1° Meeting Italiano Internazionale congiunto su POH & FOP
1st International Italian Joint Meeting on POH & FOP
(Eteroplasia Ossea Progressiva e Fibrodisplasia Ossificante Progressiva)

"Verso la Luce"
Opera di Gioacchino Loporchio

POH: Diagnostic diagrams

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.

POH: CLINICAL FEATURES (1)

- 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 rugous scar.
- Deep nodules tend to become deeper involving deepest soft tissues, muscles and tendons

POH: CLINICAL FEATURES (2)

- The ossifications put on a network-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.

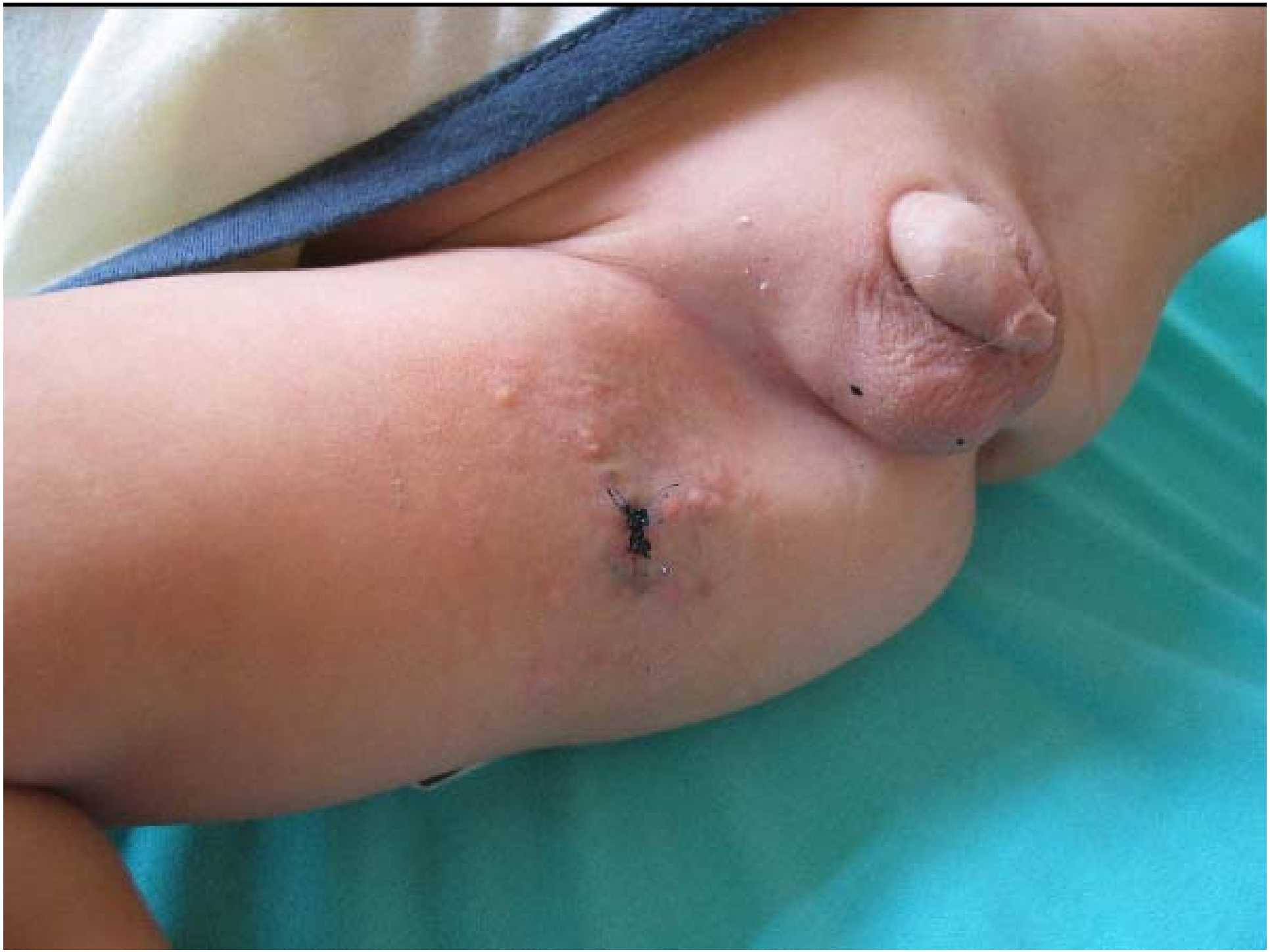
POH: CLINICAL FEATURES (3)

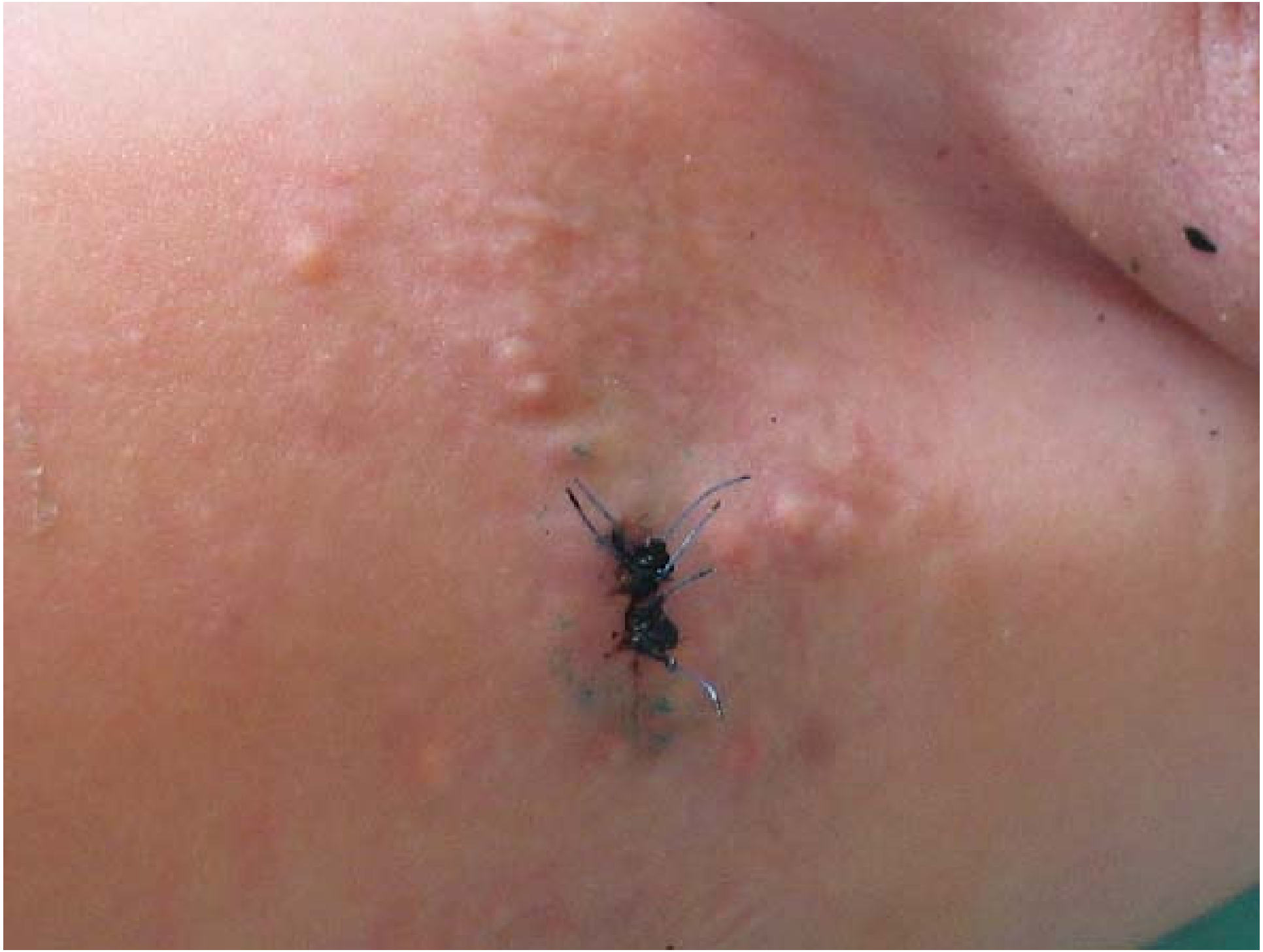
- Typically it is not combined with hormone imbalance or primary malformations of skeletal muscle apparatus or other organs.
- Laboratory findings are always normal.
- POH must be differenziated from other disease with ectopic ossification

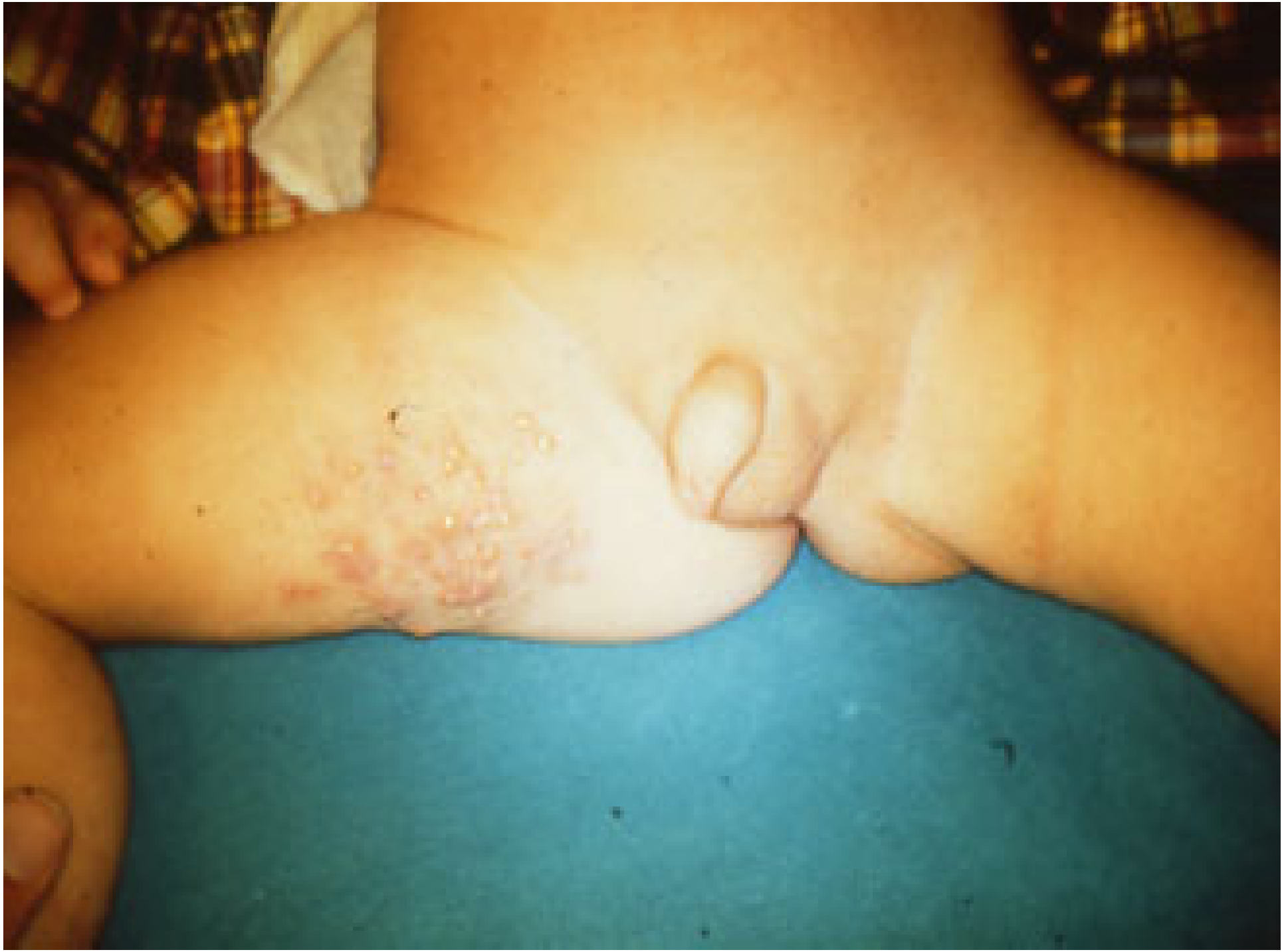
LABORATORY FINDINGS

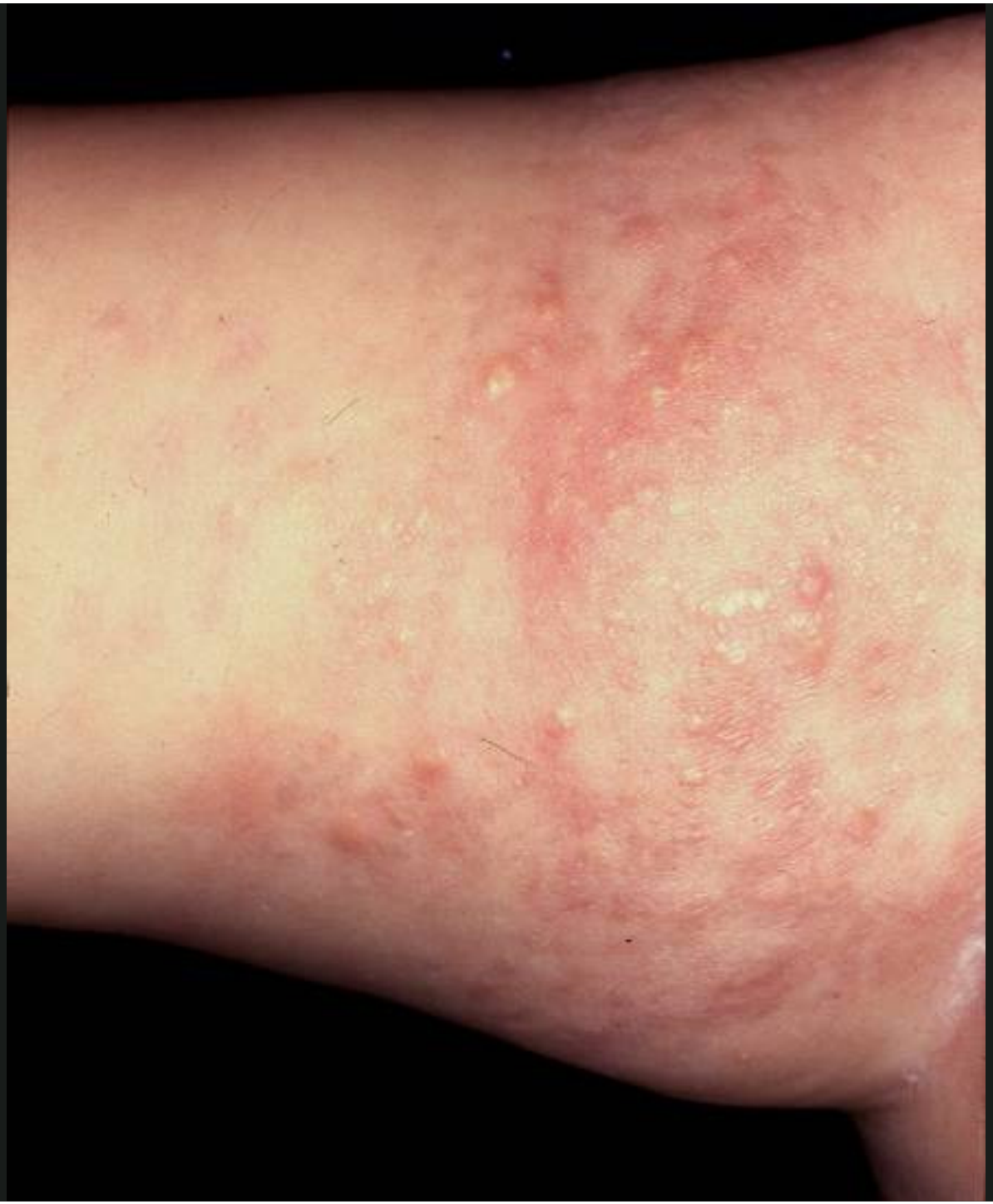
- Red cells 3,480,000; white cells 10,800; haematocrit 29.4; hb 9; MCV 84; total protein 5.8 g/dl; albumin 4.1 mg%ml; globulin : alpha 1 0.13, alpha 2 0.68, beta 0.54, gamma 0.29 mg%ml; blood calcium 9.1 mg%ml; phosphorus 6.0 mg%ml; sodium 136 mEq/l; potassium 5.2 mEq/l; IgG 37.1 i.u./ml (normal range 63.5 +/- 18.9); IgA 1.0 i.u./ml (normal range 28.7 +/- 9.4); IgM 49.4 i.u./ml (normal range 111 +/- 43.3). Urinary output of creatinine 55mg/24 hrs, phosphate 87mg/24hrs. Alkaline phosphatase 376mU/ml (normal range 150/479). Blood urate 4.7mg%ml, urea 13mg/dl, creatinine 0.8, ESR 11 (1°hr); parathormone 0.23mg (normal range 0.20 - 0.90)

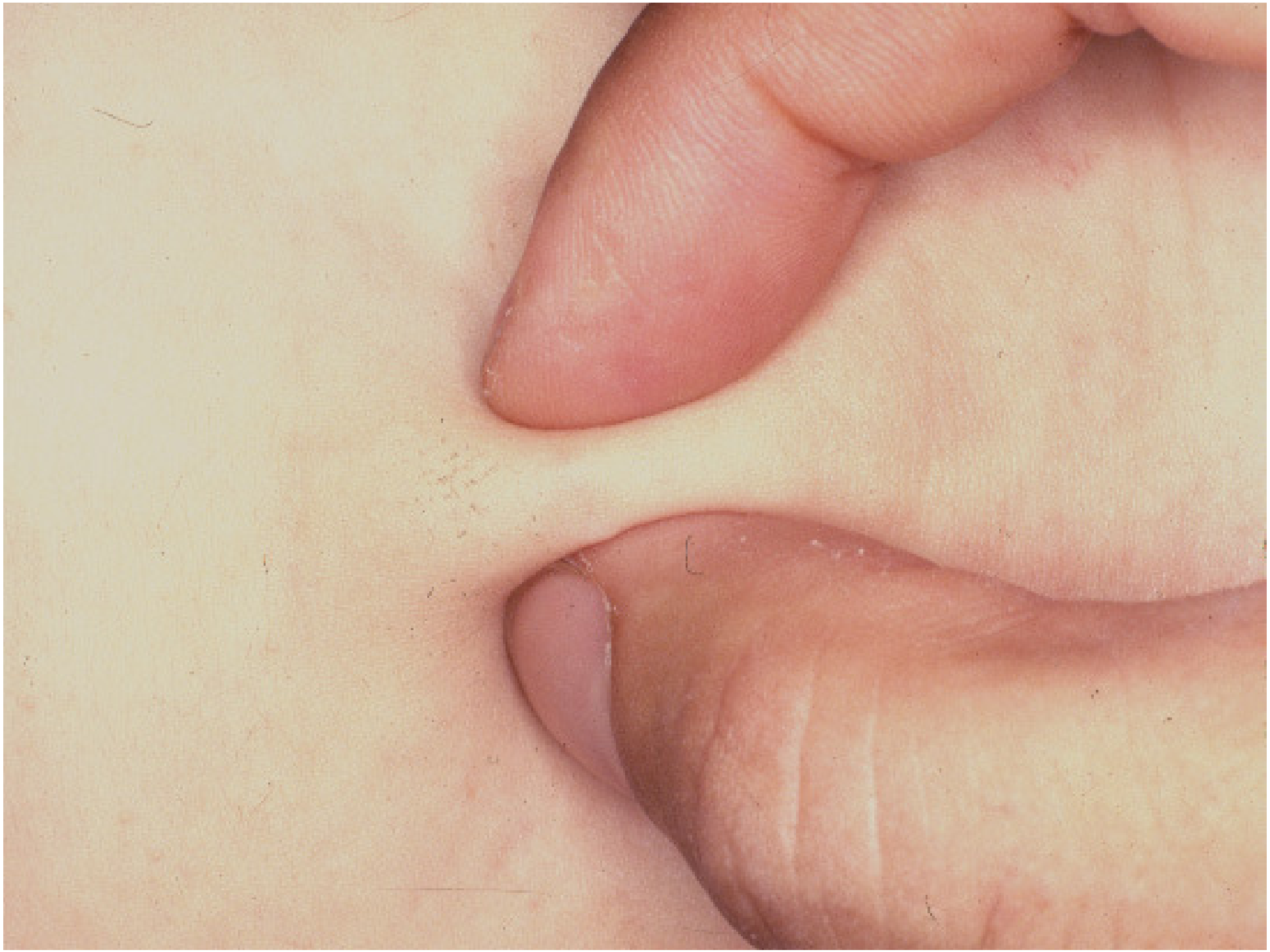
NORMAL

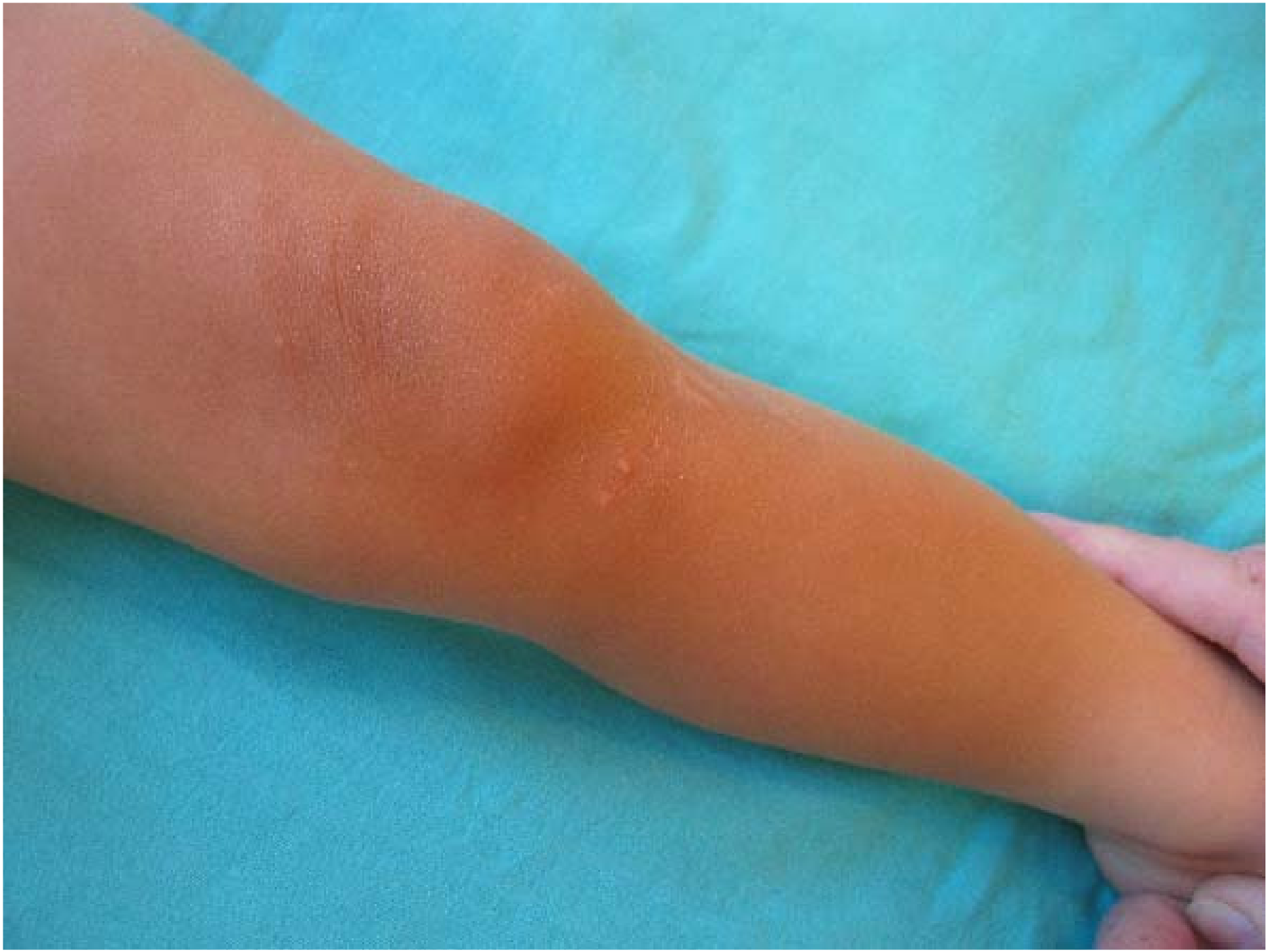


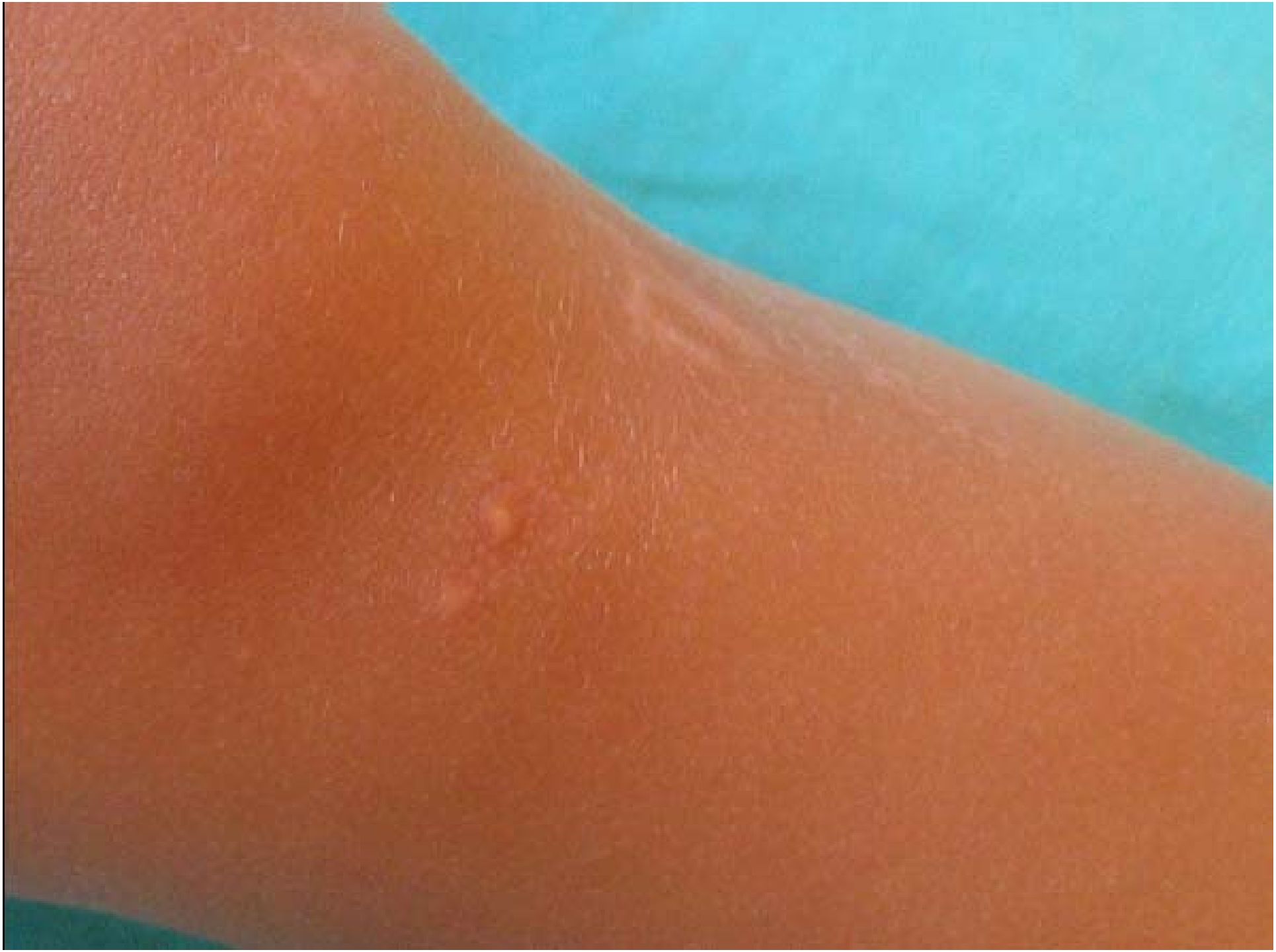


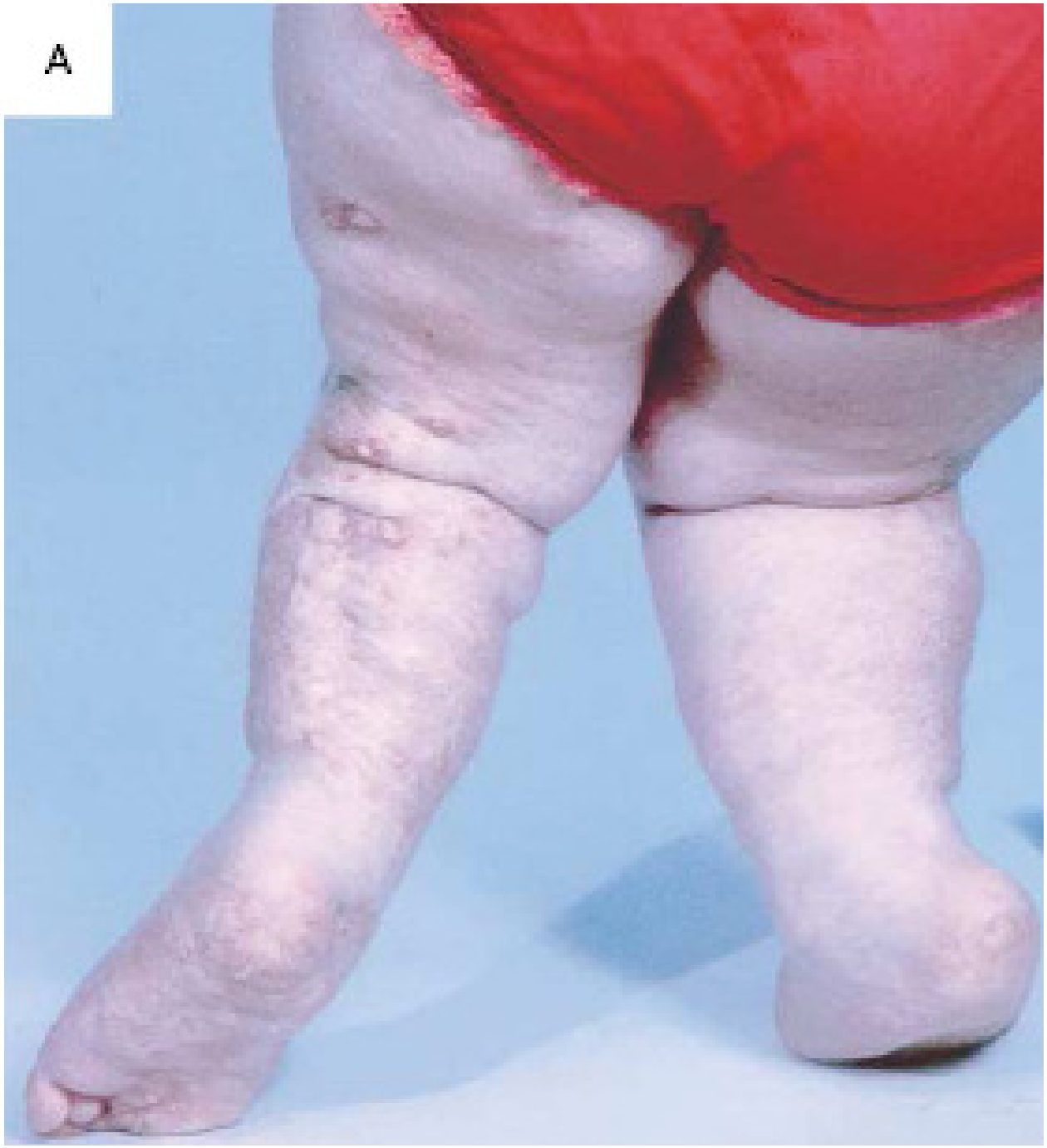


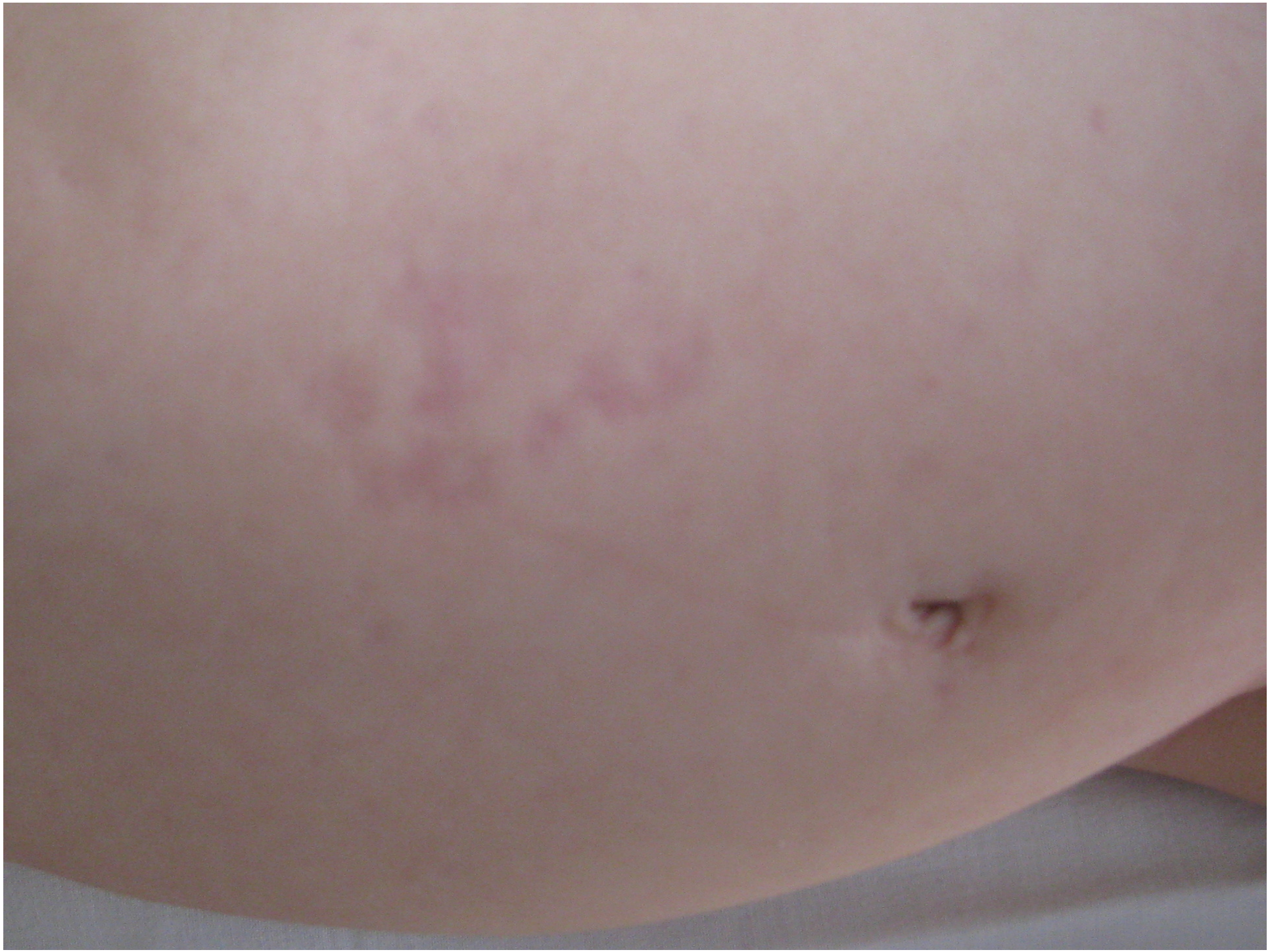


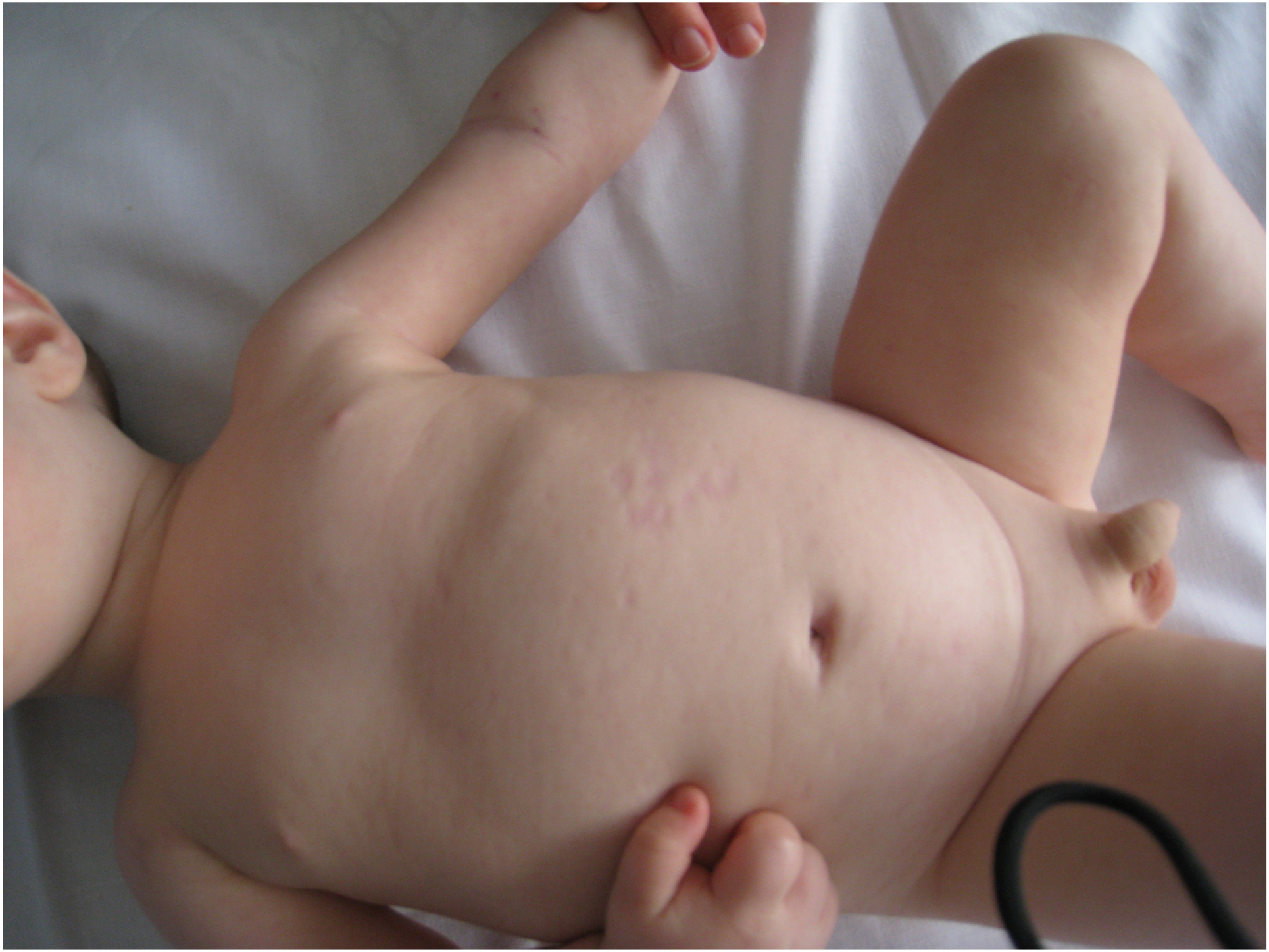


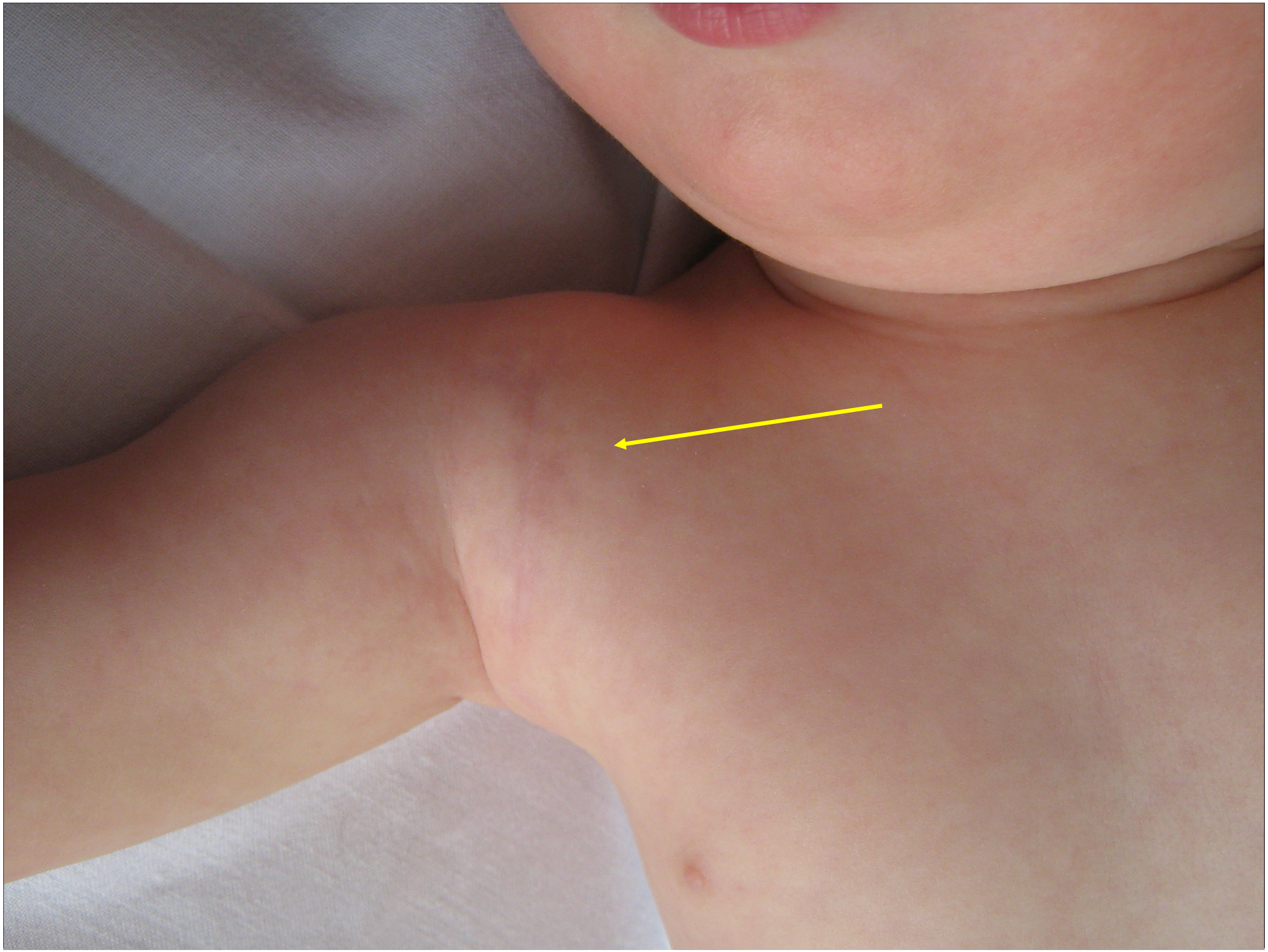


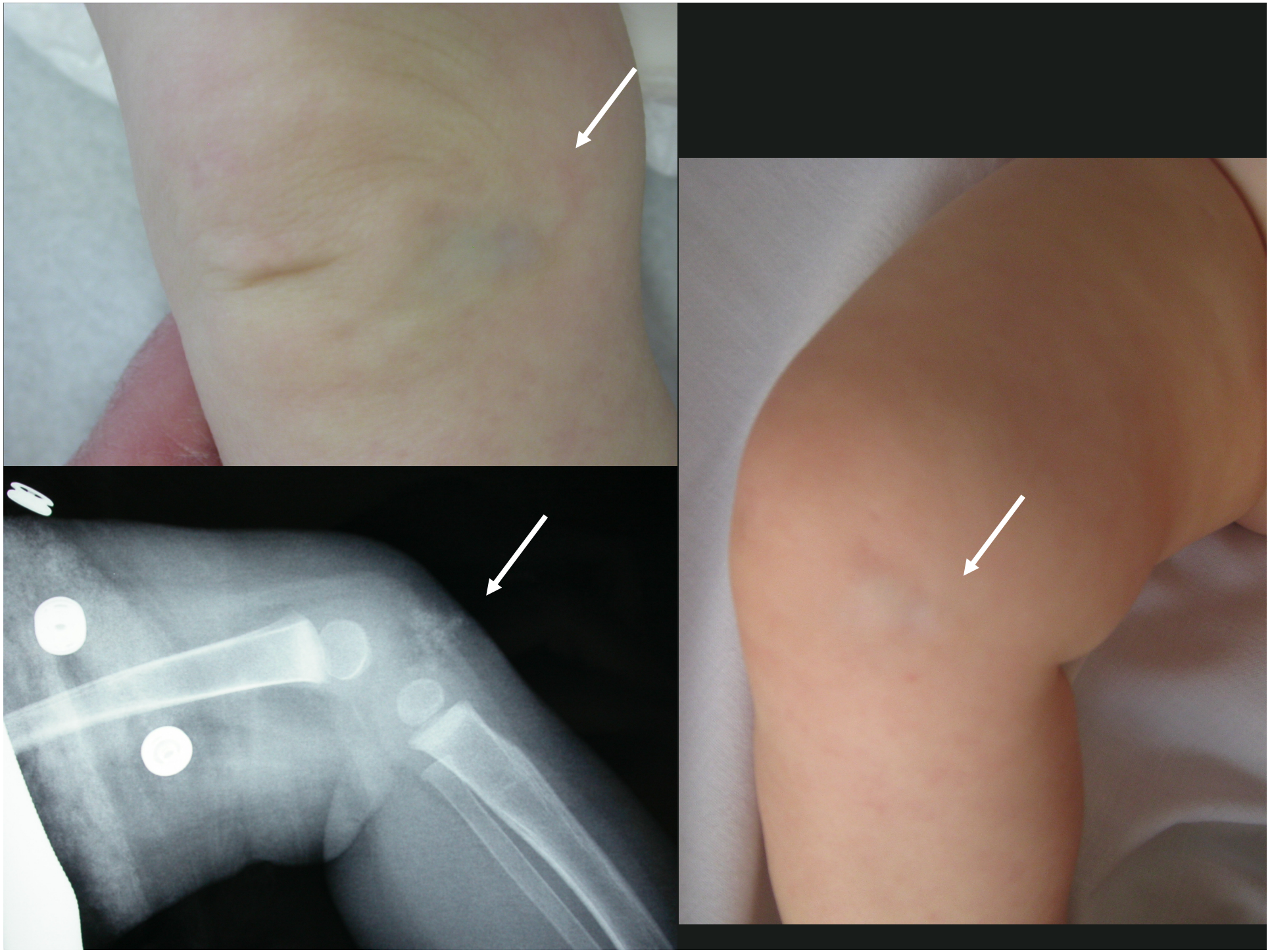



A







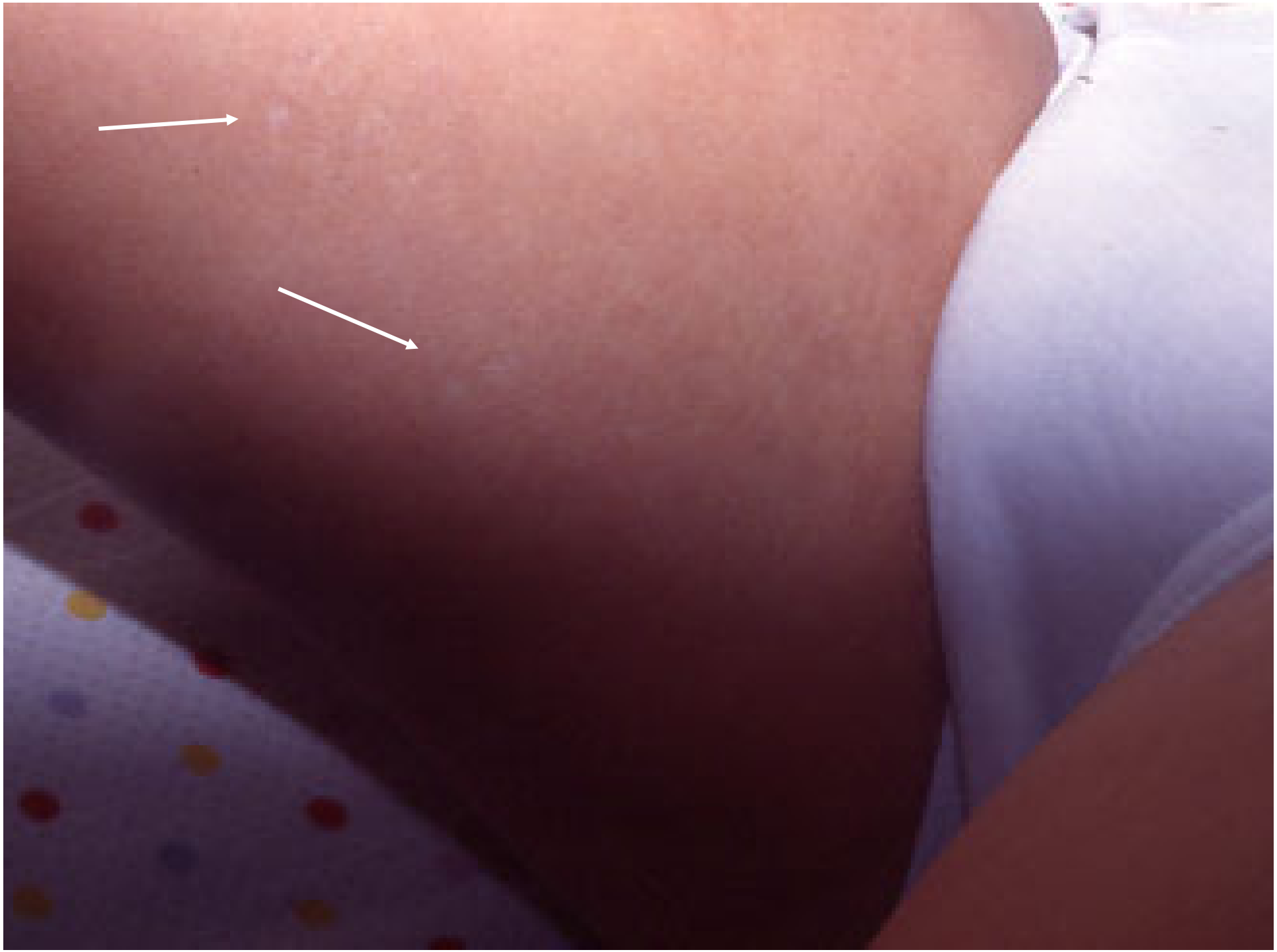


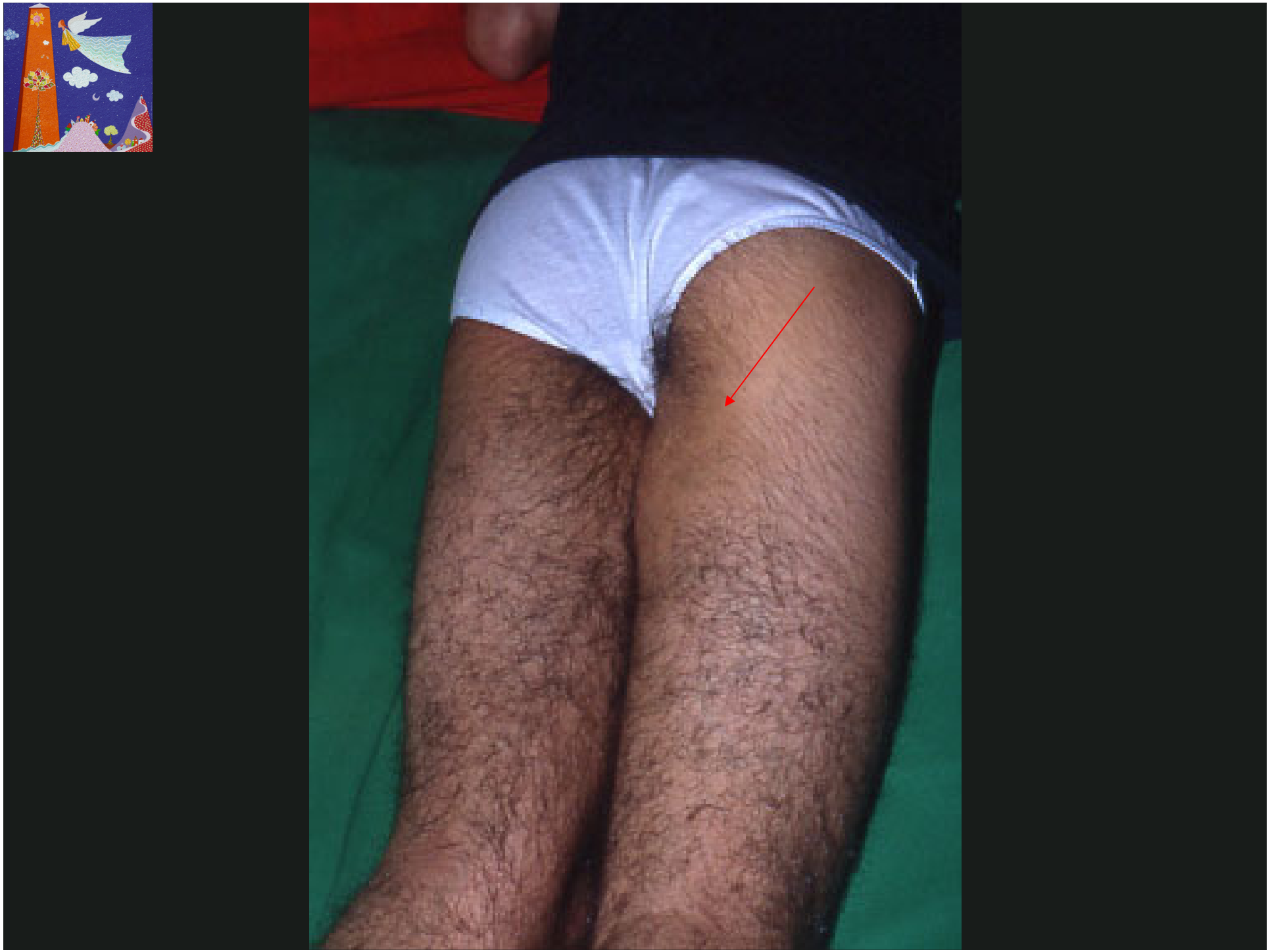
POH: COURSE

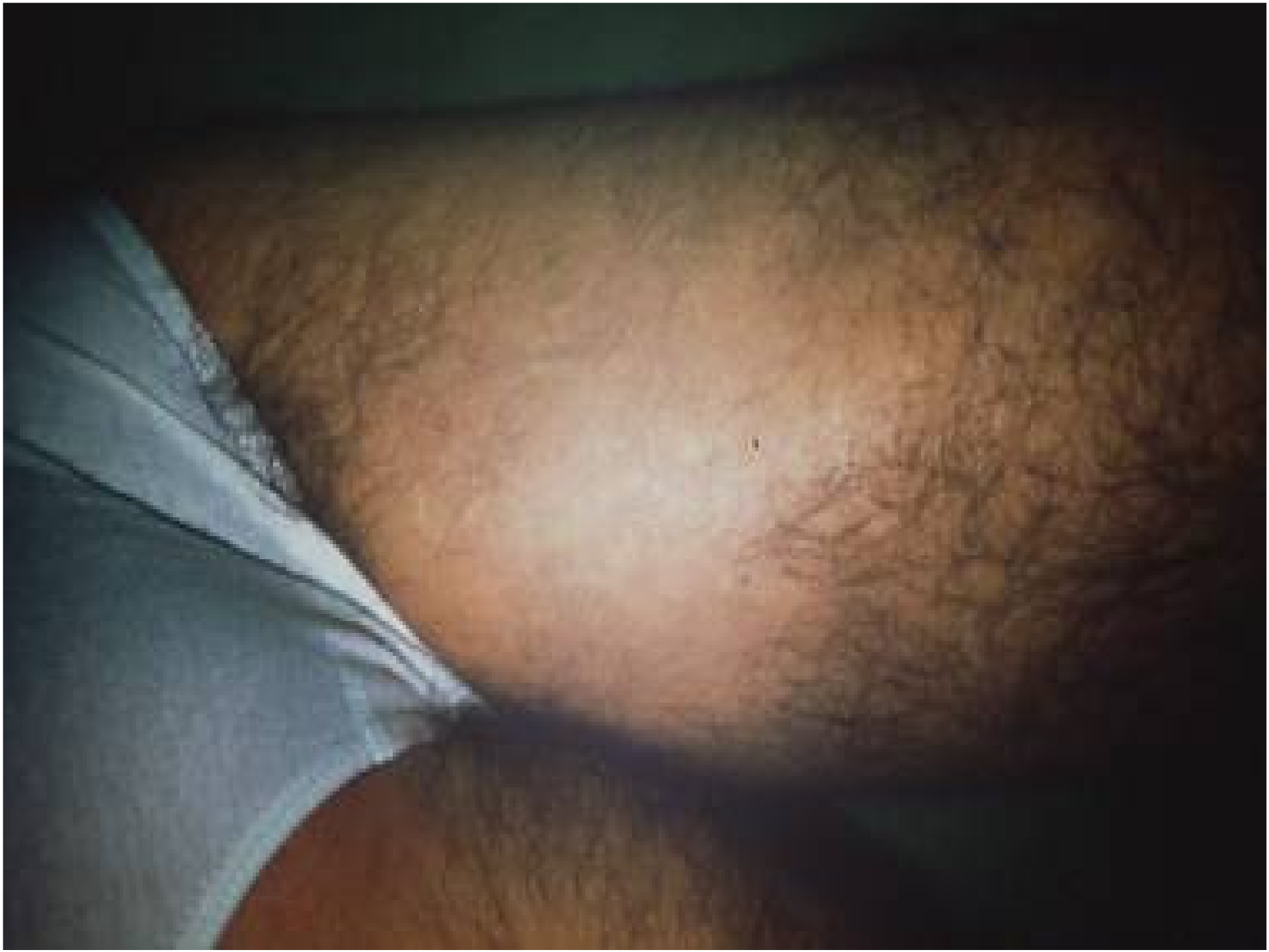
The variable course is characterized by alternate phases of slower and faster production of ectopic bone, without apparent reasons.

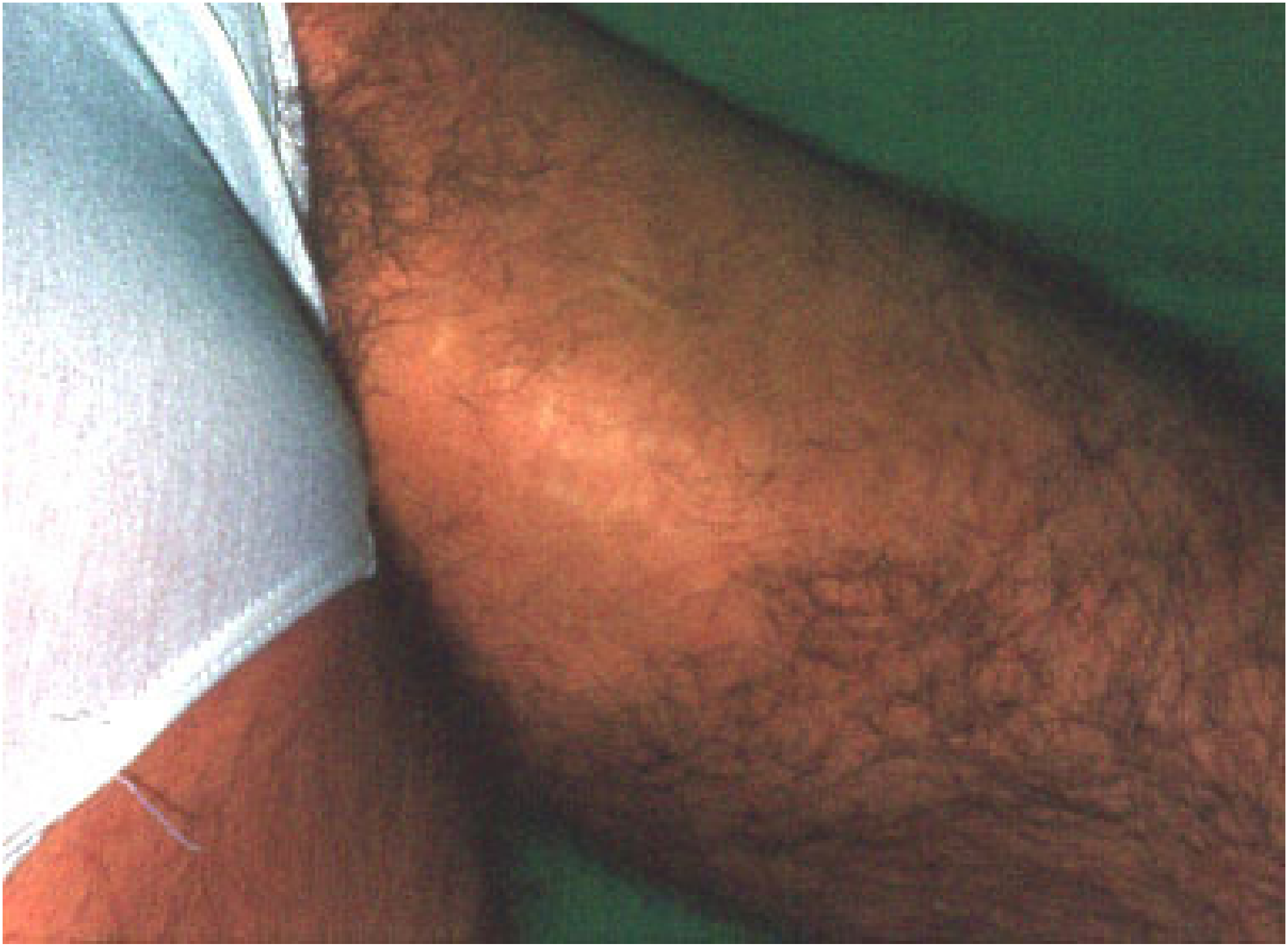
However there are not phases of sudden relapse or diffusion as flare-up type ossifications.

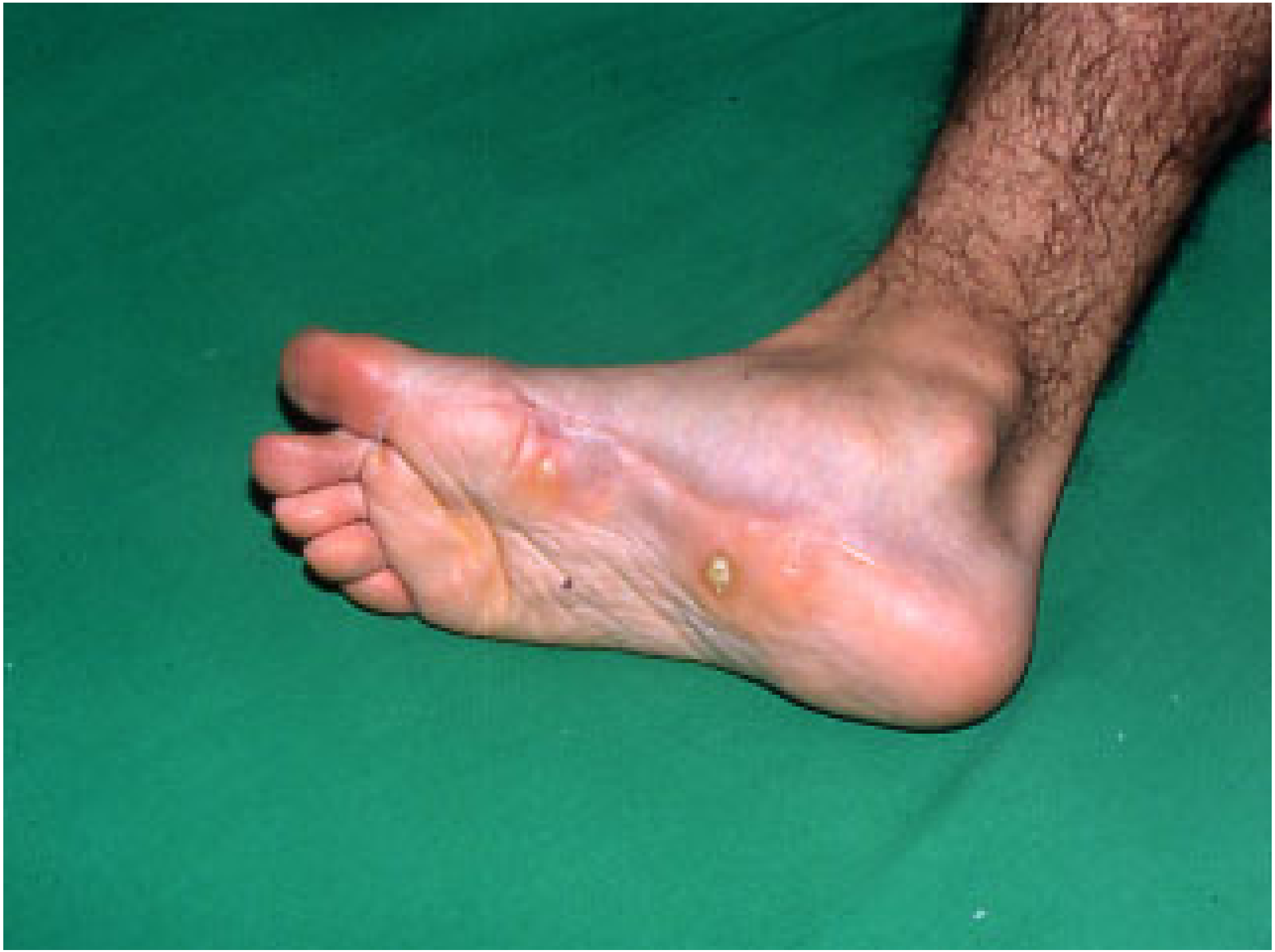
Often there is Pain, sometimes very hard to treat, caused by pressure of bony formations on surrounding tissues, or when limb growth is blocked.





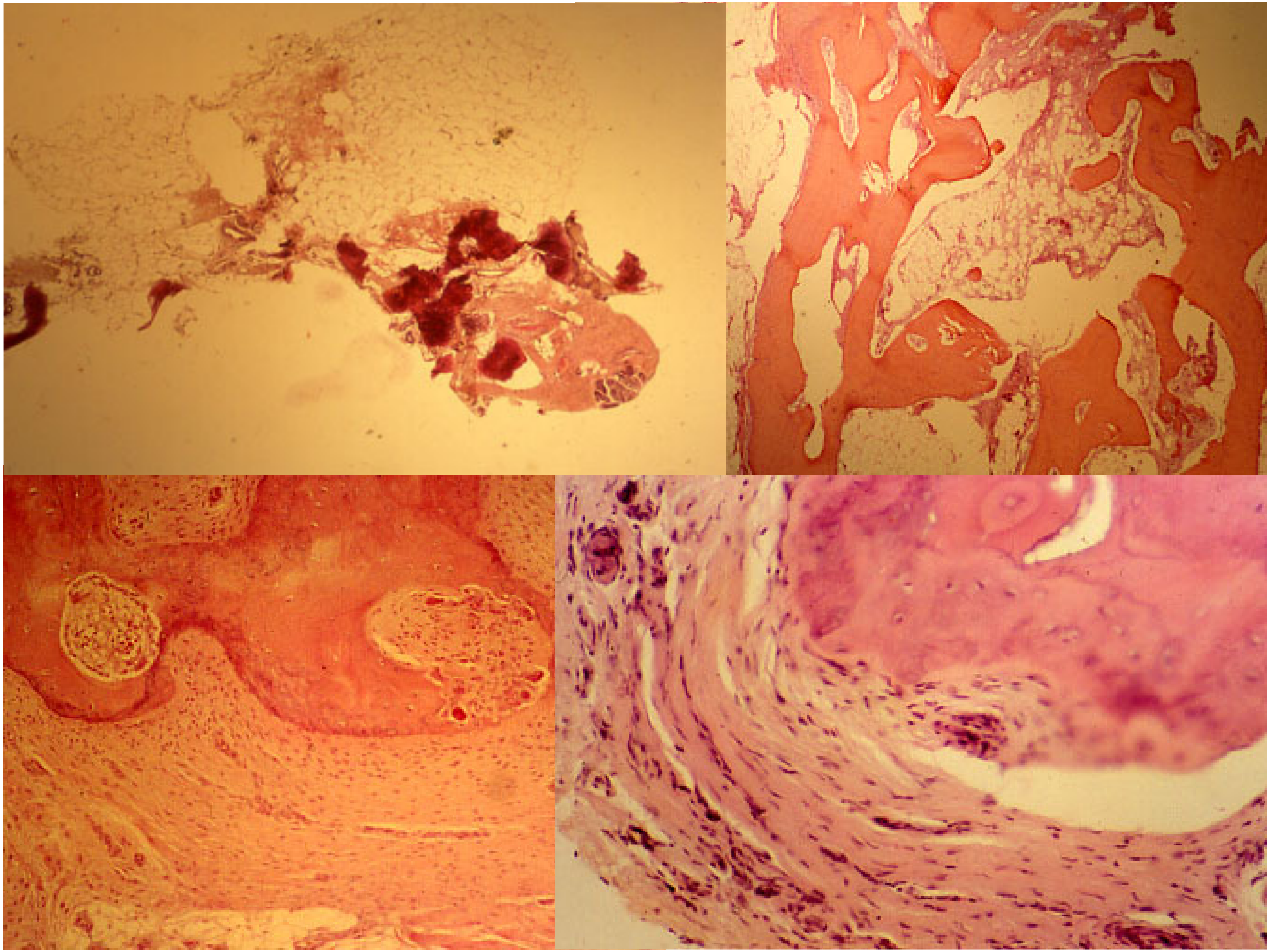






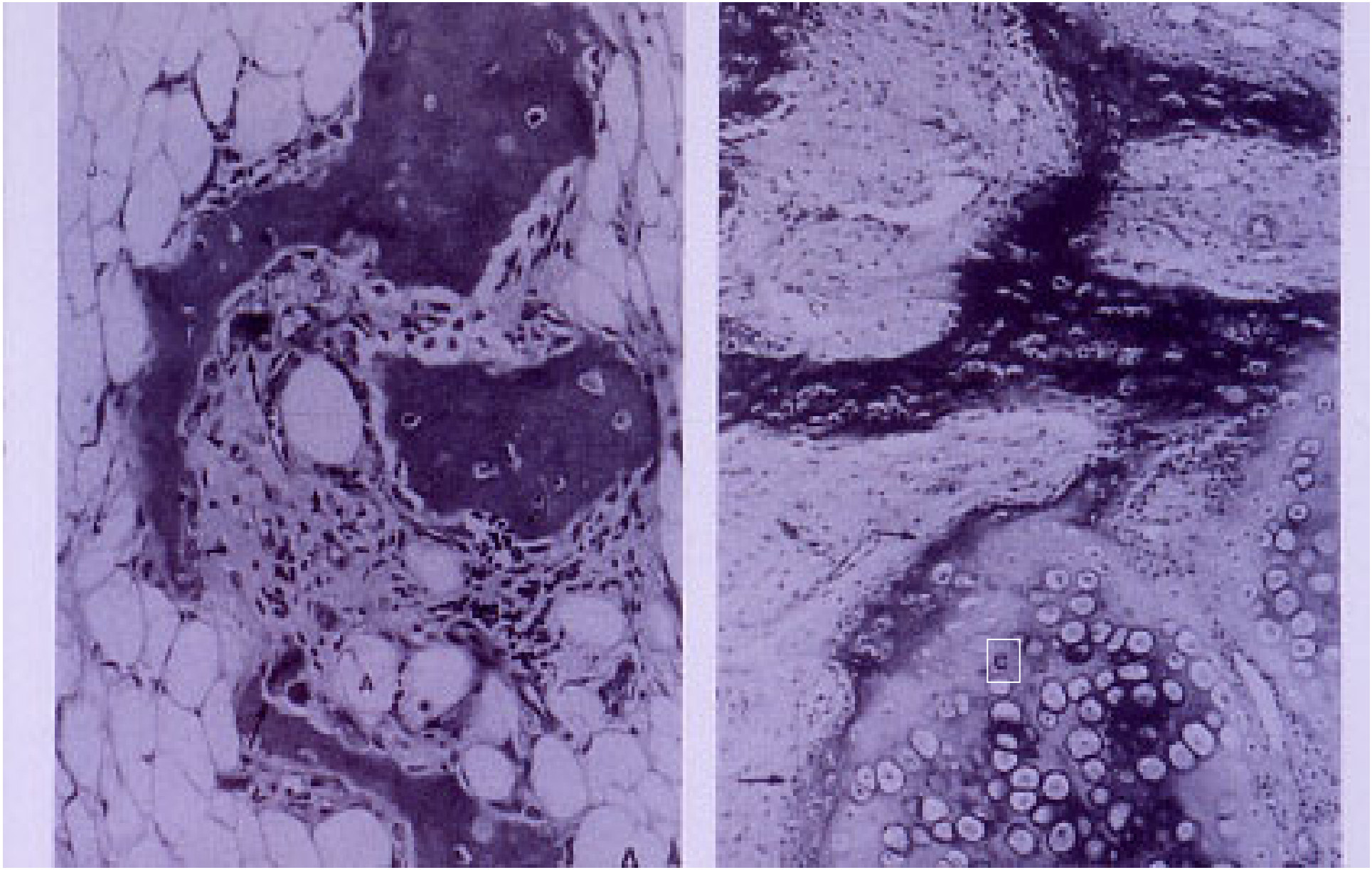
POH : ISTOPATHOLOGY

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

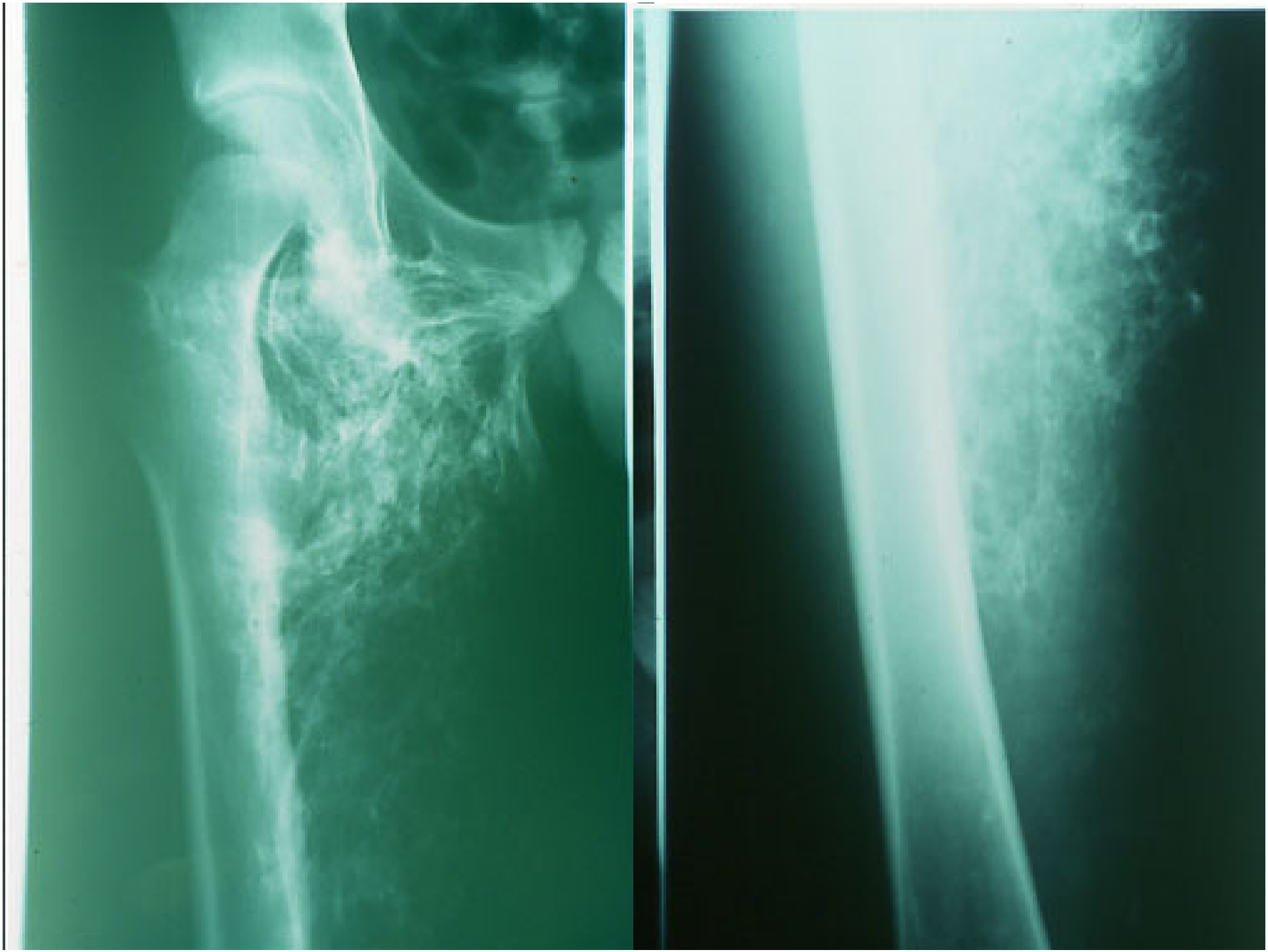


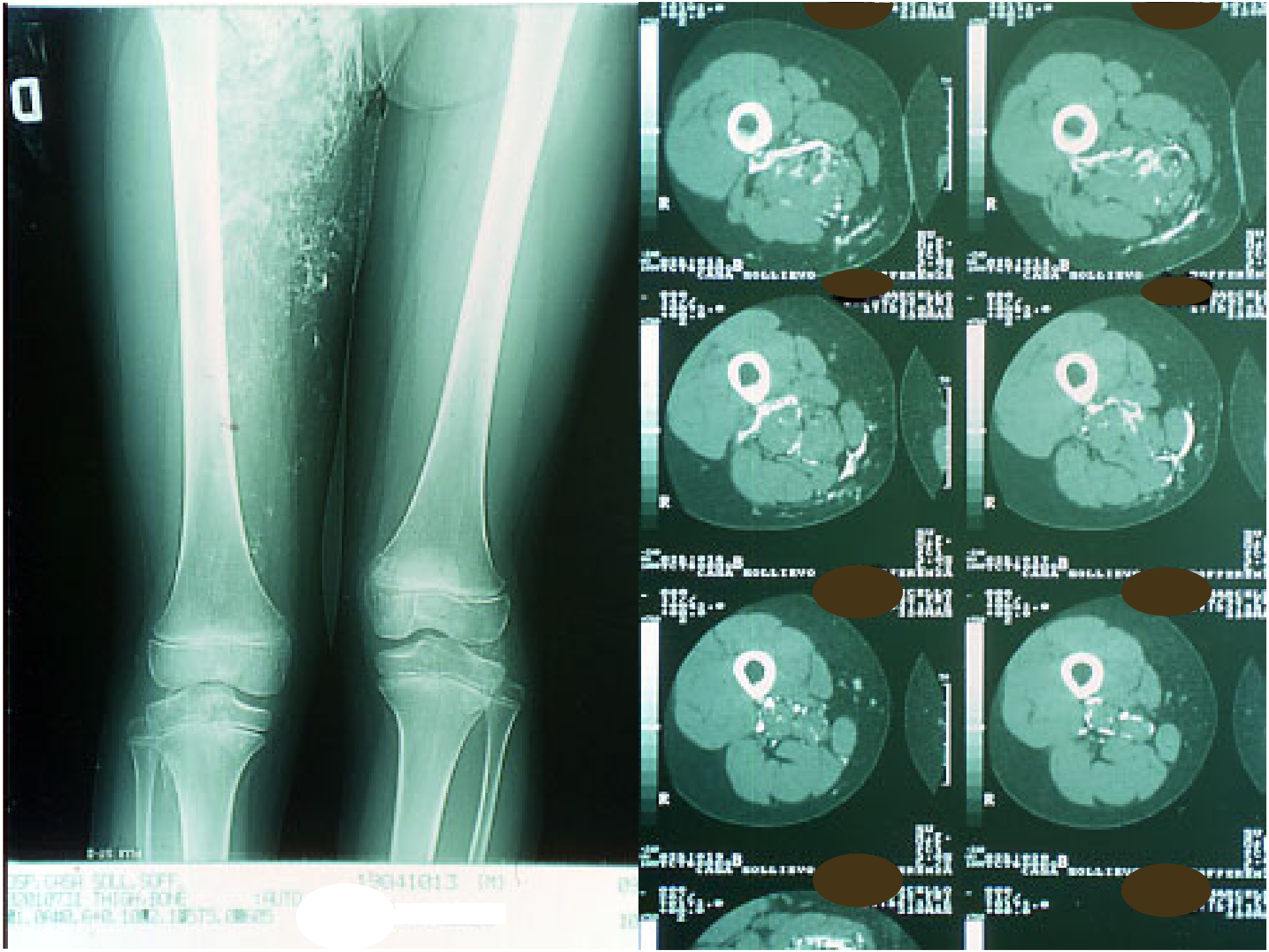
From Kaplan FS, Shore EM, J Bone Min Res.2000

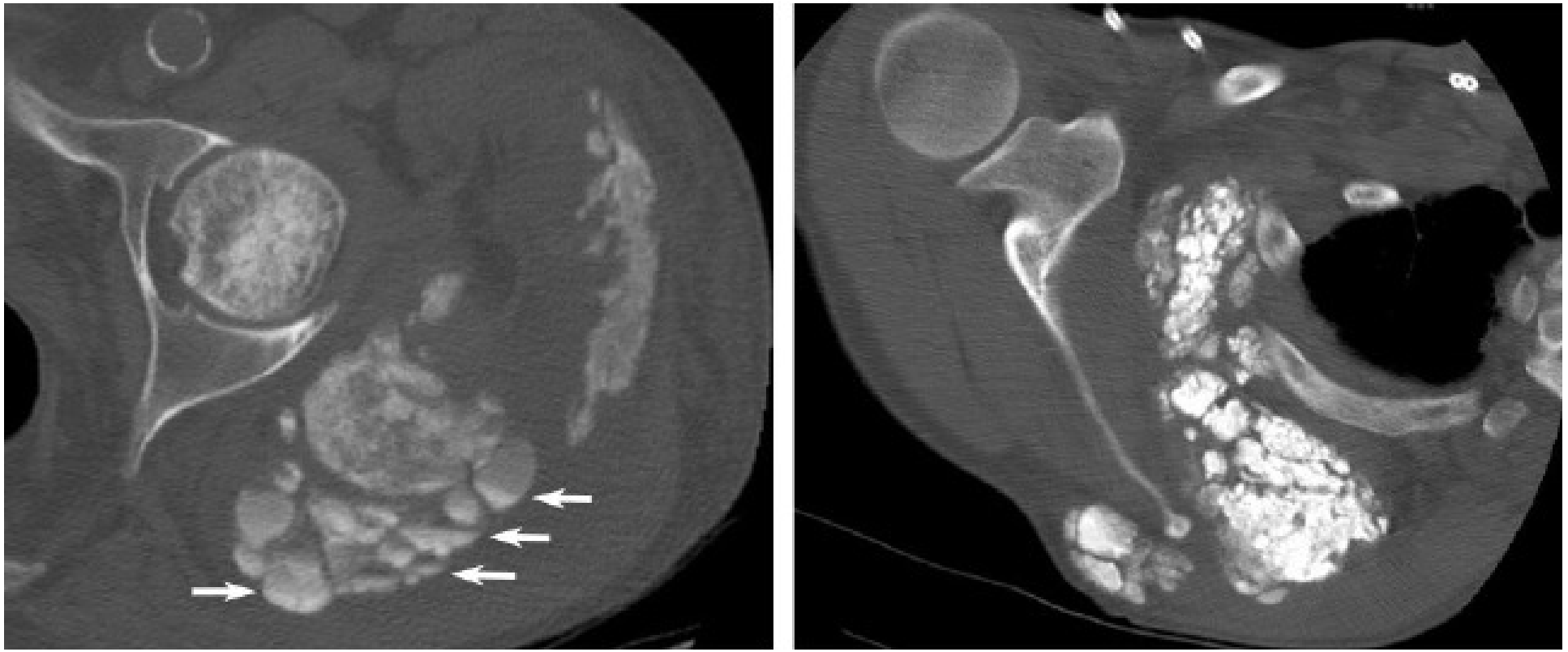
P.O.H. : RADIOLOGY

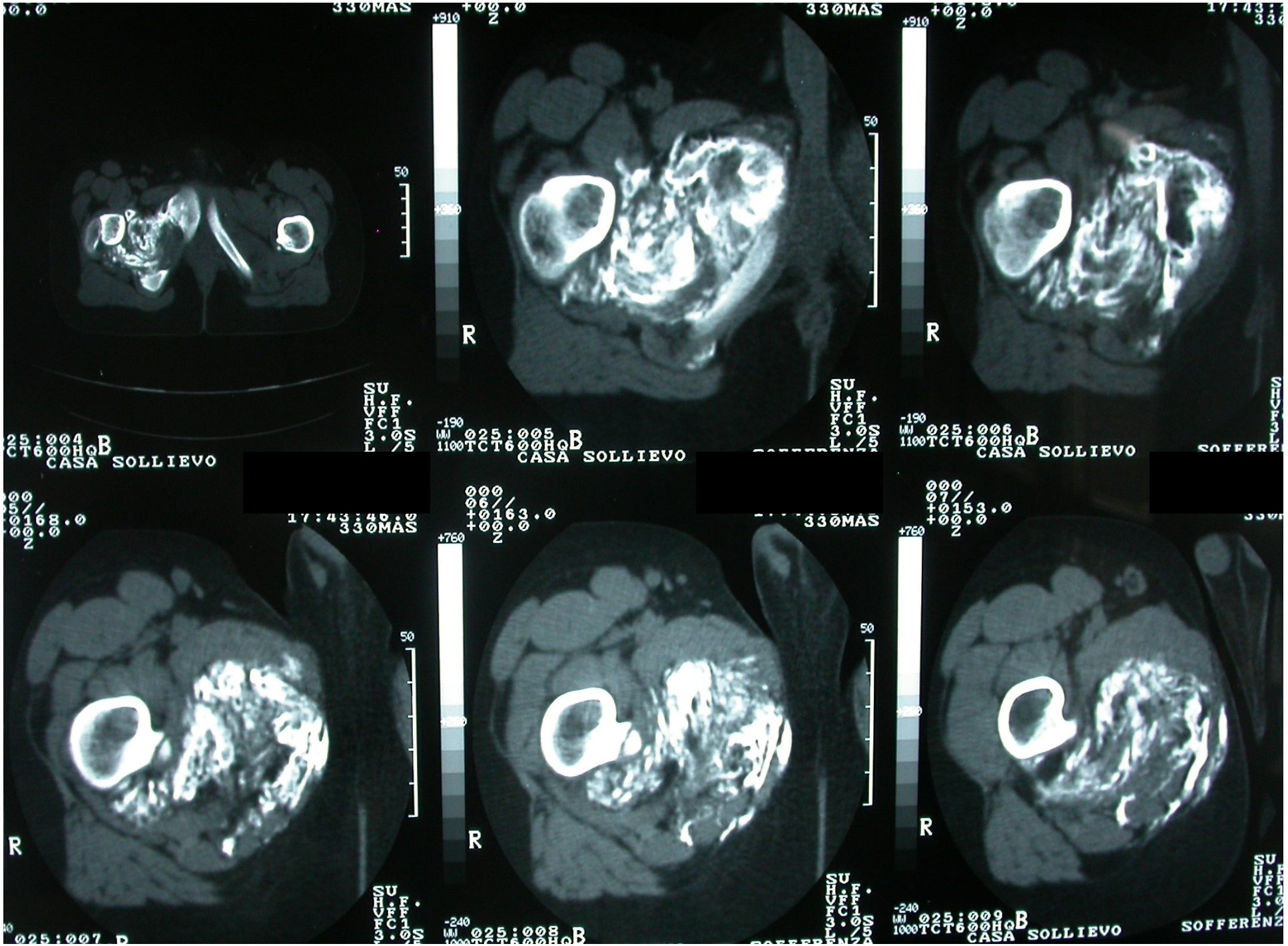
The radiological aspect is quite characteristic.

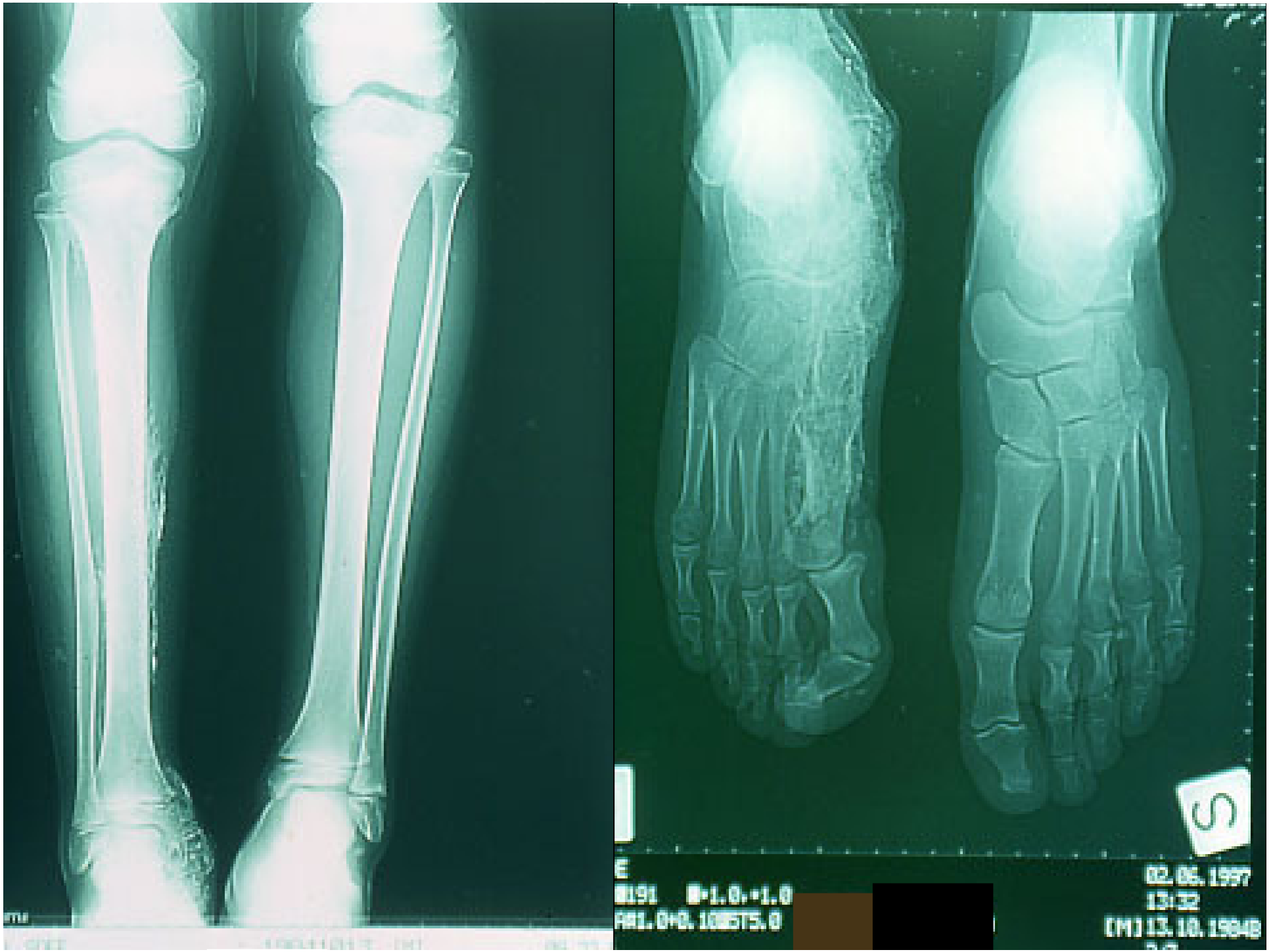
- The bone formations put on a network- or lace-like aspect, sometimes vaguely lacunar, full of gaps, corresponding to those “vine shoots” that become deeper in the tissues following neurovascular-connective bundle seen at macroscopic examination.
- Secondary deformity

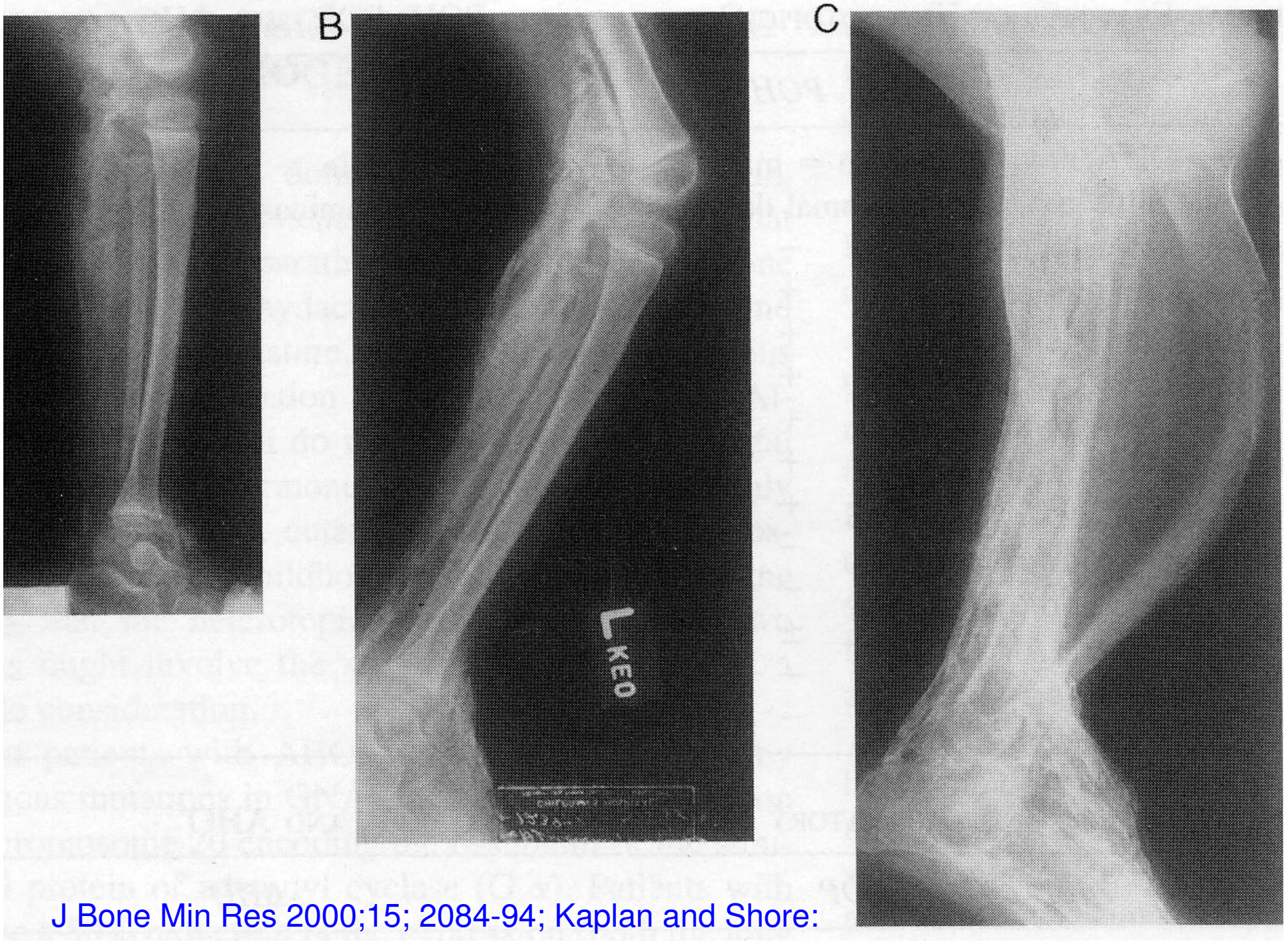







330MAS
+910
50
R
CASA SOLLIEVO
SOFFERENZA


S
02.06.1997
13:32
13.10.1984



J Bone Min Res 2000;15; 2084-94; Kaplan and Shore:

GENETICS

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

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 (network - 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 ASPECT

POH : DIAGNOSI DIFFERENZIALE

	POH	FOP	AHO	OC
➢ FORMATION OF ECTOPIC BONE	+	+	+	+
➢ INHERITANCE	GNAS	ACVR1	GNAS	GNAS
➢ MEMBRANEOUS BONE	+	-	+	+
➢ ENDOCHONDRAL BONE	-	+	-	-
➢ SKIN INVOLVEMENT	+	-	+	+
➢ INVOLVEMENT OF FAT TISSUE	+	-	+	+
➢ INVOLVEMENT OF MUSCLES	+	+	-	-

From Kaplan FS, modified,1996

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

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	+	-	+	+

Adegbite et al. Am J Med Gen 2008

POH : DIAGNOSI DIFFERENZIALE (2)

	POH	FOP	AHO	OC
➢ MALFORMATION OF BIG TOE	-	+	-	-
➢ SKIN TO MUSCLE PROGRESSION	+	-	-	-
➢ SEVERE IMMOBILIZZATION	+	+	-	-
➢ SEVERE SCOLIOSIS	-	+	-	-
➢ HORMONE IMBALANCE	-	-	+	-
➢ POST-INIECTIONS BONE FORMATION	-	+	-	-
➢ SEVERE FLARE-UPS	-	+	-	-

From Kaplan FS, modified,1996

DIAGNOSTIC DIAGRAM

- **MEDICAL EXAMINATION** rash – nodules, morphological aspect, articular blocks **(d.d. AHO, FOP)**
- **FAMILY ANAMNESIS (sometimes mute)**
- **BIOPSY (ossification, non calcium deposit)**
- **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)**
- **GNAS GENE MUTATION (to confirm clinical diagnosis , but may be present also in AHO and OC, and may be absent in all)**

Diagnostic and mutational spectrum of progressive osseous heteroplasia (POH) and other forms of GNAS-based heterotopic ossification.

- Age of onset
- Presence and location of HO
- Depth of HO
- Progression of HO
- Istopathology of HO
- AHO features
- Endocrine evaluation

GNAS mutation analysis

Adegbite N.S. et al. Am J Med Genet A. 2008 Jul Am J Med Genet A. 2008 Jul

DIAGNOSTIC DIAGRAM

MEDICAL EXAMINAT.

MORPHOLOGICAL ASPECT
RASH – NODULES
ARTICULAR BLOCKS

ANAMNESIS

BIOPSY → CALCIFICATION (*CALCINOSIS*)
OSSIFICATION

LABOR. FINDINGS
(Ca – P – PhAl
PTH – CaU – TSH)

[-] → **POH – OC**
PPHP

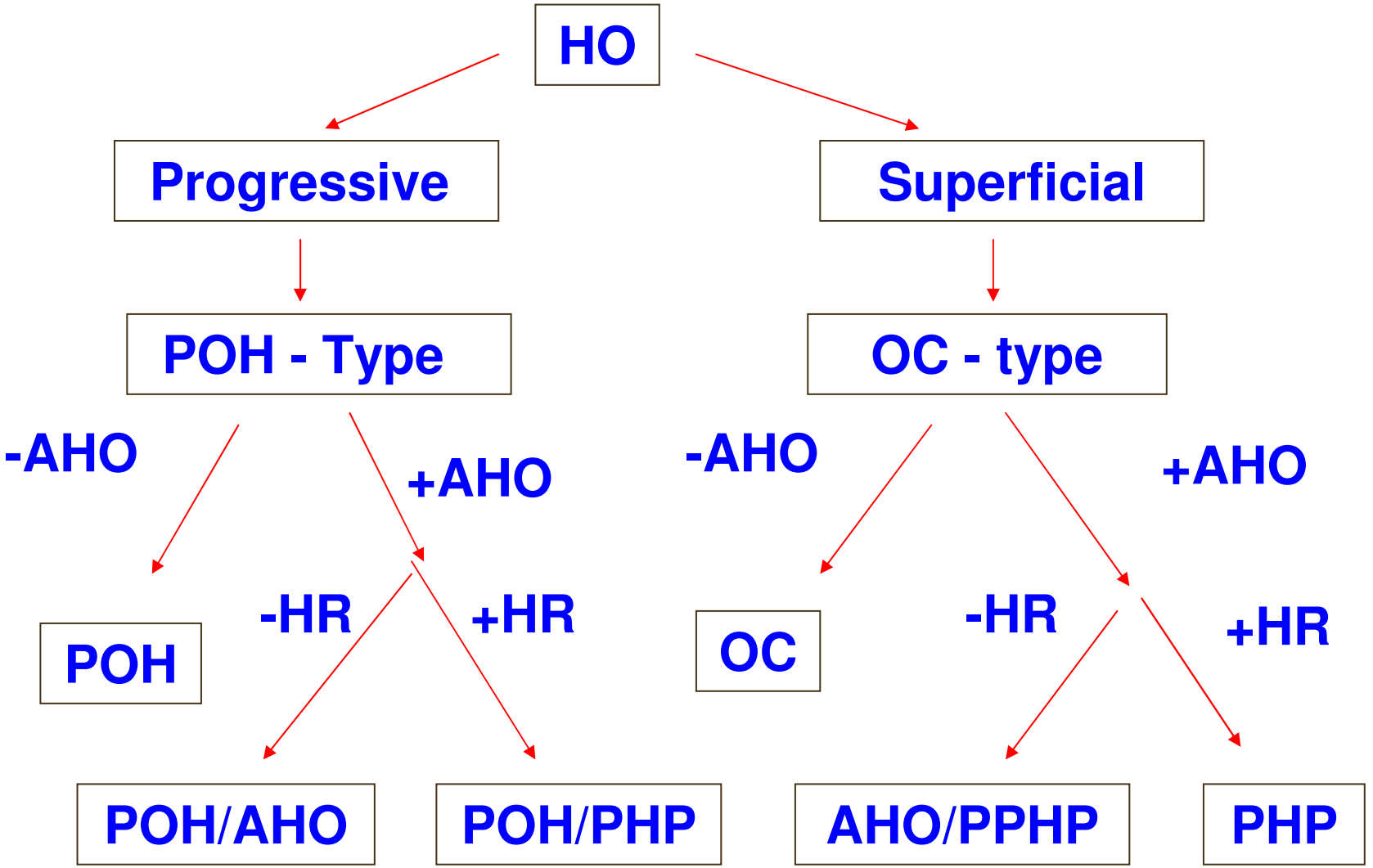
[+] → **PHPIa**

IMAGING
(Rx – ETG – CTscan)
DEEP OSSIFIC.

NO → **PPHP – PHPIa – OC**

YES → **POH**

DIAGNOSTIC DIAGRAM



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

- Esistono casi sporadici (mutazioni) e casi familiari, ma nella valutazione della familiarità bisogna tener conto del fatto che:
- Alcuni Autori hanno inoltre osservato l'assenza di manifestazioni fenotipiche in 2 soggetti portatori di mutazioni GNAS, componenti di famiglie con altri membri affetti. (mancata penetranza?mosaicismo?)
- In uno studio in 5 casi su 18 non si sono evidenziati mutazioni GNAS
- Le mutazioni del gene GNAS possono portare anche a AHO, ma anche all'OC e nella stessa famiglia!

- Le mutazioni inattivanti del gene GNAS quando ereditate per via materna danno PHPIa
- Quando ereditate per via paterna danno PPHP o POH
- Conferma da studi sui casi familiari
- Nei casi sporadici la mutazione nella POH insorge sempre sull'allele paterno

Dobbiamo quindi pensare che La forma clinica classica di POH è un estremo di un ampio spettro di condizioni patologiche geneticamente correlate.

Da considerare quindi come fenotipi differenti da mutazioni dello stesso gene (mutazioni alleliche)

È da considerare che

- La proteina $G_s\alpha$ viene normalm. espressa biallelicam. in molti tesssuti (1 solo allele è insufficiente: aploinsufficienza), ma non in tutti
- L'imprinting genomico fa si che prevalga la comparsa dell'una o altra patologia (descritti soggetti con patologie associate!)
- Probabilm. intervengono altri prodotti dello stesso gene [almeno 3 sotto osservazione: uno trascritto solo dall'allele materno (NESP55), due da quello paterno (1A e XLαs)]
- È possibile che intervenga un secondo gene
- È possibile l'effetto di altri loci adiacenti

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)**
- **INIBITORI ANGIOGENESI**
- **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 qui 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!*)

Grazie!

Associazione Italiana per l'Eteroplasia Ossea Progressiva ONLUS