Histol Histopath (1992) 7: 47-55

Histology and Histopathology

Scrotal angiokeratoma (Fordyce): histopathological and ultrastructural findings

L. Gioglio[1], C. Porta[2], M. Moroni[2], G. Nastasi[2] and I. Gangarossa[3]

[1]Institute of Human Anatomy and [2]Institute of Medical Pathology I, University of Pavia, Pavia and [3]Division of Dermatology, Bassini Hospital, Cinisello Balsamo, Italy

Summary. Bioptic findings related to four cases of scrotal angiokeratoma-Fordyce, were studied under light and electron microscopy.

A particular heterogeneity of the structural and ultrastructural patterns typical of this lesion was thus observed.

Light microscopy study pointed out, in particular, different degrees of dilation of papillary vessels, whereas ultrastructural study highlighted marked alterations of endothelial cells with structural and quantitative modifications of cytoplasmic organelles.

Key words: Angiokeratoma-Fordyce, Histopathological study, Ultrastructural study

Introduction

The term angiokeratoma refers to several vascular skin lesions which are macroscopically verrucoid-like and histologically characterized by a marked dilation of the vessels of the papillary dermis, which tend to form vascular lacunae, and by hyperkeratosis and achantosis of the overlying epidermis.

Besides the systemic thesaurismotic form known as Fabry's disease (Fabry, 1898), at least four types of angiokeratoma with cutaneous localization have been described (Imperial and Hellwig, 1967a): the Mibelli type, the circumscribed angiokeratoma, the multiple angiokeratoma and the Fordyce type, which was first described in 1896 in a 60-year-old man (Fordyce, 1896). They share similar light microscopical features although they differ from each other in the clinical pattern and localization.

Scrotal angiokeratoma can be easily observed in old, debilitated men, occasionally affected by malignant abdominal neoplasms or, on the contrary, in young subjects undergoing intense physical activity (recruits, athletes, labourers, etc) (Imperial and Hellwig, 1967b).

The most frequent symptom is a sensation of heaviness and tension at the scrotum accompained by irritation, bleding to varying extents, and macerative phenomena with possible superinduced infections (Wile and Belote, 1928; Imperial and Hellwig, 1967b), even though patients could also be totally asymptomatic.

The epidemiological and clinical peculiarities of scrotal angiokeratoma can be easily explained on the basis of anatomy and characteristics of the venous drainage at the scrotum. In old and debilitated individuals the dartos muscle, which supports the scrotal vessels, is particularly relaxed, and flaccidity of the scrotal sac itself is a common finding. However, intense physical activity and high temperature can also cause relaxation of the dartos so as to favour dilation in the scrotal venous system. In this manner, the increase in pressure and the consequent venous stasis cause an enlargement and symptomatic worsening of the vascular lesions which are characteristic of this disease.

Since the left pampiniform plexus has a less efficient drainage system than the right one, as it leads at right angle and, in most cases with no valves, into the left renal vein, instead of leading directly into the vena cava, it can be understood why the left side is mostly affected by angiokeratoma-Fordyce, and why this disease is often associated with varicocele (Sutton, 1911; Agger and Osmundsen, 1970).

This report presents a histological and ultrastructural study of four cases of scrotal angiokeratoma-Fordyce.

Materials and methods

We observed four patients, hospitalized for

Offprint requests to: Dr. Luciana Gioglio, Ph.D., Istituto di Anatomia Umana Normale, Università di Pavia, Via Forlanini 8, I-27100 Pavia, Italy

different reasons (3 alcoholic cirrhosis and 1 left renal cell carcinoma) who, during objective examination, showed the presence at the scrotum of papulo-nodular elements with variable diameter (from 0.1 to 0.5 cm), hard-elastic consistency and an apparently fibro-angiomatous constitution.

Light microscopy

Fragments of scrotal skin affected by the lesion were removed bioptically, fixed in 10% formalin and included in paraffin according to conventional histological procedures.

Sections of approximately 5 μm thickness were obtained from the fragments thus treated and were stained with haematoxylin-eosin. Some sections were also stained with orcein according to the Unna-Tänzer-Livini method for highlighting elastic fibres.

Electron microscopy

Fragments of skin affected by the lesion were fixed in 4% glutaraldehyde under phosphate buffer at pH 7.4 for 12 hours.

After short rinses under phosphate buffer, the fragments were postfixed in 1% osmium tetroxide under phosphate buffer for 1 hour, dehydrated in ethanol and epoxypropane, then included in Epon 812 and finally cut into semi-thin sections (approximately 1 μm thick) and ultra-thin sections (approximately 600 Å thick).

The semi-thin sections were stained with toluidine blue and observed under a light microscope in order to select the most significant fields for subsequent ultrastructural analysis.

The ultra-thin sections, contrasted with uranyl acetate and lead citrate, were finally examined under a Zeiss EM 109 electron microscope.

Results

Light microscopy

The fragments of skin affected by the lesions showed a marked dilation of papillary veins, capillaries and arterioles, which tended to assume the appearance of lacunae or vascular lakes delimited by a thin but continuous endothelial wall; these lacunae appeared to be clustered in groups between which long epidermal crests penetrate, surrounding these groups incompletely (Fig. 1).

In many cases it was possible to observe small calibre venous vessels, the wall of which being formed by endothelial cells which protruded into the vessel

Fig. 1. Fragment of scrotal skin showing the typical structural alterations of angiokeratoma. Hyperkeratosis and achantosis characterize the epidermis (E), whereas severely dilated papillary vessels (asterisk) and long epidermal crests (arrow) are observed in the underlying dermis. x 63

Fig. 2. Vessels with normal or moderately increased calibre (arrow) are present both next to the large lacunae (asterisk) and outside the epidermal crests. x 160

Fig. 3. The lacunae (asterisk) are delimited by a thin but continous endothelial wall and the surrounding epidermis has basal cells which contain large clear vacuoles (arrow). x 196

Fig. 4. An image of the dermis highlighting a decrease in elastic fibres (arrow). Orcein stain. x 725

lumen (Fig. 2), immediately below these lacunae, between them and the epidermal crests.

The epidermis which covers these lacunae was characterized by hyperkeratosis and achantosis and by the presence of basal cells which contained large clear vesicles in their cytoplasm (Fig. 3).

In other points of the lesions, the papillary dermis was characterized by the presence of normal-calibre vessels alternating with others with a larger than normal calibre. The wall of these vessels was made up of endothelial cells which were more or less flattened in relation to the diameter of the vessel being considered.

The epidermis showed neither hyperkeratosis nor marked achantosis; only a small increase in the epidermal crests.

Regardless of the point of the lesion observed, at the base of the dermal papillae there were vessels with larger than normal calibre, delimited by a thin endothelial wall.

Inside the vessels examined were found erythrocytes, amorphous substance or thrombi.

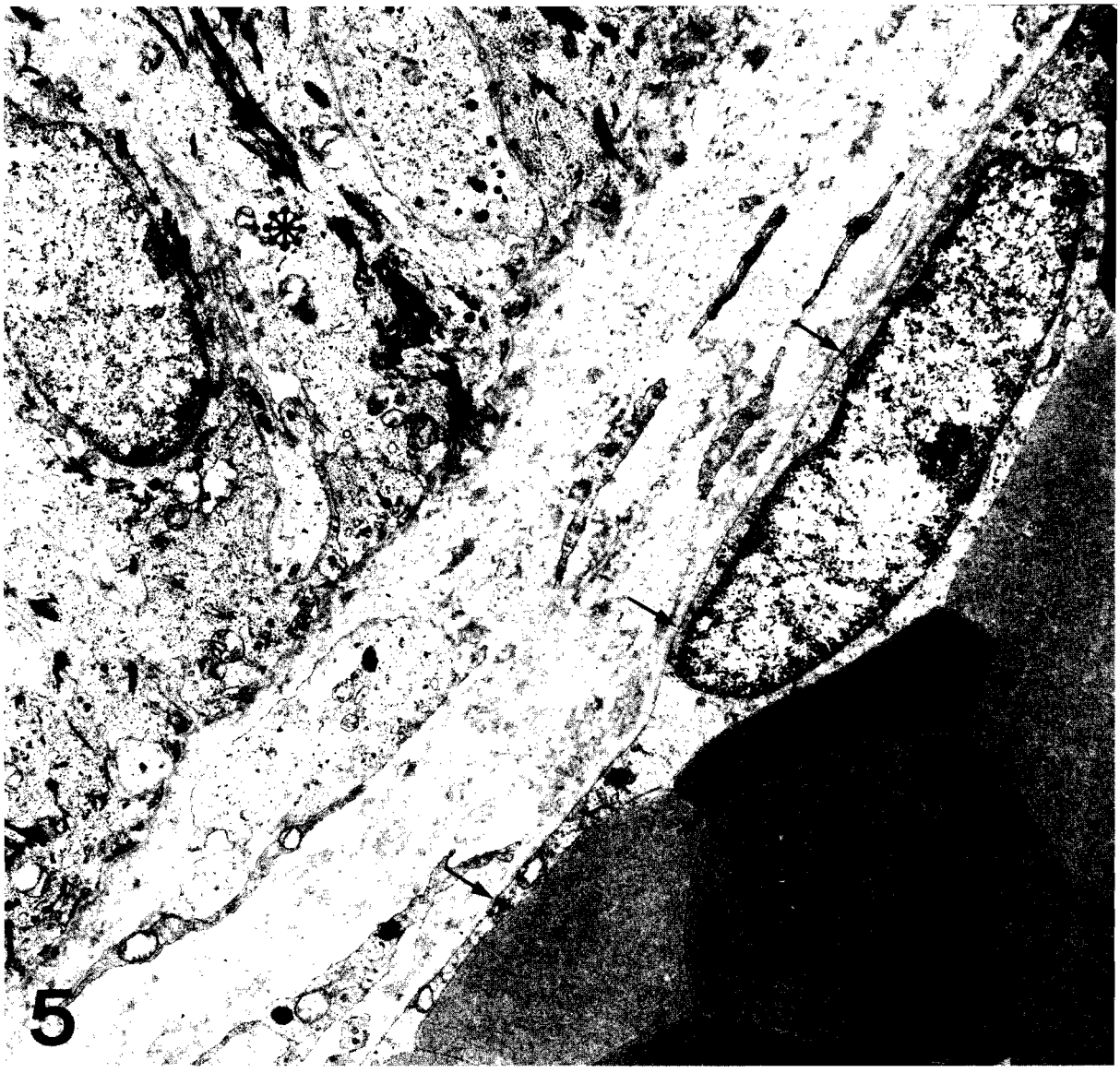

Fig. 5. Electron microscopy image clearly showing that the large lacunae (star) are delimited by a very thin endothelial wall (arrow) and are separated from the surrounding epidermis (asterisk) by the interposition of a thin layer of connective tissue. × 9,000

In papillary dermis we observed an extremely modest inflammatory reaction; a decrease in the elastic fibrillary component was observed throughout the dermis, as shown by the orcein stains (Fig. 4).

Electron microscopy

Ultrastructural observation, which followed histological observation, allowed us to define more precisely the characteristics of the endothelial cells of the papillary vessel wall, which could have a normal, enlarged or greatly enlarged calibre.

The large vascular lacunae appeared to be delimited by an endothelial wall; the cells of this wall being very thin, and microfilaments, pinocytosis vesicles and vacuoles with a scarcely electron-opaque content, with a diameter varying between 2,000 and 4,000 Å, were observed in its cytoplasm (Fig. 5). Cytoplasmatic organelles, such as mitochondria and endoplasmic reticulum, were scarce (Fig. 6).

Some of these vacuoles showed a double layer membrane and structures similar to mitochondrial crests within the vacuoles themselves (Figs. 7, 8a,b). Multivesicle bodies were also observed in some endothelial cells (Fig. 9).

The epidermis which surrounded the lacunae was characterized by the presence of cells which contained scarcely electron-opaque vacuoles with variable diameter (Fig. 10a). In basal cells, these vacuoles could flow together to occupy most of the cytoplasm and push the nucleus close to cell membrane (Fig. 10b).

Fig. 6. The endothelial cells of the wall of large lacunae are characterized by the presence of microfilaments (star), pinocytosis vesicles (arrow) and vacuoles which contain scarcely electron-opaque material (tip of arrow). × 21,000

Fig. 7. Endothelial cell containing scarcely electron-opaque vacuoles characterized by a double layer membrane (tip of arrow). × 32,000

Fig. 8a. Endothelial cell containing scarcely electron-opaque vacuoles characterized by a double layer membrane and by structures similar to mitochondrial crests. × 28,000

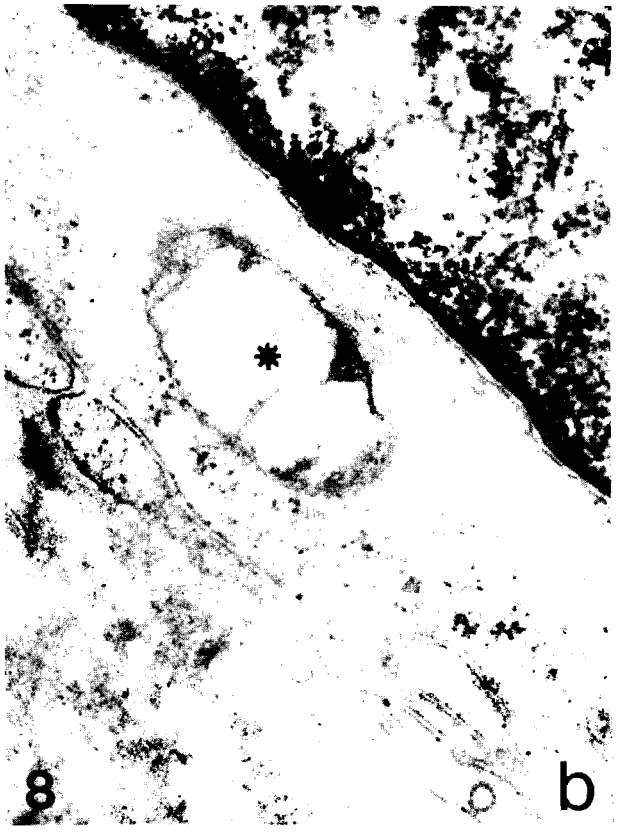

Fig. 8b. High magnification of a vacuole (asterisk) in which the double layer membrane and structures similar to mitochondrial crests are particularly evident. × 36,000

Fig. 9. Multi-vesicular bodies present in some endothelial cells (asterisk). × 20,000

Fig. 10a. The cells of the epidermis which surrounds the large lacunae have several intracytoplasmatic vacuoles with a low degree of electron opacity (arrow) × 8,800

Fig. 10b. In some cases a single vacuole occupies most of the cytoplasm of these cells (asterisk). A thickened basal membrane separates the epidermis from the underlying dermis (arrow). × 10,000

The basal membrane, which separates the epidermis from the underlying dermis, was thickened, especially at the lacunae (Fig. 10b), which were always separated from the surrounding epithelium by the interposition not only of the basal membrane, but also of a very thin layer of connective tissue (Fig. 5).

The vessels with a smaller degree of dilation, located at the base of the dermal papillae, had an endothelium constituted by round or oval cells, contained a normal cytoplasmic set (Fig. 11a) and their surface directed toward the vessel lumen could have endolumenal cytoplasmic evagination (Fig. 11b).

Ultrastructural investigation has pointed out, externally to the cells of the vascular endothelium, some smooth muscle cells arranged in a discontinous layer (Fig. 11a). Finally, the scarce presence of elastic fibres, which had already been pointed out during light-microscopy examination of the histological preparations, was confirmed.

Discussion

Our observations, in accordance with the data of Imperial (Imperial and Hellwig, 1967c), Sutton (Sutton, 1911) and Braverman (Braverman and Ken-Yen, 1983; Braverman, 1989), attest that angiokeratoma-Fordyce is distinguished by the presence of very dilated papillary vessels joined by vessels of a smaller diameter. Moreover, it was possible to evidence some moderately dilated vessels at the base of the dermal papillae that, for localization and for anatomic traits of the paries, can be considered as post capillary venules. On the contrary, the vessels that connect papillary lacunae and the vessels that are in the profound region of the dermis, traced by Braverman in the angiokeratoma-Fabry (Braverman and Ken-Yen, 1983), have not been pointed out.

The endothelial cells of the lacunae were characterized by a minimum thickness, as well as by the presence of vacuoles scarcely electron-opaque, comparable to the large clear vacuoles traced by Voglino in a case of Angiokeratoma-Fabry (Voglino et al., 1988). Moreover, in some endothelial cells, the vacuoles showed a double membrane and crests similar to those of mitochondria, similarly to the description of the inclusions which characterize the endothelial cells of angiokeratoma-Fabry, made by Hashimoto (Hashimoto et al., 1976).

Such vacuoles can therefore be considered as altered mitochondria. In fact, mitochondria are the first cytoplasmic organelles to modify when there is a

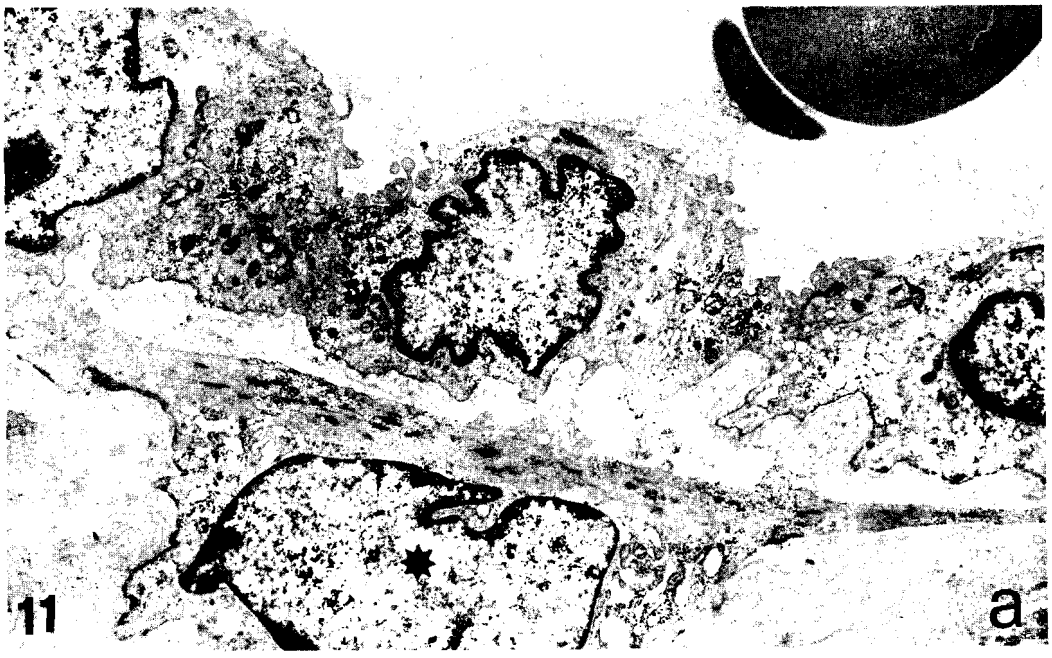

Fig. 11a. The less dilated vessels are delimited by an endothelium with round cells, outside which some smooth muscle cells can be seen (star). × 5,800

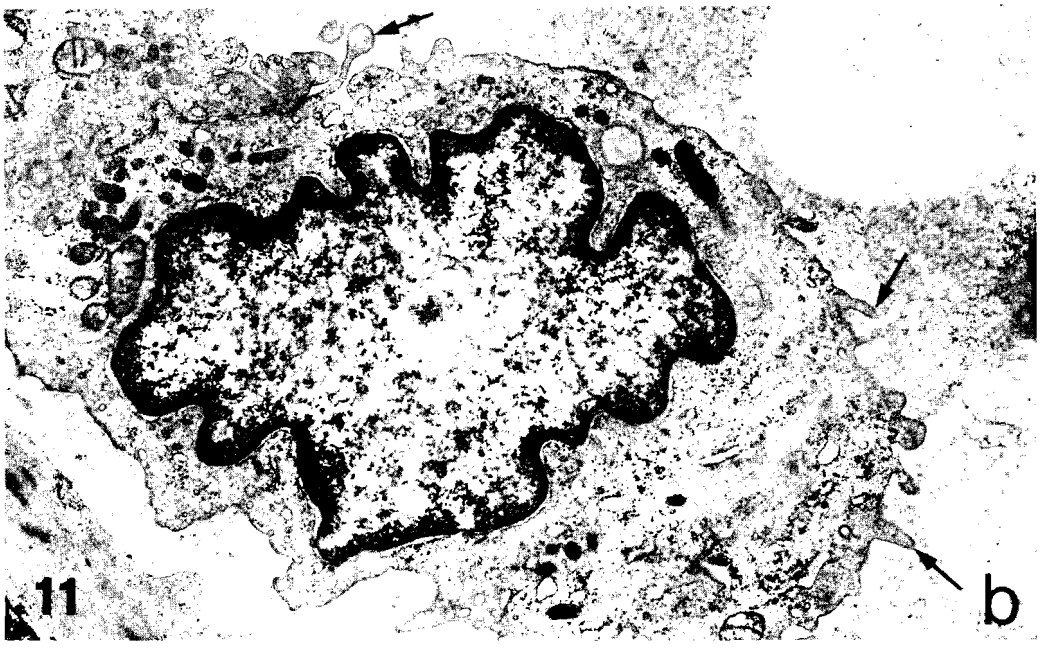

Fig. 11b. Detail of the preceding image showing that these endothelial cells have a normal cytoplasmatic set and several cytoplasmatic evaginations at their lumenal surface (arrow). × 13,600

cellular lesion and, as known, may be subject to swelling, as far as to assume the appearance of wide vacuoles. On the contrary, in the endothelial cells the small electron-dense bodies, traced by Karlsmark in vulvar angiokeratoma (Karlsmark et al., 1988) have not been evidenced, pathology that the author considers a variant of the angiokeratoma of the scrotum.

Our observations definitely allow us to point out that there is an affinity between the morphological alterations that characterized the angiokeratoma of the scrotum and the angiokeratoma-Fabry, even though it is a matter of pathologies of different etiology. In our opinion such anatomic alteration, in particular the presence of vacuoles in the endothelial cells, may be related to the stasis that follows the dilation of the vessels which characterize such pathologies, with consequent structural and quantitative alterations in the cytoplasmatic organelles. The presence of vacuoles in the cytoplasm of the basal cells and of the cells of the stratum spinosum is to be considered the consequence of the venous stasis; as a matter of fact, they may be the effect of alterations in the osmotic exchanges between the extracellular and the intracellular environment.

References

Agger P. and Osmundsen P.E. (1970). Angiokeratoma of the scrotum (Fordyce): a case report on response to surgical treatment of varicocele. Acta Derm. Venereol. (Stockh) 50, 221-224.

Braverman I.M. and Ken-Yen A. (1983). Ultrastructure and three-dimensional reconstruction of several macular and papular teleangiectases. J. Invest. Dermatol. 81, 489-497.

Braverman I.M. (1989). Ultrastructure and organization of the cutaneous microvasculature in normal and pathological states. J. Invest. Dermatol. 93 (Suppl. 2),25-95.

Fabry J. (1898). Ein beitrag zur kenntniss der purpura haemorragica (*Purpura papulosa haemorrhagica hebrae).* Arch. Derm. Syphil. (Berlin) 43, 187-200.

Fordyce J.A. (1896). Angiokeratoma of the scrotum. J. Cutan. Genitourin. Dis. 14, 81-87.

Hashimoto K., Lieberman P. and Nelson L. Jr. (1976). Angiokeratoma corporis diffusum (Fabry disease). A lysosomial disease. Arch. Dermatol. 112, 1416-1423.

Imperial R. and Helwig E.B. (1967a). Angiokeratoma. A clinical pathological study. Arch. Dermatol. (Chicago) 43, 187-200.

Imperial R. and Helwig E.B. (1967b). Angiokeratoma of the scrotum (Fordyce type). J. Urol. 98, 379-387.

Imperial R. and Helwig E.B. (1967c). Angiokeratoma of the vulva. Obstet. Gynecol. 29, 307-312.

Karlsmark T., Weissmann K. and Kobayashi T. (1988). Ultrastructure of angiokeratoma vulvae. Acta Derm. Venereol. (Stockholm) 68, 80-82.

Sutton R.L. (1911). A clinical and histolopathologic study of angiokeratoma of the scrotum. JAMA 57, 189-192.

Voglino A., Paradisi M., Dompé G., Onetti-Muda A. and Faraggiana T. (1988). Angiokeratoma corporis diffusum (Fabry's disease) with unusual features in a female patient. Am. J. Dermatopathol. 10, 343-348.

Wile U.J. and Belote G.H. (1928). Angiokeratoma; confused clinical and pathological picture. Arch. Derm. Syphil. 18, 501-513.

Accepted June 20, 1991