Introduction

Symmetrical peripheral gangrene (SPG) is a disease that causes symmetric ischemic necrosis of the peripheral limbs without proximal arterial occlusion. This concept was proposed by Hutchinson et al. in 1891. SPG is defined as a result of marked elevation of blood catecholamine levels during septic shock and micro-thrombosis with disseminated intravascular coagulation (DIC), resulting in symmetric ischemia of the peripheral limbs and necrosis of the fingers and toes. Various pathogens cause bacteremia with a high proportion of pneumococcal pneumonia in Japan, with an estimated mortality rate of approximately 30%–43% for pneumococcal SPG. Withdrawal from sepsis is expected to have a life-threatening prognosis, corresponding necrosis of the extremities after withdrawal from the underlying disease often requires amputation which implicates prolonged course of treatment.

We report a case of SPG in a patient who underwent living-donor liver transplantation. In this case, the patient developed posttransplant lymphoproliferative disorders (PTLDs) after long-term use of immunosuppressive drugs wherein administration of R-CHOP therapy (R) rituximab (Rituxan), (C) cyclophosphamide, (H) doxorubicin hydrochloride, (O) vincristine (Oncovin, Vincasar PFS), (P) prednisolone, R-CHOP is a combination of five drugs that work together to target and kill cancer cells. It’s a first-line treatment for aggressive non-Hodgkin’s lymphoma] was the initial management. However, pneumococcal pneumonia was complicated by immunosuppressive conditions, thus septic shock complications resulted to SPG. In this case, symmetric necrosis of the peripheral extremities and necrosis of the nasal tip, apex of the tongue, central part of the lip, and tip of the penis were also observed. This is the first report of the development of SPG after living-donor liver transplantation. Necrosis extended beyond the extremities to the peripheral bloodstream with characterization of the symmetry.

Key words: liver transplantation, Symmetrical Peripheral Gangrene

Case Report

A Case of Symmetrical Peripheral Gangrene Secondary to Liver Transplantation

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ABSTRACT

Symmetrical peripheral gangrene (SPG) is a symmetric ischemic necrosis of the peripheral extremities without proximal arterial occlusion. We encountered an immunocompromised patient with pneumococcal pneumonia complicated by septic shock leading to SPG after chemotherapy for posttransplant lymphoproliferative disorders (PTLDs) secondary to the use of immunosuppressants after living-donor liver transplantation. In this case, symmetric necrosis of the peripheral extremities and necrosis of the nasal tip, apex of the tongue, central part of the lip, and tip of the penis were also observed. This is the first report of the development of SPG after living-donor liver transplantation. Necrosis extended beyond the extremities to the peripheral bloodstream with characterization of the symmetry.

Key words: liver transplantation, Symmetrical Peripheral Gangrene

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rejection. Ten months prior, the patient developed PTLDs and was induced to remission with seven courses of R-CHOP therapy but had reversible myelosuppression. The patient had a history of having borderline diabetes mellitus, chronic kidney disease (G4A0), previous lacunar infarction, hyperuricemia, atrial fibrillation, and prostatic hypertrophy.

The patient visited the emergency outpatient clinic because of fever, diarrhea, and cough. Laboratory data on admission (Table 1) revealed severe inflammation and renal dysfunction. The respiratory condition gradually deteriorated and ventilator management by endotracheal intubation was performed. The patient was diagnosed with septic shock based on the blood culture, and DIC associated with severe pneumococcal pneumonia. Management was facilitated through the administration of vasoconstrictors, low-molecular-weight heparin, antithrombin preparation, fresh frozen human plasma, intravenous gamma globulin, and ABPC (Ampicillin). The vasoconstrictors administered included noradrenaline (3.3 µg/kg/min) between 1st and 3rd day of illness, adrenaline (1.66 µg/kg/min) between 1st and 2nd day of illness, dobutamine hydrochloride (1.1 µg/kg/min) between 2nd and 6th day of illness, and vasopressin (0.55 µg/kg/min) between 1st and 4th day of illness. Continuous hemodiafiltration was introduced for the acute aggravation of chronic renal insufficiency. The patient was weaned from the respirator on the 23rd day of illness. The patient was transferred to the general ward on 42nd day of illness when his general condition stabilized.

Skin changes were not observed in the arm and leg, although reddish-purple discoloration of the lips was observed on admission. The ischemic changes in the lips, nose, fingers, and toes gradually progressed, and the patient was referred to our department on the 9th day of illness. At the first visit to our department, purpura was observed on the anterior surface of both lower legs and a dark purple discoloration was observed from the sole of the foot to the heel (Fig. 1). The dorsalis pedis artery and posterior tibial artery were palpated and both toes were cold and partially gangrenous. Purpura and blistering were observed in both hands and black discoloration was observed in the fingertips of both hands. Necrosis was also observed in the nasal tip, apex of the tongue, central part of the lip, mandible, and tip of the penis. It was determined that the proximal artery was not occluded based on the results of the transcutaneous oxygen pressure on the 4th day of illness, lower limb arterial ultrasound on the 5th day of illness, and transcutaneous Doppler sonogram on the 9th day of illness.

Tissue necrosis due to temporary impairment of peripheral blood flow was also considered. The necrosis of the limbs was penetrative and there was a possibility of bone exposure, thus dry management was performed for the purpose of infection control until demarcation. For other sites, the necrosis was superficial and the possibility of bone/cartilage exposure was low, thus spontaneous loss and epithelialization of necrotic tissue were attempted in a wet environment. Gangrene was evident at the first visit to our department and epithelialization was observed at the site of purpura and blistering. The nasal tip, apex of the tongue, central part of the lip, and tip of the penis were epithelialized, but two-thirds of the lips were unsalvageable.

The toes showed dry gangrene, but marginal maceration and signs of infection were observed 4 months after onset; therefore, debridement including amputation was performed. On the right foot, the hallux was amputated at the interphalangeal joint, and the third toe was amputated at the proximal interphalangeal joint. The metatarsal incision of the fifth toe and phleom cutis of the plantar skin were open wounds (Fig. 2a and b). The left foot was also excised into a lump of skin necrosis on the sole of

| Table 1. Laboratory data on admission |
|--------------------------------------|
| **Hematology**                       | **Biochemical analysis** |
| WBC 0.93×10⁹/mm³                     | Na 135 mEq/l             |
| RBC 469×10⁴/mm³                      | K 3.5 mEq/l              |
| Hb 13.4 g/dl                         | Cl 101 mEq/l             |
| Hct 39.8 %                           | Alb 3.4 g/dl             |
| Pt 10.9×10⁹/mm³                      | AST 32 U/l               |
|                                      | ALT 13 U/l               |
| **Hemostasis**                       | LDH 419 U/l              |
| PT (INR) 1.19                        | T.bil 1.6 mg/dl          |
| APTT 30.2 sec                        | Cre 2.51 mg/dl           |
|                                      | CRP 19.82 mg/dl          |
|                                      | CK 322 U/l               |

WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, Hct: hematocrit, Plt: platelet, PT(INR): prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, Na: natrium, K: kalium, Cl: chlorine, Alb: albumin, AST: Aspartate Aminotransferase, ALT: Alanine aminotransferase, LDH: lactate dehydrogenase, T.bil: total bilirubin, Cre: creatine, CRP: C-reactive protein, CK: Creatine Kinase
the foot with amputation of the metatarsal bones of the halluxes, fourth, and fifth toes, amputation of the proximal phalanx of the second toe, and detachment of the third toe metatarsophalangeal joint wherein the incision was made as an open wound (Fig. 2e and f). Debridement was minimized as closure of wounds were facilitated using skin grafts. The extent of the postoperative ulcer on the right foot was minimal but with partial bone exposure. Therefore, negative pressure wound therapy with instillation and dwell time (NPWTi-d) therapy was performed. On the other hand, the extent of the postoperative ulcer on the left foot was large and many necrotic tissues remained. Therefore, negative pressure wound therapy with continuous irrigation (NPWTci) was performed in the infected layer. Six months after the onset of the disease, the defect was closed with skin grafts from both groin regions (Fig. 2c, d, g, and h).

Because both fingers remained dry and necrotic, conservative treatment was continued with the expectation that the necrotic area would fall off spontaneously. Approximately 6 months after onset, the patient experienced almost spontaneous withdrawal, the residual site was sharply resected, and epithelialization was anticipated by ointment treatment (Fig. 3a, b, d, and e). Seven months after onset, only small ulcers persisted below the right middle fingernail and below the left thumb, index finger, and middle fingernail (Fig. 3c, and f).

Autonomic neuropathy was observed from the time of septic shock and the patient was unable to sit for a long time. The patient was transferred 7 months after onset for rehabilitation of joint contracture and disuse syndrome due to prolonged bed rest. At this time, the wounds on both feet were already healed (Fig. 4a, and b). The upper lip was unsalvageable in two-thirds of the left lip (Fig. 4c). The patient continued rehabilitation.

Fig. 1. Appearance on the 9th day of illness. Necrosis was observed in the lips, papilla of the tongue (a), and apex of the nose (b). A dark purple discoloration and blistering were observed from the sole of the foot to the heel. Both toes partially resulted in gangrenes (c) and (d). Purpura and blistering were observed in both hands, and black discoloration was observed in the fingertips of both hands (e, f).
after being transferred to another hospital; however, he died of pneumonia and urinary tract infection 11 months after the onset of sepsis.

Discussion

SPG is defined as a symmetric ischemic necrosis of the peripheral limbs without proximal arterial occlusion. Causes include hypoperfusion such as cardiogenic shock, vasospasm such as Raynaud syndrome, microvascular occlusion such as cold agglutinin, snakebite wounds, and infections. Infections are particularly caused by acute infectious purpura fulminans, which is caused by hypoperfusion due to infection, DIC, and immunologic abnormalities. Although the definite pathology is still unknown, it is hypothesized to be caused by elevated blood catecholamine levels in the blood. In Japan, Streptococcus pneumoniae is the major cause of SPG. In other countries, meningococci are the major cause of sepsis in SPG cases.

In this case, the patient had to take immunosuppressive drugs for a long time after liver transplantation, which led to the development of PTLDs. The patient received R-CHOP therapy but became immunocompromised due to irreversible myelosuppression. His immunocompromised state resulted in the development of severe pneumococcal pneumonia secondary to sepsis. In addition, it was hypothesized that the administration of high catecholamines to maintain blood pressure due to septic shock reduced peripheral blood flow and resulted in the development of SPG.

There is currently no consensus on the timing of debridement of peripheral necrotic tissue caused by SPG. If the central artery is not occluded, as in the case of blue toe syndrome, and the terminal necrosis is caused only by the most peripheral arterial occlusion, it is common to wait conservatively until a demarcation is made and tissue is preserved as much as possible. In SPG, before performing surgery, it is recommended to wait for a demarcation while waiting for stability of the general condition. Because many of the previously reported SPGs are not myelosuppressed, withdrawal from sepsis by treating the underlying diseases such as pneumonia and urinary tract infections may be associated with a relatively low risk of wound infection. In this case, demarcation occurred 1 month after the onset. However, it took 4 months for the general condition to settle because this patient had irreversible myelosuppression and the wound was still susceptible to infection even after withdrawal from sepsis due to pneumonia. Therefore, careful management of the wound was necessary although general wound treatment was continued.

As described above, in the case of SPG, the patient usually

Fig. 2. Treatment course for both feet.
The toes showed dry gangrene (a)(e). Four months after onset, debridement, including amputation, was performed (b)(f). After NPWTi-d therapy on the right foot ulcer (c) and NPWTci therapy on the left foot ulcer (g), good granulations were observed. Six months after onset, split-thickness skin grafting from both groins was performed (d)(h).
Fig. 3. Treatment course for both fingers. The fingertips of both hands were dry and necrotic (a)(d). Six months after the onset, the residual site was debrided (b)(e). Seven months after onset, only small ulcers persisted below the right middle fingernail (c). Only small ulcers persisted below the left thumb, index finger, and middle finger (f).

Fig. 4. Appearance after 7 months after onset. Both feet were epithelialized (a)(b). Two-thirds of the upper lip was unsalvageable; therefore, he had difficulty using straws (c).
requires longer periods of intensive care followed by longer wound rest. Contractures can be prevented with passive rehabilitation for joints distal to necrotic areas such as the knee and elbow, even under severe general conditions. However, this is a dilemma because movements of the tendon near the infected site possibly spread bacteria to the distal tendons, such as the fingers and toes. In this patient, rehabilitation intervention for the large joint was performed with avoidance of tendon movement near the infection site; however, the duration of treatment from the onset of pneumonia was prolonged, resulting in generalized contracture of the joints, leading to decreased ADL and cognitive function. After wound healing, it was difficult to shift to long-term sitting training and standing training due to instability of the foot scar, autonomic neuropathy, and joint contractures.

Historical significance of SPG was reported initially by Hutchinson et al. in 1891. It has been emphasized that necrosis in the periphery of the limbs is symmetric; however, if it is assumed that the increase in blood catecholamine concentration causes peripheral blood flow failure then there is a corresponding assumption that necrosis occurs in other peripheral blood flow areas. In this case, necrosis was also observed in the tongue, lip, apex of the nose, and tip of the penis, which protruded from the body and required wound management. Although many of the punctate purpura and blistering areas developed epithelialization by avoiding dryness, necrosis of the lip progressed, and two-thirds of the upper lip was unsalvageable.

Conclusion

We encountered a case of SPG secondary to pneumococcal pneumonia in an immunocompromised patient with PTLDs caused by the use of immunosuppressants after living-donor liver transplantation. The patient was vulnerable to infection, thus careful local control was necessary. Appropriate judgment of the timing for debridement resulted in patient survival and wound healing. However, there are still minor complications leading to decreased ADLs with long-term bed rest.

COI statement

The authors declare no conflicts of interest associated with this manuscript.

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