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Skeletal Fluorosis: A Case of Inhalant Abuse Leading to a Diagnosis of Colon Cancer

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Abstract

Skeletal fluorosis is a long-term bone disease that develops when prolonged fluoride toxicity leads to osteosclerosis and bone deformities that result in crippling pain and debility. The disease is endemic to many countries due to environmental or industrial exposures. However, rare cases in the United States have been reported from various causes including heavy toothpaste ingestion, excessive tea consumption, voriconazole use, and inhalant abuse. Here, we present a case of a 41-year-old man who presented for weight loss and severe joint pains due to bony sclerotic lesions found on X-rays. Social history revealed that he had been recreationally inhaling compressed air dusters used for cleaning electronics. Owing to concern for malignancy, he underwent an extensive work-up which led to a diagnosis of colon cancer, but positron emission tomography/computed tomography (PET/CT) and bone biopsy were unexpectedly negative for metastatic bone disease. Further characterization of his lesions by skeletal survey led to a diagnosis of skeletal fluorosis secondary to inhalant abuse. As in this patient, the disease can be difficult for clinicians to recognize as it can be mistaken for various boney diseases such as metastatic cancer. However, once there is clinical suspicion for skeletal fluorosis, various tests to help confirm the diagnosis can include serum and urine fluoride levels, skeletal survey, and bone ash fluoride concentration. Treatment of skeletal fluorosis primarily involves cessation of fluoride exposure, and recovery can take years. Ultimately, further study is required to develop recommendations and guidelines for diagnosis, management, and prognosis of the disease in the United States.

Keywords

skeletal fluorosis, inhalant abuse, colon cancer, 1,1-difluoroethane

Inroduction

Skeletal fluorosis is a long-term disorder of bone metabolism arising from long-term fluoride toxicity.[1] The condition diffusely affects bone and connective tissue, and common presentations include osteosclerosis, periosteal bone formation, and ossification of connective tissue and muscles. In patients, symptoms can manifest as crippling pain and loss of mobility.[2,3]

Endemic skeletal fluorosis affects millions of people across nearly 25 countries, primarily in Asia and Africa.[4] These regions most commonly develop fluoride toxicity from consumption of groundwater with high concentrations of fluoride. Other common means of toxicity include inhalation of fluoride gasses from volcanic activity or industrial exposure from coal burning, brick making, aluminum smelting, and industrial waste.[4-6] In the United States, skeletal fluorosis is rare and has been reported to develop via uncommon means of toxicity including toothpaste ingestion, excessive tea consumption, voriconazole treatment, and inhalant abuse.[6-10]

Diagnosis, particularly in the United States, can prove to be difficult because the condition is not commonly seen by clinicians. In addition, the differential for the presentation can be broad and includes metabolic disorders, malignancy, and hematologic disorders.[1] Here, we present a case of

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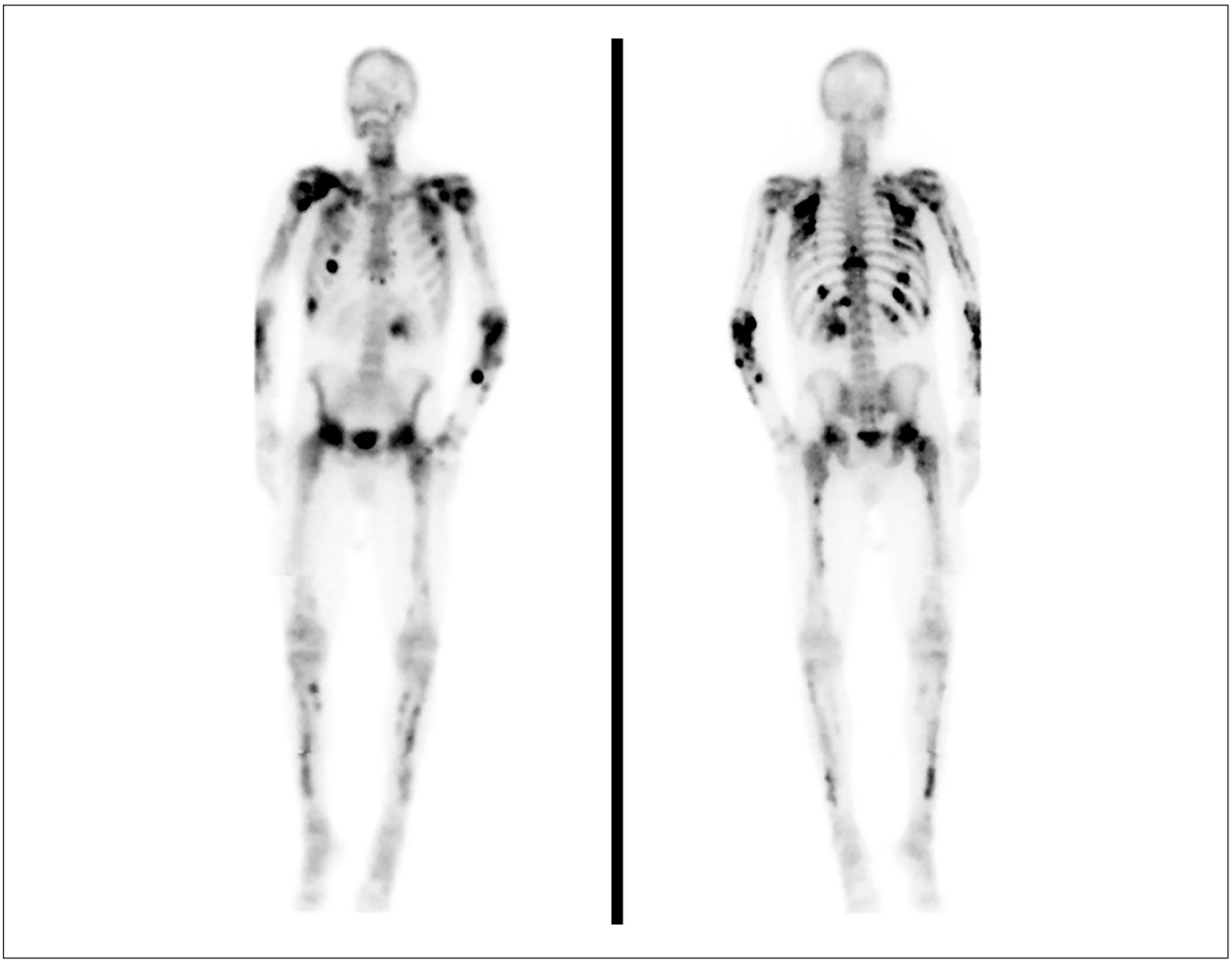

Figure 1. Skeletal scintigraphy showing anterior (left) and posterior (right) views of the patient's skeleton with numerous foci of uptake within the skull, cervical spine, thoracic spine, lumbar spine, long bones, ribs, and pelvis.

skeletal fluorosis secondary to inhalant abuse that incidentally led to a diagnosis of colon cancer.

Case Report

A 41-year-old man with a past medical history of type-2 diabetes, hypertension, gastroesophageal reflux disease, depression, and posttraumatic stress disorder presented for a 2-month history of severe, diffuse joint pain, and 50-pound weight loss over 6 months. His only medications were losartan, metformin, alogliptin, and glipizide. Social history was notable for heavy alcohol, tobacco, and cannabis use, but the patient had remained abstinent from all of these for 6 months prior to presentation. Family history was only notable for a mother who had died of breast cancer. On physical exam, he had tender, boney nodules throughout his upper and lower extremities. Palpation of his anterior and posterior ribs elicited diffuse tenderness. Mobility in his shoulders and lumbar spine were severely restricted due to pain.

Two months prior to presentation, he had established care with an oncologist due to concerns for malignancy after X-rays showed multiple sites of fractures and periosteal reactions in his ribs, radius, ulna, and humerus. Serum alkaline phosphatase at that time was noted to be 1018 IU/L (reference range: 48-121 IU/L) without elevation in total bilirubin, alanine aminotransferase, or aspartate aminotransferase. His oncologist subsequently ordered a whole-body nuclear bone scan (Figure 1), which revealed numerous foci of abnormal bone activity in the skull, long bones, ribs, pelvis, and spine concerning for metastatic osseous disease. These findings prompted an extensive work-up to locate a suspected primary malignancy. Serum protein electrophoresis was negative for multiple myeloma. Prostate-specific antigen was within normal limits. Bone marrow biopsy revealed no evidence of malignancy, and bone biopsy of a right scapular lesion was negative for any metastatic disease. Computed tomography of the chest, abdomen, and pelvis with intravenous contrast revealed a possible mass lesion involving the

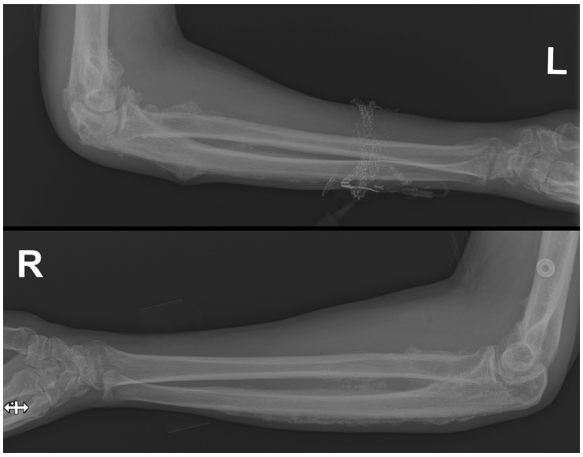

Figure 2. X-rays of the left and right forearms depicting prominent osseous proliferation along the elbows, radii, and ulnas.

pancreas and stomach. Further evaluation with endoscopic ultrasound showed no evidence of pancreatic or gastric malignancy but did reveal Barrett's esophagus and a gastric bezoar that was likely misinterpreted as a mass on CT.

Following this work-up from his oncologist, he was admitted for pain control, and detailed history from the patient revealed that he had been recreationally inhaling compressed air dusters used for cleaning electronics. He reported inhaling upward of 10 cans per day for approximately 1 year. Initial laboratories redemonstrated elevated alkaline phosphatase without elevation in other hepatic function markers. Vitamin D was noted to be 31 ng/mL (reference range: 30-100 ng/mL). Serum calcium was 8.9 mg/dL (reference range: 8.4-10.6 mg/dL) and serum phosphorous was 3.2 mg/dL (reference range: 2.5-4.5 mg/dL). Positron emission tomography/computed tomography (PET/CT) revealed increased radiotracer uptake in the sigmoid colon but no uptake at any of his bony lesions to suggest metastatic disease. He then underwent colonoscopy showing a partially circumferential ulcerated mass in the sigmoid colon with a biopsy positive for adenocarcinoma.

Given the negative uptake of his bony lesions on PET/CT, there was concern for skeletal fluorosis. Serum and urine fluoride testing were unable to be performed as this testing was not available within the admitting institution. Additional diagnostic options were reviewed, and the patient underwent skeletal survey. This revealed osseous proliferation most prominently visualized in the elbows (Figure 2), shoulders (Figure 3), and hands (Figure 4) highly consistent with skeletal fluorosis. Based on his history, physical exam, and imaging findings, a clinical diagnosis of skeletal fluorosis was made.

Once diagnosed, the patient was motivated to forgo any further inhalant abuse. He was referred to a substance use disorder recovery program and started on cholecalciferol at discharge. Ultimately, the patient underwent curative laparoscopic sigmoid colectomy as definitive treatment for his adenocarcinoma. At the time of this report, he has yet to follow-up with any clinician regarding his skeletal fluorosis or inhalant abuse.

Discussion

1,1-Difluoroethane is a propellant used in compressed gasses that is commonly inhaled for its ability to produce central nervous system depression and euphoria.[11,12] Once ingested, the lipophilic compound is able to cross the blood–brain barrier and exert its effects which are short-lived, lasting only minutes. The accessibility, cost, and brief duration of intoxication make 1,1-difluoroethane in computer dusters a highly desirable substance for recreational use.[11,13] Such was the case with this patient who was able to afford and inhale upward of 10 cans per day.

Acute adverse effects of 1,1-difluoroethane ingestion can include loss of consciousness, angioedema, respiratory depression, frostbite at sites of inhalation, rhabdomyolysis, cardiomyopathy, and psychosis.[11] Long-term use can result in dependence and increased systemic fluoride concentrations.[13,14] In our patient, fluoride toxicity from his heavy and prolonged inhalant abuse lead to skeletal fluorosis, a rare condition in the United States.

Skeletal fluorosis in relation to 1,1-difluoroethane develops when repetitive inhalation leads to accumulation of fluoride in the body. Toxic levels of fluoride disrupt the balance of osteoblastic and osteoclastic activity, thereby resulting in dysregulation of bone formation and breakdown. In addition, the uptake of fluoride into bone results in the conversion of the normal bone mineral, hydroxyapatite, into fluorapatite. Fluorapatite results in increased bone density, but the bone is of lower quality making it more brittle. Bone containing fluorapatite is also more resistant to the effects of parathyroid hormone which results in calcium redistribution to the bone and decreased serum calcium. This can then lead to secondary hyperparathyroidism that leaches calcium from healthy bone. The net result of these processes is osteosclerosis, skeletal abnormalities, and loss of bone flexibility resulting in fractures.[15,16]

These skeletal abnormalities can vary between individuals with skeletal fluorosis, but several common features exist. The major clinical sign is osteosclerosis of the axial skeleton.[17] Additional boney findings include new periosteal bone formation, development of osteophytes, and trabecular blurring or haziness. Connective tissue findings include ossification of ligaments and tendons.[3,18,19]

Based on these physical and radiologic findings, skeletal fluorosis can be divided into preclinical and clinical phases. In the preclinical phase, patients are typically asymptomatic but may have slight increases in bone mass. The disease then progresses to phase I, the first symptomatic phase. Patients

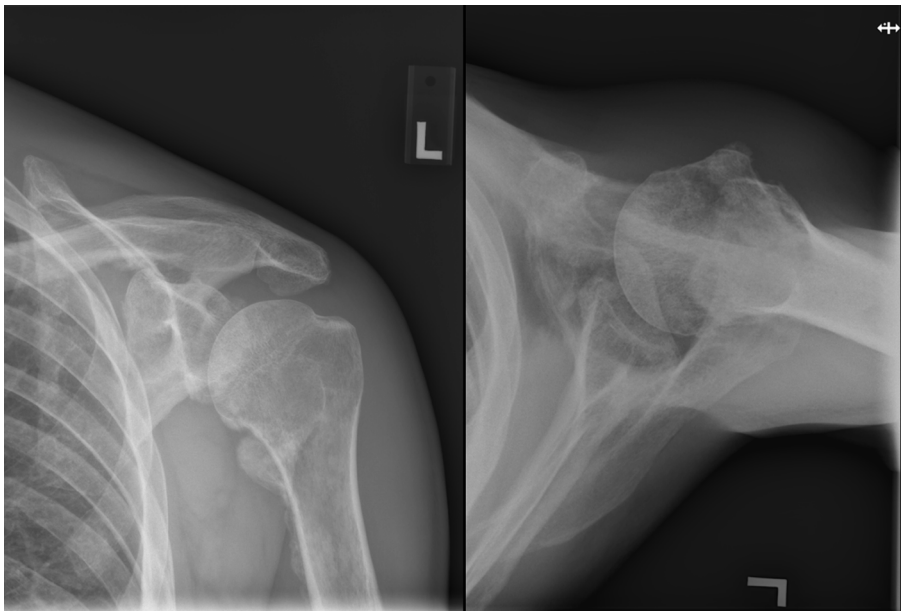

Figure 3. A left shoulder X-ray depicting a mottled appearance of the proximal humeral diaphysis and cortex. Proliferative periosteal bone formation and periostitis can be noted at the glenoid and from the metaphysis to the proximal humeral diaphysis. In addition, there are areas of mild proliferation along the undersurface of the clavicle. Similar findings were noted on the right shoulder.

present with random joint pains, stiffness of joints, and osteosclerosis of their pelvis and vertebral column. As the disease advances to phase II, patients will develop arthritic symptoms, calcification of ligaments, increased cancellous bone, and progressing osteosclerosis. Finally, in stage III, the patient will develop loss of range of motion in joints, calcifications in vertebral ligaments, deformities of the spine and major joints, muscle wasting, and spinal cord compression. Ultimately, the patient is left in a crippled and debilitated state. Based on our patient's symptoms, we suspect that he was most likely in stage II and progressing into stage III. He had severe arthritic symptoms and significant osteosclerosis of his long bones to suggest phase II. However, he also had significant muscle wasting from weight loss and impaired range of motion in his shoulders and spine concerning for phase III.[20]

Given the unclear distinction in the patient's phase, a bone ash fluoride concentration could have been utilized in the staging process. Quantitative analysis for bone ash fluoride concentration from a bone biopsy is the gold standard for diagnosis and can be used to determine clinical phases of skeletal fluorosis.[1,20,21] Each phase has been correlated with a specific ranges of bone ash fluoride concentrations. The preclinical phase involves concentrations of 3500 to 5500 mg F/kg. Phases I, II, and II are associated with concentrations of 6000 to 7000, 7500 to 9000, and greater than 8400 mg F/kg, respectively.[20] In our patient, bone biopsy at an outside hospital was performed prior to the suspicion for skeletal fluorosis, so no fluoride ash testing was performed. Thus, the diagnosis and staging were primarily clinical.

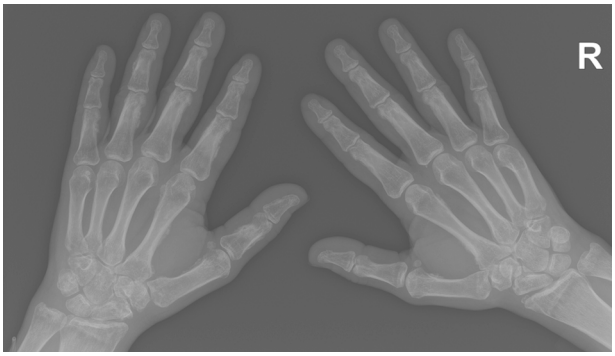

Figure 4. X-ray of the hands showing scattered areas of osseous proliferation bilaterally. This is most prominently seen along the second metacarpal of the left hand.

Aside from bone ash fluoride measurements, other serum, urine, and imaging tests can be employed to confirm the disease. Elevated serum or 24-h urine fluoride levels can support the diagnosis. However, lack of serum and urine testing in many institutions means that the diagnosis often must be clinical in conjunction with imaging studies.[14,21]

A variety of imaging studies such as skeletal survey, CT, magnetic resonance imaging (MRI), scintigraphy, and dual-energy X-ray absorptiometry, can be highly supportive of the

diagnosis.[1] The primary imaging modality in our patient was a skeletal survey which has been reported to have over 90% sensitivity in diagnosing the disease.[22] In addition, a dual-energy X-ray absorptiometry has been known to reveal osteosclerosis of the lumbar spine and femur in patients with skeletal fluorosis.[23] Furthermore, skeletal scintigraphy was performed for evaluation of metastatic disease and revealed numerous foci of uptake in the axial and appendicular skeleton. Many of these foci were not apparent on skeletal survey or CT. Bone scintigraphy has been known to reveal increased bone remodeling in areas that appear normal on other forms of imaging. For this reason, skeletal scintigraphy has been proposed as a more sensitive study than skeletal survey in the diagnosis of skeletal fluorosis.[24]

After diagnosis through these clinical and imaging findings, management of the disease is primarily supportive as there are no well-established treatments. Stopping the source of fluoride toxicity remains the most crucial aspect of recovery, and in patients who abuse inhalants, this would likely involve addiction and psychiatric interventions to prevent further abuse.[1] Additional management may include vitamin D and calcium supplementation which have shown benefit in pediatric and in vitro studies.[1] Finally, surgical intervention such as decompressive laminectomy or excision of skeletal masses may be employed to help prevent complications and morbidity from the disease.[22,25,26] Once these measures are taken, improvement in bone mineral density has been observed, but this process can take years.[27,28]

Last, while treating the patient, clinicians would need to be concerned about nonskeletal complications and risks that can arise from fluorosis. During his clinical work-up, this patient was diagnosed with sigmoid adenocarcinoma and Barrett's esophagus. These diagnoses would raise concern that fluoride toxicity can lead to gastrointestinal manifestations, specifically malignant or premalignant conditions. A limited number of studies have shown possible associations with bone, bladder, respiratory, uterine, and oropharyngeal malignancies, but no clear association with esophageal or colorectal malignancy has been established.[29] In vitro studies have shown that increased fluoride exposure can contribute to increased gastric acid secretion which could present a mechanism for Barrett's esophagus.[30-32] However, there has not been significant assessment of gastrointestinal manifestations or symptoms in human fluoridation studies to suggest that Barrett's esophagus or sigmoid adenocarcinoma could be related to fluoride toxicity.[29] In addition, the patient had developed colonic adenocarcinoma after abusing inhalants for approximately 1 year prior to presentation. In contrast, suspected malignancies in relation to fluoride toxicity have been shown to have latency periods lasting many years after exposure.[33] This would suggest that his sigmoid adenocarcinoma and Barrett's esophagus were likely incidental findings during his clinical work-up that were unrelated to his fluoride exposure. Finally, one could consider that his presentation and work-up for skeletal fluorosis led to an early diagnosis and prompt treatment of his colon cancer.

Conclusion

Skeletal fluorosis in relation to inhalant abuse is a rare entity. Given the nonspecific clinical manifestations, rapid-onset, and infrequency of cases in the United States, the disease can create a diagnostic challenge. Progression of the disease can be crippling to patients, so early identification of inhalant abuse is necessary to raise clinical suspicion and promote a more directed work-up to expedite the diagnosis. Clinicians can then focus their efforts on counseling patients regarding cessation of further inhalant abuse. After diagnosis, no clear treatment options exist aside from supportive measures and surgical management to reduce complications or disease burden. Ultimately, further study is required to understand the diagnosis, treatment, outcomes, and complications of skeletal fluorosis from inhalant abuse.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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