Juvenile hyaline fibromatosis and infantile systemic hyalinosis: The first two reported cases in the Philippines

Mariecon O. Escuadro-Chin, MD, DPDS; Patricia Anne Z. Pontejos, MD, DPDS and Marie Eleanore O. Nicolas, MD, FPDS

Hyaline Fibromatosis Syndrome (HFS) is a rare, autosomal recessive condition characterized by abnormal deposition of amorphous hyaline material in the skin, joints and visceral organs. It represents a disease spectrum with infantile systemic hyalinosis (ISH) being the severe form with deaths in the first 2 years of life and juvenile hyaline fibromatosis (JHF) being the mild form with survival to adulthood. In both disorders, mental development is normal.

The first case is a 1-year-old male with a coarse facial appearance and gingival hypertrophy, multiple painful joint contractures, frog leg deformity, and characteristic cutaneous findings of multiple erythematous plaques with cobblestone appearance on the neck, back, perianal area and hyperpigmented patches overlying malleoli and metacarpophalangeal joints. He also had recurrent upper respiratory tract infections and intractable diarrhea. The second case is a 4-year-old girl who had a coarse facial appearance, wide-based gait and multiple joint contractures. She had multiple papules and plaques on the head and neck, multiple hard masses of the scalp and digits, gingival hyperplasia and sessile perianal masses. Diagnosis of ISH and JHF, respectively were confirmed by histopathology and skeletal survey.

HFS is a rare genetic disorder and only a few are reported in literature. Our paper highlights the importance of early recognition by presenting the characteristic clinical manifestations and diagnostic work-ups; genetic counselling of both the patients and their families; and the long-term, multidisciplinary approach in the management of such conditions. To the best of our knowledge, these are the first reported cases in the Philippines.

Keywords: Hyaline fibromatosis syndrome, juvenile hyaline fibromatosis, infantile systemic hyalinosis

INTRODUCTION

Juvenile Hyaline Fibromatosis (JHF) and Infantile Systemic Hyalinosis (ISH) are previously two distinct entities that are now considered to be part of the spectrum of Hyaline Fibromatosis Syndrome (HFS) characterized by hyaline deposition in the skin and other organs.

HFS is an autosomal recessive disorder triggered by mutations of gene ANTXR2 (anthrax toxin receptor-2), also known as gene CMG2 (capillary morphogenesis gene-2), located in chromosome 4q21. After Rahman et al. (2002) mapped JHF gene locus on chromosome 4q21, Hanks et al. (2003) and Dowling et al. (2003) identified mutations in the CMG2 gene as the cause of both ISH and JHF, indicating that these disorders are allelic and part of the same phenotypic spectrum. CMG2 is a transmembrane protein that binds extracellular matrix proteins laminin and collagen IV. Abnormal CMG2-laminin contact has been demonstrated in HFS derived fibroblasts, this probably underlies their pathogenesis. The gene is expressed in all tissues with exception of the brain, a finding consistent with normal cognitive development of the affected individuals.

Multiple skin lesions, joint contractures, gingival hypertrophy, osteolyis and osteoporosis characterizes both syndromes. JHF occurs much later in infancy with a milder course and survival into adulthood. JHF typically presents with larger nodules. ISH is more severe with multiple visceral involvement, persistent diarrhea, frequent severe infections, failure to thrive.

and death before the age of two. Overlaps have been reported. HFS remains a stigmatizing and incapacitating disorder. Risks of potentially life-threatening complications in people with HFS, particularly of the ISH form may be due to persistent diarrhea, infections, and malnutrition. There is currently no cure for HFS, and treatment is supportive and generally aims to alleviate the signs and symptoms. Early recognition is invaluable in providing improved outcome of treatment and a better quality of life.

CASE REPORT 1

We describe a 9 month-old Filipino male born to non-consanguineous parents after a normal pregnancy and delivery. He presented at birth with stiffness of both knees and hyperpigmentation of skin overlying the malleoli and metacarpophalangeal joints and an erythematous soft nodule on the left gluteal area. He was also noted to be irritable on joint manipulation; despite this, he had good feeding and activity. At 2 months of age, the patient developed stiffening of both upper extremities, and the knees were already in permanent flexion. He also developed multiple erythematous papules on the neck and the back. During this time, the nodule on the left gluteal area started to ulcerate; he was admitted at the Philippine General Hospital Pediatric ward for 5 days with the diagnosis of a sacral decubitus ulcer and was given IV antibiotics. He was on constant follow up on out patient basis for recurrent upper respiratory tract infections. At 8 months-old, the patient started to have constipation with alternating diarrhea. He also developed rectal prolapse due to straining on defecation and there was increase in number of the erythematous papules on the neck and back. There are no similar conditions in the family but the patient’s older sibling has congenital cataracts.
At the time of consultation, the patient was 9 months old; he was malnourished and weighed only 6.3 kg (<5 percentile) and 70 cm (<5 percentile). Vital signs were normal. There was note of a coarse facial appearance, low set ears, depressed nasal bridge, gingival hypertrophy and clear nasal discharge. Multiple erythematous papules and plaques with cobblestone appearance were present in the neck, back and perianal area (Figure 1). There were hyperpigmented patches overlying the lateral and medial malleoli and metacarpophalangeal joints (Figure 2). All hand joints were in permanent flexion. Shoulder, elbow, hip and ankle joints all had limited range of motion. The knees were in permanent flexion causing a frog leg deformity. Tenderness on joint manipulation was also elicited for all joints. There was also note of rectal prolapse and a hypertrophic scar on the left gluteal area (Figure 3). Systemic physical examination was unremarkable as well as the neurologic and ophthalmologic examination.

Histopathology of an erythematous plaque over the nape revealed homogenous collagen in the papillary dermis with chondroid appearance (Figure 4). Vimentin immunostain was positive (Figure 5). Complete blood count and serum electrolytes were normal. Rheumatoid factor, erythrocyte sedimentation rate, C3, serum VDRL and routine urinalysis and fecalyses were unremarkable. The patient had low albumin probably secondary to a protein losing enteropathy. AST and ALT were 2x and 1.5x elevated raising the suspicion of hyaline deposition in the liver, however, Holoabdominal ultrasound was normal. Intestinal biopsy and upper GI series were however not done to confirm malabsorption. Electromyography and nerve conduction studies showed decreased compound muscle action potential for all extremities but no nerve conduction defects were found. On skeletal survey, there was generalized osteopenia signifying delayed bone growth again consistent with ISH. 12-L ECG and Chest X-rays were normal. Patient is co-managed with Pediatrics. Patient was given oral Paracetamol for pain He was referred to Rehabilitation Medicine for physiotherapy and dietician for nutritional build-up.
CASE REPORT 2

We describe a 4-year-old Filipino girl who was born to non-consanguineous parents after a normal pregnancy and delivery. Her birthweight was 2800 grams and her length was 37 cm. She was normal at birth. At one month of age, there was note of multiple skin-colored, sessile perianal masses. She also had constipation with abdominal pain and distention. At 3 months of age, she developed multiple pearly-pink, pruritic papules and confluent plaques on the head and neck. These progressively increased with age. At nine months of age, patient developed multiple hard non-painful nodules over the scalp, digits and toes. She was also noted to have coarse fascies, low-based ears and broad, infiltrated nose with a depressed bridge. At 1-year of age, there was noted pain upon passive and active movements of the shoulders and elbows. She became irritable when lifted by the arms or dressed. At 2 years of age, there was note of gingival hypertrophy and malpositioned teeth. She had difficulty in reaching objects and combing her hair. She was described to have a characteristic wide-based gait and was unable to catch up with playmates when running. She easily loses balance and falls. Intellect and fine motor skills were at par with age. There are no similar conditions in the family.

At the time of consultation, the patient was 4-years-old. She was malnourished with short stature. She weighed 13.6 kg (<5 percentile) and was 99cm (<5 percentile) in height. Vital signs were normal. Patient has coarse fascies characterized as large, infiltrated, low set ears and a broad infiltrated nose with a depressed nasal bridge. There was marked gingival hypertrophy with malpositioned carious teeth (Figure 6). She had characteristic skin lesions as manifested by multiple confluent, pearly papules with excoriations on the forehead, around the alae nasi, cheeks, chin, earlobes, and neck (Figure 7). There were multiple hard, non-movable, non-tender nodules on the scalp. Many sharply demarcated translucent and doughy nodules with erosions and excoriations were present on the proximal and distal interphalangeal joints of both fingers and toes (Figure 8). Multiple flesh-colored sessile nodules were on the perianal area (Figure 9). She had a limited range of motion over both shoulders and elbows associated with pain on movement. Her gait was wide-based. Her feet showed pes planus. Systemic physical examination was unremarkable as well as the neurologic and ophthalmologic examination.

Histopathology of lesional biopsy specimens from the nape and gingiva revealed a flattened epidermis with an abundance of homogeneous, amorphous, eosinophilic extracellular matrix that contained spindle shaped cells in the dermis (Figure 10). The amorphous material was Periodic acid-Schiff positive and Diastase resistant but did not stain with Alcian blue (Figure 11A). The spindle-shaped cells stained with Vimentin (Figure 11B).

Hematologic and biochemical investigations were normal including complete blood count, electrolytes, renal and liver function tests, rheumatoid factor, erythrocyte sedimentation
rate, C3, serum VDRL and routine urinalysis and fecal examination. Skeletal radiography showed well-defined osseous lucencies in both parietooccipital and distal metaphyseal region of the left humerus (Figure 12). Chest X-ray, Holoabdominal ultrasonography and 12-L ECG were all normal.

Patient was given oral Paracetamol for pain relief and topical antibiotics for secondarily infected lesions. Patient underwent serial excision of perianal masses. She was referred to Pediatrics for co-management, Rehabilitation Medicine for physiotherapy, dietician for nutritional build-up and Dental Services for gingivectomy and oral care.

DISCUSSION

HFS is a rare genetic disorder. ISH and JHF represent both ends of the spectrum. ISH and JHF has a prevalence of <1/1000000 cases. Less than 20 cases of ISH have been reported in literature and only about 70 cases of JHF have been reported. There is no apparent ethnic or gender predilection.

Originally, ISH and JHF were considered as two distinct entities on the basis of onset, with ISH manifesting in the first few weeks of life and JHF at a later onset. However, subsequent work demonstrated that both forms of hyalinosis were caused by mutations in the CMG2 gene (also known as ANTXR2), indicating that these disorders are allelic and part of the same phenotypic spectrum, now known as HFS. While the precise physiologic function of this protein is currently unknown, it was demonstrated to encode a transmembrane protein that links itself to laminin and collagen IV, which suggests alteration in adhesion of the basement membrane to the extracellular matrix and in endothelial cell morphogenesis. This alteration causes extravasation of hyaline material through the basement membrane to the perivascular space, which would explain histological findings observed in both diseases. The gene is expressed in all tissues with exception of the brain, a finding consistent with normal cognitive development of the affected individuals.

The more severe form ISH manifests in the first weeks of life by painful swelling of the skin and the large joints as well as edema of the skin. Overtime, affected individuals develop cutaneous tumors over regions of chronic mechanical stimulation, such as the gingiva, the perianal region, the alae nasi, the external ears and the nuchal region of the skull. In addition, patients suffer from flexion contractures of the joints and osteolytic lesions of the long bones and distal phalanges. ISH may lead to death in the first 2 years of life because of chronic malabsorption and diarrhea or pulmonary infection. Patients suffering from the milder form, JHF, usually do not present with these complications and do not have the infantile painful phase, but do present with cutaneous tumors and debilitating loss of joint mobility. The onset of JHF is later in infancy, usually with severe pain on movement, progressive joint contractures, and pearly papules of the face and neck. These papules eventually coalesce and most often occur on the alae nasi, around the mouth, behind the ears, and the nape. The first sign of joint involvement may be difficulty in leg extension. Complete immobility occurs much later at the age of 4 usually with flexion contractures. In contrast to ISH, larger nodules characterize JHF. These large cutaneous tumors occur on the scalp, trunk, and extremities. They may be soft or...
hard and calcified and may eventually ulcerate. Perianal masses develop and grow slowly. Doughy nodules occur on the hands. The skin may be thickened and hyperpigmented over joints. Gingival hypertrophy is prominent leading to irregular teeth growth. Problems with hygiene lead to tooth decay. Difficulty in mastication may contribute to malnutrition. Punched out osteolysis usually occurs, especially in the terminal phalanges. Osteopenia, osteoporosis, and short stature have been described. Cognitive development is normal and patients survive into adulthood.

Other disorders that may share similar features with JHF and ISH include Lipoid Proteinosis of Urbach and Wiethe, Winchester Syndrome, and Multicentric Infantile Myofibromatosis. Lipoid Proteinosis is a rare autosomal recessive genodermatosis also characterized by deposition of hyaline material in the skin, mucosa and viscera. Patients of this case initially present with inflammatory, vesicular and crusted eruptions and later become diffuse, thickened and waxy in appearance. Patients, however, present with hoarseness, temporal lobe calcification, seizures, learning disabilities and rage attacks. Winchester Syndrome, an extremely rare connective tissue disease is characterized by patches of thickened, hyperpigmented skin with hypertrichosis; gingival hypertrophy, severe joint contractures, generalized osteoporosis, and corneal opacities. In Multicentric Infantile Myofibromatosis, patients present with multiple nodules in the skin, subcutis, muscle, bone and internal organs brought about by hyperproliferation of myofibroblasts. The gums and joints are spared.

Other deposition disorders that may share similar symptoms include Farber Disease, Mucolipidosis and Stiff skin syndrome. Farber Disease is characterized by accumulation of ceramide with progressive tissue destruction particularly of the joints, liver, lungs and nervous system. Patient presents with painful joint contractures, progressive hoarseness and skin nodules over bony prominences. However, patients usually have neurologic involvement and do not present with hyperpigmented patches compared to HFS. Patients die by the age of 2, usually from lung disease. Mucolipidoses are a group of autosomal recessive disorders characterized by accumulation of mucolipids and mucopolysaccharides. One subtype is I-cell disease characterized with coarse facial features, gingival thickening, joint contractures, dysostosis, organomegaly and recurrent respiratory tract infections. Patients usually die before 7 years old due to congestive heart failure or respiratory tract infections. Another subtype is Pseudohurler polydystrophy, a less severe form of I-cell disease characterized with coarse facial features, joint stiffness, scoliosis, deformities of the hand, corneal clouding, mental retardation and heart disease. Skin findings in HFS usually distinguish from these two. Stiff skin syndrome is characterized by mucopolysaccharide deposition with thickened skin, flexion contractures, recurrent episodes of stiffness and spasms, stiff gait and early deaths.

The diagnosis of JHF and ISH is based on clinical findings, histopathologic demonstration of hyaline deposition and molecular genetic testing. The discovery that CMG2 mutations result in the allelic disorders JHF and ISH, provides a noninvasive molecular diagnostic tool, defines these two diseases as being on either end of the same disease spectrum, and highlights novel information on the in vivo function of this integrin-like cell surface molecule and its role in key developmental and physiological processes. Histopathological demonstration of hyaline material in the dermis confirms the clinical diagnosis. The hyaline material appears as an amorphous eosinophilic substance that is Periodic acid Schiff (PAS) positive and Diastase resistant. The spindle-shaped fibroblasts dispersed in abundant amounts of hyaline material are Vimentin positive.

Electron microscopy demonstrates cells filled with fine, fibrillar material with an enlarged endoplasmic reticulum and Golgi apparatus. Internal organ involvement (gastrointestinal tract, lymph nodes, spleen, cardiac muscle, skeletal muscle, thyroid gland, adrenal gland, lungs) with hyaline deposition has been reported with HFS. Intestinal biopsy and imaging may show villous atrophy, edema, lymphangiectasia and hyalinosis. Imaging shows rapid transit time in real-time upper GI imaging studies. Abdominal distention, intractable diarrhea, and elevated fecal alpha-1 antitrypsin levels characterize a protein losing enteropathy in ISH patients. Skeletal survey shows osteopenia, periosteal reactions and lucent lesions. These skeletal changes usually affect the long bones and axial skeleton. Myopathic changes on muscle biopsy may be evident. Appropriate evaluations may be necessary when internal organ involvement is suspected. Risk of cardiomyopathy prompts a cardiovascular evaluation. Hearing, eyesight and mental development are almost always normal.

There is no specific treatment for HFS. The severity of HFS can vary broadly. The long-term prognosis depends on how severely the patient is affected. Overall, the prognosis is poor, especially for those with systemic involvement. In all patients, it is important to establish the extent through complete nutritional evaluation, evaluation for immune deficiency, evaluations for internal organ involvement and genetic counselling.

Pain management is the mainstay treatment in patients with ISH and JHF. Non-steroidal anti-inflammatory drugs (NSAIDs), opiates and possibly gabapentin may be used for pain control. Gentle handling is a necessity and splinting of affected joints may provide comfort. Referral to a pain management specialist may be helpful and palliative care may be an option for severe cases. Skin lesions involving the intertriginous areas are prone to dermatitis and secondary skin infections and should be addressed promptly. Lesions that obstruct the airway or interfere with oral intake are particularly problematic. Partial gingivectomy for gingival overgrowth offer short term improvement and may be repeated as necessary.
in 2007 combined full mouth gingivectomy with consistent oral hygiene and concluded aesthetic and functional success in a two year follow-up.3,4 Proteolytic enzymes has also been tried for gingival hypertrophy but no significant regression was noted.3,5 Recurrent excision of cutaneous tumors may be done for cosmetics and improved function.5,27,36,37 Bedford et al. attempted intralesional steroid injections for dermal lesions with very limited response.35 Raney et al. used chemotherapy, radiotherapy and endocrine-based therapy (antiestrogens and progesterational agents) for recurrent or unresectable fibromatosis in children and showed regression of tumors in some of the patients.38 Perianal masses can be resected but with a high recurrence rate. Nakipoglu et al. in his report of the rehabilitation of 3 siblings with JHF, demonstrated the great value of rehabilitation in preventing contractures and their progression, and in stopping functional loss.39 Gentle physiotherapy of painful contractures can be carried out.33,36 The contractures can also be diminished by capsulotomy, but improvement is transient.3,35 Although the prognosis is good with capsulotomy, the final outcome is that patients are left with deformities.40 Orthopedic Surgery followed by local radiotherapy and physiotherapy may be tried for intraosseous lesions, however, functional prognosis is poor 41. O’Neill and Kasser stated that operative release is contraindicated, as it can result in activation of hyaline fibromatosis.42 In contrast, Suzuki et al. believe that when gentle physical therapy fails to improve range of motion, surgery is indicated.43 Oral Penicillamine has been used in some cases and improved joint mobility and flexibility with variable success.30,37 Therapeutic trials with dimethyl sulfoxide, ketotifen and calcitriol have been attempted to decrease contractures, however, improvements were transient.44 Routine nutritional assessment is appropriate. Periodic assessment for gastrointestinal malabsorption may aid in optimizing nutritional status. Nasogastric tube or gastrostomy tube feeding may be considered. Co-management with a nutritionist is recommended. Chronic diarrhea and protein-losing enteropathy with subsequent edema are treated with hydration and albumin infusions; an effective long-term treatment is lacking. The effectiveness of dietary therapies with intestinal lymphangiectasia is not known.45,46 Because of the rarity of JHF and ISH, there is no sufficient experience concerning the effectiveness and long-term results of these treatments. Given the chronic nature of this disorder and the patients having normal intelligence, family counseling should be considered in order to develop coping strategies for both the patient and the immediate family. The Inherited Systemic Hyalinoses remain a stigmatizing, incapacitating and sometimes fatal disorder with no satisfactory treatment.47 The discovery of the responsible mutations provide the basis for diagnostic testing, genetic counseling for families and a potential target for gene therapy in the future. Early recognition is invaluable in providing improved outcome of treatment. We highlight the value of early recognition and diagnosis, genetic counselling and multi disciplinary approach in the management of HFS.

REFERENCES


