Primer hiperoksalüri tip 1 olguları

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PRİMER HIPEROKSALÜRILI IKI KARDEŞTE TANı VE IZLEM

THE DIAGNOSIS AND FOLLOW-UP IN TWO BROTHERS WITH PRIMARY HYPEROXALURIA

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ÖZET

Son dönem böbrek hastalığına ulaşmış, bilateral böbrek taş hastalığı saptanan 16 yaşında erkek hastaya kronik hemodiyaliz tedavisi başlandıktan sonra, böbrek taş hastalığı ve tekrarlayan idrar yolu enfeksiyonları nedeni ile total nefrektomi uygulandı. Nefrektomi materyali oksalozis ile uyumlu bulundu. Olgunun dörtbuçuk yaşındaki erkek kardeşi incelendiğinde, idrarda yüksek oksalat atılımı bulundu ve primer hiperoksalüri tanısı aldı. Özellikle soygeçmişinde böbrek taş hastalığı olan, kronik böbrek yetmezliği nedeni ile böbrek transplantasyonuna hazırlanan hastalarda, ülkemizde akraba evliliğinin sıklığı da gözönüne alınarak primer hiperoksalüri için daha yakından inceleme yapılması gerekmektedir.

Primer hiperoksalüri ile ilişkili klinik ve laboratuvar verilerin kısıtlılığı nedeni ile, kronik hemodiyaliz programında bulunan nefrokalsinozis ve/veya böbrek taş hastalığı olan olgularda doku incelemesi etyolojinin aydınlatılmasını sağlayabilir.

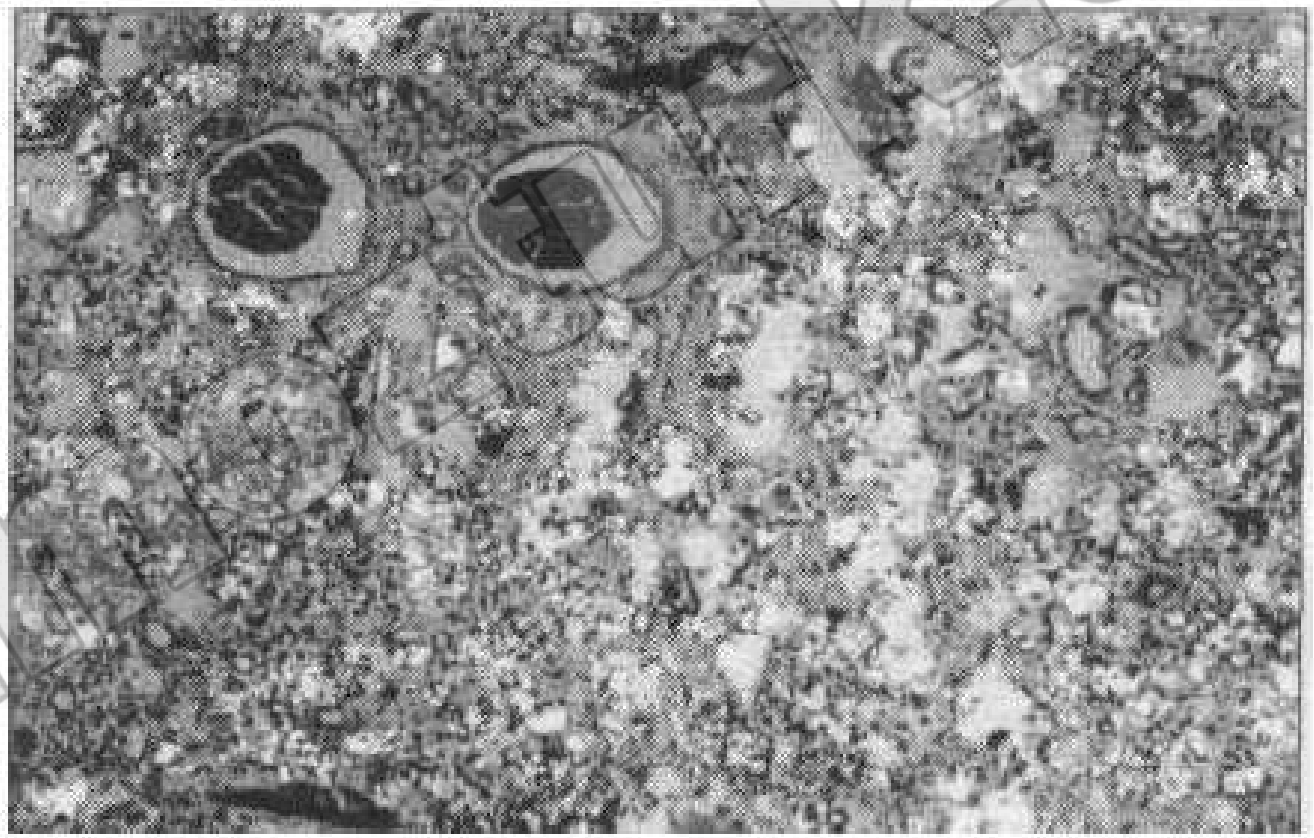
SUMMARY

A 16 year old boy with end stage renal disease secondary to bilateral urolithiasis underwent bilateral nephrectomy because of recurrent urinary tract infections.Histopathologic examination of the renal tissue was compatible with oxalosis.After that, the ounger brother of the patient was found to excrete high levels of oxalate in the urine.Thus, the diagnosis of primary hyperoxaluria was made in these siblings.

We think that the patients being evaluated for renal transplantation due to end stage renal disease and having a family history of urolithiasis should also be evaluated for primary hyperoxaluria, taking the high rate of consanguinous marriage in our population into consideration.However, it is difficult to make the diagnosis of primary renal disease after end stage renal disease ensues.Thus, in the patients with nephrocalcinosis and / or renal stones undergoing to chronic hemodialysis, evaluation of the renal tissue could be considered in revealing the underlying etiology, since the clinical and laboratory data related to primary hyperoxaluria are limited.

Olgu 1

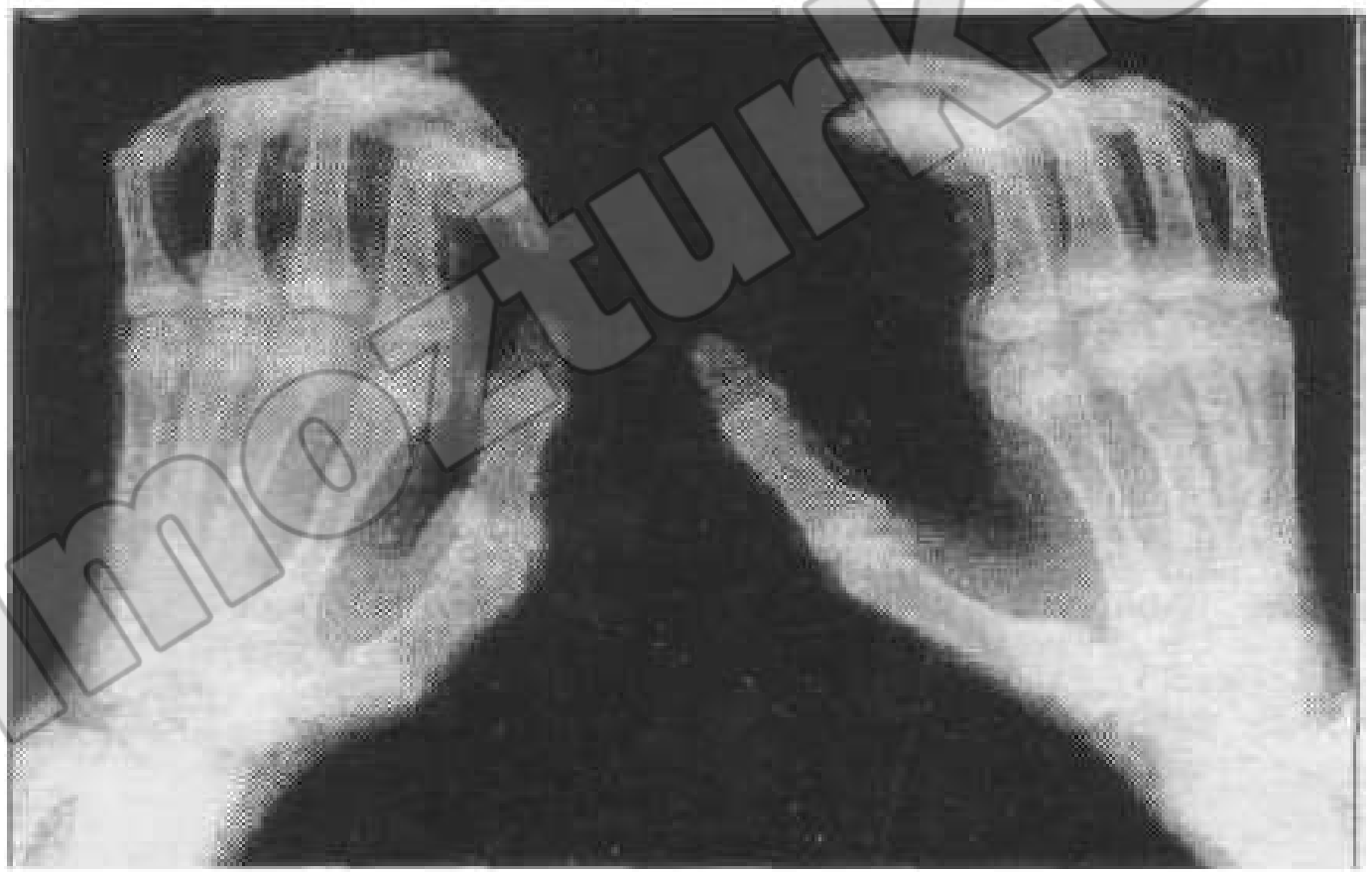
- Nefrektomi materyalinin patolojik incelemesi



Resim 1: Polarize ışıkta tübüler lümenleri dolduran, parankim içine ilerlemiş, tüm korteks ve medullada yaygın olarak bulunan oksalat kristallerinin görünümü

Olgu 1

- Vasküler CaOx Birikimi: İskemik hasar, polinörit
- İlerleyici kemik ve eklem hasarı
- Retinal lezyon yok



Resim 2: Osteopeni, epifiz-metafiz ilişkisinin yitirilmesi ve damar cidarlarında kalsiyum oksalat akümülasyonuna bağlı izlenebilen damar yapıları içeren direkt radyografi

Primary Hyperoxaluria: Simultaneous Combined Liver and Kidney Transplantation from a Living Related Donor

Ibrahim Astarcioglu, Sedat Karademir, Hüseyin Gülay, Seymen Bora, Hüseyin Astarcioglu, Salih Kavukcu, Mehmet Türkmen, and Alper Soylu

Primary hyperoxaluria type 1 (PH1) is a rare inherited metabolic disorder in which deficiency of the liver enzyme AGT leads to renal failure and systemic oxalosis. Timely, combined cadaveric liver-kidney transplantation (LKT) is recommended for end-stage renal failure (ESRF) caused by PH1; however, the shortage of cadaveric organs has generated enthusiasm for living-related transplantation in years. Recently, successful sequential LKT from the same living donor has been reported in a child with PH1. We present a sister-to-brother simultaneous LKT in a pediatric patient who suffered from PH1 with ESRF. Twelve months after transplantation, his daily urine oxalate excretion was decreased from 160 mg to 19.5 mg with normal liver and renal allograft functions. In addition to the well-known advantages of living organ transplantation, simultaneous LKT may facilitate early postoperative hemodynamic stability and may induce immunotolerance and allow for low-dose immunosuppression. (*Liver Transpl 2003;9:433-436.*)

tial LKT from living donors have been successfully performed for PH1.[4,5] To date, there have been no reports describing combined simultaneous LKT from the same living donor in the treatment of PH1 complicated with ESRF.

Case

A 9-year-old boy (32 kg) with hyperoxaluria, nephrocalcinosis, and urinary tract infection progressed to ESRF, with a glomerular filtration rate (GFR) of 18 mL/min/1.73 m^2 despite maximal medical management; he commenced dialysis in September, 2001. His older brother (20 years old) had died of severe systemic oxalosis and uremia waiting for a suitable combined cadaveric donor. His sister (19 years old, 65 kg) decided

Ardışık Karaciğer ve Böbrek Tx

- Yoğun HD ile doku CaOx depoları azaltılabilir

Yamauchi T. NDT 2001

Kombine Karaciğer –Böbrek Tx

- Erken kombine Tx ile doku oksalat yükünün artması önlenir
- Post-op sıvı dengesi kolaylaşır
- Uzun dönem HD ve riskleri önlenir
- İmmünolojik avantaj

Watts RWE. NDT 1991
Elis SR. NDT 2000
Rasmussen A. Transplantation 1995
Jeyarajah DE. Transplantation 1997

Table 1. Postoperative Liver and Kidney Graft Function

Postoperative days	1	3	7	15	30	60	120	240	300
AST (U/L)	102	45	34	27	24	22	24	23	21
Bilirubin (mg/dL)	0.99	0.93	0.93	0.87	0.8	0.76	0.82	0.56	0.62
PT (sec)	38	18.2	20.6	17.4	14.6	12.5	12.3	12.1	12.8
BUN (mg/dL)	24.5	8	21	16.7	18.7	16.5	14.2	11.4	12.4
Creatinine (mg/dL)	2	0.6	0.5	0.8	1.2	1	0.9	0.8	0.8
Oxalate (mg/24 h urine)	160	133	147	58	51	48	44	27	21

Combined Liver-Kidney Transplantation and Follow-Up in Primary Hyperoxaluria Treatment: Report of Three Cases

S. Kavukçu, M. Türkmen, A. Soylu, B. Kasap, Y. Öztürk, S. Karademir, S. Bora, İ. Astarcıoğlu, and H. Gülay

Transplantation Proceedings, 40, 316–319 (2008)

ABSTRACT

Introduction. Primary hyperoxaluria type-1 (PH1) is an autosomal recessive disorder caused by impaired activity of the hepatic peroxisomal alanine-glyoxilate aminotransferase, which leads to end-stage renal disease (ESRD) and requires combined liver-kidney transplantation (CLKT). Herein, we have reported 3 children diagnosed with PH1 who received CLKT.

Case 1. A 4.5-year-old boy with an elder brother diagnosed with PH1 was diagnosed during family screening when the sonography showed multiple calculi. Within 5 years he experienced flank pain, hematuria attacks, and anuric phases due to obstruction and received hemodialysis (HD) when ESRD appeared. CLKT was performed from his full-match sister at the age of 9.5. He is doing well at 5.5 years.

Case 2. A 7-year-old boy was admitted with polyuria, polydypsia, and stomach pain with renal stones on sonography. PD was instituted when serum creatinine and BUN levels were measured as high values. At the age of 10, CKLT was performed from his mother. His liver and renal function tests are well at 14 months after CKLT.

Case 3. A 2.5-year-old girl had attacks of dark urine without any pain; renal stones were imaged on sonography. She was diagnosed with PH1 and operated on several times due to obstruction. She received peritoneal dialysis and a cadaveric CLKT was performed when she was 9 years old. At the age of 16, she experienced chronic allograft nephropathy requiring HD and subsequent cadaveric donor renal transplantation at 1.5 years after inititation of HD.

Conclusion. Herein, we have presented the favorable clinical outcomes of patients with CKLT to indicate the validity of this treatment choice for PH1.

Tanı

Olgu 1

Klinik bulgular (kardeşinde PH1 bulguları, kendisinde böbrek taş hastalığı ve kronik böbrek hastalığı) ve hiperoksalüri*

Olgu 2

- Karaciğer dokusunda AGT enzim aktivitesi: 2.5 μmol/h/mg protein (aralık 19.1–47.9)

Olgu 3

- AGXT gen mutasyonu (Almanya)

* Daha sonra AGXT mutasyonu gösterildi

Table 1. Clinical and Laboratory Documentation of the Patients

	Case 1	Case 2	Case 3
Complaint	None	Polydipsia, frequency, abdominal pain	Dark urine
Age at diagnosis	4.5 y	7 y	2 y
History	Multiple renal stones were incidentally encountered by abdominal USG, which was performed for having an elder brother with the diagnosis of PH1	Dialysis was started when renal function tests were simultaneously found impaired in addition to nephrolithiasis.	Recurrent operations due to renal stones
Parental consanguinity	—	+ (1°)	+ (1°)
History of the disease in relatives	+	—	—
Age at the beginning of renal replacement	9.5 y	7 y	6 y
Type of renal replacement	PD + HD	PD	PD
Age at CLKT	9.5 y	10 y	9 y
Donor type	Living donor (elder sister)	Living donor (mother)	Cadaver
Rejection			
Renal	—	—	+
Hepatic	—	—	+
Re-transplantation			
Renal	—	—	+ (17,5 y)
Hepatic	—	—	—
Posttransplantation follow-up duration			
1st transplantation	5.5 y	14 m	8 y
2nd transplantation	—	—	6 m
Latest laboratory values			
BUN	24.1	24.4	9.9
Creatinine	1.26	1.00	0.83
AST	22	58	31
ALT	16	37	44
T.bil/D.bil	0.69/0.23	0.34/0.11	0.22/0.03
GGT	13	65	133
T.pr/alb	7.4/4.9	5.4/3.5	6.8/4.5

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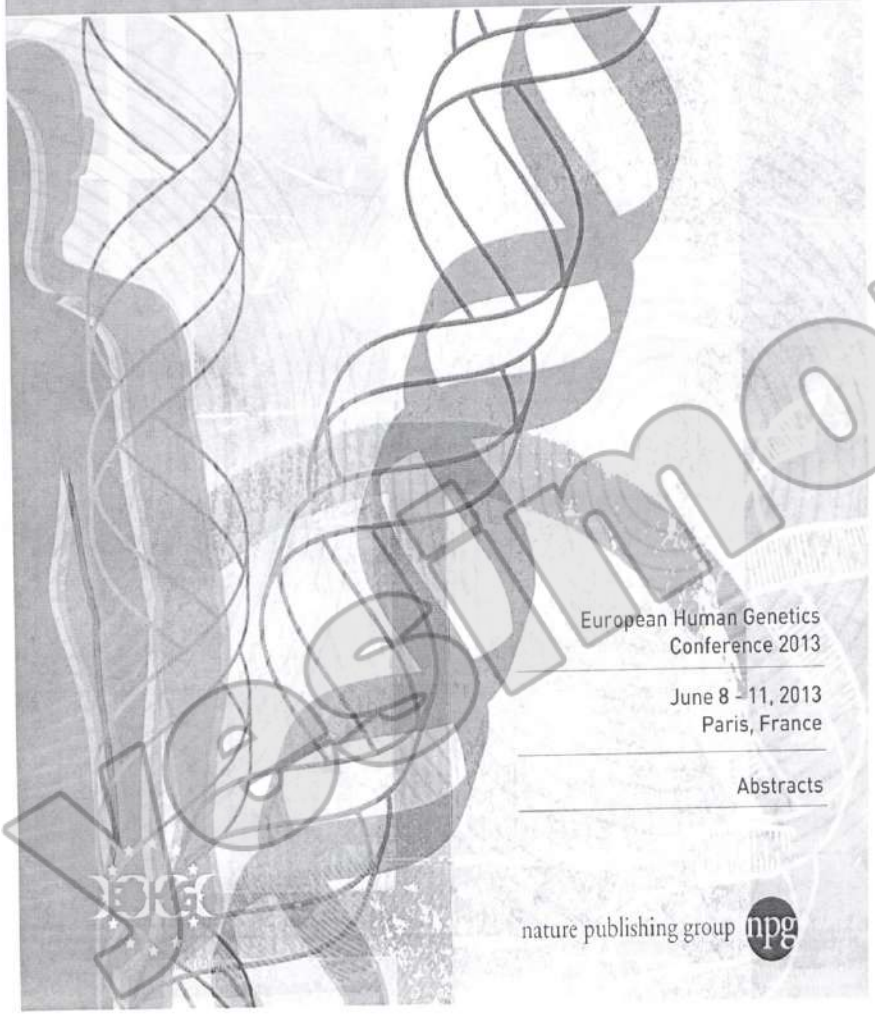

P04.34

Mutation analysis of the *AGXT* gene in combined liver-kidney and isolated liver transplanted six children for primary hyperoxaluria type 1: a single center experience

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Primary hyperoxaluria type I (PH1) is an autosomal recessive rare disorder, characterized by progressive kidney failure, caused by mutations in the alanine: glyoxylate aminotransferase (*AGXT*) gene which leads to the failure of the alanine: glyoxylate aminotransferase activity in the liver. Although targeted sequence analysis of exons 1, 4 and 7 of *AGXT* has been proposed for first line genetic testing, the sequence of the entire coding region is recommended. We aimed to detect the *AGXT* gene mutations causing PH1 in combined liver-kidney, isolated liver, sequential kidney and liver-kidney transplanted six Turkish children (Five male) with phenotypic characteristics of PH1. Median age at diagnosis was 119 months (Range 42-178 months). The entire coding region including exon intron boundaries of the *AGXT* gene were sequenced in patients.

We detected six mutations PH1causing and two minor allele polymorphism in six patients. The entire patients had at least one PH1 related mutation. Patient 1 had homozygous minor allele polymorphisms Pro11Leu in exon 1 and Ile340Met in exon 10, and mutation Met195Arg in exon 5.

Patient 2 had homozygous mutation c. 33_34insC in exon 1. Patient 3 was compound heterozygous for mutations Gly170Arg in exon 4 and c.846+1G>A in intron 8 and heterozygous minor allele polymorphisms Ile340Met in exon 10. Patient 4 had homozygous mutation c.823-824dupAG in exon 8. Patient 5 and 6 had homozygous mutation c.976delG in exon 10. Mutational analysis of the *AGXT* gene in PH1 patients can be a useful tool for establishing the diagnosis and choosing an appropriate therapeutic strategy.

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	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Complaint	Abd. pain, polyuria, polydipsia	Family history	Recurrent stones	Recurrent stones	Abdominal pain	Family history
Clinical find.	Nephrolithiasis, ESRD	Nephrolithiasis	Nephrolithiasis, ESRD	Nephrolithiasis	Nephrolithiasis, ESRD	Nephrolithiasis
Age at diagnosis (months)	118	42	173	108	178	120
Family hist. of disease	Sister	Brother (Exitus)	-	Brother	+	+
Age at CLKT (months)	123	115	176	118	180	168
Donor type	Living (mother)	Living (sister)	Living (sister)	Living (father)	Living (mother)	Living (father)
Transplant	CLKT	CLKT	CLKT	LT	CLKT	LT
$U_{oxalate}$ (mmol/1.73m^2/24h)	0.52	1.5	2.12	1.52	Unknown	Unknown
AGT activity	Low	Unknown	Unknown	Low	Unknown	Unknown

The entire coding region including exon intron boundaries of the *AGXT* gene were sequenced in patients and their family.

We detected six mutations PH1causing and two minor allele polymorphism in six patients.

Locat.	Sequence variant	Codon/ effect	Case	Major (Pro11) or minor (Leu11) haplotype	In vitro AGTactivity (% of normal) or how proven	Freqcy in controls	SNP db	Molecular phenotype	Reference
Exon 1	c.32C>T	p.Pro11Leu	1 (H)	minor	64% (Lumb and Danpure, 2000)	0.20	rs34116584	5% of AGT rerouted from peroxisomes to mitochondria	(Purdue et al., 1990)
Exon 10	c.1020A>G	p.Ile340Met	1 (H) 3 (h)	minor (occasion. major)	76-117% (Lumb and Danpure. 2000)	0.15	rs4426527	Little or none	(Purdue et al., 1992)
Exon 4	c. 508G>A	p.Gly170Arg	3 (h)	major	40% on minor, 68% on major (Lumb and Danpure, 2000)			Peroxisome to mitochondrion mistargeting	(Purdue et al., 1990)
Exon 5	c.584T>G	p.Met195Arg	1 (H)	minor	No other mutation found				(Frishberg et al., 2005)
Exon 1	c.33delC	p.Lys12fs	2 (H)	major				Frameshift	(Pirulli et al., 1999)
Exon 8	c.823_824dupAG	p.Ser275fs	4 (H)	unknown				Frameshift	(Yuen, et al., 2004)
Exon 10	c.976delG	p.Val326fs	5,6 (H)	major				Frameshift	(Pirulli et al., 1999)
Intron 8	c.846+1G>A		3 (h)	unknown				splice site mutation	(Williams et al.,2009)

No	K/E	Tanı yaşı	Yakınma	Tanı yöntemi	SDBY yaşı	Transplant	Son kreatinin	Son GFR	Mortalite
1	E	12	SDBY, taş	Klinik, patoloji	12	-	-	-	Ex
2	E	4	Öykü, taş	Klinik*, Aile öykü	9	CLKT (canlı)	1.39	70	-
3	K	2	Taş	Mutasyon	6	CLKT (kadavra) (Almanya) KT x 2 (kadavra)	1.08	73	-
4	E	7	Taş	Enzim*	10	CLKT (canlı)	1.38	73	-
5	E	16	SDBY, taş	Enzim*	16	CLKT (canlı)	1.44	61 (2015)	-
6	K	12	Öykü, taş	Aile öykü, klinik*	20	LT (canlı)	6.38	9 (2014)	-
7	E	10	Taş	Enzim*	13	CLKT (canlı)	1.22	75 (2015)	-
8	E	7	Taş	Enzim*	-	LT (canlı)	0.66	90	-
9	E	17	SDBY, taş	Aile öykü, klinik*	17	CLKT (canlı)	1.2	88	-
10	E	4	SDBY, taş	Mutasyon	8 ay	-	-	-	Ex

J Child Orthop (2008) 2:205–210
DOI 10.1007/s11832-008-0082-4

ORIGINAL CLINICAL ARTICLE

Skeletal features of primary hyperoxaluria type 1, revisited

Samer El Hage · Ismat Ghanem · André Baradhi · Chebel Mourani · Samir Mallat · Fernand Dagher · Khalil Kharrat

- Kemik semptomları diyaliz başlangıcından 1-2 yıl sonra ortaya çıkar.

- Bazı radyolojik bulgular oksalosis için patognomoniktir:

✓ Dens metafizyel bant (DMB)
✓ Lusent metafizyel bant (LMB)
✓ Vertebral osteokondensasyon

✓ DMB genişliği α SDBH süresi

✓ DMB'ın büyüme plağına uzaklığı α diyaliz süresi

✓ LMB sadece SDBH hastalarında görülür; tipik olarak uzun kemiklerde fizis ile komşu DMB arasında bulunur

✓ Vertebral kondensasyonlar önce süperior ve inferior vertebral endplate bölgesinde olur ve "rugger-jersey spine" görüntüsü oluşturu

Table 1 Clinical and radiographic skeletal manifestations for each patient. *DMB* dense metaphyseal band, *LMB* lucent metaphyseal band

Patient (gender)	Age (years)	Renal function	Duration of dialysis	DMB	LMB	Spondylolysis	Fractures	Bone pain	Urinary lithiasis	Nephrocalcinosis
1 (Female)	8	ESRD	4½ years	+	+	−	+	+	+	−
2 (Male)	10	ESRD	1 year	+	+	−	−	+	+	+
3 (Female)	15	ESRD	2½ years	+	+	+	−	+	+	+
4 (Male)	2	ESRD	3 months (peritoneal)	+	+	−	+	+	+	+
5 (Female)	16	Severe failure	−	−	−	−	−	−	+	+
6 (Female)	4	Moderate failure	−	−	−	−	−	−	+	−
7 (Male)	16	Moderate failure	−	−	−	−	−	−	+	+
8 (Female)	7	Moderate failure	−	−	−	+	−	−	+	−
9 (Female)	6	Moderate failure	−	±	−	+	−	−	+	−
10 (Female)	2	Moderate failure	−	±	−	−	−	−	+	−
11 (Male)	17	Mild failure	−	−	−	−	−	−	−	−
12 (Male)	9	Mild failure	−	−	−	−	−	−	+	−

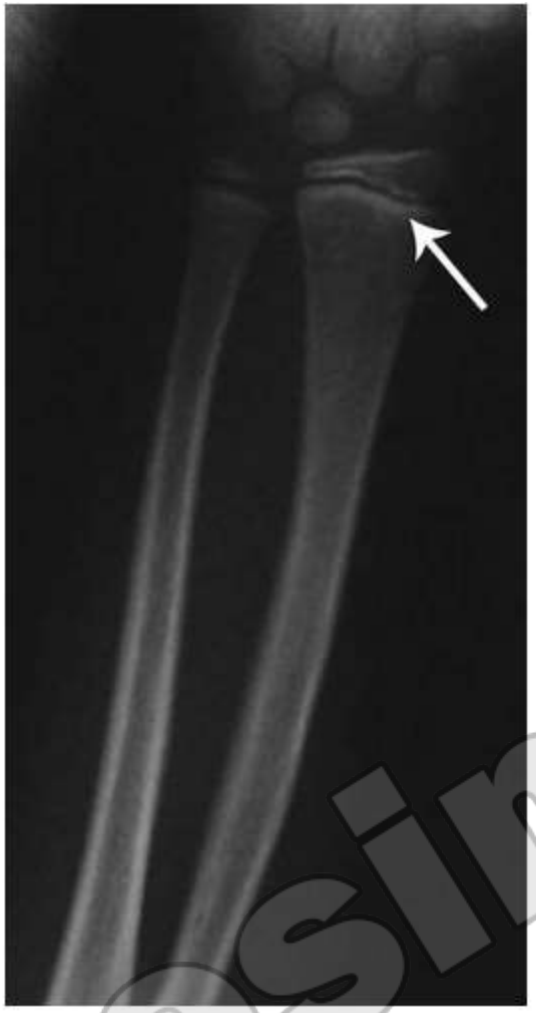


Fig. 1 Anteroposterior (AP) radiograph of the wrist of a 10-year-old patient (patient 2) showing an early dense metaphyseal band (DMB) on the metaphyseal aspect of the distal radial physis

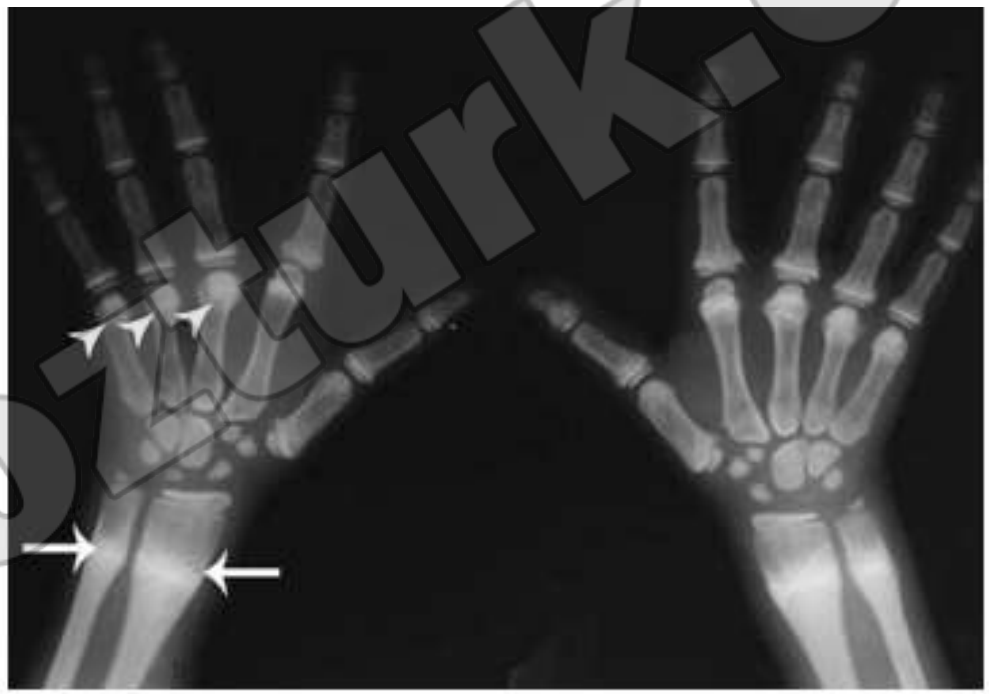


Fig. 2 Anteroposterior (AP) radiograph of both hands of an 8-year-old patient undergoing dialysis (patient 1) showing late dense metaphyseal bands (DMBs; *arrows*). Note their width and their distance from the growth plates, compared with that shown in Fig. 1. Also, note the fractures of the distal aspect of the third, fourth and fifth metacarpals (*arrow heads*)

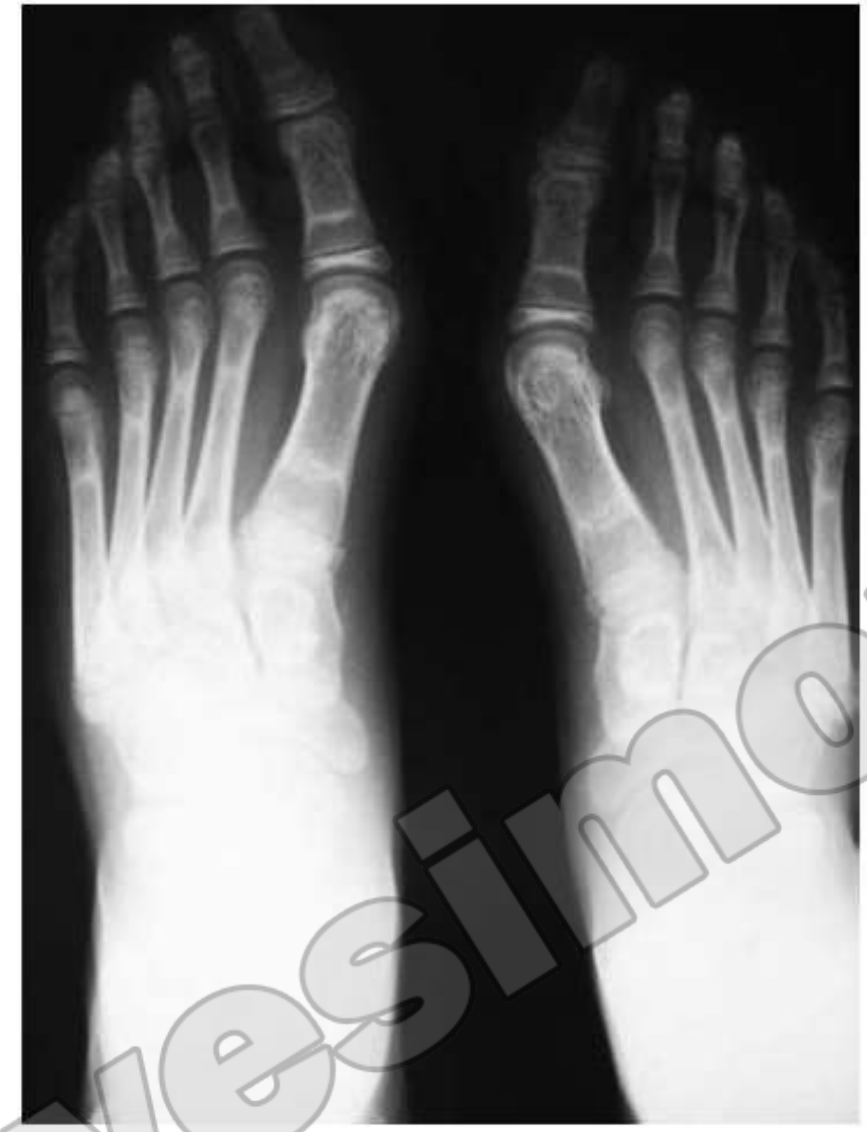


Fig. 3 Standing dorsoplantar radiograph of both feet in a 15-year-old patient (patient 3) showing lucent metaphyseal bands (LMBs) and dense metaphyseal bands (DMBs) in the proximal aspect of the first metatarsals

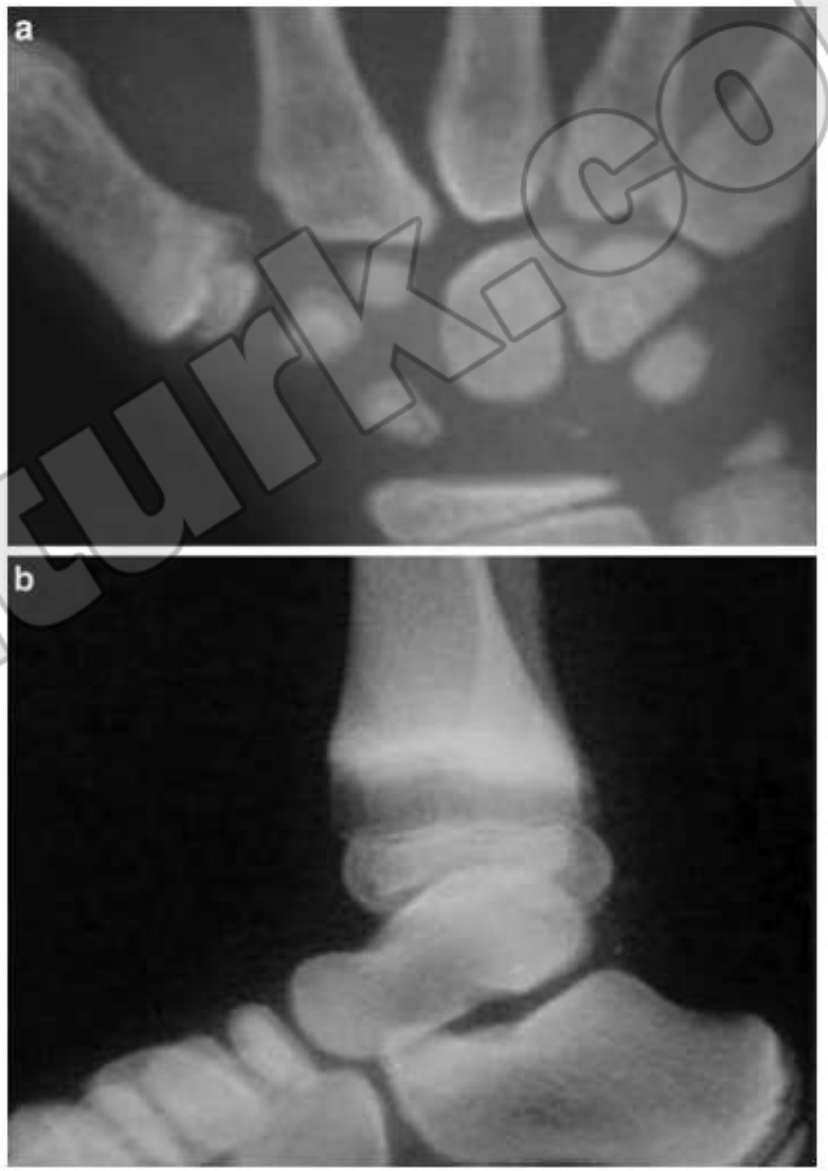


Fig. 4 a Anteroposterior (AP) radiograph of the wrist of patient 1 showing lucent rings surrounding the scaphoid and the trapezium. **b** Lateral radiograph of the left ankle of patient 3 showing lucent rings around the talus and navicular

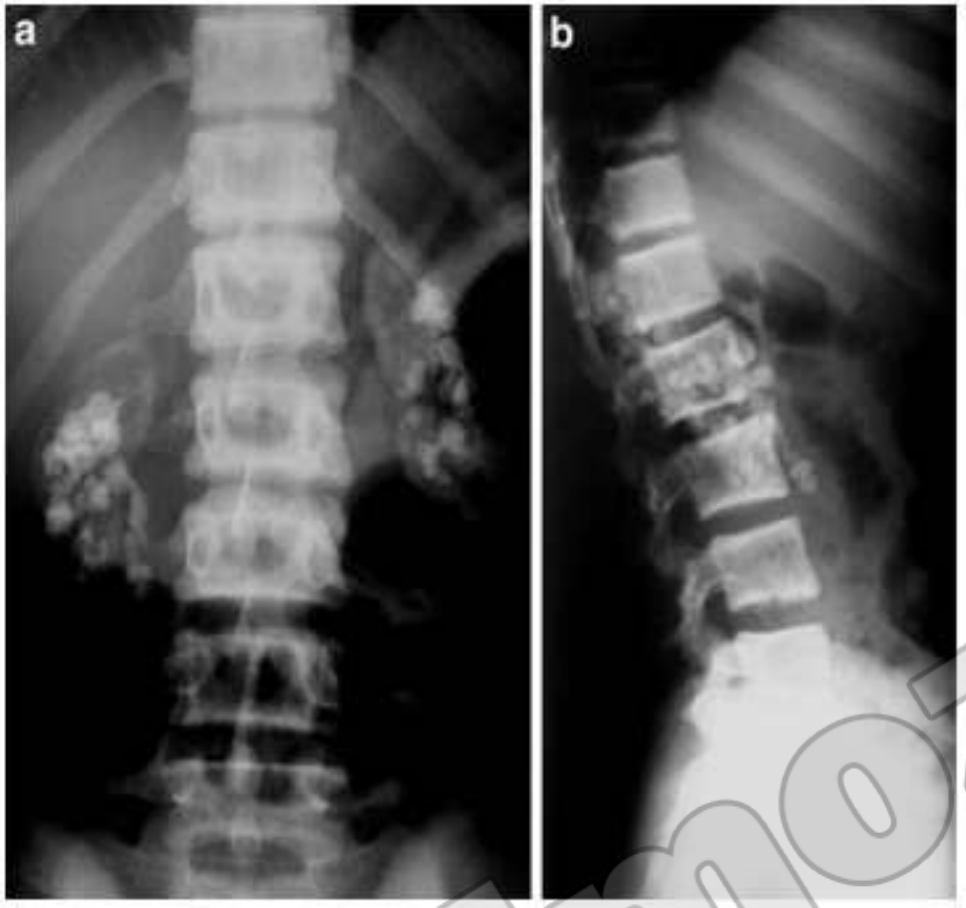


Fig. 5 Anteroposterior (AP; a) and lateral (b) radiographs showing the sclerotic superior and inferior end plates realizing a rugger-jersey spine appearance in a 10-year-old patient (patient 2). Also note the characteristic image of nephrocalcinosis

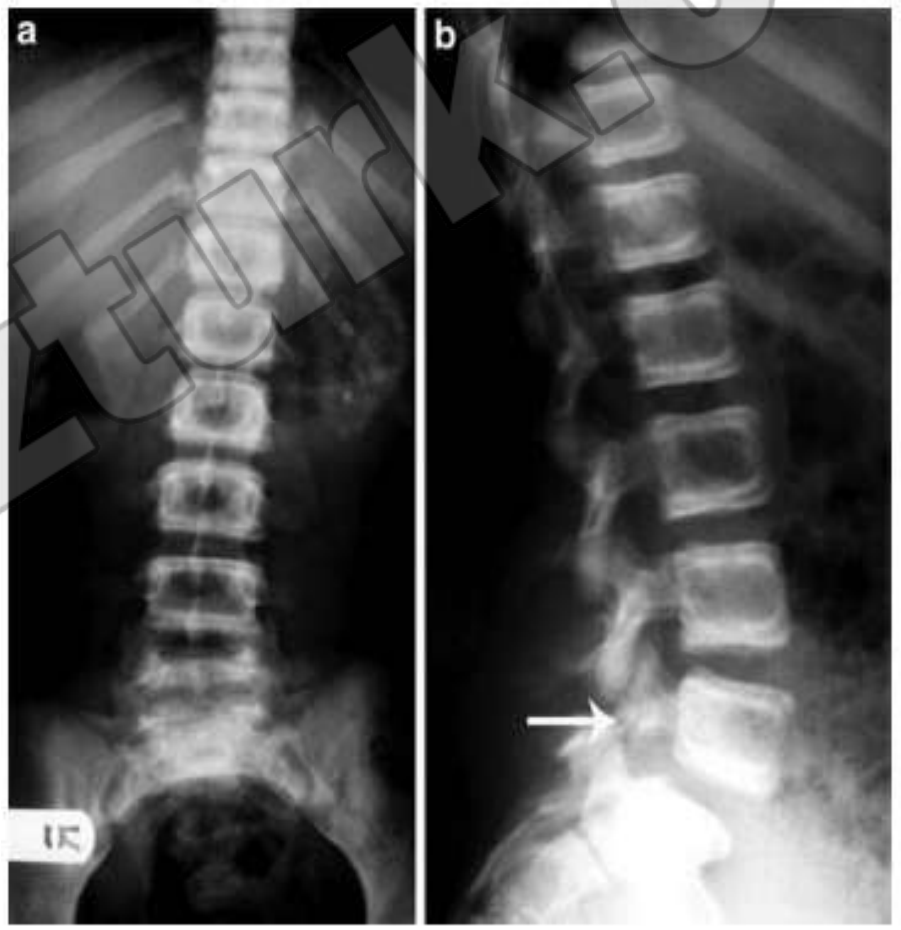
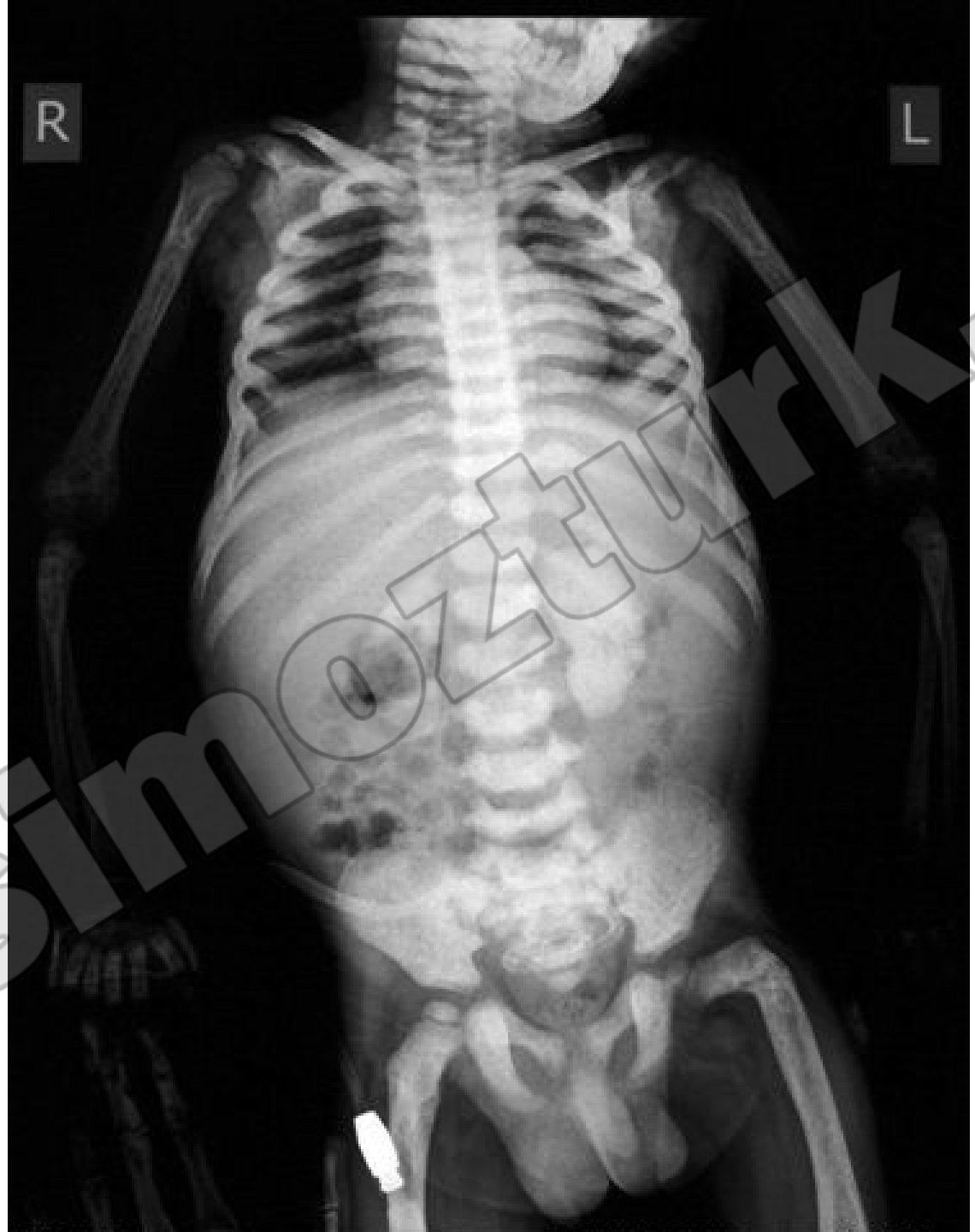
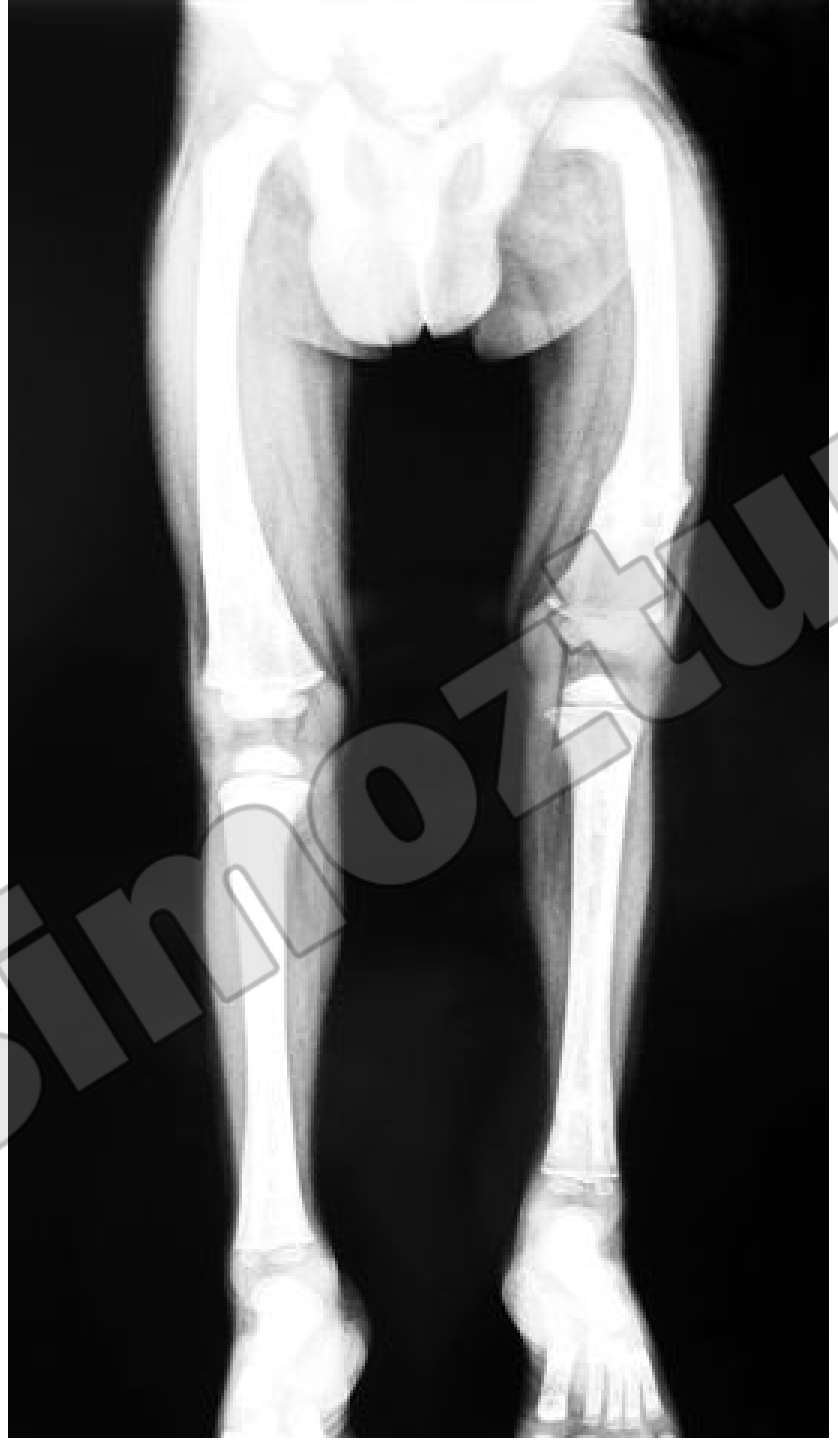
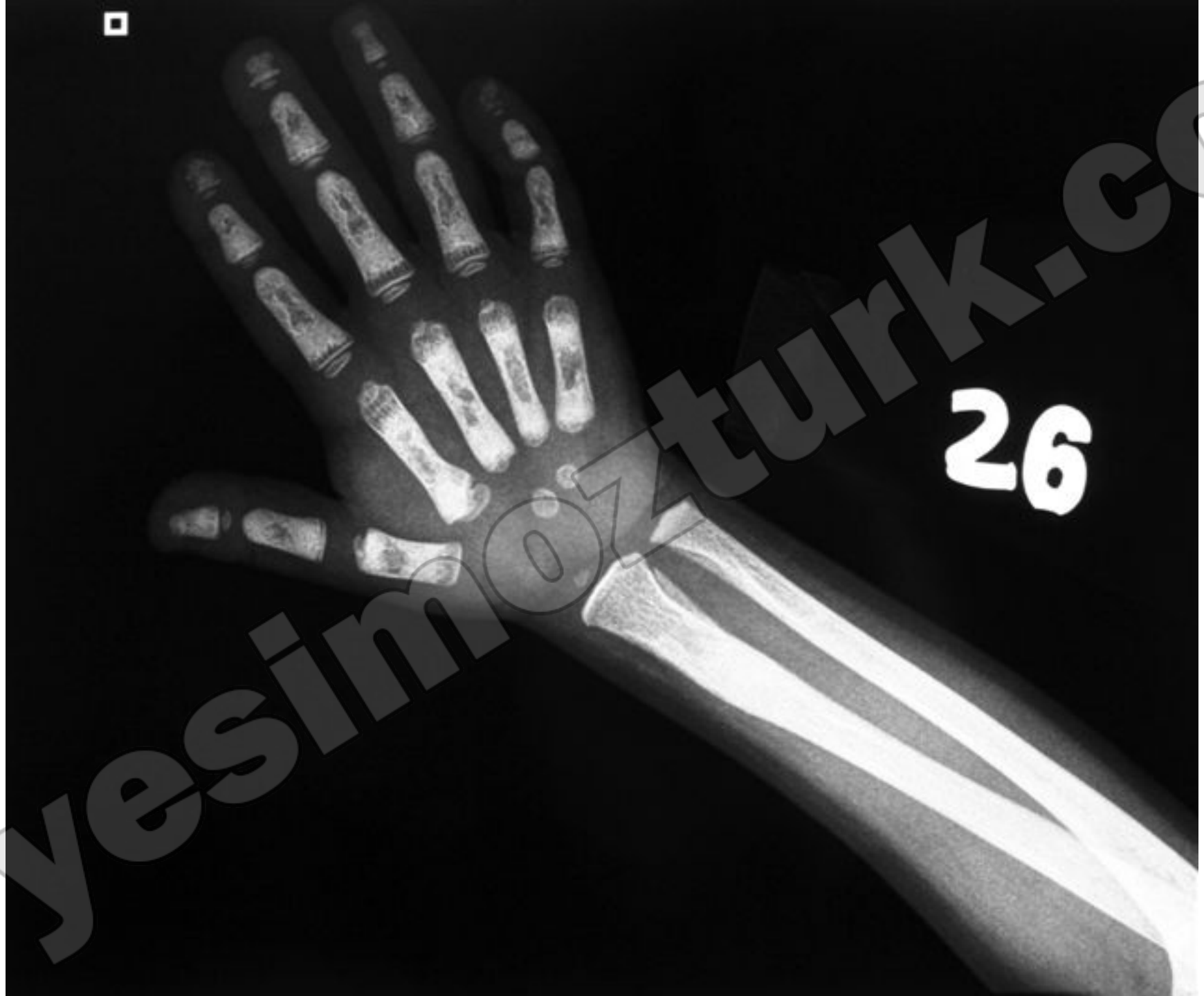
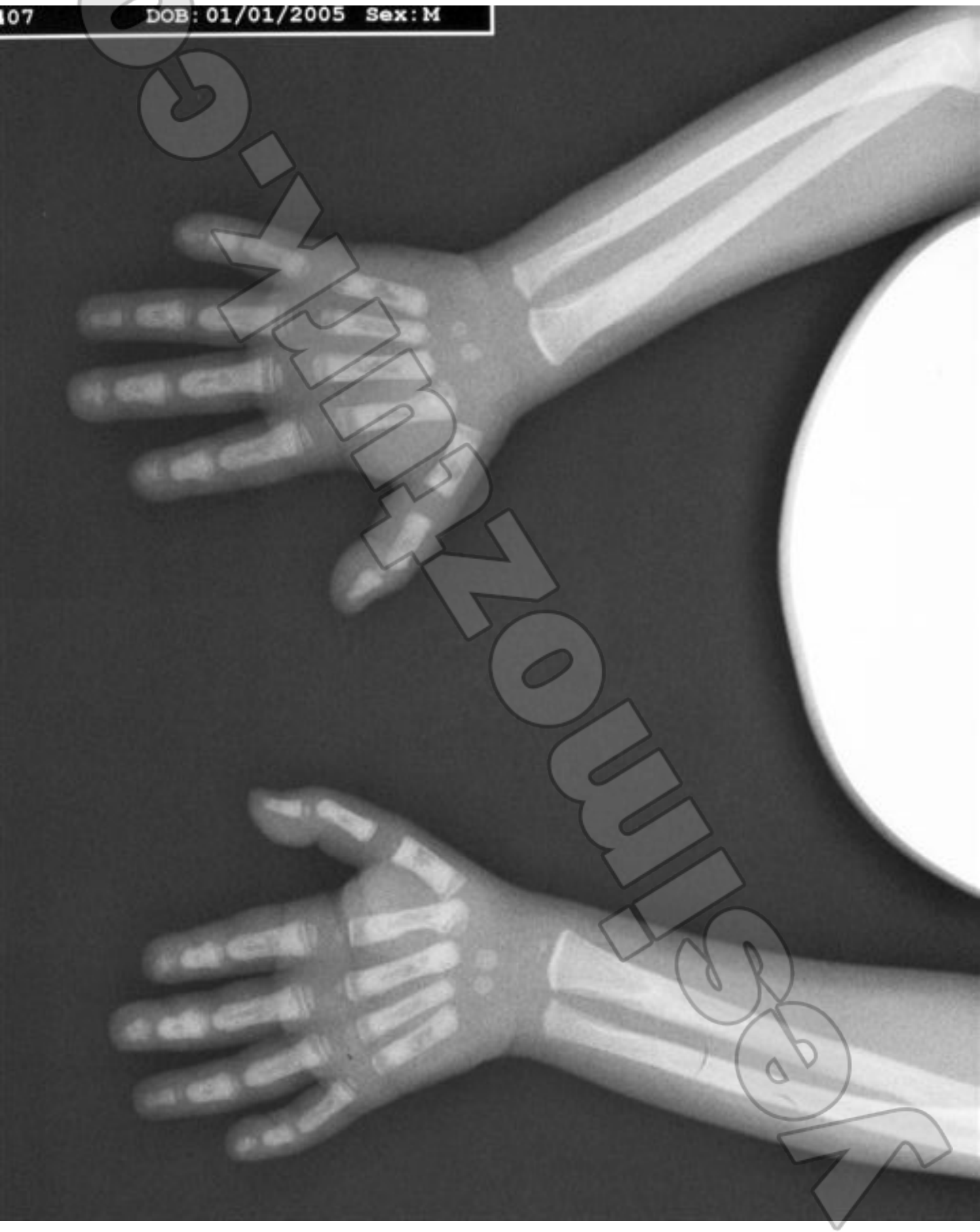


Fig. 6 Anteroposterior (AP; a) and lateral (b) radiographs of the lumbar spine in a 15-year-old patient (patient 3) showing the characteristic bone-within-a-bone appearance. Note the spondylolysis (*arrow*) with a grade-1 slip of L5 over S1 on the lateral view





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DOB: 01/01/2005 Sex: M