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**Author/s:**

Wee, E;Nikpour, M;Balta, S;Williams, RA;Kelly, RI

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# Title Page – Brief Report

## Lymphocytic thrombophilic arteritis complicated by systemic involvement

Running head:

LTA complicated by systemic involvement

Authors:

- Dr Edmund Wee<sup>1</sup>
- Dr Mandana Nikpour<sup>2</sup>
- Dr Showan Balta<sup>3</sup>
- Prof. Richard A Williams<sup>3</sup>
- Dr Robert I Kelly<sup>1</sup>

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Institution:

- <sup>1</sup>Department of Dermatology, St Vincent's Hospital Melbourne
- <sup>2</sup>Department of Rheumatology, St Vincent's Hospital Melbourne
- <sup>3</sup>Department of Anatomical Pathology, St Vincent's Hospital Melbourne
  - 41 Victoria Parade Fitzroy VIC 3065

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Contact details for corresponding author:

- Dr Edmund Wee
- [Edmundwee1@gmail.com](mailto:Edmundwee1@gmail.com)
- Postal Address:  
Department of Dermatology  
St Vincent's Hospital Melbourne  
41 Victoria Parade Fitzroy VIC 3065
- Mobile: 0419907818

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## **Lymphocytic thrombophilic arteritis complicated by systemic involvement**

### **Abstract**

Lymphocytic thrombophilic arteritis (LTA) is a recently described entity defined by a primary lymphocytic vasculitis. LTA usually presents with persistent widespread livedo racemosa or macular hyperpigmentation on the limbs and typically has a chronic indolent course. We describe a patient that presented with clinical and histological findings consistent with LTA, and later developed bilateral focal testicular infarcts as well as an acute median nerve neuropathy. To our knowledge, this is the first account of LTA associated with subsequent systemic involvement, highlighting the importance of close long-term observation in patients with this condition.

### **Keywords**

Lymphocytic thrombophilic arteritis, macular arteritis, lymphocytic vasculitis, cutaneous polyarteritis nodosa, livedo racemosa

### **Learning Points**

- Lymphocytic thrombophilic arteritis (LTA) is a recently described entity defined by a primary lymphocytic vasculitis, and typically has a chronic indolent course.
- We describe a case of LTA associated with subsequent internal organ involvement, highlighting the importance of close long-term observation.

### **Introduction**

Lymphocytic thrombophilic arteritis (LTA), or macular lymphocytic arteritis, is a recently described entity defined by a primary lymphocytic vasculitis. Pathologically, the condition is characterized by dense lymphocytic inflammation affecting small to medium sized arteries in the deep dermis and upper subcutis, associated with fibrin deposition and a distinct luminal fibrin ring.<sup>1</sup> Clinically, LTA most commonly presents with persistent widespread livedo racemosa or macular hyperpigmentation on the limbs and typically has a chronic indolent course.<sup>1</sup> While some previous cases have been associated with

peripheral neuropathy<sup>2</sup> or ulceration<sup>3</sup>, none have been accompanied by internal organ involvement. We describe a case of LTA associated with the development of bilateral focal testicular infarcts and an acute median nerve neuropathy.

### Case Report

A 26-year-old Caucasian man presented with a 1-year history of persistent livedo racemosa that initially developed over his thighs and later involved the legs, buttocks, lower trunk and arms (Figure 1). There were no associated nodules, ulceration, purpura or atrophie blanche. A skin biopsy with serial sections from the centre of the reticulate pattern on his buttocks revealed dense lymphocytic inflammation and infiltration of a medium sized artery at the dermal subcutaneous junction. This was associated with fibrin deposition in the wall and lumen of the vessel, as well as a luminal fibrin ring (Figure 2). The patient was otherwise well, and his past medical history was significant only for smoking 1-2 cigarettes daily as well as a Chiari malformation managed with craniocervical decompression several years earlier. There was no family history of thrombophilia or connective tissue disease. Initial investigations for associated underlying causes revealed heterozygosity for prothrombin gene mutation and only a slightly raised rheumatoid factor (28; normal <14 IU/ml) (Table 1). Given the clinical presentation and histological findings, the patient was diagnosed with LTA. The patient was trialed on a combination of aspirin 100mg in addition to dipyridamole 200mg daily, as well as nifedipine 40mg daily, with minimal improvement. He was subsequently continued on aspirin 100mg daily only.

Over the following 5 years, the patient noted occasional bilateral testicular discomfort, and was referred to a urologist after experiencing an episode of severe right testicular pain lasting several days. Testicular ultrasound demonstrated a well-defined hypoechoic region in the superior pole of the right testis (25mm in size) that was avascular and consistent with a focal infarct. Tumor markers, urine microscopy and culture as well as a flexible cystoscopy were unremarkable, and the patient was closely monitored. He subsequently suffered from a similar episode of severe left testicular pain 6 months later. A

repeat ultrasound indicated that the previous right-sided testicular infarct was resolving, but that a new infarct (7mm in size) had developed in the inferior pole of the left testis (Figure 3). The patient was continued on aspirin, commenced on pentoxifylline 400mg three times daily, and referred for sperm banking.

Although the patient remained systemically well, 3 months later, he developed sudden onset shooting pain, paraesthesia and weakness in his left hand. Neurological examination revealed reduced sensation and weakness in the median nerve distribution of the left hand. Carpal tunnel release surgery was performed but failed to relieve his symptoms. A nerve conduction study confirmed the presence of a proximal left median nerve neuropathy above the elbow, with severe axonal degeneration.

Given the progression of symptoms and ongoing left hand pain, the patient was commenced on prednisolone 40mg/day and admitted to hospital for multidisciplinary assessment. Repeat investigations revealed an increase in rheumatoid factor levels (60; normal<14 IU/ml), as well as a high titre of antibodies against cyclic citrullinated peptides (CCP) (>250; normal<20 U/ml) (Table 1). An ultrasound of the left median nerve in the upper arm revealed diffuse nerve enlargement in keeping with neuritis. A computed tomography (CT) aortobifemoral angiogram was performed, but did not identify any focal arterial aneurysms or stenosis in the abdomen and lower limbs to suggest systemic polyarteritis nodosa (PAN). Magnetic resonance angiogram (MRA) imaging of the brain revealed some irregularity in the contour of the right anterior inferior cerebellar artery as well as bilateral superior cerebellar arteries, but these changes were not suggestive of vasculitis. The patient was treated with a course of pulsed methylprednisolone (three 1g intravenous doses) followed by prednisolone 40 mg daily. Rivaroxaban 15 mg daily was initiated to treat the thrombophilic component of LTA. Two infusions of rituximab 1 gm at weeks 0 and 2 were also administered. Aspirin 100mg daily and pentoxifylline 400mg three times daily were continued. Testicular and nerve biopsies were not performed as the results were considered unlikely to alter management.

In the subsequent two months, there was significant improvement in left hand function, and a reduction in neuropathic pain. Over six of follow-up, prednisolone has been tapered to 5 mg daily with plans to taper to 0 mg. No further testicular infarcts have arisen, though the livedo racemosa remains unchanged. No further features of systemic vasculitis have arisen.

## **Discussion**

There has been speculation that LTA may represent an indolent non-nodule forming variant of cutaneous polyarteritis nodosa (CPAN), underscored by the finding that the subacute and reparative stages of CPAN may occasionally have a predominantly lymphocytic infiltrate.<sup>2</sup> However, more than thirty cases of LTA have been reported with typical clinical findings that have been consistently associated with a lymphocytic vasculitis in which neutrophils were absent or rare. Recent publications questioning the existence of LTA as a separate entity to CPAN<sup>2</sup> have had significant methodological weaknesses.<sup>9,10</sup>

In our patient, the diagnosis of LTA was based on a correlation of clinical and pathological findings including persistent widespread livedo racemosa and typical histological features of lymphocytic arteritis with a prominent fibrin ring, as well as an absence of systemic involvement at presentation. While a diagnosis of systemic polyarteritis nodosa (PAN) was considered in the setting of subsequent testicular involvement and mononeuritis,<sup>4</sup> other common features of CPAN and PAN such as acute onset, purpura, nodules, inflammatory ulceration, fever, arthralgia and myalgia were absent.<sup>5</sup> Cutaneous histology with serial sections revealed the absence of neutrophilic infiltrate, and abdominal CT angiography demonstrated a lack of focal arterial aneurysms or stenosis. Importantly, CPAN itself rarely progresses to PAN and only two such cases are documented in the literature.<sup>5</sup> CPAN and PAN were thus considered unlikely based on the clinical presentation, histological and radiologic findings.

The pathophysiology of LTA remains uncertain. Some cases have been associated with autoimmune antibodies and/or heterozygosity for pro-thrombotic mutations, suggesting that both immunological and thrombophilic factors may contribute to pathogenesis.<sup>1</sup> Our patient had high titres of rheumatoid factor and anti-CCP antibodies in the absence of an inflammatory arthritis, suggestive of an autoimmune predisposition.<sup>6</sup> While testicular and nerve biopsies were not performed, the radiological findings as well as the sudden onset of the neurologic and testicular symptoms are consistent with a vasculitic process.

Pro-thrombotic factors could also have contributed to the presentation of LTA in our patient, who was heterozygous for prothrombin gene mutation. Previous reports have highlighted a possible relationship between LTA and livedoid vasculopathy based on an overlap of clinical and histological findings.<sup>3</sup> Some skin manifestations of LTA have also been found to be responsive to treatments such as aspirin and pentoxifylline.<sup>3</sup> This suggests that, similar to livedoid vasculopathy, pro-coagulant factors that contribute to the fibrin deposition evident on histology may play a significant role in the pathogenesis of LTA.

Our patient was treated with systemic corticosteroids and rituximab in addition to rivaroxaban, aspirin and pentoxifylline, to manage the systemic inflammatory and thrombophilic aspects of the condition, respectively. He responded well with significant recovery in median nerve function and no further focal testicular infarcts.

In summary, we describe a patient that presented with clinical and histological findings consistent with LTA, and later developed bilateral focal testicular infarcts as well as an acute median nerve neuropathy. To our knowledge, this is the first account of a patient presenting with clinical and histological features of LTA with subsequent internal organ involvement. This case highlights the importance of close long-term observation in these patients.

Further clinicopathologic studies will be beneficial in clarifying the nosology of LTA and the potential for systemic involvement.

## References

1. Lee JS, Kossard S, McGrath MA. Lymphocytic thrombophilic arteritis: a newly described medium-sized vessel arteritis of the skin. *Arch Dermatol* 2008; 144: 1175-82.
2. Shen S, Williams RA, Kelly RI. Neuropathy in a patient with lymphocytic thrombophilic arteritis. *Australas J Dermatol* 2013; 54: e28-32.
3. Llamas-Velasco M, Garcia-Martin P, Sanchez-Perez J, et al. Macular lymphocytic arteritis: first clinical presentation with ulcers. *J Cutan Pathol* 2013; 40: 424-7.
4. Pagnoux C, Seror R, Henegar C, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum* 2010; 62: 616-26.
5. Morgan AJ, Schwartz RA. Cutaneous polyarteritis nodosa: a comprehensive review. *Int J Dermatol* 2010; 49: 750-6.
6. Nielen MM, van Schaardenburg D, Reesink HW, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum* 2004; 50: 380-6.

## Figure Legends

**Figure 1.** Dermatologic presentation of patient with widespread livedo racemosa over right (left panel) and left (right panel) thighs. This was also present over the lower trunk, buttocks and arms.

**Figure 2.** Histology (X10) under haematoxylin and eosin staining showing dense lymphocytic inflammation infiltrating walls of a medium sized artery at the dermal subcutaneous junction, with fibrin deposition giving rise to a distinct luminal fibrin ring.

**Figure 3.** Ultrasound of the left testis demonstrating a well-defined hypoechoic wedge-shaped region in the inferior pole consistent with an infarct 7mm in diameter.

**Table 1. Blood tests performed in patient with LTA associated with subsequent systemic progression**

Blood Test	Result
Rheumatoid Factor	60IU/ml (normal<14)
Anti-CCP Antibodies	>250U/ml (normal<20)
ANA	Negative
ENA	Negative
ANCA	Negative
Proteinase 3-ANCA	Negative
Myeloperoxidase-ANCA	Negative
C3	Normal
C4	Normal
Prothrombin gene mutation	Heterozygous (G20210A)
Factor V Leiden	Negative
Antithrombin III	Normal
Protein C	Normal
Protein S	Normal
Lupus anticoagulant	Negative
Anti-cardiolipin Antibodies	Negative

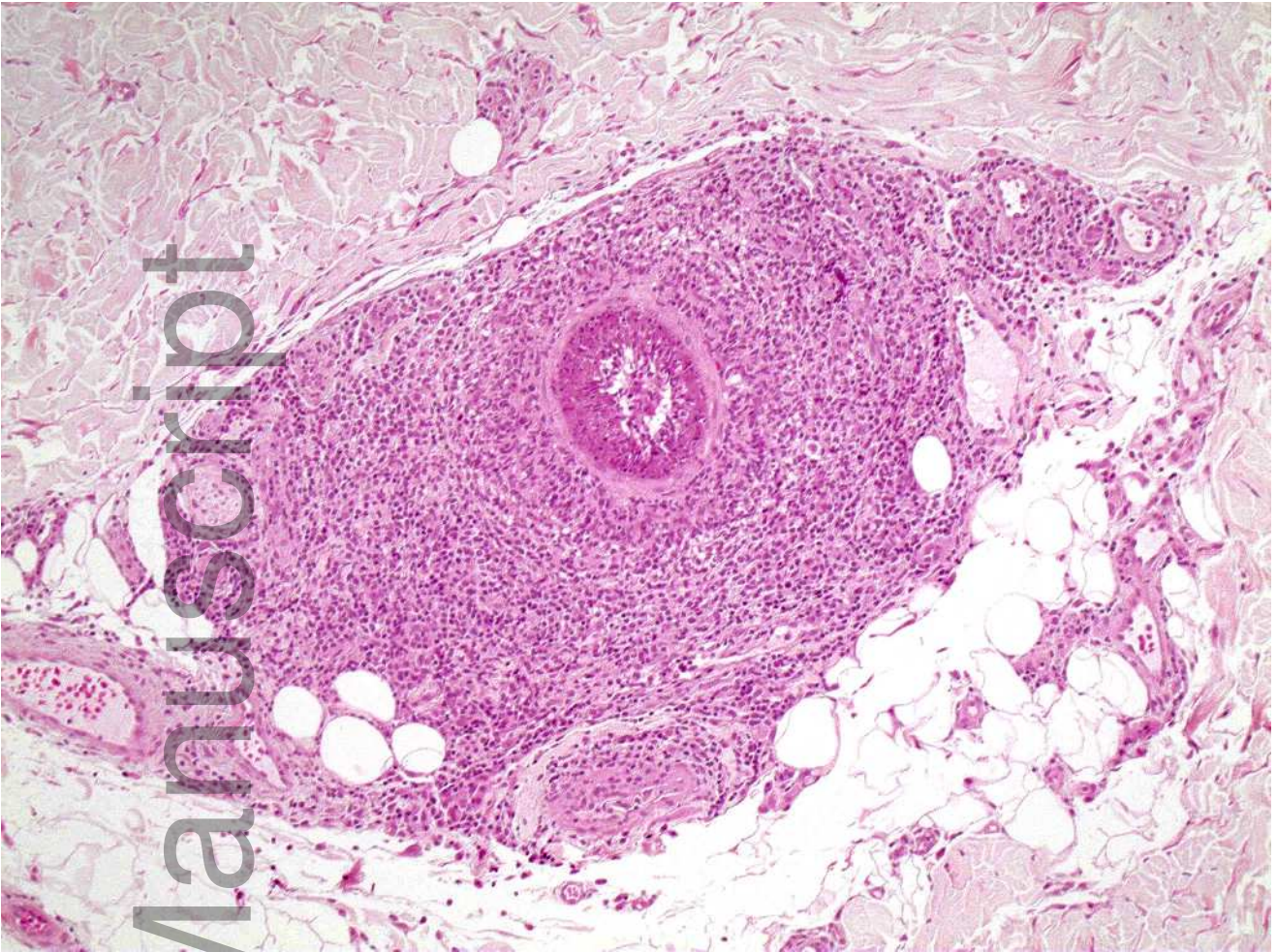
Anti-beta 2 glycoprotein	Negative
Antibodies	Negative
Cryoglobulin	Negative
FBE	Normal
ESR	30mm/h
CRP	Normal
Hepatitis B Serology	Negative
Hepatitis C Serology	Negative
HIV Serology	Negative
Quantiferon-TB	Negative
SPEP	Negative
TSH	Normal

CCP, cyclic citrullinated peptide; ANA, anti-nuclear antibody; ENA, extractable nuclear antigen; ANCA, anti-neutrophil cytoplasmic antibody; C3, complement factor 3; C4, complement factor 4; FBE, full blood examination; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SPEP, serum protein electrophoresis; TB, tuberculosis; TSH, thyroid stimulating hormone



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