5° MEETING F.O.P. 5th FOP CONFERENCE

"Verso la Luce"
Opera di Gioacchino Loporchio

POH: Clinical features

U.O. Pediatria - Cerignola (FG)
dr Roberto Bufo
Presidente IPOHA Onlus

POH: DEFINITION

- Progressive osseous heteroplasia (POH) is a rare autosomal dominant developmental disorder of mesenchimal differentiation. Most cases are caused by a GNAS inactivating mutation (20q13.2)
- Is characterized by heterotopic ossification that progresses from skin and subcutaneous tissues into deep connective tissues.
- Finally POH affects muscle fasciae, muscles and tendons and then comes out to be a highly disabling disease.

GENETICS

- Most cases are caused by a ***GNAS inactivating mutation*** with reduced activity of Gsα (20q13.2-q13.3), paternally inherited.
- ***About 35%*** of POH patients ***haven't GNAS mutation*** (*Adegbite 2008*)
- There are some unaffected ♂ people with GNAS mutation, that have POH daughters and AHO grandsons (***mosaicism? non-penetrant carriers?***) (*Shore 2002*)
- The same mutation may cause: PPHP – OC if ***paternally inherited***, or PHPIa if ***maternally inherited***

GENETICS

- Clinic may also be influenced by:
  - "Genomic Imprinting"
  - the levels of other GNAS transcript form (Nesp55, XLαs, A/B)
  - other indipendent modifier genes
  - Adjacent gene

POH: CLINICAL FEATURES

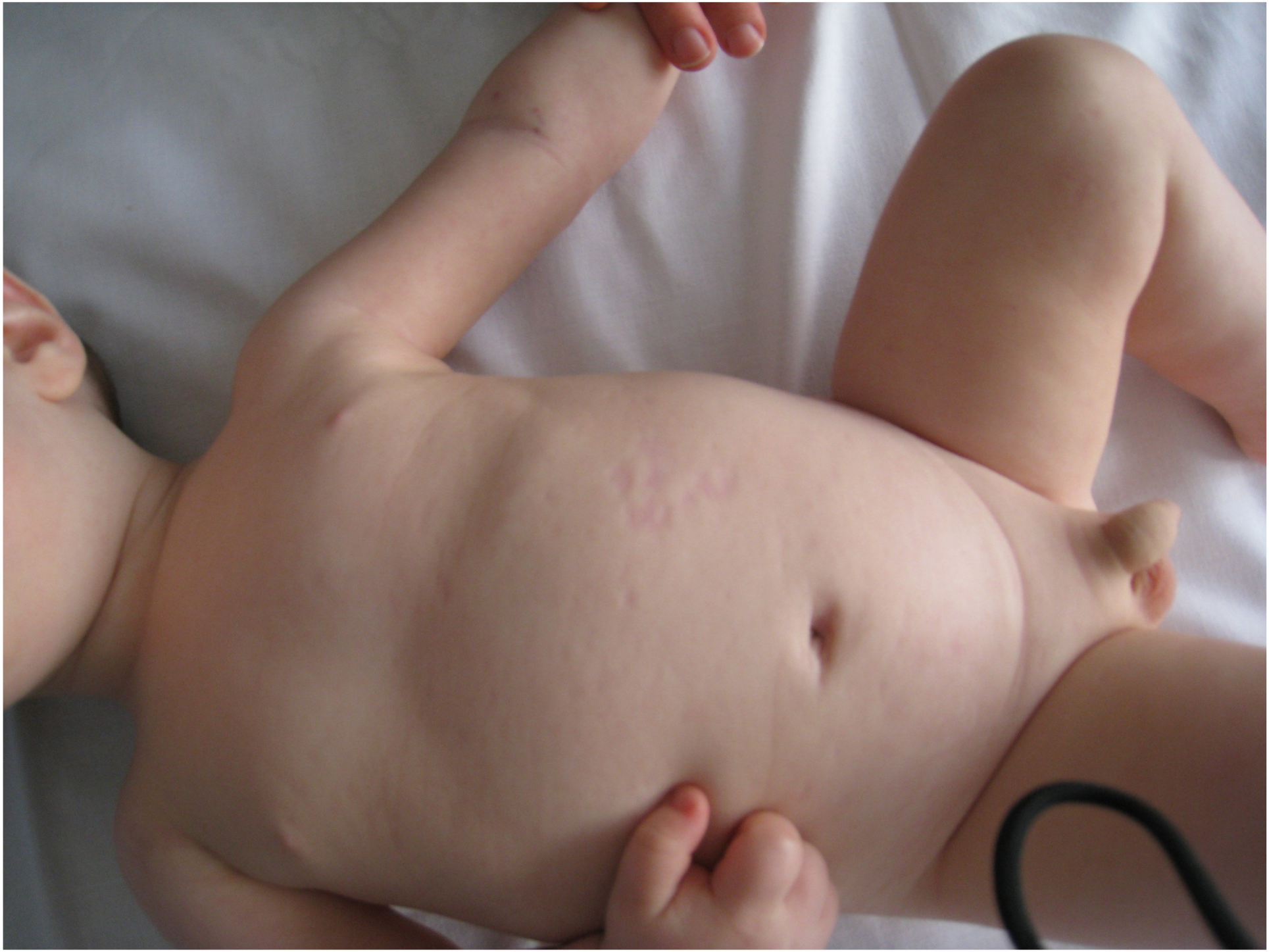
- Present at **birth** or in the first months of life.
- Small hard **rice-grain** nodules often confluent in plaques with a **gritty consistency**, at first skin-like coloured and then yellowish. It's possible an atrophic erythematous rash with some nodules within maculae.
- Asymmetric and random distribution (mosaicism?) Especially on the limbs.
- **Superficial nodules** often extrude some chalk-like material and disappear leaving some not very visible rough scar.
- **Deep nodules** tend to become deeper involving deepest soft tissues, muscles and tendons

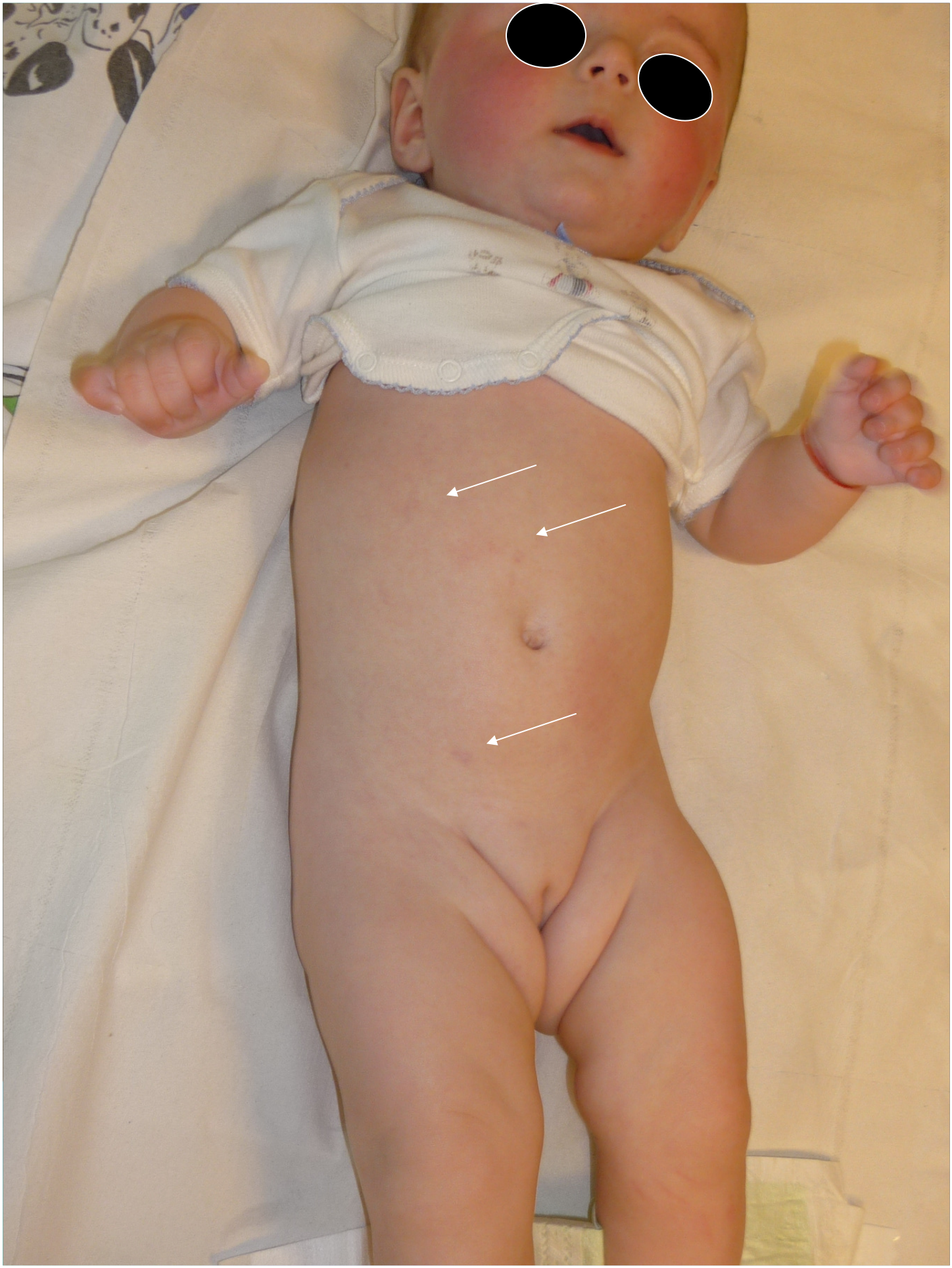
POH: CLINICAL FEATURES

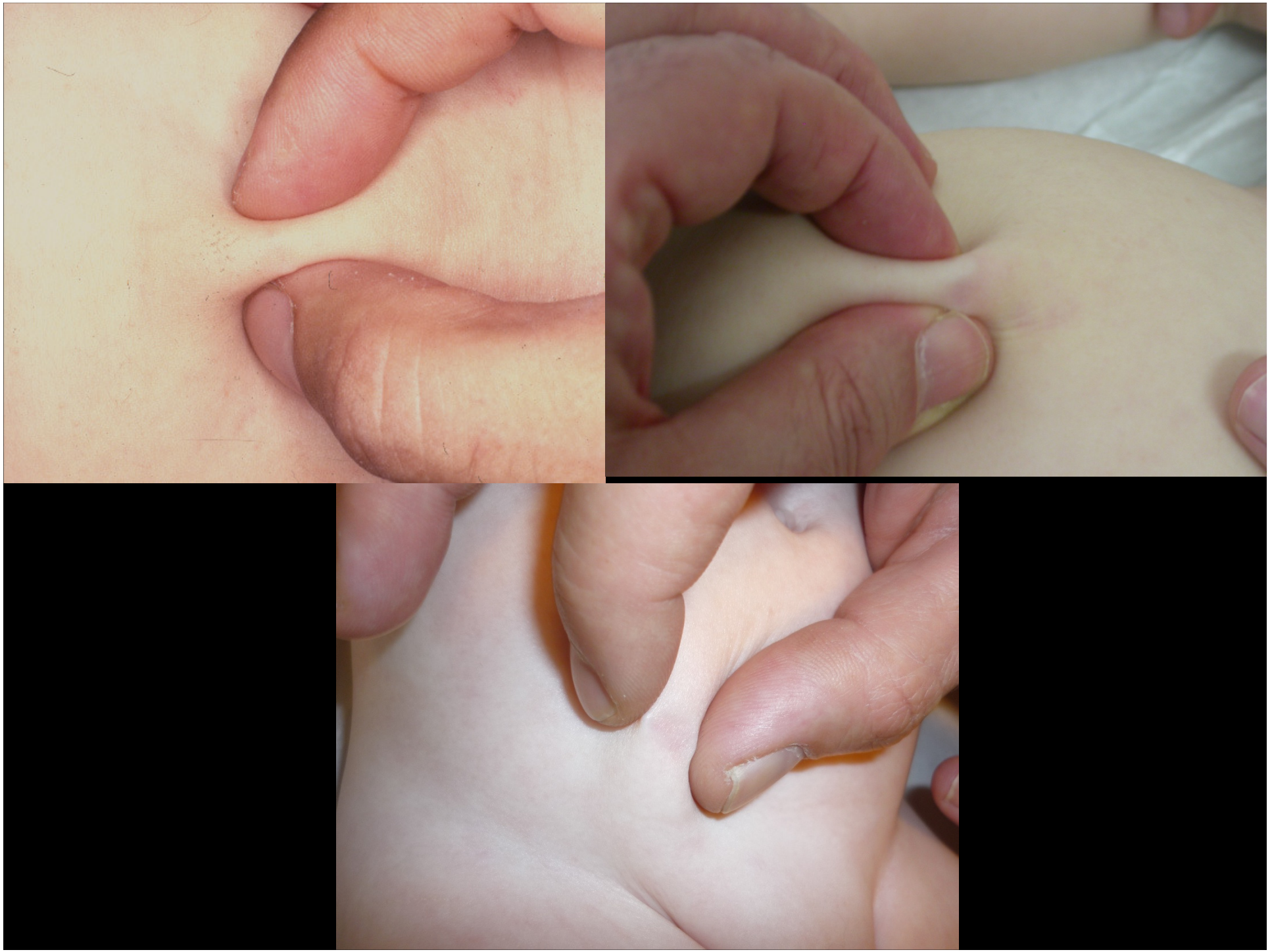
- The ossifications put on a web-like aspect following the vessels and the nerves in their course and giving them a sort of a "cocoon", exoskeleton, generally without never spreading all over them, sometimes breaking off tendons.
- The osseous ramifications close to the joints cross them and make bridges bringing about functional limitations and articular blocks, sometimes causing reduced growth of a limb, with even serious disabling injuries.

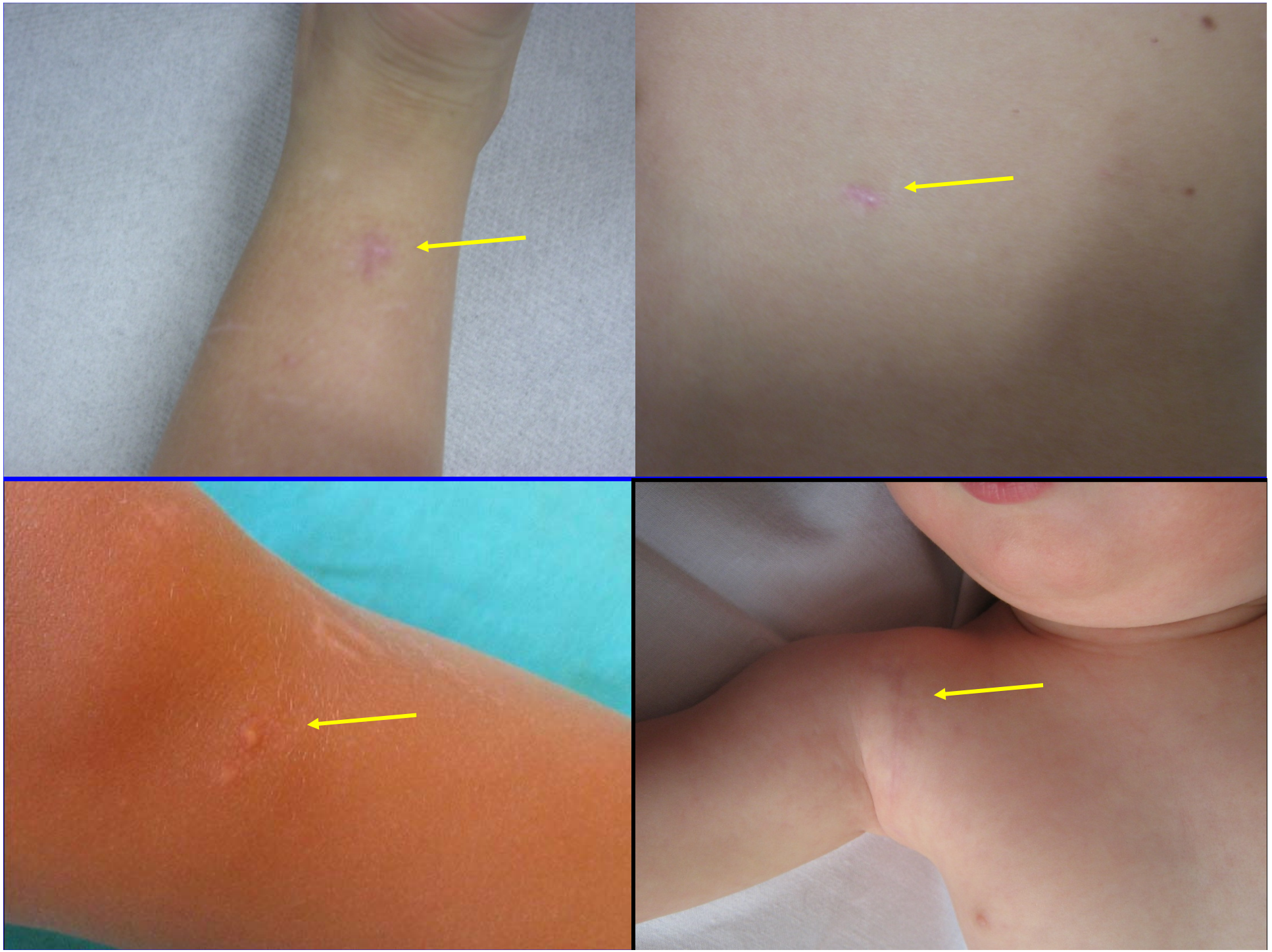
POH: CLINICAL FEATURES

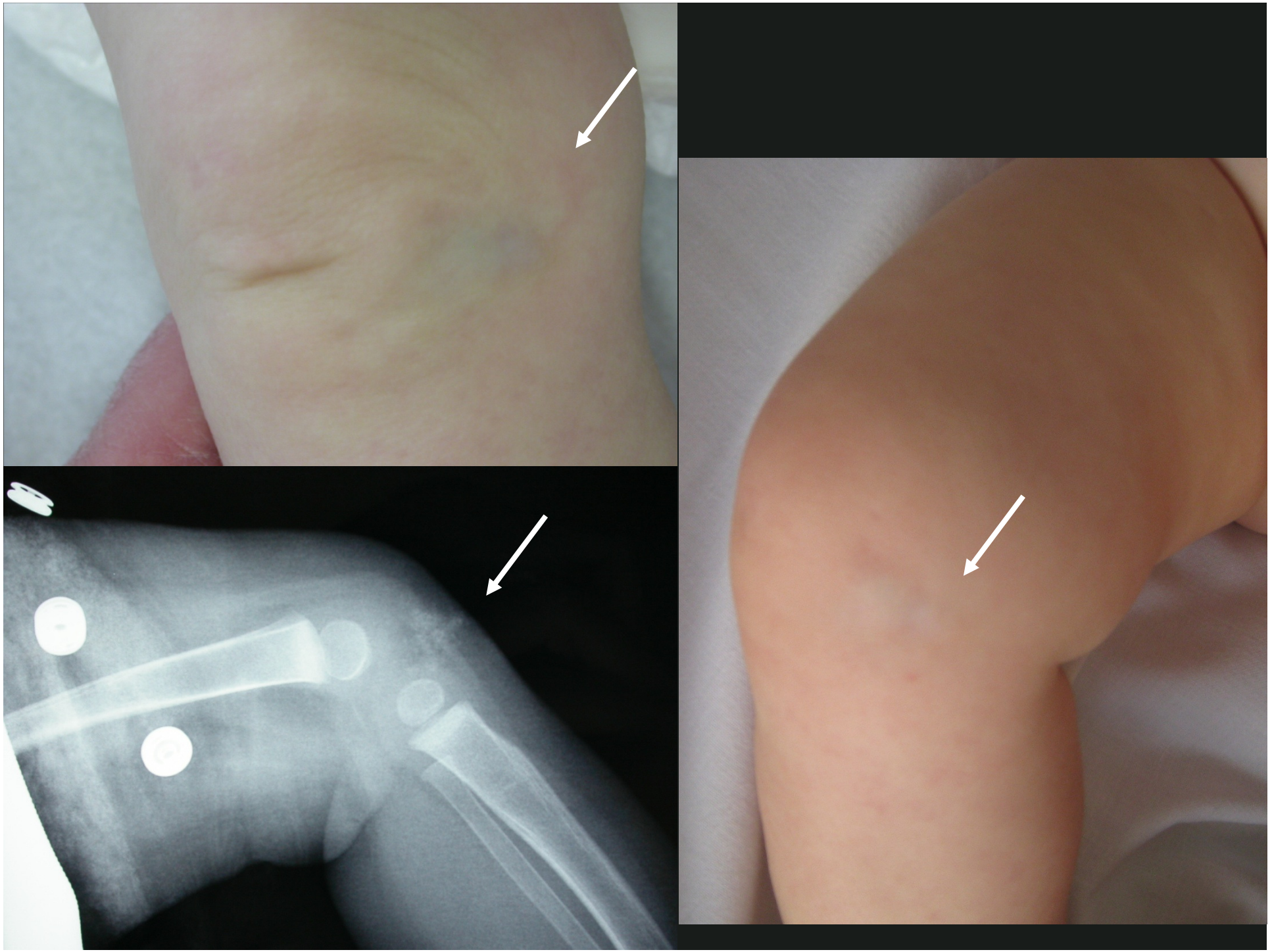
- Typically it is not combined with hormone imbalance or primary malformations of skeletal muscle apparatus or other organs.
- Laboratory findings are always normal.
- POH must be differentiated from other disease with ectopic ossification

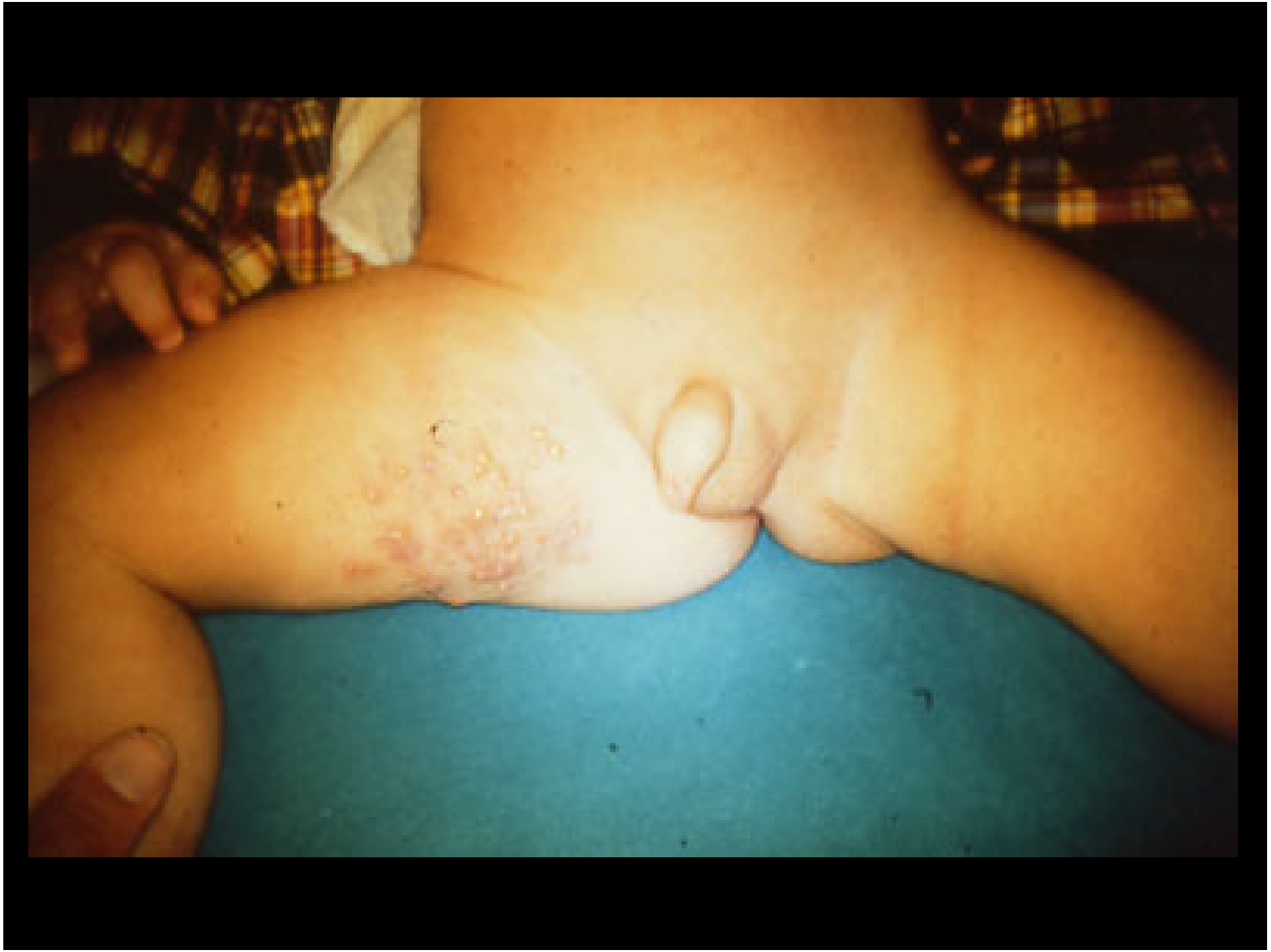


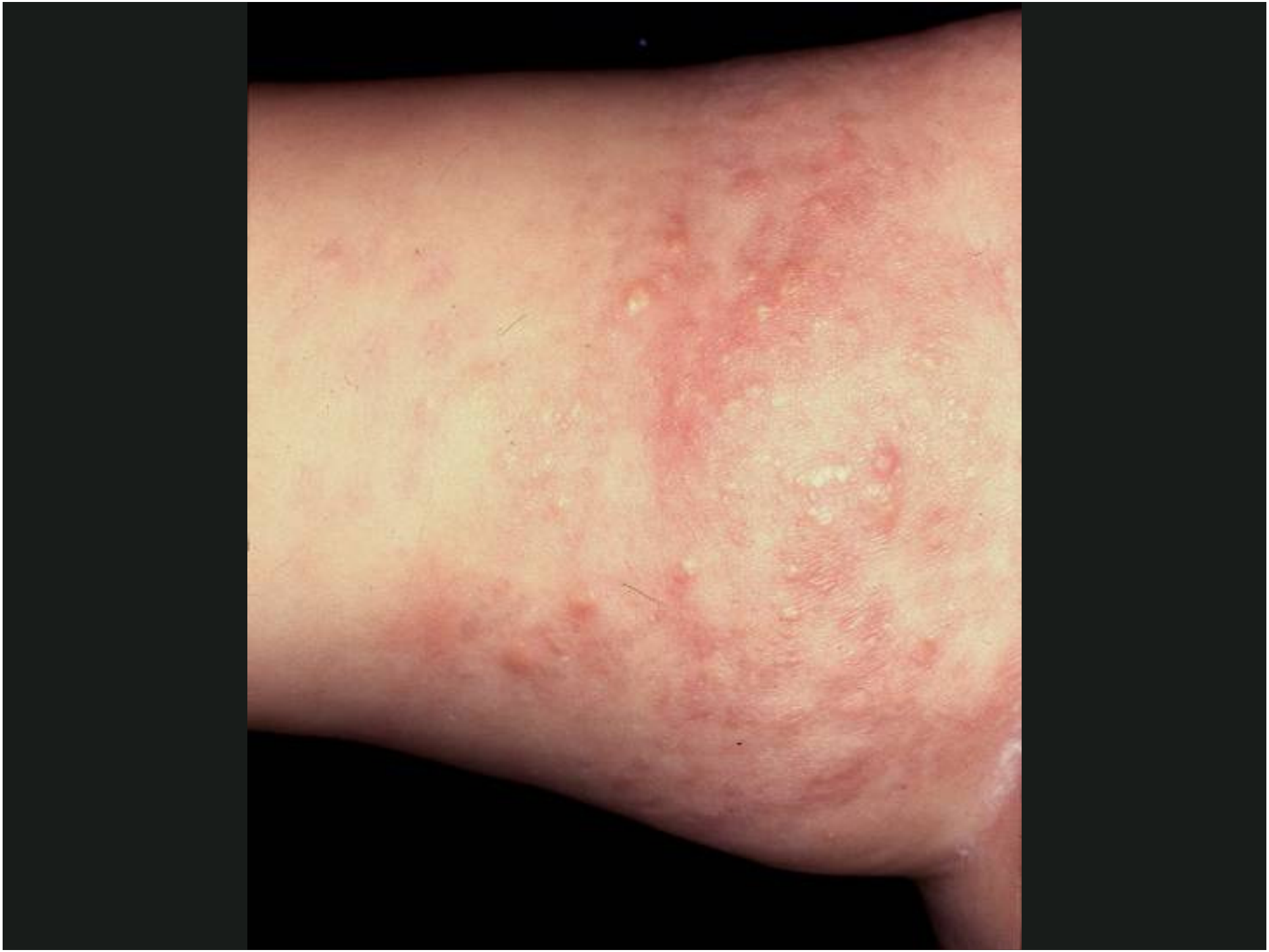








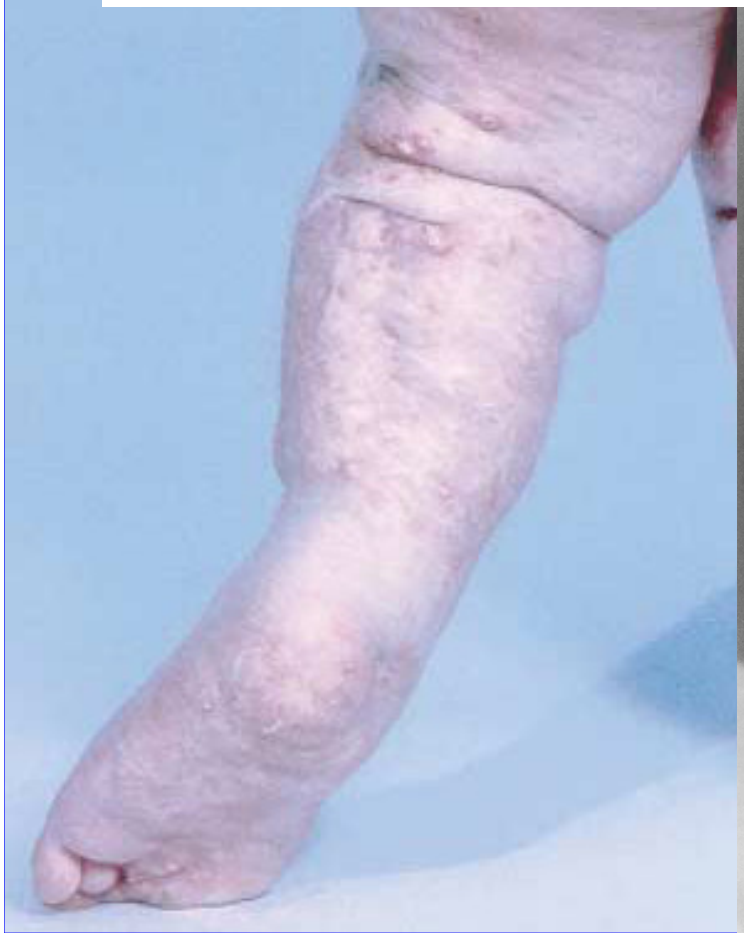


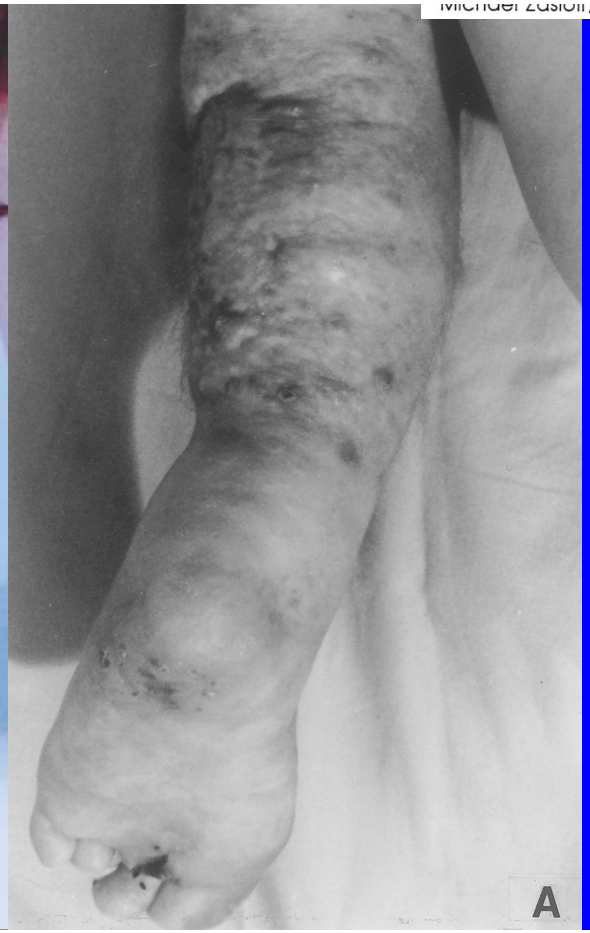


Progressive Osseous Heteroplasia: a Distinct Developmental Disorder of Heterotopic Ossification

Two New Case Reports and Follow-up of Three Previously Reported Cases*

BY FREDERICK S. KAPLAN, M.D.†, PHILADELPHIA, RANDALL CRAVER, M.D.‡, G. DEAN MacEWEN, M.D.‡, NEW ORLEANS, LOUISIANA, FRANCIS H. GANNON, M.D.§, GERALD FINKEL, M.D.§, GREGORY HAHN, B.A.†, JEFFREY TABAS, M.D.†, PHILADELPHIA, R. J. McKINLAY GARDNER, M.B., CH.B.¶, DUNEDIN, NEW ZEALAND, AND MICHAEL A. ZASLOFF, M.D., PH.D.†, PHILADELPHIA, PENNSYLVANIA





Case Report

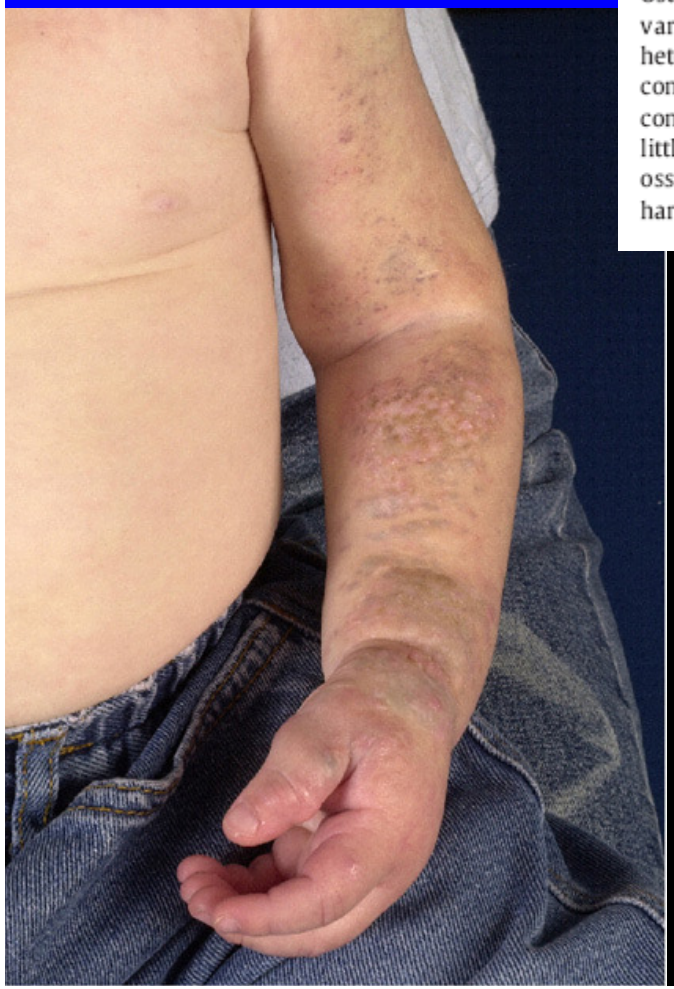
Bone

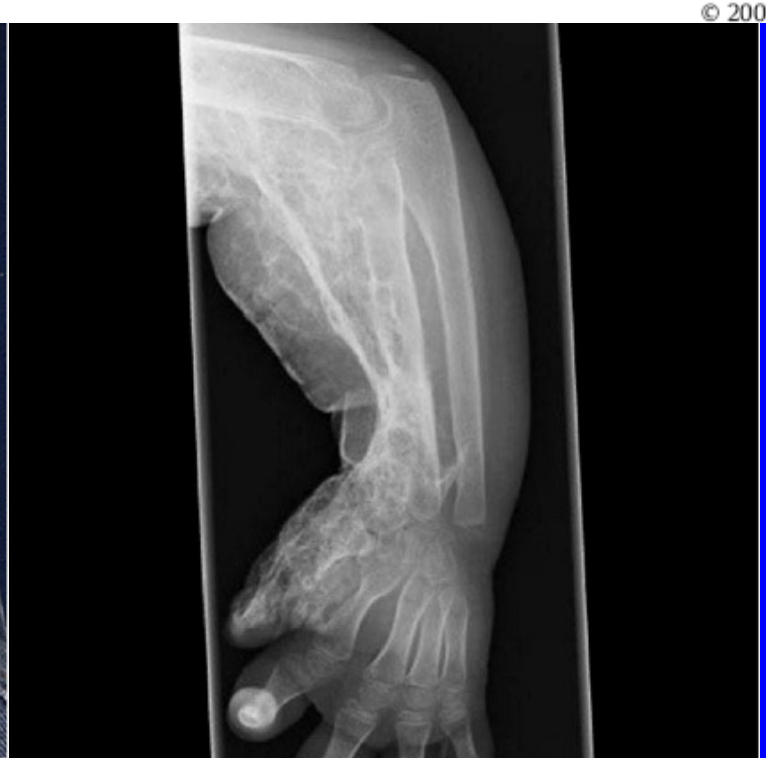
GNAS-associated disorders of cutaneous ossification: Two different clinical presentations

R.J. Schimmel [a,1], S.G.M.A. Pasmans [a,*,1], M. Xu [b], S.A.E. Stadhouders-Keet [c], E.M. Shore [d], F.S. Kaplan [e], N.M. Wulffraat [f]

A B S T R A C T

Progressive osseous heteroplasia (POH) is a rare genetic disorder characterized by dermal ossification during infancy and progressive ossification into deep connective tissue during childhood. POH is at the severe end of a spectrum of *GNAS*-associated ossification disorders that include osteoma cutis and Albright Hereditary Osteodystrophy (AHO). Here we describe two girls who have different clinical presentations that reflect the variable expression of *GNAS*-associated disorders of cutaneous ossification. Each girl had a novel heterozygous inactivating mutation in the *GNAS* gene. One girl had POH limited to the left arm with severe contractures and growth retardation resulting from progressive heterotopic ossification in the deep connective tissues. The other girl had AHO with widespread, superficial heterotopic ossification but with little functional impairment. While there is presently no treatment or prevention for *GNAS*-associated ossification disorders, early diagnosis is important for genetic counselling and for prevention of iatrogenic harm.





Eur J Dermatol 2009; 19 (3): 214-5

Felicidade SANTIAGO
Ricardo VIEIRA
Margarida CORDEIRO
Óscar TELLECHEA
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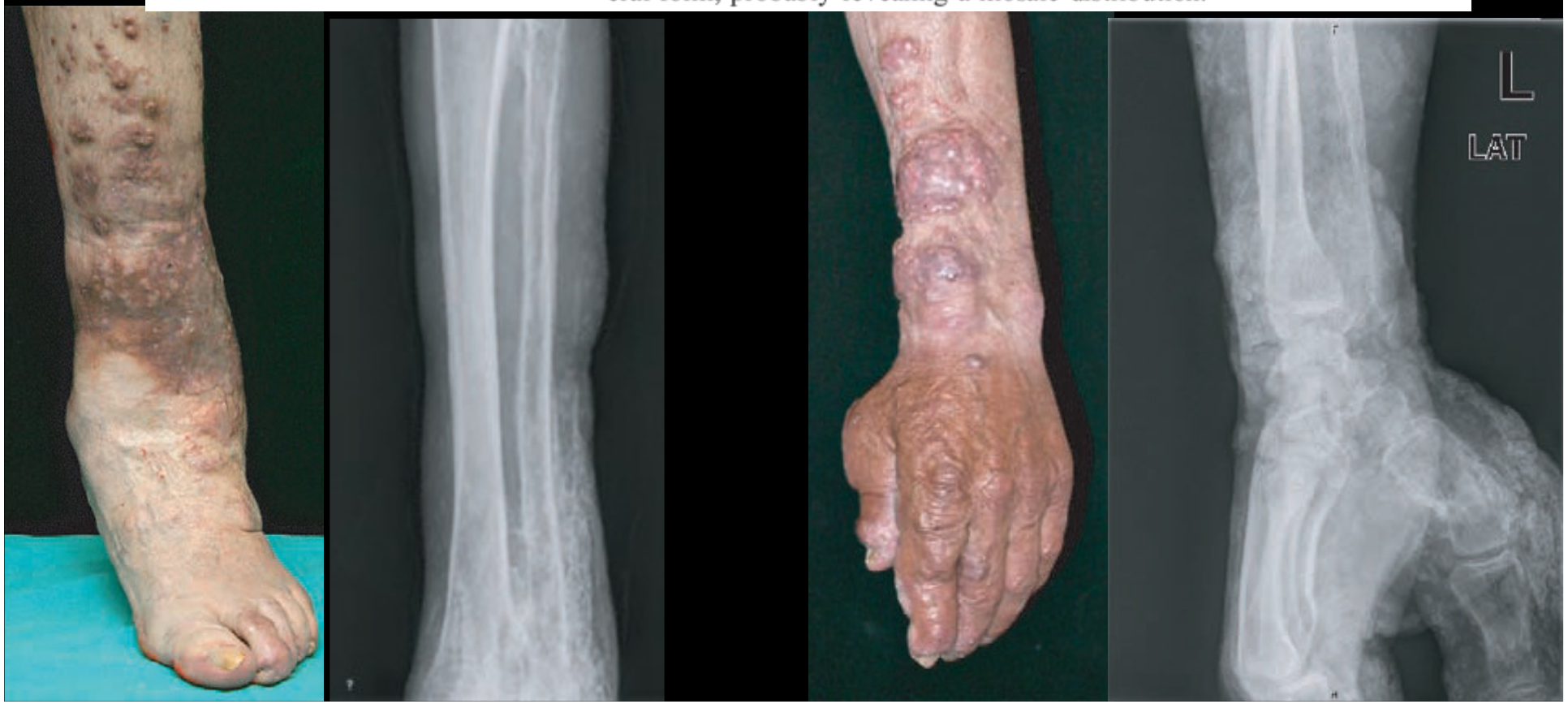
Unilateral progressive osseous heteroplasia

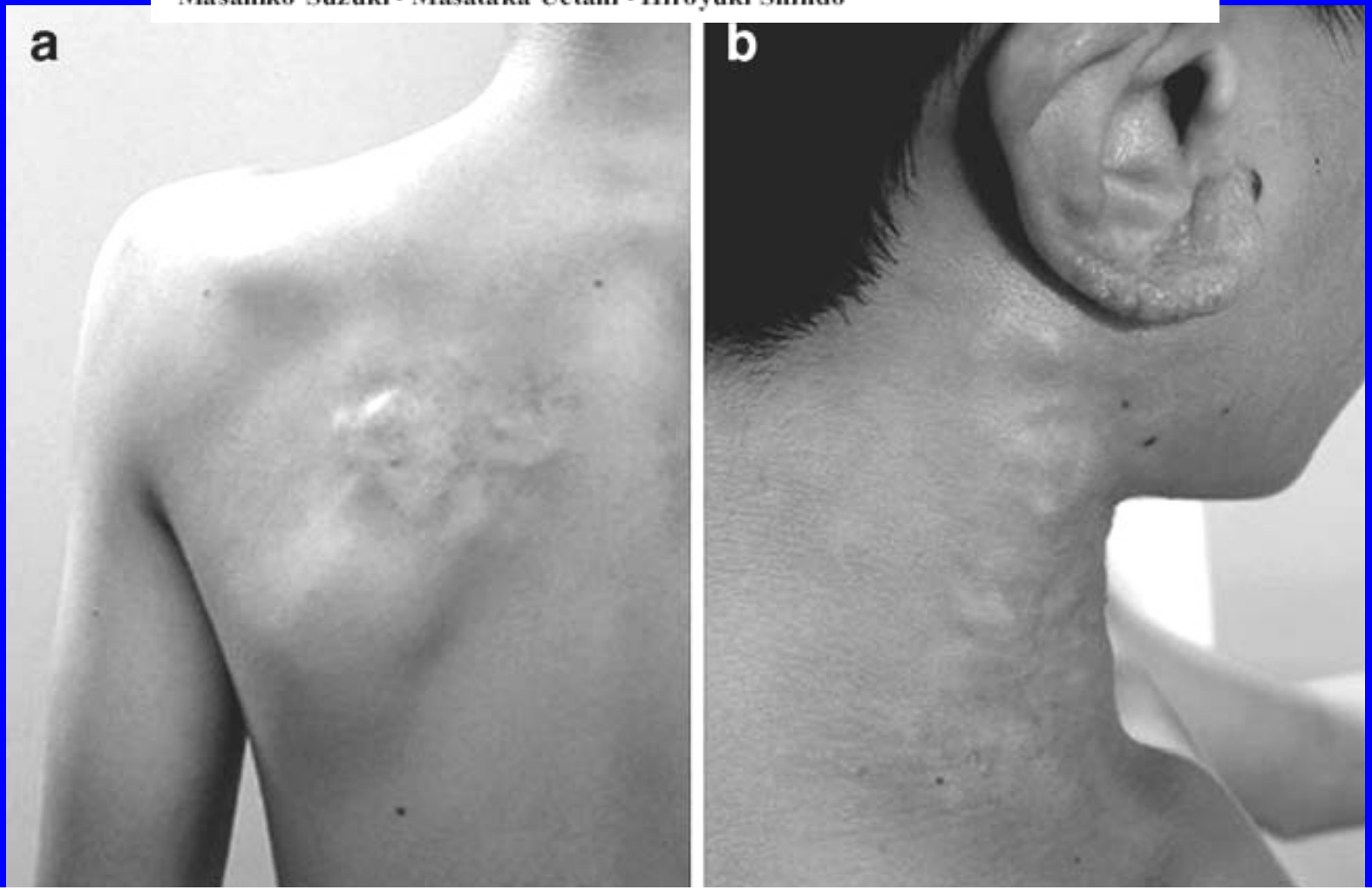
A 50-year-old male patient presented with firm subcutaneous nodules and plaques with a gritty texture, unilaterally affecting the left side of the trunk and the left limbs. These lesions had had a progressive course since early childhood and caused functional impairment. There was no family history of similar disorders. No phospho-calcium metabolism abnormalities were observed. Biopsies of the affected areas demonstrated osteoma cutis. Analysis of DNA showed no mutation of the GNAS gene. The clinical features were consistent with progressive osseous heteroplasia, atypically presented in a unilateral form, probably revealing a mosaic distribution.

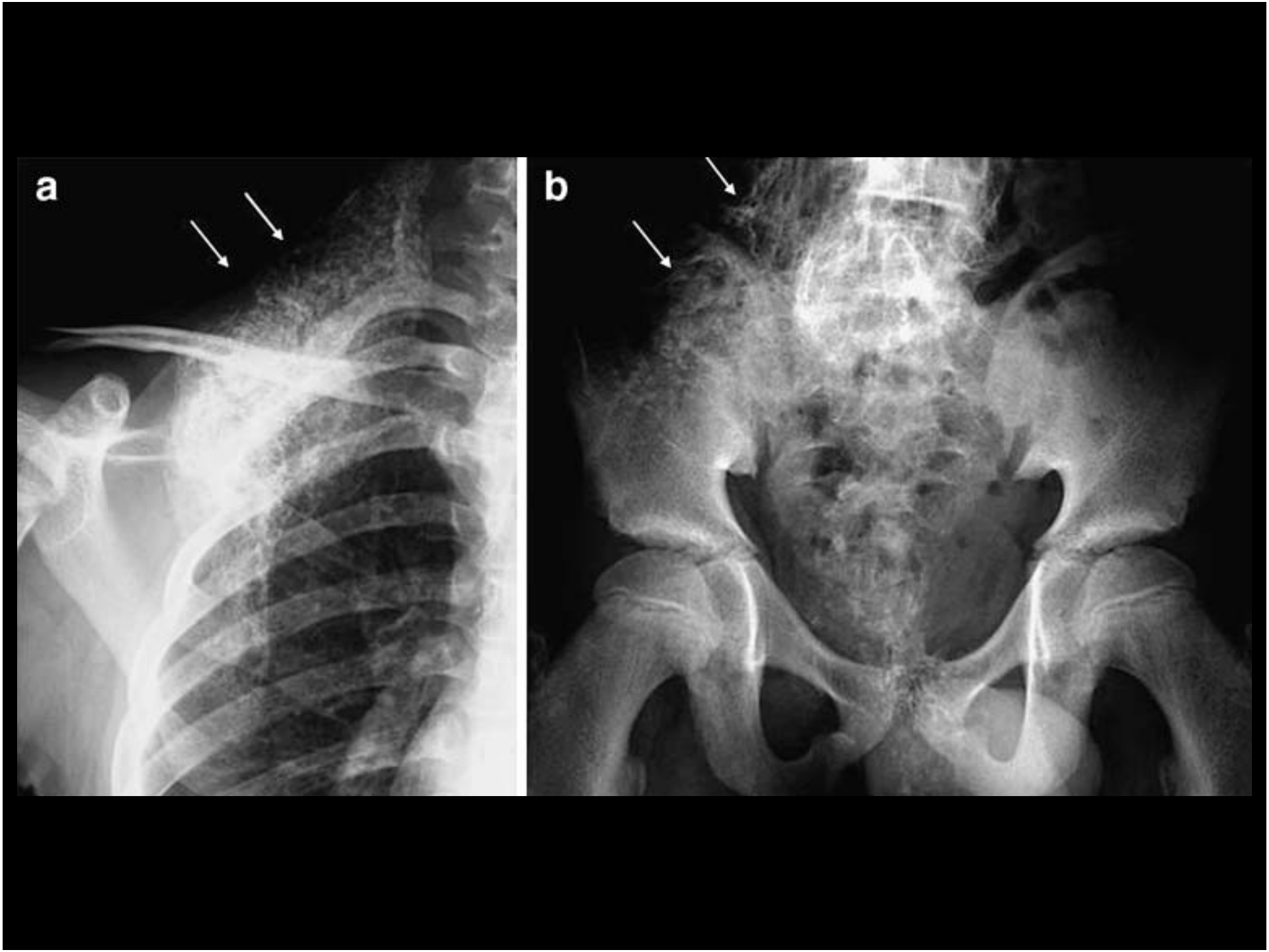


Skeletal Radiol (2008) 37:563–567
DOI 10.1007/s00256-008-0469-9

A case of progressive osseous heteroplasia: a first case in Japan

Kenji Kumagai · Katsuaki Motomura · Masayuki Egashira · Masato Tomita · Masahiko Suzuki · Masataka Uetani · Hiroyuki Shindo




a
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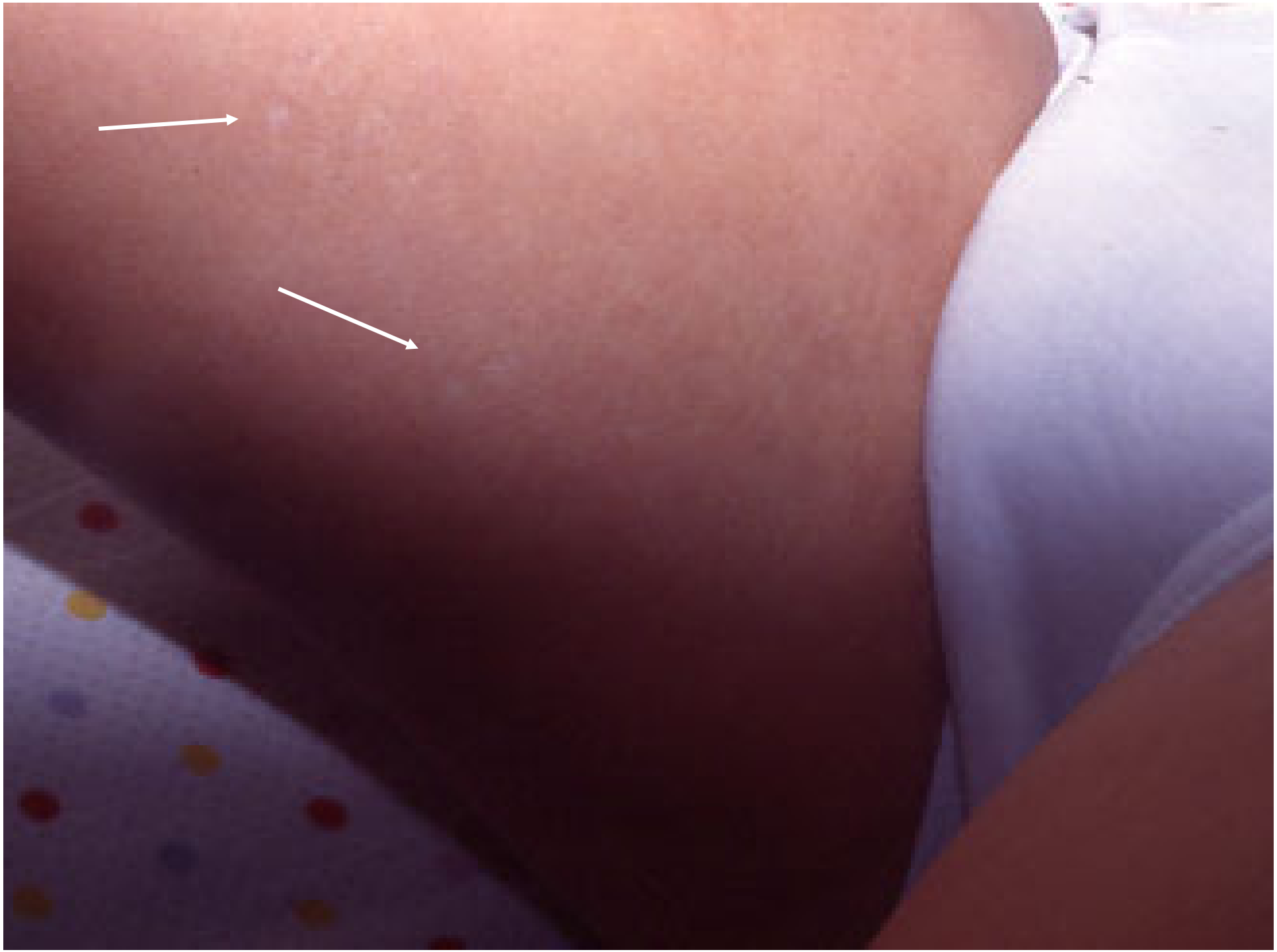
POH: COURSE

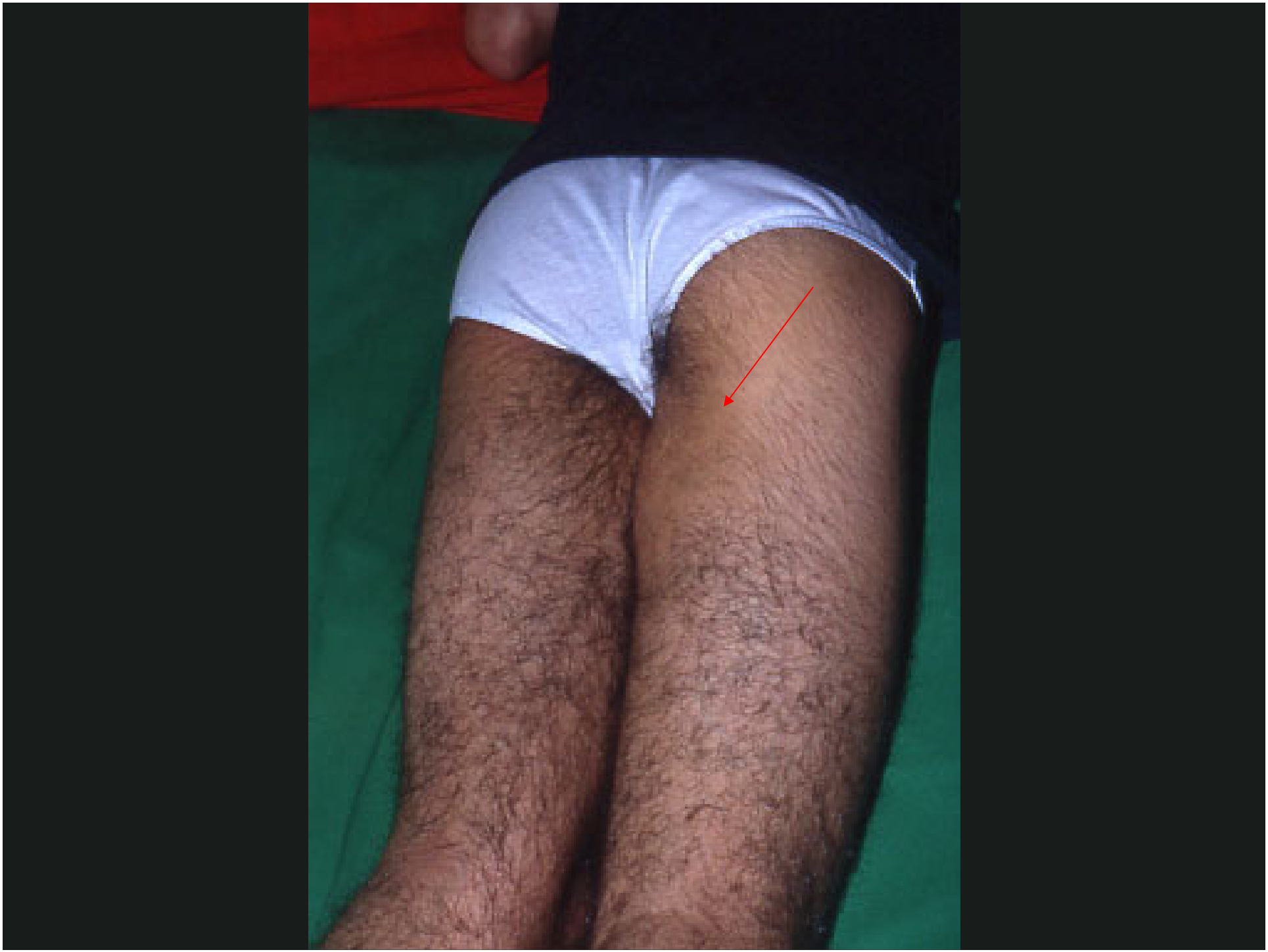
The variable course is characterized by ***alternate phases*** of slower and faster production of ectopic bone, without apparent reasons.

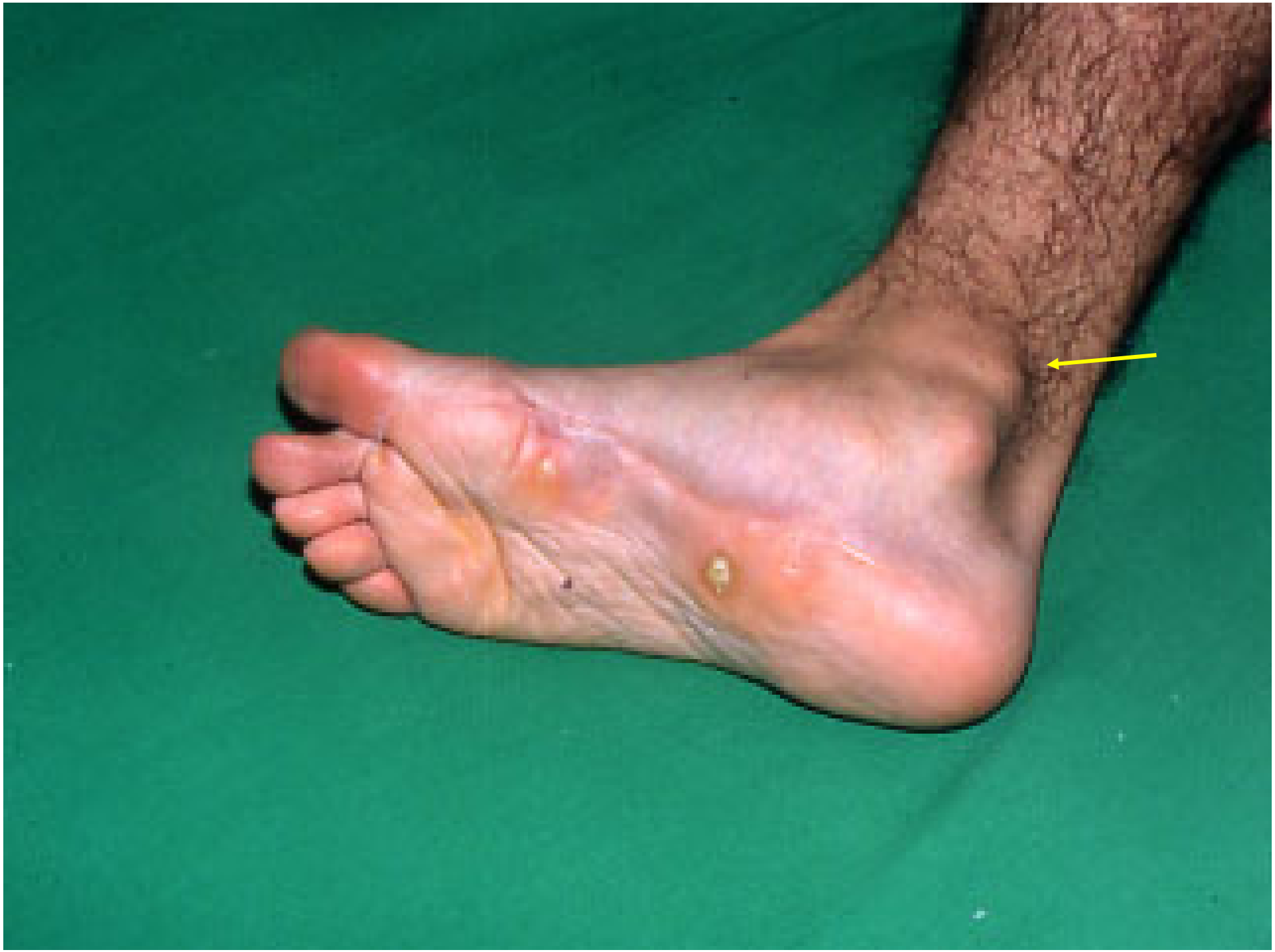
However there are *not* phases of sudden relapse or diffusion as *flare-up* type ossifications.

The course is very slow in ***adulthood***

Sometimes there is ***Pain***, also very hard to treat, caused by pressure of bony formations on surrounding tissues and structures, or when limb growth is blocked.







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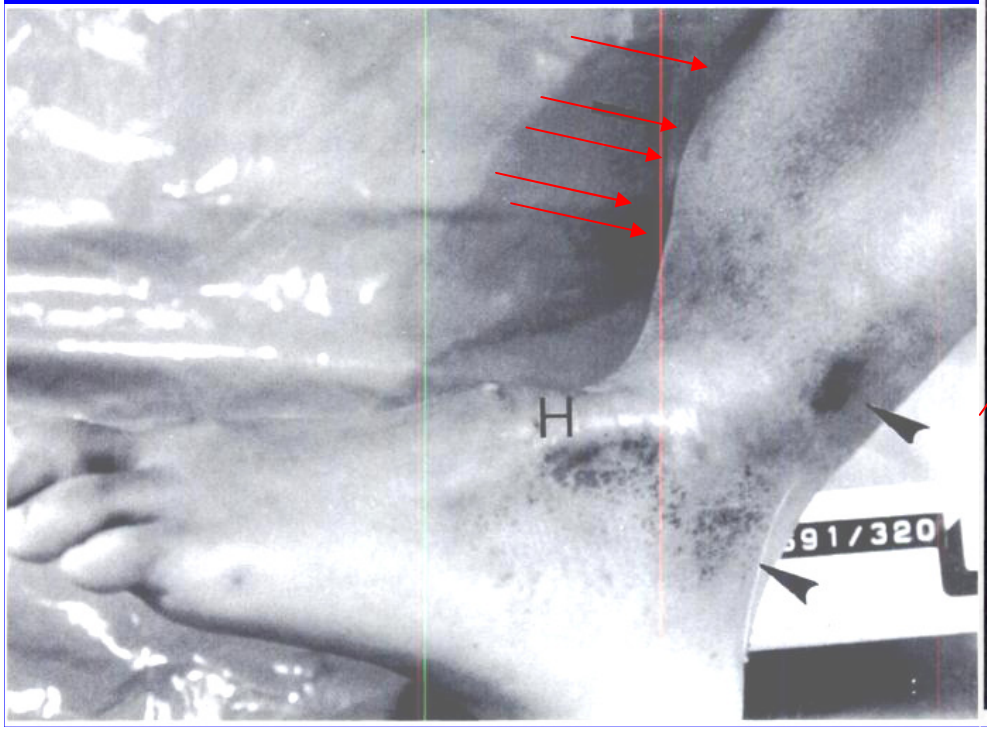
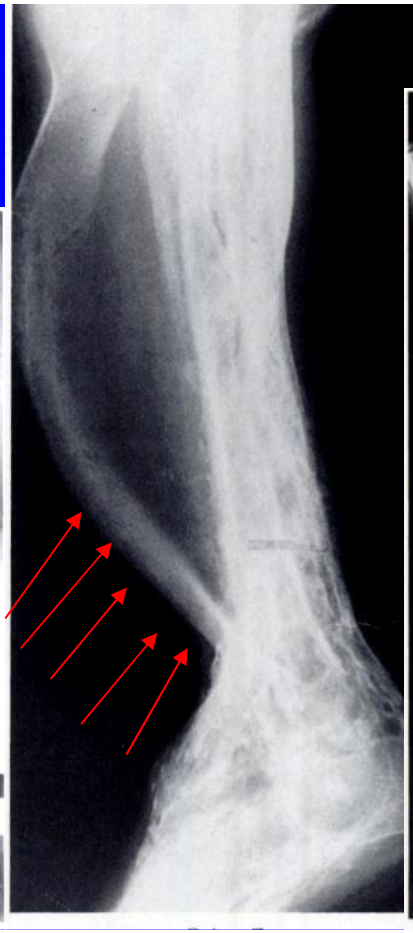
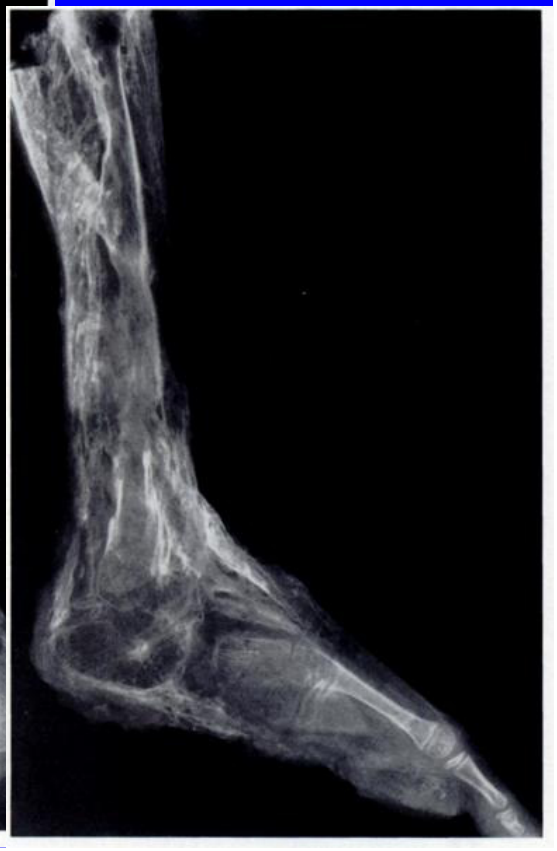






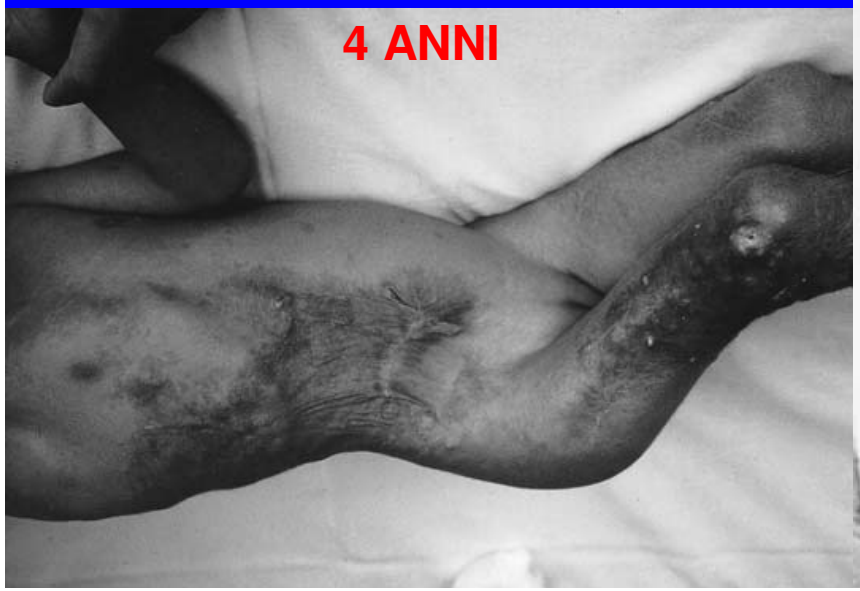
THE JOURNAL OF BONE & JOINT SURGERY (Br)

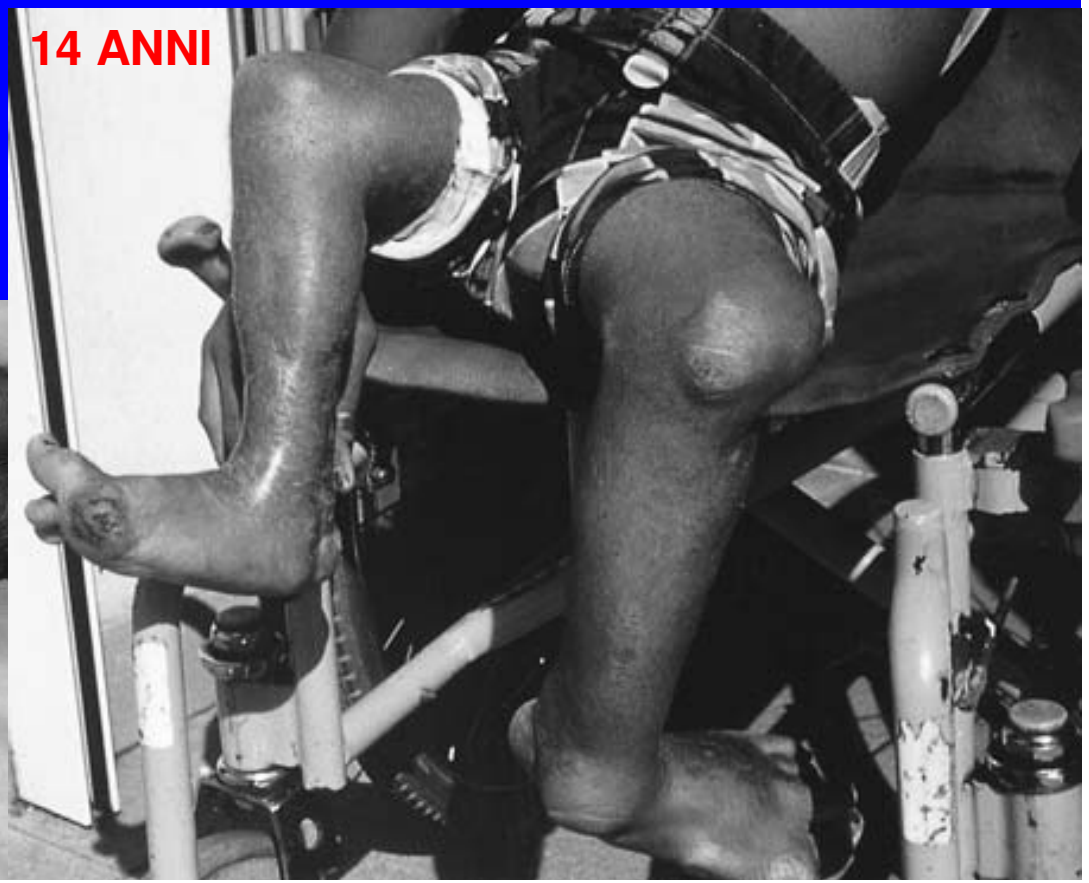
Progressive osseous heteroplasia

REPORT OF A FAMILY

J. Andoni Urtizberea, Hervé Testart, François Cartault, Liliane Boccon-Gibod, Martine Le Merrer, Frederick S. Kaplan

From the Hôpital d'Enfants, St Denis de la Réunion, France

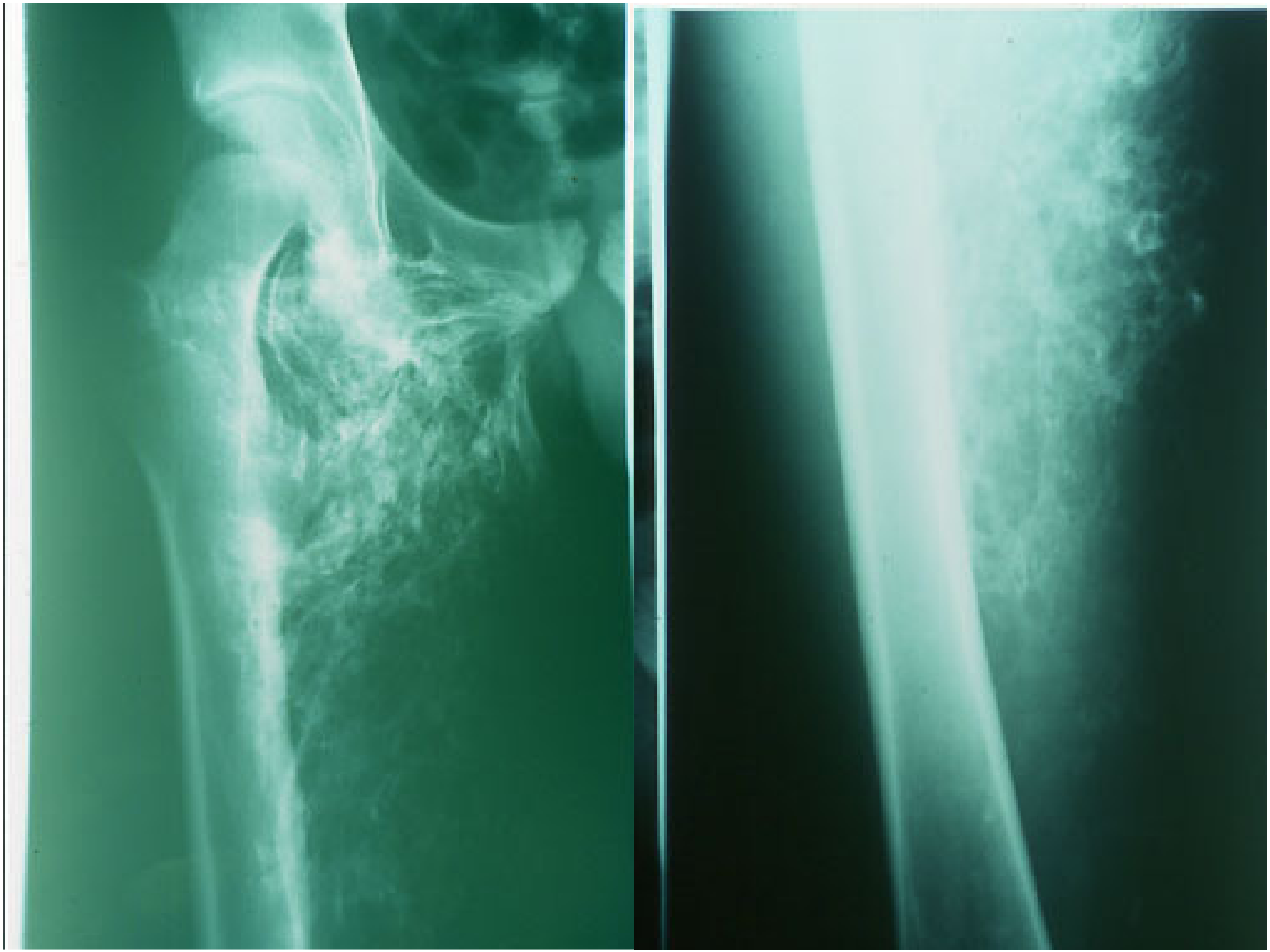


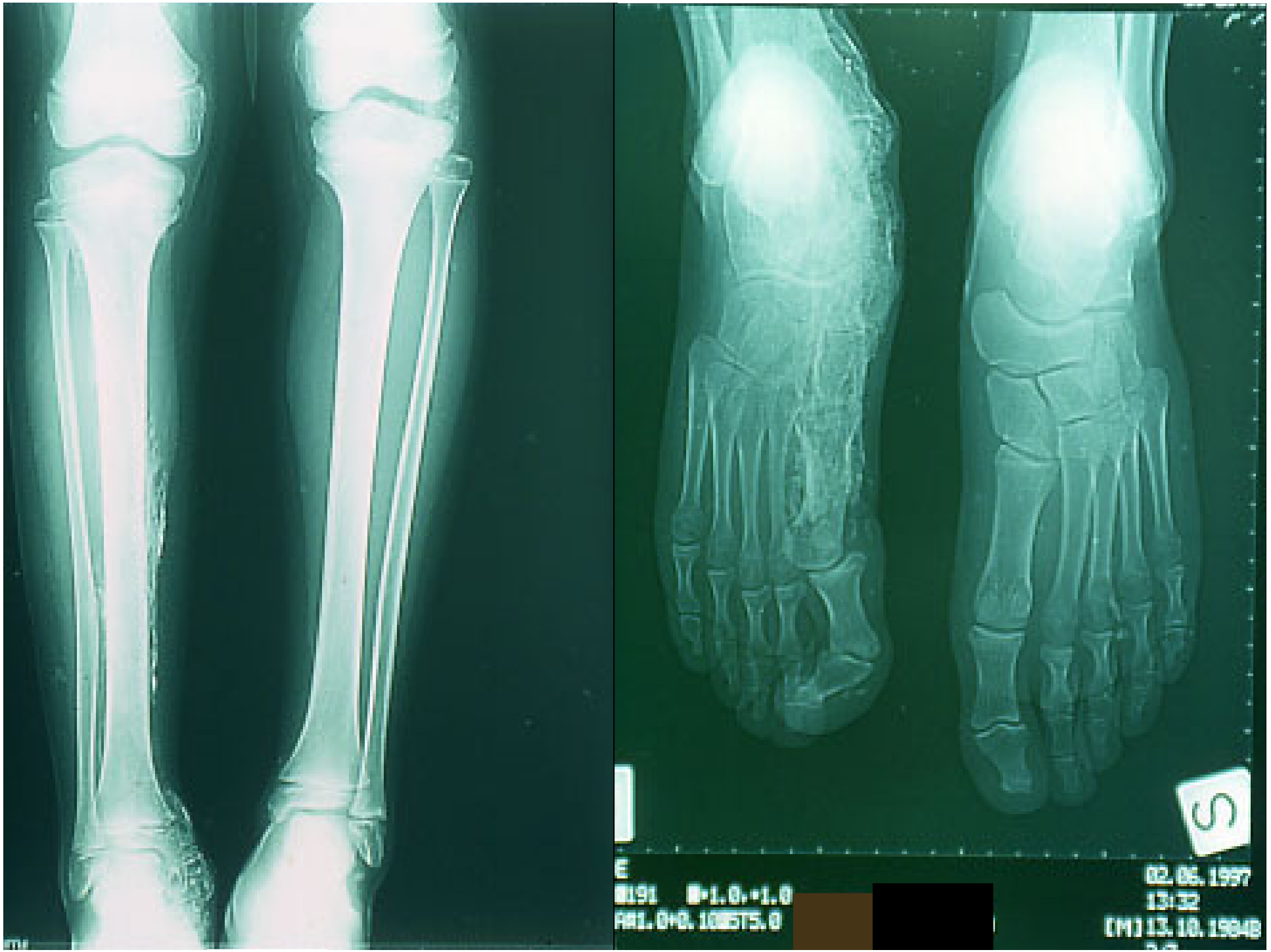


P.O.H. : RADIOLOGY

The radiological aspect is quite characteristic.

- The bone formations put on a ***web-*** or ***lace-like*** aspect, sometimes vaguely lacunar, full of gaps, corresponding to those "***vine shoots***" that become deeper in the tissues following neurovascular-connective bundle seen at macroscopic examination.
- <u>Secondary</u> deformity

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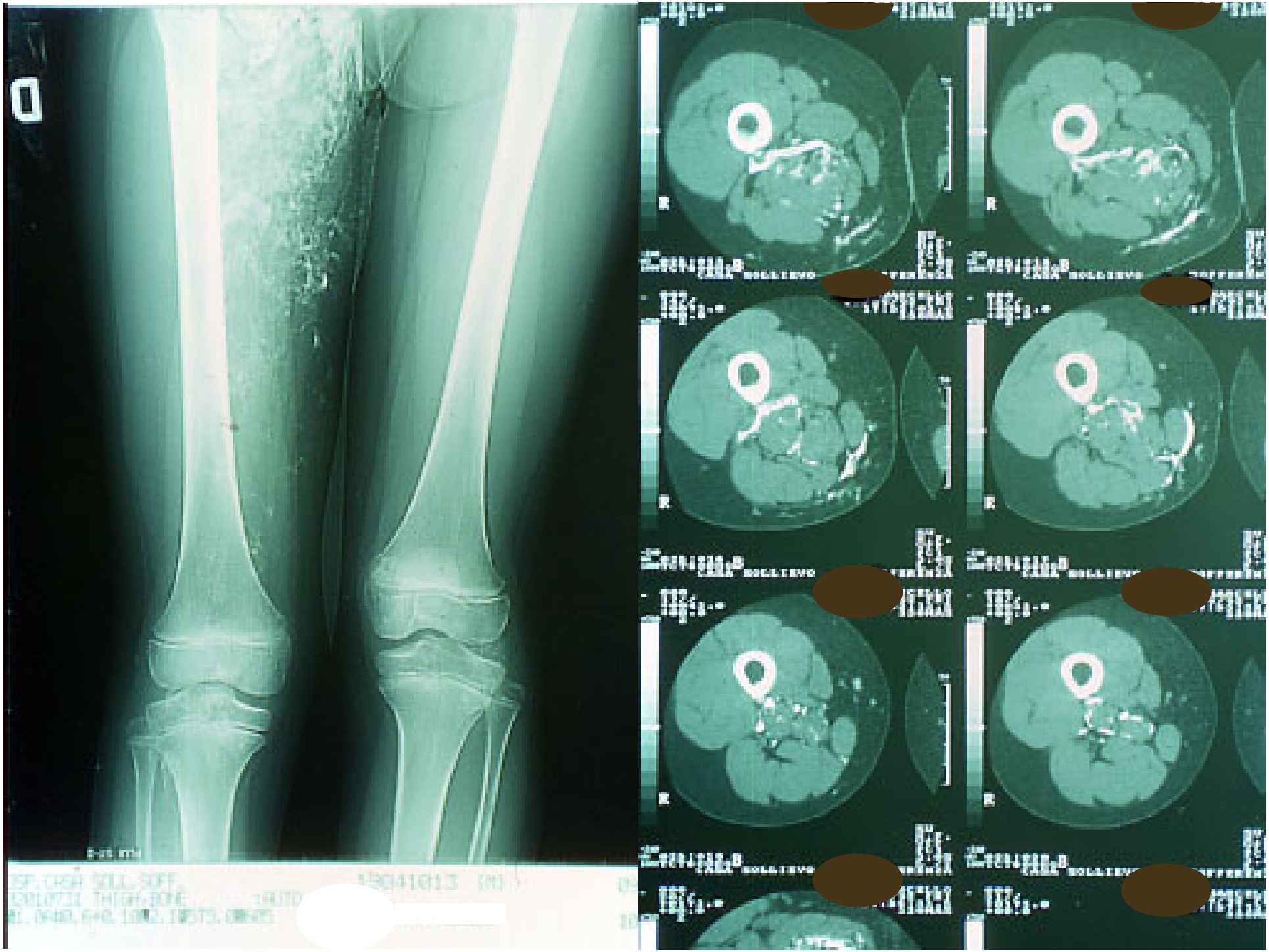

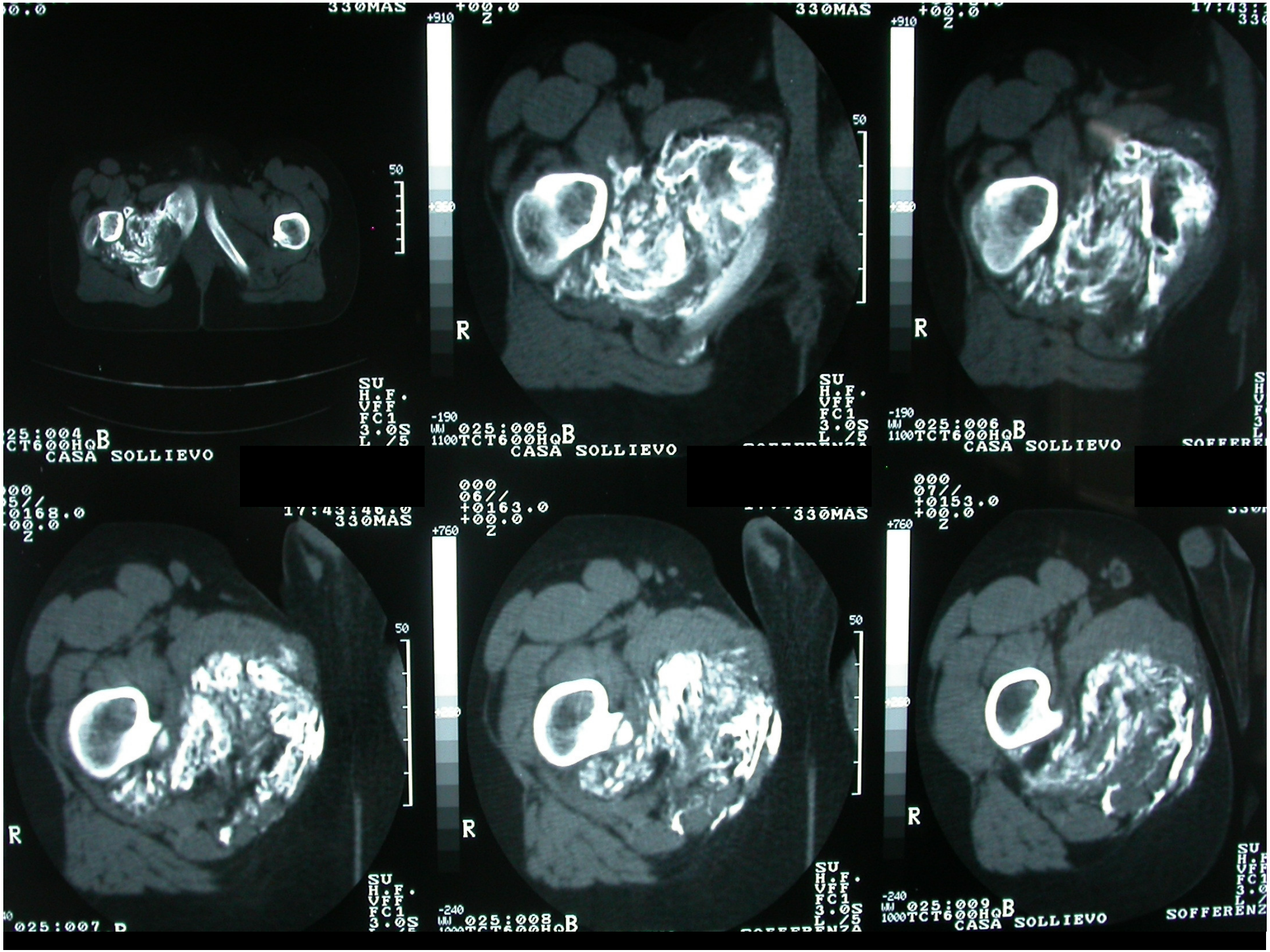
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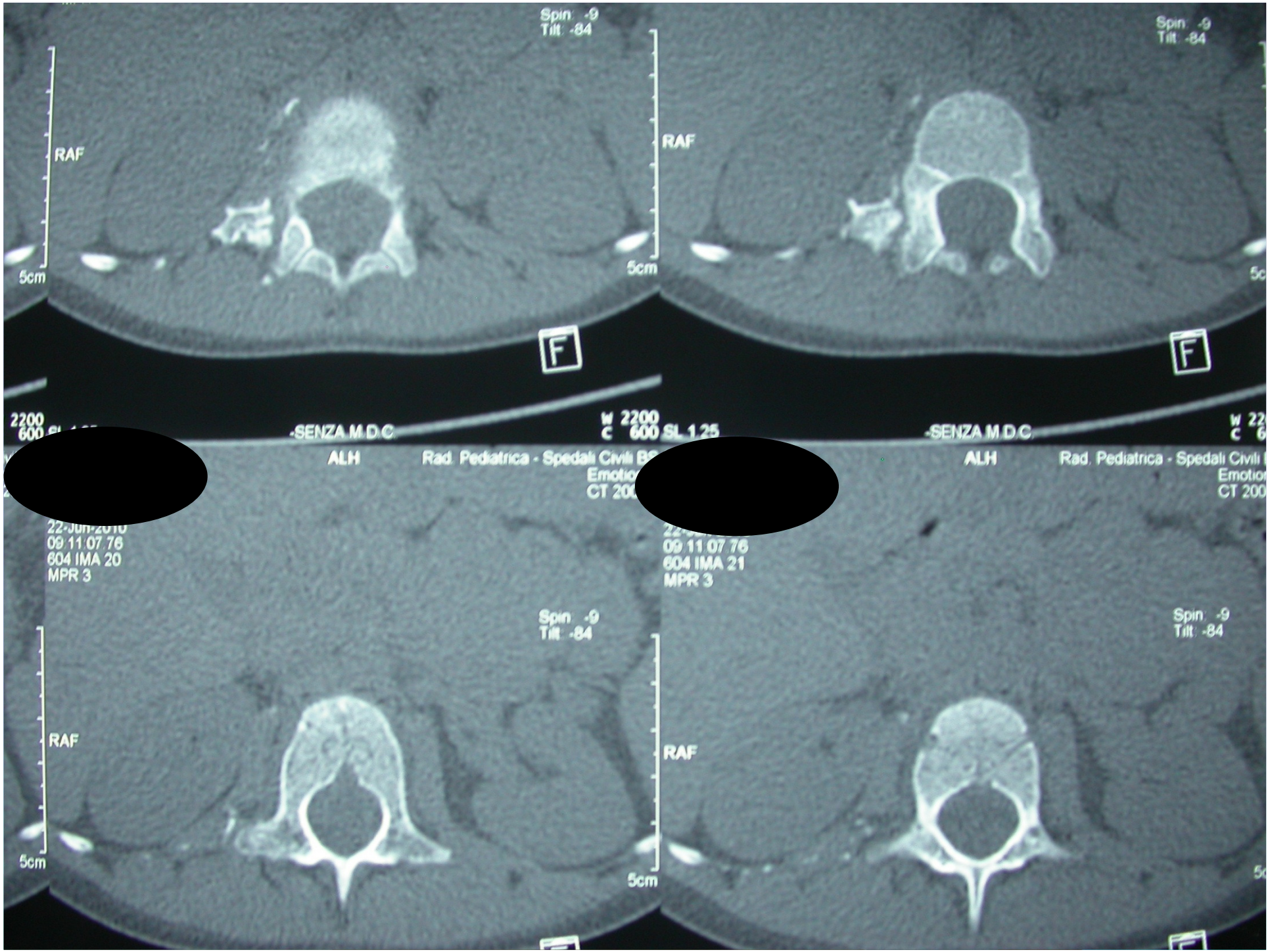
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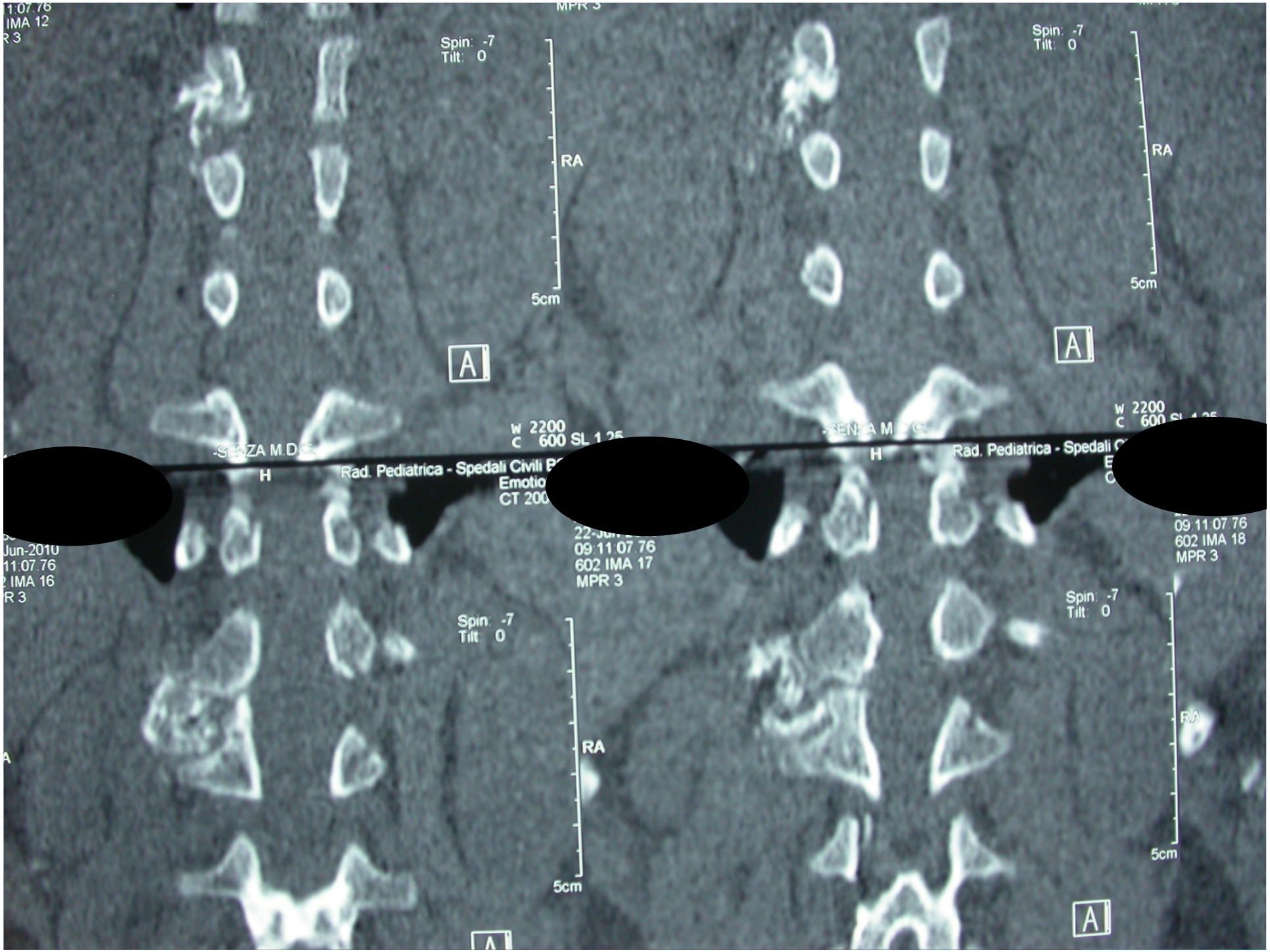
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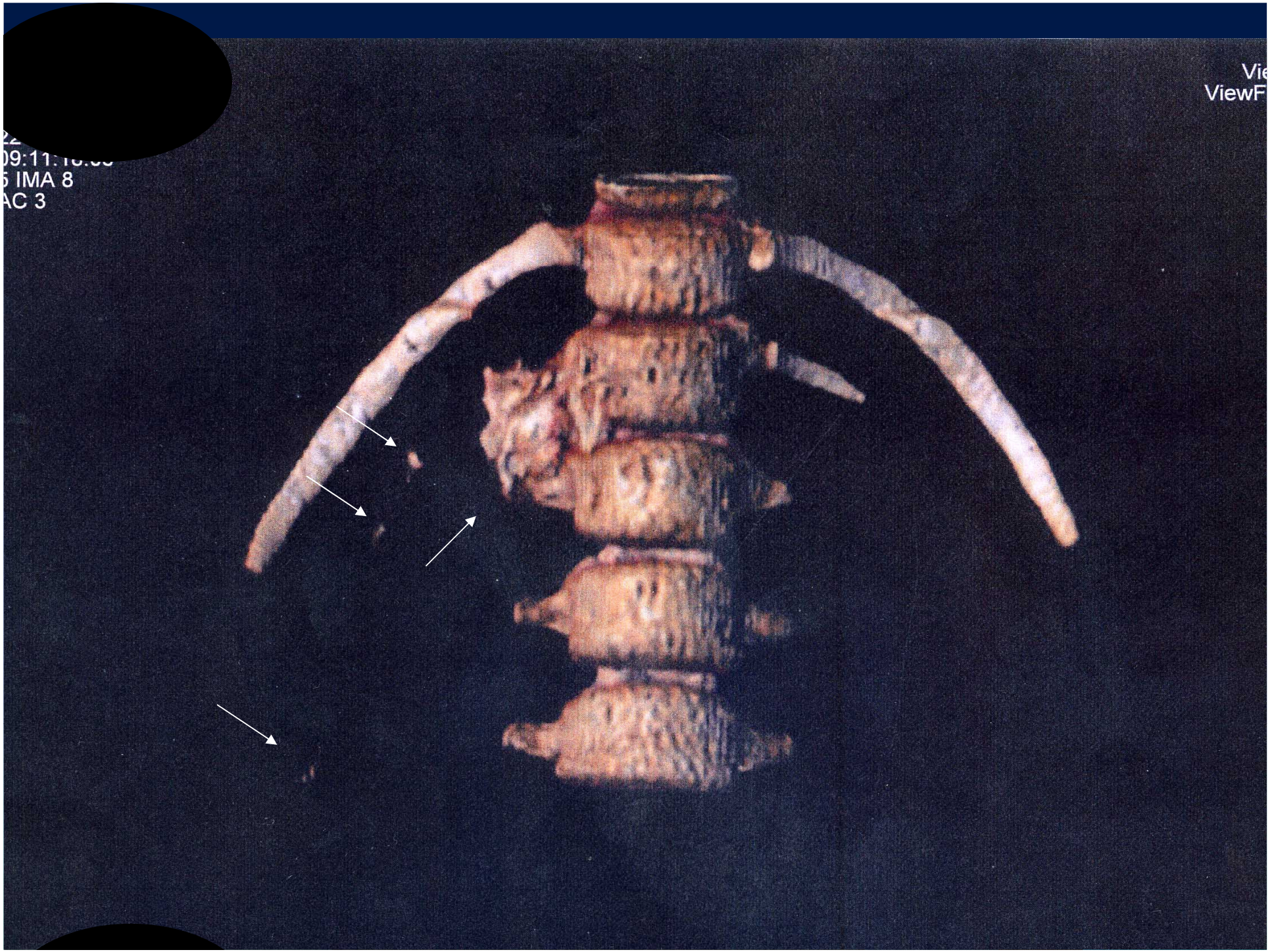
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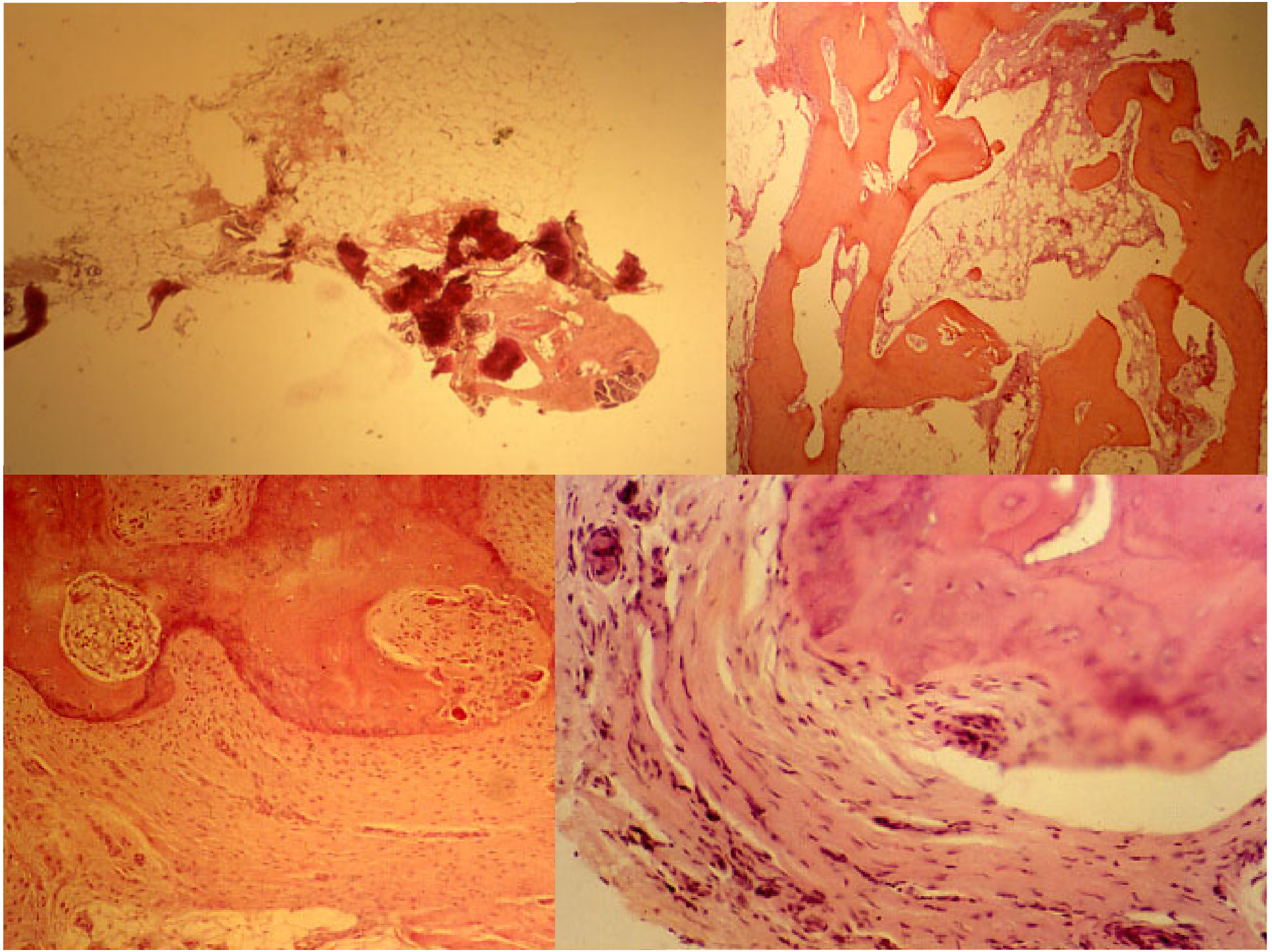
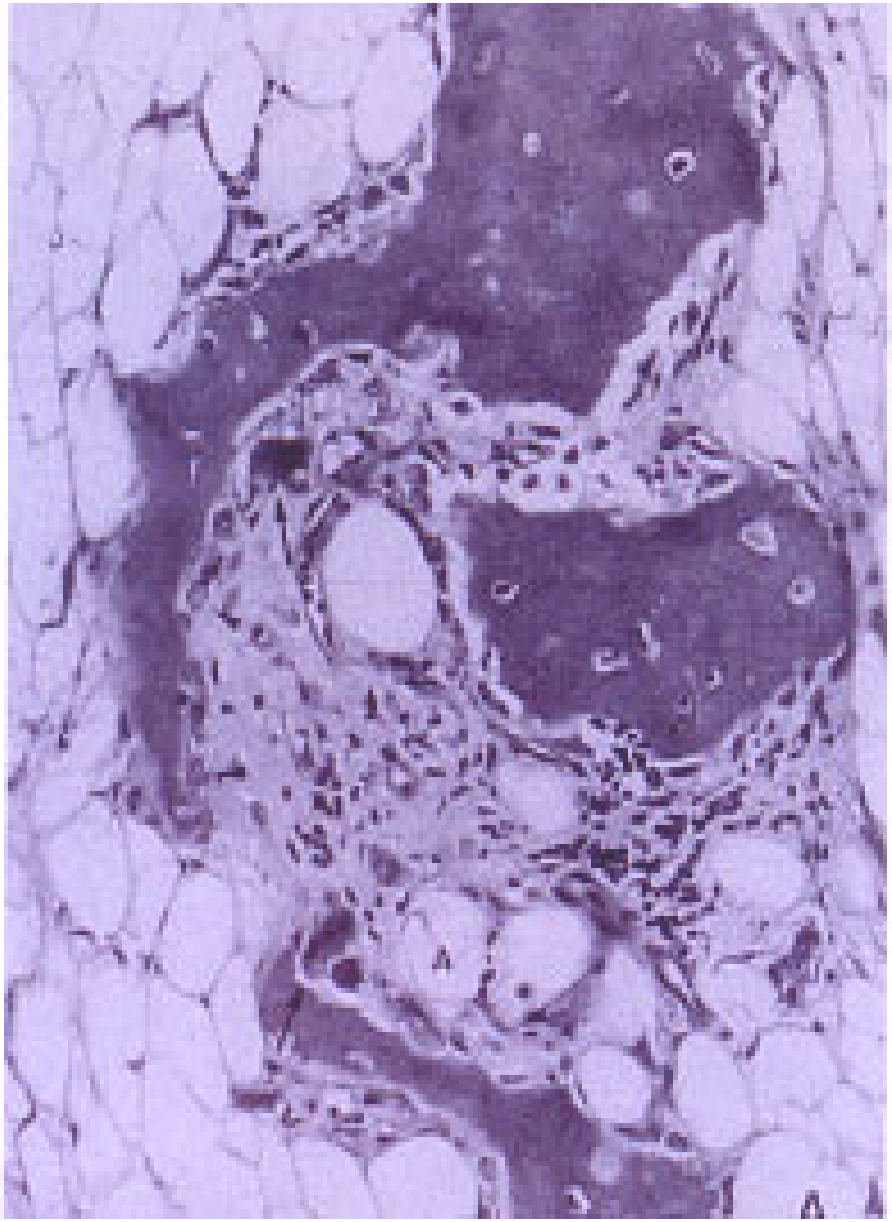
POH : ISTOPATHOLOGY

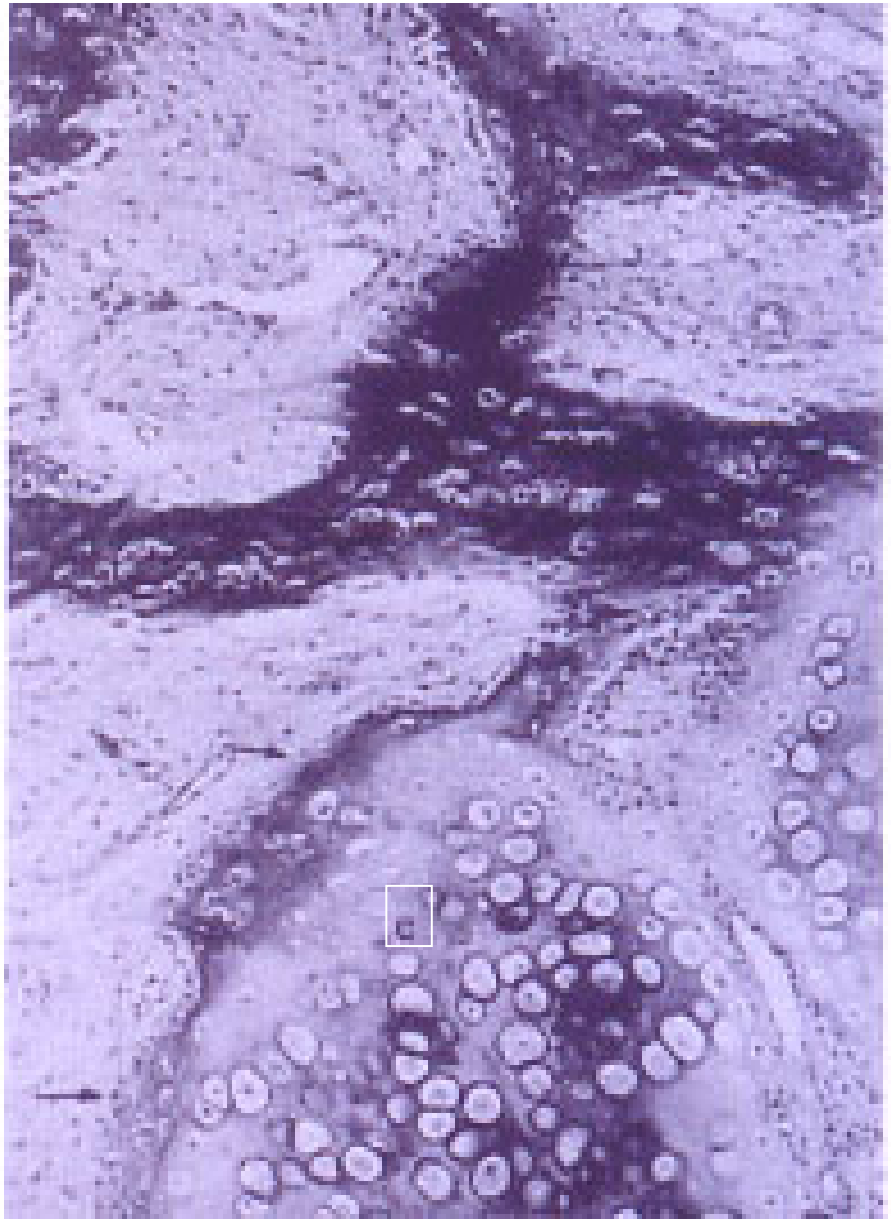
On light microscopy: generally the neoformed bone is of a direct ***membranous derivation***, except for some rare islets of endochondral osseous tissue (30%). The latter are found alone in single cases (20%), contrary to the FOP where the endochondral ossification is prevailing.



POH

FOP





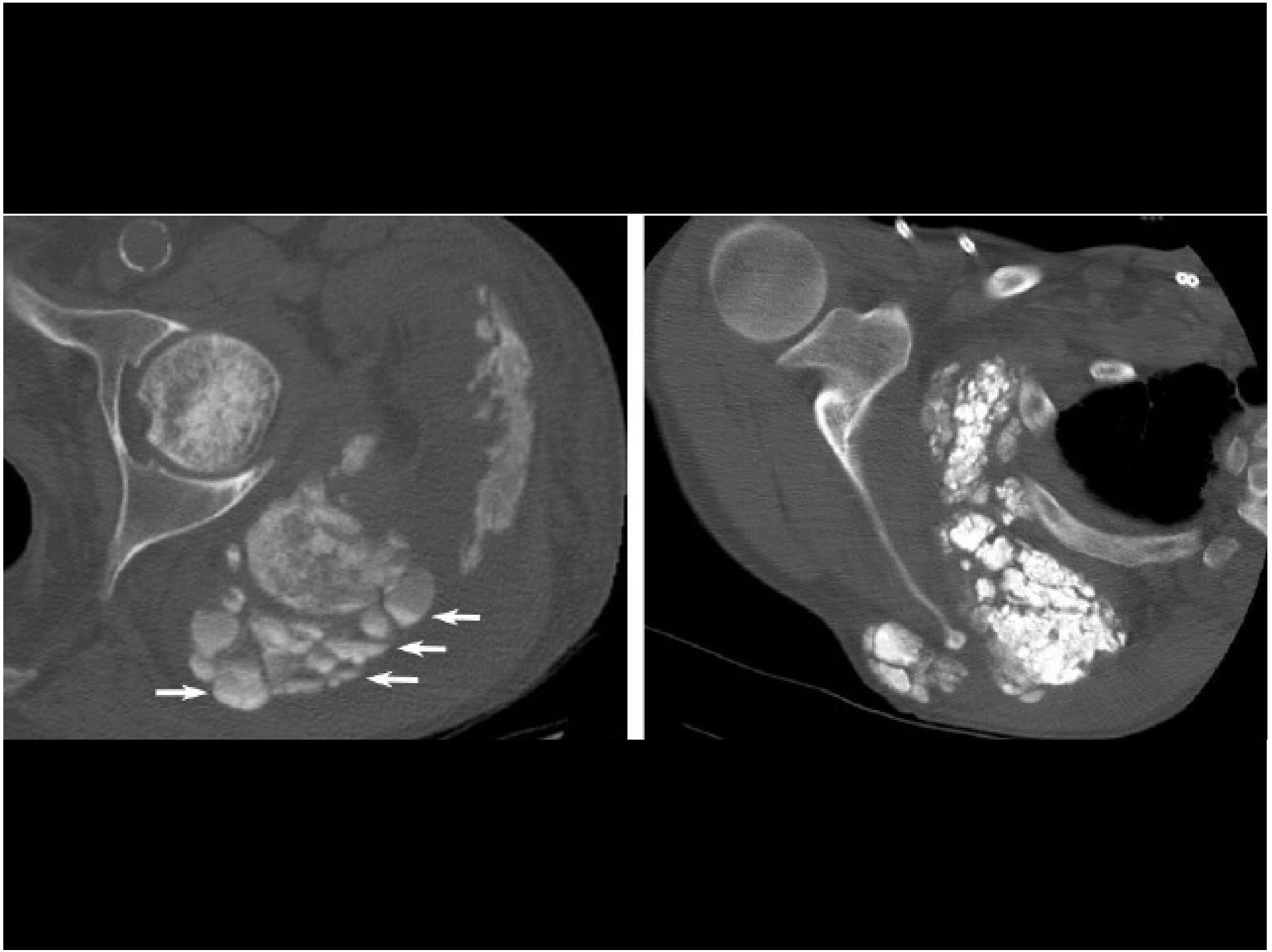
From Kaplan FS, Shore EM, J Bone Min Res.2000

POH (MIM 166350): DIAGNOSTICAL CRITERIA

- Peculiar skin features (rash, nodules)
- Normal mental development, no dysmorphic aspect
- No primitive skeletal malformations
- Normal laboratory and endocrinol. findings
- Histopathology (intramembranous predominant ossification)
- Progressive ossification into deepest tissues
- Radiological aspect (web-like - cocoon)
- GNAS inactivating mutation (probable)
- Familiarity (possible)

P.O.H. : DIFFERENTIAL DIAGNOSIS

- FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (MYOSITIS OSSIFICANS) (FOP)
- ALBRIGHT'S HEREDITARY OSTEODYSTROPHY (AHO)
- OSTEOMA CUTIS (OC)
- CALCINOSIS



FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)(1)

- AUTOSOMAL DOMINANT TRANSMISSION (ACVR1 gene mutation)
- PROGRESSIVE HETEROTOPIC OSTEOGENESIS
- CONGENITAL MALFORMATION OF THE BIG TOES
- ONSET IN THE 1ST DECADE OF LIFE
- PAINFUL NODULES OF POST-INFLAMMATORY FIBROPROLIFERATIVE TISSUE INVOLVING TENDONS, LIGAMENTS AND CONNECTIVE TISSUE OF SKELETAL MUSCLE
- ENDOCHONDRAL OSSIFICATION
- PROGRESSIVELY IMMOBILIZZATION OF THE JOINTS OF THE AXIAL AND APPENDICULAR SKELETON

FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)(2)

- BONE FORMATION CAN BE TRIGGERED BY BLUNT TRAUMA, BUT IT MOST OFTEN OCCURS SPONTANEOUSLY
- EXCISSION IS FUTILE AS THE TRAUMA LEADS TO THE STIMULATION OF NEW OSSIFICATION, ALSO BIOPSY IS TO AVOID!
- THE DIAPHRAGM, EXTRAOCULAR MUSCLES, CARDIAC AND SMOOTH MUSCLES ARE SPARED
- THE SKIN IS ALWAYS SPARED
- PREMATURE DEATH OFTEN RESULTS FROM RESPIRATORY FAILURE (RESTRICTION OF THE THORACIC CAGE) OR FROM INANITION (ANKYLOSIS OF THE JAW)

ALBRIGHT'S HEREDITARY OSTEODYSTROPHY (AHO)

- **PPHP (MIM 300800)**
  - ✓ ECTOPIC BONE FORMATIONS (CUTIS AND SUBCUTIS)
  - ✓ PERIOSTEAL EROSIONS
  - ✓ OBESITY, ROUND FACE, ALTERED HEIGHT – WEIGHT RATIO
  - ✓ SHORT METACARPAL AND METATARSAL BONES
  - ✓ MENTAL IMPAIRMENT
  - ✓ INACTIVATING MUTATION OF GNAS GENE (PATERNALLY)
- **PHPIa (MIM 103580)**
  - ✓ ALL THE PREVIOUS +
  - ✓ HORMONE RESISTANCE (TSH, FSH, LH, ACTH)
  - ✓ >PTH (NORMAL IN PPHP)
  - ✓ HYPOCALCEMIA (LATE ONSET, INCOSTANT)
  - ✓ INTRACRANIAL CALCIFICATIONS
  - ✓ SOMETIMES DIABETES
  - ✓ INACTIVATING MUTATION OF GNAS GENE (MATERNALLY)

Osteoma Cutis

- AUTOSOMAL DOMINANT TRASMISSION WITH INACTIVATING MUTATION OF GNAS GENE
- DERMAL AND SUBCUTANEOUS HETEROTOPIC OSSIFICATION
- AT BIRTH OR 1ST YEAR OF LIFE
- ABSENCE OF TRAUMA, INFECTIONS, METABOLIC OR ENDOCRINE ABNORMALITIES
- NEVER PROGRESSED TO DEEPER TISSUE
- NO PRIMITIVE SKELETAL MALFORMATIONS, NO DYSMORPHIC FEATURES

Clinical characteristics of POH and other GNAS-based disorders of superficial heterotopic ossification (HO)

Adegbite et al. Am J Med Gen 2008

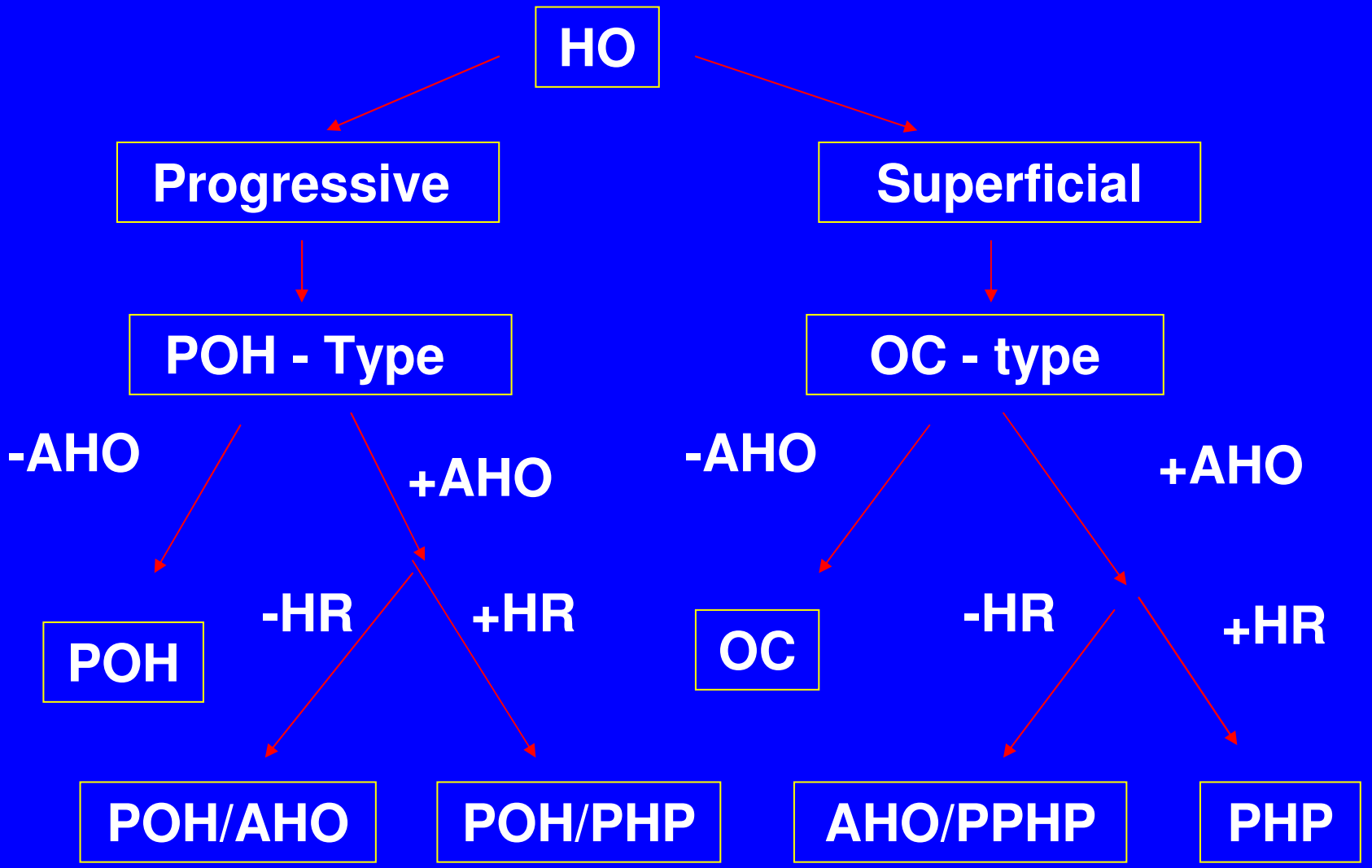
Diagnosis	n	Superficial HO	Deep HO	>2 AHO Features	PTH Resistance
POH	52	+	+	-	-
POH/AHO	6	+	+	+	-
POH/PHP1a	5	+	+	+	+
OSTEOMA CUTIS	26	+	-	-	-
AHO	10	+	-	+	-
PHP1a	12	+	-	+	+

DIAGNOSTIC DIAGRAM

- **MEDICAL EXAMINATION** rash – nodules, morphological aspect, articular blocks **(d.d. AHO, FOP)**
- **PERSONAL (IUGR – growth retard. infancy) AND FAMILY ANAMNESIS (sometimes mute)**
- **LABORATORY FINDINGS** (calcium, phosphorus, alk. phosphatasis, PTH, TSH, calciuria)**(d.d. AHO)**
- **RX TOTAL BODY – CT Scan** to detect deep bony lesions and lack of visceral calcifications **(d.d. OC and CALCINOSIS)**
- **BIOPSY (ossification, non calcium deposit)**
- **GNAS GENE MUTATION (to confirm clinical diagnosis , but may be present also in AHO and OC, and may be absent in all)**

DIAGNOSTIC DIAGRAM

da Adegbite et al. Am J Med Genet. A 2008



THERAPEUTIC ATTEMPTS

Presently, there are no effective treatments to modify natural history of disease or to prevent ossifications

- **DIPHOSPHONATES: ETHIDRONATE, PAMIDRONATE**
- **FANS : INDOMETHACIN, ANTI COX-II,**
- **AMINOPHYLLINE (cAMP)**
- **ANGIOGENESIS INHIBITOR**
- **SURGICAL TREATMENT**
- **RADIATION THERAPY(?)**
- **GENIC THERAPY : FUTURE AND HOPE!**
- **PHYSIOTHERAPY**

PERCHÉ NE STIAMO PARLANDO?

- Far conoscere l'esistenza di questa patologia o meglio di questi malati con i loro bisogni socio-sanitari
- Importanza della diagnosi precoce da parte di Neonatologi, Pediatri e Dermatologi Pediatri
- Aumentare le diagnosi e quindi le possibilità di studio
- Evitare trattamenti aggressivi inutili e dannosi
- Avvio verso centro di riferimento

A CHI È UTILE LA RICERCA SULLA POH

- Ai bambini affetti e le loro famiglie
- Alla comprensione di patologie + comuni della formazione ossea (a cominciare dalle ossificazioni eterotopiche acquisite e poi alle anomalie congenite degli arti, osteoporosi, cancro osseo, osteoartrosi, riparazione anomala di fratture) **attraverso la comprensione di tutti i meccanismi molecolari alla base dell'osteogenesi.**

COSA ABBIAMO IMPARATO

- Esiste una malattia rara con ossificazioni eterotopiche notevolmente invalidante
- È abbastanza facile da diagnosticare da parte del Neonatologo, Pediatra e Dermatologo Pediatra seguendo i criteri diagnostici descritti
- Non ha terapia al momento
- C'é bisogno ancora di molta ricerca per dare risposte a questi malati
- Questa ricerca puó essere utile a tante malattie piú comuni

CONSIDERAZIONI CONCLUSIVE

- L'esistenza delle malattie "Rare" deve essere meglio resa nota anche al medico pratico, ma sicuramente in questo caso sono i pediatri, i neonatologi, i dermatologi, gli ortopedici e anche i ginecologi a dover intervenire, anche per il "counseling" (diagnosi prenatale, diagnosi pre-impianto)
- Se la diagnosi precoce è sempre importante, nelle malattie rare lo è ancora di più
- Collaborazione con centri di riferimento internazionale
- Continuare a studiare per comprendere i meccanismi intrinseci di regolazione del metabolismo dell'osso e trovare una terapia!
- Riconoscimento, finalmente, da parte del Sistema Sanitario Nazionale

Cosa Possiamo fare di più?!?

1. Versamento su c.c. postale n. 30708853
2. Bonifico bancario a BancoPosta IBAN:IT82 K076 0115 7000 0003 0[illegible]3 853 (deducibile/detra[illegible]di dich[illegible]*versi!*)
3. "5 [illegible]ndo nella dic[illegible]ione dei redditi alla voce "5 per mille" il codice fiscale n. **90017210718** (*non ti costa nulla, ma dai tanto!*)

Ass. It. Eteroplasia Ossea Progressiva ONLUS

Grazie!