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Farber Disease Case Study: Don’t Miss the Diagnosis

Announcer:
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Dr. Sutton:
Hello, I'm Dr. Reid Sutton from Baylor College of Medicine and I will be presenting a case of a 14-year-old male whose initial presentation was at about 17 months of age where parents had noted difficulty walking. He was referred to a pediatric orthopedic surgeon who noted subcutaneous nodules on the soles of the feet as well as on the arms and the legs.

Physical examination and X-rays revealed synovial thickening of the elbows, wrists, knees, and ankles. And on physical examination, there were flexion contractures of the fingers as well as limited range of motion at the ankles. And in addition, there seemed to be pain with passive range of motion at the limits of the end of the range of motion. Family history is notable for an older brother with Blau syndrome and both parents are well. And so this individual was diagnosed with Blau syndrome. Blau syndrome is an autoimmune granulomatous inflammation involving the skin, the eyes, and the joints. It may present as a papular red rash, which may be transient and then individuals can develop arthritis as well as minimally erosive swelling of the wrists, ankles, knees, and elbows. Presentation is typically before four years of age.

In addition, individuals with Blau syndrome develop progressive flexion contractures of the fingers as well as non-caseating granulomas of the skin, subcutaneous tissue and joints. Uveitis is often present, which can lead to glaucoma and less common features include cranial neuropathies as well as arthritis. Blau syndrome is due to heterozygous pathogenic variants in the NOD2 gene which results in aberrent NF-κB signaling. So back to our case, he was initially treated with naproxen sodium and methotrexate at 30 months of age due to limited improvement. Etanercept was added as a weekly injection. At 34 months of age, it was thought that there may be some improvement in walking as by subjective parental report, but no significant change was noted at three and a half years of age.

The note from the rheumatologist noted that he had not been doing well mainly because of ongoing diffuse arthritis continued development of new subcutaneous nodules, occasional low-grade fevers, and based upon these findings, prednisone and adalimumab were added to his regimen. About six months later, there still was no improvement with joint pain and limited mobility, difficulty wearing splints due to pressure on nodules and joint contractures, continued intermittent fevers and therefore the adalimumab was stopped. The dose of methotrexate was increased and IV solumedrol and IV etanercept were added back to the regimen.

Diagnostic studies around this time included radiographs and laboratory studies on X-rays. There were multiple areas of soft tissue prominence in the periarticular regions that were noted and thought to represent synovial inflammation or cysts. There was mild elevation of the sedimentation rate as well as aldolase enzyme, but other studies including creatine kinase with enzyme fractionation, IgA, IgM, IgG levels, complete blood count, lactate dehydrogenase, c-reactive protein and lysozyme were all normal. Sequencing of the NOD2 gene was performed and revealed a deep intronic variant. The laboratory reported this as a Crohn's syndrome susceptibility allele in individuals of Eastern European Jewish ancestry. However, it was also known to occur with about a 10% incidence in an unaffected

white population.

The interpretation in the clinic notes from the treating physicians noted that it was not known if this variant was pathogenic. In the intervening 10 years, there was continued progression of subcutaneous nodules and joint contractures is seen in the images on the right with the nodules in the hands the antihelix of the ear and the soles of the feet. In addition to continued immune modulating, medications that were prescribed, multiple surgeries and injections of the nodules were performed to try to improve pain and mobility with limited success. An autoimmune gene panel was sent. There were no pathogenic variants detected in the NOD2 gene.

However, in the ASAH1 gene, there was a stop-gain variant that was interpreted as pathogenic and an intronic variant that was interpreted as likely pathogenic. These were confirmed in trans by parental testing and were also confirmed in the older sibling. ASAH1 is related to a spectrum of disorders that range from infantile onset fiber disease to spinal muscular atrophy with progressive myoclonic epilepsy. The pathogenicity of these alleles was further confirmed by leukocyte acid ceramic enzyme activity where this individual had about a 3% enzyme activity level compared to controls. So there is a range of disorders related to ASAH1.

This includes classic Farber disease or type one which is the most common form. Onset is typically within the first week of life. And the classic triad of this Farber disease is progressive joint deformity, subcutaneous nodules of the joints and pressure points as well as a hoarse cry that's due to granulomas of the larynx and epiglottis. Other features that may occur include lower motor neuron disease, a macular cherry red spot, and pulmonary infiltration and the life expectancy is typically less than two years of age.

Type two is also called intermediate Farber disease with onset at about eight months of age, but otherwise similar symptoms to type one. Type three or mild Farber disease typically has onset after one year of age, and individuals with this form of disease are often misdiagnosed as juvenile idiopathic arthritis. About half of these will have a neurologic involvement and life expectancy is into the teens. Type four is a neonatal-visceral form which is principally enlarged liver and spleen of neonatal onset without the classic triad seen in classic Farber disease. And then type five is the neurologic form where there is normal development for the first month of life followed by developmental regression refractory epilepsy, and paraparesis. Thank you for your time and I hope you found the case educational.

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