Case Report

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New insights on fibrodysplasia ossificans progressiva: discussion of an autoptic case report and brief literature review

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SUMMARY Fibrodysplasia ossificans progressiva (FOP) is a rare genetic condition with soft tissue progressive ossification, leading to severe disability. We describe a 27-years-old female affected by FOP who died after a fall. An autopsy was performed. Upper and lower extremities resulted in fixed flexion, with kyphoscoliosis of the spine and chest wall deformity. Moreover, a cranial fracture was pointed out. At histology, atypical abundance of *corpora amylacea* in gray matter was observed. In a sample of macroscopically non-affected muscular tissue, small areas with necrosis of myocytes and hyperplasia of fibroblasts were seen in light microscopy, with intracellular inorganic dystrophic inclusions in transmission electron microscopy. Thyroid gland histology showed diffuse lymphocytic infiltration. Postmortem examination of FOP patients provided precious information about involvement of other tissues, suggesting an initial and widespread inflammatory/dystrophic phase, to be further investigated, because it might reveal new insights about a FOP mutation cascade.

Keywords fibrodysplasia ossificans progressiva, thyroiditis, fibrosis, *corpora amylacea*, transmission electron microscopy

1. Introduction

Fibrodysplasia ossificans progressiva (FOP) is a rare (1/2,000,000 inhabitants) autosomal dominant disorder, characterized by progressive bone formation in soft tissues, due to the mutation of the activin receptor 1/activin receptor-like kinase 2 (ACVR1/ALK2, c.617 G>A, R206H) gene encoding for bone morphogenetic protein type-1 Receptor (BMPR1) (*1-5*). The hyperactivity and widespread dysregulation of the downstream bone morphogenetic protein (BMP) signaling pathway, mainly due to the receptor alteration, causes progressive heterotopic ossification of soft connective tissues (*6,7*). Heterotopic ossification in FOP patients takes place in two phases: inflammation and destruction of connective tissues (phase 1) and bone formation (phase 2). This is further divided into three sub-stages: fibroproliferation and angiogenesis (2A), chondrogenesis (2B), and osteogenesis (2C) (*8*). Moreover, bone morphogenetic proteins, as pleiotropic growth factors, have also important functions in cell proliferation, migration and differentiation. The ossification of muscles, tendons, ligaments and other connective tissues, in association with congenital skeletal malformations, leads to a severe reduction of joint mobility and therefore to severe disability (*9*). Literature data reports a median age of death of 40 years (*3,10*). The most frequently causes of death in FOP patients are thoracic insufficiency syndrome, recurrent respiratory infections or accidental traumas.

The aim of this study is to present postmortem findings in a FOP case, which provides novel insights about the FOP pathological picture. We believe in the importance of forensic pathology also from the point of view of a deeper understanding of rare disease's pathophysiology. Indeed, postmortem data, including gross examination and histology, can add essential information to the clinical picture, providing valuable information potentially helpful in the management and treatment of patients (*11*).

2. Case Report

2.1. Patient's history

This case report describes the postmortem findings

of a 27-year-old female affected by FOP. The patient showed mobility limitations since childhood, but the diagnosis was made only at the age of 23, after she underwent orthopedic surgery for right coxo-femoral joint ossification, On this occasion the subject of a myositis ossificans was brought about. No neurological or thyroidal symptoms were reported. No anatomical nor electrocardiographic anomalies were reported. Brain MRI showed a thin T2- and FLAIR-hyperintense and T1-isointense tissue streak, without contrast enhancement, behind the brain bulb, in the foramina of Luschka and along the ventro-lateral margin of the pontine protuberance; a brainstem dysmorphism characterized by a small posterior protrusion of the *tegmentum pontis* and a very slight FLAIR-hyperintensity in the *nuclei dentati*. A genetic test confirmed the diagnosis, with classical R206H mutation. Radiological findings (CT) showed diffuse muscular calcification (Figure 1).

The patient had severe gait impairment, being able to walk only for short distances, with crutches, and she required her parents' aid in almost the totality of daily activities. The subject was found by her parents at the foot of the stairs, with head injuries and blood spread around. A cardiovascular resuscitation procedure was unsuccessfully carried out by rescuers. Due to the unclear circumstances and the report of a fall, a judicial autopsy was ordered.

2.2. Autopsy

2.2.1. External examination

Rigor mortis was difficult to evaluate due to firm rigidity caused by muscle stiffness and joint fixation. The upper extremities were diffusely and hardly fixed in flexion, abduction and intra-rotation, in particular the left elbow joint, which was fixed in flexion at 80°. There was a major head trauma, with a laceration of the scalp in the vertex region. The skull below was extensively fractured. Periorbital hematoma, as well as bruises in the left forearm, in the back side of the left hand and in the right leg, were also observed. Hand arthrogryposis was seen bilaterally. An old linear scar was seen in the right trochanteric region, due to previous hip orthopedic surgery. There was kyphoscoliosis of the spine and major deformity of the chest wall, similar to *pectus carenatus*. Hallux valgus was observed bilaterally.

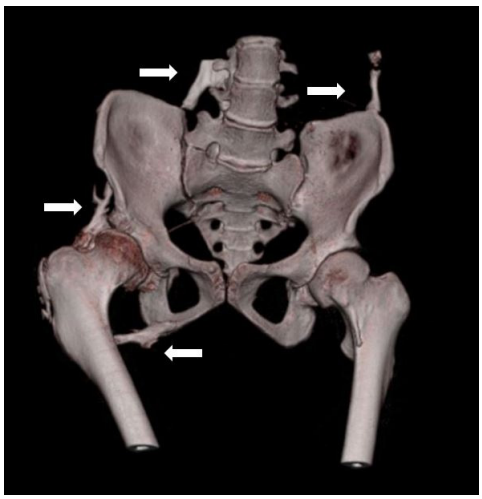

Figure 1. 3D reconstruction of pelvis joint from TC images. White arrows point to diffuse, band-like, ectopic calcifications.

2.2.2. Internal examination

A diastatic median fracture, originating from the vertex and ending next to the *sella turcica*, along the fused metopic suture and across the *anterior fossa cranica*, was observed, together with diffuse subdural and subarachnoid hemorrhage, especially in the cerebellum and around the brainstem. Ogival palate with teeth overcrowding was seen. The thoracic cavity was severely reduced in volume and diverted to the right. The spine was intact, whereas ribs were fractured on both sides (on the right: II, III, IV ribs; on the left: II and III), with hemorrhagic infiltrate. Left pectoralis major muscle's tendon was completely ossified like an accessory rib (0.7 cm in width × 3 cm in length). Both lungs showed some subpleural petechiae, edema and congestion. Heart and liver did not show macroscopic or microscopic alterations. The thyroid gland was macroscopically regular.

2.3. Light microscopy investigation

Tissues were fixed in 10% neutral buffered formalin (formaldehyde solution) for 24 hours. Samples taken from brain, heart, lungs, liver, spleen, kidney, thyroid, ovary, and *quadriceps femoris* muscle were routinely processed and stained with Hematoxylin & Eosin (H&E). Microscopic sections of the brain demonstrated recent cerebral hemorrhage and fields of initial post-mortem autolysis; moreover, in the superficial layer of the cerebral cortex, an abnormally high number of amyloid bodies was observed (Figure 2: A, H&E 200×; B, H&E 400×). Microscopic sections of the lungs showed acute emphysema and endo-alveolar hemorrhage, with areas of edema.

The thyroid gland showed diffuse lymphocytic infiltration, sometimes organized in follicles, and fibrosis (Figure 2: C, H&E 40×; D, H&E 200×). In a histological sample of muscular tissue (right quadriceps femoris), small areas with necrosis of myocytes and hyperplasia of fibroblasts were seen, defining an initial thin fibrosis (Figure 3: A, H&E 100×; B, H&E 200×; C, H&E 200×).

2.4. Transmission Electron Microscopy investigation

To study in depth the muscular histopathologic findings and to investigate possible precocious cellular

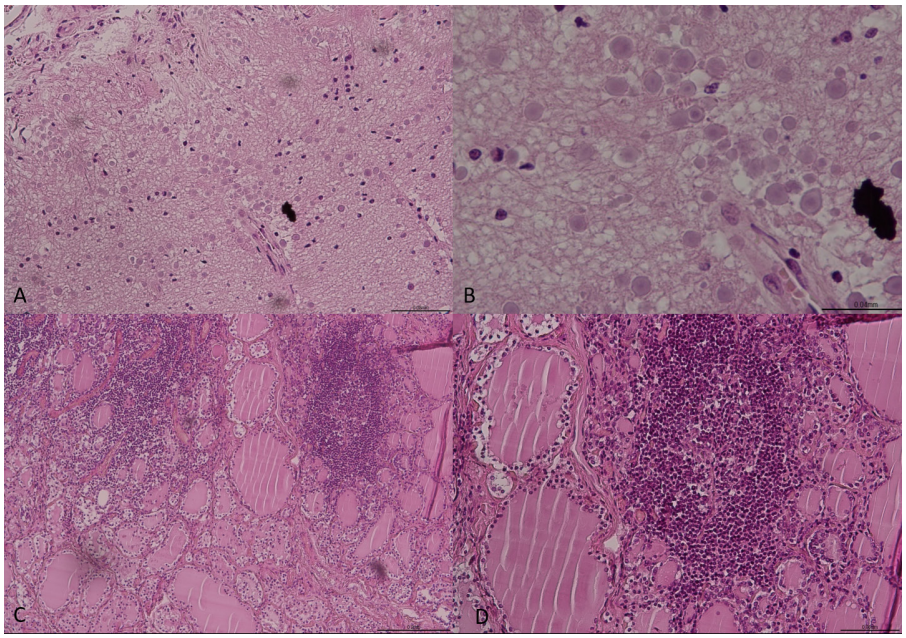

Figure 2. (A) Brain tissue under light microscopy (H&E, 200×): plenty of *corpora amylacea* in the superficial layer of the cerebral cortex. Top left a section of subarachnoid blood vessel; **(B) Brain tissue under light microscopy (H&E, 400×):** plenty of *corpora amylacea* in the superficial layer of the cerebral cortex; **(C) Thyroid under light microscopy (H&E, 40×):** lymphocytic infiltration surrounding follicles, filled with colloid; **(D) Thyroid under light microscopy (H&E, 200×):** detail of the lymphocytic infiltration.

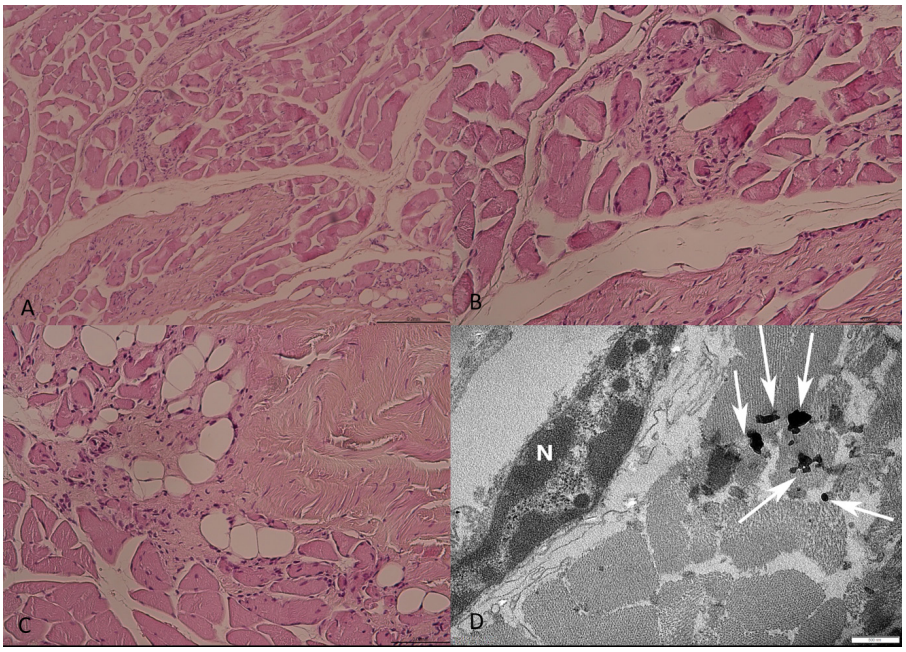

Figure 3. (A) Skeletal muscle (*quadriceps femoris*) under light microscopy (H&E, 100×): field of fibrosis in a contest of myocytes' degeneration. Mild post-mortum dissociation of the tissue; **(B) Skeletal muscle (*quadriceps femoris*) under light microscopy (H&E, 200×):** detail of fibroblast hyperplasia; **(C) skeletal muscle (*quadriceps femoris*) under light microscopy (H&E, 200×):** myocytes' degeneration with fibroblast hyperplasia; **(D) Skeletal muscle (*quadriceps femoris*) transmission electron microscopy in transverse section (18000×):** ultrastructural spatial arrangement of cytoskeletal myofibers, as thick (myosin) and thin (actin) dots. Top left: N for nucleus with nucleoli. In cytoplasm, among myofibers, white arrows point to numerous hyperdense cell's inclusions.

alterations, further ultrastructural analysis was performed on the unharmed quadriceps femoris muscle. Muscular samples were immediately fixed in 4% glutaraldehyde (in 0.1 M Na-cacodylate buffer, pH 7.4) overnight at 4 °C. After post-fixation in 2% osmium tetroxide for 1h, samples were dehydrated in an ethanol series and embedded in resin (Epon 812 mixture). Semi-thin sections were stained with Toluidine blue and observed using an Eclipse 600 microscope (Nikon, Tokyo, Japan) equipped with a TrueChrome II S digital camera system (Tucson Photonics, Fuzhou, China). Ultra-thin sections were stained with uranyl acetate and lead citrate and

observed using a Morgagni 268D TEM, Field Emission Inc, (Philips, Eindhoven, Netherlands) equipped with a Morada digital camera (Olympus, Tokyo, Japan).

In physiological transverse sections the architecture of cytoskeletal proteins and their ultrastructural spatial arrangement are evident and can be seen in Figure 3D (TEM, 18000×) as thick and thin dots, representing thick (myosin) and thin filaments (actin).

In one sample, in transverse section, among myofibers, numerous hyperdense inclusions are seen inside cells (white arrows). Inclusions appear as amorphous, inorganic debris.

3. Discussion

The cause of death of the young woman was identified as a severe head and brain trauma. The fall down the stairs was due to intense and diffuse joint rigidity causing difficulty in walking. The manner of death was classified as accidental.

The first remarkable finding that emerged from the postmortem examination is the abnormally high amount of cerebral amyloid bodies (*corpora amylacea*), absolutely unusual in young individuals. In fact, these amorphous bodies, distributed under the leptomeningeal coat or around blood vessels, are dystrophic inclusions of astrocytes typically found in aged brains, but often also in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, as well as in temporal lobe epilepsy. Similar polyglucosan bodies are found in the nervous tissue of juvenile myoclonic epilepsy, a genetic form of epilepsy called Lafora disease, and in the adult polyglucosan bodies disease (APBD), caused by the alteration of glycogen synthesis and storage (*12-14*). The patient did not show any neurological symptoms, so the clinical significance of the numerous *corpora amylacea* remains unclear. On the contrary, brainstem dysmorphism and FLAIR-hyperintensity in the *nuclei dentati* are consistent with Severino *et al.* findings, suggesting that the ACVR1/ALK2 gene mutation reverberates in the central nervous system (CNS) (*15*). Some other Authors had tried to explain the frequent but non-specific CNS anomalies as focal inflammation and demyelination (*16-18*).

The finding of muscle cell degeneration, with fibroblast hyperplasia, in macroscopically non-affected muscles, may indicate that the disease is in the 1-2A phase (necro-inflammation and fibroblast differentiation) of the endochondral ossification's process. The transmission electron microscopy evaluation reveals the presence of intracellular degenerative inclusions, as hyperdense inorganic dystrophic debris, that could represent foci of early calcification, although not typical of fibroproliferative areas (*19*). Their aspect seems to confirm the light microscopy findings of initial cellular degeneration, in a macroscopically normal muscle.

Future studies are requested to explain why the pathologic process affected only axial skeletal muscles, sparing other skeletal muscles such as the diaphragm, the tongue and the extraocular muscles; on the other hand, it is well known that smooth muscles are not involved. Some authors had also suggested the role of striated muscle microenvironment, with related specific growth factors, and muscle-restricted stem cells, with a peculiar capacity of BMP-dependent osteogenic differentiation in culture. Wosczyna *et al.* identified and characterized a population of Tie2+PDGFRa+Sca-1+ multipotent mesenchymal progenitors, that reside in the skeletal muscle *interstitium* and represent a significant cell-of-origin for heterotopic ossification in the mouse, contributing to all stages of heterotopic ossification, including the pre-cartilage mesenchyme, and suggesting that the recruitment of Tie2+ (angiopoietin receptor) progenitors in the skeletogenic pathway represent an early key event in the induction of heterotopic bone formation (*20,21*). The analysis of this abnormal evolution of soft tissue could be dramatically significative for the prevention of the rigidity and disability.

Moreover, post-natal FOP flare-ups and the variety of inflammatory cells in the FOP lesions strongly implicate an underlying immunological component. This suggests that FOP pathogenesis is more complex and inflammation-related. In fact, BMP and Activin ligands, that interact with ACVR1 signaling, have critical regulatory functions also in the immune system (*22,23*). A new article of Haviv *et al.*, which saw high levels of IL-1β, proposes even the inclusion of FOP in auto-inflammatory syndromes (*24*). The crosstalk between the morphogenetic and immunological pathways thus regulates normal tissue maintenance and wound healing. This *immunological* hypothesis aligns with the identification, even in the absence of clinical symptoms, of lymphocytic thyroiditis, as in all FOP cases described in the report of Wentworth *et al.* It is not fully understood if the ACVR1 mutation and BMP's altered function directly affect immunity regulation, or if chronic inflammation must be a reactive phenomenon of an unknown thyroid alteration, caused by the mutation cascade itself. Interestingly, BMP pleiotropic signaling is also related to papillary thyroid cancer, found in one FOP patient in Wentworth's report and not in the present case, and that BMP is linked with epithelial-mesenchymal transition and cell regulation (*25-27*), as to say that an altered BMP pathway could induce an anomalous proliferation of thyroid cells, recruiting *editing* T lymphocytes (chronic thyroiditis), and eventually leading to neoplasia.

All the classical features of FOP disease, together with atypical features, reported in the literature, are briefly reviewed in Table 1. Among the unusual findings, neurological and thyroid alterations were mentioned and deserve special attention. For Kaplan *et al.* all the classical and common variable features of FOP, as well as many of the atypical features evaluated in his

Table 1. Summary of the features of FOP disease reported in literature

Features	Chile (*n* = 1) (*Ref. 17*)	Colombia (*n* = 2) (*Ref. 29*)	Spain (*n* = 24) (*Ref. 30*)	China (*n* = 72) (*Ref. 1*)	California (*n* = 3) (*Ref. 3*)	Italy (*n* = 1) Our patient
Genetic variant p.R206H on gene ACVR1	1/1	2/2	14/16	70/72	3/3	1/1
Osteo-skeletal abnormalities						
First toe malformation	1/1	2/2	21/24	70/72	3	1/1
Heterotopic ossification	1/1	2/2	24/24	72/72	3/3	1/1
Scoliosis	1/1	2/2	7/24	NR	3/3	1/1
Ankylosis	1/1	NR	2/24	72/72	3/3	1/1
Micrognatia	1/1	2/2	NR	NR	NR	0
Neuronal abnormalities						
White matter anomalies (at MRI)	1/1	NR	NR	NR	1/3	1/1
CNS cancer	NR	NR	NR	NR	0	0
Corpora amylacea	NR	NR	NR	NR	NR	1/1
Neurological symptoms						
Intellectual disability	1/1	2/2	1/24	NR	NR	0
Epilepsy	NR	NR	NR	NR	NR	0
Migraine	NR	NR	NR	NR	2/3	0
Deafness	NR	0	7/24	12/72	0	0
Thyroid alterations						
Lymphocytic thyroiditis	NR	NR	NR	NR	3/3	1/1
Thyroid papillary cancer	NR	NR	NR	NR	1/3	0
Alopecia	0	0	5/24	NR	NR	0
Teeth anomalies	0	2/2	4/24	NR	NR	1/1
Renal agenesia	1/1	NR	NR	NR	0	0
ECG conduction anomalies	NR	NR	NR	NR	NR	0

NR: not reported; 0: not present.

study, could plausibly be ascribed to dysregulation of the ACVR1 signaling pathway, responsible at the very beginning of a widespread dystrophic/dysmorphic phase (*28*).

4. Conclusion

In conclusion, it appears that the influence of mutated ACVR1 is not restricted to soft tissues, and the effects of alteration in this pathway has to be more thoroughly investigated. Forensic studies could significantly improve the comprehension of the disease physiopathology, identifying precocious tissue alterations and allowing earlier diagnosis with better patient management. Thanks to the new law no. 10/2020, FOP patients' body donation in Italy must be encouraged.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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