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Non-Endemic Skeletal Fluorosis: Causes And Associated Secondary Hyperparathyroidism (Case Report and Literature Review)

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Abstract

Skeletal fluorosis (SF) is endemic primarily in regions with fluoride (F)-contaminated well water, but can reflect other types of chronic F exposure. Calcium (Ca) and vitamin D (D) deficiency can exacerbate SF. A 51-year-old man with years of musculoskeletal pain and opiate use was hypocalcemic with secondary hyperparathyroidism upon manifesting recurrent long bone fractures. He smoked cigarettes, drank large amounts of cola beverage, and consumed little dietary Ca. Then, after 5 months of Ca and D_3 supplementation, serum 25(OH)D was 21 ng/mL (Nl, 30–100), corrected serum Ca had normalized from 7.8 to 9.4 mg/dL (Nl, 8.5–10.1), alkaline phosphatase (ALP) had decreased from 1080 to 539 U/L (Nl, 46–116), yet parathyroid hormone (PTH) had increased from 133 to 327 pg/mL (Nl, 8.7–77.1). Radiographs revealed generalized osteosclerosis and a cystic osteopenic area in the left femoral neck and intertrochanteric region. DXA BMD Z-scores were +7.4 and +0.4 at the lumbar spine and "1/3" radius, respectively. Bone

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Author contributions:

All authors helped write and approved the submitted manuscript. FJC organized the diagnostic studies and drafted and finalized this document. MS-G detailed the patient's clinical findings. SM conducted and interpreted the mutation analyses. WHM and DJV delineated the radiological and histopathological features, respectively. VNB managed the illustrations. DW and MPW helped guide the investigations and manuscript completion.

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scintigraphy showed increased uptake in two ribs, periarticular areas, and proximal left femur at the site of a subsequent atraumatic fracture. Elevated serum collagen type I C-telopeptide 2513 pg/mL (Nl, 87–345) and osteocalcin >300 ng/mL (Nl, 9–38) indicated rapid bone turnover. Negative studies included hepatitis C Ab, prostate-specific antigen, serum and urine electrophoresis, and Ion Torrent mutation analysis for dense or high-turnover skeletal diseases. After discovering markedly elevated F concentrations in his plasma [4.84 mg/L (Nl, 0.02–0.08)] and spot urine [42.6 mg/L (Nl, 0.2–3.2)], a two-year history emerged of “huffing” computer cleaner containing difluoroethane. Non-decalcified histology of a subsequent right femur fracture showed increased osteoblasts and osteoclasts and excessive osteoid. A 24-hour urine collection contained 27 mg/L F (Nl, 0.2–3.2) and < 2 mg/dL Ca. Then, 19 months after “huffing” cessation and improved Ca and D_3 intake, yet with persisting bone pain, serum PTH was normal (52 pg/mL) and serum ALP and urine F had decreased to 248 U/L and 3.3 mg/L, respectively. Our experience combined with 15 publications in PubMed concerning unusual causes of non-endemic SF where the F source became known (19 cases in all) revealed: 11 instances from high consumption of black tea and/or F-containing toothpaste, 1 due to geophagia of F-rich soil, and 7 due to “recreational” inhalation of F-containing vapors. Circulating PTH measured in 13 was substantially elevated in 2 (including ours) and mildly increased in 2. Their SF severity, including bone turnover rate, seemed to reflect cumulative F exposure, renal function, and Ca and D status. Several factors appeared to condition our patient’s skeletal disease: i) direct anabolic effects of toxic amounts of F on his skeleton, ii) secondary hyperparathyroidism from degradation-resistant fluorapatite bone crystals and low dietary Ca, and iii) impaired mineralization of excessive osteoid due to hypocalcemia.

Keywords

atypical femoral fracture; bone pain; bone scan; difluoroethane; DXA; elevated bone mass; fluoride; fluorocarbon; fluorocarbon inhalation; fluorosis; hip fracture; “huffing”; hyperparathyroidism; hyperplastic callus; hypertrophic callus; hypocalcemia; osteolysis; osteomalacia; osteoporosis; osteosclerosis; periostitis; tea consumption

II) Introduction:

Skeletal fluorosis (SF) was first recognized in 1932.[1] We now know SF affects millions living in endemic areas worldwide where well water is contaminated with fluoride (F) leached from volcanic rock, primarily the Indian subcontinent,[2] China,[3] and Africa.[4] SF prevalence may be increasing as surface waters become polluted and more water wells are bored.[4] Release of F into the air from indoor coal combustion causes SF in some regions, especially rural China.[5] General health, diet, and renal capacity to excrete F condition the severity of SF, with advancing age, male sex, low socioeconomic status, poor nutrition, and alcohol and tobacco use apparently associated with severe endemic disease.[2] Non-endemic explanations for SF include consumption of poor quality “brick” tea[3] in Asia, and elsewhere excessive amounts of commercial black tea.[6–8] F exposure can also occur by dust inhalation in a number of industries, leading to wide acceptance of SF as an occupational disease.[1,9] In the 1970s and 1980s, F was evaluated for osteoporosis because F has anabolic effects on bone.[10] However, meta-analyses indicated that despite increases

in bone mineral density (BMD), fracture risk was not decreased,[11,12] and longer duration[11] or higher doses[12] of F were associated with more non-vertebral fractures. Since 1965, *periostitis deformans* has been recognized as a complication of SF, having been noted in a series of 28 cases of SF from drinking wine containing toxic amounts of F.[13] Periostitis deformans is more recently reported to occur in 5–50% of individuals receiving F-rich voriconazole for prophylaxis or treatment of fungal infections.[14] SF has also been reported from the anti-inflammatory, niflumic acid.[15] Other causes are rare and often obscure with delayed diagnosis.[7,16] We report a middle-aged man with severe SF from fluorocarbon inhalation abuse called “huffing”, and likely exacerbated by dietary calcium (Ca) insufficiency. Huffing can increase suicide risk and cause neurologic and cognitive deficits, acute kidney injury, hepatotoxicity, and cardiac arrhythmia with sudden death.[17,18] The skeletal consequences are poorly understood. We also provide a review of non-endemic SF, unrelated to medicinal or industrial exposure, reported in the American and European literature and highlight the F sources, impact on Ca metabolism, and bone pathophysiology.

III) Patient and Methods:

A) Medical History:

This 51-year-old morbidly obese Caucasian man was referred by his family physician for unexplained secondary hyperparathyroidism found upon discovery of hypocalcemia when he was admitted with a left femur fracture. His medical history was significant during the previous two years for three long bone fractures. The first was an atraumatic right femoral neck fracture treated with arthroplasty at another institution. The second was a displaced traumatic right humerus fracture complicated by radial nerve entrapment. One month later, the third break involved his left proximal femoral shaft while climbing steps without trauma. Bone scintigraphy prior to this fracture showed increased uptake in two ribs, periarticular areas, and where the femur would subsequently break. Surgical pathology showed no bone malignancy. Because radiographs had revealed osteosclerosis of his spine and pelvis and CT had indicated a cystic osteopenic area in the left femoral neck (see Radiographic Findings), he had been evaluated first by our oncology service. Hepatitis C Ab, prostate-specific antigen, and serum and urine protein electrophoresis were negative. In his “30s”, he had had rib fractures including one during chiropractic “adjustment”. He denied height loss or recent dental issues. Opiates had been used for many years for unexplained, chronic, diffuse, musculoskeletal pain. Hypogonadotropic hypogonadism attributed to opiate use had been treated with transdermal testosterone, although used inconsistently. Prior to his limb fractures, he had gained 100 lbs over 20 years attributed to sedentary habits from pain. His diet included ~ 72 ounces of a dark cola beverage daily and no milk or milk-containing products. He used no supplements, smoked 1–2 packs of cigarettes daily for 30 years, and denied alcohol consumption. Although he had had dental issues in the distant past, he denied recent difficulty with his teeth. His family history was unremarkable for bone disease, bone or joint pain, short stature, or height loss.

His height, 67 inches (1.70 meters), was within the lowest reference quartile. He weighed 280 lbs (127 kg), with a BMI of 44. A cane helped his antalgic gait. He had a deformed right

humerus, diminished right hand dorsiflexion, and seemingly swollen hands and fingers, but no dental or skull abnormalities.

B) Biochemical Findings:

Skeletal remodeling was evaluated using bone turnover markers (BTMs), including serum osteocalcin (OCN) and collagen type I C-telopeptide (CTX) quantitated by electro-chemiluminescence and immunoassay, respectively, at Quest Diagnostics Nichols Institute (Chantilly, VA, USA). Plasma F was quantitated using the Ion-Selective Electrode (ISE) assay at Mayo Clinical Laboratories (Rochester, MN, USA) and Quest Diagnostics. Urinary F was quantitated using Ion-Specific Electrode potentiometry at Quest Diagnostics and LabCorp (Burlington, NC, USA).

Biochemical evaluation at the time of his left femur fracture and then upon referral to us five months later indicated prompt resolution of his hypocalcemia after treatment with oral calcium carbonate with subsequent addition of vitamin D_3. In his serum were normal phosphorus and magnesium levels, slightly low serum 25-hydroxyvitamin D [25(OH)D], and elevated alkaline phosphatase (ALP), intact parathyroid hormone (PTH), 1,25-dihydroxyvitamin D, CTX, and OCN. Two months later, urine Ca was undetectable at < 2 mg/dL (Table 1).

C) SF Diagnosis and Treatment:

Due to his rapid bone remodeling, diffuse osteosclerosis especially of the spine and pelvis, long tubular bone cortical thickening, and abundant callus formation at the right humerus fracture (see Radiological Findings), SF was suspected. Subsequently, serum and spot urine F levels were found to be significantly elevated at 4.84 mg/L (Nl, 0.02–0.08) and 42.6 mg/L (Nl, 0.2 −3.2), respectively. However, he denied high F exposure including from excess black tea,[6–8,19–22] ingestion of toothpaste,[16,21,23] or inhalation of a fluorocarbon.[17,24–28] Then, his mother revealed that he had inhaled several times daily for 2–3 years, reportedly for pain control, computer ‘duster’ that we found contains difluoroethane (DFE). Subsequently, the patient confirmed this practice, using Dust-Off (Falcon Safety Products, Branchburg, JN, USA), but despite his skeletal disease indicating more prolonged exposure was adamant the duration was not longer.

Six months after referral, the patient experienced right thigh pain and was diagnosed with a stress fracture at the tip of the right femoral prosthesis. The lesion progressed to a transverse fracture requiring open reduction and internal fixation with a femoral plate. The orthopedic surgeon commented the bone was “soft”. A specimen from the surgical site was fixed in 70% alcohol, embedded in methylmethacrylate, sectioned, and stained with Goldner trichrome (see Histopathological Findings). Following prolonged hospitalization first to treat a surgical wound infection and sepsis, and then inpatient rehabilitation, he ceased “huffing” and was prescribed Ca 600 mg orally BID and vitamin D_3 5000 IU orally daily.

Three months after discharge, serum 25(OH)D was normal and plasma and spot urine F were lower, but serum ALP remained substantially elevated. Dual-energy X-ray absorptiometry (DXA) reflecting a 13-month comparison showed his L_2-L_4 spine bone mineral density (BMD) Z-score +7.7 and T-score +8.3 had not changed significantly.

Although anteroposterior and lateral lumbar spine radiographs appeared unchanged, vertebra L_1 was not included in the spine BMD determination because it was an "outlier" having Z- and T-scores of +10.5 and +11.0, respectively (15.8% increase in BMD). At the 1/3 radius, BMD had increased by 6.3%, having Z- and T-scores of +1.1 and +1.0, respectively (see Radiological Findings).

Subsequently, he reported no further huffing and had decreased cola consumption but with difficulty complying with Ca and vitamin D_3 supplementation. Plasma and urine F levels, though decreasing, remained elevated. Then, 19 months after F exposure reportedly ceased, serum PTH had normalized. He had no subsequent fractures, but diffuse pain continued as he weaned off methadone while requiring a motorized wheelchair for mobility.

D) Mutation Analysis:

Informed written consent for mutation analysis of dense bone disease genes was obtained from the patient as approved by the Human Research Protection Office for our research laboratory at Washington University School of Medicine; St. Louis, MO, USA. The coding regions and adjacent mRNA splice sites for all five exons of *TNFRSF11B* encoding OPG and exon 1 of *TNFRSF11A* encoding RANK were Sanger-sequenced using previously described methods.[29,30] The coding regions and adjacent mRNA splice sites of 35 genes involved in bone turnover or elevated bone mass, specifically *TNFRSF11A (RANK), TNFRSF11B (OPG), TNFSF11 (RANKL), VCP, SQSTM1, TGFB1, IFITM5, MAFB, CSF1, CSFR1, TRAF6, RELA, RELB, REL, NFKB1, NFKB2, TFEB, CA2, CLCN7, CTSK (CATHEPSIN K), OSTM1, PLEKHM1, TCIRG1, SOST, SLC29A3, LRP4, LRP5, LRP6, SNX10, FAM206, FAM123B (AMER1), TYROBP, LEMD3, DLX3, and PTDSS1* were examined using our Ion Torrent Next Generation Sequencing (NGS) system (ThermoFisher Scientific, Waltham, MA, USA).[31]

E) Literature Review:

We performed, on March 18th, 2020, a literature search using key words "skeletal fluorosis case report" to capture articles indexed in PubMed (https://www.ncbi.nlm.nih.gov/Pubmed). Cases of endemic SF, those from F treatment of osteoporosis, voriconazole, wine, industrial exposure, or uncertain F exposure sources were excluded.

IV) Results:

A) Mutation Analyses:

Evaluation for high-turnover and elevated bone mass diseases was negative, including examination of *TNFRSF11B* encoding OPG and exon 1 of *TNFRSF11A* encoding RANK, as well as NGS using our Ion Torrent panel.

B) Radiological Findings:

Multiple radiographs were available for review including a skeletal survey showing predominately diffuse osteosclerosis of the axial skeleton. Skull radiographs demonstrated slight osteosclerosis and diploic thickening and a prominent external occipital protuberance,

the site of the insertion of the ligamentum nuchi and muscles including the trapezius (Figure 1).

The cervical spine was diffusely osteosclerotic involving the neural arches as well as the vertebral bodies. There was right carotid calcification and extensive laryngeal cartilage calcification (Figure 2).

The thoracic and lumbar spine, ribs, and pelvis were diffusely osteosclerotic. Degenerative spine changes included osteophytosis. There was some calcification in the sacrotuberous ligaments (Figure 3).

The right femoral head was replaced with a prosthesis and subsequently a periprosthetic right femur fracture was reduced and fixated. The left proximal femur had a benign appearing cystic osteopenic area in the femoral neck and developed a subtrochanteric insufficiency fracture (Figure 3E and Figure 4).

The left humerus was diffusely osteosclerotic with cortical thickening, an enlarged deltoid muscle insertion, and periosteal bone formation distally (Figure 5). There was periosteal bone formation in the left ulna and interosseous calcification. Calcifications were present at the shoulder.

The right humerus showed an oblique fracture in the mid shaft and six months later increased fracture angulation and hyperplastic callus (Figure 6). Periosteal new bone was present distal to the fracture, and streaks of ossification in the muscle planes medial to the fracture. Periosteal new bone affected the ulna. Interosseous membrane calcification was present.

The hands and wrists showed soft tissue calcifications, some mild osteosclerosis and cortical thickening, and focal areas of metaphyseal sclerosis. No periostitis deformans was seen (Figure 7).

Technetium bone scintigraphy showed intense periarticular uptake at the knees, feet, wrist, and hand along with increased uptake at the fracture sites including several ribs (Figure 8).

BMD assessed by DXA using a Lunar iDXA instrument, ME200288 (GE Healthcare, Chicago, IL, USA) was substantially elevated at his L_1-L_4 spine where the Z- and T-scores were reported to be +7.4 and +8.3, respectively, but nearly average at the “1/3” radius where the Z- and T-scores were reported to be +0.4 and +0.3, respectively. Accordingly, his axial but not appendicular BMD was elevated. Trabecular bone score (TBS) Z-score was +2.1, suggesting robust cancellous bone structure, but now appreciated in SF to be misleading because there is poor bone quality.[24]

Hence, the radiological changes suggesting SF were the diffuse osteosclerosis especially of the spine and pelvis, cortical thickening of the tubular bones, abundant callus formation of the right humerus fracture, interosseous membrane calcification in the forearms, periosteal new bone formation in the tubular bones, calcification in the sacrotuberous ligaments, ossification in the muscle and ligamentous insertions including possibly the external occipital protuberance, and the excessive laryngeal cartilage calcification.

C) Histopathological Findings:

The specimen from the second right femur fracture showed extensive unmineralized osteoid suggesting osteomalacia (Figure 9). However, the patient had not received tetracycline "labeling" for definitive assessment of a mineralization defect. Most of the osteoid surface was covered by osteoblasts. The marrow spaces were fibrotic, with prominent blood vessels and no obvious normal hematopoietic elements. Some osteoclasts were normally apposed to the bone surface, while others were rounded and off the bone. The high number of osteoblasts and osteoclasts and marrow fibrosis, elevated BTMs (see Biochemical Findings), and increased uptake of radionuclide on bone scan of non-fractured sites (see Radiological Findings) were in keeping with high bone turnover likely with some delay in mineralization.

V) Discussion:

Our patient developed SF, from huffing of a fluorocarbon, complicated by secondary hyperparathyroidism.

A) Fluoride Metabolism and Toxicity:

F is an essential micronutrient[32] that is rapidly absorbed into the circulation from the stomach and small intestine. Interaction with other nutrients may influence F bioavailability.[33] Ca, aluminum, magnesium, and chloride reportedly reduce gut F absorption whereas phosphate, sulfate, protein, and fat may cause increases.[33] Approximately 50% of absorbed F deposits in the skeleton with a half-life of approximately 7 years,[7,20,32] whereas the rest is excreted by the kidneys.[7] Thus, the F level in urine reflects acute and/or chronic F exposure. F accumulates in the dentition and skeleton where it hardens tooth enamel and stabilizes bone matrix by attracting calcium ions.[33] F substitutes for hydroxyl ions in hydroxyapatite, which becomes fluorapatite or fluorohydroxyapatite.[32] Such crystals are more compact, less soluble, and more stable than hydroxyapatite and resist skeletal resorption.[7] Due to its better blood supply, F accumulation occurs more in cancellous than cortical bone.[2] Additionally, F directly stimulates osteoblasts and thereby bone formation,[7,32] with toxic levels causing osteosclerosis and exostosis. However, areas of osteomalacia and osteoporosis may also occur.[32]

Direct quantification of F in a bone specimen is the "gold standard" for documenting SF, but SF is typically diagnosed from 24-hour urine F content. Notably, F content of fingernail clippings can also reveal chronic F exposure.[7]

F exposure of 3–4 mg ingested daily is considered adequate to reduce tooth decay.[7] Per the US Environmental Protection Agency (EPA), SF occurs with ingestion of more than 10 mg daily for more than 10 years.[20] However, the dose and duration of F in relation to bone health likely varies in each individual depending on mode of access and other factors influencing the skeleton.

B) Non-Endemic Skeletal Fluorosis:

1) Fluoride Source: The case reports revealed by our PubMed search dated to 1978 and showed increased frequency since 2005 (Table 2). The 19 cases included the 14 discussed by

Tucci et al in 2017.[24] We briefly described our patient at a medical meeting in 2019.[34] Subsequently, three additional cases were identified. One published in the French literature in 2005 was attributed to toothpaste ingestion,[23] and one (in abstract form only) was attributed to eating soil in Arizona, USA (1981).[35]

Approximately half of these 19 cases were attributed, in part[21,22] or completely,[6–8,19,22] to chronic consumption of large amounts of various types of black tea. The estimated daily intake of F from this tea ranged from 13–74 mg spanning >20 years. All of these instances occurred in women, age range 47–67 years. Here, F from soil accumulates in the tea plant (*Camelia sinensis*) and is released after the leaves are baked to prepare the beverage. Thus, brewed, instant, and bottled tea can be the source of F.[6–8,22]

Seven of the 19 cases were attributed to “recreational” inhalation of F-containing vapors, i.e., “huffing”. Huffing fluorocarbons can lead to euphoria, and abuse or dependence in 10–50% of cases.[25] The first, reported 42 years ago by Klemmer and Hadler,[27] involved an operating room nurse admitted to a clinical research unit for a puzzling bone disease who was discovered in possession of cotton wadding soaked in methoxyflurane (an anesthetic). Her serum and urine F levels were much higher than ever subsequently recorded, likely explained by specimen collection shortly after inhalation. She stopped this practice, and a decade later was healthy (Nortin Hadler, MD, personal communication). Subsequently, the inhalation source for others was typically aerosolized computer cleaners. However, no data has established the dose or duration of inhaled F underlying skeletal toxicity.

Unfortunately, the extent and consequences of such inhalation abuse are largely underappreciated, yet regarded as a “hidden epidemic”.[18] Estimates in 2012 indicated > 2,000,000 people over age 12 years in the USA had used “inhalants”.[37] Computer dusters contain F as DFE or tetrafluoroethane (TFE), and are widely available and inexpensive. The abuse risks neurologic and cognitive deficits, acute kidney injury, hepatotoxicity, sudden death due to cardiac arrhythmia, and suicide.[17,18] Nearly one-third of the 30 inhalant abuse deaths in North Carolina between 2000 and 2008 were attributed to exposure to computer duster.[18]

2) Clinical features: SF from any cause is suspected based on symptoms, including bone and joint pain and deformities, fractures, and poor dentition together with various radiological features. Wang et al[38] reviewed the radiographic findings of 127 pediatric and adult patients with endemic SF and found, by decreasing prevalence, calcified ligament attachments in 89%, growth lines (remnants from “transient disorders of calcium/phosphorus metabolism occurring during growth”) in 70%, osteosclerosis in 43%, osteopenia in 40%, and diaphyseal widening in 28%. Osteosclerosis of the spine and pelvis with osteopenia of the long bones was common.[38] Calcification of the sacrotuberous ligament is considered a characteristic feature.[39] Periosteal hyperostosis (“periostitis deformans”) affecting tubular bones, especially the hands, is recognized in some instances of SF.[1,24]

In the case reports found of non-endemic SF, bone and/or joint pain and osteosclerosis, primarily of the axial skeleton, were invariably present. Decreased range of motion,

kyphosis, and stiffness were frequent complaints. Elevation of serum ALP in the majority of cases was consistent with increased bone remodeling or osteomalacia. Increased periarticular radio-isotope uptake on skeletal scintigraphy, as in our patient (total 7 cases), was common and considered reflective of accelerated bone remodeling or osteomalacia.[24] Some patients exhibited periostitis, others ligament calcifications, osteophytes, exostoses, or exuberant callus at fracture sites. In some cases, including ours, atraumatic or stress fractures involved areas of osteopenia. Associated factors were poor Ca nutrition including anorexia nervosa,[20,22] elevated circulating PTH (our case), or D insufficiency.[24]

DXA was performed in 13 of these 20 cases, with some authors reporting BMD T-scores, while others provided more appropriate Z-scores[40] (Table 3). BMD was always high at the lumbar spine, but more variable at the femoral neck and total hip; being elevated in most, normal in three cases,[22,23] and in the “osteopenic” range in one postmenopausal woman with a history of anorexia nervosa.[22] Forearm BMD measured in five cases was normal for age in four and in the “osteopenic” range in one. Thus, in non-endemic SF, areal BMD seems to reflect a greater osteosclerotic effect of F in cancellous compared to cortical bone. DXA evaluation may suggest SF particularly when there is significantly increased axial but not distal appendicular bone mass although TBS assessment and finite element analysis[24] may be misleading because underlying bone quality is poor.

3) Secondary Hyperparathyroidism: Our patient with SF was referred uniquely for evaluation of endocrinopathy; i.e., unexplained secondary hyperparathyroidism. Hyperparathyroidism in SF was apparently first described in 1973 by Teotia[41] based on investigation of 20 patients with endemic SF manifesting typical radiologic features, five of whom also had radiologic and histologic findings of secondary hyperparathyroidism along with high serum levels of PTH. Srivastava et al[42] described secondary hyperparathyroidism in 1989 in their study of five family members consuming well water with high F concentration. The family was poor, including their nutrition involving Ca. Serum Ca and 25(OH)D were low in one family member but normal in the others, yet all had elevated circulating PTH, ALP, and OCN indicative of high bone turnover. In a study from Turkey in 2011, Koroglu et al[32] found mean serum PTH level was elevated in endemic SF despite mean serum Ca and 25(OH)D levels equivalent to controls. The authors postulated that in SF with adequate dietary Ca osteosclerosis dominates, whereas dietary Ca inadequacy causes secondary hyperparathyroidism featuring areas of osteosclerosis and osteoporosis.[32]

In 1997, Chadha and Kumar[43] described a woman with endemic SF in India who presented like our patient with progressive hip pain followed by a pathologic fracture of a femoral neck. Similarly, radiographs showed a large osteolytic lesion of the femoral neck. Four years later, she had persistent diffuse bone pain including of her hips and a pseudofracture was found in the contralateral femoral neck. A Looser zone (i.e., pseudofracture) was also found in a rib, and bone resorption was evident in her phalanges and metacarpals. Mild hypocalcemia, elevated serum ALP, and very high serum and urine F levels were documented. SF seemed associated with osteomalacia, secondary hyperparathyroidism, and a large resorptive cavity in the femoral neck.

Our review of non-endemic SF case reports revealed circulating PTH levels with reference ranges were reported in 13 of the 19 patients including our patient, and was elevated in four. Two of these four cases had mild elevation of PTH and two significant elevations. In our case, PTH was > 4x the upper limit of the normal range (ULN) while initially he was also strikingly hypocalcemic. None of the other cases reviewed were hypocalcemic.

F interferes with Ca homeostasis in animals. Xu et al[44] studied circulating PTH levels in rats exposed to high amounts of F with or without a low Ca diet. Circulating Ca decreased and PTH increased in a time-dependent manner with the extent of F exposure, and was highest in the low Ca, F-exposed group. They concluded that PTH acts importantly in SF, particularly in the setting of Ca deficiency. Excess F seems to disrupt mineral homeostasis while also directly affecting osteoblasts. In SF, increased avidity of the skeleton for Ca may cause osteosclerosis from increased Ca uptake in areas taking up F (predominantly cancellous bone), diminish circulating Ca levels and thereby engender secondary hyperparathyroidism followed by increased bone turnover, and calciopenic osteomalacia or osteoporosis at other sites.

4) Fluoride Assay: In all 19 instances of non-endemic SF we reviewed, the diagnosis was made by measuring F concentration in blood, urine, nail clippings, and/or bone. However, F quantitation involved different assays and units of measurement. Thus, we present data as multiples of the ULN (Table 2). F in serum or plasma ranged from 1.5 to 130 times elevated, in urine 3.3 to 16 times elevated, in finger and toe nails 1.5 to 5.9 times elevated, and in bone 7.4–18 times elevated. No significant correlation was identified between F levels and SF severity in terms of fractures, bone deformities, markers of bone turnover, or degree of secondary hyperparathyroidism. This matches the lack of linear relationship between F concentration in drinking water and development of endemic SF.[32] Notably, F levels in blood and urine are expected to vary depending on renal function and time since F exposure. Therefore, bone F levels would be expected to provide the best reflection of the severity of SF disease because F is released slowly from the skeleton. However, quantitation of bone F is not readily available.

5) Treatment: There is no established medical treatment for SF other than protection from F exposure along with adequate mineral and vitamin D to mineralize the skeleton. If F ingestion continues, oral calcium might reduce F absorption by binding it in the GI tract.[33] Although symptoms may improve over months,[16] full recovery takes years due to the long half-life of skeletal F.[7,16] A brief report of a postmenopausal woman with SF recounted BMD normalizing rapidly once estrogen replacement therapy stopped, consistent with the pace at which SF reverses depending on the rate of bone turnover.[45] Teriparatide has been proposed to hasten recovery by increasing bone turnover, but there is little data to support this treatment.[19] In fact, during recovery from SF, nephrolithiasis (Ca oxalate stones) may become a chronic problem due to unloading of excess mineral from the skeleton.[7,16]

6) Our Patient: Our patient had several classic radiologic features of SF, including axial osteosclerosis, exuberant callus formation at the site of a humerus fracture, periosteal bone formation, and conspicuous sacrotuberous ligament calcification. Also, his bone scan showed diffuse periarticular uptake. His serum ALP, CTX, and OCN levels were

significantly elevated indicating rapid bone remodeling. Secondary hyperparathyroidism, likely a consequence of his SF and diet, was also evident at presentation. Despite obesity he had poor intake of dietary Ca, tobacco and opiate abuse, as well as hypogonadism -- all potentially contributing to his skeletal disease.[46] High intake of cola beverage has been associated with altered bone metabolism, low BMD, and fractures in human and animal studies.[47] However, it is controversial whether this association involves a direct adverse effect of phosphate or concomitant poor Ca nutrition.[47] Because phosphate is thought to increase uptake of F[33] his cola consumption may have exacerbated his SF.

We postulate that our patient's forearm BMD increased with treatment of his SF due to mineralization of areas of osteomalacia. He has not developed kidney stones, but we will monitor him for hypercalciuria and nephrolithiasis.[16]

He reminds us of the prevalence of fluorocarbon inhalation, and how it may be difficult to uncover. If clinical findings suggest SF, F levels in blood and urine, preferably a 24-hour collection, should be obtained mindful that the patient may not disclose this practice. Prompt diagnosis is crucial because "huffing" has multiple morbidities and can lead to death.

7) Conclusion: Although SF is described in radiology textbooks,[48] it is not indexed in several canonical textbooks of internal medicine[49,50] endocrinology[51,52] or metabolic bone disease.[46] This absence is regrettable given its prevalence worldwide. Indeed, we wonder, from the high prevalence of endemic SF, if SF is the most common metabolic bone disease. Non-endemic SF, with its unusual causes, or endemic SF in an individual who has relocated to a non-endemic region, may go undetected because of its broad-ranging presentation and laboratory findings that depend on the duration and magnitude of F exposure and renal function, dietary Ca, and other factors influencing bone health. The differential diagnosis of chronic bone or joint pain, elevated axial bone mass, and rapid bone remodeling, with or without, osteomalacia, fractures, or hyperparathyroidism, must include SF.

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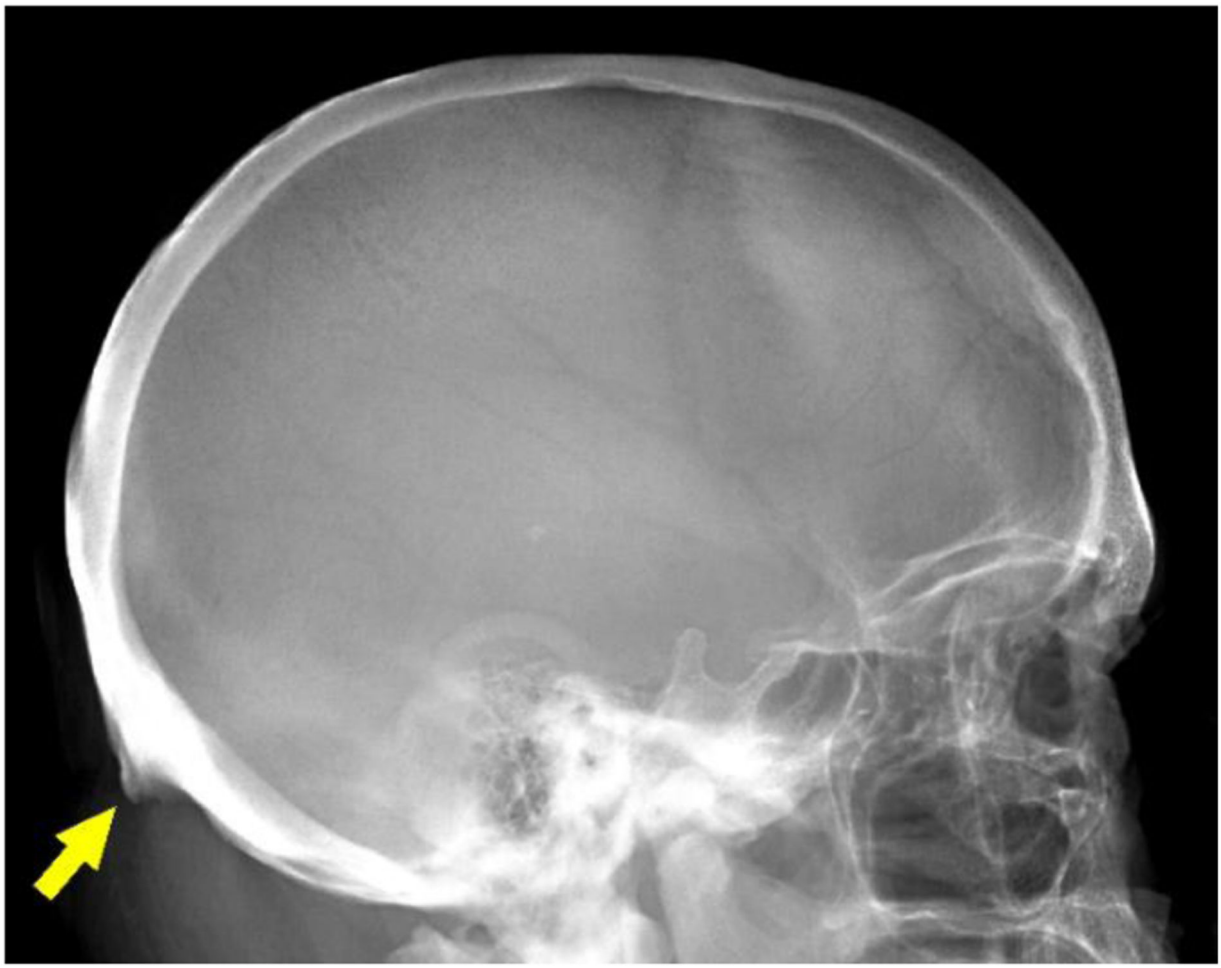

Figure 1.
Lateral skull radiograph shows osteosclerosis with diplopic thickening and a prominent external occipital protuberance (arrow).

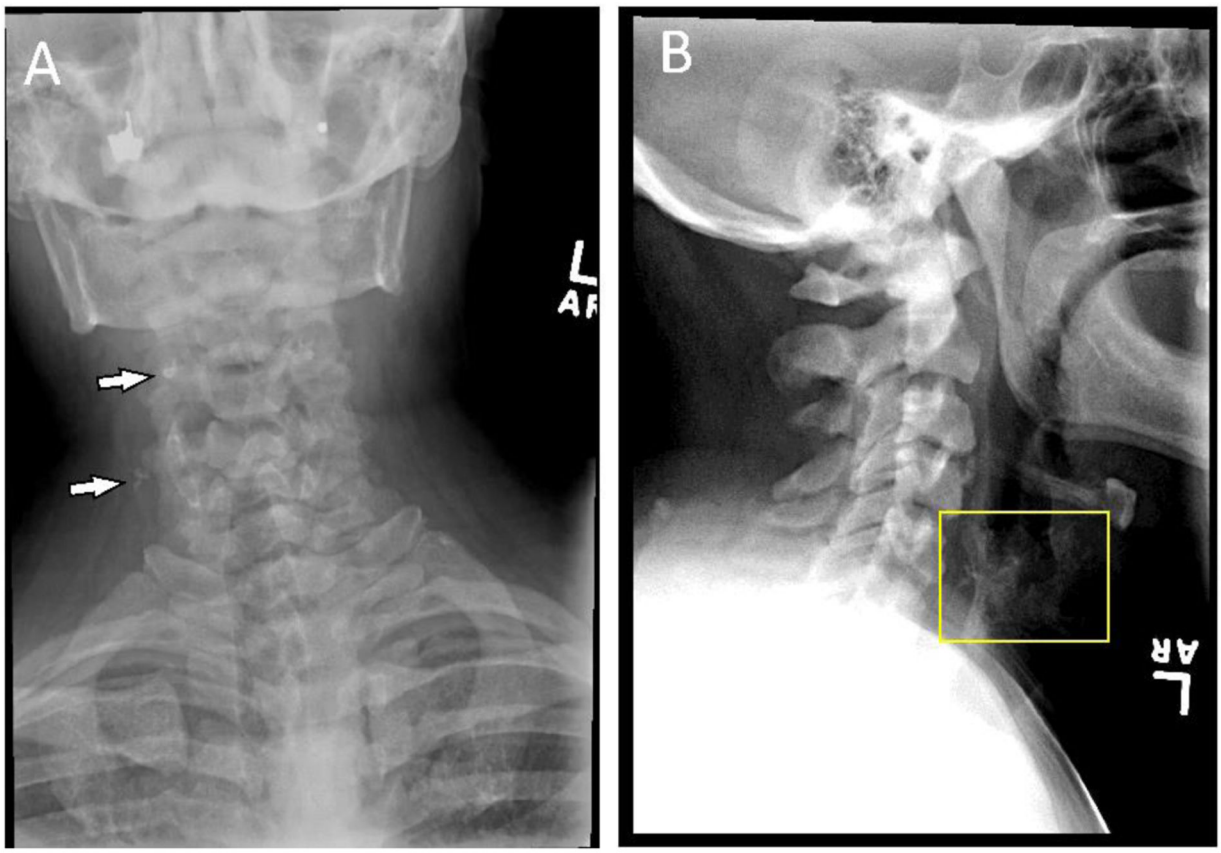

Figure 2:
Radiographs of the anterior-posterior (A) and lateral (B) cervical spine show diffuse osteosclerosis of the vertebral bodies and neural arches, right carotid calcification (arrows), and extensive laryngeal cartilage calcification (box).

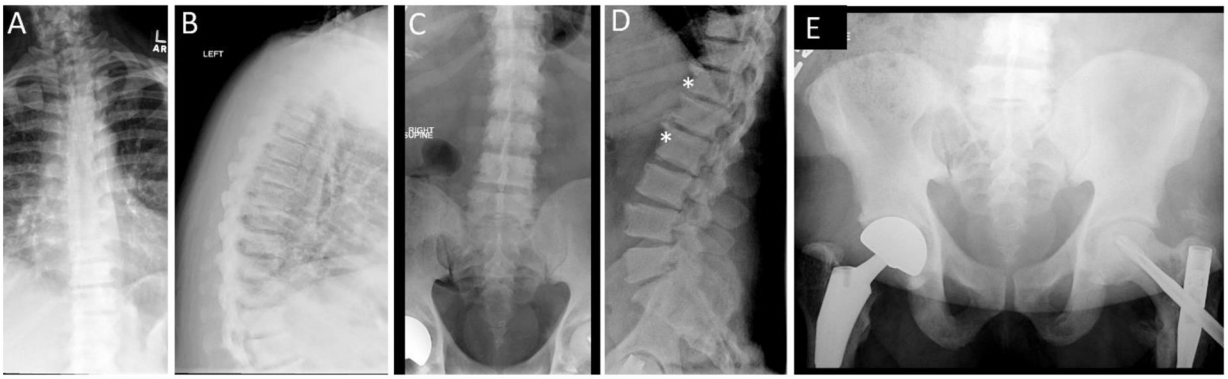

Figure 3.

Radiographs of the anterior-posterior (AP) and lateral thoracic (A, B) and lumbar (C, D) spine show diffuse osteosclerosis and degenerative changes including osteophytosis (*). Diffuse osteosclerosis affects the pelvis (E) and lower lumbar spine. The right hip has a prosthesis and left hip orthopedic hardware.

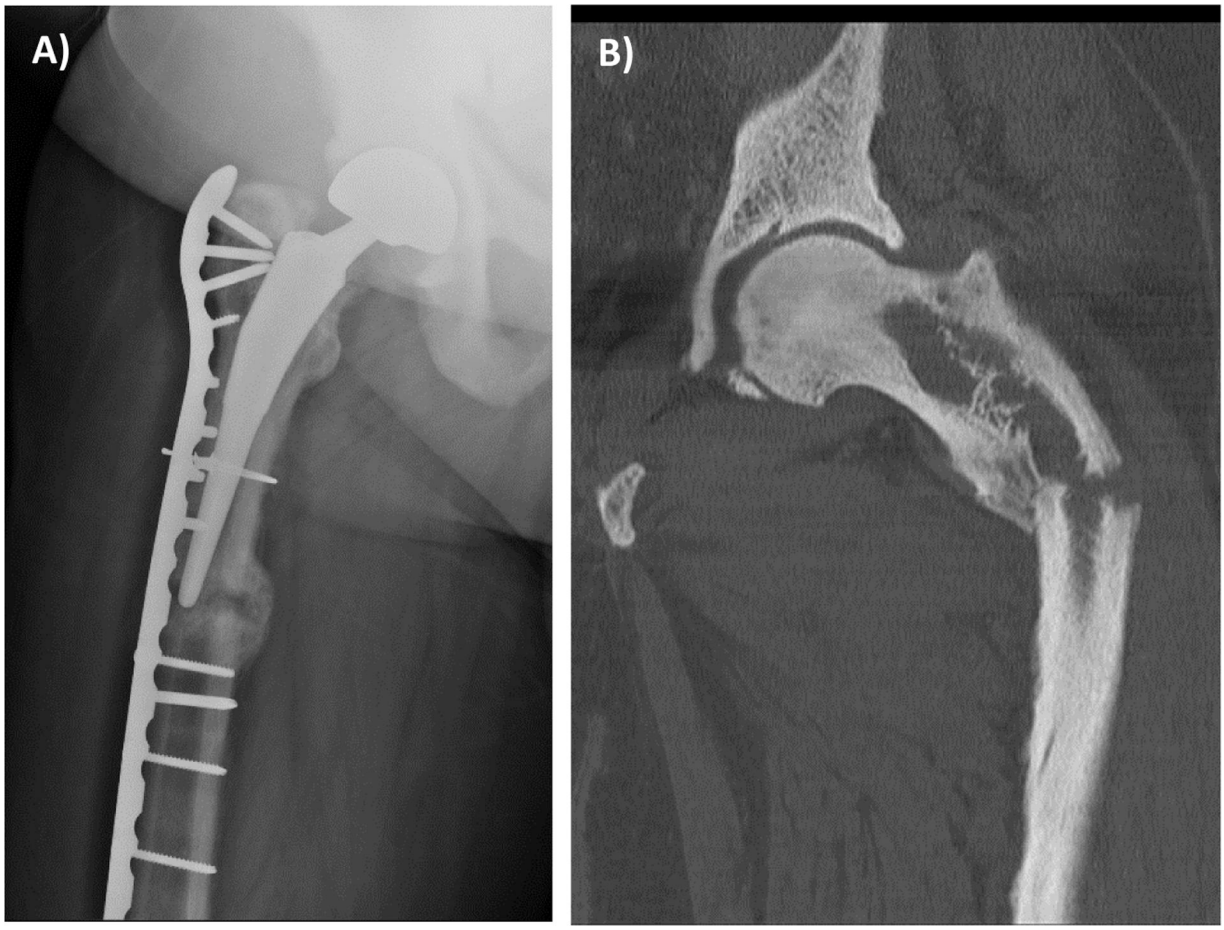

Figure 4:
Radiograph of the proximal right femur (A) showing a healing transverse fracture at the distal tip of the femoral prosthesis, and treatment with a femoral plate and screws. CT of the left hip (B) showing a cystic osteopenic neck and a subtrochanteric fracture. Note the irregularity of the femoral shaft distal to the fracture.

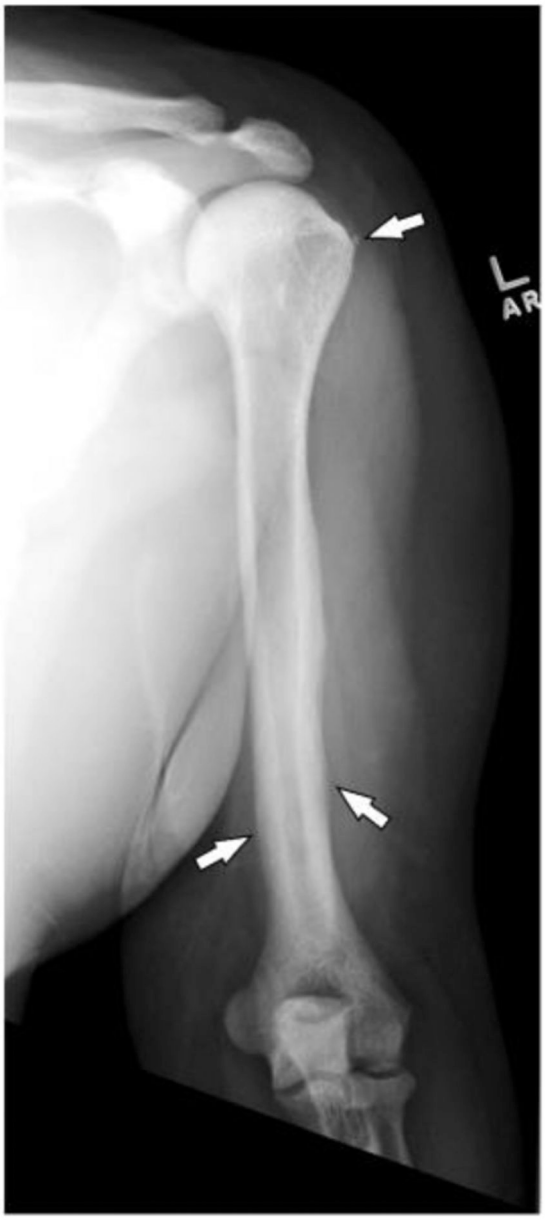

Figure 5.

Radiograph of left humerus shows osteosclerosis, cortical thickening, an enlarged deltoid muscle insertion, periosteal bone formations in the distal humerus (arrows) and proximal ulna, and calcification about the shoulder (arrow)

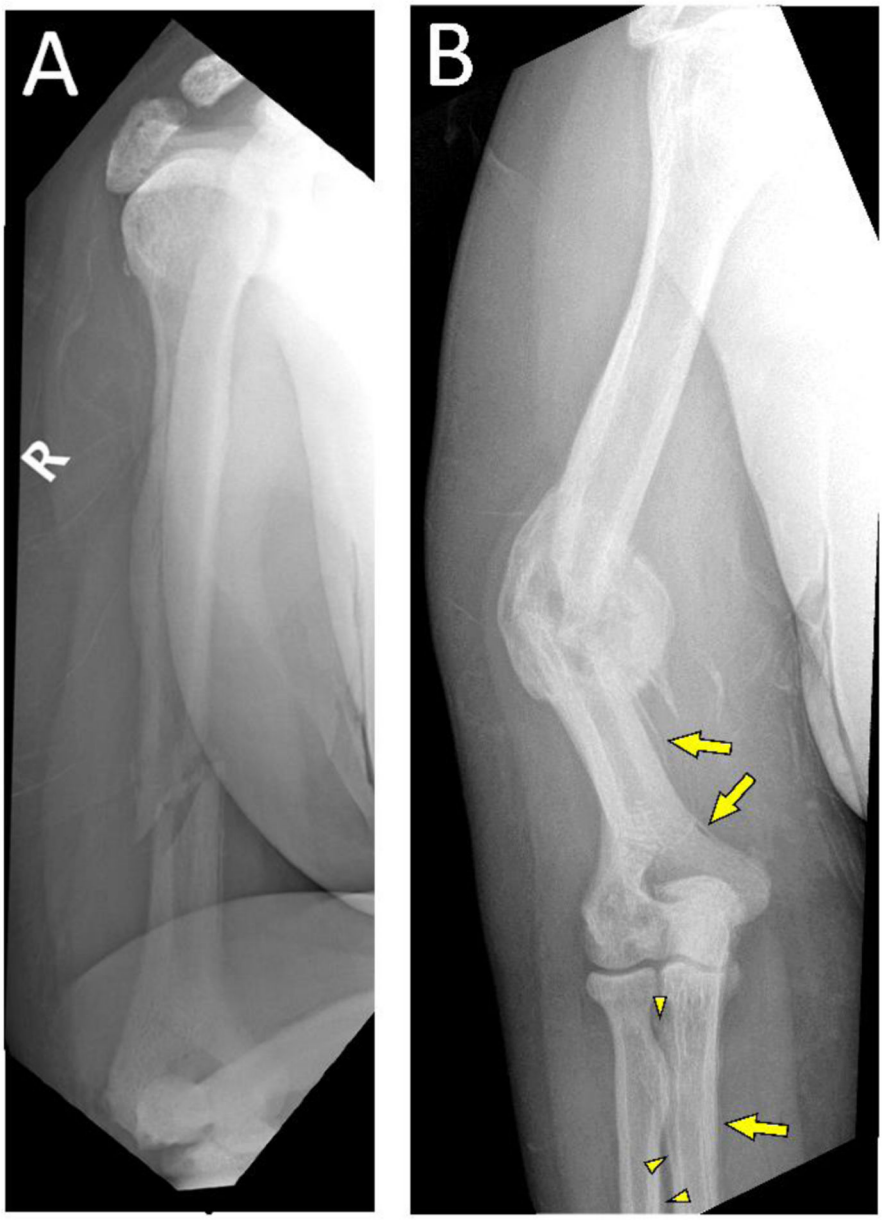

Figure 6:
Radiographs of the right humerus. Initial (A) and six months later (B) The follow up at 6 months shows an oblique mid humerus fracture with increased angulation and hyperplastic callus. There are linear streaks of ossification in the muscle planes adjacent to the fracture and periosteal new bone formation of the distal humerus and all along the radius (arrows) and interosseous membrane of the forearm (arrow heads).

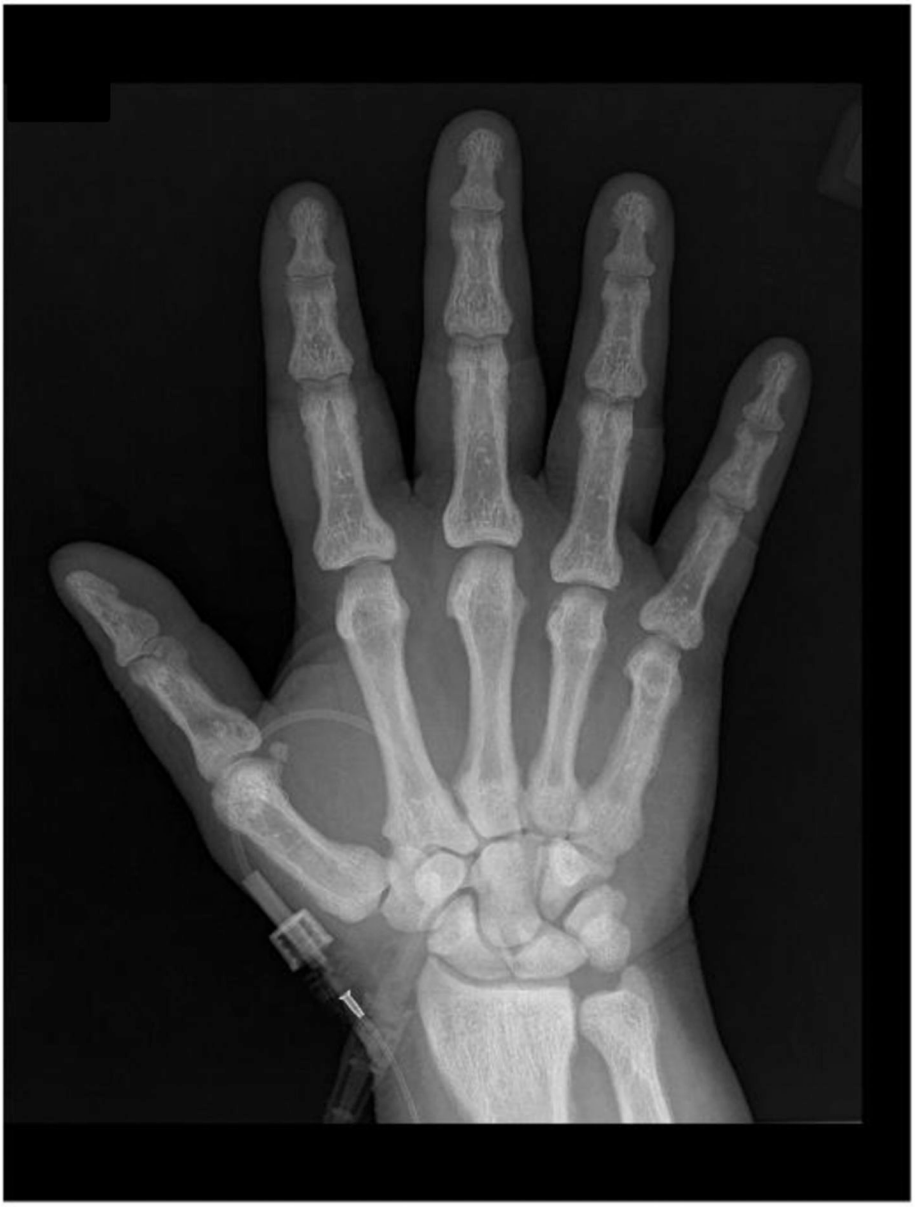

Figure 7:
PA radiograph of left hand shows osteosclerosis, cortical thickening, coarse trabeculae, periosteal new bone formation, focal areas of osteosclerosis, and interosseous membrane calcification between the distal radius and ulna.

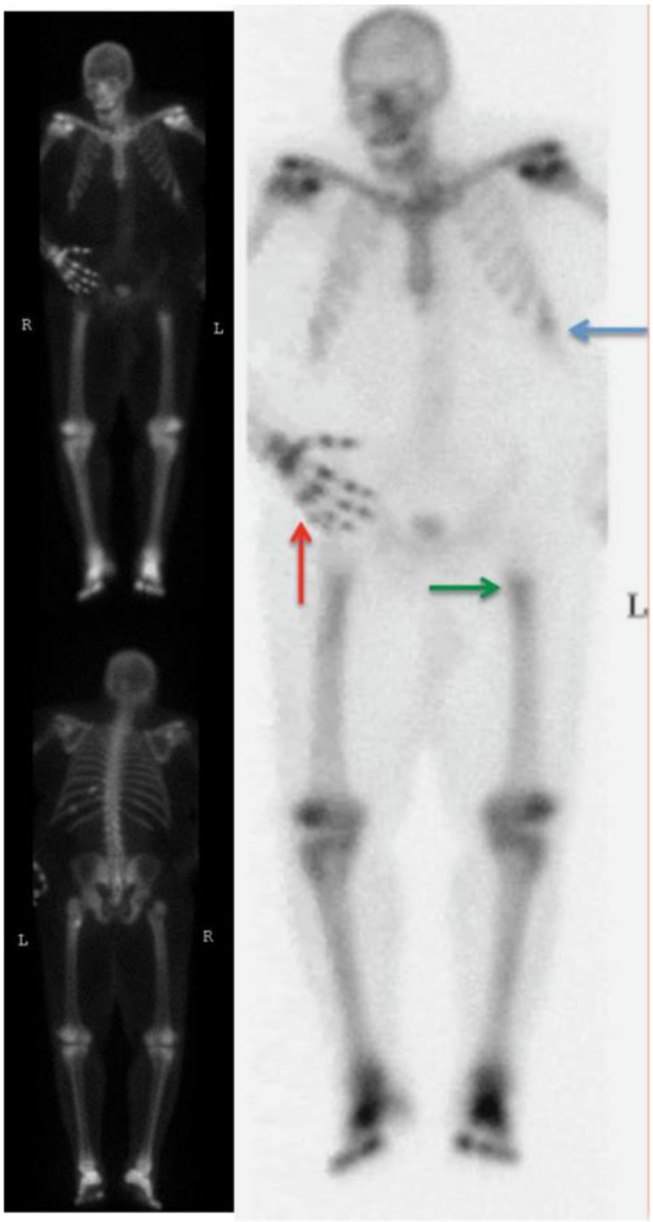

Figure 8.

Technetium bone scintigraphy shows intense periarticular uptake at the knees, feet, right wrist and hand, along with increased uptake at the fracture sites including several ribs (arrows).

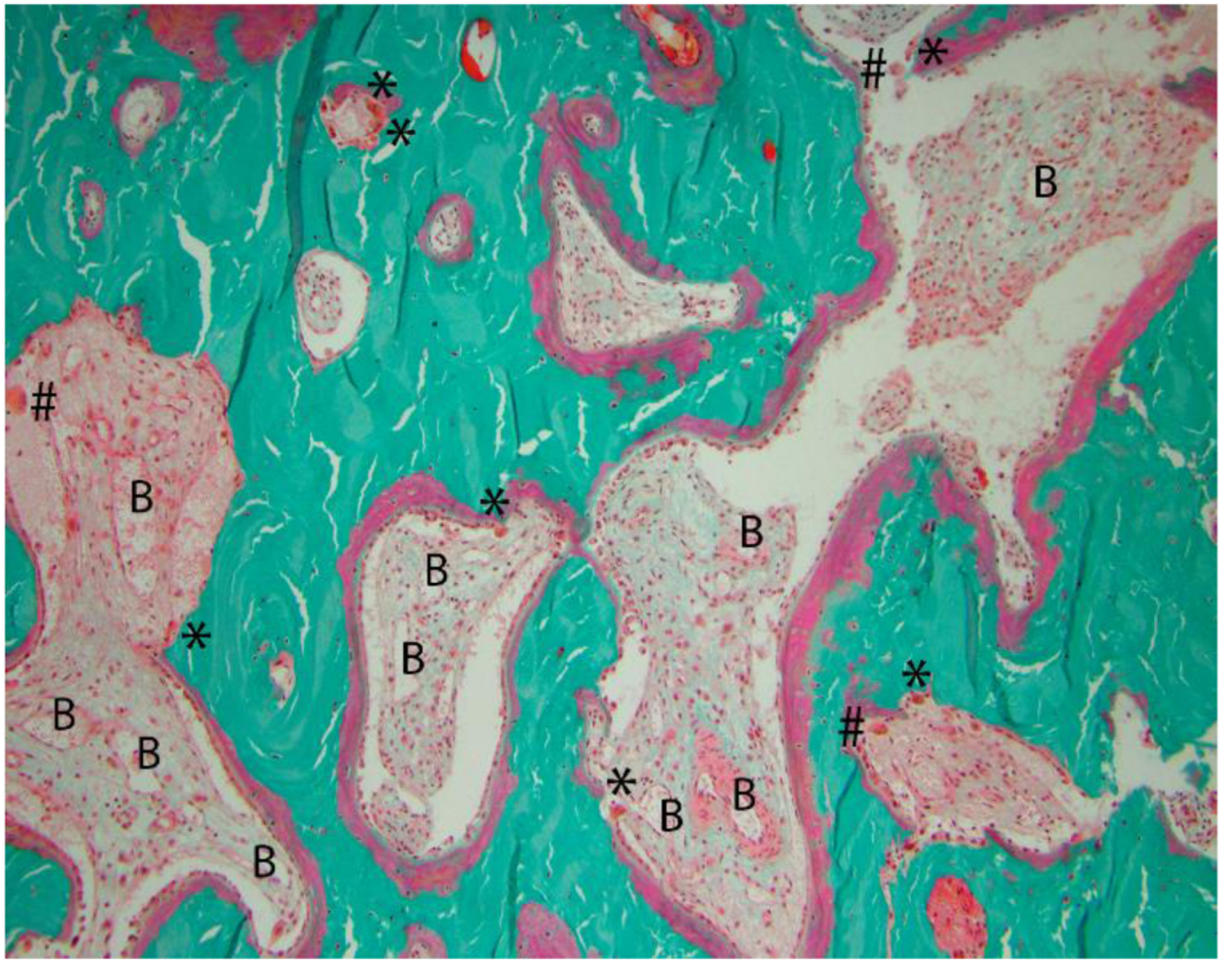

Figure 9:

Surgical Bone Biopsy:

Goldner trichrome stain of undecalcified bone obtained at right femoral fracture repair. Osteoid (pink) is present on most bone surfaces, covered by cuboidal osteoblasts (10x magnification).

KEY:

*, polarized osteoclast on bone surface.

#, rounded osteoclast, likely apoptotic

B, blood vessels

Table 1:

Patient's Mineral and Skeletal Biochemistry *

Months before or after referral	**−19**	**−7**	**−6**	**−5**	**Referral**	**+4**	**+6**	**+10**	**+14**	**+17**	**+18**	**+25**
Fracture location	Right femoral neck		Right humerus	Left femur			Right femur					
SERUM												
Calcium (corrected) (8.5–10.2 mg/dL)		7.6		7.8	9.4	9.0		9.2	9.4	9.2		10.2
Magnesium (1.8–2.4 mg/dL)				2.5								
Phosphorus (2.3–4.7 mg/dL)				2.5	3.7							
25(OH)vitamin D[a] (30–100 ng/mL					21	26		36	31		23	
$1,25(OH)_2$vitamin D[b] (18–72 pg/mL)					100							
PTH (Intact) (9–77 pg/mL)				133	327	311		161	144			56
Alkaline phosphatase (46–116 U/L)		708		1080	539	815		832				248
Creatinine (0.72–1.25 mg/dL)		0.7		1.06	0.62	0.84		0.61	0.71	0.78		0.81
C-telopeptide[c] (87–345 pg/mL)						2513						
Osteocalcin[d] (9–38 ng/mL)						>300						
Fluoride[e] (0.02–0.08 mg/L)						4.84		0.62			0.36	
URINE												
24 hr calcium (volume = 3.4 L)							<2 mg/dL					
24 hr Cr (950–2490 mg)							1761					
24 hr fluoride[f] (volume=3.4 L) (0.2–3.2 mg/L)							27.1					
Spot fluoride[f] (0.2–3.2 mg/L)						42.6		34.1	8.2		13.0	3.3
Fluoride (0–3 mg/gm cr)						80	52	43	23		22	14

*Assays:

a – in house;

b,c,d, - Quest;

e - Mayo, Quest;

f – LabCorp

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Table 2 –

Unusual Instances Of Skeletal Fluorosis

Ref no.	Author(s)	Year	Age/ Sex	F-Source	Est.F-Daily Intake (mg)	Dur (yrs)	Clinical Presentation	Radiology Findings	Initial laboratory findings							
									[F] Blood X ULN	[F] Urine X ULN	[F] Tissue High	ALP X ULN	PTH X ULN	25(OH)D ng/mL	cCa mg/ dL	Cr mg/ dL
27	Klemmer & Hadler	1978	27F	Inhaled anesthetic[@]			DBP, CRI, SC nodules	AOS, PD, bone scan uptake	130[+]	16[+]	Bone	4.3	1.6	13.4	9.8	
35	Fisher et al[#]	1981	F	Soil		20	DBP, CRI	GOS			Bone					
6	Whyte et al	2005	52F	tea	37–74	>30	Back pain and stiffness, joint pain, dental problems	AOS, LC, osteophytes		5.5		nl	nl	nl	nl	nl
23	Roos et al	2005	45F	toothpaste	66	>5	Pain, swelling of fingers, dental problems	PD, bone scan uptake	1.7	16		3.5	1.3	20.4	8.8	
22	Hallanger et al	2007	50F	tea	56		DBP, CRI, kyphosis, smoker	GOS	4.8		Bone	17		12	9.9	2.1
			67F[^]	tea	13		Foot fracture, kyphosis, anorexia (BMI 15)	AOS	3.9			1.45	nl	19	9.7	1.3
			60F	tea + toothpaste	17		DBP, rib fractures, anorexia (BMI 17), smoker	AOS	2.6			nl	nl	54	9.8	1.5
			62F[^]	tea	14	30	Joint pain, CRI, high BMD (Screening DXA)	AOS, LC	4.3			nl	nl	25	9.9	1.7
16	Kurland et al	2007	52M	toothpaste			Stiff neck, joint pains	AOS, LC, SSO, bone scan uptake	1.7	24	Bone	1.8	nl	nl	nl	1.3
17	Little et al	2008	33M	Inhaled DFE			Fractures from motor vehicle accident	Exostoses, heterotopic bone								
7	Whyte et al	2008	49F	tea	44	37	DBP, LE fracture	AOS, PD, LC, bone scan uptake	1.5	6.0	Nails	1.4	nl	42	9.1	1.1

Ref no.	Author(s)	Year	Age/ Sex	F-Source	Est.F-Daily Intake (mg)	Dur (yrs)	Clinical Presentation	Radiology Findings	Initial laboratory findings							
									[F] Blood X ULN	[F] Urine X ULN	[F] Tissue High	ALP X ULN	PTH X ULN	25(OH)D ng/mL	cCa mg/ dL	Cr mg/ dL
8	Izuora et al	2011	48F	tea	19–37	30+	DBP, joint pain, kyphosis, smoker	GOS, LC, IOMC, SSO, STO, bone scan uptake	2.8	3.3	Nails	3.2	3.1	11	9.0	nl
21	Joshi et al	2011	53F	tea+ toothpaste	15		Foot fracture, dental problems, cerebral palsy	AOS, LC, SSO, profuse callus	17	10	Bone Nails	nl	nl	nl	nl	
19	Kakamanu & Sudhaker	2013	47F	tea	>20	17	DBP, dental problems	AOS, IOMC	4.3							
36	Rackoff et al	2015	70M	Inhaled Freon		2	LE nodules, heroin use, smoker	AOS, LC, SSO, STO, exostoses	49 [+]					49	9.5	1.3
24	Tucci et al [*]	2017 [*]	28M	Inhaled DFE		3–4	Hip ankylosis, kyphosis, femur fracture, UE bone deformities	GOS, PD, LC, IOMC, SSO, exostoses, focal osteopenia, bone scan uptake	2	5.9	Bone	1.8	nl	14	9.0	
25	Peicher & Maalouf	2017	33M	Inhaled DFE		3	Back pain, loss of lumbar-lordosis	GOS	14			2.6	nl	32	9.6	0.94
28	Ponce et al	2019	27M	Inhaled DFE		1	UE & LE painless nodules, syncope, frostbite	PD, exostoses	3.8	16		5.2		10		
	Our Patient	2020	51M	Inhaled DFE		2–3	DBP, fractures, obese, poor diet, opiate use, smoker	AOS, LC, IOMC, STO, osteophytes, soft tissue calcification, profuse callus, focal osteopenia, bone scan uptake	61	8.5		4.6	4.2	21	7.6	0.7

ALP = serum alkaline phosphatase, 25OHD = serum 25 hydroxy vitamin D, AN = anorexia nervosa, AOS = axial osteosclerosis, BMD = bone mineral density , BMI = body mass index, cCa = corrected serum calcium, Cr = serum creatinine, CRI = chronic renal insufficiency, DBP = diffuse bone pain, DFE = difluoroethane in computer duster, [F] = fluoride concentration, GOS = generalized osteosclerosis, IOMC = interosseous membrane calcification, LC = ligament calcifications or ossifications, LE = lower extremity, nl = reported as normal (lab values not provided), PD = periostitis deformans, PTH = serum intact parathyroid hormone, SC = subcutaneous, SSO = sacrospinous calcification or ossification, STO = sacrotuberous ligament calcification or ossification, UE = upper extremity, X ULN = times upper limit of normal

Blank boxes indicate this information was not available.

Abstract only available.

* This case was reported also by Cohen et al (ref 26) in 2014 and by Tucci et al as an ASBMR abstract 2013

^ Follow up on these 2 cases was reported 11 years later (ref 20)

@ methoxyfluoroethane

+ no normal range given so our assay normal range was used to estimate X ULN

Table 3 –

DXA Bone Mineral Density Reported In Non-Endemic SF

Ref.	Age/Sex	L1–L4 Spine		Total hip		Femoral neck		1/3 radius	
Score		Z	T	Z	T	Z	T	Z	T
Whyte 2005[6]	52 F	10.3		2.1					
Roos 2005[23]	45 F		+4				−0.3		
Hallinger 2007[22]	50 F		+5.3				+2.5		
	67 F	+4.7^	+2.3			+0.4	−1.7		
	60 F		+1.9				−0.5		
	62 F	+7.2^	+6.1			+2.0	+0.9		
Kurland 2007[16]	52 M	+14.3				+6.6		−0.6	
Whyte 2008[7]	49F	+10.3		+2.8					
Izuora 2011[8]	48 F	+9.9		+5.0					
Joshi 2011[21]	53 F		+12*		+8.7*				−1.8
Tucci 2017[24]	28 M	+6.2		+3.0		+4.8		−0.2	
Peicher 2017[25]	33 M	+10.7		+6.5				+1.0	
Our case	51 M	+7.4	+8.3					+0.4	+0.3

*First of serial measurements after SF diagnosis

^Original Z-scores were reported in a follow-up publication[20]