DR ANGELA TEWARI (Orcid ID : 0000-0002-8789-7353)

Article type : Research Letter

Post-zygotic mosaicism in a woman with Goltz syndrome mimics segmental angioma serpiginosum

A. Tewari,[1] L. Alarcon,[2] K. Gordon, S. Mansour,[3] V. Akhras[1]

Departments of [1]Dermatology, [2]Histopathology, and [3]Clinical Genetics, St George's Hospital, Tooting, London, UK

Corresponding Author: Angela Tewari
E-mail: angela.tewari@kcl.ac.uk
ORCID: 0000-0002-8789-7353

Funding: None
Conflicts of interest: None to declare

A 30-year-old Caucasian woman with no relevant medical history or family history presented to dermatology with a benign fibrous papule on her nose and was incidentally found to have an unusual rash on her legs. It had developed after birth, was itchy and aggravated by hot weather. She had no previous miscarriages and had a healthy 2-year-old daughter. On examination there were red, scaly plaques and areas of dermal atrophy in a blaschkoid distribution on the lower left leg (Fig 1a) and a linear punctate eruption over the right inner thigh (Fig 1b). Dermoscopy of the lesions showed presence of vascular clods arranged in clusters on a background of reticulate fine vessels (Fig 1c), which initially raised the differential of a capillary naevoid eruption, blaschkoid Darier's or inflammatory linear verrucous epidermal naevus. A skin biopsy demonstrated dilated vascular channels (Fig 1d), capillary ectasia, and normal epidermal histology. D240 stain was negative. These findings were in keeping with a possible diagnosis of angioma serpiginosum (AS). On further review, subtle, linear dermal atrophy at the anterior neck (Fig 1e) could be seen. There were no hair, teeth, mucosal or bony abnormalities. Following a literature review of AS, sanger sequencing of the DNA extracted directly from the affected skin was organized which identified a high level of a heterozygous, frameshift mutation *c.858_859delGT* in the *PORCN* gene. This was not identified in the DNA extracted from blood lymphocytes. The histology slides were reviewed and fat deposits at the mid papillary dermis and perivascular space could be seen, a feature seen in Goltz syndrome (Fig 1f).

Segmental AS is a benign naevoid entity which usually presents sporadically in women. On the other hand, examples of parent to child transmission of non-segmental AS have been described [1, 2]. The classic red, oval or round lagoons of segmental AS seen on dermoscopy are caused by congenital hyperplasia or ectasia of preexisting dermal capillaries and clinically this is seen as grouped punctate,

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.17823

violaceous or red macules with incomplete blanching on pressure, arranged in a segmental, serpiginous pattern. AS with oesophageal papillomatosis and nail dystrophy has been proposed in a 3-generation family [3] *with a familial microdeletion* involving the *PORCN* gene (Xp11.3-Xq12) [4] in all affected females. Happle (2009), however, has interpreted this family as having a variant of Goltz syndrome or Focal Dermal hypoplasia (FDH) [5].

Goltz syndrome, or FDH, is an X linked dominant condition affecting the embryonic development of ectodermal (hair, nails, teeth, skin and central nervous system) and mesodermal (skeletal, urogenital and eyes) tissues [6]. At least 4 types of cutaneous involvement are described: 1) polymorphic atrophy-like depressions 2) striations 3) verrucoid papillomas of the skin and mucous membranes 4) lipomatous lesions. Histological prominence of dilated superficial capillaries in keeping with AS has been described [7], as well as non-specific inflammation (eosinophils and lymphocytes) and fat lobules occupying the dermis. Fat deposits probably relate to a combination of localized dysplasia of proliferating connective tissue cells and subcutaneous fat herniation into empty spaces due to dermal aplasia [6,7].

Our patient had a post-zygotic, mosaic mutation identified in the affected skin accounting for the sporadic presentation and her mild phenotype. This finding may have reproductive risks. If she carries this mutation in her germ line, this could give rise to FDH in her offspring with loss of affected male pregnancies and a risk of having an affected female who would most probably be more severely affected (functional X-chromosome mosaicism/germline mutation). The blaschkoid distribution of the lesions in classic, familial FDH and the variable severity is due to random X inactivation [8]. In our case, there are two reasons for the blaschkoid distribution, - the post-zygotic mosaicism and random X inactivation.

Post-zygotic mosaicism has recently been described in two women [8] who both had non specific histopathology, but had more pronounced cutaneous disease than our patient. The first patient had syndactyly of the $2^{nd}/3^{rd}$ and $4^{th}/5^{th}$ fingers of the left hand along with extensive right sided, linear, hyperpigmented and atrophic lesions, and the second patient had left $3^{rd}/4^{th}$ fingernail involvement and also extensive left sided and right flank, hyperpigmented and atrophic cutaneous streaking. The patients had mutations in the *PORCN* gene (in either saliva or lesional skin) but not in DNA extracted from peripheral blood lymphocytes [8,9].

In our patient, despite features of AS on histology, the diagnosis of FDH was considered due to subtle dermal atrophy on the neck, subsequently confirmed with genetic testing and review of histology. Our case highlights how patients who are labeled with AS, may in fact be a forme-fruste of FDH and

should be screened for mutations in the *PORCN* gene preferably on DNA extracted directly from the affected skin.

References

[1] Marriott PJ, Munro DD, Ryan T. Angioma serpiginosum--familial incidence. Br J Dermatol 1975;**93**(6):701-6

[2] Sandhu K, Gupta S Angioma Serpiginosum: report of 2 unusual cases J Eur Acad Dermatol Venereol 2005;**19**(5): 127-128

[3] Blinkenberg EO, Brendehaug A, Sandvik AK, et al. Angioma serpiginosum with oesophageal papillomatosis is an X-linked dominant condition that maps to Xp11.3-Xq12. European Journal of Human Genetics 2007;**15**(5):543-7

[4] Houge G, Oeffner F, Grzeschik KH. An Xp11.23 deletion containing PORCN may also cause angioma serpiginosum, a cosmetic skin disease associated with extreme skewing of X-inactivation. European Journal of Human Genetics 2008;**16**(9):1027-8

[5] Happle R. Angioma serpiginosum is not caused by PORCN mutations. European Journal of Human Genetics 2009;**17**(7):881-2;

[6] Ko CJ, Antaya RJ, Zubek A et al Revisiting histopathological findings in Goltz Syndrome J Cutan Pathol 2016;**43**(5):418-421

[7] Ishil N, Baba N, Kanaizuka I et al Histopathological study of focal dermal hypoplasia (Goltz Syndrome) Clin Exp Dermatol 1992 ;**17**(1): 24-6

[8] Heinz L, Bourrat E, Vabres P et al. Mosaicism due to postzygotic mutations in women with focal dermal hypoplasia. Br J Dermatol 2018; Jul 19:1-5

[9] Severino-Freire M, Maza A, Lombardi MP et al Mosaic Focal Dermal Hypolasia in Two Female patients Acta Demato Venereologica 2017; **97**(7): 853-854

Figure Legends:
Fig 1a: red, scaly plaques and areas of dermal atrophy in a blaschkoid distribution on the lower left leg.
Fig 1b: linear punctuate eruption over the right inner thigh.
Fig 1c: dermoscopy of the lesions showing presence of vascular close arranged in clusters on a background of reticulate fine vessels.
Fig 1d: low power skin biopsy showing dilated vascular channels, capillary ectasia and normal epidermal histology.
Fig 1e: subtle dermal atrophy at the anterior neck.
Fig 1f: fat deposits in the mid papillary dermis and perivascular space