An Unusual Presentation of Neurofibromatosis Type 2
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INTRODUCTION
Coffin-Siris Syndrome is a rare genetic disorder with just over 60 individuals diagnosed within a span of 30 years1. A coexisting diagnosis of Neurofibromatosis Type 2 (NF2) is an unusual occurrence, with no other known cases currently reported in the literature. Hence, the clinical presentation as well as the unique radiologic and pathologic correlations are discussed.

CASE REPORT
A 27-year-old male with a history of Coffin-Siris Syndrome presented with progressive neurological dysfunction below the level of T11. An MRI of the spine and CT myelogram showed several paraspinal lesions in regions T11-L3 which were surgically resected and found to be consistent with schwannoma. An MRI of the brain and head displayed a mass consistent with schwannoma likely involving cranial nerves 7-10 extending into the hypoglossal canal, multiple smaller masses on the right lower cranial nerves, bilateral chronic otomastoiditis, and a left lateral tongue mass. By history, the patient reported bilateral hearing loss and chronic otorhea, but denied worsening dysphagia or threatening signs of airway obstruction. Examination revealed coarse facies, short stature, severe MR, significant 5th digit nail hypoplasia, lower extremity weakness and spasticity- all findings consistent with Coffin-Siris Syndrome. Ear exam showed left-sided otorhea and bilateral tympanic membrane perforations. He also showed evidence of macroglossia and a palpable firm, rubbery left lateral tongue mass, approximately 2.5x2.1 cm, not involving the tongue base. An FNA of the left tongue mass showed spindle cells with immunohistochemical stains favoring neural origin. Given the lack of urgency, a conservative treatment plan was implemented to clinically monitor the tongue mass until worsening symptoms warranted surgical intervention.

Further neuro-otologic workup was performed. Pt had a presumed diagnosis of Neurofibromatosis Type 2 (NF2) based on the presence of a left vestibular schwannoma before the age of 30 and multiple spinal schwannomas. A CT of his temporal bones was obtained showing bilateral sclerotic mastoid cavities and chronic changes consistent with otomastoiditis. Sedated ABRs showed bilateral moderately-severe to severe mixed hearing loss in low frequencies and sensorineural hearing loss in mid to high frequencies. No surgical intervention was initiated given the active MRSA infection as well as the family’s decision to refrain from surgical treatment at the time.

A follow-up MRI was obtained 3 months later showing progressive schwannomatosis. Further genetic evaluation was performed and his NF2 genetic test was found to be negative. Pediatric hematology/oncology recommended medical chemotherapy to treat the multifocal progressive schwannomas. Consequently, the patient is currently participating in a new clinical trial involving Avastin therapy for the treatment of progressive schwannomatosis. He will undergo therapy for 8 weeks after which he will be reimaged to monitor for clinical response to treatment.

DISCUSSION
In 1970, Coffin and Siris reported 3 female patients with a distinct clinical pattern, including severe mental retardation, growth delay, coarse facies, lax joints, and hypoplastic or absent fifth distal phalanges and nails2,3. Since then, additional cases of Coffin-Siris Syndrome have been reported, representing a rare genetic disorder with just over 60 individuals diagnosed within a span of 30 years1. Etiology of this syndrome remains unknown. Although the inheritance pattern is undetermined, most cases are reported as autosomal recessive, but autosomal dominant has been infrequently described2. Patients typically have a normal karyotype. No biochemical, molecular, or cytogenetic diagnostic tests exist and specific diagnostic criteria is not well established1. Diagnosis is based solely on clinical findings. Significant variable phenotypic manifestations may involve multiple organ systems. Specific head and neck features include coarse facies (eg. flat nasal bridge, broad nose, wide mouth, thick lips, high arched palate, abnormal ears), ptosis, short philtrum, abnormal delayed dentition, hearing loss, chronic otitis media, and macroglossia4-6. Minimal criteria for diagnosis include developmental delay, coarse facial appearance, hirsutism, hypoplastic or absent fifth fingerprints/toenails, or fifth distal phalanges5. Additional findings to support a diagnosis include feeding difficulties, frequent infections, delayed dentition, and cardiac defects1.

Neurofibromatosis Type 2 (NF2) is a genetic neurocutaneous disorder with numerous manifestations and wide phenotypic variability. The incidence is estimated approximately 1:40,0007. More than 200 mutations have been identified on the NF2 gene (merlin) on chromosome 22. A negative NF2 genetic test, however, does not exclude a diagnosis, as the test is not able to identify all NF2 gene mutations. Inheritance patterns is autosomal dominant with 95% gene penetrance. Fifty percent have no family history, representing a new germ line mutation7. Bilateral vestibular schwannomas is the hallmark sign of NF2. Symptoms typically manifest in the second and third decades with variable clinical presentation. Fifty percent present with hearing loss that is often progressive with poor speech discrimination7. Other manifestations include juvenile subcapsular lenticular opacities, retinal abnormalities, and muscular weakness. Greater than 80% develop spinal schwannomas, warranting all patients to obtain a baseline MRI of the spine8. Intracranal involvement ranges between 4-7%, but may be higher9,10. The tongue is the most common site for intracranal neurofibromas and may involve the lips, palate, buccal mucosa, gingiva, and floor of mouth11,12. Macroglossia and enlargement of fungiform papillae are commonly seen. Specific diagnostic criteria for NF2 has been well established.

Coexisting diagnosis of Coffin-Siris Syndrome and Neurofibromatosis Type 2 is an unusual occurrence, with no other known cases currently reported in the literature. It is unclear if the multiple schwannomas are related to the patient’s underlying Coffin-Siris Syndrome or represent coincidental findings involving 2 separate disorders. In addition, this case may represent a new variant of Coffin-Siris Syndrome. Although the inheritance pattern of Coffin-Siris Syndrome is nonconclusive and NF2 is autosomal dominant, frequent new mutations can occur and may involve chromosome alteration encompassing both the NF2 locus and putative Coffin-Siris locus. Alternatively, other unreported cases may exist due to incomplete diagnostic testing or lack of formal documentation in the literature. Nonetheless, the association between these 2 disease processes is significant and warrants further investigation.

REFERENCES