



Case report

ITGB (Integrin subunit beta) 3 mutation involved in pulmonary hemorrhage and osteopetrosis

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A B S T R A C T

We report on a previously healthy infant who presented with pulmonary hemorrhage due to a rare hematologic disorder. He also had imaging and laboratory studies suggestive of osteopetrosis. A genetic testing uncovered a previously known integrin gene possibly involving both hematologic and bone tissues; however, the latter has been described only in mouse models.

1. Introduction

Pulmonary hemorrhage (PH) in infants is a rare condition [1]. In some cases, PH is large enough that infants may need mechanical ventilation or die. Prompt management of the airway and ventilation is vital, and a subsequent visualization of the upper and lower airways will help to determine source of bleeding. Once stable, an intense evaluation must follow to determine etiology because an accurate diagnosis will be crucial for management and prognosis. Etiologies of PH are typically classified as caused by infectious agents, malignancy, trauma, vasculitis, coagulopathy, cardiac diseases, toxins, drugs, congenital lung malformations, and idiopathic entities. Genetic studies are rarely used to determine disease but can become very useful when etiology is unclear.

2. Case report

A 5-week-old male infant, who was born full term, presented to the emergency department with a sudden episode of limpness, cyanosis, and apnea. At exam, he had petechiae over his face and chest, and frothy pinkish oral secretions. During intubation, a significant amount of blood was observed inside his endotracheal tube. His initial tests revealed a decrease in the hematocrit concentration level (20.9%), platelet count (96,000 per microliter) and fibrinogen level (114 mg/dl). A chest radiograph showed diffuse ground glass opacification of both lung fields (Fig. 1A). Ampicillin and gentamicin were started and discontinued after five days because all his culture results came back negative. Infant remained in critical state and on mechanical ventilation for 1 week.

An echocardiogram revealed a patent foramen ovale with a left to

right shunt however, there was no evidence of pulmonary hypertension. Brain MRI displayed bi-frontal subdural fluid collections with diffuse patchy-meningeal enhancement, which raised concern for non-accidental trauma. Further radiological examination was performed because of suspected abuse. A skeletal survey exhibited unusual “bone-within-bone” appearance in all metacarpal and proximal phalanx of bones (Fig. 1B, black arrows) of the hands and feet. This imaging appearance was suggestive of either metabolic disorder or genetic condition. Therefore, tests for levels of urine organic amino acids, plasma amino acids, acyl carnitine, beta-glucosidase, hemoglobin electrophoresis, and urine storage disease panel levels were sent and reported as normal. A “bone-within-bone” appearance was associated with osteopetrosis and initial tests to evaluate this condition were reported as normal. (Parathyroid hormone (PTH) (normal range), vitamin D levels [1,25 OH (113 pg/mL, normal range) and 25 OH (19 ng/nL, normal range 20–50 ng/nL)], collagen type 1 C-telopeptide (CTX) (809 pg/mL, normal range. A marker of bone resorption) and creatine kinase BB (CKBB) (6%, elevated. Range is zero)). Interestingly, levels of pro-collagen 1 N terminal propeptide (P1NP) (1010 µg/L, normal range 22–105 µg/L. A marker of bone formation) were elevated and, a DEXA scan demonstrated high-normal bone mineral density and bone mineral content for age. In light of these results, an extended genetic panel for osteopetrosis that included CLCN7, TCIRG1, OSTM1, SOST, SNX10, PLEKHM1, TNFRSF11A, TNFSF11, CA2, IKBKG and ITGB3 was ordered. Two months later, his whole exome sequencing study revealed a mutation in the ITGB (Integrin subunit beta) 3 gene.

Among other studies, his initial bronchoalveolar lavage was positive for hemosiderin in more than 50% of total alveolar macrophages. Subsequent bronchoscopies demonstrated a declining percentage of hemosiderin-laden macrophages. First bronchoalveolar lavage was

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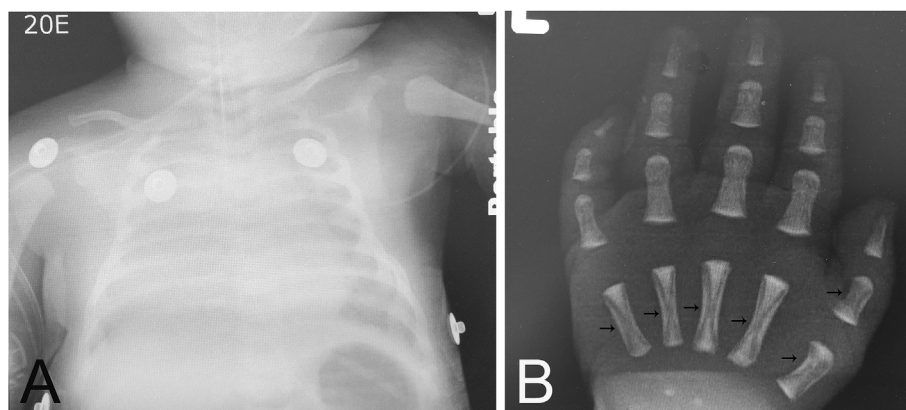


Fig. 1. Imaging studies (A) chest radiograph with diffuse ground glass opacification of both lung fields. (B) “bone-within-bone” appearance in all metacarpal and proximal phalanx of bones (black arrows) of the left hand.

positive for cytomegalovirus and since there was no viremia and clinical status improved, treatment was not considered. Fungi and bacteria cultures were negative after 7 days.

Our patient was discharged 3 weeks after admission on prednisolone that was tapered over 3 months. He did not have any other episode of pulmonary hemorrhage; however, he had significant nose and mouth bleeding that were treated with aminocaproic acid solution or recombinant Factor VIIa (NovoSeven). He tended to bruise easily and developed petechiae on his face when he cried or strained to stool. Fortunately, he did not develop any fractures or bony pain. He was doing very well from an osteopetrosis standpoint at 30 months of age.

3. Discussion

The diagnosis of pulmonary hemorrhage in infants is an elusive task. Its sudden onset in an apparently healthy infant can result in a life-threatening event [2]. A myriad of diagnoses have been proposed, among them are hematologic entities such as thrombocytopenia, congenital or acquired coagulopathies, transient vitamin K deficiency, and other bleeding disorders. Our case is the first to suggest a relation between a hematologic condition and a bone disorder. The infant's exome sequencing study revealed a homozygous D145Y missense mutation (aspartic acid to tyrosine) in the ITGB3 gene.

Pathogenic variants in the ITGB3 gene are characterized by failure of platelet aggregation and absent or diminished clot retraction. Mutations affecting either the ITGA2B or ITGB3 genes have been found in Glanzmann's thrombasthenia (GT) [2], an autosomal recessive disorder. ITGB3 mutation is also known to cause osteopetrosis in animal models but has not been linked to human osteopetrosis to our knowledge.

GT is associated with abnormal integrin α Ib β 3, formerly known as glycoprotein IIb/IIIa (GpIIb/IIIa), which is an integrin aggregation receptor on platelets. Many point mutations and polymorphisms have been found in α Ib β 3 complex of patients with GT. Missense and nonsense mutations, deletions, and insertions seem to cause premature termination or splice site defects. Some of these mutations affect the ligand-binding and recognition properties of the heterodimeric complex, while others affect the receptor activation [3]. This receptor is activated when the platelet is stimulated by ADP, epinephrine, collagen, or thrombin. GpIIb/IIIa is essential to blood coagulation since the activated receptor has the ability to bind fibrinogen (as well as von Willebrand factor, fibronectin and vitronectin), which is required for fibrinogen-dependent platelet-platelet interaction (aggregation). Although only two types of glycoproteins (IIb and IIIa) are affected in GT, the mutation diversity is high in this bleeding disorder. No significant correlation has been found between bleeding severity and the type of mutation in GT.

ITGA2B or ITGB3 genes are closely located at chromosome 17q21.31–32 but are independently expressed. Consanguinity contributes to a greater frequency of GT in some ethnic groups (e.g. Iraqi Jews, Palestinian Arabs, French Gypsies) [2]. Our patient's parents are originally from Central America and have a distal family history of consanguinity (parents are third cousins).

The bleeding tendency in GT is variable and there is no adequate prophylactic therapy for it. Platelets and antifibrinolytics have been the standard of care for signs of significant bleeding. Unfortunately, some patients with GT develop alloantibodies to platelet, making them refractory to transfusion treatments. Recently, the FDA approved the use of recombinant factor VIIa (NovoSeven) [2] for bleeding or procedures as a preventative measure for patients with GT. Patients who have severe disease and platelet refractoriness are offered bone marrow transplant as a curative option [4].

In addition to GT, our patient has osteopetrosis, an extremely rare inherited disorder where the bones become more brittle and denser. Mild osteopetrosis may not cause significant problems, however, severe forms can result in stunted growth, deformity, and increased likelihood of fractures. Our patient has bone changes consistent with this diagnosis.

ITGB3 mutations causing both GT and osteopetrosis have been described in mouse models but not in humans [2].

Progressive osteopetrosis may lead to bone marrow failure [5]. In our infant, bone marrow transplant could be a potential therapeutic option since both GT and osteopetrosis may be treated with this approach. Unfortunately, bone marrow transplant is a procedure not without potential for significant morbidity and mortality.

Finally, our patient's parents received genetic counseling because they had 25% risk of recurrence of this recessive disorder. Prognosis of our patient's descendants will depend if his spouse is a carrier or not.

We present a rare cause of pulmonary hemorrhage in infants and speculate that presence of bone abnormalities may alert clinicians to consider genetic studies and further referral for specialized care.

Conflict of interest

We have no financial relationships relevant to this article to disclose.

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