Diagnosis and treatment of digitocutaneous dysplasia, a rare infantile digital fibromatosis: a case report

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Introduction

Digitocutaneous dysplasia, also termed osseous terminal dysplasia with pigmentary defects, is a recently described pathology. In 1974, Bloem et al. [5] discussed the association between digital fibromas and pigmentary lesions. In 1998, Horii et al. [13] published a case report with similar characteristics associated with facial dysmorphism and metacarpal involvement. These authors were the first to describe a syndrome that embraced all these features. Recently, in 2010, Sun et al. [28] published the etiology of this pathology, FLNA gene mutation, with X-linked dominant transmission. This gene codifies filamin A, a protein essential in cytoskeleton formation.

Published cases with digitocutaneous dysplasia are rare, with only 19 patients from nine different families [2, 3, 6, 7, 19, 21, 30], with exceptional isolated cases [15, 20]. In all of these cases, there were similar clinical findings that defined digitocutaneous dysplasia, such as multiple digital fibromas, dental anomalies, osseous alterations, and dysmorphic changes [13].

Fibromas associated with infantile digital fibromatosis have a high risk of recurrence when they are removed and they tend to autoresolve with time [20]. For fibromas associated with dysplasia digitocutaneous, the response to excision or other treatments is still not well defined. Consultation of a newborn female in our center, who presented with severe digital fibromas, encouraged us to carefully review the literature and examine the therapeutic possibilities.

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Case Report

We report an unweaned female baby of Spanish nationality. She was evaluated in our center for the first time because of tumoral digital lesions. Her parents were healthy and there was no consanguinity. Written permission from the patient's parents was obtained to publish the patient's information and photographs.

Clinical Characteristics

We observed various characteristics associated with digitocutaneous dysplasia (Table 1) [6]. These characteristics included rounded hyperpigmented skin lesions in the malar zone and nose, a pigmented cutaneous temporal bilateral atrophy in a linear drawing, ptosis, epicanthus, telecanthus, hypertelorism, microphthalmia, frontal bulge, low set ears, papillomas on the lips, and a palatine fissure (Figs. 1, 2, 3, 4, and 5).

Table 1 Clinical findings in digitocutaneous dysplasia [6, 15, 21, 28]

Non-osseous digital alterations (hand and feet)
Fibromas
Osseous alterations
Lack of organization of phalanges and metacarpus
Lack of organization of metatarsus
Clinodactyly
Brachydactyly
Syndactyly
Camptodactyly
Alteration of long bones in extremities
Articular abnormality
Tendinous affection with generalized contracture [13]
Cutaneous alterations
Periocular pigmented spot
Pigmented linear lesions in frontal and temporal area
Dysmorphic facies
Hyperterolism
Epicantus
Lagophthalmus
Widen nose
Microftalmy
Telecantus
Iris colobome
Prominent lips
Other alterations
Palatine fissure
Cysts on the lips
Oval foramen
Dental fissures

Fig. 1 Fibromas in right hand

Fig. 2 Fibromas in left foot

In the hands and feet, we found the cause of consultation, which was tumoral lesions that were subcutaneous, solid, not painful, and without mobility. From their clinical appearance, they were compatible with digital fibromas. Histological study showed proliferation of fusiform cells with a growing storiform pattern, in the shape of a fascicle. The lesions affected the superficial dermis and extended up to subcutaneous adipose tissue, surrounding the cutaneous structures. Cells were separated by a collagenized stroma, and there were no inclusion bodies in the cytoplasm when stained with hematoxylin–eosin or Masson's trichrome. Histochemical study showed that desmin was strongly positive, actin was only focally positive, and beta-catenin was negative (cytoplasmic positivity).

The progressive increase in size of the fibromas caused digital flexion contracture and, subsequently, significant functional impotence. Moreover, in the right hand, the patient presented with a simple incomplete syndactyly of the third space. Furthermore, there was also bilateral thumb hypoplasia with minimal shortening. Therefore, they were type I hypoplastic thumbs, according to Blauth's classification modified by Manske and Goldfarb [23]. As a result, no treatment appeared to be necessary [22, 29].

Fig. 3 Cysts on the lips

Fig. 4 Periocular pigmented spots

This syndrome, digitocutaneous dysplasia, like many others, presents with some clinical heterogeneity. Other alterations such as ocular, genitourinary, cardiovascular, osseous, and dental malformations, as well as alteration of psychomotor development, are possible. In our patient, only an oval foramen was present.

Complementary Study

In an osseous X-ray study, we found isolated osseous digital dysplasia in the hands and feet, with metacarpal malformation and thumb hypoplasia (Fig. 6a, b). Other tests were carried out. An abdominal ultrasound scan was normal. A neonatal brain ultrasound scan showed a subependymal cyst of unknown origin. A cardiologic ultrasound scan showed an oval foramen. A genitourinary ultrasound scan did not rule out any distortion at this level. Genetic study confirmed the initial diagnosis. An FLNA gene mutation was identified, confirming that the patient was affected by digitocutaneous dysplasia.

Fig. 5 Pigmented linear lesions

Treatment

The first treatment applied was systemic corticosteroids, with dexamethasone in a dose of 1.9 mg/kg/day, for 4 days. Because of the lack of response to this treatment, a descending dose period, of four more days' duration, was started.

In 2010, Holmes et al. [12] published a retrospective case series of digital fibromatosis. They found that the average recurrence was similar between the group treated with surgical excision and that treated with intralesional corticoids, but there was a smaller percentage of complications and morbidity in the group treated with intralesional corticoids. Based on these findings, and because systemic corticoids did not have any response, we applied intralesional treatment. Under sedation, between 1 and 2 ml of dexamethasone was administered to the second and third fingers of the left hand. A total of three doses were administered with an interval of 20 days. We did not see any significant response after an observational period of 10 months.

Another therapeutic possibility for our patient was excisional surgery. In patients affected by digital fibromatosis, surgery must be restricted to cases with severe functional limitation because it involves a high average recurrence [26] and because various cases of spontaneous regression have been described [1, 4, 11, 14, 17, 18, 24]. In contrast, in fibromas associated with digital dysplasia, Horii et al. [13] consider that lesions with the best evolution are those treated with surgical excision (at 21 months old). We decided to extirpate some of the lesions when our patient was 16 months old and suffering from severe disability because no treatment had yielded a proper response. The lesions selected were at the third and fourth toes of both feet. While operating on the left foot, we discovered that the lesions had aggressively infiltrated the surrounding tissue. As a result, partial excision was not possible, and the only possibility was amputation of the toes. Lesions on the right foot were smaller and partial excision was feasible. The skin defect was covered with an inguinal autologous graft. Histological study showed the same characteristics mentioned above, including proliferation of fusiform cells with a collagen structure, with areas of fascicular growth and a polypoid morphology. This proliferation had an infiltrative shape reaching underlying adipose tissue and surrounding cartilage. Fusiform cells were arranged around annexes, affecting adipose tissue, and some of these lesions were identified in perpendicular fascicles in the superficial dermis. This extensive involvement indicated aggressive local progression. The epidermis showed irregular acanthosis with hyper- and parakeratosis. Foci of chronic inflammation were observed, as well as some figures of mitosis. Inclusion bodies were not found, as expected in digitocutaneous dysplasia. Cells mainly expressed desmin, but also expressed alpha-smooth muscular actin, intracytoplasmic beta-catenin, and vimentin, negative to CD99 and CD34 (Table 2).

Fig. 6 **a** Right hand X-ray. **b** Left foot X-ray

Extirpated lesions had not recurred after 4 months. In contrast to digital fibromatosis, excisional surgery does not cause aggressive recurrence of lesions [13]. The rest of the lesions maintained the same size, causing the same functional limitation as before surgery.

We tried a fourth therapeutic line with local cryotherapy on the third toe of the right foot and the fourth finger of the left hand. Liquid nitrogen was applied several times, under general anesthesia, at -40°C for 10 s until lesions were

totally covered (Fig. 7). Unfortunately, this option was not effective and the lesions remained of the same size.

After 20 months of observation from the last treatment, which was cryotherapy, digital lesions appeared to be less aggressive and less disabling. Partial regression has been observed as the patient has grown up. We conclude that time appears to be an effective treatment for digitocutaneous dysplasia. Digital lesions appear to be less aggressive as the patient grows up.

Table 2 Histological findings in fibromas associated with digitocutaneous dysplasia

A. Fusiform cells arriving to superficial dermis. Epidermic irregular acanthosis with hyper- and parakeratosis	B. Proliferation of cells with fascicular shape, surrounding skin structures	C. Cells with elongated nucleus, without atypia. There are no inclusion bodies	D. Masson's trichrome stain: collagenized stroma without inclusion bodies	E. Fusiform cells positive to desmin

Fig. 7 Cryotherapy on the third toe of the right foot

Discussion

The pathology of digitocutaneous dysplasia is currently described as a syndrome of X-linked dominant transmission, and it is lethal in XY embryos [1, 11]. Bacino et al. [2] published a family series of four generations with ten affected women. In 2000, Breuning et al. [6] reported a girl affected by digitocutaneous dysplasia whose mother presented with recurrent digital fibromas. Because all these published patients were female, we conclude that genetic transmission follows a genetic pattern linked to X for various reasons. Only women are affected and there is suspected mortality in males. Studies of X inactivation show minimal involvement in carrier patients [3, 31].

In 2000, Zhang et al. [31] found the genetic representation in Xq27.3-Xqter. In 2010, Sun et al. [28] found that the FLNA gene is responsible for this digitocutaneous syndrome, or terminal osseous dysplasia, with skin involvement. Mutation of the FLNA gene might produce multiple clinical alterations and syndromes. Our patient presented with the specific defined mutation, c.5217G>A, in the FLNA gene [28], which confirmed the clinical and histological suspicion of digitocutaneous dysplasia.

Histological findings from our patient included characteristics as strictly defined above [9, 20]. In brief, in digital fibromatosis, eosinophilic inclusion bodies are systematically found, which are not found in lesions associated with digitocutaneous dysplasia [15]. Moreover, digitocutaneous dysplasia presents with fibroblastic cells that are clearly

positive for desmin. Additionally, fibroblastic cells are positive for alpha-smooth muscular actin, vimentin, CD10, and beta-catenin (but only intracytoplasmic). In contrast, cells do not express CD34, CD99, or CD117. These findings are similar to those by Drut et al. [9], with the exception of actin. While Drut et al. describe that cells in digitocutaneous dysplasia are negative for alpha-smooth muscle actin, we found a positive response in our patient. In summary, in the current study, although there were multiple histochemical stains that were positive in this pathology, the most characteristic of these was desmin. All of these histochemical considerations are summarized in Table 3.

Differential diagnosis of digitocutaneous dysplasia may be difficult, and it is always important to consider other pathologies, such as Gorlin–Goltz syndrome (skin focal hypoplasia) [10], Proteus syndrome, and type I neurofibromatosis. Other differential diagnoses include focal facial skin dysplasia [29], Setleis syndrome [27], fibrosarcoma, Koenen tumor, and juvenile hyaline fibromatosis.

Ishii et al., Laskin et al., and Niamba et al. [14, 20, 24] observed that isolated digital fibromas have a higher average recurrence when operated on than when conservatively treated, with up to 47 % of complications and 73 % recurrence in Laskin's series. Excision surgery is only recommended when pain or functional limitations exist [16]. Holmes et al. [12] observed that in digital fibromatosis, the risk of recurrence is higher when operating than when applying intralesional corticoids, but this finding was not significant ($p=0.3$). They concluded that recurrence is more aggressive with the first treatment.

Niamba et al. [24] described that in some cases, fibromas associated with digital fibromatosis regress spontaneously after some time of observation. There are some reports on the autoresolution of these digital fibromas [1, 4, 8, 14], but none of these patients suffered from digitocutaneous dysplasia. In our patient, partial regression occurred, but there was no total resolution.

Oh et al. [25] published excellent results obtained with local fluorouracil infiltration in a patient with digital fibromatosis. They obtained total resolution without recurrence with five injections. We decided not to proceed with this treatment because of the possible adverse effects and the lack of scientific and statistical evidence.

Table 3 Histochemical findings in fibromas associated with digitocutaneous dysplasia

	Inclusion bodies [11, 27]	Alpha-smooth actin muscular [12, 27]	Vimentin [6]	Desmin	CD10 [12]	Beta-catenin [12] [6]	CD34 [6]	CD99, CD117 [12]
Digital fibromatosis	+	+	+	+ [12]	+	+	?	+
Digitocutaneous dysplasia	–	Slightly +	+	+++	+	Nucleus –, cytoplasm +	–	–

Conclusions

Histological study of digital lesions clearly differentiates the two pathologies of infantile digital fibromatosis from digitocutaneous dysplasia. Infantile digital fibromatosis presents with eosinophilic inclusion bodies, while dysplasia does not. The latter pathology presents with a characteristic positivity for desmin.

Currently, the final diagnosis of digitocutaneous dysplasia is confirmed by genetic study of the FLNA gene. Only one mutation has been reported in this gene, causing digitocutaneous dysplasia, and it was found in our patient. Therefore, molecular testing for the FLNA gene in case of clinical suspicion of digitocutaneous dysplasia is highly recommended. The FLNA gene is located in the Xq28 region and codifies filamin A, a cytoprotein of cytoskeleton.

Digital fibromatosis and digitocutaneous dysplasia are different pathologies [12, 13]. Digital fibromatosis responds to intralesional corticoids [12] and has a high average recurrence with surgical extirpation. Digitocutaneous dysplasia does not respond aggressively to excision. Digitocutaneous dysplasia presents with a minimum response to multiple treatments, subsiding partially with time. Further studies are required to find an appropriate treatment for this infrequent pathology.

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Conflict of Interest All authors declare that they have no conflicts of interest, commercial associations, or intent of financial gain regarding this research.

References

1. Azam SH, Nicholas JL. Recurring infantile digital fibromatosis: report of two cases. *J Pediatr Surg*. 1995;30:89–90. PMID: 7722838.
2. Bacino CA, Stockton DW, Sierra RA, et al. Terminal osseous dysplasia and pigmentary defects: clinical characterization of a novel male lethal X-linked syndrome. *Am J Med Genet*. 2000;94:102–12.
3. Baroncini A, Castelluccio P, Morleo M, et al. Terminal osseous dysplasia with pigmentary defects: clinical description of a new family. *Am J Med Genet A*. 2007;143 A:51–7. PMID: 17152064.
4. Beckett JH, Jacobs AH. Recurring infantile digital tumor of childhood: a review. *Pediatrics*. 1977;59:401–6.
5. Bloem JJ, Vuzevski VD, Huffstadt AJC. Recurring digital fibroma of infancy. *J Bone Joint Surg Br*. 1974;56B:746–51.
6. Breuning MH, Oranje AP, Langemeijer RA, et al. Recurrent digital fibroma, focal dermal hypoplasia, and limb malformations. *Am J Med Genet*. 2000;94:91–101.
7. Brunetti-Pierri N, Lachman R, Lee K, et al. Terminal osseous dysplasia with pigmentary defects (TODPD): follow-up of the first reported family, characterization of the radiological phenotype, and refinement of the linkage region. *Am J Med Genet Part A*. 2010;152A:1825–31.
8. Dabney KW, MacEwen GD, Davis NE. Recurring digital fibrous tumor of childhood: case report with long-term follow-up and review of the literature. *J Pediatr Orthop*. 1986;6:612–7. PMID: 3760175.
9. Drut R, Pedemonte L, Rositto A. Noninclusion-body infantile digital fibromatosis: a lesion heralding terminal osseous dysplasia and pigmentary defects syndrome. *Int J Surg Pathol*. 2005;13:181–4.
10. Goltz RW, Peterson WC, Gorlin RJ, et al. Focal dermal hypoplasia. *Arch Dermatol*. 1962;86:708–17.
11. Guadagnini E, Durango A, Perich L. Fibromatosis digital infantil. *Derm Venez*. 1995;33:135–7.
12. Holmes WJM, Mishra A, McArthur P. Intra-lesional steroid for the management of symptomatic infantile digital fibromatosis. *J Plast Reconstr Aesthet Surg*. 2010;64:632–7.
13. Horii E, Sugiura Y, Nakamura R. A syndrome of digital fibromas, facial pigmentary dysplasia, and metatarsal disorganization. *Am J Med Genet*. 1998;80:1–5.
14. Ishii N, Matsui K, Ichiyama S, et al. A case of infantile digital fibromatosis showing spontaneous regression. *Br J Dermatol*. 1989;121:129–33.
15. Izadpanah A, Hogeling M, Buka RL, et al. Digitocutaneous dysplasia. *J Am Acad Dermatol*. 2007;56:S6–9.
16. Kang SK, Chang SE, Choi JH, et al. A case of congenital infantile digital fibromatosis. *Pediatr Dermatol*. 2002;19:462–3.
17. Kanwar AJ, Kaur S, Thami GP, et al. Congenital infantile digital fibromatosis. *Pediatr Dermatol*. 2002;19:370–1.
18. Kawaguchi M, Mitsuhashi Y, Hizumi Y, et al. A case of infantile digital fibromatosis with spontaneous regression. *J Dermatol*. 1998;25:523–6.
19. Kokitsu-Nakata NM, Antunes LF, Guion-Almeida ML. Terminal osseous dysplasia and pigmentary defects in a Brazilian girl. *Am J Med Genet A*. 2008;146A:2698–700.
20. Laskin W, Miettinen M, Fetsch J. Infantile digital fibroma/fibromatosis a clinicopathologic and immunohistochemical study of 69 tumors from 57 patients with long-term follow-up. *Am J Surg Pathol*. 2009;33:1–13.
21. Lin BP, Lin MI, Bericoher WC. Clinical manifestations of terminal osseous dysplasia and pigmentary defects in a young girl. *Oral Surg Oral Med Oral Pathol Radiol Endod*. 2003;95:607–13.
22. Lister G. Reconstruction of the hypoplastic thumb. *Clin Orthop Relat Res*. 1985;95:52–65.
23. Manske PR, Goldfarb CA. Congenital failure of formation of the upper limb. *Hand Clin*. 2009;25:157–70.
24. Niamba P, Léauté-Labrèze C, Boralevi F, et al. Further documentation of spontaneous regression of infantile digital fibromatosis. *Pediatr Dermatol*. 2007;24:280–4.
25. Oh CK, Son HS, Kwon YW, et al. Intralesional fluoracil injection in infantile digital fibromatosis. *Arch Dermatol*. 2005;141:549–50.
26. Reye RD. Recurring digital fibrous tumor of childhood. *Arch Pathol*. 1965;80:228–31.
27. Setleis H, Kramer B, Valcarcel M, et al. Congenital ectodermal dysplasia of the face. *Pediatrics*. 1963;32:540–8.
28. Sun Y, Almomani R, Aten E, et al. Terminal osseous dysplasia is caused by a single recurrent mutation in the FLNA gene. *Am J Hum Genet*. 2010;87:146–53.
29. Tay SC, Moran SL, Shin AY, et al. The hypoplastic thumb. *J Am Acad Orthop Surg*. 2006;14:354–66.
30. Wells JM, Weedon D. Focal facial dermal dysplasia or aplasia cutis congenita: a case with a hair collar. *Australas J Dermatol*. 2001;42:129–31.
31. Zhang W, Amir R, Stockton DW, et al. Terminal osseous dysplasia with pigmentary defects maps to human chromosome Xq27.3-qxqter. *Am J Hum Genet*. 2000;66:1461–4.