Case 24-2014: A 27-Year-Old Man with Severe Osteoporosis and Multiple Bone Fractures

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**Presentation of Case**

Dr. Joel B. Krier (Pediatrics): A 27-year-old man was seen in the outpatient endocrinology clinic at this hospital because of severe osteoporosis and multiple bone fractures.

The patient had been born to a 23-year-old primigravida mother after 40 weeks of uncomplicated gestation. His mother noted that he had intensely blue sclerae at birth; physical examination was otherwise normal. The patient's postnatal course was normal, and he was discharged home. When he was approximately 1 year of age, mild delays in speech and gross motor development were noted by his parents and pediatrician, including weakness of the leg muscles and poor body control. He began walking at 16 to 17 months of age and shortly thereafter had the first of multiple fractures. He had had more than 12 fractures before he started school, and approximately 20 fractures before he was 10 years of age; these fractures resulted from minor trauma, twisting injuries, falls, and collisions that occurred during typical childhood daily activities and play. During early childhood, mild cognitive impairment and speech difficulties were diagnosed and speech therapy was initiated. By the time he started elementary school, his language development had reportedly “caught up” with that of his peers, and he did not require additional speech therapy. He reportedly had mild cognitive challenges in school, for which he was granted extra time on tests and received special-education services, but he attended mainstream classes and graduated from high school. Ankle tendon-release surgery was performed during childhood to improve the range of motion; contracture of the left ankle persisted. Physical therapy was performed. A bone-mineral-density (BMD) assessment performed in childhood was reportedly normal. An evaluation by a geneticist at another hospital during the patient’s early childhood reportedly showed no evidence of chromosomal abnormalities. There was a clinical suspicion of the fragile X syndrome, but definitive testing was not available at the time.

When he was in his 20s, the patient began participating in a sports activity program for youth with disabilities, and fractures occurred with an increased frequency; he had had a total of approximately 30 fractures by the time he was 27 years of age. Fractures predominantly involved the ribs, hands, feet, and ankles and did not include fractures of the long bones or compression fractures. Laboratory evaluation for secondary osteoporosis, performed at a second hospital, was reportedly negative. Four months before this evaluation, BMD assessment with the use of dual-energy X-ray absorptiometry (DXA) was performed at this hospital, and the results were reportedly consistent with severe osteoporosis (T score of -3.5 in the lumbar spine). The patient was referred to the endocrinology service for further evaluation.

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x-ray absorptiometry (DEXA) revealed severe osteoporosis. The next month, a 24-hour urine collection contained 120 mg (3 mmol) of calcium and a normal level of creatinine; other test results are shown in Table 1. Approximately 1 month before this evaluation, a bone scan performed at another hospital reportedly showed increased technetium uptake in two ribs on the left side, as well as in the right ankle, left hindfoot, and midshaft of both tibias, findings that were thought to represent fractures. He was referred to the endocrinology clinic at this hospital.

The medical history was obtained from the patient and his mother. He had asymptomatic hypothyroidism, hypercholesterolemia, and vitiligo. He reported pain, which he rated at 2 on a scale of 0 to 10 (with 10 indicating the most severe pain), “muscle cramps” in his groin and knees on weight-bearing, occasional pain in his upper body, and occasional palpitations. In the past, he had had bleeding and infections of his toenails after self-induced trauma, as well as acid reflux. He had no history of hearing loss, joint dislocations, nephrolithiasis, eating disorders, lactose intolerance, or celiac disease. Medications included vitamin D₃, atorvastatin, and levothy-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults†</th>
<th>3 Mo before This Presentation, at Another Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/liter)</td>
<td>135–145</td>
<td>138</td>
</tr>
<tr>
<td>Potassium (mmol/liter)</td>
<td>3.4–4.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Carbon dioxide (mmol/liter)</td>
<td>21–33</td>
<td>19</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.60–1.50</td>
<td>0.56</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.5–10.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>2.6–4.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>40–115</td>
<td>136</td>
</tr>
<tr>
<td>Alkaline phosphatase bone isoenzyme (%)</td>
<td>28–66</td>
<td>70</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D (ng/ml)</td>
<td>&gt;32</td>
<td>20</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml)</td>
<td>10–65</td>
<td>39</td>
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<tr>
<td>N-terminal telopeptide (μg/liter)</td>
<td>30–110</td>
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<tr>
<td>C-terminal telopeptide (pg/ml)</td>
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<td>Thyrotopin (μU/ml)</td>
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<tr>
<td>Thyroxine (μg/dl)</td>
<td>4.5–10.9</td>
<td>7.9</td>
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<tr>
<td>Thyroid peroxidase antibodies (IU/ml)</td>
<td>&lt;35, negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Tissue transglutaminase IgA antibodies (U/ml)</td>
<td>&lt;4.0, negative</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Sex hormone–binding globulin (nmol/liter)</td>
<td>10–50</td>
<td>25</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>250–1100</td>
<td>537</td>
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<tr>
<td>Serum protein electrophoresis</td>
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<tr>
<td>Cholesterol (mg/dl)</td>
<td>Total</td>
<td>&lt;200 (desirable)</td>
</tr>
<tr>
<td></td>
<td>Low-density lipoprotein</td>
<td>&lt;130 (desirable)</td>
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<tr>
<td></td>
<td>High-density lipoprotein</td>
<td>35–100</td>
</tr>
<tr>
<td></td>
<td>Triglycerides (mg/dl)</td>
<td>0–150</td>
</tr>
<tr>
<td></td>
<td>Glycated hemoglobin (%)</td>
<td>3.80–6.40</td>
</tr>
</tbody>
</table>

* To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496. To convert the values for thyroxine to nanomoles per liter, multiply by 12.87. To convert the values for testosterone to nanomoles per liter, multiply by 0.03467. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
roxine sodium. He had no known allergies. His diet included dairy products (one or two glasses of milk daily and several servings of cheese per week) and two to three cans of carbonated soft drinks daily. He exercised with light weights and a stationary bike; walking was occasionally limited by leg pain. He lived with his parents and a sibling, had graduated from a community college with an associate’s degree, and worked part-time in a service industry. He had casual social contacts through various hobbies. Although he had a few good friends in high school, he was “not very social” as an adult. He spent time in his room playing online games, worrying, and picking his toenails, which he described as an obsessive behavior. He did not smoke, drink alcohol, or use illicit drugs. His mother was of French Canadian and Native American ancestry and his father of Dutch and English ancestry. His maternal aunt had osteoporosis and had multiple fractures after 45 years of age after falls, his father had hypertension and hypercholesterolemia, his maternal grandmother and uncles had diabetes mellitus type 2, and his sisters were healthy.

On examination, the blood pressure was 125/86 mm Hg, the pulse 67 beats per minute, the height 167 cm (9th percentile), the weight 70 kg (70th percentile), the head circumference 56 cm (73rd percentile), and the body-mass index 25.1. The patient looked older than his stated age and had a prominent forehead, lower jaw, and nasal bridge, as well as a thickened nose and receded hairline. The teeth were short, wide-spaced, and discolored (not opalescent), with some periodontal disease, and the palate and uvula were normal. The sclerae were pale blue. There was slight central obesity, some muscle wasting of extremities, and normal virilization and testes. The small joints of the hands and fingers had notable laxity, with a score of 2 out of 9 on the Beighton scale of hypermobility (the two fifth digits could each dorsiflex more than 90 degrees); the large joints were mildly contracted. There were patches of vitiligo, as well as hyperpigmentation that was consistent with sun exposure, with no pigmented striae or bruising. He had truncal hypotonia, mild kyphosis, and no scoliosis or vertebral tenderness. He generally spoke with a flat affect but had insight, made jokes at times, and expressed anxiety about being undressed during physical examination. The remainder of the examination was normal.

Calcium supplementation and continuation of vitamin D supplementation and thyroid-replacement therapy were recommended. Exercise with weight-bearing and strength training was also advised.

Two months later, diagnostic tests were performed.

**DIFFERENTIAL DIAGNOSIS**

**Dr. Michael Mannstadt:** The history of this 27-year-old man is most notable for numerous fractures that have occurred since early childhood and recent BMD assessment with the use of DEXA revealing severe osteoporosis. Since the problem of multiple bone fractures and osteoporosis is the major feature in this case, I will construct my differential diagnosis around bone fragility and will use some of the other findings, including unusual facial features, pale blue sclerae, discolored and wide-spaced dentition, and joint laxity, to narrow the list of possible diagnoses.

**OSTEOMALACIA AND RICKETS**

Osteoporosis, a disease of low bone mass, has to be distinguished from osteomalacia, a defect in the mineralization of the bony matrix. Both osteoporosis and osteomalacia can result in low BMD readings. Conditions (e.g., hypophosphatemia) that lead to osteomalacia in adults will lead to rickets if present during skeletal growth. This patient is unlikely to have had rickets, since he does not have bowing of the legs or other typical manifestations of the disease. In addition, he has no laboratory evidence of hypocalcemia, hypophosphatemia, elevated or low levels of alkaline phosphatase (in osteomalacia and hypophosphatasia, respectively), or severe vitamin D deficiency. Radiographs of bones, which can show widened metaphyses in rickets and pseudofractures in osteomalacia, would be useful to obtain. If we were evaluating this patient when he was a child, the finding of multiple unexplained fractures should prompt consideration of nonaccidental injury or child abuse.

**OSTEOPOROSIS**

Osteoporosis can be defined as “a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.”¹ The World Health Organization (WHO) defines osteoporosis in adults with the use of BMD criteria,² but for children, there is no WHO definition of osteoporosis and the interpretation of BMD mea-
measurements is more complex, since bone size and density change rapidly with growth. Therefore, evidence of bone fragility (the presence of atraumatic fractures) in combination with low BMD adjusted for bone size becomes key in defining osteoporosis in children. This patient had an impressive number of atraumatic fractures starting in early childhood; therefore, we can assume that he had osteoporosis as a child, which has persisted throughout his life. In constructing a differential diagnosis for this patient, it is important to determine whether osteoporosis developed because of a primary bone disorder (primary osteoporosis) or as a result of another medical condition (secondary osteoporosis).

SECONDARY OSTEOPOROSIS

Could this patient have a chronic illness that is causing secondary osteoporosis? Celiac disease is a condition that may develop during childhood and causes chronic diarrhea and malabsorption and can result in bone loss and secondary hyperparathyroidism. Although celiac disease is often difficult to diagnose, this patient had no evidence of gastrointestinal symptoms as a child or an adult, and before his most recent presentation, he had a negative test for tissue transglutaminase IgA antibodies, which make the diagnosis of celiac disease unlikely.

Endocrine disorders including hyperthyroidism, hypogonadism, and Cushing's syndrome have been associated with the development of secondary osteoporosis. However, normal results of testosterone and thyroid studies and no clear evidence on physical examination to suggest hypercortisolism or hypogonadism make these diagnoses unlikely in this patient.

Other causes of secondary osteoporosis include the chronic use of immunosuppressive therapy or such medications as glucocorticoids, neuromuscular disease (cerebral palsy), and environmental factors (e.g., malnutrition and lead exposure). These features are inconsistent with this patient's history.

PRIMARY BONE DISORDERS

The occurrence of fractures in early childhood and the absence of obvious secondary causes of osteoporosis point to a primary bone disorder (Table 2). Idiopathic juvenile osteoporosis is characterized by fractures occurring 2 to 3 years before the onset of puberty followed by spontaneous remission several years later. This typical manifestation clearly differs from that in this patient, since fractures developed throughout his life without evidence of remission. Therefore, a heritable disorder of connective tissue is the most likely diagnosis for this patient.

OSTEOPATHIES

Osteoporosis is the most prevalent heritable disorder of connective tissue. This patient presents with the hallmark features of this disease: bone fragility, blue sclerae, and dental disease. This genetic disorder is caused by mutations either in genes encoding one of the two types of alpha chains of type I collagen (90% of cases, classic osteogenesis imperfecta) or in genes with protein products that are involved in the proper folding and processing of type I collagen (10% of cases, newer types of osteogenesis imperfecta). Type I collagen is the major structural protein in bone, tendon, ligaments, and dentin and consists of two alpha-1 chains (encoded by COLIA1) and one alpha-2 chain (encoded by COLIA2) that fold into a triple helix (Fig. 1).

Mutations in type I collagen can occur sporadically or as an autosomal-dominant trait. More than 800 distinct mutations in either COLIA1 or COLIA2 have been reported. The functional absence of one allele, caused by nonsense mutations or frameshift mutations, leads to a quantitative defect and a mild clinical phenotype. In contrast, missense mutations disrupt the proper helical structure at the site of the mutation and delay the triple-helix formation, leading to overmodification of the collagen chains. A single missense mutation in one of the collagen chains can therefore lead to a dominant negative effect with a more severe phenotype by impairing the stability of the entire collagen helix. The abnormalities in collagen lead to fragile bones, blue sclerae, hyperextensible joints, and

Table 2. Causes of Primary Osteoporosis.

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Idiopathic juvenile osteoporosis (starts 2 to 3 yr before puberty, and remission is spontaneous)</td>
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<tr>
<td>Heritable disorders of connective tissue</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
</tr>
<tr>
<td>Ehlers–Danlos syndrome</td>
</tr>
<tr>
<td>Osteoporosis pseudoglioma</td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
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<td>Homocystinuria</td>
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Dentinogenesis imperfecta. These abnormalities match this patient’s clinical syndrome.

**Other Rare Disorders**

Other connective-tissue disorders are possible but unlikely in this patient. Fractures are not the main feature in the Ehlers–Danlos syndrome, and the patient does not have the arachnodactyly and tall stature seen in Marfan’s syndrome or the blindness seen in osteoporosis pseudoglioma.

Rare diseases caused by mutations in genes that are important for the formation of osteoblasts should also be considered. However, extraskeletal features are not part of X-linked osteoporosis (plastin 3 [PLS3] mutations), and this patient did not have the dysplastic features seen in cleidocranial dysplasia (RUNX2 mutations) or the acro-osteolysis and facial features that are typical of the Hajdu–Cheney syndrome (NOTCH2 mutations).

This patient has many of the classic features of osteogenesis imperfecta, but cognitive impairment, delay in speech development, and self-
mutilation are not typically associated with this disease. His presentation could be called “osteogenesis imperfecta plus.” It is possible that the atypical features occurred in this patient by chance. Alternatively, he could have a contiguous gene condition, a chromosomal deletion syndrome affecting multiple functionally unrelated loci that are physically close. A contiguous gene syndrome has been described in two members of a family who were affected with osteogenesis imperfecta and who also presented with an intellectual disability, similar to that in this patient. The molecular defect in that case was identified as a large genomic deletion of 17q21, leading to a loss of \( \text{COL1A1} \) and several other genes. Depending on the function of the neighboring genes, an affected patient could present with seemingly unrelated symptoms. Although osteogenesis imperfecta is mainly a clinical diagnosis, genetic evaluation through sequencing of the genes for type I collagen (\( \text{COL1A1} \) and \( \text{COL1A2} \)) and microdeletion analysis should be considered in this patient.

**DR. MICHAEL MANNSTADT’S DIAGNOSIS**

Osteogenesis imperfecta, possibly part of a contiguous gene syndrome.

**CLINICAL IMPRESSION**

Dr. Angela E. Lin (Genetics): When we evaluated this patient, we thought his medical history and clinical presentation were most consistent with osteogenesis imperfecta, without dentinogenesis imperfecta or apparent hearing loss. He did not fit into any of the traditional Silence classification groups or expanded phenotypes. Review of the four-generation pedigree did not show any relatives with consanguinity, fractures, blue sclerae, joint laxity, hearing loss, abnormal teeth, or intellectual disability. Because of the co-occurrence of intellectual disability and features of an autism spectrum disorder, our clinical diagnosis was a genomic disorder (contiguous gene syndrome). Although the patient lacked classic features of the fragile X syndrome, we thought this entity should be definitively ruled out because of potential reproductive risks for his female relatives and because this possible diagnosis had been lingering since the patient’s childhood. To clarify these diagnoses, we recommended genetic testing.

**PATHOLOGICAL DISCUSSION**

Dr. Long P. Le: To evaluate for osteogenesis imperfecta, the patient’s blood sample was sent to a reference laboratory for Sanger sequencing of the coding regions and flanking intronic regions of \( \text{COL1A1} \) and \( \text{COL1A2} \). No mutations were detected in either \( \text{COL1A1} \) or \( \text{COL1A2} \). Although heterozygosity for polymorphic variants was identified along the gene \( \text{COL1A2} \), only homozygosity for polymorphic variants was detected in \( \text{COL1A1} \). A lack of heterozygosity in either gene is atypical, and this finding may be consistent with a rare deletion of the gene \( \text{COL1A1} \). Deletion and duplication analysis of \( \text{COL1A1} \) by array-based comparative genomic hybridization (CGH) was recommended.

Because of the skepticism surrounding the long-standing diagnosis of the fragile X syndrome as a basis for the patient’s intellectual and social limitations, genetic testing was performed; the results were not consistent with the fragile X syndrome. Array-based CGH was also performed to evaluate the patient’s developmental delay and intellectual disability. Array-based CGH is a common technique performed in clinical laboratories to assess for copy-number variations at a coverage and resolution that are high enough to enable genomewide analysis. Copy-number variations are gains or losses of several kilobases to hundreds of kilobases of genomic DNA. They have been implicated in many congenital disorders and in cancer but are also present in healthy persons. Since 2010, both the International Standard Cytogenetic Array Consortium and the American College of Medical Genetics and Genomics have recommended array-based CGH as first-tier cytogenetic testing for unexplained developmental delay and intellectual disability, autism spectrum disorder, and multiple congenital anomalies because of its relatively high diagnostic yield.

The patient’s blood DNA was tested, and in addition to a number of benign polymorphic copy-number changes, the results show a hemizygous interstitial deletion at 17q21.33 spanning approximately 1.025 Mb. This contiguous gene
Deletion encompasses at least 28 genes, one of which is COL1A1 and is most likely the cause of the osteogenesis imperfecta type I phenotype in this patient (Fig. 2). Another affected gene of interest in the copy-number loss is DLX3 (distal-less homeobox 3). The autosomal dominant loss-of-function mutations in DLX3 have been associated with amelogenesis imperfecta (hypomaturation–hypoplastic type, with taurodontism) and the tricho–dento–osseous syndrome. Both conditions show abnormal growth of the molar teeth and a tooth-enamel defect, increased BMD, and curly hair. Perhaps this gene defect may partially explain the patient’s noted dentition. The hemizygous loss of the remaining genes could be responsible for the patient’s developmental delay, intellectual disability, and social limitations; however, because of a lack of definitive functional evidence, it is unclear which of those genes are causative.

Because of the size and content of the hemizygous copy loss, the evidence in the literature, and the patient’s clinical presentation, the detected contiguous gene deletion in this case was interpreted as pathogenic. The features of the patient’s disease are consistent with atypical osteogenesis imperfecta type I combined with a complex phenotype of developmental delay and intellectual disability.

**Figure 2. Genetic Studies.**

Array-based comparative genomic hybridization was performed on a blood specimen. Labeled DNA from the patient’s blood was comparatively hybridized against control DNA. A hemizygous interstitial deletion at 17q21.33, involving 60 oligonucleotide probes and spanning approximately 1.025 Mb, was detected. The y axis shows the log2 ratio of patient signals versus control signals, and the x axis shows the chromosome 17 base position in megabases (hg19 human genome reference sequence). Black squares represent probes showing signal within the normal range; green squares represent probes showing signal indicative of copy-number loss. Gray bars represent known genes in this region. The arrow denotes the one-copy deletion of the COL1A1 gene.

**Follow-Up.**

Dr. Krier: The determination that this patient did not have the fragile X syndrome was an important finding for the patient and his family, given the many years that the possibility of the diagnosis had lingered. We considered the implications for the patient’s family of his diagnosis of atypical osteogenesis imperfecta, since he has two sisters in early adulthood, neither of whom has yet had children. Because of the lack of relevant family history and presumed high penetrance of the COL1A1 deletion, our suspicion is that the patient has a de novo deletion; we recommended testing his parents for the deletion for confirmation. If testing were negative, con-
cern regarding risk in his sisters would be minimized. The patient did not respond to our invitations to return for continued medical care and genetics counseling and has since been lost to follow-up.

Dr. Lloyd Axelson (Medicine): If the patient had returned, would you have recommended therapy with a bisphosphonate or another treatment to decrease the risk of recurrent fractures?

Dr. Mannstadt: Bisphosphonates and teriparatide are not approved therapies for osteogenesis imperfecta, although there are limited data to support their use. I would consider the administration of bisphosphonates or teriparatide in this patient, especially because of his recurrent fractures as an adult. Of course, the relative paucity of data from clinical trials and the potential risks associated with bisphosphonate and teriparatide therapy would have to be discussed with the patient.

**Final Diagnosis**

Contiguous gene deletion involving COL1A1, resulting in osteogenesis imperfecta type I, and other genes possibly related to the patient’s complex phenotype.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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**References**


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