A Filipino Child with Cleidocranial Dysplasia and Acute Leukemia: A Case Report

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ABSTRACT

Cleidocranial dysplasia (CCD) is an autosomal dominant skeletal dysplasia whose most common features include late closure of fontanelles, absent or hypoplastic clavicles, and dental abnormalities. This disorder is primarily due to mutations in RUNX2 (CBFA1) gene. Here we present a Filipino child with clinical and radiologic features of CCD who was also diagnosed with B-cell acute lymphoblastic leukemia (ALL). On history, the patient's father and paternal grandfather also presented with short stature and similar facial features. Association of leukemia and CCD has been noted in the literature. Hence, this report adds to the potential role of RUNX2 gene in leukemogenesis. With the potential predisposition to developing leukemia, this provides implications in genetic counselling and possible recommendations for surveillance later on.

Key Words: cleidocranial dysplasia, leukemia, autosomal dominant

INTRODUCTION

Cleidocranial dysplasia (CCD) is an autosomal dominant skeletal dysplasia characterized by the classic triad of late closure of the fontanels, absent or hypoplastic clavicles, and dental anomalies. Short stature is mostly observed in these patients, who are shorter than their unaffected siblings. Dental anomalies may include the presence of supernumerary teeth, delayed eruption of permanent teeth, and the presence of the second permanent molar with the primary teeth.[1]

CCD has a prevalence of 1 in 1,000,000. Among patients with this skeletal dysplasia, there are only a handful of reported cases, with only 2 pediatric cases.[2] The association of these 2 conditions may be explained by the potential role of the RUNX2 gene mutation. RUNX2 or the runt-related transcription factor 2 gene located in chromosome 6p21, plays a major role in bone and cartilage formation.[3] It is the implicated gene in the majority of cases of cleidocranial dysplasia. The role of RUNX2 in the development and progression of specific tumor types like leukemia are being investigated using experimental animal studies.[2]

We present the case of a 15-year-old boy with short stature, open anterior fontanel, absent clavicles, hypertelorism, and dental anomalies consistent with cleidocranial dysplasia. In the clinical work-up, acute lymphoblastic leukemia was diagnosed.

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CASE PRESENTATION

We are presented with a 15-year-old male with fever. He was born full term to a then 23-year-old gravida 2 para 1 (1001) mother via spontaneous vaginal delivery. At birth, he was already noted to have similar features as his father and paternal grandfather. Hence, though with short stature and characteristic facial features, no consult was done. He was developmentally at par with age, apparently well and has never been hospitalized until 1 week prior to consult, when he presented with fever, associated with easy bruisability and gum bleeding. On work-up, complete blood count showed an elevated white blood cell count of 60.2 x 10^9/L (reference value: 4.5-11.0 x 10^9/L). The patient was then worked-up for acute leukemia. Due to the presence of short stature and facial features, the patient was referred for dysmorphology evaluation.

The patient was second of a sibship of six born to a healthy non-consanguineous union of Filipino descent. The mother and the other siblings are of normal height. The father and the paternal grandfather, have the same condition as the patient, also presenting with short stature and similar facial features (Figure 1).

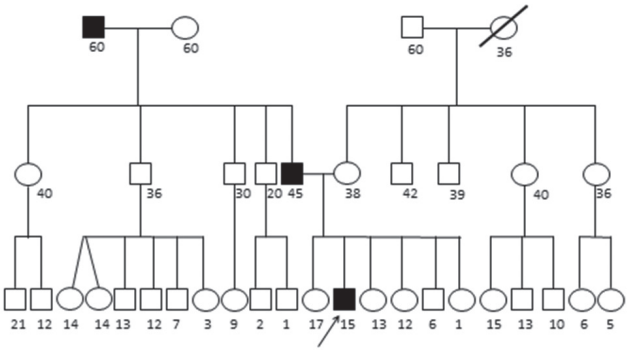

Figure 1. Three-generation pedigree and family medical history of the patient showing the autosomal dominant mode of inheritance of cleidocranial dysplasia.

On physical examination, the patient has relative macrocephaly, with weight and height both below the 3rd percentile. He has frontal bossing, hypertelorism, depressed nasal bridge, palpably absent clavicles, crowding of teeth and malocclusion. There was note of subconjunctival haemorrhage on the right eye and gum bleeding but no note of cervical, inguinal and axillary lymphadenopathies. Cardiac and pulmonary examinations were unremarkable. There was note of hepatomegaly but no splenomegaly. The father was also examined and was noted to have short stature, frontal bossing, hypertelorism, depressed nasal bridge, sloping shoulders, and absent clavicles on palpation, just like the patient (Figure 2).

On radiographic evaluation, the patient is brachycephalic with a cephalic index of 97.1 (N: 72.8–87.7) and microcephalic with a modulus of 16.3 (N: 16.6–18.8. There is also the persistence of the posterior fontanelle. Based on the Greulich Pyle, the patient's left hand and wrist most closely resemble the standard for a 12- to 13-year-old male. The cervical spine is also straightened (Figure 3).

Genetic counselling was done. The condition being autosomal dominant, it was explained to the family that the recurrence risk for every pregnancy of an affected individual is 50%. They were advised of the possible skeletal and orthopaedic complications, which would warrant close monitoring. They were also advised the runt-related transcription factor 2 (RUNX2) molecular testing but due to the more pressing medical problem, the family opted to delay genetic diagnostics.

The patient was subsequently diagnosed with B-cell acute lymphoblastic leukemia (ALL). Based on the patient's age and initial white blood cell count, the patient was classified as high risk. Chemotherapy was started using the International Society of Pediatric Oncology (SIOP) Paediatric Oncology in Developing Countries (PODC) graduated intensity ALL regimen 2. During the course of the chemotherapy, the patient was noted to have poor response to Prednisone. He was on interim maintenance phase of the chemotherapy regimen when he succumbed due to relapse.

Figure 2. (A and B) Features of the patient, which include frontal bossing, depressed nasal bridge, hypertelorism, relative prognathism, and sloping shoulders; **(C)** Dental anomalies, such as crowding and malocclusion; **(D)** Father with short stature, frontal bossing, hypertelorism, depressed nasal bridge and sloping shoulders.

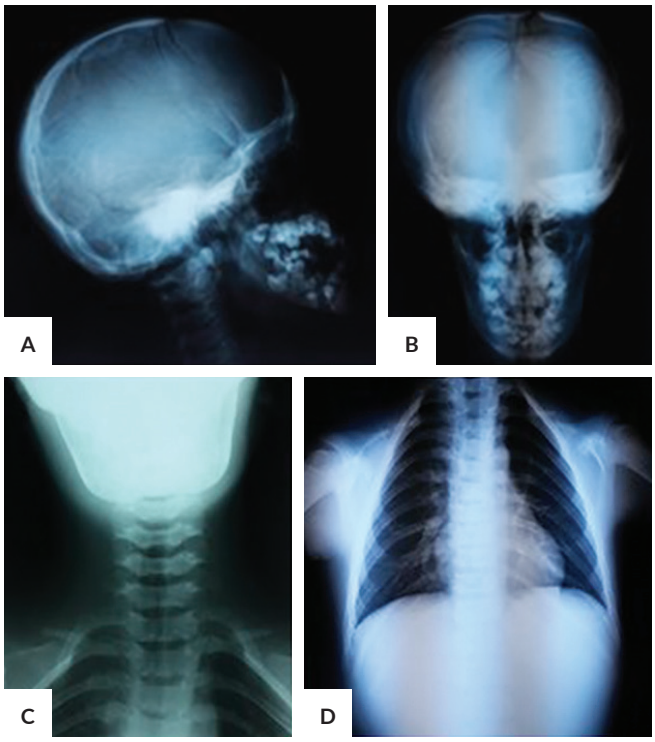

Figure 3. (A and B) Open sutures, multiple wormian bones, patent fontanels, hypoplasia of the maxilla, and dental crowding; **(C and D)** Hypoplastic clavicles and cone-shaped thorax on radiograph.

DISCUSSION

Based on both clinical features and radiologic characteristics, the patient has cleidocranial dysplasia (Tables 1 and 2). Although the name suggests primary involvement of cranial and clavicular abnormalities, this condition has long been recognized to involve the entire skeletal system.[4] As shown in Table 2, involvement of spine, thorax and shoulders, extremities and dentition are also recognized in this condition. In addition, a pedigree showing a three-generation involvement reinforces the diagnosis since it is inherited in an autosomal dominant manner. However, for other cases wherein the proband is the only one involved in the family, the likelihood of a de novo mutation is high.

RUNX2 is the gene implicated in cleidocranial dysplasia. This gene is known to function as a master transcription factor for osteogenesis. It interacts with a number of proteins and regulates several cellular events thru posttranslational modifications. RUNX2 is also known for its diversified function in different tissues of the body, such as a regulation in osteoblast differentiation, role in skeletal morphogenesis, tooth development, vasculogenesis and chondrogenesis. Hence, the features of cleidocranial dysplasia can be explained by the gene's involvement in these processes.[5] In addition, RUNX2 interacts with cell cycle regulators like the p53 tumor suppressor, which is the master regulator of the cell cycle.[6]

This skeletal dysplasia's association with malignancy has been reported before. The first case on acute myeloid leukemia (AML) developing in a RUNX2 haploinsufficient background was previously reported. A female with cleidocranial dysplasia presenting with recurrent infections was worked-up and was diagnosed with AML. Leukemic blast analysis and skin biopsy revealed RUNX2–R190Q mutation. In this report, however, it is still uncertain whether the

Table 1. Comparison of Clinical Features of our patient with the previously reported cases of Cleidocranial Dysplasia

Present	Absent
Skull	
Brachycephaly[1,4]	
Frontal and parietal bossing[1,2,4,9]	
Open sutures and fontanels[4,9]	
Relative prognathism[1,4]	
Soft skull in infancy[4]	
Depressed nasal bridge[1,4]	
Hypertelorism[1,4,9]	
Thorax and shoulders	
Ability to bring shoulders together[1,4]	Respiratory distress at early age[4]
Narrow, sloping shoulders[4,8,9]	
Increased mobility[1,4]	
Spine	
	Scoliosis[4]
	Kyphosis[4]
Hands	
Brachydactyly[4]	Tapering of fingers[4,8]
Nail dysplasia/hypoplasia[4]	
Short/broad thumbs[4]	
Clinodactyly of 5th finger[4]	
Dentition	
Delayed eruption[1,4]	Normal deciduous dentition[4]
Crowding, malocclusion[1,4]	Supernumerary teeth[1,4]

Table 2. Comparison of Radiologic Features of our patient with the previously reported cases of Cleidocranial Dysplasia

Present	Absent
Multiple wormian bones[1,4,8]	Segmental calvarial thickening[4]
Unossified sutures and patent fontanelles[1,4,8]	Dysplastic changes in the bassiocciput[4]
Hypoplasia of maxilla[4]	Delayed mineralization[4]
Calcification of nasal bone delayed or missing[4]	Cervical ribs, missing ribs[4]
Hypoplastic sinuses (paranasal, frontal, mastoid)[4]	Widening of sacroiliac joints[4]
Hypoplastic, aplastic, or discontinuous clavicles[3,4,8,9]	Large femoral neck, large epiphyses[4]
Cone shaped thorax[4,8]	Spondylolysis and spondylolisthesis[4]
Hypoplastic scapulae[4]	Spina bifida occulta[4]
Delayed ossification of pubic bone[4]	Short middle phalanges and metacarpals/tarsals III-V[4]
Hypoplasia of iliac wings[4]	Accessory epiphyses especially of 2nd metacarpal[4]
Hemivertebrae, posterior wedging[4]	Long 2nd metacarpal[4]
Hypoplastic distal phalanges[4]	Cone-shaped epiphyses[4]
Impacted, supernumerary teeth[1,4]	

RUNX2 mutation contributed to the development of AML. If not directly, the mutation may have caused up-regulation of RUNX2 which may be involved in leukemogenesis.[7]

In the pediatric population, there were two reported cases of the association of cleidocranial dysplasia with leukemia. A child with CCD who developed AML was noted to have a heterozygous mutation on direct sequencing of RUNX2 gene. The mother, brother and maternal cousin were also noted to carry the same RUNX2 p.R225Q mutation. In another report, a 3-year-old boy was with CCD was diagnosed with B-cell acute lymphoblastic leukemia. On molecular genetic testing, he had a missense mutation in exon 3 of RUNX2 (c.674G>A) resulting in the replacement of arginine with glutamine at residue 225 (p.Arg225Gln). Cytogenetic studies showed a chromosomal rearrangement leading to ETV6(TEL)-RUNX1(AML1) fusion with loss of wild-type ETV6 in his leukemic cells. Interaction between RUNX1 and RUNX2 was thus suggested. It was suggested that in children with CCD, RUNX2 mutations may act as the "second hit" required for cells expressing ETV6-RUNX1 fusion to undergo leukemic transformation. Given these reports, patients with CCD may be predisposed to developing leukemia.[2,8]

CONCLUSION

With the knowledge of a possible predisposition to certain diseases, this provides an implication in genetic counselling, which is an integral part on the management of patients and families with CCD. It is an autosomal dominant condition, hence the chances of an affected individual passing on the condition to his or her offspring is 50%. This additional information on this condition may help the family to make more informed medical and personal decisions. This report may also contribute in the data needed for a possible recommendation in the future for surveillance in children with a leukemia-predisposing condition.

Ethical Consideration

Informed consent was obtained from the parent of the patient for publication of this case report and the accompanying images.

Statement of Authorship

All authors participated in writing the paper and approved the final version submitted.

Author Disclosure

All authors declared no conflicts of interest.

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REFERENCES

1. Nagaraj T, Nigam H, Balraj L, Gogula S. Cleidocranial dysplasia: A rare case report. J Med Radiol Pathol Surg. 2016 Nov-Dec; 3:9–12.
2. Callea M, Bellacchio E, Fattori F, Bertini E, Callea F, Cammarata-Scalisi F. Acute myeloid leukemia in a 3 years old child with cleidocranial dysplasia. Leuk Lymphoma. 2016 Sep; 57(9):2189-91.
3. Jaruga A, Hordyjewska E, Kandzierski G, Tylzanowski P. Cleidocranial dysplasia and RUNX2 – clinical phenotype-genotype correlation. Clin Genet. 2016 Nov; 90(5):393-402.
4. Mundlos S. Cleidocranial dysplasia: clinical and molecular genetics. J Med Genet. 1999 Mar; 36(3):177–82.
5. Vimalraj S, Arumugam B, Miranda PJ, Selvamurugan N. Runx2: Structure, function, and phosphorylation in osteoblast differentiation. Int J Biol Macromol. 2015; 78:202–8.
6. Wysokinski D, Blasiak J, Pawlowska E. Role of RUNX2 in breast carcinogenesis. Int J Mol Sci. 2015 Sep; 16(9):20969–93.
7. Schnerch D, Lausch E, Becker H, Felthaus J, Pfeifer D, Mundlos S, et al. Up-regulation of RUNX2 in acute myeloid leukemia in a patient with an inherent RUNX2 haploinsufficiency and cleidocranial dysplasia. Leuk Lymphoma. 2014 Aug; 55(8):1930–2.
8. Gardham A, Forsythe E, Goulden N. One in 10 million: a case of cleidocranial dysplasia and acute lymphoblastic leukaemia – more than just a coincidence? Clin Dysmorphol. 2012 Jul; 21(3):170–1.
9. Konda KC, Katkuri D, Reddy KV, Rajan J, Lewis LE. Familial Cleidocranial Dysplasia in a Neonate: A Case Report. Iran J Neonatol. 2018 Jun; 9(2):83-6.