

## Farber`s Disease: A Case Report

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### Abstract

**Background:** Farber`s disease also known as disseminated lipogranulomatosis is a very rare disorder of lipid metabolism inherited in autosomal recessive pattern. It is primarily a childhood disorder with defect in ceramide degradation due to deficiency of acid ceramidase within the lysosomes. Clinical features include joint pain and swelling, subcutaneous nodules along with a hoarse voice. In the absence of typical features diagnosis is made either by, measurement of acid ceramidase activity within the cultured skin fibroblasts, white blood cells, amniocytes or by documenting typical histopathological findings on skin/ subcutaneous tissue biopsy. Stem cell transplantation has an important role in treatment of patients who present without any central nervous system findings.

**Case presentation:** We present a case of 2 years old boy diagnosed as juvenile idiopathic arthritis. Detailed history and examination pointed out a possibility of Farber`s disease. Histopathology of a skin nodule confirmed the diagnosis.

**Conclusion :** Farber`s disease being a very rare entity can often be misdiagnosed as juvenile idiopathic arthritis due to many similarities between the two at the time of presentation. This is the second recorded case of Farber`s disease in Pakistan.

**Key words:** Farber`s disease, disseminated lipogranulomatosis, scid ceramidase, juvenile idiopathic arthritis.

### Introduction

Farber`s disease is a very rare, autosomal recessive disorder first described by Sidney Farber in 1957 and named it "disseminated lipogranulomatosis" (Farber et al, 1957).<sup>1</sup> It is an inherited metabolic disorder due to deficiency of lysosomal acid ceramidase, this leads to accumulation of ceramide within the tissues.<sup>2</sup> The underlying pathology is an ASAH1 gene mutation that encodes acid ceramidase.<sup>3</sup> Typically a triad of subcutaneous nodules, joint pain and progressively deformed joints, and hoarseness of voice due to laryngeal involvement is present early on. The subcutaneous nodules are usually present near the joints, most commonly involving the interphalangeal,

wrist, elbow and ankle joints, or over areas of mechanical pressure. This leads to painful joints and subsequently to progressive joint stiffness, limitation of movement due to contractures and finally to immobilization and deformation of joints.<sup>4</sup> Other organs involved include liver, lungs, heart, spleen, lymph nodes and the nervous system.<sup>5, 6</sup> Seven different phenotypes of the disease have been described.<sup>7</sup> Subtype 1 is the classical form with early subcutaneous nodules, joint involvement and hoarseness. Neurological involvement and pulmonary involvement occurs later on.<sup>4</sup> Subtype 2 and 3 show little or no neurological involvement but subcutaneous nodules, joint pain and contractures, hoarseness,

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**Contribution of Authors:** Dr Syed Afaq Ahmed and Dr Anwar-ul- Haq were involved in diagnosis of the case on histopathology. Dr. Muhammad Erfan drafted the paper, searched the literature and contributed to paper writing. All authors approved the final manuscript. □

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failure to thrive and respiratory involvement occurs<sup>4</sup>. Subtype 4 present with severe neurological deterioration and large hepatosplenomegaly in the neonatal period.<sup>8</sup> Subtype 5 has a progressive CNS dysfunction.<sup>9</sup> Subtype 6 is combination of subtype 1 and Sandhoff disease<sup>10</sup> Subtype 7 has combined deficiencies: glucocerebrosidase, galactocerebrosidase and ceramidase<sup>11</sup>. Patients with the CNS involvement generally have a grave prognosis<sup>7</sup>. Indeed apart from subtype 7, the most severe form is subtype 4.<sup>12-14</sup> Death due to pulmonary involvement mainly interstitial pneumonia may also occur. Milder forms of the disease have also been recognized, these are those subset of patients who do not have CNS involvement and are often misdiagnosed as having juvenile idiopathic arthritis<sup>15</sup>. In a typical case the triad of subcutaneous nodules, joint and laryngeal involvement is sufficient to make the diagnosis, however, in atypical cases or where in doubt, disease confirmation can be done via measurement of acid ceramidase activity, that is <6% of control values as measured in leucocytes, amniocytes or in the cultured skin fibroblasts<sup>4</sup>; or by looking for the typical histopathological features on biopsy- foam cells in the early lesions and granulomas together with foam cells in more advanced nodules. Diagnosis can also be made by measuring Ceramide levels using mass spectrometry or chromatography. Hematopoietic stem cell transplant is the cornerstone of treatment in patients without the CNS involvement.<sup>16</sup>

### Case presentation

A 2 years old boy presented in the pediatrics outpatient department for the evaluation of intermittent fever, joint pains and joint nodules. (Figure 1). History from the mother revealed that the boy was the firstborn; gestation and the neonatal period were without any complications. The parents were related. Detailed history showed that the first symptoms appeared at the 5<sup>th</sup> month of age with pain during movement of hands. By the 6<sup>th</sup> month the patient developed swelling, involving the small joints of hand and feet. The patient was subsequently diagnosed with and treated for juvenile idiopathic arthritis. Medications initially included NSAIDS and

subsequently oral methotrexate and steroids. However the patient continued to have joint pains and started developing joint nodules first involving the interphalangeal joints and metacarpal joints of the hand (Figure. 2 & 3) and subsequently the interphalangeal joints of the feet Figure. 4). By this time around 1.5 year of age the patient had also developed a hoarse voice. 18 months into treatment the patient's pain and joint movement had improved a little. Patient now started developing intermittent fever and shortness of breath. He was diagnosed and treated for asthma and pneumonia on two occasions within 2 months duration.



Figure 1. Patient with Farber's disease



Figure 2. Interphalangeal and metacarpal joint involvement



Figure 3. Interphalangeal and metacarpal joint involvement

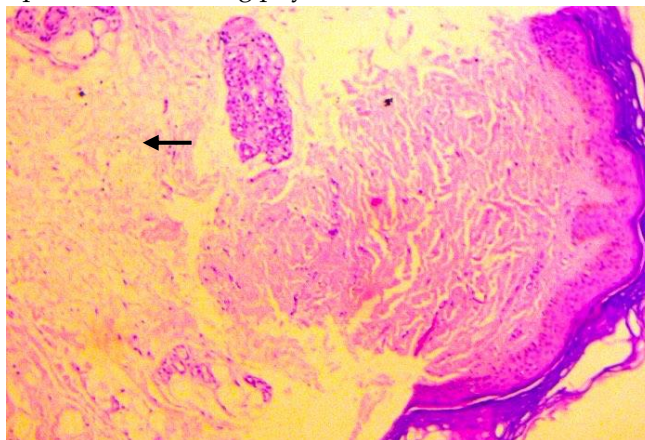


**Figure 4. Involvement of interphalangeal joint-feet**

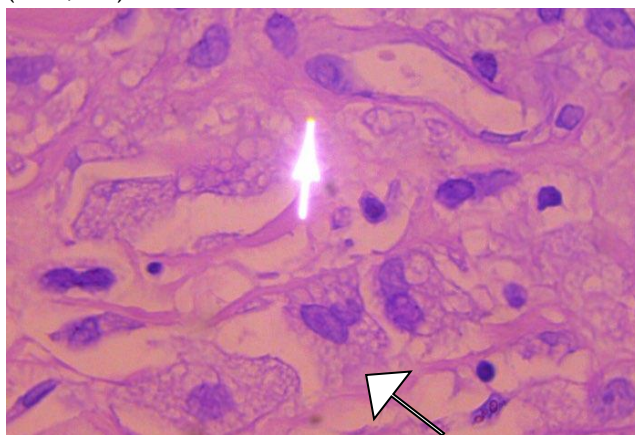
Considering the development of skin nodules, hoarse voice and recurrent respiratory tract infections, diagnosis of Farber lipogranulomatosis was suggested and the patient referred to the dermatology unit for evaluation and biopsy of the subcutaneous nodule (as the other confirmatory tests for the disease are lacking in the country). On examination the patient was of average built and height, normal for his age. Vitals were within normal limits except for an increased respiratory rate- 30 breaths per minute. Systemic examination revealed bilateral, biphasic, polyphonic rhonchi with a prolonged expiratory phase. CVS and GIT examination was normal. CNS examination showed no focal deficit. Cranial nerves were intact. No motor or sensory loss was noted. Local examination showed bilateral involvement of interphalangeal and metacarpal joints with slight flexion deformity of the hands (Figure. 2 & 3). There was no swelling. Interphalangeal joints of the feet were also involved (Figure.4).

The skin Subcutaneous nodule biopsy from the left hand interphalangeal joint was taken for histopathology. The microscopic sections revealed hyperkeratosis, slight to moderate atrophy of the epidermis. The dermis had increased collagen content. The small dermal vessels were telangiectatic and compressed by moderately large xanthomatous cells with distinctly bubbly cytoplasm. Fairly large number of these cells were identified. (Figure 5& 6). The dermis and subcutaneous tissue also displayed increased number of capillaries and fibrosis (Figure 7). The findings were quite consistent with Farber's

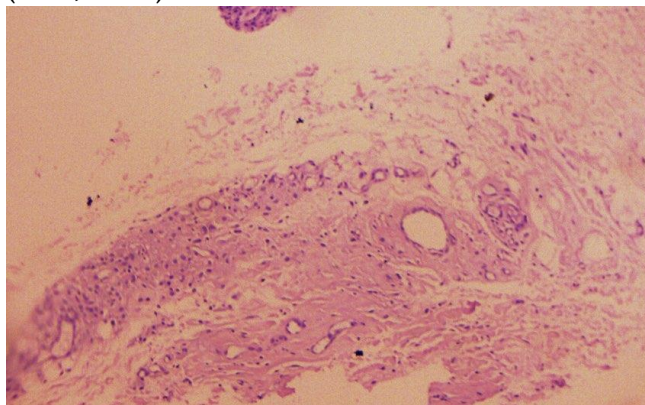
disease. The patient's family was counseled about the nature of the disease, its course and the possible treatment option. They were also advised strict follow-ups with the treating physicians.



**Figure 5. Biopsy of subcutaneous nodule showing cluster of storage cells as they become vacuolar (black arrow) (H&E, x40)**



**Figure 6. Foam cells (lipid Leiden macrophages) (H&E, x1000)**



**Figure 7. Dense fibrovascular stroma with adjacent foam cells (H&E, x100)**

## Discussion

80 cases of Farber's disease have been reported so far<sup>17</sup>. The clinical presentation of Farber's disease consists of joint pain and swelling along with development of subcutaneous skin nodules, usually in the vicinity of or on the joints- interphalangeal, wrist, elbow and ankle joints, or over points of mechanical pressure. The joint pain, swelling and subcutaneous nodules lead to limitation of motion and subsequently development of contractures. Hoarseness of voice is also noted to be cardinal feature of Farber's disease. Our patient had all these features starting with joint pain, swelling, subcutaneous nodules and a hoarse voice.

Hepatomegaly or hepatosplenomegaly occurs in 25% of patients. Beside the major manifestations other organs like lungs, liver, lymph nodes, heart and nervous system may also be involved. But these were not present in our case. Depending on the severity and clinical manifestations seven different phenotypes have been identified. Our patient had milder form of the disease without CNS involvement.

In a typical case the triad of joint involvement, a subcutaneous and laryngeal nodule is enough to make the diagnosis. However, in an atypical case diagnosis can be confirmed by measuring the acid ceramidase level, also mass spectrometry and chromatography to measure ceramide levels can be used for diagnosis; unfortunately these modalities are not available in the country. Another approach is to look for classical histopathological finding on biopsy of skin nodules. These findings include presence of granulomatous inflammation along with foam cells and a fibrovascular stroma. Our case had findings of foams cells along with fibrovascular stroma. Absence of granuloma in our case may be due to the early stage of the disease.

Due to its rare occurrence many patients are misdiagnosed as having juvenile idiopathic arthritis, as happened in our case. Early onset, nodule formation around joints, deposits of lipogranuloma in other sites, and hoarseness of voice etc help to differentiate it from JIA.

Hematopoietic stem cell transplantation can be used to treat patients of Farber's disease without CNS

involvement. This is the preferred treatment in our case.

Further work is needed to come up with a definite treatment of this rare entity, especially in those patients who have CNS involvement.

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