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SCIENTIFIC ARTICLE

Radiological features of Paget disease of bone associated with VCP myopathy

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Abstract
Objective Mutations in the Valosin-containing protein (VCP) gene cause a unique disorder characterized by classic Paget disease of bone (PDB), inclusion body myopathy, and frontotemporal dementia (IBMPFD). Our objective was to analyze the radiographic features of PDB associated with VCP mutations since there is a dearth of literature on the PDB component of VCP disease.
Materials and methods Radiographic bone surveys were examined in 23 individuals with VCP mutation and compared with their unaffected relatives. Laboratory testing relevant for VCP disease was performed in all individuals.
Results Of the 17 affected individuals with clinical manifestations of VCP disease, 16 of whom had myopathy, radiographic analysis revealed classic PDB in 11 individuals (65%). The mean age of diagnosis for myopathy was 43.8 years and for PDB was 38.1 years of age. Radiological evidence of PDB was seen in one individual (16%) amongst six clinically asymptomatic VCP mutation carriers. Alkaline phosphatase was a useful marker for diagnosing PDB in VCP disease.
Conclusions Radiographic findings of classic PDB are seen in 52% of individuals carrying VCP mutations at a significantly younger age than conventional PDB. Screening for PDB is warranted in at-risk individuals because of the benefit of early treatment with the new powerful bisphosphonates that hold the potential for prevention of disease.

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Keywords IBMPFD · Inclusion body myopathy · Paget's disease of bone · Alkaline phosphatase · Valosin-containing protein · Frontotemporal dementia · Presymptomatic

Introduction

Paget disease of bone (PDB), also known as osteitis deformans, was first described by Sir James Paget in 1877 [1]. PDB is a common condition characterized by focal increases in bone turnover affecting one or more sites throughout the skeleton. Genetic factors play an important role in the pathogenesis of PDB and several genes in the NFkB pathway have been identified to cause PDB and related syndromes [2]. An important relatively new disorder that provides insight in the pathogenesis of PDB is Inclusion Body Myopathy, Paget's disease of bone and frontotemporal dementia (IBMPFD) [3]. IBMPFD is a highly penetrant autosomal dominant progressive disorder that maps to chromosome 9p21-p12 [4]. It is caused by mutations in the gene encoding Valosin-containing protein (VCP) [5]. VCP a member of the type II AAA adenosine triphosphatase (ATPase associated with diverse cellular activities) family is an essential component of various cellular pathways [6].

Previous radiographic data on PDB in patients with VCP mutations is limited [3, 4, 7]. This article is a first systematic review of the radiographic findings of PDB in individuals with VCP mutations from nine families.

Materials and methods

Thirty-three subjects from nine families with IBMPFD were studied to detect PDB-associated radiographic changes and laboratory testing relevant for VCP disease including serum creatinine phosphokinase (CK) concentration, serum alkaline phosphatase (ALP) concentration, and urine concentrations of pyridinoline (PYD) and deoxypyridinoline (DPD). The 'affected' group included 17 individuals (eight males/nine females (8M/9F), age range 41–67 years, mean age 53.4 years) with one or more clinical feature of VCP disease. There were **six** carriers (2M/4F, age range 33–40 years, mean age 35.8 years) with mutations in VCP but with no obvious clinical manifestations and ten first-degree 'unaffected' relatives (6M/4F, age range 37–72 years, mean age 52.8 years) who did not carry the familial mutation and served as controls.

The following criteria were used for diagnosing myopathy in these subjects:

1. Adult-onset, slowly progressive distal and proximal muscle weakness with initial involvement of the hip and shoulder girdle muscle groups.
2. Abnormal, waddling gait; inability to raise the arms; difficulty in climbing stairs; and mild weakness of the hands.
3. Generalized reduction or absence of tendon reflexes, normal nerve conduction.
4. Light microscopy of muscle biopsy revealing single or multiple rimmed vacuoles and cytoplasmic VCP- and ubiquitin-positive inclusions. Absence of inflammatory change helps distinguish IBMPFD myopathy from sporadic inclusion body myositis (Fig. 1).

Prior diagnosis of PDB was based on clinical features of pain, bony tenderness on physical examination, elevated levels of alkaline phosphatase (ALP) in blood and skeletal radiographs suggestive of PDB.

Surveys included radiographic study of the skull, spine, chest, pelvis and hips, and long bones (humerus and femur). Initial readings of the radiographs were done blinded to the clinical status and were performed by an experienced board certified musculoskeletal radiologist (JT) and research fellow (FF). A second review also included the senior author who disclosed the VCP mutation status of the individuals.

Radiographic findings of PDB were classified according to standardized criteria [8, 9]:

1. Cortical thickening, coarse and thickened bone trabeculae and bone sclerosis and enlargement.
2. Advancing edge ("cutting cone") of osseous rarefaction or "the blade of grass" lesion; zone of rarefaction, osteoporosis circumscripta, cotton-wool, and thickening in the skull;
3. Widening of bones, and sclerotic areas, in the pelvis, thickening of iliopectineal line or brim sign; enlargement

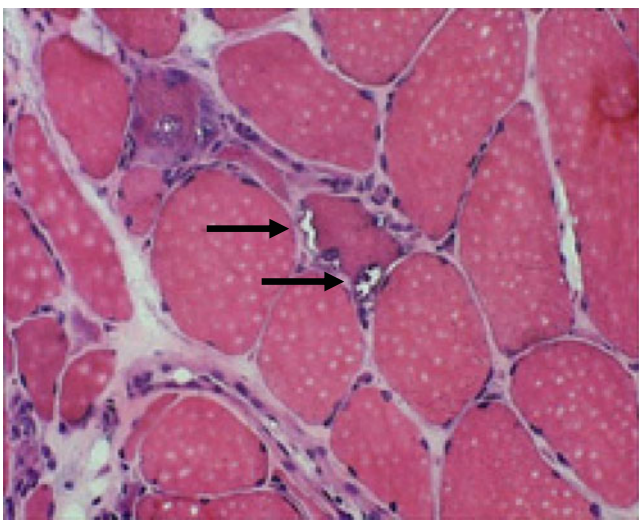

Fig. 1 Histology of muscle fiber. Muscle fiber from right quadriceps from a 41-year-old man with PDB and myopathy revealed moderately severe, chronic-active myopathy with variation in fiber diameter and rimmed vacuoles (*arrows*)

of the vertebral body, trabecular coarsening, thickening of cortices (picture framing), ivory vertebrae or vertical stripping in the spine; enlargement of the bone, flame shaped appearance (advancing edges) in the long bone.

Radiographic findings and laboratory data were reviewed in the three groups. Laboratory data were compared using analysis of variance with pair wise *t* tests adjusted for multiple comparisons using the Tukey method.

Blood and urine were collected according to standard practice and concentrations of serum alkaline phosphatase (ALP), serum CK and urine concentrations of pyridinoline (PYD) and deoxypyridinoline (DPD) were measured.

Results

The clinical and radiographic findings in 23 individuals including six presymptomatic/asymptomatic carriers and ten control subjects are summarized in Tables 1, 2, and 3. The clinically affected group consisted of eight males and nine females. Of the 17 affected individuals with clinical manifestations of VCP disease, 16 also had myopathy, 11 (65%) also had clinical and radiological features of PDB; one individual had isolated PDB and one individual had all three components of the disease. Radiographic analysis revealed evidence of PDB in a clinically asymptomatic individual positive for a VCP mutation (16%). There were five individuals who carried the VCP mutation but who did not show any clinical and/or radiographic evidence of VCP disease including PDB. No evidence of PDB was seen in ten VCP negative first-degree relatives who served as controls. Average age of onset for myopathy was 43.8 years and for PDB was 38.1 years of age.

Spine changes Thoracic spine involvement was seen in four VCP-affected patients, two with sclerotic changes, three revealed bony enlargement, of which two had picture framing (Figs. 2 and 3). Lumbar spine involvement was seen in six patients, one with coarse trabeculae, three demonstrated enlargement of the vertebral body, and one showed end-plate sclerosis. Cervical spine enlargement of the vertebral body was seen in one patient.

Pelvis Thickening of iliopectineal line was observed in three VCP-affected patients, one had enlargement of iliac bone, one had coarse trabecular findings, and two had lucency of the ileum and greater trochanter, respectively (Fig. 4).

Long bones Femur involvement was seen in three VCP-affected patients, two with cortical thickening, one showed sclerosis; one demonstrated expansion of the femoral condyles, two showed coarse trabeculae of proximal or distal area, and one had long osteolytic lucency of the proximal shaft of femur (Fig. 5). Humerus involvement was seen in two patients, one with coarse trabeculae, and two showed cortical thickening of the shaft humerus (Fig. 6).

Skull Skull involvement was seen in five VCP-affected patients, all demonstrated diffuses or focal irregular thickening, two with sclerosis of calvarium, three showed widening of diploic space, and two with focal area of lucency or osteolytic area. Interestingly, changes of hyperostosis frontalis interna, a benign entity, were seen in six individuals among affected and unaffected individuals. Cortical thickening of wing of scapula was seen in one individual and one had involvement of the clavicle. One

Table 1 Demographic and lab data

	Affected (n=17)			Carrier (n=6)			Non-mutation carrier (n=10)			
	M/F	% M	% F	M/F	% M	% F	M/F	% M	% F	p-value[++]
Gender	8/9	47%	53%	2/4	33%	67%	6/4	60%	40%	0.58
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	p-value[+]
Age	53.4	9.3	41-67	35.8	3.1	33-40	52.8	12.6	37-72	0.002
Alkaline Phosphatase	184.3	186.1	58-782	70.5	9.0	58-83	74.5	50.2	46-213	0.089
Pyridinoline[a]	51.7	26.0	20.6-99.8	36.2	9.3	24.2-47.0	33.4	5.2	26.2-37.8	0.254
Deoxypyrodinoline[b]	11.6	7.8	3.9-28.8	7.3	3.7	2.4-11.2	7.2	1.2	5.8-8.6	0.320
CPK	175.6	107.4	54-473	85.0	39.8	54-160	126.4	51.2	75-202	0.074

M Male, *F* Female *SD* Standard deviation

[++] Chi-square test (2df)

[+] F-test

[a] N per group = 10, 4, and 4

[b] N per group = 9, 4, and 4

Table 2 Clinical and radiological data

Clinical data											Radiological data							
No.	Patient ID	Age (Y)	SEX	Mutation	Clinical diagnosis	Myopathy onset (Y)	Paget-onset (Y)	Dementia-onset (Y)	CPK level	ALP Levels	Skull	Lumbar	Thoracic	Scapula	Humerus	Femur	Pelvis	Clavicle
VCP affected patients																		
1	02-002	56	M	R155C	Myopathy	45	-	-	255	85	-	-	-	-	-	-	-	-
2	15-003	61	M	R155H	Myopathy	45	-	-	145	93	-	-	-	-	-	-	-	-
3	24-001	66	F	R159C	Myopathy	50	-	-	159	89	-	-	-	-	-	-	-	-
4	30-002	41	M	L198W	Myopathy	34	-	-	94	58	-	-	-	-	-	-	-	-
5	02-001	47	F	R155C	Myopathy	47	-	-	54	74	-	-	-	-	-	-	-	-
6	24-002	60	F	R159C	Myopathy	60	-	-	115	85	-	-	-	-	-	-	-	-
7	16-006	56	F	R155H	Myopathy	48	-	-	203	75	-	-	-	-	-	-	-	-
8	30-001	67	M	L198W	Myopathy Paget	37	50	-	62	782	+	-	-	-	-	-	-	-
9	01-001	59	F	R155H	Myopathy Paget	33	37	-	192	127	-	+	+	-	-	-	-	-
10	01-003	43	M	R155H	Myopathy Paget	43	33	-	200	236	+	+	+		-	-	+	+
11	04-004	64	M	R155H	Myopathy, Paget	41	40	-	9	225	-	-	-	-	-	+	+	-
12	15-002	58	F	R155H	Myopathy Paget	51	35	-	99	183	-	-	-	-	-	+	-	-
13	30-002	41	F	L198W	Myopathy Paget	35	39	-	473	59	+	-	-	-	-	-	-	-
14	01-004	56	F	R155H	Myopathy Paget	45	40	-	96	71	-	+	-	+	+	+	-	-
15	16-001	49	M	R155H	Myopathy Paget Dementia	45	32	47	324	397	-	+	-	-	-	-	+	-
16	03-001	42	M	R155H	Myopathy Paget	41	42	-	266	124	+	+	+	-	+	-	-	-
17	01-005	41	F	R155H	Paget		31	-	150	370	-	+	+	-	-	-	-	-
Mean		53.4				43.8	38.5		170	184.3								
Data Summaries			8M 9F		Myopathy 16/17 (94%) PDB 10/17 (59%)						4/10 40%	6/10 60%	4/10 40%	1/10 10%	2/10 20%	3/10 30%	3/10 30%	1/10 10%
VCP carrier patients																		
18	03-003	33	F	R155H	No symptoms	-	33	-	72	75	+	-	-	-	-	-	+	-
19	30-003	39	F	L198W	Depression	-	-	-	56	63	-	-	-	-	-	-	-	-
20	02-003	34	M	R155C	Normal	-	-	-	97	74	-	-	-	-	-	-	-	-
21	16-003	40	F	R155H	Normal	-	-	-	71	83	-	-	-	-	-	-	-	-
22	33-002	33	M	R191Q	Normal	-	-	-	160	58	-	-	-	-	-	-	-	-
23	02-004	36	F	R155C	Normal	-	-	-	54	70	-	-	-	-	-	-	-	-
Mean		36.4							85	70.5								
VCP unaffected patients																		
24	02-005	55	M		Normal	-	-	-	202	46	-	-	-	-	-	-	-	-
25	01-002	67	M		Normal	-	-	-	180	213	-	-	-	-	-	-	-	-
26	03-002	72	M		Normal	-	-	-	90	51	-	-	-	-	-	-	-	-
27	16-002	43	F		Normal	-	-	-	76	57	-	-	-	-	-	-	-	-
28	33-001	68	M		Normal	-	-	-	75	70	-	-	-	-	-	-	-	-
29	16-004	41	M		Normal	-	-	-	162	52	-	-	-	-	-	-	-	-

30	16-005	48	F		Normal	-	-	-		95	47	-	-	-	-	-	-	-	-	-
31	16-007	42	F		Normal	-	-	-		89	62	-	-	-	-	-	-	-	-	-
32	30-005	37	M		Normal	-	-	-		192	60	-	-	-	-	-	-	-	-	-
33	33-003	55	F		Normal	-	-	-		103	87	-	-	-	-	-	-	-	-	-
Mean		44.6								126	74.5									

Columns 7, 8, and 9 include ages of onset of myopathy, Paget and frontotemporal dementia in years

CPK Creatinine phosphokinase level (normal 4–120 U/l), *ALP* Alkaline phosphatase (normal 30–120 U/l)

Radiological data in columns 12–19 indicate if PDB changes were seen in skull, lumbar, thoracic spine, scapula, humerus, femur, pelvis, and clavicle

individual had diaphragmatic eventration, a feature associated with congenital myopathies or phrenic nerve palsy.

Laboratory results Elevated levels of alkaline phosphatase (ALP) indicates abnormal osteoblast activity [9] and can be an effective tool in the diagnosis and monitoring of therapy of PDB in at-risk individuals. ALP levels study showed significantly higher ALP levels in individuals with radiological features of Paget (n=10; mean=257.4) than unaffected (n=10; mean=74.5, SE=15.87), and carrier (n=6; mean=70.5)) (p=0.012). After adjustment for multiple comparisons, ALP levels were significantly higher in PDB compared to asymptomatic individuals (p=0.041) and controls (p=0.020). Only 60% (6/10) of our patients with PDB had ALP higher than 141 U/L as some were on treatment or had localized skeleton involvement. Differences between unaffected and carriers were not statistically significant.

High levels of pyridinoline (PYD >31 IU/l) and deoxypyridinoline (DPYD >6.8 IU/l) breakdown products of bone collagen are used to gauge osteoclast activity. PYD and DPYD levels were higher in individuals with Paget than unaffecteds and carriers, however, these differences were not statistically significant.

Creatine kinase (CK) levels in 15 patients with myopathy showed that CK levels were higher in affected than in unaffected individuals and carriers, however, these differences were not significant.

Discussion

Inclusion body myopathy associated with Paget's disease of the bone and frontotemporal dementia, (IBMPFD, OMIM 167320), is a progressive and ultimately a lethal condition with an onset usually in the 30s to 40s, showing autosomal dominant inheritance. The disease was mapped to 9p13.3-12 and subsequently attributed to being caused by mutations in the gene encoding Valosin-containing protein (VCP) [3, 4]. VCP myopathy is associated with weakness and atrophy of the skeletal muscles of the pelvic and shoulder girdle muscles in 90% of individuals [3, 4, 10]. Affected individuals exhibit scapular winging and die from progressive muscle weakness, and cardiac and respiratory failure, typically in their 40s to 60s [3, 7]. Histologically, patients show the presence of rimmed vacuoles and TDP-43 positive large ubiquitinated inclusion bodies in the muscles [3, 5, 7, 11]. Electron micrographs of affected skeletal muscle demonstrated prominent tubulofilamentous inclusions within myonuclei. Patients with VCP disease may also be clinically diagnosed with limb girdle muscular dystrophy (LGMD), facioscapular muscular dystrophy, scapuloperoneal muscular dystrophy, or amyotrophic lateral sclerosis (ALS) [7, 12–14].

Table 3 Details of bone surveys

Individual	Region	Details of radiological features
8	Skull	Skull: Thickened calvarium
9	T10, L3	Skull: Hyperostosis frontalis interna
		T10: Sclerotic changes of the vertebral body with slight enlargement of vertebral body
		L3: Enlargement and coarse trabeculae of the vertebral body and picture framing
		Right ileum: Small lytic changes
10	Skull, C5, Left Ileum, L3, L4, T7, T12	Skull: Thickened calvarium with widening of diploic space and focal area of lucency at posterior occiput
		C5: Slightly thicker than normal
		T7, T12: Sclerotic changes of the vertebral body, with slight enlargement of vertebral body
		L3: Slight enlargement of vertebral body
		Ileum: Thickening of iliopectineal line
11	Left femur, Left ileum	Left femur: Coarse trabeculae of proximal femur with a long osteolytic lucency of the proximal shaft of femur
		Left ileum: Coarse trabecular and thickening of iliopectineal line
12	Right femur	Right femur: Thickening and sclerosis with expansion of the femoral condyles with coarse trabeculae of distal femur
13	Skull	Skull: Diffuse thickening and sclerosis of calvarium with widening of diploic space
		Thoracic spine: Mild scoliosis
14	Right humerus, Left scapula, L5, Right femur	Right humerus: Thickening from proximal to distal humerus. Left scapula: Thickening
		L5: Picture framing
		Right femur: Thickening from proximal to distal
		Right hemidiaphragm: Elevated, suggesting muscle disease or phrenic nerve palsy
		L5/S1: degenerative joint disease
15	Right ileum, L1	L1: Picture framing and enlargement of vertebral body
		Right ileum: Thickening of iliopectineal line enlargement of right iliac bone
16	T11, L3	Skull: Hyperostosis frontalis interna
		T11, L3: Picture framing
17	Skull, T12, L1, L2, Right humerus	Skull: Parietal and occipital: irregular thickening
		T12, L1: Picture framing and enlargement of vertebral body
		L2: Upper end plate sclerosis
		Right humerus: Proximal thicker than normal with increased coarsening
18	Skull	Skull: Diffuses thickening and sclerosis of calvarium with the widening of diploic space and also osteolytic changes in the parietal bon
		Lumbar spine: scoliosis
		Pelvis: symmetrical lucencies of greater trochanter with sclerotic margin

The disease seldom appears before the age of 40 years, and the overall prevalence of PDB has been estimated at 3% of the European population [8–10] and up to 2–3% of the US population aged over 60 years [9], reaching about 10% in 90-year-olds in the general population [1]. The highest prevalence is in the UK, but PDB is also common in Australia, New Zealand, North America, and countries of Western Europe, especially in France [1]. Noteworthy, the incidence of PDB seems to be higher in the rural areas than in urban areas [1]. Epidemiological data suggest a fall in prevalence and in clinical severity of the condition in the last 30 years in developed countries; a possible explanation of this could reside in changes in prevalence of environmental triggers and/or in changes of ethnic make-up of the populations [1, 2]. PBD is a metabolic bone disease characterized by localized, rapid bone remodeling due to over activity of abnormally large, multinucleated osteoclasts [9]. Histologically, evaluation of these osteoclasts shows nuclear filamentous inclusions of 15 to 18 nm paired helical filaments similar to that seen in IBM [9, 15]. The precise etiology and pathogenesis of PDB remain unknown; however, current evidence suggests that both genetic and

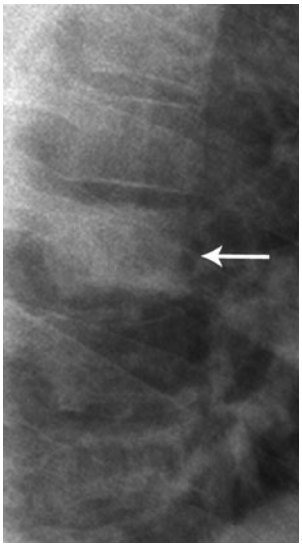

Fig. 2 Lateral radiograph of thoracic spine in a 43-year-old man with PDB and myopathy shows sclerotic changes of the vertebral body at the level of T7 (*arrow*) with slight enlargement of vertebral body

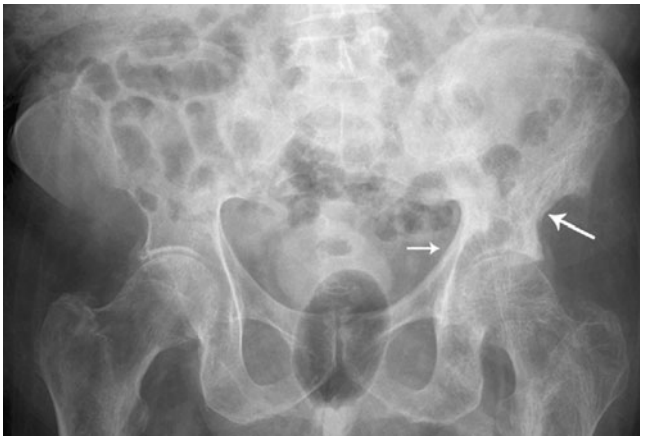

Fig. 4 AP radiograph of pelvis in a 64-year-old man with PDB and myopathy shows diffuse sclerosis of the left innominate bone with enlargement and coarse trabeculae (*long arrow*). There is thickening of the left iliopectineal line (*short arrow*). Lucency is also noted in the great trochanter and ischium in the left and right side

environmental factors contribute to the pathogenesis of PDB, supported by longstanding observation of the familial clustering of PDB, and identification of several disparate gene mutations as a cause of PDB [1, 2, 8, 16, 17]. In our study, PDB presents early (mean 38.1 years) with typical distribution in the spine, pelvis, and skull in the majority of individuals.

Conventional Pagets has radiographic changes which could be lytic, sclerotic, or mixed. Radiographic findings of PDB in individuals with VCP gene mutations are generally associated with blastic and sclerotic changes with bone expansion and coarse bony trabeculae and cortical thickening. Lytic changes are less commonly observed in comparison to conventional Pagets.

Eekhoff et al. reported findings on skeletal radiographs, considered the gold standard for diagnosing PDB, and ALP from the Rotterdam study [18]. ALP was a useful marker in our study and individuals with higher serum levels had a higher risk for radiologically diagnosed PDB, however, 11/26 (42%) individuals with PDB diagnosed radiologically had a normal serum ALP suggesting that active PBD restricted to a small region of the skeleton may have little or no effect on the circulating levels of ALP or collagen degradation products. Overall, in our study, ALP, DPYD, and PYD levels were higher in affected patients. Sixty percent of our patients with PDB had high ALP. However, normal ALP was seen in individuals with radiological findings of PDB, most likely due to localized skeleton involvement.

VCP disease is characterized by clinical heterogeneity and variable presentation in severity of symptoms, age of onset, distribution of weakness and presence of Paget's

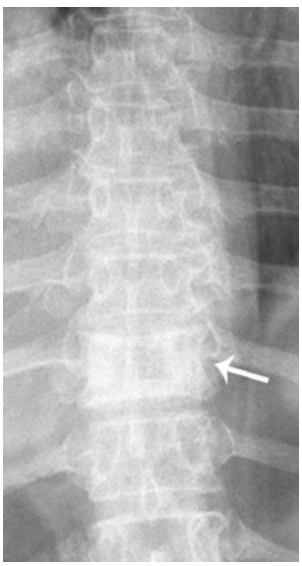

Fig. 3 AP radiograph of thoracic spine in a 59-year-old female with PDB and myopathy shows sclerosis and slight enlargement of the vertebral body at the level of T10 (*arrow*)

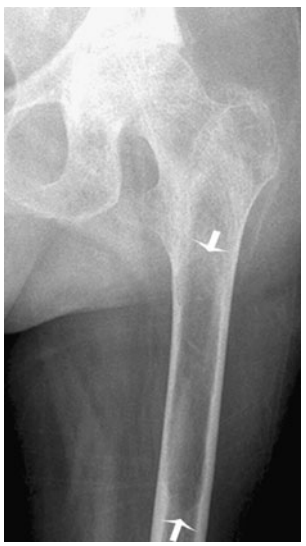

Fig. 5 AP radiograph of left femur in a 64-year-old man with PDB and myopathy shows coarsening of trabeculae of proximal shaft of femur with a long lucency or osteolytic lesion (*between two arrows*) of the proximal shaft of left femur

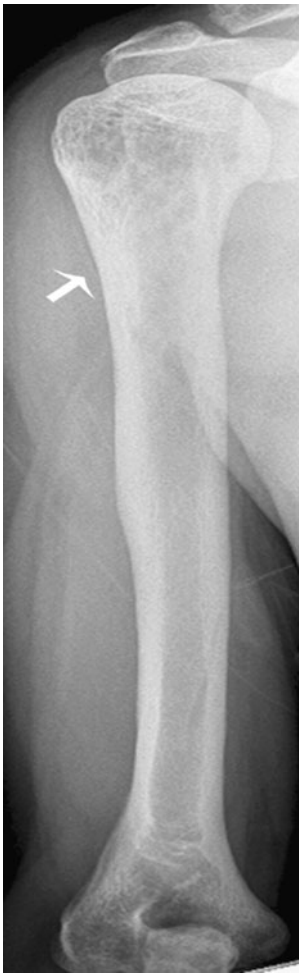

Fig. 6 AP radiograph of the humerus in a 42-year-old female with PDB shows cortical thickening (*arrow*) and bone enlargement and coarse trabeculae

disease, myopathy, or cognitive impairment. Complete manifestation of all three symptoms is seen in 12% of affected individuals. Presence of two manifestations in any combination is seen in 50% of affected individuals. Isolated myopathy, PDB, or FTD is seen in 30, 5, and 3% of affected individuals, respectively, positive for VCP mutation [19] Appropriate screening and diagnostic testing is therefore important in the VCP patient population for accurate management and prevention of under diagnosis if PDB is not actively sought among patients with a personal or family history of myopathy and/or dementia. In patients with early onset Paget disease, an underlying genetic component such as VCP or SQSTM1 should be considered specifically in the presence of a positive family history of related symptoms.

This is the first systematic comparative study of skeletal radiographs in 23 individuals from nine families with VCP mutations and their unaffected first-degree relatives.

This data indicates that all individuals at risk of inheriting VCP mutations should be screened for PDB, especially since the new bisphosphonates such as zoledronic acid and risedronate hold the potential of prevention if treatment begins in the early stages of the disease [20, 21]. Ralston et al. [21] suggested genetic testing for SQSTM1 mutations in patients with a family history of the disease so that carriers of these mutations could be kept under close surveillance for early signs of PDB. In order to study issues such as anxiety associated with having a genetic test and the potential clinical benefit of prophylactic zoledronic acid therapy versus placebo in asymptomatic patients with SQSTM1 mutations, a trial called the Zoledronate in the Prevention of Paget's disease (ZiPP) study is in progress, the primary aim of which is to determine whether bisphosphonate therapy can prevent the development of elevated bone turnover and bone lesions in mutation carriers.

The results of our study aim to increase awareness of this important disorder, which will help improve diagnosis and our understanding of the pathogenesis of PDB. VCP-associated PDB is currently under-diagnosed. PDB adds significantly to the underlying morbidity of the disorder and is readily treatable with bisphosphonates, thus should be actively screened for in any individual with two or more associated features of IBMPFD, a suspicious family history or known VCP mutations [7, 11]. We suggest screening *with* alkaline phosphatase levels followed by bone scans/X-rays if PDB is suspected.

There is a rather significant age difference between Pagets in this group compared to hyperphosphatasia or juvenile Pagets. Hyperphosphatasia or so-called juvenile Pagets appears in a much younger age group and especially in children in whom the epiphyseal growth plates may still be open on radiographs. Additionally, radiographs show more diffuse bony expansion in the entire bone length and the changes often involve bilateral extremities.

One of the limitations of the study is that this is a cross-sectional study. Long-term follow-up of the clinical and radiological evaluation of these patients is therefore necessary to observe progression and outcome of these findings.

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Conflict of interest The authors declare no conflicts of interest.

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