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Skeletal Fluorosis Due To Inhalation Abuse Of A Difluoroethane-Containing Computer Cleaner

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Abstract

Skeletal fluorosis (SF) is endemic in many countries and millions of people are affected worldwide, whereas in the United States SF is rare with occasional descriptions of unique cases. We report a 28-year-old American man who was healthy until two years earlier when he gradually experienced difficulty walking and an abnormal gait, left hip pain, loss of mobility in his right wrist and forearm, and progressive deformities including enlargement of the digits of both hands. Dual-energy x-ray absorptiometry (DXA) of his lumbar spine, femoral neck, total hip, and the one-third forearm revealed bone mineral density (BMD) Z-scores of +6.2, +4.8, +3.0, and -0.2, respectively. Serum, urine, and bone fluoride levels were all elevated and ultimately explained by chronic sniffing abuse of a computer cleaner containing 1,1-difluoroethane. Our findings reflect

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Authors' roles: All authors helped write and approved the submitted manuscript. JRT diagnosed and investigated the patient's osteosclerosis. GMW performed the bone fluoride analysis, and guided interpretation of the biochemical findings. WHM and DVN characterized, illustrated, and discussed the radiological and histopathological findings, respectively. SM conducted and interpreted the mutation analyses. TMK performed the finite element analysis. MPW helped guide the patient studies and manuscript creation and finalization.

SF due to the unusual cause of inhalation abuse of difluoroethane. Because this practice seems widespread, particularly in the young, there may be many more such cases.

Keywords

Fluoride; Hyperostosis; Osteosclerosis; Periostitis

II) Introduction

Skeletal fluorosis (SF) is a major endemic problem in India, China, Japan, Mexico, Argentina, Australia, and countries in the Middle East and Africa, and is generally related to drinking well water or tea high in fluoride (F⁻) content.^(1,2) In the United States, SF is uncommon and occurrences have unusual causes.⁽³⁻⁹⁾ For example, in 1978, a nurse with painful periostitis and osteosclerosis had markedly elevated F⁻ levels in her serum, urine, and bone that were ultimately attributable to inhalation abuse of an organofluoride anesthetic.⁽³⁾ Tea drinking is popular in the United States, and consumption of extreme volumes or concentrations of the beverages prepared from *Camellia sinensis* can cause SF due to the F⁻ levels sometimes found in commercial tea preparations. In 2005, Whyte et al⁽⁴⁾ reported a woman with SF due to chronic daily intake of one to two gallons of extra-strength instant tea, and subsequently similar patients consuming instant tea⁽⁵⁾ or brewed tea.⁽⁶⁾ At the Mayo Clinic from 1997 to 2006, four patients with sclerosing bone disease had chronic intake of high volumes of tea in the face of renal compromise.⁽⁷⁾ In 2007, an enigmatic case of SF was reported in a middle-aged man apparently due to frequent dental brushing and perhaps surreptitious ingestion of toothpaste.⁽⁸⁾ In 2013, Kakumanu and Rao published the radiographs showing SF affecting a woman who consumed tea daily that was made from 100 to 150 tea bags.⁽⁹⁾

Herein, we report a young man who presented with progressive pain and ankylosis of a hip, abnormal gait, advancing deformation of his hands and upper extremities, and limited mobility due to inhalation abuse of a computer cleaner containing 1,1-difluoroethane.

III) Case Report

In 2010, this 28-year-old American office worker had been healthy until two years earlier when he developed difficulty walking, an abnormal gait, pain in the anterior left hip, loss of movement of his right forearm and wrist, and progressive deformities including enlargement of bone in both hands. Then, an orthopedic surgeon noted his asymmetric gait and flexion contractures of 20 and 35 degrees of the right and left hips, respectively. The left hip also lacked internal and external rotation, with flexion to 80 degrees. Marked bony masses were present along the phalanges of all digits in his hands. A large bony excrescence overlay the lateral aspect of his left elbow where pronation was 70 degrees and supination zero degrees. Interphalangeal motion was limited in both hands. Imaging studies revealed multiple exostoses, ossification of the capsule of the left hip nearly with ankylosis, and multiple surface lesions along the radius and about the left elbow (see Radiological Findings). Blood chemistry profile showed increased serum alkaline phosphatase (ALP) activity of 227 U/L (NI, 40-130), but normal calcium, albumin and intact parathyroid hormone (PTH) levels at 9

mg/dl, 4.3 g/dl, and 53 pg/ml (NI, 10-66), respectively. Serum 25(OH)D was low at 14 ng/ml (NI, 32-100) and 1,25(OH)₂D elevated at 91 pg/ml (NI, 10-75). Urine N-telopeptide/creatinine (NTx/Cr) ratio was markedly increased at 283 nM BCE/mM Cr (NI, 3-51). Complete blood count reflected his history of thalassemia minor; Hb 12 gm/dl (NI, 13.5 to 16), Hct 37% (NI, 37 to 47), and MCV 64 (NI, 80 to 98) with serum total bilirubin 0.7 (NI, 0.2 to 1.3), iron 77 mcg/dl (NI, 49 to 181), and ferritin 105 ng/ml (NI, 22 to 322).

In September 2010, the patient was referred to us for continuing expansion of the bones of his hands (Figure 1). Weight was 142 lbs and height 66 inches. He was stooped, walked tilted to the left, and had ankylosis of the left hip with limited mobility. Serum 25(OH)D was 17 ng/ml, 1,25(OH)₂D 104 pg/ml (NI, 18-64), and bone-specific alkaline phosphatase (BSALP) 70 ug/L (NI, 20). Following vitamin D supplementation, serum 25(OH)D rose to 38 ng/ml. Radiographs demonstrated marked periostitis deformans in his hands (Figure 2) and high bone density in his spine. Whole-body bone scintigraphy revealed areas of mild diffuse increased uptake in the shoulders, hips, knees, feet, ankles, and wrists (Figure 3). Computed tomography (CT) showed diffuse trabecular heterogeneity with a generalized increase in bone density that was more striking in his left upper extremity than pelvis. Prominent hypertrophic spurring was present at the acetabular margins. The findings were not simply ectopic mineralization from metastatic or dystrophic calcification, but bone in large part emanating from skeletal surfaces yet not conventional periosteal new bone formation. Areas of relative radiolucency and a coarse trabecular pattern suggested rare disorders of high bone turnover with skeletal expansion (see Radiological Findings).⁽¹⁰⁾

Reminiscent of our patient's presentation was the report of Little et al⁽¹¹⁾ in 2008 of a 33-year-old man who, during loss of consciousness, crashed his car and sustained multiple fractures. He was intoxicated from inhaling an aerosol propellant containing 1,1-difluoroethane, C₂H₄F₂, used in "dust spray" cans.⁽¹¹⁾ Several months after orthopedic repairs, radiographs revealed rapid pathologic bone formation about a proximal humeral metaphysis, proximal femur, elbow, and soft tissues. Aerosol abuse was considered the etiology of his skeletal changes.⁽¹¹⁾ Accordingly, in May 2011, we questioned our patient. He admitted to regularly sniffing for 3 to 4 years a computer cleaner, Dust Off[®], for its highs. This stopped 5 months later in October 2011. The F⁻ content of his municipal water was at acceptable levels. Dual-energy x-ray absorptiometry (DXA) revealed his BMD Z-scores and T-scores both at +6.2 in his spine, +4.8 and +4.7, respectively, at the femoral neck, and both +3.0 at the total hip. The forearm "one-third" Z-score was -0.2.

In February 2012, left hip arthrotomy for ankylosis included extensive osteochondroplasty of the femoral head and neck and prophylactic pinning of the femoral neck. Six months later, hip function was markedly improved and his gait was nearly normal. We studied femoral exostosis fragments by histopathological analysis (see Histopathological Findings) and by F⁻ analysis. Two 300-micron sections of the bone specimen had been embedded in methacrylate and dry-ashed at 600°C overnight. The ash was pulverized with a stainless steel mortar and pestle into a finely divided, pure-white powder. The bone ash and appropriate F⁻ standards were analyzed for F⁻ using the ion-specific electrode following overnight hexamethyldisiloxane-facilitated diffusion.⁽¹²⁾ The bone F⁻ concentration was markedly elevated at 16.4 gm F⁻/kg of ash (NI, ~ 0.5 – 1.2).⁽¹³⁾

Six months after reportedly no longer “sniffing”, the patient's plasma F⁻ level (Quest Diagnostics) was still elevated at 0.16 mg/L (NI, 0.08) and 24-hour urine F⁻ (Quest Nichols Institute/Chantilly, Chantilly, VA) was still elevated at 18.9 mg/L (NI, 0.2-3.2).

In January 2013, after *in vivo* tetracycline labeling, transiliac crest bone biopsy was unsuccessful due to the extremely hard bone. Later, he complained of severe pain in the left hip due to a pathologic fracture around a femoral screw placed during hip exploration. The fracture later healed.

In July 2013, finite element analysis (FEA) based on a CT scan of his proximal left femur was performed (O.N. Diagnostics, Berkeley, CA) to estimate the overall femoral strength (in units of Newtons, N) during a simulated sideways fall (see Results).⁽¹⁴⁾ As is the protocol for that analysis, it was assumed that the bone material quality was normal. Volumetric BMD was also measured for the trabecular and cortical compartments. For that analysis, the “cortical bone” was defined as any bone having a volumetric density of more than 1.0 g/cm³ or being within 3 mm of the periosteal surface, but not necessarily histologically “cortical bone”.

In February 2014, serum chemistry profile included serum ALP of 31 U/L (NI, 42-121), PTH 21 pg/ml (NI, 12-88), 25(OH)D 37 ng/ml, and F⁻ 2.9 umol/L (NI, 0-4), and urine NTx/Cr was normal at 55 nmol/mmol.

In 2014, BMD was essentially unchanged compared to 2011 and 2012. He no longer “sniffed” and was doing well, walking more normally, and regularly “working out”. In 2015, he expressed no interest for follow-up.

Following informed written consent, we performed mutation analyses to search for genetic contributions to his high bone mass and rapid skeletal turnover using our published methods.⁽¹⁵⁻¹⁷⁾ We studied all coding exons and adjacent mRNA splice sites for the three major genes involved in RANK signaling: *TNFRSF11A* encoding RANK, *TNFRSF11B* encoding osteoprotegerin (OPG), and *TNFSF11* encoding RANKL. No mutations were identified.

IV) Results

A) Radiographic Features of Skeletal Fluorosis

Radiographs available from our patient to characterize and illustrate his SF included the images at presentation and two years later upon referral together with CT images of his left upper extremity and pelvis and proximal femurs before arthroplasty.

In the hands, marked tumoriform proliferating periosteal bone involved the tubular bone of the middle and proximal phalanges of his hands; less so on the metacarpals (Figure 2). These periosteal pseudotumors (“periostitis deformans”) are characteristic of SF. The distal phalanges showed exostoses at the distal interphalangeal joints. The proliferations were bone with striated trabeculae projecting at right angles to the shafts showing sharply demarcated outer margins, but irregular or wavy contours. The underlying cortex may have been completely lost, and replaced by bone extending out from the medullary cavity. Proliferations extended off some carpal bones along with the distal radius and ulna where

marginal osteophytes were at the radiocarpal joints. These periosteal bony proliferations were decreased and smoother on later radiographs. However, none disappeared.

Pelvic radiographs showed diffuse osteosclerosis including the sacrum (Figure 4). Marked osteophyte formations affected the hips, greater on the left where bone bridged the acetabulum to the femoral neck. Capsular calcifications involved both hips. Small marginal bone proliferations affected the pubic and ischial bones, trochanters, lateral iliac bone margins, and superior and inferior iliac spines. Sacrospinous ligament calcification was apparent on the left. Osteophytes formed at the inferior aspects of the sacroiliac joints, and periosteal new bone on the femora. The proximal femoral neck showed focal osteopenia with cystic changes, seen best on the pelvic CT. Mild improvement was apparent on the last radiograph.

The lateral spine demonstrated uniformly osteosclerotic vertebral bodies and neural arches (Supplementary Appendix, Figures 1-3). The thoracic and lumbosacral spine exhibited no osseous bridging, ligamentous calcifications, ossifications, abnormalities in shape, or rugger jersey appearance. Small bony excrescences projected from the neural arches and the anterior vertebral bodies. The scapulae were osteosclerotic, had irregularity of their lateral margins from periosteal bone proliferations, as did the proximal humeri and outer clavicles. In the chest, uniform osteosclerosis was apparent in the ribs and clavicles without expansion of these bones (Supplementary Appendix, Figure 2).

The elbows showed proliferating periosteal new bone on each side of the elbow joint (Figure 5) that was smoother and smaller on the later radiographs. The joints were spared. Some proximal interosseous fusion affected the forearm bones. CT of the left forearm showed multiple periosteal excrescences off the radius and ulna along with intraosseous membrane ossification.

The bones at the knees were osteopenic. The right cruciate ligament was calcified. Irregular periosteal thickenings affected the femora, tibia, and fibulae. Patellar and marginal osteophytes occurred at the joints. Radiolucencies were noted in the acetabuli, femoral necks, and intertrochanteric regions without cortical disruption. Partial ossification affected the left radial ulnar interosseous membrane.

The foot bones were uniformly osteosclerotic in the tarsals along with marginal irregularities. The metatarsals and phalanges had periosteal irregular bone formation along the shafts greatest in the fifth metatarsals and phalanges. Periostitis deformans was greater in the hands than the feet.

B) Histopathological Findings

The specimen from the hip arthrotomy consisted largely of highly vascularized and entirely lamellar cortical bone (Figure 6A-C). Both cortical and trabecular bone exhibited many surfaces showing bone formation, with osteoid, osteoblasts, and incorporation of the single tetracycline label administered before surgery (Figure 6D). Osteoclasts were present, particularly in typical cutting cones in the cortex, but were not increased or abnormal in shape (not shown). The articular surface on one fragment showed disorganized

chondrocytes, damage to the surface cartilage, and increased subchondral bone typical of osteoarthritis (Figure 6E,F).

C) Finite Element Analysis

With his history of a nondisplaced femoral neck fracture, the results from the FEA strength analysis indicated that the patient's bone material quality was likely not normal since otherwise – if it were normal – the overall bone would be too strong to sustain a non-traumatic fracture. Assuming normal bone material quality, the FEA-estimated overall femoral strength was 11,920 N. This value is about two-fold higher than expected for an average 30-year-old white male⁽¹⁸⁾ and clinically, a femoral strength value of more than 5,000 N indicates a low risk of fracture. Further, analysis of the volumetric BMD for the trabecular and cortical compartments indicated that the mass of the “cortical bone” was highly elevated compared to the mass of the trabecular bone (63.3 g versus 28.3 g, ratio = 2.24) compared with a ratio of approximately 0.90, on average, ranging from 0.6-1.2, for white males under age 65 (data on file at O.N. Diagnostics).

V) Discussion

F⁻ is widely distributed throughout the earth's crust, and reportedly the Earth's 13th or 17th most abundant element.⁽¹⁹⁻²³⁾ Volcanos even when seemingly inactive, are the major natural source of environmental F⁻.^(19,24) Industrial processes such as aluminum smelting, coal burning, cement and phosphate fertilizer production, and brick and ceramic firing are other important environmental sources of fluorine and F⁻.^(19,24)

Chronic F⁻ intoxication was first described in India in 1937.⁽²⁵⁾ Generally, SF results from imbibing over years large quantities of F⁻ in drinking water from wells, which can affect the teeth, skeleton, and secondarily the nervous system.⁽²⁾ In the largest series of 1065 cases of SF, significantly high levels of F⁻ were found in blood, urine, and bone.⁽²⁾ In 1952, “periostitis deformans” was characterized in Spain in six patients with hyperostosing polyostotic disease,⁽²⁶⁾ and in 1965 attributed to wine with high F⁻ levels,⁽²⁷⁾ as subsequently verified in 28 additional cases.⁽²⁸⁾ In China, water-related and coal-combustion fluorosis were treated vigorously in the 1950s and 1970s.⁽²⁹⁾ SF was additionally discovered in Asia in the 1980s due to consumption of inferior quality “brick” tea made from the twigs, berries, and old leaves of the tea plant *Camellia sinensis*. In Tibet, a survey of SF in adults revealed habitual consumption of brick tea with high F⁻ content, a food intimately related to the Tibetan lifestyle.⁽²⁹⁾ There, daily F⁻ intake reached 12 mg, of which 99% originated from brick tea-containing foods. Nearly 90% of affected individuals had symptomatic joint dysfunction, with their SF more severe compared to water-type and coal-type fluorosis.⁽²⁹⁾

Other causes of SF are unusual, as we reviewed above for the USA.⁽³⁻⁹⁾ In 2005, a French woman developed SF from brushing her teeth 18 times daily.⁽³⁰⁾ She swallowed her fluoridated toothpaste for its taste, providing an estimated 69 mg of F⁻ daily.⁽³⁰⁾ In 2011, an English woman with markedly increased BMD reported consumption of large amounts of tea and toothpaste high in F⁻ content.⁽³¹⁾ Recently, periostitis and periostitis deformans followed transplantation of lung, liver, heart, or stem cells because of subsequent long-term

therapy with the potent F⁻-containing antifungal agent voriconazole.⁽³²⁻³⁴⁾ Now, many such antifungal agents and other pharmaceuticals contain F⁻.⁽³⁵⁾

Beginning in the 1960s, sudden death from cardiac arrhythmia, hypercapnia, and stress occurred in young Americans following sniffing inhalation of volatile hydrocarbons such as trichloroethane and fluorinated refrigerants.⁽³⁶⁾ Serious and fatal automobile accidents occurred due to driver unconsciousness or erratic behavior from inhalation of a difluoroethane duster. Corpses were discovered alongside a canister of duster.^(37,38) Post-mortem examination showed high difluoroethane concentrations in the blood and in a number of organs and tissues.^(37,38) In 2014, Chitkara et al⁽³⁹⁾ reported periostitis deformans, subperiosteal hematomas, ectopic calcifications, and a serum F⁻ level of 3.9 mg/dl (NI, < 0.2) from chronic “huffing” of Freon® or inhaling a chlorofluorocarbon gas from a plastic bag. Inhalation for two years of Freon® by a 72-year-old man caused numerous hard fixed masses on all extremities. Radiographs revealed multiple exostoses, a radio-dense pelvis, and densely calcified ligaments and cartilage. His serum F⁻ level was 3.9 mg/l.⁽⁴⁰⁾

The radiographic features of chronic F⁻ toxicity include the classic, virtually pathognomonic, periosteal hyperostosis, which can become profound and is termed periostitis deformans. It can affect any tubular bone, but may be most apparent in the hands. These large periosteal nodules project out from the bone with a defined, round, wavy, or multicircular margin that cloaks the bone. Striated trabeculae extend out at right angles to the shaft. The underlying cortex may be lost with bone extending out from the medullary cavity. MRI has shown thick irregular periosteal edema along the cortical surfaces.⁽³⁵⁾ These bony outcroppings can regress as high F⁻ levels subside. Larger joints may have large marginal osteophytes of endosteal or periosteal origin that expand and block joints and create bizarre shapes. Typical are large osseous lamellae extending into the interosseous membranes of the forearm and leg. Bone nodules may occur in tendon sheaths or muscles. Initially, the ones may become osteopenic. Axially, osteosclerosis includes trabecular condensation creating dense ribs, vertebrae, and pelvis. The skull is typically spared. Vertebral osteophytes encroach on the spinal canal and inter-vertebral foramen. Bony excrescences develop at leg ligamentous attachments; e.g., the iliac crests, ischial tuberosities, and sacrospinous ligaments. Calcification can affect the paraspinal, intraspinal, and posterior longitudinal ligaments. The bony findings of SF from Freon®, F⁻-contaminated water or certain Spanish wines, or voriconazole are similar.

Our patient apparently had SF due to inhalation abuse of a commercial duster containing difluoroethane. SF was suggested by his periostitis deformans and increased spine and hip BMD, and confirmed by increased F⁻ levels in his blood, urine, and bone. Our patient's femur fractured during attempted iliac crest biopsy. In 8,266 Chinese adults, overall fracture risk and hip fracture risk were significantly increased at drinking-water levels of F⁻ exceeding 4.32 mg/L.⁽⁴¹⁾ In the early 1990s, high-dose F⁻ given to osteoporotic women increased cancellous BMD, but cortical BMD decreased, and skeletal fragility increased, with no significant reduction in fractures.⁽⁴²⁻⁴⁴⁾ Exposure to high levels of F⁻ weakens bone without appreciably altering BMD.⁽⁴⁵⁾

The safety materials from Falcon Safety Products, Inc. (Branchburg, NJ) concerning its product Dust-Off[®], described the potential of fire and explosion, and frostbite with liquid contact.⁽⁴⁶⁾ Animal studies were in keeping with deleterious effects on the central nervous system, lungs, heart, kidneys, and bone marrow. In man, inhalation effects included central nervous system depression, incoordination, and unconsciousness as well as cough and dyspnea, respiratory depression, arrhythmias, cardiac arrest, and sudden death.⁽⁴⁶⁾ However, except for bone marrow effects in animals, there was no mention of deleterious skeletal effects in man. When we asked Falcon Safety Products, Inc. about urinary F⁻ levels in individuals inhaling Dust-Off[®], their toxicologists indicated that the difluoroethane was poorly metabolized, and even the small amount that might be metabolized is not metabolized entirely to F⁻.⁽⁴⁷⁾ Also, with a typical short inhalation, elimination from the body is via rapid exhalation of unmetabolized substance.⁽⁴⁷⁾

SF is slowly reversible after cessation of F⁻ intake, but the elevated skeletal mass and F⁻ content lasts many years.^(8,48) In 2007, we reported that nine years after cessation of excessive F⁻ intake, radiographs revealed a decrease in sclerosis and coarsening of trabeculae, particularly in the lumbar vertebral bodies.⁽⁸⁾ There was a reduction in DXA BMD of 23.6% and 15.1% in lumbar spine and femoral neck (with Z-scores of +9.3 and +4.8), respectively.⁽⁸⁾ After 8.5 years, bone F⁻ was reduced by 36%, but was still 10 times the reference value. Furthermore, a chronic problem developed soon after excessive F⁻ intake stopped and excess skeletal mineral was lost -- hypercalciuria and calcium oxalate nephrolithiasis.⁽⁸⁾ It is not clear how long any residual effects of F⁻ last on the material quality of the bone tissue itself — presumably remodeling over time replaces any inferior quality bone tissue with new normal bone. In our patient, BMD remained markedly elevated at his spine and hip three years after “huffing” stopped.

In summary, as demonstrated in our patient, relatively rapid development of periostitis, a sclerotic skeleton, periostitis deformans, and calcification or ossification of ligaments, tendons, and interosseous membranes should raise suspicion of SF. The diagnosis is supported by elevated blood and urine F⁻ levels and confirmed by increased bone F⁻ content. Cessation of excessive F⁻ exposure, including huffing abuse, can gradually alleviate musculoskeletal symptoms, but elevated BMD can persist for years. Careful follow-up, including attention to urinary calcium excretion and therapy of hypercalciuria, may prevent renal calcium stone disease.⁽⁸⁾

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Qian J, Susheela AK, Mudgal A, Keast G. Fluoride in water: an overview. *Waterfront*. 1999; 13:11–13.
2. Jolly SS, Singh BM, Mathur OC. Endemic fluorosis in Punjab (India). *Amer J Med*. 1969; 47:553–563. [PubMed: 5822978]
3. Klemmer PJ, Hadler NM. Subacute fluorosis: A consequence of abuse of an organofluoride anesthetic. *Ann Int Med*. 1978; 89(1):607–611. [PubMed: 717928]
4. Whyte MP, Essmeyer K, Gannon FH, Reinus WR. Skeletal fluorosis and instant tea. *Amer J Med*. 2005; 118:78–82. [PubMed: 15639213]
5. Whyte MP, Totty WG, Lim VT, Whitford GM. Skeletal fluorosis from instant tea. *J Bone Miner Res*. 2008; 23:759–769. [PubMed: 18179362]
6. Izuora K, Twombly JG, Whitford GM, Totty WG, Pacifici R, Whyte MP. Skeletal fluorosis from brewed tea. *J Clin Endocrinol Metab*. 2011; 96:2318–2324. [PubMed: 21593111]
7. Hallanger Johnson JE, Kearns AE, Doran PM, Khoo TK, Wermers RA. Fluoride-related bone disease associated with habitual tea consumption. *Mayo Clin Proc*. 2007; 82(6):719–724. [PubMed: 17550752]
8. Kurland ES, Schulman RC, Zerwekh JE, Dempster DW, Reinus WR, Whyte MP. Recovery from skeletal fluorosis (an enigmatic, American case). *J Bone Miner Res*. 2007; 22(1):163–170. [PubMed: 17014382]
9. Kakumanu N, Rao SD. Skeletal fluorosis due to excessive tea drinking. *NEJM*. 2013; 368(12):1140. [PubMed: 23514291]
10. Whyte MP. Mendelian Disorders of RANKL/OPG/RANK Signaling. In: Thakker, RV, Whyte MP, Eisman, J., Igarashi, T., editors. *Genetics of Bone Biology and Skeletal Disease*. Elsevier (Academic Press); San Diego, CA: 2013. p. 309-24.
11. Little J, Hileman B, Ziran BH. Inhalant abuse of 1,1-difluoroethane (DFE) leading to heterotopic ossification: a case report. *Patient Safety in Surgery*. 2008; 2(28):1–5. [PubMed: 18271949]
12. Whitford, GM. Some characteristics of fluoride analysis with the electrode. In: Myers, HM., editor. *The Metabolism and Toxicity of Fluoride*. 2nd. S Karger; Basel: 1996. p. 24-29.
13. Martinez-Mier EA, Cury JA, Heilman JR, et al. Development of gold standard ion-selective electrode-based methods for fluoride analysis. *Caries Res*. 2011; 45:3–12. [PubMed: 21160184]
14. Keaveny TM. Biomechanical computed tomography—noninvasive bone strength analysis using clinical computed tomography scans. *Ann NY Acad Sci*. 2010; 1192:57–65. [PubMed: 20392218]
15. Schafer AL, Mumm S, El-Sayed I, McAlister WH, Horvai AE, Tom AM, Hsiao EC, Schaefer FV, Collins MT, Anderson MS, Whyte MP, Shoback DM. Panostotic expansile bone disease with massive jaw tumor formation and a novel mutation in the signal peptide of RANK. *J Bone Miner Res*. 2014; 29:911–21. [PubMed: 24014458]
16. Whyte MP, Obrecht SE, Finnegan PM, Jones JL, Podgornik MN, McAlister WH, Mumm S. Osteoprotegerin deficiency and juvenile Paget's disease. *New Engl J Med*. 2002; 347:175–84. [PubMed: 12124406]
17. Whyte MP, Totty WH, Novack DV, Zhang X, Wenkert D, Mumm S. Camurati-Engelmann disease: unique variant featuring a novel mutation in TGFBI encoding transforming growth factor beta I and a missense change in TNFSF11 encoding RANK Ligand. *J Bone Miner Res*. 2011; 26:920–33. [PubMed: 21541994]
18. Keaveny TM, Kopperdahl DL, Melton LI, Hoffmann PF, Amin S, Riggs BL, Khosla S. Age-dependence of femoral strength in white women and men. *J Bone Miner Res*. 2010; 25:994–1001. [PubMed: 19874201]
19. Weinstein, LH., Davison, A. *Fluorides in the environment: effects on plants and animals*. CABI Publishing; Cambridge, MA: 2003.
20. Smith FA, Hodge HC. Airborne fluorides and man. Part I. *Critical Reviews in Environmental Control*. 1979; 8:293–371.
21. Fleischer, M. Circular No 285. US Geological Survey; Washington, DC: 1953. Recent estimates of the relative abundance of the elements in the Earth's crust.

22. Bell, M., Largent, E., Ludwig, T., Muhler, J., Stookey, G. Monograph Series No 59. World Health Organization; Geneva: 1970. Fluorides and human health.
23. Biological, NAS. effects of air pollutants: fluorides. National Academy of Sciences; Washington, DC: 1971.
24. D'Alessandro W. Human fluorosis related to volcanic activity: a review. Istituto Nazionale di Feofisica e Vulcanologia – Sezione di Palermo, via La Malfa, Palermo, Italy. 2006; 153:90146.
25. Shortt HE, Crobert FR, Barnard TW, Nayar ASM. Endemic fluorosis in the Madras presidency. *Indian J Med Res.* 1937; 25:553–568.
26. Soriano M. Periostitis deformans. *Ann Rheum Dis.* 1952; 11:154–161. [PubMed: 14933999]
27. Soriano M. Periostitis deformans: Un nuevo tipo de fluorosis osea en el hombre. La fluosis vinica. *Rev Clin Espan.* 1965; 97:375–388. [PubMed: 5847606]
28. Soriano M, Manchon F. Radiological aspects of a new type of bone fluorosis, periostitis deformans. *Radiology.* 1966; 87(6):1089–1094. [PubMed: 5926232]
29. Cao J, Zhao Y, Liu J, Xirao R, Danzeng S, Daji D, Yan Y. Brick tea fluoride as a main source of adult fluorosis. *Food and Chemical Toxicology.* 2003; 41:535–542. [PubMed: 12615125]
30. Roos J, Dumolard A, Bourget S, Grange L, Rousseau A, Gaudin P, Calop J, Jivin R. Osteofluorosis caused by excess use of toothpaste. *Presse Med.* 2005; 34:1518–1520. [PubMed: 16301964]
31. Joshi S, Hlaing T, Whitford GM, Compston JE. Skeletal fluorosis due to excessive tea and toothpaste consumption. *Osteoporosis Int.* 2011; 22:2557–2560.
32. Lustenberger, DP., Granata, JD., Scharschmidt, TJ. Periostitis secondary to prolonged voriconazole therapy in a lung transplant recipient; *Orthopedics.* Nov, 2011 p. e793-e796. ORTHOSuperSite.com
33. Becce F, Malghem J, Lecouvet FE, Vande Berg BC, Omoumi P. Clinical Images: Voriconazole-induced periostitis deformans. *Arthritis and Rheum Letters.* 2012; 64(10):3490.
34. Bucknor MD, Gross AJ, Link TM. Voriconazole-induced periostitis in two post-transplant patients. *Musculoskeletal Radiology.* 2013; 7(8):10–17.
35. Davis DL. Voriconazole-related periostitis presenting on magnetic resonance imaging. *Mineral and Bone Metabolism, the Official Journal of the Italian Society of Orthopaedics and Medicine (Orto Med).* 2015; 12(1):78–81.
36. Bass M. Sudden sniffing death. *JAMA.* 1970; 212(12):2075–2079. [PubMed: 5467774]
37. Hahn T, Avella J, Lehrer M. A motor vehicle accident fatality involving the inhalation of 1,1-difluoroethane. *J Analytical Toxicology.* 2006; 30:638–642.
38. Rahi, H. Toxicology. Vol. 12. The New York State Poison Centers: A Quarterly Publication; Jul 2007. A “duster” inhalational exposure with drugs leads to death.
39. Chitkara M, Rackoff PJ, Eltran LS. Multiple painless masses: periostitis deformans secondary to fluoride intoxication. *Skeletal Radiology.* 2014; 43:555–556.
40. Rackoff P. Clinical images: Skeletal fluorosis – a tricky diagnosis. *Arthritis and Rheum.* 2015; 67:2701.
41. Li Y, Liang C, Slemenda CW, Ji R, Sun S, Cao J, Emsley C, Ma F, Wu Y, Ying P, Zhang Y, Gao S, Zhang W, Katz B, Niu S, Cao S, Johnston C. Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. *J Bone Miner Res.* 2001; 16(5):932–939. [PubMed: 11341339]
42. Riggs BL, Hodgson SF, O'Fallon WM, Chao EYS, Wahner HW, Muhs JM, Cedel SL, Melton LJ III. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *NEJM.* Mar.1990 :802–809. [PubMed: 2407957]
43. Kleerekoper M, Peterson EL, Nelson DA, Phillips E, Schork MA, Tilley BC, Parfitt AM. A randomized trial of sodium fluoride as a treatment for postmenopausal osteoporosis. *Osteoporosis Int.* 1991; 1:155–161.
44. Haguenaer D, Welch V, Shea B, Tugwell P, Adachi JD, Wells G. Fluoride for the treatment of postmenopausal osteoporotic fractures: a meta-analysis. *Osteoporosis Int.* 2000; 11:727–738.
45. Silva MJ, Ulrich SR. In vitro sodium fluoride exposure decreases torsional and bending strength and increases ductility of mouse femora. *J Biomech.* 2000; 33(2):231–234. [PubMed: 10653038]
46. Falcon Safety Products, Inc., Branchburg, NJ 08876
47. Communication with John Flaagan of Falcon Safety Products, Inc. January 16, 2013.

48. Cundy T. Recovery from skeletal fluorosis. *J Bone Miner Res.* 2007; 22(9):1475. [PubMed: 17539735]

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Figure 1. Patient's Right Hand
Bony masses due to periostitis deformans are present along the phalanges of all digits.

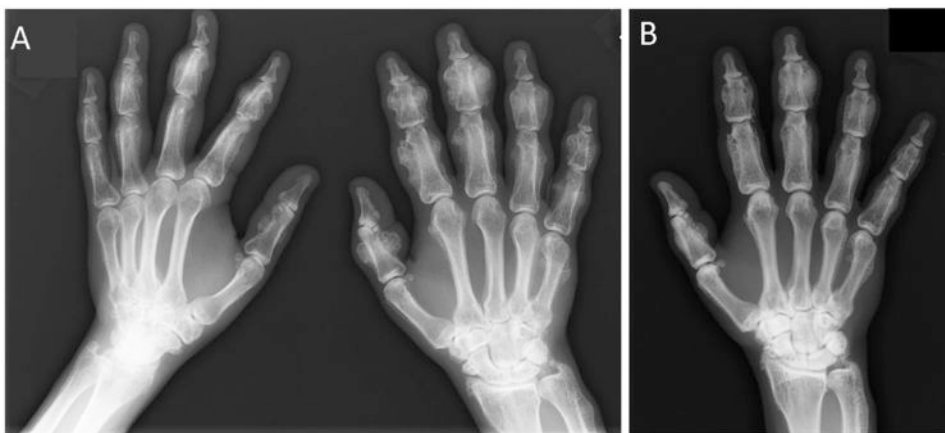


Figure 2. Radiographs of the patient's hands

(A) Postero-anterior radiograph at age 28 years, while continuing to “huff”, demonstrates marked proliferating periosteal new bone (periostitis deformans) at many tubular bones (greatest in the proximal and middle phalanges) with some loss of the underlying cortex in the larger excrescences. The proliferations are bony with undulating peripheral margins that have distinct surfaces. Proliferations are also seen coming off the carpal bones, as well as off the radius and ulna.

(B) Nearly two years later, after cessation of “huffing”, the proliferations have decreased and have smoother outer margins.

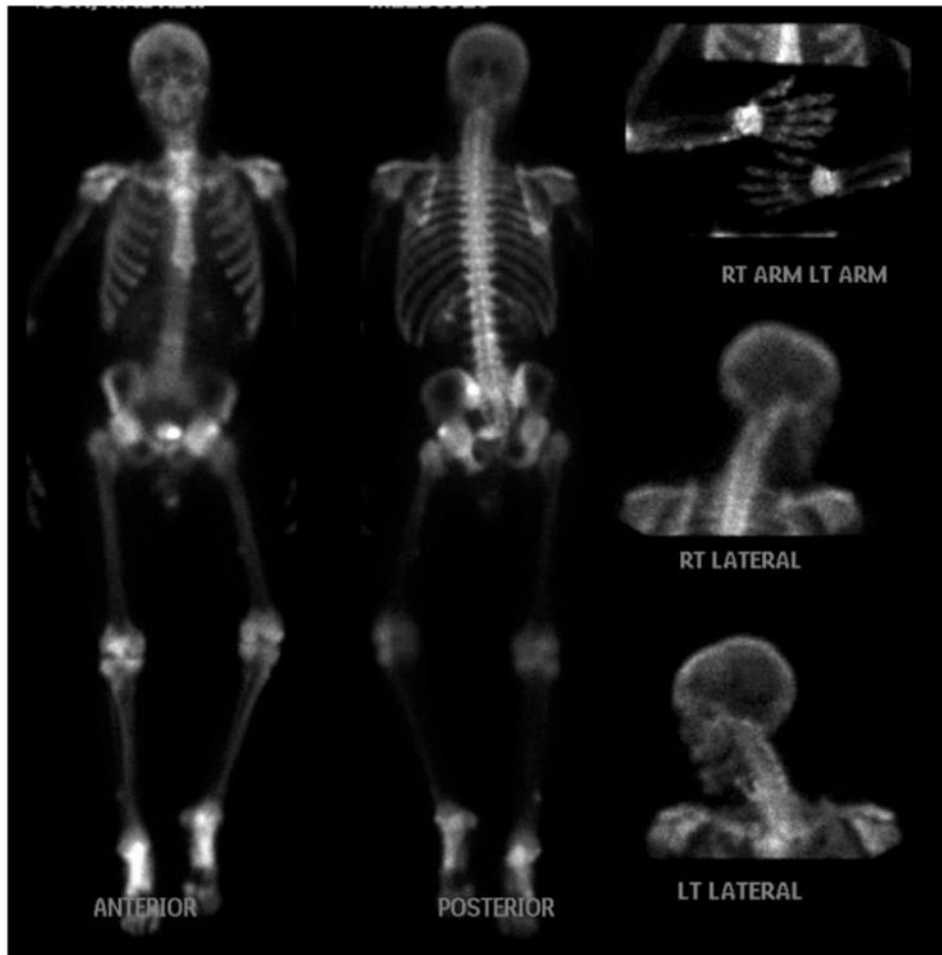


Figure 3. Bone scintigram

Mild diffuse increased uptake is present at the shoulders, hips, knees, ankles, wrists, and feet.

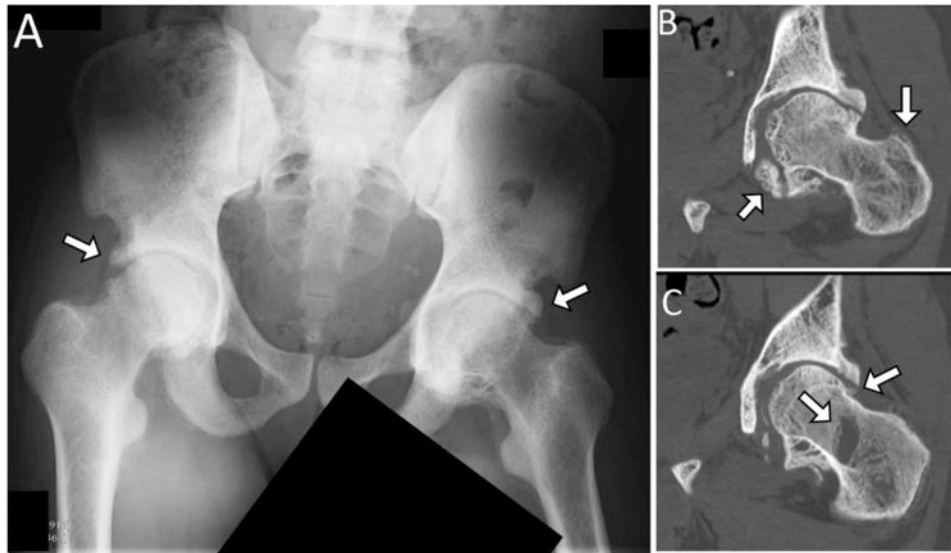


Figure 4. Patient Radiographs and CT of the Pelvis and Femoral Neck

(A) Antero-posterior pelvis shows diffuse osteosclerosis with marked osteophyte formations about the hips (arrows) greater on the left. Small marginal proliferations project off all the bones, but are not well shown.

(B) CT of the left hip shows marked marginal osteophytes and bridging capsular and neck ossifications and impingement deformities (arrows).

(C) CT shows cystic osteopenic changes in the femoral neck (arrows).



Figure 5. Patient Radiographs and CT of Left Elbow

Antero-posterior (A) and lateral (B) radiographs of the left elbow show new bone on each side of the elbow joint (arrows). CT shows osteophytes (C arrow) and periosteal new bone formations (D arrow).

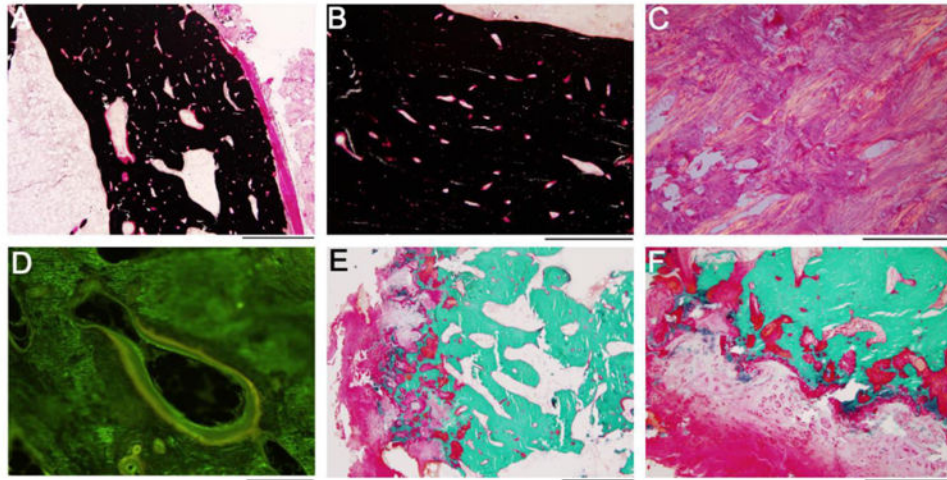


Figure 6. Histology of Femoral Tissue

A,B) Low and higher power images of von Kossa-stained cortex show robust cortical bone and highlight an abundance of vascular channels. **C)** Visualization of an H&E stained image of cortex under polarized light demonstrates lamellar bone. **D)** Fluorescence imaging of an unstained section shows mineralization associated with osteoid, consistent with high levels of bone formation. **E,F)** Goldner trichrome stained sections of a fragment from an articular surface show irregular and disrupted cartilage, with regenerative nests of chondrocytes, and an abnormal osteochondral interface. Scale bars A,E = 1 mm; B,C,F = 500 μ m; D = 200 μ m.