Are great toes always abnormal in patients with fibrodysplasia ossificans progressiva?

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Sir,

We read with interest a recent paper by Kartal-Kaess and colleagues [3] reporting a child who had episodic and progressive heterotopic ossification along with congenitally malformed great toes. On the basis of these findings, a clinical diagnosis of fibrodysplasia ossificans progressiva (FOP) was made and was confirmed by DNA sequence analysis which revealed the classical FOP mutation in the *ACVR1* gene (c.617G>A). The authors concluded that all classically affected patients have congenital malformations of the great toe, and this finding helps in establishing the diagnosis of FOP.

Recently, a few studies [1, 2] analyzed phenotypic variations in patients with FOP along with mutations in the *ACVR1* gene. In the largest study on FOP, so far, Kaplan [2] identified 20 patients with atypical phenotypes, of which five had normal great toes (clinically and radiologically). Also, in a study of Italian patients with FOP, Bocciardi [1] described a patient of FOP with normal toes. All these patients were diagnosed with FOP but experienced episodes of heterotopic soft tissue ossification of milder severity and had mutations in the *ACVR1* gene other than the classical c.617G>A. All the above patients [1, 2] were in their second or third decade of life. We had a similar experience when a child was referred to us for staging of a suspected sarcoma. In addition to sheets of calcification in the paraspinal region on imaging, we noted short broad femoral necks bilaterally with an osteochondroma in the right femur neck and short and broad first metatarsal. Both great toes however were clinically and

radiologically normal. A diagnosis of FOP was then rendered based on the clinicoradiologic features; a mutation analysis was however not performed.

The report by Kartal-Kaess et al. [3] should thus be interpreted with the important caveat that although almost all patients with FOP have great toe abnormalities, the diagnosis can by no means be ruled out in patients with *normal* great toes. These patients, particularly those presenting after the first decade, can have a FOP variant with milder clinical course. In such patients, the diagnosis can be based on the clinical history and other characteristic-associated skeletal abnormalities, as seen in our patient. In equivocal cases, the DNA sequence analysis can provide confirmation, thus avoiding a potential missed diagnosis of FOP.

Conflict of Interest/Financial Disclosures None.

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