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Pathogenesis of Telangiectasia in Scleroderma

Tiffany L. Mould and Peter J. Roberts-Thomson

SUMMARY **Scleroderma (progressive systemic sclerosis) is a systemic autoimmune disorder characterised by skin sclerosis, calcinosis and changes in microvasculature. The etiology of the disease is unknown but both genetic and environmental factors have been implicated. Telangiectasia (macroscopically visible dilated skin vessels) occurring primarily on the hands and face, are a prominent feature in scleroderma and are present in the majority of patients. Similarly, telangiectasia are found in patients with hereditary hemorrhagic telangiectasia (HHT), a mutational disorder of the germline genes endoglin and ALK-1, members of the TGFβ receptor family, expressed on endothelial cells. Our study investigated the number, distribution and microscopic characteristics of telangiectasia in both limited (n = 29) and diffuse scleroderma (n = 9) and compared findings with 3 patients with HHT. In limited scleroderma, the mean number of telangiectasia (hand and face) was 36 (0-150) compared with 23 (0-135) in diffuse scleroderma. A significant correlation was observed between the number of telangiectasia on the face and on the hands (p = 0.014). The total number of telangiectasia correlated significantly with the disease duration (p = 0.009). The spatial distribution of the telangiectasia appeared to be random on both hands and foreface in contrast with the distribution of subcutaneous calcification of the hands which occurred predominantly on the distal and flexor surfaces of the first, second and fifth digits. Nailfold microscopic capillaroscopy was performed on 12 patients. No significant correlation was observed between capillary diameter or density and with total number of telangiectasia observed macroscopically. The distribution and microscopic appearance of telangiectasia in scleroderma appeared very similar to those observed in HHT. In view of these similarities we therefore conclude that telangiectactic development in scleroderma may be associated with disorders of the TGFb receptor family proteins found on the microvasculature.**

Telangiectasia are simply defined as visibly dilated blood vessels in the skin and are subdivided into several morphological groups.[1] Patients with telangiectasia due to irradiation, sun exposure or topical steroid therapy can usually be easily identified by the associated dermal atrophy and pigmentary changes. Angiomas can be distinguished by a central punctum, which is often pulsating and they may have radiating capillaries. Causes in this group include the Campbell de Morgan spots commonly found in the elderly and the spider naevi found in pregnancy and liver disease. Linear telangiectasia are a group of net like telangiectasia, which are a feature of essential telangiectasia and ataxia telangiectasia, the latter being a rare hereditary disease of childhood whereby there is a failure of DNA repair leading to neurological and immunological defects.

It is common to find telangiectasia associated with connective tissue diseases, particularly scleroderma, overlap syndromes and dermatomyositis.[2] Scleroderma is a disease characterized by skin sclerosis, subcutaneous calcification and microvascular abnormalities. These telangiectasia are "mat" in type. They are broad macules up to 1-2 mm in diameter and polygonal or oval in shape. They are distributed over the hands and face, as well as the mucosal surfaces and the latter may bleed with substantial gastrointestinal blood loss. Scleroderma

From the Department of Immunology, Allergy and Arthritis, Flinders Medical Centre, Bedford Park, South Australia, 5042.
Correspondence: Peter J. Roberts-Thomson

has an etio-pathogenesis which is largely unknown. It involves abnormalities of fibroblasts and collagen, the vascular endothelium and the immune system. Vascular changes are seen early in the process, and it is thought that endothelial cells may also be important in the genesis of fibrotic response.

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant condition, characterized by the development of telangiectasia in later years.[3] The telangiectasia are similarly mat like, and have the same distribution of the face, hands and mucosal surfaces. One subset of this condition also leads to arteriovenous (AV) malformations of the lungs and liver. In 1997, the pathogenesis of this condition was elucidated. It is now known to relate to a mutational disorder of the TGFβ receptor proteins, endoglin or ALK1, found on the endothelial cell.[3]

Our aims in the present study were to determine the site, extent and clinical associations of telangiectasia of the hands and face in patients with scleroderma and to correlate these findings with the results of nail fold capillaroscopy and also the extent and distribution of subcutaneous calcification as determined radiologically. The second part of our study was to compare these vascular findings with those in patients with hereditary hemorrhagic telangiectasia.

METHODS

Patients and controls

Thirty eight patients with scleroderma were selected from the South Australian Scleroderma Register.[4] Of these, 29 have a limited disease, and 9 had diffuse disease. Their hands and face were examined with the number, size (< 1 mm and > 1 mm) and distribution of telangiectasia mapped. The disease duration, serologic type and smoking history were noted for each patient.

Three patients with HHT were studied, two having prominent facial and hand telangiectasia and one with evidence of a pulmonary AV malformation.

Fifty patients who were attending the Rheumatology/Immunology Outpatient Clinic for conditions other than connective tissue disorders were also included as controls.

Nailfold capillaroscopy and video image analysis

This was performed as previously described[5] in 12 patients with scleroderma (all with limited disease) and in 3 patients with HHT. Nailfold capillaroscopy was performed on the ring finger of each hand. The capillaries were visualized by a Micro-Orient microscope with 60x magnification. Cold light was provided by Euromex fibre optic light source. A Sony CCD color camera was attached to the microscope and was linked to a NEC MultiSync 3 FG computer. To visualize the capillaries, a drop of microscope oil was placed on the nail bed to reduce the refractive error. The capillaries were then digitized using the Video Pro software. A minimum of 4 images of each finger were captured. Measurements were calibrated according to a biopsy ruler and were measured in micrometers. Video image analysis techniques were then used to analyze the data. Capillary diameter was taken to be the maximum width of the loop. Only well visualized capillaries were measured. A minimum of 6 images were analyzed in each subject. Mean capillary diameter was then calculated for each subject. Capillary density was measured by counting well visualized capillaries on a minimum of 6 images per patient. The capillaries were marked and counted. An average number of capillaries was calculated for each subject.

Subcutaneous calcification

The site and extent of subcutaneous calcification of the hands were determined by an examination of the hand radiographs in 11 patients with limited scleroderma as previously described.[6]

Statistical analysis

All data are presented as mean ± standard deviation. Statistical analysis was performed using the Chi-square or the Wilcoxon Rank Sum test. Differences were considered significant when p values were less than 0.01. Relationships between two variables were assessed using linear regression.

RESULTS:

Analysis of telangiectasia was performed in 38 patients with scleroderma and 50 control patients. The average age of the patients with limited scleroderma was 63.4 years (range 34-90 years), and diffuse 48.4 years (range 26-63 years). The male/female ratio for limited and diffuse disease was 3:26 and 3:6, respectively. None of the patients were current smokers. The mean number of telangiectasia in the limited group was 35 (0-150) and 23 (0-135) in the diffuse group (Fig. 1). Ten percent of the telangiectasia were > 1 mm in size. There was a highly significant cor-

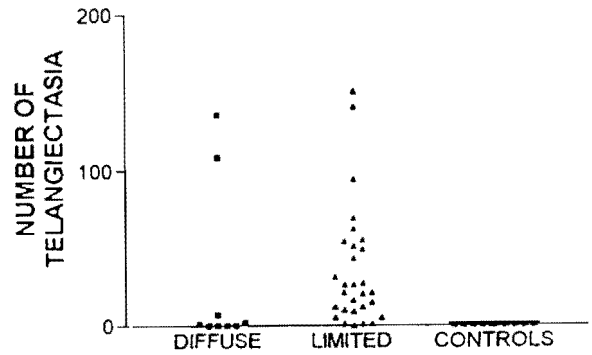

Fig. 1 Total number of telangiectasia (hands and face) observed in patients with diffuse scleroderma, limited scleroderma and in rheumatic control subjects.

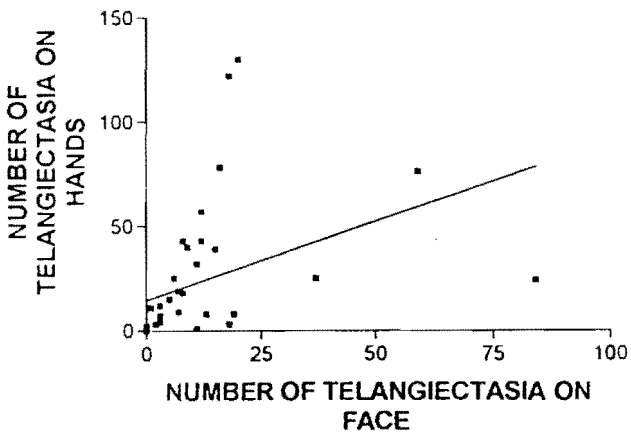

Fig. 2 Correlation of number of telangiectasia on hands versus number on face and lips ($p = 0.014$).

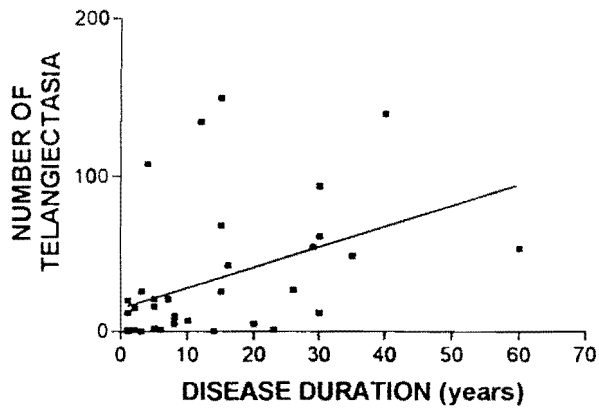

Fig. 3 Correlation of total number of telangiectasia (hands and face) with disease duration ($p = 0.009$).

relation between the number of telangiectasia on the hands compared with the face (Fig. 2, $p = 0.014$), with no significant difference between the limited and diffuse groups. The number of telangiectasia in both groups was also significantly correlated with the duration of the disease (Fig. 3, $p = 0.009$). The spacial distribution of telangiectasia appeared to be random on both the foreface and the hands in both limited and diffuse scleroderma (Fig. 4). This contrasted with the distribution of calcinosis, which was found maximally on the flexor surfaces of the thumb, index and fifth finger.[6] No correlation was observed between the surface area of calcification and total number of telangiectasia ($p = 0.67$). None of the control patients demonstrated any mat type telangiectasia of the hands and face. Nailfold capillaroscopy was performed in 12 patients with limited scleroderma. No significant correlation was observed between total number of telangiectasia and with capillary diameter ($p = 0.97$) or with capillary density ($p = 0.66$). In 3 patients with HHT, the number and distribution of the telangiectasia was similar to that found in patients with scleroderma (Fig. 4) Similarly, the appearance of the telangiectasia as observed microscopically also appeared similar (Fig. 5).

DISCUSSION

The essential findings from this study were that telangiectasia of the hands and face occurred commonly in scleroderma, particularly in the limited subtype; there was a significant correlation between the number of telangiectasia on the face and hands and that this number increases with disease duration; no correlation was observed between the number of telangiec-

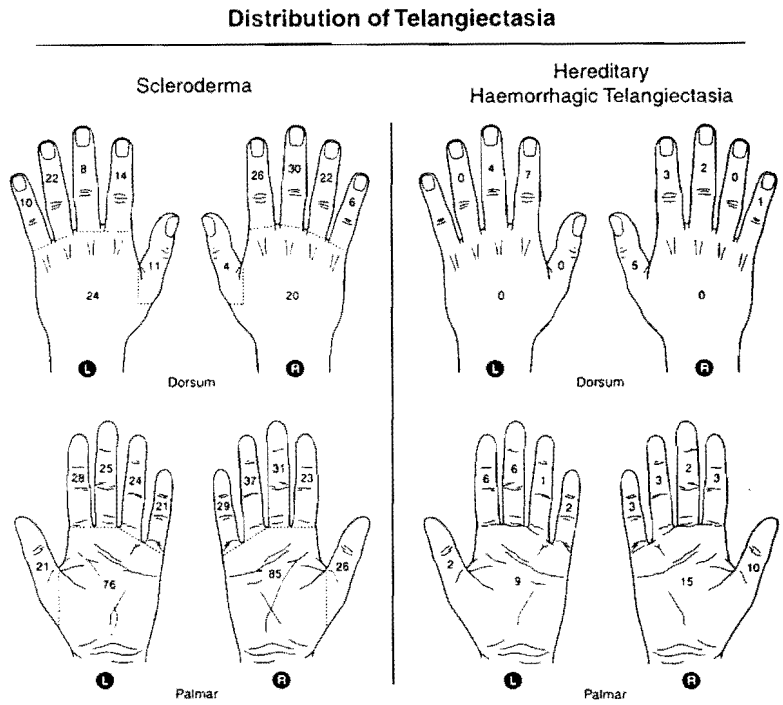

Fig. 4 Total number of telangiectasia observed in different spatial segments of the hands (illustrating random distribution) in a) scleroderma and b) hereditary hemorrhagic telangiectasia.

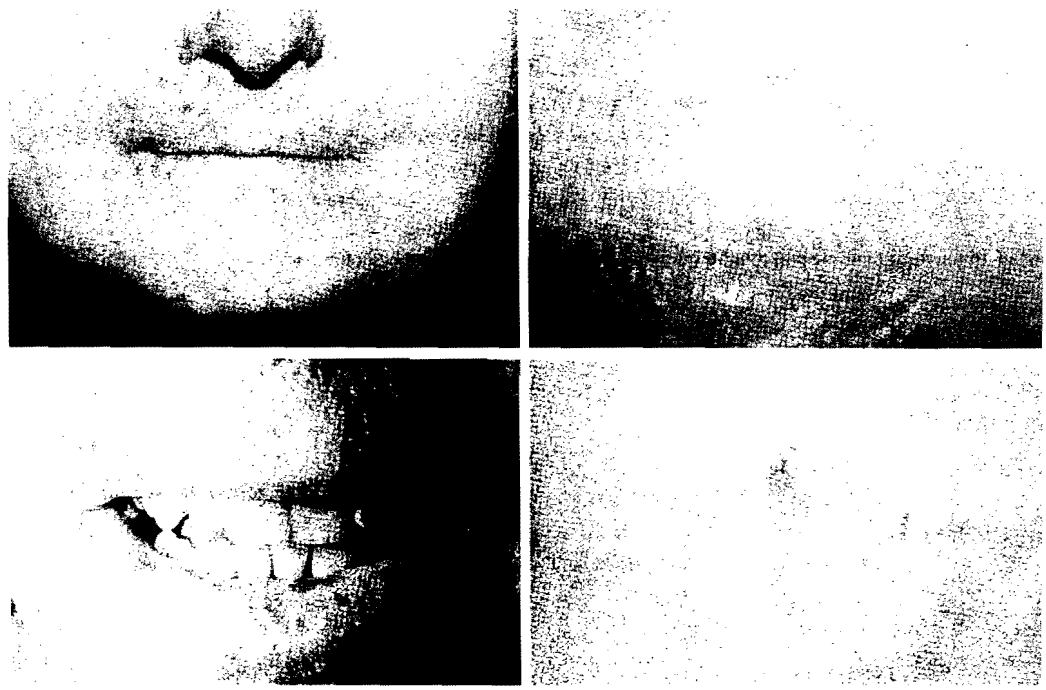

Fig. 5 Facial telangiectasia and nailfold capillary characteristics in A) patient with scleroderma (upper panels) and B) patient with hereditary hemorrhagic telangiectasia (lower panels).

Table 1 Similarities of telangiectasia in scleroderma and hereditary hemorrhagic telangiectasia

	Scleroderma	Hereditary hemorrhagic telangiectasia
Cause	?	Mutation in TGFβ receptor
Telangiectasia	++	++
Distribution	Hands/face/mucosa	Hands/face/mucosa
Nailfold capillary abnormalities	++	+/-
Mucosal bleeding	+	++

tasia and the nailfold capillary diameter or density; the site of telangiectasia appears to occur without specific spatial localization on the hands and foreface (in contrast to the restricted site of subcutaneous calcinosis of the hands) and finally, the distribution and microscopic appearances of telangiectasia found in HHT were similar to those found in scleroderma.

The etio-pathogenesis of telangiectasia in scleroderma is unknown. Presumably the telangiectasia occur as an angiogenic response to endothelial injury as microscopic capillaroscopy reveals extensive derangment and destruction to the microvasculature throughout many organs of the body in this disease. This proposition would be compatible with the increased number of telangiectasia seen with disease duration. The site of telangiectasia in scleroderma is of some interest, predominating on the hands, face and mucosa and to date there is no adequate explanation why the telangiectasia are found at these locations. Perhaps the explanation relates to the nature of the endothelium of the microvasculature at these sites.

We initially predicted that the number of telangiectasia seen in our patients would correlate positively with capillary diameter as assessed by a microscopic capillaroscopy of the nail fold capillary bed of the fourth finger. No significant correlation was observed. Whether this lack of significant correlation represents a type-II error with significance to be achieved in large studies or whether no such relationships exists, will require further study. The distribution and microscopic appearances of a telangiectasia seen in three patients with HHT were similar to those in our scleroderma patients. Indeed, nailfold capillary abnormalities were observed in two patients with HHT although generally they were more focal than the more generalized changed seen in scleroderma. HHT is now recognized as a genetic disorder involving mutations of the genes encoding for endoglin and ALT-1 components of the TGFβ receptor seen in high levels of endothelial cells.[3] The TGFβ receptors are responsible for a variety of effects on development and homeostasis of the endothelial cells. In particular, TGFβ modulate many aspects of vascular architecture as well as influencing matrix formation and basement membrane deposition and maturation. Because of the similarities in location, size and microscopic characteristics of the telangiectasia in scleroderma and HHT (Table 1), it is an attractive hypothesis that the pathogenesis of the telangiectasia in scleroderma will involve acquired disorders of the TGFβ receptor. To date, there is little data concerning the TGFβ receptor in scleroderma although Kawakami and colleagues[7] have reported the over expression (2 fold) of this receptor on scleroderma fibroblasts. Furthermore, a recent study reports elevated levels of connective tissue growth factor, a down stream protein of TGFβ receptor, in scleroderma.[8] However, Zhou and colleagues[9] revealed no evidence that genetic polymorphisms of the TGFβ receptor were associated with scleroderma in a native American population. Further studies will be required to explore the possible role of TGFβ receptor and/or its abnormalities in scleroderma.

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