Type of article: Case Report

Title: Leprosy & gangrene: A rare association; role of anti phospholipid antibodies.

Abstract:

Background:
Leprosy still remains an important public health problem for many parts of the world. An association of gangrene with leprosy is a rare one & can have a number of causative mechanisms. We present a case with Leprosy & gangrene with positive anti phopholipid antibody titers.

Case presentation
A 50-year-old non-diabetic, non-hypertensive lady presented with 2 months history of progressive gangrene of bilateral toes. She was found to have madarosis & hypopigmented, hypoesthetic macular lesions on the upper limb & thighs. Bilateral ulnar & popliteal nerves were thickened. A skin biopsy of the lesions revealed borderline tuberculoid leprosy. She did not have any evidence of thromboembolic episode or atherosclerosis. ACLA was positive at presentation & also on another occasion 6 weeks later. ACLAs were of the IgM type on both occasions. Lupus Anticoagulant & β 2 GPI antibody were negative. DOPPLER of the lower limb arteries did not reveal any abnormality. Patient was successfully treated with multi-drug antileprotics & anticoagulation.

Conclusions:
Infectious aPLAs should be recognized as a cause of thrombosis in Leprosy. Appropriate anticoagulation can salvage limb function.

List of abbreviations:
anPLAs—anti phospholipid antibodies
aCLa – anti cardiolipin antibody
β2 GPI -- β2 Glycoprotein I
ANCA – anti neutrophil cytoplasmic antibody
Case presentation:
A 50-year-old non-diabetic, non-hypertensive lady presented with 2 months history of progressive blackish discoloration of the toes bilaterally. Examination revealed gangrene of the Right great toe, 2nd toe & early gangrenous changes in the 3rd toe. All the peripheral arteries were well felt, there was no radiofemoral delay. There was no cardiac murmur or a carotid bruit.

She was found to have madarosis & hypopigmented, hypoesthetic macular lesions on the upper limb & thighs. Bilateral ulnar & popliteal nerves were thickened. A skin biopsy of the lesions revealed borderline tuberculoid leprosy. Erythrocyte sedimentation rate was 105, lipid profile & fasting sugars were normal & anti neutrophil cytoplasmic antibody (ANCA) negative.

Anti cardiolipin antibody (ACLA) was positive at presentation & also on another occasion 6 weeks later. ACLAs were of the IgM type on both occasions. Lupus Anticoagulant & β 2 GPI (β2 Glycoprotein I) antibody were negative. DOPPLER of the lower limb arteries did not reveal any abnormality. The patient improved with the multi drug anti leprotics & anticoagulation. By 6 weeks, there was no progression of/ fresh gangrene & the pre gangrenous changes in the 3rd toe had resolved.

Discussion:
Antiphospholipid antibodies (aPL) are a group of heterogeneous autoantibodies, which have been reported in many autoimmune diseases, and in the antiphospholipid syndrome (APS) which is characterised by raised levels of aPL, thrombosis, recurrent fetal loss, thrombocytopenia. Although raised levels of the ACLAs were first reported in autoimmune diseases, their prevalence is now known to be more widespread. Elevated serum levels of these ACLAs have been shown in various infections like Syphilis, HIV disease, HCV disease, tuberculosis, cytomegalovirus infection [1]. Loizou S et al studied 112 patients with leprosy & found ACL in 29%, anti β2 GPI in 89% & anti-Prothrombin
in 21% patients [2]. It is hypothesized that infections may trigger the induction of aPL in certain predisposed individuals. Molecular mimicry has been invoked as a probable explanation for this occurrence [3]. The aPL seen in autoimmune conditions were found to be different from those seen in infectious conditions in that the binding of the aPL to phospholipid is enhanced by the cofactor β2GPI (i.e. β2GPI dependent) in autoimmune conditions such as SLE and primary APS, whereas the infectious aPL do not require this cofactor to enhance the binding (i.e. β2GPI independent). The infectious aPL were thus rendered non-thrombogenic. Although the infection related ACLA are usually non-pathogenic, there is also the possibility that these non-pathogenic "infectious" ACLA, might in some susceptible subjects with the right genetic HLA background, mutate at the CDR3 domain of the ACLA binding site for β2GPI, which determines the pathogenicity of ACLA antibodies [4].

A similar picture has been seen in leprosy, wherein the ACLA may be β2GPI dependent as is found with autoimmune diseases, particularly in patients with the multibacillary type of leprosy [5]. The clinical implications of this β2GPI dependency are seen in Lucio’s phenomenon in which the histopathological findings are related to microvascular thromboses in the absence of inflammatory infiltration of the vessel walls. Levy et al demonstrated that this type of leprosy was associated with β2GPI dependency of the ACLA [6]. Apart from this evidence of microscopic thrombosis, frank gangrene in association with leprosy is a rare entity.

Gangrene of the extremities in leprosy can have mechanisms other than aPLA alone. Vascular changes in the form of intimal thickening & medial infiltration are known to occur in leprosy. Embolisation & resultant grafting of the Virchow cells has been found to lead to obstruction of the vessels [7]. Four such cases of arterial obstruction have been described; 2 of them being occlusion of the posterior tibial artery by lepromatous infiltration [8]. Arteriographic abnormalities such as occlusion, narrowing, tortuosity, dilatation, poststenotic dilatation, irregularity and incomplete filling of the lumen have been found in the digital circulation in more than 75-94% of leprosy patients [9]. Nerve trunk hypertrophy secondary to lepromatous process can lead to arterial entrapment in the osteoligamentous channels. This entrapment as well as the irritation of
sympathetic fibers can lead to spasm of the vessels & resultant vascular compromise to the distal extremity. This has been confirmed with angiography & reversal of the spasm as well as the vascular compromise seen after release of the roof of the osteoligamentous channel [7].

Our patient did not have any clinical or laboratory markers of atherosclerosis or embolism, DOPPLER of the lower limbs did not reveal any vascular obstruction involving the medium size arteries. In the absence of any other hypercoagulable states, aPLA remains the most probable cause of the digital gangrene.

**Conclusions:**
Infectious aPLAs should be recognized as a cause of thrombosis in Leprosy. Appropriate anticoagulation can salvage limb function. However, other mechanisms of gangrene need careful evaluation & appropriate management.

**Competing interests:**
No competing interests to declare.

**Authors' contributions:**
SA & LB carried out the study and conceived of the study. SA drafted the manuscript & LB reviewed the same. Both authors read and approved the final manuscript.

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Written consent was obtained from the patient for the clinical photograph as well as publication of study.

**Reference:**


