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Clinical study on single-organ cutaneous small vessels vasculitis: a retrospective observational study

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Abstract. – OBJECTIVE: Single-organ cutaneous small-vessel vasculitis (SoCSVV) is an inflammatory skin-limited vascular disease affecting the dermal and/or hypodermal vessel wall. Pathogenetically, idiopathic forms are described, as well as the induction from different triggers, such as infections, drugs, and vaccines. Following the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic outbreak, cases of cutaneous vasculitis induced by both COVID-19 and COVID-19 vaccinations have been reported in literature. The aim of this study is to provide the most recent evidence on new etiological factors, clinical features, and management of the SoCSVV.

PATIENTS AND METHODS: We included 42 patients (22 women, 20 men) with SoCSVV and no systemic involvement in the study. The mean age of the patients was 57.3 years. Palpable purpura was the most frequent clinical manifestation (38 cases-90.4%). All patients were diagnosed with leukocytoclastic vasculitis by skin biopsy.

RESULTS: The etiological factors were as follows: idiopathic in 9 (21%) patients, drug-related in 19 (45%) patients, COVID-19 infection-related in 5 (12%) patients, post-COVID-19 vaccination in 5 (12%) patients, paraneoplastic in 2 (5%) patients, and drug and infection and sepsis in 1 patient each. Among the drug-related cases, 16 (84%) were antibiotic-related, and most of them were beta-lactam antibiotics. Eosinophilia was present in skin biopsy in the cases related to vaccination and drugs, while intense necrosis and vascular damage in the skin were observed in the cases related to COVID-19 infection, unlike the others. A rapid resolution was observed with the cessation of drugs and short-term steroid treatment for the precipitating factors.

CONCLUSIONS: SoCSVV is usually associated with drugs, preceding infections, and vaccines. COVID-19 infection and COVID-19 vaccinations have been reported as new etiological factors. SoCSVV indicates that the disease seems to be a mild, self-limiting illness with a good clinical result.

Key Words:
Cutaneous small-vessel vasculitis, Etiology, COVID-19, COVID-19 vaccines, Drug.

Introduction

Systemic vasculitides are a group of diseases involving vascular inflammation, often affecting multiple vessels and organs. Less frequently, vasculitis can manifest in a localized form, indicating a restricted presentation of systemic vasculitis or vascular inflammation that is restricted to a single organ or system[1-3]. To help differentiate between the two types of localized vasculitis, the 2012 Revised International Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides[4] recommended the use of the term single-organ vasculitis (SOV) for definition purposes "vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a systemic vasculitis"[4]. Currently, SOV includes cutaneous small vessel vasculitis, cutaneous arteritis, primary central nervous system (CNS) vasculitis, isolated aortitis, and other related conditions[4]. Single-organ cutaneous small-vessel vasculitis (SoCSVV) predominantly affects small blood vessels without any detectable involvement of the non-cutaneous organs. In order to diagnose skin-limited vasculitis, one must first rule out important systemic manifestations (such as renal, joint, pulmonary, neurological, and gastrointestinal complications) as well as underlying conditions that affect management and prognosis. Patients might also develop systemic manifestations over time, necessitating close follow-up. CSVV can also have a number of identifiable causes, such as medication, infections such as Coronavirus Disease 2019 (COVID-19), and vaccination against COVID-19, allergens, immune-mediated conditions, and malignancies, most frequently hematologic[5-13]. In adults, the most common causes are drugs and infectious agents[5,9,11]. Nevertheless, in around half of the cases, no underlying cause is found[9-11,14].

The purpose of our study is to provide the most recent evidence on new etiologies, clinical

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features, and management of the SoCSVV, with a particular focus on the COVID-19 pandemic.

Patients and Methods

The study included 42 patients who were diagnosed histopathologically with leukocytoclastic vasculitis according to the 2012 International Chapel Hill Meeting between January 2020 and January 2023 and admitted to our clinic. The following data were recorded for each case: age, gender, medical and family history, systemic diseases and medications; lesion characteristics (duration, location, type, and symptoms); extra-cutaneous findings; previous or current infections (including COVID-19), antibiotics used, malignancy status, vaccinations received in the last 6 months; possible etiological factors; laboratory findings and treatment options. Complete blood count, liver and renal function tests, urinalysis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), coagulation, human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) syphilis serology, antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), C3 and C4 levels, cryoglobulinemia, rheumatoid factor, extractable nuclear antigens (ENA), streptococcal antibodies, abdomen ultrasound examination, chest radiography, fecal occult blood tests (FOBT), and skin biopsy were performed in all patients. Direct immunofluorescence (DIF) tests for IgA, IgG, IgM, and C3 were analyzed in the skin biopsy. However, the analysis of the SARS-CoV-2 PCR test in the skin biopsy could not be performed due to insufficient resources and material. Patients with cutaneous small vessel vasculitis were included. Patients with systemic vasculitis or who developed systemic manifestations during follow-up were excluded. Only patients with at least 6 months of follow-up were included. Data were obtained retrospectively from patient files. Ethical approval was obtained from the local ethics committee (approval date: 03/15/2023, number: ESH/GOEK 2023/6).

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 23.0 software (IBM Corp., Armonk, NY, USA). When evaluating the study data, quantitative variables were determined by mean, standard deviation, median, minimum and maximum values; qualitative variables were indicated by descriptive statistical methods such as frequency and percentage. If $p<0.05$, the difference between the means was considered significant.

Results

There were 22 female and 20 male patients. The mean age of our patients at the onset of disease was 57.3 years (range 22-84 years). None of the patients had any history of autoimmune diseases or allergies. Diabetes mellitus (n=5, 11.9%) and hypertension (n=10, 23.8%) were the most common comorbidities. All patients were negative for anti-nuclear antibody, dsDNA, complement c3 and c4, ENA panel, rheumatoid factor, myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA. These tests were performed to rule out systemic vasculitis. All patients were also negative for cryoglobulinemia and syphilis, HIV, HBV, and HCV infections. Among the inflammatory markers, the mean CRP level was 125 mg/L (range 0-5) in COVID-19-positive patients, 13 mg/L in patients who developed vasculitis after COVID-19 vaccination, and 15 mg/L in drug-related patients.

The cutaneous manifestations of leukocytoclastic vasculitis are summarized in Table I. Palpable purpura was the most common initial symptom and the most frequent clinical manifestation (n=38). Lesions occurred mainly on the lower extremities (n=36), especially the lower legs, but were also present on the trunk, buttocks, and upper extremities in a significant number of patients (n=13).

Possible triggering events are summarized in Table II. We could not detect any triggering event in nine patients (21.4%). Recent drug intake was detected in 19 patients (45.2%). Sixteen patients developed rashes after antibiotic use. Antibiotics, especially amoxicillin/clavulanic acid, were the most frequently recorded drugs,

Table I. Patents data.

Cutaneous manifestations	No. of patients (%)
Palpable purpura	38 (90.4)
Non-palpable purpura	4 (9.5)
Urticarial lesions	5 (11.9)
Ulcers	4 (9.5)
Bullae	5 (11.9)
Pustules	3 (7.1)
Papulovesicular	3 (7.1)
Digital ischemia	1 (2.3)

followed by ampicillin/sulbactam, ciprofloxacin, and cefuroxime axetil. Seven patients had upper respiratory tract infections, two had pneumonia, two had urinary tract infections, two had gastroenteritis, two had cellulitis, and one had a burn. All patients who received antibiotics had a negative COVID-19 PCR test.

The mean time between antibiotic intake and symptom onset was 14.6±6.7 days (range 7-30 days). Three patients developed palpable purpuric lesions after starting different drugs. One patient developed lesions after six days of naproxen sodium, another after five days of rivaroxaban, and the last after three days of erlotinib for lung adenocarcinoma. Histopathological analysis revealed increased eosinophilia in 27 patients. Tissue eosinophilia was present in all patients who were suspected of having drug-related or vaccine-related vasculitis. Peripheral blood eosinophilia was within normal limits in these patients. Drug association was established based on the temporal relationship between the suspected drug and the rash, the regression of the rash with the discontinuation of the suspected drug, and the absence of any other factor in the patient's history that could cause the rash. Imaging procedures with accompanying weight loss revealed lung small cell carcinoma in one patient and renal cell carcinoma in another patient.

The mean time between the onset of purpuric rash and skin biopsy was 4.2 days (range 2-25 days) in patients. DIF analysis should be performed without exception, especially when dealing with early lesions. This is due to the potential disappearance of immune deposits in lesions that have already elapsed 48 hours. Five patients had active SARS-CoV-2 infection. Their clinical features are shown in Table III. The mean time between SARS-CoV-2 infection and vasculitis onset was 11.8 days (range 7-18 days). All patients developed vasculitis while hospitalized. One patient had a co-infection of SARS-CoV-2 and C. pneumoniae and received levofloxacin treatment. However, vasculitis was present before levofloxacin treatment. One patient had previously received one dose of the Sinovac vaccine. The lesions were necrotic in character in this patient, unlike the others. Histopathological analysis showed prominent fibrin deposition and necrosis, unlike the others. The tests for anti-cardiolipin, anti-beta2 GP I antibodies, and lupus anticoagulant, which were requested for possible antiphospholipid antibody syndrome in these patients, were negative. DIF tests for Immunoglobulin A (IgA), IgG, IgM, and C3 were negative. There was no eosinophilia in the tissue histopathologically.

Table II. Etiology and associated conditions of single-organ cutaneous small-vessel vasculitis.

Etiology or association	No. of patients (%)
Idiopathic	9 (21.4)
Drug-induced	19 (45.2)
Amoxicillin/clavulanic acid	6 (14.2)
Ampicillin/sulbactam	3 (7.1)
Ciprofloxacin	2 (4.7)
Cefuroxime axetil	2 (4.7)
Metronidazole	1 (2.3)
Moxifloxacin	1 (2.3)
Ceftriaxone	1 (2.3)
Naproxen sodium	1 (2.3)
Rivaroxaban	1 (2.3)
Erlotinib	1(2.3)
Drug and infection	1 (2.3)
Bacterial sepsis	1 (2.3)
Paraneoplastic	
Small cell lung carcinoma	1 (2.3)
Renal cell carcinoma	1 (2.3)
COVID-19 infection	5 (11.9)
COVID-19 vaccination	5 (11.9)

Vasculitis developed in five patients after COVID-19 vaccination. Their clinical features are shown in Table IV. Three patients received the Pfizer-BioNTech vaccine, and two patients received the Sinovac-CoronaVac vaccine. Vasculitis developed in four patients after the second dose and in one patient after the first dose. These patients had no history of infection and no drug use before vasculitis. The mean time between vaccination and vasculitis onset was 6.4 days (range 3-10 days). Histopathological examination revealed eosinophilic infiltration in 5 patients. DIF tests for IgA, IgG, IgM, and C3 were negative.

Spontaneous resolution occurred in 3 patients. Corticosteroid treatment was started in 37 patients. The corticosteroid dose varied from 0.5 to 1 mg/kg/day depending on the severity, extent, and necrosis of the lesions. In 2 patients with COVID-19 infection, vasculitis, and pneumonia, all lesions resolved with a 10-day course of methylprednisolone 40 mg/day. In those who had COVID-19 infection without pneumonia, the lesions resolved with a one-week course of methylprednisolone 16 mg/day. The lesions were less extensive and nonnecrotic in patients who developed vasculitis after vaccination. In five patients, the lesions resolved with a 20-day corticosteroid treatment. In two patients, the lesions relapsed when the steroid treatment was reduced. Azathioprine was added to the steroid treatment

Table III. Clinical and histological findings in patients with COVID-19-associated SoCSVV.

Case No.	Sex	Age	Time to infection	Clinical presentation	Histology	SARS-CoV-2 infection	non-COVID active infection	Drug
1	M	73	15	Purpuric macules, papules and hemorrhagic bullae on legs	Fibrinoid necrosis of vessel walls and leukocytoclasis red blood cell extravasation	Positive (PCR)	*Pneumonia, C. pneumoniae*	levofloxacin
2	M	81	12	Purple palpable purpura, necrotic lesions on periumblical area, lower legs and feet	Perivascular neutrophil, lymphocyte infiltrate, leukocytoclasis in the dermis and fibrin deposition	Positive (PCR)	N/A	N/A
3	F	49	14	Petechial, purpuric rash and necrotic lesions on both feet and ankles	Perivascular neutrophilic İnfiltrate, leucocytoclasis red blood cell extravasation and fibrin deposition	Positive (PCR)	N/A	N/A
4	M	52	8	Painful hemorrhagic bullae, necrotic lesions on trunk, arms and legs	Heavy neutrophilic infiltrate in small vessel wall, fibrinoid necrosis and extravasation of red blood cells	Positive (PCR)	N/A	N/A
5	F	58	10	Annular and urticarial lesions with purpuric component on trunk and limbs	Neutrophilic perivascular inflammation, karyorrhexis, fibrinoid necrosis and red blood cell extravasation	Positive (PCR)	N/A	N/A

C. pneumoniae; Chlamydia pneumoniae, N/A; Not available.

Table IV. Summary of five cutaneous vasculitis cases caused by administration of the COVID-19 vaccination.

Case No.	Sex	Age	Clinical history	Dose	Histology	Outcome
1	F	36	Patient developed a rash on the face, trunk and extremities 1 week after the second dose of the Pfizer vaccine	second	Lymphocyte mediated interface dermatitis with papillary dermal edema and an accompanying brisk perivascular interstitial lymphocytic and eosinophils infiltrate	Recovered
2	F	68	Patient developed a papulovesicular rash developed 3 days after receiving the first dose of the Pfizer vaccine	first	Interstitial neutrophilia, eosinophils and leukocytoclasia with hemorrhage	Recovered
3	F	48	Patient developed with palpable purpura over both ankles associated with burning sensation, 5 days following second dose of the Pfizer vaccine	second	Small vessels in dermis showing plump endothelial cells surrounded by perivascular mixed inflammatory infiltrate and eosinophils infiltrate with karyorrhectic debris and extravasation of red blood cells	Recovered
4	F	72	The patient developed a generalized erythematous papulovesicular eruption 1 week following the Sinovac (Coronavac) vaccine	second	Fibrinoid necrosis of blood vessels walls with neutrophilic fragments, and a few eosinophils on skin spescimen	Recovered
5	F	60	Patient experienced petechial macules on hands and pink blanching macules, papule and purpura on arms, chest, and legs that developed 10 days after receiving the Sinovac (Coronavac) vaccine	second	Interface dermatitis with dermal edema and a superficial lymphocytic, and eosinophils infiltrate and fibrinoid necrosis	Recovered

of these patients. Remission was achieved in the 6th month, and their treatments were stopped.

Discussion

The evaluation of a patient with suspected cutaneous leukocytoclastic vasculitis (CLA) must focus on verifying the diagnosis, identifying the underlying cause, and ruling out substantial organ impairment. Conducting a thorough investigation into the possible inciting factor is crucial, as resolution of the CLA may follow upon its removal. Cutaneous vasculitis can represent a primary or idiopathic process, a secondary process associated with another systemic, often chronic inflammatory disease, or an eruption triggered by infection or recent drug ingestion[15]. SoCSVV is a type of vasculitis that only involves the skin and does not have any systemic manifestations. However, it should be followed up closely because it could be an early sign of a more extensive vasculitis. SoCSVV is a syndrome that can result from different causes. Its annual incidence is 15-30 per million[16]. The lesions are usually bilaterally symmetrical and are located below the waist in areas affected by gravity or tight clothing. Palpable purpura is the predominant clinical manifestation and the main initial symptom. Other skin manifestations are urticaria, nodules, hemorrhagic vesicles and bullae, pustules, crusted ulcers, or livedo reticularis. Of our cases, 38 (90.4%) presented with palpable purpura, 5 (11.9%) with urticarial lesions, 4 (9.5%) with ulcers, and 5 (11.9%) with hemorrhagic bullae. Hemorrhagic bullae and skin necrosis were significantly more common, especially in patients with vasculitis due to COVID-19 infection. In addition, these patients had extensive lesions not only in the lower extremities but also in the upper extremities and trunk.

A wide variety of factors can cause CSVV, including drugs, infections, systemic diseases, vaccines, malignancy, and, rarely, dietary factors[17,18]. In such cases, elimination of the underlying cause may resolve CSVV[19,20]. Idiopathic CSVV is a diagnosis of exclusion that can only be made when no underlying cause or systemic vasculitis is found[13,17]. It accounts for 30-60% of cases.

Almost all classes of drugs have been associated with CSVV, but penicillins, cephalosporins, sulfonamides, phenytoin, and allopurinol have been most often related[13,21]. Drugs may act as haptens to stimulate an immune response. Certain infections, such as hepatitis due to hepatitis B or C virus, HIV, chronic bacteremia and other viruses, may also be associated with CSVV[22]. CSVV has been reported with SARS-CoV-2 infections and vaccination[23,24]. The rate of idiopathic SoCSVV in our study was 21.4%. This is slightly lower than the studies in the literature, which may be due to our low number of cases. In these cases, no pathology, such as drug use, previous infection, vaccination, or malignancy, was detected. No recurrence or new disease was detected in their 6-month follow-ups. Environmental pollutants, workplaces, diet contents, and other factors may have played a role in this patient group. However, we could not detect them.

Drug-associated SoCSVV was seen in 45.2% (n=19) of our patients. 84.2% (n=16) of the patients with suspected drug-associated SoCSVV were caused by antibiotics. The most common antibiotics were amoxicillin/clavulanic acid and ampicillin/sulbactam. Beta-lactam antibiotics are generally the most common group causing vasculitis[13]. Similarly, they were frequent in our study. Additionally, our study was conducted during the COVID-19 pandemic. We can say that we observed antibiotic-associated SoCSVV more frequently during this period, as hospital admissions with possible COVID-19 infection increased, and antibiotics were often used for negative COVID-19 patients.

Skin manifestations of COVID-19 continue to be reported, and there have been attempts to classify them in the literature, with initial prevalence estimates suggesting that dermatological signs would be present in 1.8 to 20.4% of COVID-19 patients[25,26]. Several studies[27,28] have identified groups of skin conditions that are indicative of skin vascular damage, including chilblain-like lesions, acral ischemia, acral vasculitis, livedo reticularis, livedo racemosa, purpuric "vasculitic" rash or petechial eruptions. Until now, the exact pathogenic mechanisms of COVID-19-associated CV have not been clarified. The SARS-CoV-2 virus results from extensive viral-induced inflammation, which leads to endothelial activation and initiation of intravascular coagulation. SARS-CoV-2 reaches the nasopharyngeal respiratory epithelium, which expresses angiotensin-converting enzyme (ACE) 2, a receptor for the virus. The virus then replicates in the alveoli[29]. Despite being present in normal skin, ACE2 is found in the dermis and subcutaneous capillaries and veins, where incomplete viral particles known as pseudoviruses have been observed to bind. Subsequently, an accelerated state of thrombosis, activation of complement, cytokine storm inclu-

ding interleukin (IL)-6, and immune activation mediated by T-cells and B-cells is believed to occur[30,31]. All of these mechanisms contribute to the inflammatory microenvironment in the skin, which may attract innate and adaptive immune cells and result in the spread of inflammation to the vessel wall, causing vasculitis. Five of our patients tested positive for SARS-CoV-2 PCR, and their rashes were more hemorrhagic, bullous, and necrotic. Histopathological examinations revealed fibrin deposition and necrosis in these patients. These patients had higher levels of acute phase reactants than the others, but they responded well to steroid treatment, and their lesions disappeared in a short time. Low molecular weight heparin treatment was given for 6 weeks due to the presence of fibrin deposition and necrosis. We think that the combination of immunosuppressive and anticoagulant therapy in these patients contributed to better outcomes.

The link between vasculitis and vaccination in terms of pathogenesis is not clear. However, it may involve immune complexes and antibody deposition in the walls of blood vessels[32]. The vaccine proteins are similar in structure to the wild-type viral antigens and could potentially trigger a pro-inflammatory cascade similar to that triggered by the viral protein. Thus, vaccine antigens have the potential to trigger B/T cells, leading to the formation of antibodies and subsequent deposition of immune complexes in small vessels. In addition, previous research[33] has pointed to the involvement of the Th1 response and has proposed that interferon-gamma is a critical requirement for the activation of vascular inflammation. Therefore, the whole virus-inactivated SARS-CoV-2 vaccine primarily stimulates a Th1-biased response, which may lead to the induction of inflammation in the vessel wall[34]. Almost all existing COVID-19 vaccines have been associated with CV, e.g., mRNA vaccines (Pfizer BioNTech), mRNA-1273 (Moderna), adenoviral vector-based vaccines (ChAdOx1 nCoV-19; Oxford-AstraZeneca), and inactivated vaccines (Covaxin, Sinovac). COVID-19 vaccines, particularly mRNA and other next-generation vaccines may trigger the development of autoimmune-inflammatory rheumatic diseases, particularly RA, in a predisposing setting of genetic and/or environmental factors[35]. Twelve out of the 22 (54.5%) cases were diagnosed with rheumatoid arthritis, two with SLE, and the remaining eight patients each with leukocytoclastic vasculitis, Sjogren's syndrome, psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, mixed connective tissue disease, eosinophilic granulomatosis with polyangiitis, and inflammatory myositis, respectively[35]. Vasculitis induced by drugs and vaccines is considered to occur within a range of 1 to 6 weeks[36]. In many cases, these were localized skin lesions without systemic involvement that resolved spontaneously or with systemic treatment. Five of our patients presented with vasculitis after COVID-19 vaccination. Histopathologically, all patients had eosinophilia in the affected tissue. Acute phase reactants were mildly elevated. They fully recovered within 20 days of treatment. They were advised not to receive the same vaccine again. Vasculitis may antedate the discovery of the malignancy, coincide with it, occur after the malignancy has already been recognized, or provide a clue to a recurrence[37]. The frequency of associated malignancy was reported to be 8% of patients from a series of individuals with cutaneous vasculitis[38]. Treatment and prognosis of paraneoplastic vasculitis depends on the underlying neoplasm. In our cases, the skin lesions disappeared after the surgery for renal cell carcinoma (RCC) in the first case and after the first cycle of chemotherapy for lung adenocarcinoma in the second case.

In the histopathological examination of patients with drug- and vaccine-induced vasculitis, eosinophilia was detected in the tissue in all patients. This suggested an etiological role of drugs or vaccines, DIF was negative due to the skin biopsy being performed 48 hours later, which indicates that an early biopsy within the first 48 hours of the lesions is necessary to determine the etiological factors.

Limitations

One of the most important limitations of this study is the small number of patients and the retrospective design of our study. Due to the lack of material and equipment, another limitation of the study was that virus isolation could not be performed from skin biopsies in SARS-CoV-2 PCR-positive patients. The time between the onset of purpuric lesions and skin biopsy among patients was 4.2 days (2-25 days). This may have contributed to the negative DIF staining.

Conclusions

According to the 2012 CHCC definitions, SoC-SVV should be differentiated from other LCVs.

SoCSVV is a benign form of vasculitis confined to the skin. In this study, we frequently observed antibiotic-induced, COVID-19 infection and vaccine-induced vasculitis as it was conducted during the COVID-19 pandemic. We can say that vascular obliterations, fibrin deposition, and necrosis were prominent in vasculitis associated with COVID-19-related vasculitis and that CRP was higher than the others. We can also say that eosinophilia was intense in the biopsies of vaccine-induced and antibiotic-induced vasculitis. In many cases, these were self-limiting skin lesions, solved spontaneously or after systemic treatment.

Conflict of Interest
The author declares that they have no conflict of interest.

Ethics Approval
This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics Committee Approval was obtained from the Eskişehir State Hospital Clinical Study Ethics Committee (ESH/GOEK 2023/6).

Informed Consent
Written informed consent was obtained from the study participants.

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Data Availability
Data information can be obtained from the author upon request.

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