Leukocytoclastic vasculitis in transplant recipients: A case series of 7 patients

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Key words: immmunosuppression; leukocytoclastic vasculitis; purpura; small-vessel disease; transplant recipients; vasculitis.

INTRODUCTION

Leukocytoclastic vasculitis (LCV) is a small-vessel vasculitis that is usually limited to the skin but may cause systemic small-vessel disease. LCV commonly presents with petechiae or palpable purpuric papules or plaques that may coalesce, ulcerate, or form hemorrhagic bullae (Fig 1). The pathogenesis of LCV involves the formation of immune complexes that deposit within small vessels and induce damage.[1] Medications are the most frequent cause of LCV, although infections, malignancies, and connective tissue disease are other reported causes.[2,3] Commonly associated medications that induce LCV include penicillins, cephalosporins, sulfonamides, phenytoin, allopurinol, aminocaproic acid, azathioprine, methotrexate, and streptokinase. With medication-induced LCV, symptoms typically develop within 10 days of antigen exposure, owing to time required for developing antigen-antibody complexes.[4] The presence of perivascular IgG or IgM deposition detected via direct immunofluorescence (DIF) suggests immune complex–induced LCV, which has a favorable prognosis.[2,5,6] IgA deposition within the skin lesion biopsy suggests Henoch-Schonlein purpura/IgA vasculitis, which is more frequent and severe than non–IgA-associated LCV.[6] Detection of vascular IgA deposition is suggestive of associated renal and gastrointestinal involvement by vasculitis.[7,8]

There is limited literature regarding LCV in the transplant population, likely because of overall immunosuppression in these patients that may prevent this disease. In transplant recipients (TRs), sirolimus has been reported to cause LCV.[9,10] To evaluate the causes and outcomes of LCV in TR, we performed a retrospective study to evaluate the clinical features of TRs in whom LCV developed, along with reviewing their management and outcomes.

Abbreviations used:

DIF: Direct immunofluorescence
LCV: Leukocytoclastic vasculitis
TRs: Transplant recipients

PATIENTS AND METHODS

A retrospective chart review of all records of TRs with biopsy-proven LCV at the Mayo Clinic Rochester within the last 10 years was performed with Institutional Review Board Approval. Based on these criteria, 7 patients were included. Each patient's medical records were reviewed, and demographic data, medical history, pathology, and disease course were evaluated. When determining the etiology of LCV in each patient, we considered short-term (recently introduced drugs or infections) and long-term (chronic disease) factors. Affected area was determined based on the location of LCV lesions and split into 3 groups: (1) upper extremity—from the shoulder to the digits, (2) lower extremity—from the hips to the toes, and (3) trunk—the anterior or posterior torso. Evidence of immunoglobulins within skin biopsy was determined using DIF. Patient outcome was determined via thorough chart review. Resolution of disease implies that all LCV-related lesions cleared and the patient remained disease free.

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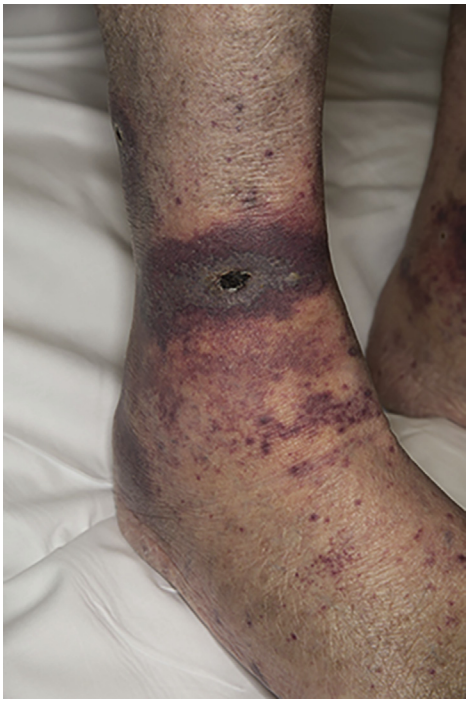

Fig 1. LCV presenting with palpable purpura and petechiae on the lower extremity of patient 7.

RESULTS

The clinical data of all patients is summarized in Table I. A total of 7 white patients, 6 men (86%) and 1 woman (14%), all with biopsy confirmed LCV were included in this study. The mean age of patients at biopsy was 62.5 years (range, 33-85 years). The average number of years between transplant and disease onset was 7 years (range, 1-17 years). All patients presented with palpable purpura without ulceration and had an eventual resolution of lesions. No patients had active or chronic hepatitis B or C. Five (71.4%) patients tested negative for cytoplasmic antineutrophil cytoplasmic antibodies (ANCA), perinuclear ANCA, antinuclear antibody or elevated complement. Patient 2 had a kidney transplant because of granulomatosis with polyangiitis and thus a positive cytoplasmic ANCA test result. Patient 4 tested positive for antinuclear antibody (3.0 U) but no other symptoms of connective tissue disease. None of the patients went on to have systemic disease, and none had recurrence of LCV symptoms. All 7 patients (100%) had involvement of lower extremity, either alone (43%) or in combination with involvement of upper extremity (43%) or trunk (14%). The most common associated transplant was kidney (71%), with liver (14%) and kidney/pancreas cotransplant (14%) making up the remainder. No patient was on sirolimus as an immunosuppressant, but 5 (71.4%) were immunosuppressed using tacrolimus. DIF failed to detect any immunoglobulin in 43% of patients, whereas 29% had a positive result for IgA only, 14% for IgM only, and 14% for IgM and IgA. The etiology of LCV in most patients was idiopathic (71%). In the remaining patients, LCV was caused by IgA vasculitis (14%) and cryoglobulinemia (14%). LCV lesions resolved for all 7 patients. Patients 5 and 7 had resolution of lesions without the use of a therapeutic agent. In patient 5, the cessation of tacrolimus was sufficient; patient 7 was treated with supportive care. Topical corticosteroids (29%), dapsone (29%), and prednisone (14%) were successful treatment options used in the remaining patients.

DISCUSSION

There are numerous triggers for the development of LCV; however, in most patients in this study, the inciting factor was unknown. However, an underlying cause was found in 2 of the TRs: IgA vasculitis and cryoglobulinemia. Patient 3, who had cutaneous IgA vasculitis, had 3 failed renal transplants owing to IgA nephropathy. This finding may explain the presence of IgA on DIF. Patient 6 had LCV attributed to cryoglobulinemia, likely owing to his chronic hepatitis C infection before liver transplant. Regardless of etiology, resolution of lesions was noted in all patients. Within the TR population, sirolimus is the most frequently reported trigger for disease.[9,10] Our patients were immunosuppressed with tacrolimus, mycophenolate mofetil, and cyclosporine. Five patients were immunosuppressed with tacrolimus. Although an association between tacrolimus and LCV development is lacking in the literature, such an association has been reported in US Food and Drug Administration research reports.[11] Additionally, the cessation of tacrolimus in patient 5 led to symptom resolution. None of our 7 patients were immunosuppressed with sirolimus. These findings suggest that TR care providers should consider other causes of LCV aside from medications. Bacterial, viral, fungal, and protozoan infections have all been reported to induce LCV; given TRs susceptibility to infections, there may need to be a high suspicion for infection-related causes. Upper respiratory tract infections have been linked with LCV development, most commonly attributed to *Streptoccocus*.[12] Viruses within the herpesvirus family are capable of causing vascular inflammation in immunosuppressed patients.[13] Given the increased likelihood of infection in TRs, we hypothesize that a mild underlying infection may be responsible for LCV development in some of our patients. Although there was no evidence of overwhelming infection in any of our patients, it is plausible that a mild upper

Table I. Clinical data of 7 transplant recipients with leukocytoclastic vasculitis

Patient	Sex	Age at biopsy, y	Affected area	Transplant type	Reason for transplantation	Immunosuppressant at biopsy	DIF	Underlying condition	Treatment
1	F	33	UE and LE	Kidney	Type 1 diabetes mellitus	T, CS	Negative	U	Dapsone
2	M	80	LE	Kidney	c-ANCA vasculitis	T	Negative	U	Topicals
3	M	62	UE and LE	Kidney	IgA nephropathy	None	IgA^+	I	Dapsone
4	M	43	LE	Kidney	IgA nephropathy	MM	Negative	U	Topicals
5	M	67	UE and LE	Kidney/ Pancreas	Type 1 diabetes mellitus	MM, T	IgA^+	U	Stopped tacrolimus
6	M	64	LE and trunk	Liver	Hepatocellular carcinoma	T	IgM^+	C	Prednisone
7	M	85	LE	Kidney	Hypertensive nephrosclerosis	T	IgA^+, IgM^+	U	Supportive care

C, Cryoglobulinemia; *CS*, cyclosporine; *DIF*, direct immunofluorescence; *I*, Cutaneous IgA vasculitis; *LE*, lower extremity; *MM*, mycophenolate mofetil; *T*, tacrolimus; *U*, unknown; *UE*, upper extremity.

respiratory tract infection or other infection may have been overlooked.

We describe herein the first analytical review of TRs in whom LCV developed. None of our patients went on to have systemic vasculitis and had overall resolution of the disease. It's essential for TR care providers to effectively recognize and manage LCV to prevent morbidity associated with this condition. Further studies are needed to find etiologic factors and specific treatment plans within this population.

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