Scalp nodules as a presenting sign of fibrodysplasia ossificans progressiva: A register-based study

Maryam Piram, MD,[a,f] Martine Le Merrer, MD,[b,d,f] Valérie Bughin,[e,f] Yves De Prost, MD, PhD,[a,e,f] Sylvie Fraitag, MD,[c,e,f] and Christine Bodemer, MD, PhD[a,f,e,g]
Paris, France

Background: Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder characterized by progressive ossification of soft tissues. Clinical diagnosis is important because trauma from lesional biopsies can exacerbate the disease.

Objective: We sought to evaluate the frequency of scalp nodules as the presenting manifestation of FOP.

Methods: We describe 3 infants with FOP who presented with multiple neonatal scalp nodules. We reviewed all 43 cases of this disorder in the French FOP registry.

Results: Scalp nodules were found in 40% of cases and usually represented the first manifestation of the disease. All 43 patients had characteristic skeletal malformations involving the great toes (n = 43), fingers (n = 12), and vertebrae (n = 3). Other abnormalities were cerebral malformations (n = 1) and alopecia (n = 2). Histopathologic analysis did not contribute to the differential diagnosis and was interpreted as cranial fasciitis in two patients.

Limitations: Our study was retrospective, and the presence or absence of scalp nodules was not always recorded.

Conclusion: Neonatal scalp nodules associated with a characteristic malformation of the great toes are a common presentation of FOP. Physicians should be aware that lesional biopsies can exacerbate the disease and must therefore be avoided. A diagnosis of classic FOP can be confirmed by molecular genetic studies. (J Am Acad Dermatol 2011;64:97-101.)

Key words: fibrodysplasia ossificans progressiva; hallux valgus; heterotopic ossification; neonatal nodules; nodular fasciitis.

Fibrodysplasia ossificans progressiva (FOP) is a catastrophic genetic disorder of the musculoskeletal system characterized by gradual and irreversible soft-tissue ossification.

The course of FOP consists of cranial to caudal, dorsal to ventral, and proximal to distal ossification after spontaneous, postinfectious, or posttraumatic exacerbations, which leads to ankylosis of all major joints. The gene mutation responsible for FOP has been recently identified.[1] There is currently no effective way of halting the progression of this terrible disease. Prevention of soft-tissue injuries, muscle damage, and falls is the cornerstone of FOP management.[2] Early clinical diagnosis is of the utmost importance to avoid harmful diagnostic and treatment procedures. The association of a characteristic congenital malformation of the great toes with tender soft-tissue swellings is highly evocative of FOP.

We describe 3 infants with FOP who presented with neonatal scalp nodules. We reviewed the French FOP register to examine the frequency of

From the Departments of Dermatology,[a] Genetics,[b] and Pathology,[c] and Reference Center for Genetic Bone Diseases,[d] National Reference Centre for Genodermatoses,[e] Groupe Hospitalier Necker Enfants-Malades, Assistance Publique Hôpitaux de Paris[f]; and René Descartes University, Paris V.[g]

Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication April 9, 2010.

Reprint requests: Christine Bodemer, MD, PhD, Department of Dermatology, Groupe Hospitalier Necker Enfants-Malades, 149 Rue de Sèvres, 75015 Paris, France. E-mail: christine.bodemer@nck.aphp.fr.

Published online November 9, 2010.
0190-9622/$36.00

doi:10.1016/j.jaad.2010.04.025

scalp nodules and other clinical signs that may assist with early diagnosis.

METHODS

Three children were referred to our dermatology department between 2004 and 2007, two for evaluation of multiple scalp nodules and one with scalp and cervical nodules. All 3 patients were subsequently given the diagnosis of FOP. We reviewed the French national FOP register, which contains the records of 43 patients (our 3 patients and 40 others) treated in Groupe Hospitalier Necker Enfants-Malades in Paris from 1979 to 2007.

CAPSULE SUMMARY

- Multiple scalp nodules in neonates can be a presenting sign of fibrodysplasia ossificans progressiva (FOP).
- The association of a characteristic congenital malformation of the great toes with tender soft-tissue swellings is highly evocative of FOP.
- Trauma from lesional biopsies may exacerbate FOP and should therefore be avoided.
- The diagnosis of classic FOP can be confirmed by molecular genetic studies.

RESULTS

Case presentation

Clinical and radiologic features. The clinical features of the 3 infants are reported in Table I. The scalp nodules were large, firm, immobile, and painful only at onset (Fig 1, *A*). They grew very rapidly, sometimes reaching the size of a table-tennis ball. The overlying skin appeared normal. The parents reported several exacerbations, after which some nodules regressed spontaneously. Skull radiographs showed soft-tissue thickening only initially, with small areas of ossification 6 to 7 months later. The nodules first appeared during the neonatal period in cases 1 and 2 and in early infancy in case 3.

A diagnostic excisional biopsy was performed in cases 1 and 2, and fine-needle aspiration for cytologic studies in case 3. After surgical excision, a plaquelike indurated lesion appeared around the scars and a new nodule occurred. The clinical course was marked by frequent exacerbations, occurring spontaneously or after infections or trauma. Nodules and subcutaneous indurations developed gradually on the trunk and then on the limbs, progressing to ossification of muscle and connective tissues, and causing irreversible limitation of joint movement (Fig 1, *B*). Radiographic examination disclosed heterotopic bone formation within the soft tissues, and computed tomographic imaging showed lesions separating muscle fibers, without involving the skeleton. All 3 infants had congenital malformation of the great toes (Fig 1, *C* and *D*). Patient 3 also had partial agenesis of the hands and feet with short phalanges, median vermis hypoplasia, agenesis of the corpus callosum, and patchy alopecia.

Histopathologic findings. In patient 1, histopathologic examination of an excised scalp nodule showed proliferation of short spindle-shaped cells in the deep subcutaneous tissue and focally in superficial muscle tissue, randomly arranged within a myxoid stroma or forming short fascicles within a collagenous stroma. Thick collagen bundles were present in some areas, together with scattered mononuclear inflammatory cells and numerous small vessels. The inflammatory cells consisted mainly of T lymphocytes and a few scattered mast cells (c-kit and tryptase-positive). Some cells were smooth muscle actin-positive, and 5 of 100 cells were positive for Ki67 but negative for desmin, CD34, and S100. These findings were interpreted as consistent with nodular/cranial fasciitis (Fig 2). In patient 2, histopathologic analysis of a resected scalp nodule revealed a myofibroblastic proliferation in loose, well-vascularized subcutaneous tissue, associated, in some areas, with an abundant collagenous stroma, focally infiltrating skeletal muscle, and mild chronic inflammation. Scattered mast cells were also seen. Spindle cells were strongly positive for smooth muscle actin, weakly and focally positive for desmin, and negative for CD34 and S100. Based on these features, a diagnosis of cranial fasciitis was suspected. Fine-needle aspiration of a cervical nodule in patient 3 showed proliferation of fusiform cells infiltrating muscle, no inflammatory cells or calcification, and positive staining for smooth muscle actin. The initial diagnosis was fibromatosis.

Genetic studies. The R206H mutation in the *ACVR1* gene was detected in a DNA specimen from patient 1, confirming a diagnosis of classic FOP. Genetic testing was not performed in the other two patients.

Review of the French FOP registry cases

Including the 3 cases described above, the FOP register contained 43 cases (20 female and 23 male). The patients were born between 1954 and 2005 and had been examined in the genetics, pediatrics, or dermatology departments between 1979 and 2007. All had congenital malformation of the great toes and progressive heterotopic ossification after inflammatory soft-tissue swellings. Mean age at FOP symptom onset was 3.3 years (range 17 days-10 years), and