Human Statues: Challenges in Management of Patients with Fibrodysplasia Ossificans Progressiva

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Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder in which soft tissues transform into bone, causing patients to gradually become entombed in their own bodies. Early symptoms typically involve inflammatory lesions that are often confused with a variety of tumours and other conditions, leading to delays in diagnosis and medical procedures that may cause significant detriment. The recent discovery of the FOP gene may help to alleviate this issue, as DNA testing can allow for earlier identification of the condition. A case study is presented to exemplify the challenges faced when treating a patient with FOP, and possible complications are detailed to emphasize the consequences if precautions are not taken. With a specific gene target in sight, it is hoped that treatments can extend beyond supportive care and be able to prevent or halt this debilitating condition.

Introduction

Metamorphosis is defined as the transformation of one normal tissue or organ system into another through a pathological process. Within its realm, heterotopic ossification (HO) describes the abnormal formation of true bone within extraskeletal soft tissues. Fibrodysplasia ossificans progressiva (FOP) is an exceedingly rare genetic disorder which has, until recently, been one of medicine’s most elusive mysteries and the most disabling condition of extraskeletal ossification known in humans.

Genetics

FOP is an extremely rare condition, occurring at a population frequency of about 1 per 2 million with no ethnic, racial, gender or geographic predisposition. The severe disability of FOP results in low reproductive fitness and fewer than ten multigenerational families are known worldwide. Most cases of FOP are sporadic with only one affected individual in a family, though when observed, genetic transmission is autosomal dominant.

A recent breakthrough in the study of FOP was attained with the identification of a recurrent single nucleotide missense mutation in activin receptor IA/activin-like kinase 2 (ACVR1/ALK2). This bone morphogenic protein (BMP) type I receptor causes skeletal morphogenesis, and is therefore the first identified human metamorphogene. The mutation has been reported in all sporadic and familial cases of classic FOP worldwide, making it one of the most highly specific disease-causing mutations in the human genome.

Clinical Features

The classic presentation of FOP is defined by two clinical features: congenital malformation of the great toes and progressive HO. Congenital malformation of the great toes is the earliest phenotypic feature present in all classically affected individuals, who appear otherwise unremarkable at birth. Other skeletal anomalies often associated with FOP include developmental anomalies of the cervical spine, short malformed thumbs, clinodactyly, short broad femoral necks and proximal medial tibial osteochondromas.
During the first decade of life, children with FOP develop painful and highly inflammatory soft tissue swellings (or flare-ups) that progressively and permanently transform connective tissues into heterotopic bone.\textsuperscript{1,3} The ossification in FOP progresses in characteristic patterns that mimic normal embryonic skeletal development, with the first episodes typically occurring along the upper back and neck.\textsuperscript{1,2} However, several muscles including the diaphragm, tongue, extraocular and cardiac as well as smooth muscle are enigmatically spared from the FOP process.\textsuperscript{1}

Interestingly, the clinical features of early involvement in the axial regions differ from those seen in the appendicular regions.\textsuperscript{1,3} Even though swelling appears more rapidly than typically seen with neoplasms, the bulbous lesions which appear on the neck and back are often mistaken for tumours.\textsuperscript{1,3} In the limbs, on the other hand, the swelling is often diffuse and may be mistaken for acute thrombophlebitis.\textsuperscript{1,3}

The natural progression of the disease can also be altered by environmental factors, as any trauma leading to tissue injury has the potential to induce HO. This leads to episodes of explosive and painful new bone growth, with cumulative immobility.\textsuperscript{1,2}

**Case Report**

An 18-month-old boy from Britain presented with a brainstem lesion in need of neurosurgery. He had recently been diagnosed with FOP, and physical exam prior to surgery revealed heterotopic ossification of the dorsal and lumbar paravertebral muscles, the left sternocleidomastoid, and fusion of the C4-C6 vertebrae. Although the brainstem lesion was in this case unrelated to his FOP, his condition nonetheless complicated the procedure to remove it. His montelukast was switched to prednisone to prevent inflammation 24 hours before surgery and continued until four days post-op. Direct laryngoscopy was not possible due to the fusion of his cervical vertebrae, therefore fiberoptic broncoscopy via the nostril was necessary to intubate him. Traumatic injury was avoided by using silicon carpets and a headrest, as well as by padding every point of contact with cotton wool. Because his FOP was recognized and attended to properly, the procedure produced a favourable outcome and the child had no signs of progression of the disease at two months post-op.\textsuperscript{4}

**Complications of FOP**

The case report above illustrates some of the difficulties in managing patients with FOP. Since it is crucial to prevent exacerbations, one of the mainstays of proper care is to avoid the trauma associated with certain medical procedures. Surgeries in particular pose difficulties for patients if, as in the case report, fusion of the cervical vertebrae has occurred and impedes intubation. Anesthesia in an FOP patient can also be extremely difficult if ankylosis of the jaw is present, which could be triggered by something as simple as minor dental procedures.\textsuperscript{4,5} Biopsies are also contraindicated, but since they are the investigation of choice for most tumours, they are often performed before a diagnosis is made.

One of the most severe complications of FOP is cardiopulmonary compromise. FOP can lead to ankylosis of the costovertebral joints, ossification of the intercostal and paravertebral muscles, and progressive spinal deformity such as kyphoscoliosis or thoracic lordosis. Chest expansion is drastically limited, resulting in reduced vital capacity and restrictive lung disease. Right ventricular hypertrophy can also occur due to the thoracic insufficiency.\textsuperscript{5,7}

Patients with FOP are also more prone than the general population to kidney stones as well as conductive hearing loss due to fusion of the bones of the middle ear. They are also prone to fracture of heterotopic bone, which requires closed reduction and splinting, as well as analgesia, as in fracture of normotopic bone in any patient.\textsuperscript{5} Thus, patients should be educated about risk factors for falls to avoid precipitation of a cycle in which a fall leads to further ossification and joint ankylosis, which in turn increases the risk of future falls.\textsuperscript{5,6}
Discussion

FOP is an extremely debilitating disease. Most affected people are wheelchair-bound by their 20s and life expectancy is less than 40, as thoracic insufficiency usually occurs by this point. Patients must live with the constant knowledge that they have a progressive disease. As more and more joints and muscles become permanently ossified over time, patients with FOP are essentially trapped inside their own bodies until they can no longer move or even breathe.

The recent breakthrough discovery of the FOP gene has identified a specific target for pharmacologic therapy and allowed for the development of a DNA diagnostic test which expedites diagnosis and limits harmful interventions. However, the opportunities for insight provided by studying the FOP gene extend far beyond this rare disorder alone. That is, characterization of the underlying mechanism causing HO in FOP has much broader implications for patients with more common forms of HO and for developing tissue engineering strategies for skeletal bone and cartilage repair.

Conclusions

Due to the rarity, variable severity and episodic clinical course of FOP, clinicians often fail to associate the rapidly developing axial soft tissue swellings with the distinctive malformed great toes. When such associations are not made, FOP is commonly mistaken for other conditions, delaying proper treatment. Not surprisingly, misdiagnosed individuals often undergo a battery of unnecessary biopsies and tests that exacerbate progression of the condition. Early diagnosis and cautious management of patients with suspected FOP are therefore very important. Finally, although the current medical management of FOP is largely supportive, the goal of research continues to be the development of treatments that will prevent, halt or even reverse progression of the disease.

References