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INCORPORATED IN FLORIDA

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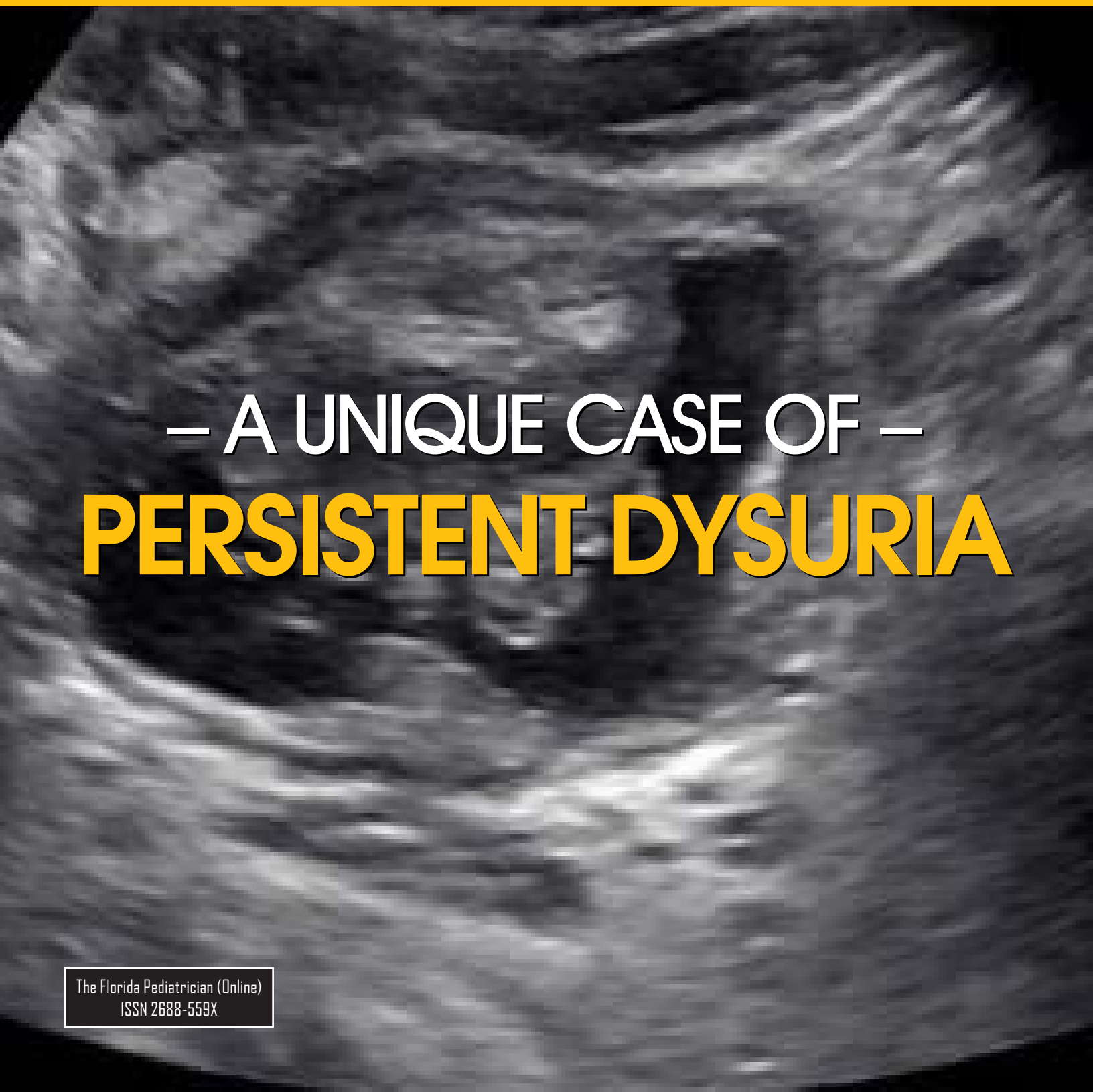

– A UNIQUE CASE OF –

PERSISTENT DYSURIA

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EDITOR'S NOTE

Dear Readers,

Well folks, it seems in Florida we are all getting a break from COVID infections, for now at least. We must stay vigilant since COVID cases are increasing in the northeast, and, historically, Florida trails the northeast by a few months to a few weeks before cases increases. Even still, this is an opportunity to immunize as many eligible children as possible with the approved COVID vaccines.

While we are getting a break from COVID, several other child health issues are requiring our attention and our advocacy.

There is an outbreak of meningococcal infections in Florida. This is a good time for pediatricians to remind their families that those who are eligible for the meningococcal vaccine should get their immunization against meningococcal infection updated. The vaccine is safe and highly effective. The meningococcal infection is usually difficult to diagnose early and can be deadly if diagnosed late, so vaccination is paramount.

There is also a mysterious strain of hepatitis that is specifically affecting children less than 6 years of age. Initially seen in several European countries, cases have now been reported in Alabama and North Carolina. Two children in Alabama required a liver transplant. Fortunately, no child has died from hepatitis. The usual causes of infectious and toxic hepatitis have been excluded in these children. Currently, adenovirus is being investigated as a possible cause. So stay tuned. In the meantime, if you see children with hepatitis and you have not diagnosed them with the usual and known causes of hepatitis, please consult your friendly infectious diseases specialist. If truly no cause of hepatitis is identified, these cases of hepatitis should be reported to local and state health departments so that they can be reported to the CDC so that additional investigations are done as needed.

Of course, the major issue facing children in Florida is an assault on good healthcare practices for children. After the first salvo of attacks by the ill-conceived decision not to support COVID vaccinations for children, additional measures are being taken to prevent good healthcare services for children. Now, treatment of gender dysphoria for children and adolescents is under attack. A missive that went out to all healthcare providers mischaracterizing the evidence supporting treatment of gender dysphoria for children and adolescents as a dangerous path on how we provide care for children in Florida. This should alarm all pediatric advocates. Healthcare decisions should be based on science and not ideology.

Documents from several professional societies have looked at this issue carefully and evaluated the risk and benefits of treatment of gender dysphoria in children and adolescents. These are complicated issues that require joint decision making that includes the patient, family, and their pediatrician. Each case is unique and the decision for treatment must be individualized. Government has no place in determining how and when a patient needs any treatment. Science and evidence should guide these decisions. This is a slippery slope and that allows government or, potentially, a legislature to become a party in the examination room and in the shared decision making process. What will be next? The physician-patient-family relationship is sacred, and we cannot let big brother dictate what science and evidence dictates and what professional societies advise after careful consideration of all aspects of transgender issue. The American Academy of Pediatrics offers excellent guidance for this issue (https://publications.aap.org/pediatrics/article/142/4/e20182162/37381/Ensuring-Comprehensive-Care-and-Support-for); the Pediatric Endocrine Society is the profession specialist organization that treats and manages these issues offers evidence based guidance (https://pedsendo.org/patient-resource/transgender-care/); the Profession Group of Endocrinologists offers a comprehensive source for information and transgender care https://www.endocrine.org/advocacy/position-statements/transgender-health).

The need for advocacy is critical, now more than ever. Your chapter, with your support, continues to work on these and other issues of importance for children. Please let us know how we can support you in your advocacy efforts.

Mobeen H. Rathore, MD, CPE, FAAP, FPIDS, FSHEA, FIDSA, FACPE
Editor, The Florida Pediatrician

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CASE REPORT

A Unique Case of Persistent Dysuria in a Pediatric Patient

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ABBREVIATIONS

UTI (Urinary Tract Infection), LE (leukocyte esterase), CFU (colony forming units), TUBRT (Transurethral Resection of Bladder Tumor); CT (computed tomography)

CASE NARRATIVE

A 10-year-old, unimmunized female, developmentally appropriate child presented with a chief complaint of painful urination, which had been ongoing for 3-4 months. She had not been evaluated by a medical provider in 7 years as mother believed in holistic medicine. Patient was reported to be a previously healthy female who was not taking any daily medications. Her initial symptoms included dysuria, feeling of pressure while urinating, and a small amount of urine leakage on underwear. Upon initial evaluation at an urgent care clinic, her symptoms were thought to be due to ligamentous or muscular strain while overstretching in ballet. Therefore, she stopped ballet. However, as her symptoms persisted, the patient was taken to the local emergency department (ED), where she was treated for a urinary tract infection (UTI). Mother could not recall details of testing at the ED or the antibiotic given and records were unavailable. Despite treatment, there was no resolution of symptoms and she developed small specks of gross blood in her urine, noted in the toilet and on the toilet paper. Hence, she presented to our primary care clinic after 1 month of persistent symptoms. On assessment, patient denied a history of fever, abdominal distention or pain, flank pain, hypertension, edema, oliguria, urinary frequency or breathing difficulty. She reported urinating approximately five times daily. She had not yet started menarche. Aside from treatment received for a UTI during her recent ED visit, the patient denied a prior history of UTI. There was no family history of recurrent UTIs or kidney pathology. She reported no history of any preceding illness to her current symptoms. No abdominal trauma or trauma to the urogenital region was reported. Family history included a sibling with a history of rheumatic fever with mitral valve involvement.

On the initial day of presentation to the primary care clinic, her vital signs were unremarkable, with BP of 95/64 mmHg. Physical exam of the urogenital region was unremarkable. Urine dip stick showed specific gravity of 1.025, pH 5.5; glucose, bilirubin and, ketones were negative, with blood large, protein of 100 mg/dL, urobilinogen of 0.2 EU/dL; nitrites were negative and leukocyte esterase (LE) was large. Urine culture showed mixed flora with multiple organisms, each <10,000 colony forming units (CFU). No treatment was provided at this visit as UTI was unlikely based on the lab results. Follow-up was arranged to repeat testing and reassess symptoms. At follow-up, the patient continued to report hematuria and dysuria and similar findings were noted on urine dip stick, including large blood and large LE. Repeat urine culture also showed mixed flora with <10,000 CFU. At this point, a bladder ultrasound was obtained, due to persistence of large blood and the patient's symptoms, which was interpreted as a complex, poly-lobulated mass arising from the dome of the urinary bladder and extending into the lumen, producing wall thickening, concerning for an invasive tumor such as rhabdomyosarcoma. The patient was referred to Urology for further evaluation. Due to a high suspicion for a malignant neoplasm, urology performed a transurethral resection of bladder tumor (TURBT) procedure. Pathology results revealed acute and chronic inflammation and partially denuded urothelium with edematous stroma indicative of polypoid cystitis. There was no evidence of malignancy. The post-operative course was uneventful, and at follow-up, the patient's symptoms had resolved with no further recurrence.

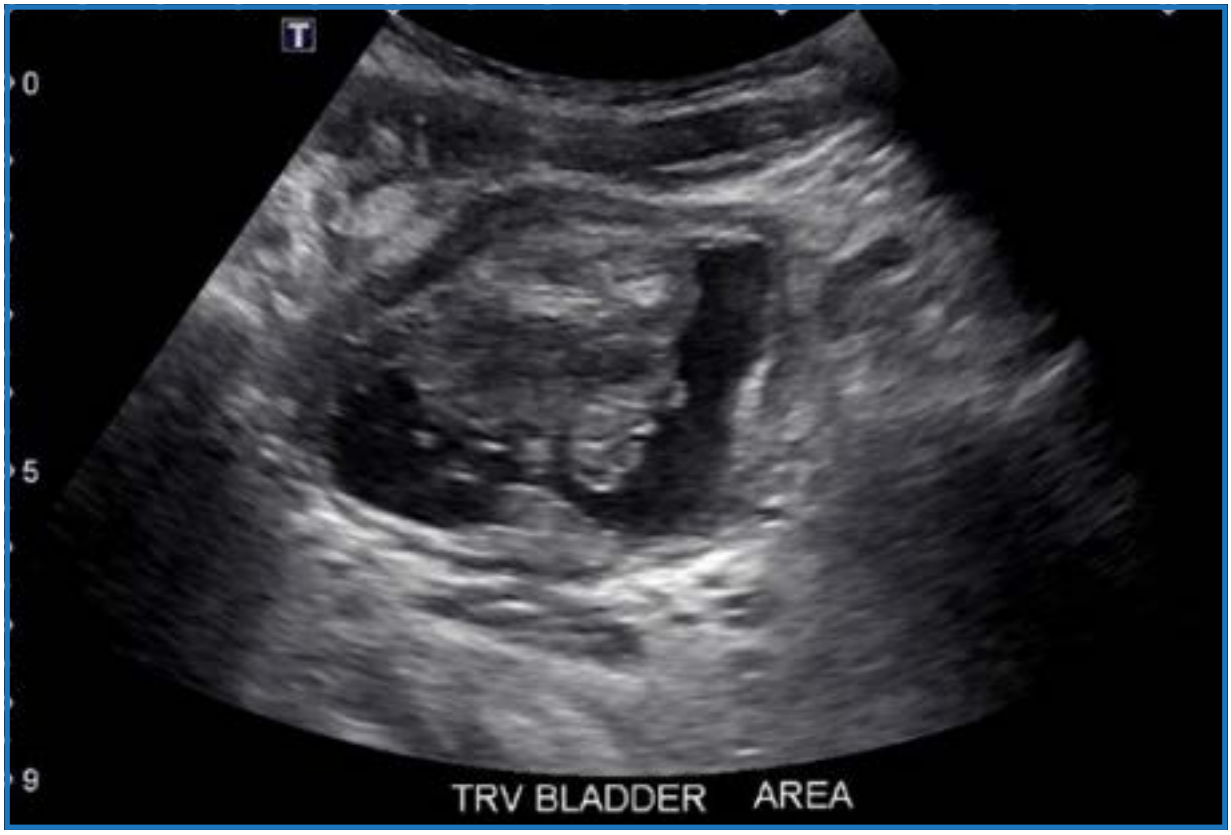

Figure 1: Transverse view of urinary bladder demonstrating bladder mass

DISCUSSION

Benign bladder masses in children are extremely rare pathologic lesions.[3] The presentation can include gross hematuria, dysuria or obstructive voiding symptoms, and urinary infection. There should be a high clinical suspicion for a neoplastic process such as rhabdomyosarcoma.[4] Polypoid cystitis, although rare in the pediatric age, is now an acknowledged cause of childhood hematuria[5], and should also be considered in a patient with persistent symptoms that are unresponsive to conservative measures or treatments.

Polypoid cystitis is a benign, reactive, exophytic urinary bladder mucosal lesion whose etiology has been attributed to chronic non-specific injury to the bladder mucosa, most commonly seen in adults.[5] Friedman and Ash first defined the diagnosis of "polypoid cystitis" in 1959. The most well-known etiology of this condition is long-standing, indwelling catheterization.[6] In addition to an indwelling catheter, other frequently cited etiological factors include vesical fistulae, radiation, tumors, and previous urological instrumentation. The location of the lesion, though it may vary, can aid in the differential diagnosis. Polypoid cystitis has mostly been observed on the dome and the posterior wall of the urinary bladder, an area in close contact

with the catheter tip. Bladder tumors are known to be rare in these locations.[6] A stepwise diagnostic approach should include urinalysis and culture, urine cytology, and imaging studies. The anatomy should be initially defined with renal and bladder ultrasonography followed by a voiding cystourethrogram (VCUG). Based on the absence of hydronephrosis in our patient, there was no indication for the VCUG. Contrast CT or magnetic resonance imaging can help define the lesion further, and cystoscopic inspection with attempts at transurethral biopsy should be the primary mode of obtaining a tissue diagnosis.[4] The usual treatment for polypoid cystitis consists of removing the source of irritation and surgical excision in the rare severely involved cases.[5]

In summary, when a polypoid lesion is found within the bladder of a patient, regardless of age and regardless of an indwelling-catheter or chronic source of irritation, polypoid cystitis should be considered as a potential etiology.

CONCLUSION

Review of the current case highlights the importance of considering a rare, in the pediatric population, but prevalent adult benign bladder mass noted with polypoid cystitis. This case will also allow Pediatricians to broaden differential diagnoses when evaluating persistent dysuria in a patient without significant urological abnormalities. Early diagnosis and treatment can ameliorate symptoms.

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CASE REPORT

First Presentation of a MED12 Mutation Causing Capillary Malformation and Hemihyperplasia

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ABSTRACT

A newborn born to a healthy mother with no complications was found to have extensive unilateral capillary malformations resembling port wine stains as well as right hemihyperplasia of the upper and lower extremities. While several genetic syndromes are associated with one of these findings, both occurring together is a rare, potentially novel presentation. The patient's DNA was examined for mutations correlated with capillary malformations and hemihyperplasia, and while no such changes were found, a variant of unknown significance in a gene known to cause other genetic disorders was found. This may be the first description of a new *MED12*-related disorder.

INTRODUCTION

Vascular lesions in the newborn population are not uncommon, frequently regress on their own, and have no associated pathological features, although some are specifically correlated with syndromic disorders. These anomalies encompass everything from vascular tumors, simple and combined malformations and major vessel anomalies to syndromic-specific malformations. Infantile hemangioma (IH), a type of benign vascular tumor, is recognized as the most common newborn vascular lesion with an estimated incidence of 5%, while port wine stain (PWS), associated most often with Sturge Weber syndrome (SWS), is found in only three to five children per 1000 live births[1,2]. PWS, unlike IH, often does not regress in childhood. Contrastingly, the lesions' color tends to darken from red to purple and even become raised and hardened after several decades. This is due to progressive dilatation of immature venule-like structures and subsequent formation of vascular nodules.

Hemihyperplasia (replacing the former term hemihypertrophy) is defined as one or several isolated areas of overgrowth of the body and represents another finding most commonly first reported at birth, with several established syndromic associations, most commonly Beckwith-Wiedemann syndrome (BWS). Although the prevalence of hemihyperplasia has been approximated at 1 in 86,000, the rate of isolated, non-syndromic findings consistent with hemihyperplasia has been more difficult to elucidate[3]. This case details a patient born with isolated findings of PWS and hemihyperplasia, as well as a genetic mutation of unknown significance, perhaps the first such composition of findings described in the literature.

PATIENT PRESENTATION

A Caucasian female infant was born via uncomplicated spontaneous vaginal delivery at 37 weeks gestation to a 25-year-old gravida 2 para 1 mother, following an uncomplicated pregnancy. Delayed cord clamping and skin-to-skin contact were performed as part of routine care. The infant was determined to be large-for-gestational age (38 weeks estimated gestational age by Ballard score), but otherwise a healthy baby girl. Apgar scores were 9 and 9 at one and five minutes, respectively. At time of delivery, confluent, blanchable regions of erythema and purpura consistent with port-wine stains (PWS) were noted across the neonate's trunk and right upper and lower extremities. The cutaneous defect was not identified anywhere on the patient's face. The remainder of the newborn physical examination was normal. Routine newborn laboratory studies, including cord and venous blood gas, transcutaneous bilirubin, and Coombs antibody test were within normal limits. There was mild hypoglycemia that corrected upon administration of oral glucose gel and the neonate was started on formula feeds per mother's request.

During her stay in the hospital, dermatology was consulted and described large segmental capillary malformations, consistent with PWS, of the right upper extremity (Figure 1), right lower extremity (Figure 2), and the lumbosacral area (Figure 3). Interestingly, the dermatology consult team also noted subtle overgrowth with moderate fullness of the soft tissues in the right upper extremity, specifically the right shoulder and axilla where the defect appeared. There was concern about several congenital disorders, but because the patient had no neurological deficits, was feeding and voiding properly, and in no acute distress, no further evaluation was warranted. Follow-up with outpatient dermatology and a lumbosacral ultrasound were scheduled and the infant was discharged home with her mother less than 48 hours after birth.

Figure 1

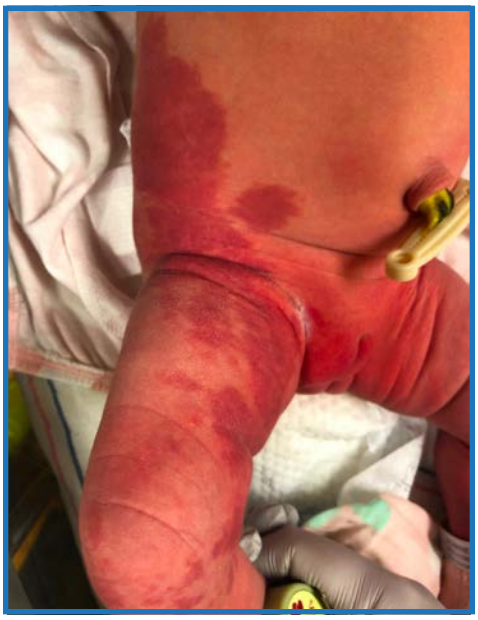

Figure 2

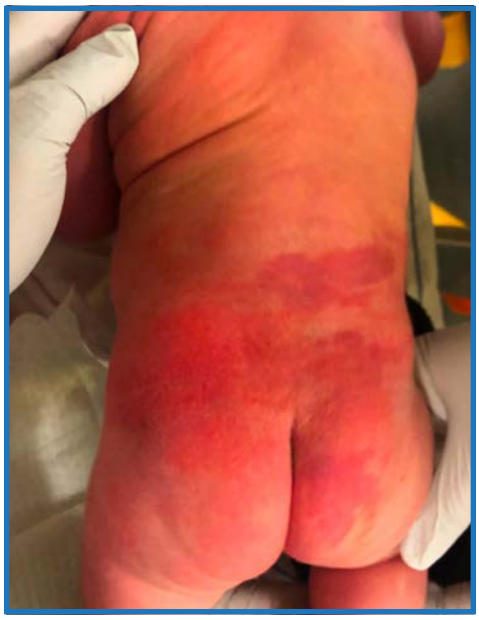

Figure 3

At 4 weeks of life the infant was meeting developmental milestones, continuing to feed and void regularly, and was progressing properly on length, weight, and head circumference growth percentiles. A spinal ultrasound showed no evidence of spinal cord tethering and was normal. Her physical examination findings were largely unchanged from birth with no changes in the growth or involvement of the PWS and no development of neurological deficits. The patient did show a moderate increase in circumference of the right proximal upper extremity compared to the left side. The patient was referred to a genetic counselor for further evaluation of the potential significance of the capillary malformation and unilateral arm overgrowth.

The genetic team first evaluated the patient at three months of age and recommended a buccal swab to be sent for pathologic gene abnormalities related to overgrowth as well as hemangiomas, including the macrocephaly-associated *PIK3CA* and *GNAQ* genes. Her DNA was negative for these two mutations; however the panel found a variant of unknown significance (VUS) in *MED12*, a gene that encodes a protein that regulates gene activity. Abnormalities in this gene are associated with several congenital disorders, none of which have findings consistent with this patient's extensive capillary malformations and hemihypertrophy. As the patient was continuing to meet milestones appropriately at six months of age, the genetics team opted to delay further diagnostic testing, including skin biopsy, until her first birthday, or in the event of new or worsening symptoms.

DISCUSSION

On initial evaluation, the genetics team was concerned primarily for macrocephaly-capillary malformation (M-CM) syndrome, caused by several *PIK3CA* gain of function mutations, which lead to superfluous activation of a cellular proliferation pathway[4]. Further investigation of neurocutaneous or congenital overgrowth disorders like SWS or BWS was not performed mainly due to the lack of other syndromic findings which are typically associated with these severe conditions. Diagnosis of M-CM syndrome depends on clinical findings of two major criteria (macrocephaly and capillary malformation) as well as one of several potential minor criteria, one of which is asymmetry or overgrowth[4]. While definitions in the literature vary slightly, the American Academy of Pediatrics denotes a head circumference >97th percentile as macrocephaly, and though the patient discussed here was nearing the upper percentiles (96th percentile at birth), she never met the clinical diagnostic criteria and by 3 months of age was within 1 standard deviation of normal at the 73rd percentile. Despite the lack of true macrocephaly, her DNA was tested for mutations in *PIK3CA* as well as *GNAQ* (most commonly associated with SWS). While these did not result in significant findings, a variant of unknown significance (VUS) was discovered in her mediator complex subunit 12 (*MED12*) gene. The initial impression that the patient's unique presentation may represent a mosaic form of M-CM syndrome was likely refuted by the results of the buccal swab, as buccal epithelial and white blood cell samples have proven to be more sensitive when probing for mosaic patterns of mutation than their serum leukocytic counterparts[5].

MED12 encodes a subunit of a multiprotein mediator complex which regulates the activity of transcription factors. Although its specific role in the transcription mediator protein multiplex is currently being studied, evidence points to its importance in cell growth, migration, and differentiation, specifically in developing neurons[6]. The exact VUS identified in the above patient was an A to G transition at base 6218 in the coding region, causing amino acid 2073 to change from glutamine to arginine. Specific mutations in the *MED12* coding region have been linked to uterine leiomyomas as well as several genetic disorders including FG syndrome, Luhan syndrome, and a specific subtype of Ohdo syndrome[7]. These three syndromes are inherited in an X-linked recessive manner and share intellectual disability as a common finding, while each is notable for distinct physical features. Interestingly, limb size abnormalities, including hemihyperplasia, and capillary malformations are absent from the list of expected physical exam findings in any of these three syndromic disorders. With that being said, all three are exceedingly rare conditions and not commonly cited in the literature. While FG syndrome and Ohdo syndrome were first described in the late 1980s, Luhan syndrome was designated later, in the early 2000s. The vast majority of data collected on *MED12*, its associated functions, and the consequences of potential coding errors has occurred since 2007. The patient described above, with a mutation in the coding region and distinct physical abnormalities may represent the first-described case of a genetic disorder. The significance of her presentation at birth as well as the linkage of the physical findings to a genetic cause, including *MED12*, will become more evident as she ages, whether or not other symptoms develop including intellectual disability. If so, more genetic testing will be required.

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RESIDENT ARTICLE

Not All Posterior Rib Fractures are Non-Accidental Trauma: Birth Records, Timing of Injury, and Time to Diagnosis Remain Paramount

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CASE REPORT

Patient 1: A 5-day-old male was transferred from an outside hospital due to concern for non-accidental trauma after three rib fractures were found on X-ray.

HISTORY OF PRESENTING ILLNESS

The infant was born via induced vaginal delivery at full term with mother reporting a very difficult delivery. After delivery, a bruise on his left arm and bruising of his abdomen were seen on physical examination. On day of life 1, the infant was increasingly fussy and inconsolable, and the maternal grandmother heard a "popping noise on his left side.". On day of life 2, new-onset crepitus was noted over the chest wall, at which point x-rays were ordered which showed a non-displaced fracture of the 6th rib on the left side and a mildly displaced fracture of the 7th and 8th rib on the left side (Figure 1). The infant was then transferred for further management and evaluation by our institution's child abuse team.

PHYSICAL EXAM

Birth exam was remarkable only for "bruising to full left forearm." Upon hospital transfer, the patient was alert and interactive with no acute distress. His length was 52 cm (85th percentile for age and sex) and weight was 3.912 kg (85th percentile). The only remarkable finding was faint purple bruising along the left forearm (Figure 2).

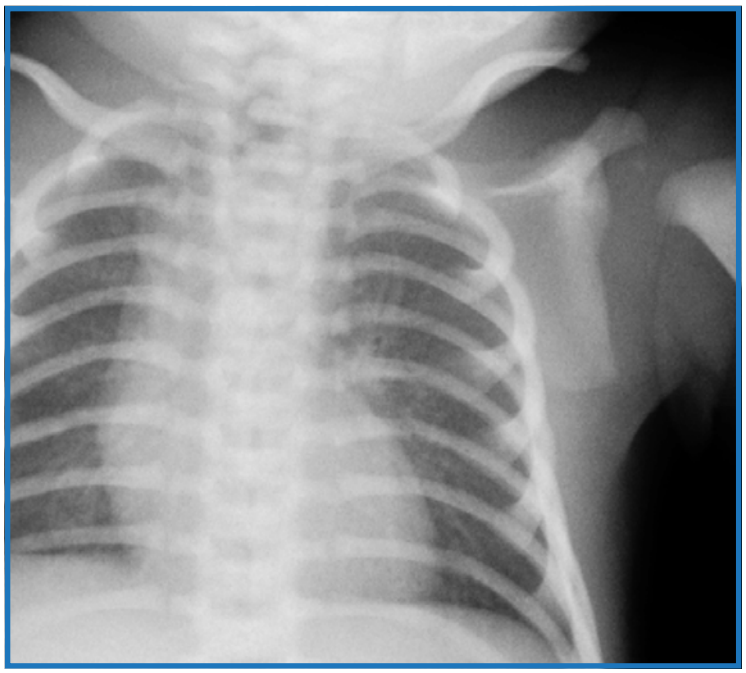

Figure 1

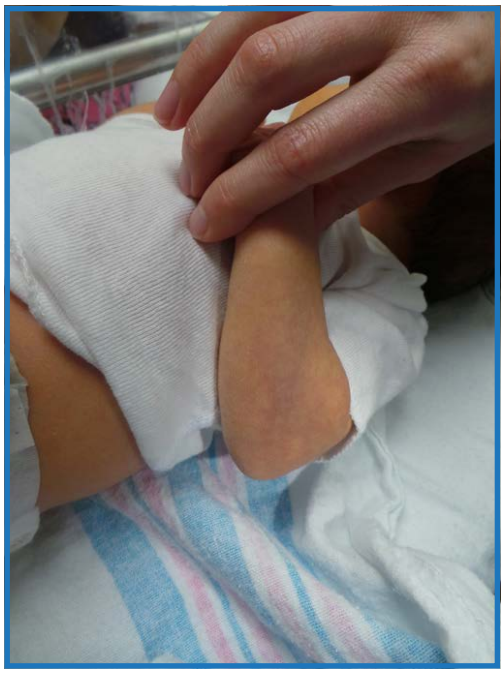

Figure 2

CONSULTATIONS/ADDITIONAL STUDIES

The obstetrician present at delivery was consulted and indicated no traumatic events occured during delivery that could have caused the rib fractures. However, upon review of medical records, the delivery was noted as "a significantly difficult birth and had evidence of some birth trauma with a bruise on the left forearm...per nursing staff, baby was 'stuck' for a little while."

After hospital transfer, a skeletal survey was performed which showed no additional fractures. Head MRI and ophthalmologic evaluation was completed and "suspect optic disc splinter hemorrhage in right eye secondary to birth trauma" was documented in the record.

Diagnosis: Multiple rib fractures due to birth trauma

Patient 2: A 16-week-old male was admitted to the hospital for concern of non-accidental trauma after 8 rib fractures were noted on chest x-ray obtained at routine cardiology follow-up in clinic.

HISTORY

The infant was born prematurely at 32 weeks' gestation via spontaneous vaginal delivery. His mother was unaware that she was pregnant and received no prenatal care. He was transferred to the NICU at a tertiary center due to respiratory distress at birth requiring intubation. He was also noted at birth to have, as noted in the medical record, "significant bruising to chest, abdomen, and face" at delivery. He was discharged home in the care of his mother after a 10-week NICU admission. During the course of this hospitalization, he was found to have a ventricular septal defect, poor feeding, and a small brain hemorrhage on head ultrasound, assumed to be associated with prematurity. He was seen in the cardiology clinic for follow-up one month after discharge, where a chest x-ray was obtained that showed multiple bilateral rib fractures in various stages of healing. He was then admitted to our institution.

PHYSICAL EXAM

Exam at our institution showed an infant measuring 19.6 inches (< 3rd percentile, adjusted for prematurity), weighing 7 lb 5.5 oz (< 5th percentile, adjusted for prematurity), with head circumference 13.9 in (< 3rd percentile, adjusted for prematurity). Auscultation of the chest revealed a loud systolic murmur. Musculoskeletal/skin exam showed no bruising, crepitus, bony deformity, or other outward signs of trauma.

CONSULTATIONS/ADDITIONAL STUDIES

NICU records from the referring hospital, including multiple chest x-rays, were provided at our request and reviewed by our pediatric radiologists. None of these records showed evidence of fracture after re-review by the child abuse team.

Skeletal survey, head CT, and eye exam were performed upon admission. Skeletal survey revealed left lateral rib fractures involving the 6th, 7th, 8th, 9th, and 10th ribs with abundant callus, as well as more acute fractures of the right lateral 7th, 8th, and 9th ribs that did not show signs of healing. No additional fractures were seen. Head CT and ophthalmologic exam revealed no further signs of trauma.

Diagnosis: Physical abuse

DISCUSSION

Most rib fractures in infants are the result of child abuse or non-accidental trauma.[1,2] These fractures result from the anterior-posterior compression by an adult squeezing the infant's chest with the greatest force occurring over the transverse process. However, as these two cases contrast, rib fractures uncommonly result from serious accidental trauma, birth related trauma, or rare genetic disorders of bone fragility.[3]

Rib fracture secondary to birth trauma is extremely rare. Multiple studies on birth trauma that collected data from a total of 115,756 traumatic live births showed no resulting rib fractures.[4] One study that looked at rib fractures in children under 12 months of age over a 3-year period at two hospitals found that of 39 infants with rib fractures, only 2.6% of the cases were caused by birth trauma.[5]

The true prevalence of rib fractures secondary to birth trauma is unknown but co-occurring injuries like dystocia and clavicular fractures may support the diagnosis. A literature review performed in 2008 found 13 cases of definitive birth-related posterior rib fractures.[4] In 12 of the 13 cases, the birth weight was high. In 7 cases, the birth was complicated by shoulder dystocia, as we believe occurred in the case of the first infant. And in 6 cases there a clavicle fracture was found ipsilateral to the rib fractures. Posterior rib fractures are believed to be quite specific for abuse; however, it should be noted that rib fractures that occur secondary to birth trauma are often located posteriorly as well, near the costovertebral junction.[5]

there is a higher prevalence of asymmetrical mid-posterior over posteromedial fractures in macrosomic neonates who are subjected to rotational forces during vaginal delivery. Ipsilateral clavicle fractures can also occur by the same mechanism. Conversely, in non-accidental trauma cases there is often a selective anterior displacement of the vertebra.[4]

Rib fractures may be more easily attributed to birth injury if diagnosed by radiograph while the newborn is still hospitalized after birth. Review of hospital medical records for type of delivery, infant size at birth, and a record or difficult or complicated delivery may also provide valuable information when assessing possibility of birth trauma. Newborns are handled frequently in the hours and days after birth, and an injury sustained at delivery should be quickly recognized by medical staff and parents.

Assessment for radiographic changes in fractures may also be useful when considering the possibility of birth-related trauma, as fractures will start to show periosteal reaction by approximately one week of age and will show callus formation between two and three weeks of age. Acute fractures in infants outside of the newborn period cannot reasonably be attributed to birth related trauma.

These cases highlight an important distinction between rib fractures due to birth trauma and rib fractures due to non-accidental trauma. The timing of presentation and review of birth records and radiographs can assist the clinician distinguishing abusive from non-abusive trauma.

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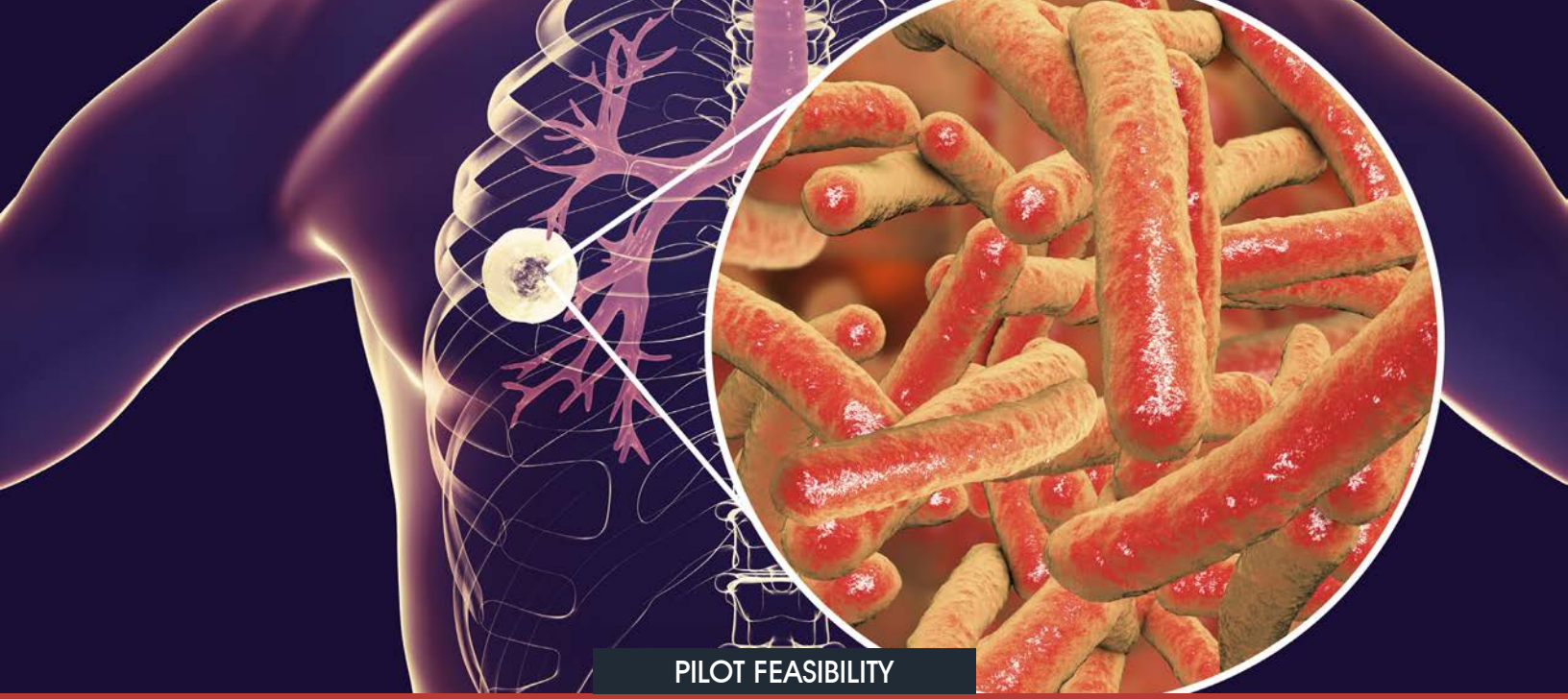

PILOT FEASIBILITY

Status Epilepticus and Hydrocephalus in a 2-Year-old Female

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INTRODUCTION

While *Mycobacterium tuberculosis* (MTB) infections remain highly prevalent throughout the world, with approximately 130 cases per 100,000 people and a constant increase in the number of new or relapsed cases[1], in the United States (US), a downward trend is reassuring. In 2018, the number of pediatric MTB infections reported in the US was 372, or 4.1%, for children younger than 14 years-old (almost half being diagnosed in children below five years), and 874, or 9.6% for the children 15 to 24 years of age. In children, the rate of extrapulmonary infections was estimated between 17-25% in certain European studies [2,3] and 32% in the US.[4] Among this US cohort of children less than 5 years-old, 80% were US-born and 64% had at least one foreign-born parent. The 2018 Centers for Disease Control and Prevention report identified that 3.8% of the extra-pulmonary infection cases were tuberculous meningitis (TBM), all ages accounted for.[5] For the pediatric population specifically, TBM with or without tuberculoma, was estimated around 20%[6] in high-prevalence areas; conversely, in the US the incidence is expected to be closer to 1-2%.[7]

PRESENTATION

A previously healthy 22-month-old female was transferred to our intensive care unit in status epilepticus. Over the course of the prior three weeks, a presumed benign viral illness had progressed to persistent febrile illness, then managed with amoxicillin followed by amoxicillin and clavulanate. Ultimately the patient exhibited neurological symptoms represented by behavior changes and focal seizure activity. Upon arrival, she was heavily sedated and intubated. Her physical exam and vital signs were unremarkable. Antibiotic therapy with cefepime, vancomycin and acyclovir were initiated.

Laboratory evaluation revealed the following: white blood cell count of 19,500/μL, neutrophils 72%, C-reactive protein 17.5 mg/dL. An initial cerebrospinal fluid (CSF) analysis showed no pleocytosis, proteinorachia less than 10mg/dL, and glucorachia less than 20mg/dL. Subsequent CSF samples shifted towards pleocytosis between 197-293/mm^3 and proteinorachia between 102-194mg/dL. The CSF gram stain, acid-fast stain, bacterial culture, molecular assay for common pathogens and MTB were negative on repeated occasions. The blood culture, HIV 4th generation assay, and cryptococcal antigen were also

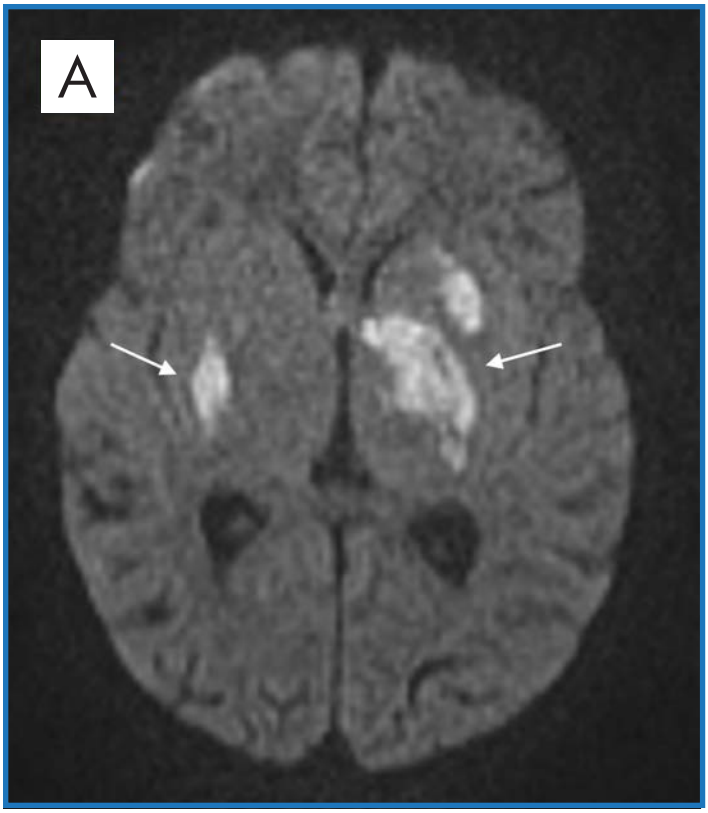

Figure A: Axial diffusion MR images of the brain demonstrating restricted diffusion in the basal ganglia bilaterally (arrows).

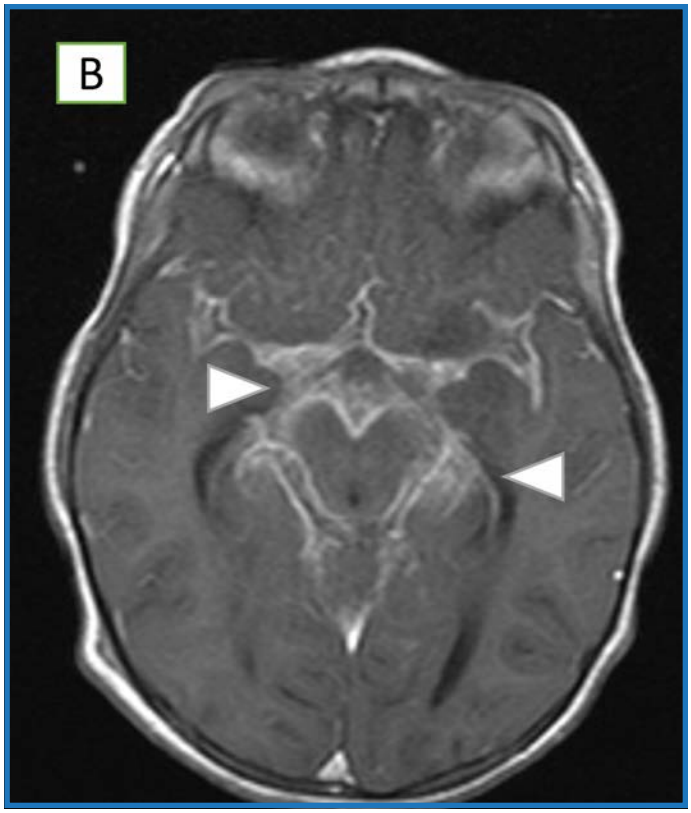

Figure B: Post-contrast T1-weighted MR images revealing diffuse enhancement in the basal cisterns and along the midbrain (arrow heads).

negative. Computed tomography revealed moderate to severe hydrocephalus and multiple hypodense lesions throughout the parenchyma (Figure 1). Tuberculous meningitis was suspected based on the clinical presentation, CSF analysis and the onset of an acute hydrocephalus. The initial tuberculin skin test (TST) was negative, but the interferon gamma-release assay (IGRA) was positive.

Following initiation of anti-tuberculous medication (isoniazid, pyrazinamide, rifampin and amikacin) we noticed worsening central nervous system (CNS) pathology (Figure 2A, 2B, 2C, and 2D). It was not until the third week of therapy that the patient become more stable, allowing extubation and de-escalation of the antiepileptic regimen. Subsequently, besides placement of a ventriculo-peritoneal shunt and a gastrostomy tube, the clinical course was uncomplicated. She completed 12 months of anti-tuberculous therapy (four drugs the first 2 months followed by 10 months of isoniazid and rifampin) without recovery of neurological functions. The main sequela were the severe neurological disability represented by pyramidal tract and basal ganglia involvement and epilepsy requiring anti-convulsive medication.

DISCUSSION

Although a rare encounter, TBM remains an ominous presentation of MTB infection. Children under the age of five, and those younger than two in particular, have the worse prognosis given their susceptibility for disseminated infection. Additional risk factors for severe presentations include HIV co-infection[8], malnutrition, recent measles infection, and immunosuppressive states.[9] The hydrocephalus, a typical radiological finding in TBM, has been found to be a poor prognostic factor by itself.[10] The neurological manifestations vary from a classical meningitis picture to cranial nerve deficits, seizure disorder and different degrees of altered mental status.[11, 12, 13]

In older children, a subtle prodrome with behavioral changes and headache is common. Tuberculous meningitis can develop in the context of miliary tuberculosis, associated or not with tuberculoma, and as an independent entity as well.[6]

The presence of altered mental status in a child who received prior antibiotic therapy usually raises concerns for a complicated bacterial infection of the CNS. The increase in the intracranial pressure, cerebral edema, cerebrovascular anomalies, extra-axial fluid collections, brain abscesses, seizures, focal deficits, and hydrocephalus are all neurological complications of bacterial meningitis. In the right epidemiologic context, TBM needs to be included in the differential diagnosis.

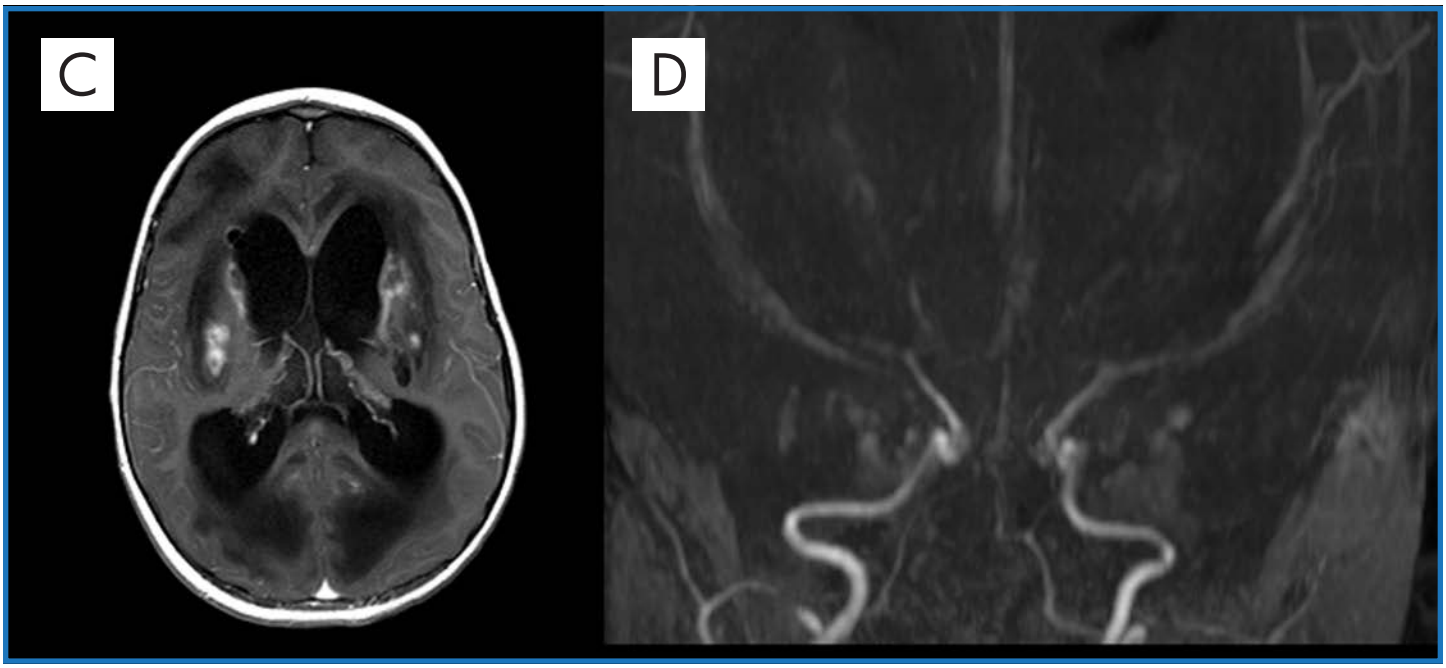

Figure C. Post-contrast axial image after 3 weeks demonstrating heterogenous enhancement in the regions of the previously noted areas of restricted diffusion, suggestive of subacute infarcts (arrows). There is moderate hydrocephalus of the lateral ventricles.

Figure D. 3D time of flight MRA of the brain demonstrates marked narrowing of the ACA and MCA's bilaterally as well as the supraclinoid and cavernous segments of the ICA's bilaterally. The posterior circulation demonstrates severe narrowing of the right vertebral and moderate narrowing of the basilar and left vertebral arteries. The PCA's are not visualized bilaterally.

A CSF analysis revealing moderate pleocytosis with lymphocytosis, proteinorachia between 100-500 mg/dL and very low glucose levels below 45mg/dL or a CSF:plasma glucose ratio <0.5 are typical findings in TBM. A paradoxical response characterized by increase in CSF neutrophil count has been described once therapy with anti-tuberculous drugs has been initiated. In rare situations, a normal CSF analysis can be observed. Identification of acid-fast bacilli (AFB) in the CSF by both staining and culture remains the most important and widely available method to diagnose CNS infection, especially in the era of increasing rates of multidrug resistance. Typically, pauci-bacillary, CSF samples result in low microbiological confirmation rates by either Ziehl-Nielson staining or culture technique in the Lowenstein-Jensen medium.[11,14] Consequently, multiple samples should be collected in order to increase the detection rate of the MTB. Access to a molecular assay decreases the need for higher CSF volumes from 5-6 ml to only 2-3 ml.[15] The GeneXpert method has an overall sensitivity of 56% although, CSF centrifugation may optimize its performance to 72-77%.[14,15] Other diagnosing methods such as antibody and antigen detection are not employed in the U. Sserology cannot differentiate acute from previous infection and cross-reactivity when other mycobacteria species have been documented.

Another piece of the puzzle facilitating the diagnosis of TBM for our patient was the positive IGRA. The severe clinical presentation was most likely responsible for the anergic tuberculous skin test. A recent meta-analysis revealed that IGRA performance from either blood or CSF was 77-78% sensitive and 61-88% specific.[16] However, similar to the molecular assays, the negative predictive value of these assays remains low, and they should not be used to rule out TBM. In comparison, the sensitivity of the TST is even lower (44% in a 2005 study), and it doesn't seem to be influenced by the nutritional status or Bacillus Calmette-Guérin vaccination.[17]

Imaging studies such as computed tomography and magnetic resonance help with the diagnosis by identifying pathognomonic intracranial changes associated with TBM[12] and help predict the outcome. The most common findings are basal meningeal enhancement (Figure 2A and 2B), infarctions in the supratentorial brain parenchyma and brain stem (Figure 2C and 2D), and hydrocephalus and are encountered in 80-90% of children with TBM, even during the first stages of the disease.[6,12]

Even though microbiological confirmation would be ideal, therapy is empirically started with a combination of anti-tuberculous drugs that include isoniazid, rifampin, pyrazinamide and either amikacin or ethambutol. After the initial 2 months of treatment, therapy is usually narrowed to isoniazid and rifampin for an additional 10 months. Penetration into the

CSF is limited for rifampin and absent for ethambutol and amikacin, resulting in a reliance on isoniazid as the most essential drug for TBM. Newer generation fluoroquinolones such as levofloxacin and moxifloxacin have optimal pharmacokinetic properties for TBM therapy based upon satisfactory susceptibility profile and excellent CSF penetration.[12] However, despite their use in the pediatric population remains restricted due to their safety profile, they are valuable options for confirmed multi-drug resistant bacilli.

The use of corticosteroids was demonstrated to improve the outcomes of TBM in both children and adult patients,[18] however, there are no randomized trials comparing different systemic steroid regimens. Some experts suggest doses between 8-12mg/day of dexamethasone for a duration of 3 weeks followed by a tapering regimen.

In the end, a multidisciplinary approach including surgical and neurosurgical specialties, rehabilitation services, and an epidemiological investigation led by the Department of Health is required for holistic management of TBM cases.

The prognosis of TBM depends largely on the patient's neurological status at presentation and the time until therapy initiation. Poor prognostic predictors include hydrocephalus, altered level of consciousness, concomitant military tuberculosis, prolonged time to therapy initiation, and lack of steroid use.[10] Mortality remains as high as 65-69% in developing countries or among patients with severe presentation, immunosuppressed state, and very young age. Among survivors, neurological sequela are reported in up to 50% of cases.[8]

CONCLUSION

Nowadays, when travel abroad and immigration processes are so common, physicians should maintain a high index of suspicion for TBM, given its high mortality and morbidity. The diagnosis might not be straight-forward during the first patient encounter, but the CSF characteristics, the neurological manifestations, the typical radiological findings, the molecular assays, and IGRA will help arrange the pieces of the puzzle. Therapy should be initiated immediately and administered for 12 months, despite the lack of confirmatory microbiological results. Finally, extra caution should be sought with children less than 2 years of age, given that they are the most susceptible when exposed to an active case of tuberculosis. Our patient survived, but faced the sequela mentioned above, including cerebral palsy, and developmental delay.

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STUDENT ARTICLE

Isolated Aural Erythromelalgia or Red Ear Syndrome

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CASE PRESENTATION

An 18-year-old Indian female presented with a one-year history of intermittent redness, burning, and warmth of her ears. The episodes occurred approximately once or twice a day and lasted for about an hour. Only one ear was affected each time but either ear was affected randomly. The episodes did not have any inciting or relieving events, resolved spontaneously, and occurred at any time of the day. There were no associated headaches or migraine episodes, and only the ears were involved without involvement of hands or feet.

Past medical history was significant for attention deficit and her medications included atomoxetine 60 mg daily and oral birth control pills for irregular menses. Review of symptoms was negative for neurological or cardiac symptoms.

On examination, the patient was an alert and oriented, well-nourished female in no acute distress. Neurological examination was intact. Head and neck examination were normal other than patchy erythema of the right ear with mild edema and increased temperature in the area of erythema. The erythematous area was well demarcated with sharp borders (Figure 1). The other ear was completely normal with no erythema (Figure 2). During the visit, the erythema progressed to involve the entire ear (Figure 3) and then abruptly cleared up (Figure 4). There was no abnormality of the temporomandibular joint and no other autonomic abnormalities. Cardiac examination was within normal limits. Patient was diagnosed with Red Ear Syndrome (RES) and provided reassurance that symptoms would get less frequent in the future. The patient presented subsequently with another episode involving the left ear in a similar fashion (Figure 5).

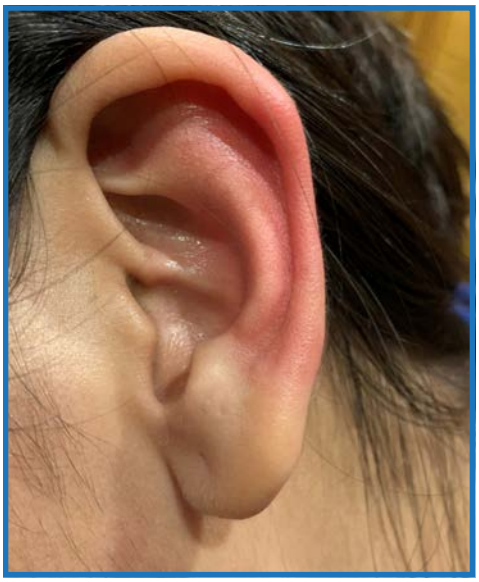

Figure 1: Limited erythema of the left ear with sharp inferior margin

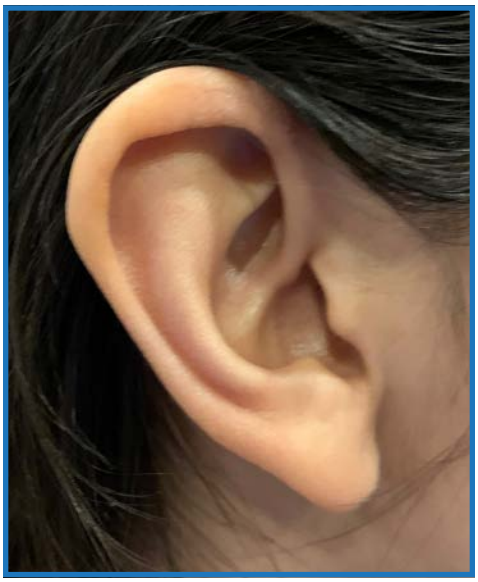

Figure 2: Uninvolved right ear

Figure 3: Progression of erythema to involve the entire ear

Figure 4: Resolution of erythema after one hour

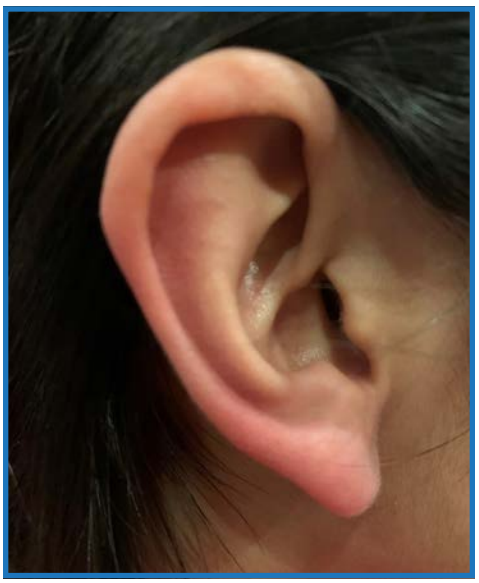

Figure 5: Involvement of the right ear at a subsequent visit

DISCUSSION

RES is an uncommon disorder typically affecting children and young adults, characterized by intermittent, recurrent episodes of redness, burning and increased temperature of one ear associated with headaches or migraines. It was first described in 1994 and has a slight female preponderance. The episodes can migrate from the ear to the jaw, neck, and even to the occiput.[1] The attacks are typically unilateral but may occur on either side, Bilateral attacks and attacks that extend to the face have also been described.[2] The cause is unknown, but one theory is that it is a form of trigeminal autonomic disorder resulting in vasodilation.

There are two types of RES. Primary RES is common in those who have migraines as children, teens, and young adults. Secondary RES affects older individuals, especially women, and is commonly seen with temporomandibular joint dysfunction (TMJD), upper spine problems, and headaches.

Common triggers that bring on a case of RES include touching or rubbing of the ear, heat or cold, stress, neck movements, exercise, hair brushing, showering, chewing, or grinding teeth.[3] Both types of red ear syndrome have been associated with various conditions, including upper cervical pathology (arachnoiditis, facet joint spondylosis and cervical root traction), glossopharyngeal and trigeminal neuralgia, TMJD, and thalamic syndrome, primary headache disorders (including migraine), chronic paroxysmal hemicranias and hemicrania continua, and the short-lasting unilateral neuralgiform headache with conjunctival injection.[4]

Proposed mechanisms are "auriculo-autonomic cephalgia" and "cervico-autonomic reflex," both of which suggest that irritation of the C3 root or great auricular nerve or great occipital nerve lead to release of vasodilator peptides from afferent nerve terminals.[2,5-7] Another suggested mechanism is that inhibition of sympathetic vasoconstriction more than activation of parasympathetic vasodilator fibers by the trigemial autonomic reflex is responsible for erythema as well as pain.[8] Others have suggested that RES is part of the spectrum of trigeminal autonomic cephalgia, a term that encompass a variety of short-lasting primary headache syndromes associated with autonomic activation.[6,9,10] There also may be a connection between the trigeminal nerve and facial parasympathetic outflow. Additionally, local damage to small nerve fibers and vessels has been considered as a possible explanation.[2]

Diagnostic criteria for RES have been proposed that require at least 20 attacks of ear pain accompanied by redness lasting up to four hours. They must occur more than once daily and must either be accompanied with a burning sensation or triggering by cutaneous or thermal stimulation.[2]

Erythromelalgia (EM) is a rare disorder characterized by intermittent episodes of redness, warmth, and intense burning pain, but typically affects the hands and feet. It has been suggested that RES associated involvement of hands and feet may be a form of erythromelalgia. It is a rare condition, with a prevalence of 0.36 to 2 per 100,000 patients and has also been classified into primary and secondary forms.[11]

Primary EM is caused by mutations in SCN9A. This gene encodes the Nav1.7 type sodium channel receptor, expressed in nociceptive neurons and normally amplifies the nociceptive pain signals. Mutations result in familial or sporadic forms of erythromelalgia through dysregulation of these neurons, with dilation of the small vessels. Primary EM may develop at any age.

Secondary EM is commonly associated with myeloproliferative disorders such as polycythemia vera and essential thrombocythemia. EM precedes the onset of the myeloproliferative disorder by 2.5 years in 85% of the cases.[11] It can also rarely occur in association with paraneoplastic disorders, diabetes, autoimmune neuropathies, as well as rheumatological and infectious diseases. Secondary EM is seen mostly in adults over 40 years of age. The distal parts of the lower and upper extremities are most commonly involved (hands, feet, fingers and toes). Rarely, symptoms may occur in the face, ears and other parts of the body. The classic description is painful, red, warm hands and feet triggered by warming and downward limb position and relieved by cooling and elevation. The attacks may last minutes to days and typically occur late in the day or night. The quality of life can be greatly affected.

Diagnosis of EM is made based on the triad of recurrent erythema, burning pain and warmth of the affected body part. Family history of EM may support genetic testing, as family planning may be impacted given 50% probability of inheriting the gene mutation in offsprings. A complete blood count should be obtained to screen for myeloprolipherative disorders.

Treatment: While spontaneous remission of symptoms may occur, most cases of RES or EM are refractory to pharmacotherapy. Therapies proposed like cooling, topical capsaicin or anesthetics, medications, or surgical sympathectomy or greater auricular nerve block have had variable responses. The various medications that have been tried include non-steroidal anti-inflammatory drugs, sodium channel blockers, calcium channel blockers, beta blockers, prostaglandins, gabapentin, tricyclic antidepressants such as amitriptyline and imipramine, and methysergide.[4]

CONCLUSION

RES is an uncommon disorder typically seen in children and young adults that is usually benign. It may be associated with erythromelalgia, or the two conditions may represent a spectrum with different preferential locations. They are both characterized by dysregulation of the autonomic nervous system and nociceptive neurons by various mechanisms. These conditions do resolve spontaneously without intervention, however therapeutic modalities may be indicated if the condition interferes with daily activities or are very bothersome to the patient. Lifestyle modifications and avoidance of migraine triggers may be useful. Referrals to otolaryngology and neurology may be warranted to rule out secondary causes of RES or EM. Genetic testing may be considered in familial cases and sporadic cases of RES with EM in young adults should trigger a workup for myeloproliferative disorders. However, in most cases, reassurance is all that is needed as it is most often a benign condition.

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