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Case Report

Reactive Angioendotheliomatosis in the Setting of Leprosy: A Previously Un-Described Association

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Abstract

Cutaneous reactive angioendotheliomatosis (CRA) is a group of benign skin disorders which comprise 3 main entities: reactive angioendotheliomatosis (RAE), intralymphatichistiocytosis and diffuse dermal angiomatosis (DDA). These disorders are characterized by vascular proliferations which are either intraluminal or periluminal. Of these, RAE is well known to arise in association with chronic systemic disorders. We report a case of a 37 year old female, who presented with multiple, painless skin coloured nodules over the extensor aspect of her upper limb and foot. She also had multiple painful, erythematous nodules over the upper as well as lower limb. Light microscopy of the painless nodules, showed features suggestive of RAE. The painful,erythematous papules of the upper limb, showed features consistent with Borderline Lepromatous Leprosy. Immunohistochemistry with CD31 and CD34 showed positivity of the spindle cells lining the capillaries, proving its vascular origin. To our knowledge, this is the first case to be reported of RAE occurring in the setting of leprosy.

Keywords: Reactive Angioendotheliomatosis; Leprosy; Skin.

Introduction

Reactive angioendotheliomatosis is a benign vascular proliferation known to arise in the setting of chronic systemic illnesses. It is a part of cutaneous reactive angiomatosis (CRA) along with intralymphatichistiocytosis, as well as diffuse dermal angiomatosis. Six entities have been described under the broad heading of CRA by Rongioletti F et al [1]. RAE is seen as erythematous patches and plaques, usually in the extremities [2], but can occur anywhere in the body.

It has known to be associated with a wide variety of disorders, of which chronic systemic disorders, infections and paraproteins are common. It is characterized by endoluminal proliferation of capillaries, which may obliterate the lumen, along with the presence of histiocytes within thesevascular lumina [3]. These lesions disappear on resolution of the underlying cause which precipitated it.

Case Report

A 37 year old female, came to the dermatology outpatient department, with complaints of painless swellings over her upper and lower limbs. She also gave a history of evanescent, painful skin lesions, over her upper and lower limb, along with complaints of fever and malaise. The duration of these symptoms was around 3 months. On examination, there were multiple erythematous papules over the flexors of her upper and lower limbs, as well as firm, well defined, skin coloured nodules over the lower limbs and foot. Her right ulnar and left common peroneal nerves were palpable and enlarged.

Light microscopy of the erythematous papules showed peri-adnexal histocytic aggregates admixed with a few lymphocytes, with a normal overlying epidermis, suggestive of Borderline Lepromatous leprosy. The nodules from the lower limb showed a

dermal lesion composed of numerous capillary sized blood vessels lined by plump endothelium, some containing erythrocytes, which were surrounded by a sparse lymphocytic infiltrate. This lesion appeared to be within a pre-existing thrombosed, large vessel in the dermis. There were no features of atypia in the lesion. Immunohistochemistry for CD34 and CD31 showed positivity for the cells lining these vessels, confirming their vascular origin.

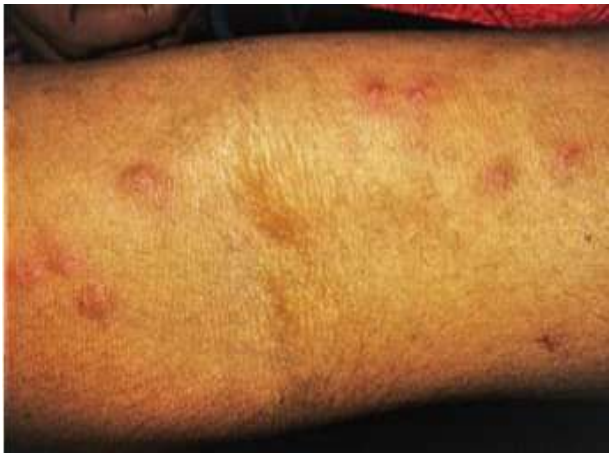

Fig. 1: Shows erythematous papules of leprosy

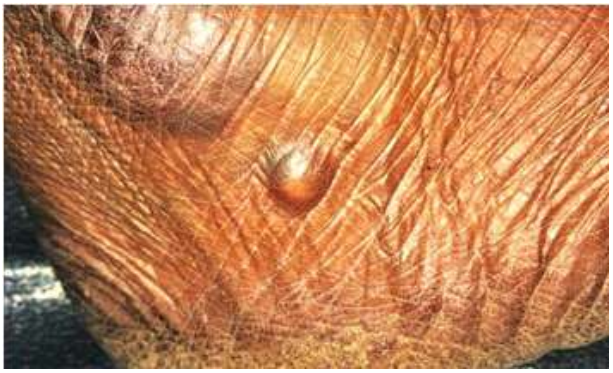

Fig. 2: Shows a firm nodule of RAE

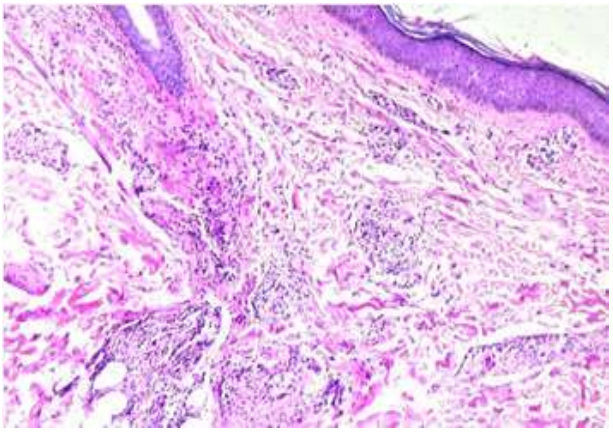

Fig. 3: Borderline lepromatous leprosy showing aggregates of histiocytes in peri-adnexal location with few admixed lymphocytes.

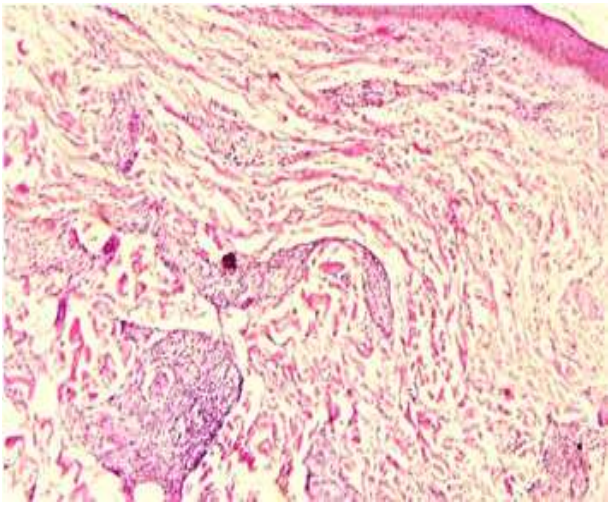

Fig. 4: Borderline lepromatous leprosy showing aggregates of histiocytes in peri-adnexal location with few admixed lymphocytes.

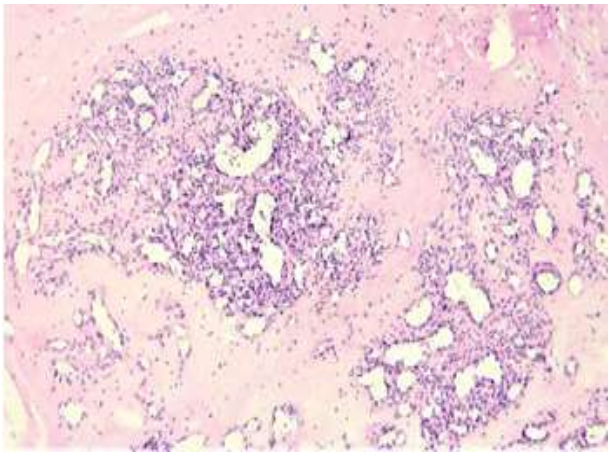

Fig. 5: Reactive angioendotheliomatosis with proliferating capillaries seen within a thrombosed vessel containing few erythrocytes.
CD34
CD31

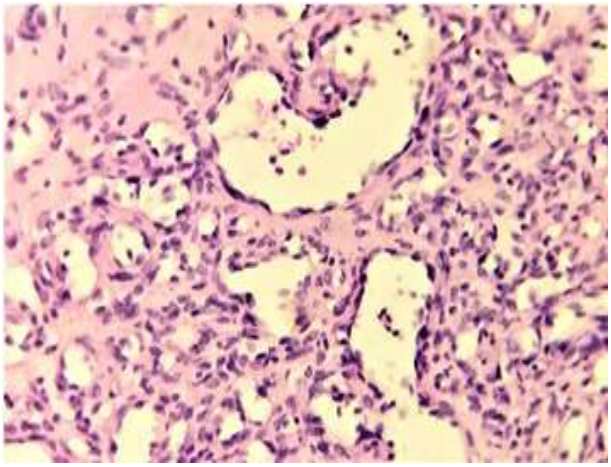

Fig. 6: Reactive angioendotheliomatosis with proliferating capillaries seen within a thrombosed vessel containing few erythrocytes.
CD34
CD31

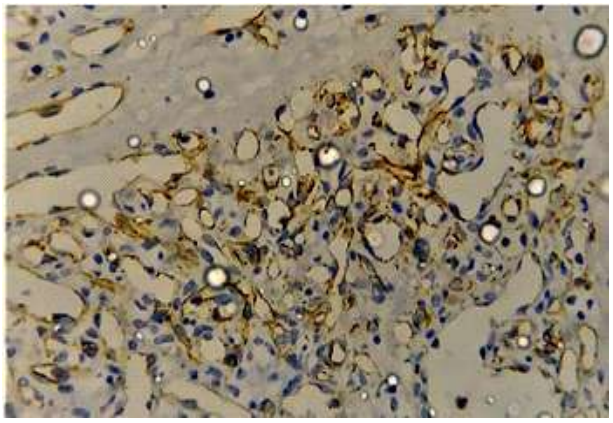

Fig. 7: Endothelial cells show positivity for CD34

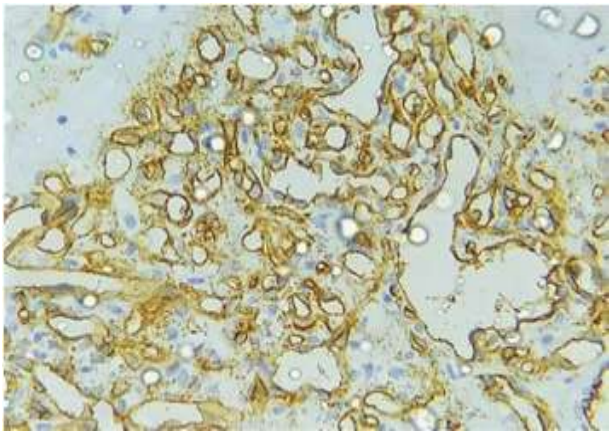

Fig. 8: Endothelial cells show positivity for CD31

Discussion

Reactive angioendotheliomatosis has been considered a benign vascular disorder, whose exact aetiopathogenesis is not yet completely understood. It was first reported by Gottron and Nikolowsky [4]. It is considered to be a marker of an underlying systemic illness [5]. It has been associated with deposition of cryoproteins within the lumen, with anti-phospholipid syndrome,as well as chronic disseminated intravascular coagulation and chronic lymphocytic leukaemia [6-9]. In a study of 15 cases by McMenamin ME et al, it was found that 11 cases had associated systemic diseases like renal disease, alcoholic cirrhosis, glioblastomamultiforme and rheumatoid arthritis [10]. Most of the reported cases have included conditions such as sub-acute bacterial endocarditis [4], tuberculosis [11], liver failure [12] and renal failure [10]. Hitherto, none of the reported cases so far show an association with leprosy.

RAE presents variably, and macules, papules, nodules and plaque formation have been reported. They may occasionally ulcerate and undergo necrosis [10].

Leprosy is a chronic granulomatous disease caused by*Mycobacterium leprae*. It manifests as neural and skin involvement and has been extensively studied. Chronic inflammation, caused by leprosy leads to release of cytokines and chemokines, which in turn causes endothelial cell activation. This causes vasodilation, proliferation and angiogenesis [13]. Certain recent studies have proven angiogenesis by demonstrating positivity for CD31 and CD105 [14]. Increased Vascular endothelial growth factor (VEGF) and tissue factor was observed in non-reactional leprosy by Noguiera MRS et al in their study [15].

It has been surmised that the proliferation of vasculature in RAE is in response to hypoxia induced by occlusive or sub-occlusive processes, especially those induced by chronic inflammatory processes. The theory that all the various types of CRA are a continuum of this evolving response to microthrombi has been proposed, with the early stages showing proliferation of histiocytes within the vascular luminaand later showing a proliferation of endothelial cells and pericytes [16]. Depending on the time of biopsy and severity of underlying condition, the variations in histological presentation have been proposed. Studies have shown that separate treatment is not needed for RAE, instead, treatment of underlying disorder will cause resolution of these lesions as well.

Leprosy shows an increase in endothelial expression and markers of angiogenesis, indicates that the same process which induces angiogenesis, may as well induce vascular proliferation seen in RAE.

Treatment of leprosy with certain anti-angiogenic factors has been speculated to reduce damage by leprosy reactions and treatment with these factors may help in the further management of leprosy [15]. RAE lesions may well respond to this line of therapy due to the same pathogenesis.

Due to strong suspicion of leprosy, but different appearing skin lesions, both the painless and painful lesions were sampled, albeit at a time gap of nearly three weeks. Further systemic illnesses were not looked for, as there was clear-cut clinical and histological evidence of leprosy in this case.

Conclusion

Leprosy, being a chronic inflammatory condition with significant angiogenesis, helps support the pathogenesis of RAE and helps explain the occurrence of two different types of lesions in the same patient. It is imperative to sample different looking lesions, to ensure that a co-existing lesion not be mistaken as being a part of the same disease. Treatment with anti-angiogenic factors may not only take care of the damage caused in leprosy by host-response, but may also aid in resolution of RAE.

Acknowledgements

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Conflicts of Interest

There are no conflicts of interest.

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