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Case Report

Recovery From Skeletal Fluorosis (an Enigmatic, American Case)

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ABSTRACT: A 52-year-old man presented with severe neck immobility and radiographic osteosclerosis. Elevated fluoride levels in serum, urine, and iliac crest bone revealed skeletal fluorosis. Nearly a decade of detailed follow-up documented considerable correction of the disorder after removal of the putative source of fluoride (toothpaste).

Introduction: Skeletal fluorosis, a crippling bone disorder, is rare in the United States, but affects millions worldwide. There are no data regarding its reversibility.
Materials and Methods: A white man presented in 1996 with neck immobility and worsening joint pains of 7-year duration. Radiographs revealed axial osteosclerosis. Bone markers were distinctly elevated. DXA of lumbar spine (LS), femoral neck (FN), and distal one-third radius showed Z scores of +14.3, +6.6, and −0.6, respectively. Transiliac crest biopsy revealed cancellous volume 4.5 times the reference mean, cortical width 3.2 times the reference mean, osteoid thickness 25 times the reference mean, and wide and diffuse tetracycline uptake documenting osteomalacia. Fluoride (F) was elevated in serum (0.34 and 0.29 mg/liter [reference range: <0.20]), urine (26 mg/liter [reference range: 0.2–1.1 mg/liter]), and iliac crest (1.8% [reference range: <0.1%]). Tap and bottled water were negative for F. Surreptitious ingestion of toothpaste was the most plausible F source.
Results: Monitoring for a decade showed that within 3 months of removal of F toothpaste, urine F dropped from 26 to 16 mg/liter (reference range: 0.2–1.1 mg/liter), to 3.9 at 14 months, and was normal (1.2 mg/liter) after 9 years. Serum F normalized within 8 months. Markers corrected by 14 months. Serum creatinine increased gradually from 1.0 (1997) to 1.3 mg/dl (2006; reference range: 0.5–1.4 mg/dl). Radiographs, after 9 years, showed decreased sclerosis of trabeculae and some decrease of sacrospinous ligament ossification. DXA, after 9 years, revealed 23.6% and 15.1% reduction in LS and FN BMD with Z scores of +9.3 and +4.8, respectively. Iliac crest, after 8.5 years, had normal osteoid surface and thickness with distinct double labels. Bone F, after 8.5 years, was 1.15% (reference range, <0.1), which was a 36% reduction (still 10 times the reference value). All arthralgias resolved within 2 years, and he never fractured, but new-onset nephrolithiasis occurred within 9 months and became a chronic problem.
Conclusions: With removal of F exposure, skeletal fluorosis is reversible, but likely impacts for decades. Patients should be monitored for impending nephrolithiasis.
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Key words: bone densitometry, bone histomorphometry, bone turnover markers, enthesopathy, fluoride, nephrolithiasis, osteoarthritis, osteosclerosis, toothpaste

INTRODUCTION

Skeletal fluorosis is a manifestation of fluoride toxicity caused by chronic ingestion or inhalation of fluoride.[1] This painful disorder develops insidiously, generally when >10 mg fluoride is consumed daily for at least 10 years.[2] Endemic skeletal fluorosis is most common where high levels of fluoride are present in well water, but it also occurs where there is industrial exposure to fluoride from dust or fumes.[1] Skeletal fluorosis is especially prevalent in parts of China, India, and Africa and affects millions of people worldwide.[3–5] Although this condition is uncommon in the United States and other developed countries, less well-known causes of chronic fluoride toxicity include

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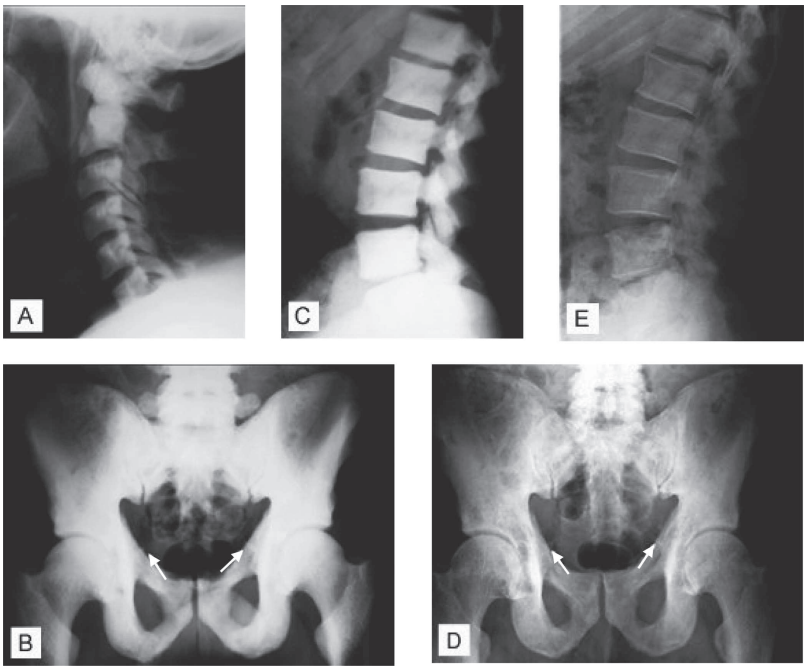

FIG. 1. (A) Lateral radiograph of the cervical spine at referral in 1996 shows sclerosis throughout the spine, but sparing of the mandible and base of the skull. Both trabecular and cortical bone content is increased. No obvious cause for limitation of motion is apparent. (B) Pelvis and (C) lateral lumbar spine from 1996 show prominent osteosclerosis with both cortical and trabecular thickening. The left sacrospinous ligament (arrow, B) is ossified. Repeat radiographs of (D) the pelvis and (E) lateral lumbar spine, after slightly >9 years after diagnosis, show improvement in the osteosclerosis but relative maintenance of the cortical thickening apparent in the original views. The left sacrospinous ligament (arrow, D) remains visible, but is somewhat improved.

fluoride supplements, certain teas and wines, and some toothpastes.[6–8] Skeletal fluorosis often results in osteosclerosis of the skeleton with significant long-term difficulties, including impaired neck and lumbar mobility, aching of the axial skeleton, kyphosis, and painful lower extremities, ultimately causing crippling and incapacitation.[1,9] Despite its prevalence and morbidity, there is no published information concerning the potential reversibility of skeletal fluorosis.

We present a case of skeletal fluorosis of uncertain etiology, which began to resolve shortly after diagnosis. Nine years of detailed follow-up studies documented the rate and pattern of correction of this disorder.

CASE REPORT

Initial presentation and evaluation

A 52-year-old white man living in New York City presented in 1996 with decreased mobility of his neck that had gradually worsened over the previous 7 years. The problem was most severe in cold weather and led to a car accident. Elevated serum alkaline phosphatase (ALP) activity had been documented for >8 years. Past medical history was significant only for hepatitis A at 20 years of age. He worked in real estate and had no known occupational or environmental exposure to toxins. Family history was unrevealing.

Physical exam showed height to be 5′ 7″, representing a loss of 3″ from his reported maximal height of 5′ 10″. His posture suggested ankylosing spondylitis, with a flexed neck and flattening of the lumbar lordosis. There were no signs of arthritis or ichthyosis, and hair had normal texture. Dentition was unremarkable without mottling. There was limited flexion and extension of his neck and low back, with full range of motion in his extremities.

Radiographs of the pelvis and cervical and lumbar spine (Figs. 1A–1C) from October 1996 showed marked osteosclerosis involving both cortical and trabecular bone. The trabeculae were coarsened throughout the visualized skeleton. The cortices in the pelvic bones, proximal femora, and posterior elements of the spine were also thickened, but there was relative sparing of vertebral endplates. The skull and mandible seemed unaffected. The pelvic radiograph showed ossification of the distal sacrospinous ligament, which is a typical (but not pathognomonic) finding in skeletal fluorosis.

Serial chest films taken over the previous 10 years showed unchanged diffuse sclerosis throughout the vertebral bodies, increasing thickness of rib cortices, and evidence of sclerosis in the scapulae and possibly humeral heads. A bone scan revealed diffuse, symmetrical, enhanced uptake at all joints. DXA (Hologic, Bedford, MA, USA) showed BMD values for the lumbar spine (L_2–L_4), femoral neck, and distal one third radius of 2.6, 1.7, and 0.8 g/cm^2, respectively, reflecting Z scores of +14.3, +6.6, and –0.6, respectively (Fig. 2). The ultradistal radius BMD was 0.48 g/cm^2, with a Z score of –0.5. The patient manifested idiopathic osteosclerosis, most significant within the axial skeleton.

Laboratory evaluation included normal serum levels of calcium, inorganic phosphate, intact PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, gamma glutamyl transferase (γ-GT), and prostate specific antigen (PSA). Serum protein electrophoresis (SPEP), 24-h urine calcium and phosphorus levels, and urine protein electrophoresis (UPEP) were all normal. Serum total creatine kinase (CK) and isoenzymes, including CK-BB, were normal and therefore provided evidence against osteopetrosis.[10] HLA-B27 was not detected, and serology was negative for hepatitis C infection.[11] Serum fluoride concentration, however, was

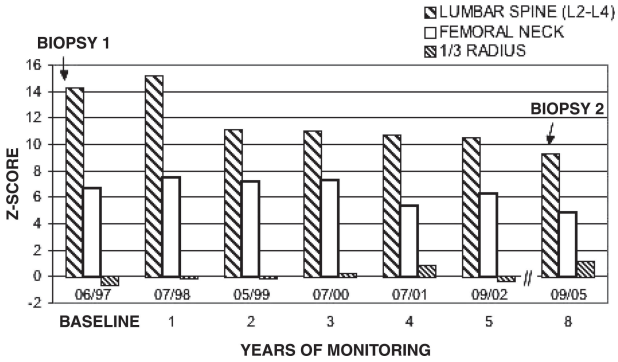

FIG. 2. Changes in BMD in a patient recovering from skeletal fluorosis: baseline and 8-year follow-up data. Z scores for BMD at the lumbar spine (L_2–L_4), femoral neck, and one third radius at presentation, yearly follow-up for years 1–5, and finally 8 years after baseline.

found twice to be elevated at 0.34 and 0.29 mg/liter (reference range: <0.20; National Medical Services, Willowgrove, PA, USA). Urinary fluoride was 26 mg/liter (reference range: 0.2–1.1; MedTox Laboratories, St Paul, MN, USA), which is also markedly elevated (Fig. 3D). Heavy metals (cadmium, arsenic, lead, and mercury) were undetectable in the urine. Biochemical markers of bone turnover were all substantially elevated (Figs. 3A–3C). Serum ALP activity was 216 U/liter (reference range: 43–120 U/liter), bone-specific ALP (BSALP) was 23 ng/ml (reference range: 4–19 ng/ml), and osteocalcin was 240 ng/ml (reference range: 8–52 ng/ml). Pyridinoline, deoxypyridinoline, and N-telopeptide of type I collagen (NTX) excretion were also substantially elevated at 250 (reference range: 20–61), 92 (reference range: 4–19), and 212 (reference range: <85) nmol BCE/mmol creat, respectively.

Iliac crest biopsy, after double tetracycline labeling (Figs. 4A–4C), showed markedly increased cancellous bone volume, increased osteoid perimeter and thickness, and diffuse tetracycline uptake without distinct fluorescent labels. These findings were consistent with osteosclerosis and osteomalacia. Bone collagen had a normal lamellar pattern. Osteoblasts were unremarkable in appearance and abundant. Osteoclasts were readily seen eroding bone. Cartilage bars were absent, thereby excluding osteopetrosis.[12]

Bone fluoride analysis[13] showed 18 times the normal level of fluoride (1.8%; reference range: <0.1%). Skeletal fluorosis was diagnosed.

Analysis of the patient's drinking water sources, including tap water (from a well) and bottled water, showed no detectable fluoride. He and his family had lived in the same residence for 22 years and drank the same type of bottled water for 10 years, and he had always worked in real estate. There was no exposure to mining, welding, or industrial use of hydrofluoric acid, nor exposure to fluoride containing insecticides, niflumic acid, or laundry powders. He stated that he did not drink tea or wine and had not chewed tobacco, inhaled snuff, or cooked with Teflon pots. To exclude an environmental source of toxicity, we measured serum and urinary fluoride levels in his wife, 50 years of age, and two daughters, 21 and 18 years of age, which were normal. Additionally, their DXA results were unremarkable at all sites. He did brush his teeth using fluoridated toothpaste, before and after all meals (minimum six times daily), kept a toothbrush at work, used nonfluoridated mouthwash two to three times each week, and had semiannual dental visits, but without fluoride treatments. Nevertheless, even after this extensive search for a source of fluoride toxicity, one could not be established. However, because of the patient's almost obsessive dental hygiene regimen, surreptitious ingestion of toothpaste seemed the most plausible. He was advised to stop using fluoridated toothpaste and substitute baking soda–based dentifrices.

Follow-up studies

Laboratory values: Within 3 months of documentation of skeletal fluorosis and education of the patient concerning fluoride excess and bone problems, as well as admonition to avoid fluoridated dental products, urine fluoride levels dropped from 26 to 16 mg/liter (reference range: 0.2–1.1 mg/liter; Fig. 3D). Eight months after diagnosis, urine fluoride declined to 7.0 mg/liter, and serum fluoride decreased from 0.34 to <0.05 mg/liter (reference range: <0.2 mg/liter). Serum ALP, which was 203 U/liter before diagnosis, corrected to 87 U/liter (reference range: 43–120 U/liter) within 8 months—the first normal value measured in 8 years (Fig. 3A). Other markers of bone formation showed clear-cut improvement within the same time-course: osteocalcin decreased from 229 to 101 ng/ml (reference range: 8–52 ng/ml; Fig. 3C) and BSALP corrected from 23 to 16 ng/ml (reference range: 4.3–19 ng/ml). Similarly, markers of bone resorption all decreased, including: pyridinoline (268 to 106 nmol BCE/ mmol creat; reference range: 20–61 nmol BCE/ mmol creat), deoxypyridinoline (100 to 39 nmol BCE/ mmol creat; reference range: 4–19 nmol BCE/ mmol creat), and NTX (212 to 125 nmol BCE/mmol creat; reference range: <85 nmol BCE/ mmol creat; Fig. 3B). Fourteen months from the time of diagnosis, all markers of bone formation and resorption had normalized (Fig. 3), whereas serum fluoride (0.10 mg/liter) remained in the normal range, but urinary fluoride remained somewhat elevated at 3.9 mg/liter (reference range: 0.2–1.1 mg/liter; Fig. 3D).

During the ensuing 9 years, all of the patient's laboratory values, other than urinary fluoride, remained normal. Urinary fluoride gradually declined to approximate the reference range; most recently (February 2005) it was 1.2 mg/liter (reference range: 0.2–1.1 mg/liter; Fig. 3D). However, serum creatinine increased gradually from 1.0 (1997), to 1.1 (2001), to 1.3 mg/dl (2006; reference range: 0.5–1.4 mg/dl).

Radiology: Radiographs obtained 9 years after baseline (Figs. 1D and 1E) showed a noticeable decrease in the sclerosis and coarsening of the trabeculae. This improvement was particularly prominent in the lumbar vertebral bodies. However, the relative decrease in sclerosis in the pelvis, proximal femora, and posterior elements of the spine was somewhat less. This suggested that reduction in the radiographic appearance of sclerosis was related more to bone loss in the trabeculae than in the cortex. The observations were corroborated by the persistence of marked cortical thickening in the pelvis and femora on the second set of

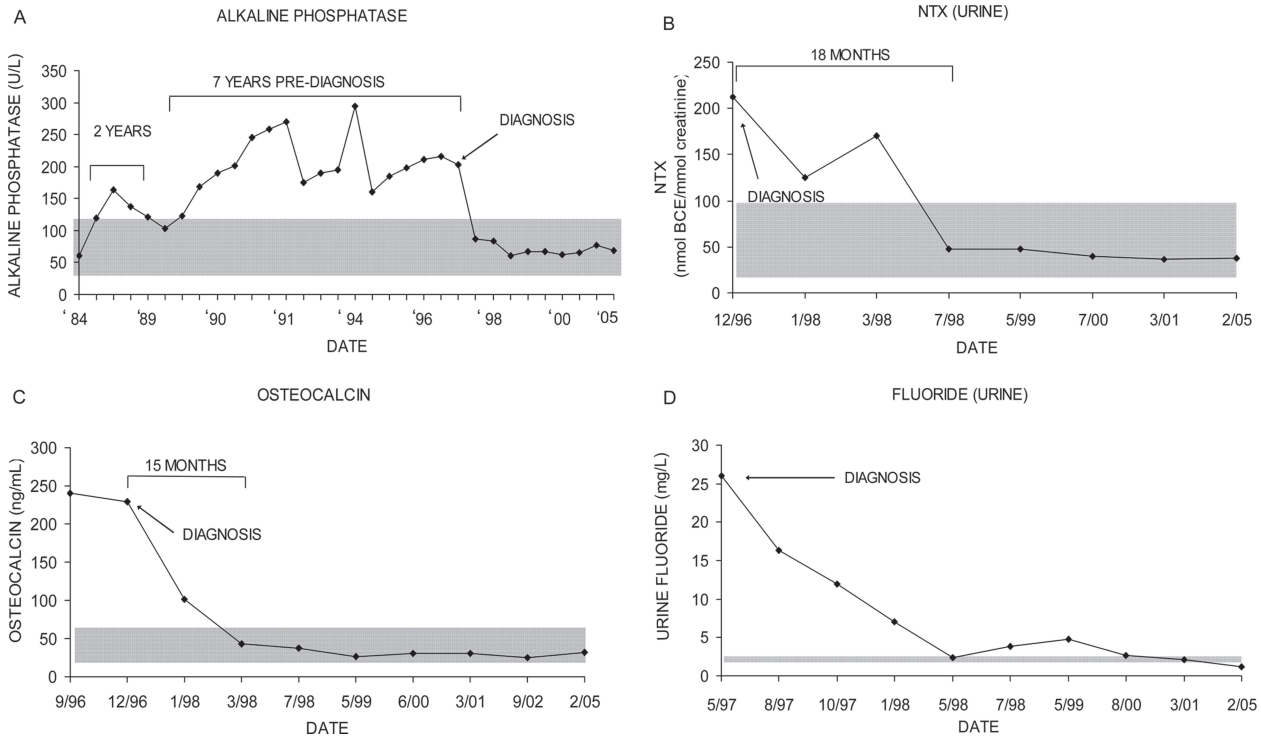

FIG. 3. Biochemical data in a patient recovering from skeletal fluorosis during 9 years of follow-up. (A) Serum alkaline phosphatase activity for the 10 years preceding diagnosis of skeletal fluorosis and during 9 years of follow-up. (B) Urinary NTX, (C) serum osteocalcin, and (D) urinary fluoride are depicted from diagnosis and over 9 years of follow-up.

images. Some decrease in ossification of the sacrospinous ligament was also noted, but it remained on the follow-up pelvic radiograph.

Bone densitometry: DXA was repeated yearly for 5 years after diagnosis and once again 3 years later (Fig. 2). In the first year, there was a 3.5% increase in BMD at the spine and a 6.3% increase in BMD at the femoral neck; spine Z score[14] increased from +14.3 to +15.2, and femoral neck Z score increased from +6.6 to +7.4. However, in the second year of follow-up, spine BMD decreased dramatically by 16.5% and femoral neck BMD declined by 2.3%. For the remaining 6 years of monitoring, BMD dropped an additional 10.6% at the spine (~1.8%/year), for a cumulative 23.6% reduction in BMD from baseline. During the same period, femoral neck BMD declined 19.1% (3.2%/year), for a cumulative 15.1% reduction from baseline. Nevertheless, the most recent DXA study, 8 years after baseline, showed spine and femoral neck Z scores of +9.3 and +4.8, respectively. Z score at the proximal one-third site of the distal radius increased gradually over 8 years from −0.6 to +1.2.

Whole body DXA scan, with percent body composition, was obtained at the most recent visit (Hologic 4500; QDR-W). The patient, now 62 years old and weighing 89 kg, had a total body BMC of 4523 g, representing 5.1% of his total body mass. Mean BMC for healthy, age-matched men of similar body weight is ~3000 g, representing a mean 3.5% of total body mass (unpublished data based on five normal subjects). Thus, almost 9 years after fluoride exposure seemed to end, our patient's skeletal burden of excess mineral (apatite) is ~1500 g (50% more than controls).

Bone histomorphometry: A contralateral, second transiliac crest biopsy was performed after 8.5 years (Figs. 4D–4F). The recent specimen revealed normal osteoid perimeter and thickness, with defined double tetracycline labels, in contrast to the initial biopsy that showed increased quantities of osteoid and diffuse labels consistent with osteomalacia. Histomorphometric parameters (Table 1), including cancellous bone volume, were still markedly elevated (46.9%; reference value: 14.7 ± 4.3 SD), with increased trabecular number and width. Cortical width was 2919 μm, >4-fold the reference value (697 ± 225 SD). Variables of bone formation and bone resorption were in the reference range. Thus, nearly 9 years after the original biopsy and removal of the fluoride source, the patient's osteomalacia had resolved, but significant osteosclerosis persisted.

Bone fluoride analysis: Identical methodology was used to separately analyze the fluoride content of both the baseline and follow-up iliac crest samples.[13] Thin sections were divided between two tared platinum crucibles and ashed overnight at 600°F. The resulting bone ash was dissolved in 1 ml of 0.5 M $HClO_4$ and brought to 10 ml with 0.5 M Na_3Citrate. This solution was too concentrated for analysis and had to be further diluted to 1:100. At follow-up analysis, two bone samples were available for study. Sample A had an ash weight of 7.0 mg. Fluoride concentration was 70 μg, yielding a bone fluoride concentration of 1.0% (70 μg fluoride/7 mg ash weight). Sample B had an ash weight of 3.8 mg and fluoride concentration of 50 μg/3.8 mg ash weight, or a fluoride concentration in original solution of 1.3%. Averaging these results, the bone fluoride of 1.15%

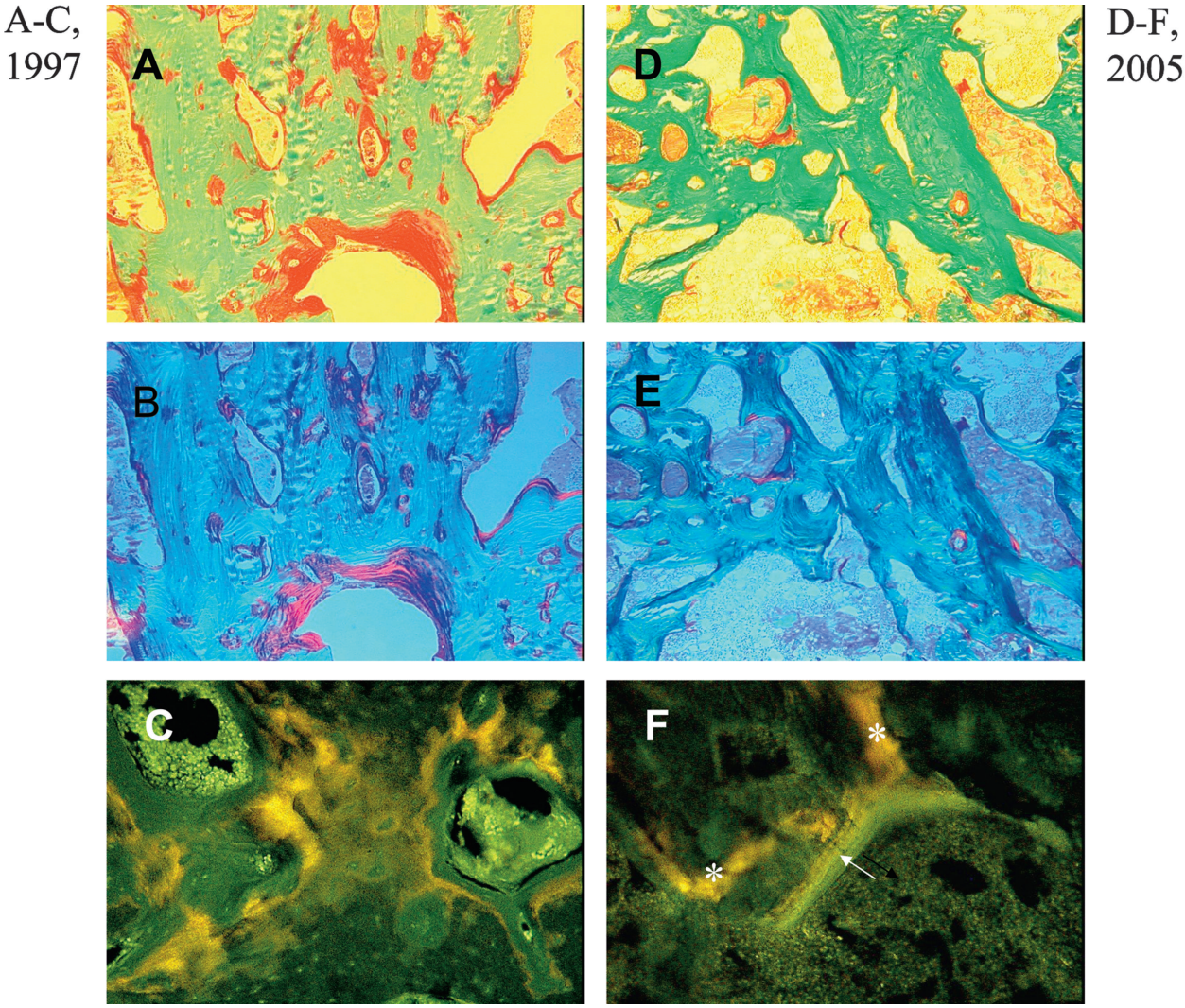

FIG. 4. Iliac crest bone morphology at (A–C) baseline and (D–F) at 8.5-year follow-up. (A) At baseline, the trabeculae are thickened and coarse, and osteoid seams (red) are extended and wide. (B) The bone tissue is of normal lamellar structure under polarized light microscopy, and (C) tetracycline uptake is broad and diffuse. (D) In the follow-up biopsy, the trabeculae are still thick and coarse, but osteoid perimeter and thickness are normal. (E) Normal lamellar structure is maintained, and (F) defined double tetracycline labels can be seen (arrow) overlying the diffuse older labels (*).

TABLE 1. COMPARISON OF PAIRED ILIAC CREST HISTOMORPHOMETRY IN A MAN WITH SKELETAL FLUOROSIS: BASELINE AND 8 YEARS AFTER CESSATION OF FLUORIDE EXPOSURE

Histomorphometric variables (units)	*Baseline: January 1997*	*Follow-up: September 2005*	*Reference range**
Cancellous bone volume (%)	61.4 ↑	46.9 ↑	14.7 ± 4.3
Trabecular width (μm)	262 ↑	218 ↑	102 ± 20
Trabecular number (#/mm^2)	2.34 ↑	2.16 ↑	1.42 ± 0.2
Trabecular separation (μm)	165 ↓	247 ↓	616 ± 138
Cortical width (μm)	3100 ↑	2,919 ↑	697 ± 225
Cancellous osteoid perimeter (%)	98.2 ↑	4.2	9.4 ± 5.8
Cancellous osteoid thickness (# of lamellae)	11	4	≤4
Cancellous eroded perimeter Surface (%)	4.11	4.09	2.80 ± 0.6
Cancellous mineralizing perimeter (%)	NM	1.39	6.84 ± 4.1
Cancellous mineral apposition rate (μm/day)	NM	0.42	0.66 ± 0.1
Bone formation rate (μm3/μm^2/day)	NM	0.007	0.043 ± 0.02
Adjusted apposition rate (μm/day)	NM	0.20	0.61 ± 0.4

* Mean ± SD.
NM, nonmeasurable.

(reference range: <0.1%) represented a 36% decline from the 1.8% value at baseline, 8.5 years previously. Nevertheless, the current fluoride content was at least 10 times the expected upper limit of normal (0.1%).

Clinical course

By ~2 years after diagnosis and apparent elimination of excess fluoride exposure, the patient had complete resolution of his neck immobility and no longer required analgesics. In fact, some improvement of joint pains and neck stiffness was evident in the first year. Height remained stable, with no decline noted over the 9 years of follow-up. Despite skeletal fluorosis, he never suffered a fracture. However, a new, important medical problem (that seemed temporally related to cessation of fluoride exposure and subsequent negative calcium balance) was renal calculus formation, with stones composed of calcium oxalate. The first episode occurred 9 months after diagnosis. He experienced numerous occurrences of nephrolithiasis over the past 7 years, requiring lithotripsy on multiple occasions. Frank hematuria occurs almost monthly. As noted above, serum creatinine has been gradually increasing, although the patient takes no nephrotoxic medications. Now he receives a regimen of potassium citrate, hydrochlorothiazide, and hydration for kidney stone prophylaxis.

DISCUSSION

This case uniquely charts the natural history of skeletal fluorosis after fluoride exposure ceases. By carefully monitoring our patient over nearly a decade, we showed that skeletal fluorosis is largely reversible. Debilitating joint symptoms can improve fairly quickly, radiographic ossification can regress, histomorphometric indices of bone remodeling can be restored, and the massive skeletal load of excess bone accrued over years of anabolic stimulation from fluoride can gradually be resorbed. However, our findings are also cautionary. Unloading the skeleton of excess mineral seems to increase urinary calcium excretion, causing nephrolithiasis and increments in serum creatinine levels. It is unclear what further morbidity will ensue if the latter problem continues unabated.

Whereas our patient with skeletal fluorosis is distinctly unusual in terms of his apparent mode of exposure to fluoride, toothpaste ingestion (reported once previously),[15] his clinical course serves as a prototype for recovery from skeletal fluorosis, a problem of great clinical significance worldwide.[3–5] Toxic levels of fluoride persist in the water sources of many countries and fluoride accumulates in the tea plant, *camellia sinensis*, tainting traditional beverages such as "brick" tea in Asia,[8] or commonly consumed modern beverages such as instant or bottled teas,[6] and pose an occupational hazard with certain industrial exposures such as arc welding.[16] With regard to fluoridated toothpaste, a typical 1-g (adult-size) strip is estimated to contain 1.1 mg of fluoride. To consume 10 mg/day, the skeletal fluorosis 10-year threshold,[2] our patient would have had to brush with this amount at least 9 times daily and swallow the majority of the rinse. While he never acknowledged this habit, a recent report documented a woman who presented similarly after brushing 18 times a day and swallowing her toothpaste simply because she enjoyed the taste.[15] Many dental studies concerning preschool children underscore the fact that routine brushing, if unsupervised, can result in inadvertent consumption of enough fluoride to exceed safety allowances.[17–19] Some interpret available scientific evidence to conclude that water fluoridation in the United States is no longer in the public's interest.[20]

Fluoride, an abundant geologic mineral, is rapidly absorbed from the stomach and proximal intestine and becomes incorporated into calcified tissues.[21] Because the fluoride ion is similar in size and charge to the hydroxyl ion, the normal component of hydroxyapatite, it can substitute to form fluorapatite.[9] The resulting crystal lattice is more compact, less soluble, and more stable than hydroxyapatite[9] and causes resistance to bone remodeling.[9,22] For these reasons, once fluoride is incorporated into skeletal architecture, especially trabecular bone,[23] its presence is prolonged.[21] Furthermore, fluoride is an anabolic agent that uncouples the remodeling process, with stimulation of bone formation in the absence of prior resorption.[9] Osteoblasts proliferate, either because fluoride enhances mitogenic signals or growth factors in bone[24] or because it inhibits phosphotyrosine phosphatase activity, thereby increasing cellular tyrosyl phosphorylation and stimulating bone cell proliferation.[25]

Considering fluoride's potent anabolic properties, and the resistance of fluorapatite to degradation, it is not surprising that steady, continuous exposure to fluoride, as seems to have occurred in our patient, causes marked skeletal accretion of bone mineral. In fact, studies from the 1990s using fluoride as a potential treatment for osteoporosis showed continued, linear increases of lumbar spine density even 6 years into treatment.[26] This contrasts sharply to recent data concerning teriparatide, another bone anabolic agent, whose effect seems to plateau after 2–3 years of daily injection.[27]

Our case, however, is especially significant because it illustrates what happens after fluoride's anabolic stimulus is removed in the setting of the excessive bone mass of skeletal fluorosis. In the first year, we observed a not surprising modest increase in trabecular bone density, which dropped precipitously in the second year. Hence, a period of continued augmentation in BMD can be expected before there is improvement. Decline in BMD after fluoride is removed has been observed previously with fluoride therapy for osteoporosis,[28] and resembles what occurs after treatment with teriparatide is discontinued.[29,30] The density changes that we observed in our patient paralleled his marked decline in urinary fluoride and occurred despite the substantial decreases in biochemical markers of bone turnover (Fig. 3). It is plausible that in the first year after fluoride exposure ceased, there was increased mineralization of the abundant osteoid (Table 1; Fig. 4). In the second year and thereafter, we can postulate that much of the bone remodeling was being driven by the skeleton's efforts to readjust its size and mass to mechanical demands (i.e., the "mechanostat" hypothesis).[31,32] The marked decline in BMD that we observed between years 1 and 2 may well be a result of mechanostat-driven remodeling of newly mineralized oste-

oid. Likely, much of the osteoid mineralization after fluoride withdrawal produced normal, hydroxyapatite-containing bone. Perhaps this "top layer" of bone, composed predominantly of hydroxyapatite, was readily resorbed, and this layer was likely substantial (as the osteoid perimeter at the time of diagnosis was 25 times normal; Table 1). However, subsequent resorption (year 2 forward), perhaps involved underlying bone composed chiefly of fluorapatite which (as noted previously) is relatively resistant to osteoclastic resorption. Thus, BMD continued to decline in years 2–8 (Fig. 2), but at a slower pace, consistent with a skeleton still retaining abundant fluorapatite.

Restoration of remodeling of our patient's sclerotic skeleton was not without its clinical consequences, as he apparently developed nephrolithiasis and perhaps mild renal impairment. If we consider that he had 50% more BMC than healthy age-matched men and that hydroxyapatite (or fluorapatite) is comprised of 40% calcium by weight {$Ca_{10}(PO_4)_6[OH]_2$; gram formula mass = 1004 g, calcium = 400 g}, the continuous bone resorption probably led to excessive renal calcium clearance. If we estimate, conservatively, that our patient might resorb a net 2% of his skeleton per year, with a current total body BMC of 4500 g, he would clear 90 g of mineral (apatite) per year (0.02 × 4500 g). This enables us to project that he would be almost 80 years old before his skeletal BMC might equal to that of average size, healthy 62-year-old men (i.e., 3000 g).

Although prolonged increase in bone mass might seem to be a positive aspect of skeletal fluorosis, and, in fact, our patient has never fractured, fluorotic bone is commonly judged to have poor quality.[9] Our patient had two measurements of bone fluoride content performed 8.5 years apart. Between the ages of 52 and 61 years, his bone fluoride declined 36%, from 1.8% to 1.15% (in specimens that contained both cortical and trabecular bone). Whereas the expected half-life of fluoride in adult bone is ~7 years,[1] fluoride clearance depends on renal function.[1] If a fluoride clearance rate of 36% per 8 years persists (and with declining renal function, fluoride clearance is likely to decline also), our patient would need to complete four "half-lives," or 32 years, before bone fluoride content would even approach the normal range of 0.1%. He would be age 94 years and, at best, would have a bone fluoride content of 0.3%. Thus, it is likely, that much of the projected, persisting, excess skeletal mass would still contain substantial amounts of fluorapatite and be brittle and more prone to fracture than skeletons containing only hydroxyapatite.[9] In fact, long-term fluoride therapy for osteoporosis was associated with more fractures, likely for this reason,[23] and we are concerned he will be at increased risk of fracture. However, he has not fractured to date, and this observation is notable because slow-release sodium fluoride has been proposed as a treatment for osteoporosis.[33]

Finally, results of the biochemistries, densitometry, and radiographs performed in this case are instructive in terms of clarifying which among these tests is optimal for the diagnosis of skeletal fluorosis, when it is considered in the differential diagnosis of sclerosing bone disorders. ALP, which is a sensitive, but nonspecific indicator of exposure to fluoride,[1] was elevated for 10 years before this patient presented with symptoms (Fig. 3A), but can be abnormal in diverse disorders such as osteomalacia from deficiency of vitamin D, Paget's bone disease, osteosarcoma, and sometimes hyperparathyroidism.[12] Elevations in ALP activity should prompt additional, more specific tests. It is worth noting that ALP, as well as serum fluoride, is diagnostically valuable only while the patient is being actively exposed to fluoride. Once fluoride has been removed, both of these indicators normalize within 8 months, possibly sooner, and are therefore of no value for assessing previous exposure to fluoride. More specific markers of bone turnover, such as serum osteocalcin and urinary NTX, are persistently elevated for about a year after fluoride exposure ceases, but are also on the decline and may therefore also be of limited diagnostic use. Urinary fluoride, however, because it reflects resorption of bone fluorapatite that continues for many years, seems to be an optimal test for detecting prior (and active) fluoride exposure. Similarly, radiographic abnormalities will be dependent on the degree of the osteosclerosis, but even in the setting of severe sclerosis can regress, as this case shows. DXA, on the other hand, is probably more sensitive at detecting subtle osteosclerosis and will likely be abnormal even if standard radiographs are less revealing.

Our patient emphasizes the importance of considering fluoride as an explanation for osteosclerosis and in diagnosing skeletal fluorosis especially in those who are at high risk from environmental or occupational exposure. Skeletal fluorosis, whether from current or remote exposure, is readily detected using axial DXA and diagnosed using urinary fluoride measurements. Eliminating the source of fluoride toxicity leads to a reversible disorder, albeit one that will likely linger and perhaps impact the patient for decades. Patients should be monitored for hypercalciuria and treated for impending nephrolithiasis. Prophylactic therapy for this complication, including hydration, limiting calcium intake, and use of thiazide diuretics, could be beneficial. With removal of fluoride, patients can achieve a fairly rapid amelioration of clinical symptomatology and forestall the development of more severe skeletal morbidity.

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