pharmacological interventions, Merendonk and colleagues used hyaluronidase to follow the disperse and dilute method [9]. Since the hyaluronidase enzyme dosage form was unavailable in our center, the dermatologists decided to start intralesional corticosteroids injection (triamcinolone acetonide suspension for injection 40 mg/mL, Hexal®; Germany) in three out of four cases; despite the patients were on systemic corticosteroids (methylprednisolone or dexamethasone). The injection sites are apparent in Figure 1D. There is controversial evidence regarding intralesional corticosteroid (mainly hydrocortisone) injections in the management of extravasations. Both outcomes, including prevention of tissue necrosis and increasing the need for surgical debridement, have been reported after intralesional corticosteroid injection. However, most of these studies focused on the extravasation of cytotoxic drugs [14]. There are several promising studies regarding intralesional triamcinolone in extravasations [15-17]. Whang *et al.* evaluated the effect of intralesional triamcinolone on ten extravasation cases and reported excellent outcomes [16]. Additionally, an experimental model showed the effectiveness of combination treatment of intralesional triamcinolone and hyaluronidase in an extravasation context [18]. As described in Table 1, four out of nine presented cases did not receive intralesional treatment (neither triamcinolone nor hyaluronidase), and all of them completely recovered. It seems that general supportive care also can be sufficient in mild to moderate conditions, while the effect of these medications on lesion resolve duration cannot be denied. As previously stated in the text, late intralesional injection in the first case (30 hours following an event) could be another justification for more complications and late recovery.

CONCLUSION

In the present study, four new cases of remdesivir infiltration, as well as a review of five previously reported ones are provided. A range of local symptoms might include mild bulging and erythema, as well as hemorrhagic ulcers and blistering. Preventive measures should be instructed in COVID-19 wards. Following our center's instructions regarding remdesivir preparation, administration, and infiltration handling could significantly reduce event severity. The most vulnerable patients should be identified and assessed more closely. Non-pharmacological interventions included discontinuing the infusion, disconnecting the tube from the catheter, aspirating the residual drug, elevating the limb, avoiding manual pressure, immobilizing the limb, applying dry and warm compresses (for 15 minutes, every 8 hours, for 48 hours), and using a non-occlusive dressing. These strategies could be effective in managing mild to moderate subjects. Intralesional triamcinolone

and/or hyaluronidase are other therapeutic options.

It is advantageous to define the pH and osmolarity of remdesivir (either concentrated or lyophilized dosage forms) reconstituted, concentrated, and final diluted solutions in different saline and dextrose-containing diluent. Accordingly, designing an experimental study to evaluate the tolerability of different remdesivir-containing solutions (excipients ± active pharmaceutical ingredients in different diluents) could be advantageous. Moreover, it will be worthwhile to evaluate their consequences on endothelium and soft tissue, as well as any potential vasoactive mechanisms.

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Authors' contributions

Vahid Reisi-Vanani: Data collection; preparations of manuscript & follow-up of the patient. Ahmad Raeisi: Data collection, and follow-up of the patient. Mina Borran: Study conception, preparations of manuscript, Supervision, and follow-up of the patient. Zakiye Ganjei: Study conception, Supervision, and follow-up of the patient. Marzieh Fattahi-Vanani: Data collection, and follow-up of the patient.

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Ethics approval and consent to participate

This study was performed in accordance with the 1975 Declaration of Helsinki and was approved by the Local Ethics Committee of Shahrekord University of Medical Sciences (IR.SKUMS.REC.1401.084).

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editors-in-Chief of this journal.

Conflict of Interest: None declared.

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