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Exploring The Unforeseen: Extrapulmonary tuberculosis (EPTB) With Rifampicin Resistance (Rr) In Cornelia De Lange Syndrome (Cdls) – A Rare Revelation

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ABSTRACT

Tuberculosis (TB) remains a major global health concern, with extrapulmonary tuberculosis (EPTB) contributing significantly to its burden. This abstract discusses the clinical manifestations, diagnosis, and management of EPTB, focusing on tuberculous lymphadenitis (TBL), the most prevalent form of EPTB. Diagnostic challenges and the importance of molecular diagnostic tools like Xpert MTB/Rif Ultra are highlighted, emphasizing the need for prompt and accurate diagnosis to initiate appropriate treatment. Additionally, the abstract explores the coexistence of Cornelia de Lange syndrome (CdLS), a multisystem disorder, in a patient with EPTB with Rifampicin Resistance (RR), underscoring the complexity of managing multiple medical conditions. The significance of a multidisciplinary approach involving pediatricians, geneticists, and infectious disease specialists is emphasized in providing comprehensive care tailored to the patient's unique needs. Long-term follow-up and supportive care are crucial for optimizing outcomes in complex medical conditions like TBL and CdLS, highlighting the importance of ongoing monitoring and intervention.

CASE REPORT

INTRODUCTION:

Tuberculosis (TB) is a communicable disease that's one of the leading causes of death worldwide (1). It spreads through coughing and primarily affects the lungs, but can also manifest in other organs such as the brain, lymph nodes, and abdomen. Before COVID-19, TB was the most common infectious cause of death, surpassing HIV/AIDS (2).

According to The Global TB Report 2020, extrapulmonary tuberculosis (EPTB) constituted 16% of the 7.5 million reported TB cases globally and 19% in South-East Asia. However, these estimates may be the tip of the iceberg, as a considerable proportion remains undiagnosed or not notified(3). In rural India, the prevalence of tuberculous lymphadenitis in children up to 14 years of age is approximately 4.4 cases per 1000. The total estimated incidence of LNTB was 30.8 per 100,000 population in India in 2013 (4).

Tuberculous Lymphadenitis (TBL) is a prevalent type of Extra Pulmonary Tuberculosis (EPTB), accounting for 35-40% of cases. There are 13 EPTB cases in our setting, including adults and pediatric age groups. Out of them, 2 are pediatric and one is Rifampicin-Resistant (RR) on Xpert, making it rare. It causes painless lumps that are usually unilateral and affect the cervical lymph node in 60-90% of cases. TBL is common among people aged 20-40 with a history of TB. Mediastinal TB may cause cough or shortness of breath(5).

The diagnosis of TBL is a challenging task that demands an array of clinical, radiologic, microbiological, and diagnostic tests to be positive for the condition. However, with the advent of high sensitivity and specificity molecular diagnostic tools, the identification of TBL has become more feasible and accurate.(Xpert MTB/Rif and Xpert Ultra have, respectively, 89% and 70% sensitivity and 86% and 100% specificity over MRS for lymph node aspirates)(6). The NTEP provides free diagnostic and therapeutic services for universal healthcare. The treatment plan for EPTB is determined by site and drug susceptibility. Incision and drainage techniques can replace surgery in some cases. Residual lymph nodes after treatment are not indicative of recurrence or treatment failure(4).

CdLS is a developmental disorder that affects multiple systems in the body. It is named after Cornelia de Lange, a Dutch pediatrician who first identified the disorder in 1933. The prevalence of CdLS ranges from 1 in 10,000 to 1 in 30,000 live births. Classic CdLS can be identified at birth by experienced pediatricians and clinical geneticists due to a unique craniofacial appearance, growth pattern and limb malformations. However, the disorder can present in a variety of ways, ranging from mild to severe. Not every person with CdLS displays the typical phenotype.(7).

Synophrys, or eyebrows that meet in the middle, is a highly indicative facial characteristic of Cornelia de Lange syndrome (CdLS). Other features such as a thin upper lip, downturned mouth corners, and small hands or feet are also common. It is important to note that a clinical score of 11 points, with at least 3 cardinal features, is required to indicate classic CdLS.(8). Here in this case report, we were depicting a case of young child with EPTB-RR and Cornelia de Lange syndrome (CdLS).

CASE REPORT:

A 10 years old female child who was a 5th born child of a non-consanguineous marriage, presented with swelling in the right area of the neck along with an inability to height gain for 6 months duration. The child was asymptomatic six months back, when she developed a swelling below the chin over the right area of the neck which was insidious in onset, gradually progressive from the size of a pea to the size of a lemon associated with an inability to gain height as compared to her younger siblings. There was no history of pain,

difficulty swallowing, fever, cough, cold, weight loss, night sweats, chest pain, and no similar swellings in other body parts.

There was no history of chronic or known systemic illness for which the child was not taking medication. The antenatal period was uneventful, and the baby was born at full term via normal vaginal route at the government hospital. The neonatal period was uneventful. Breastfeeding started soon after birth and continued until 3 years of age. She met age-appropriate milestones with average performance in school. There was no documentation of immunization to the child, but a BCG scar was visible. She consumes a mixed diet and adjusts her diet to her needs. Both parents had no formal education, and the family belongs to a lower socioeconomic scale according to the modified Kuppuswamy scale 2023.The pedigree chart of the family is depicted in Fig 1.

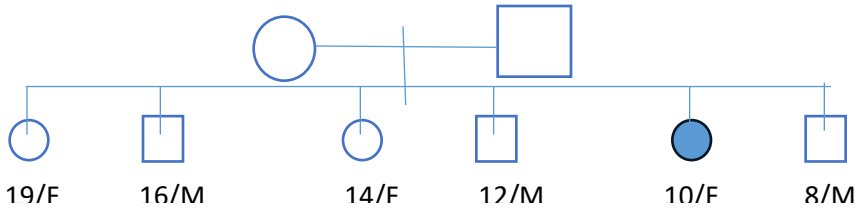

Fig 1: The Pedigree Chart

The child was active and alert during the general examination. The vital data and anthropometry appeared to be normal, as shown. Pallor and cervical lymphadenopathy at the Ia, Ib, II, and III levels were present, with no evidence of icterus, cyanosis, clubbing, or pedal edema. Thelarche and adrenarche were not achieved. Figure 2 depicts the phenotype of Cornelia de Lange syndrome (CdLS), which includes short stature, low set ears, short neck, clinodactyly, brachydactyly, and cardinal facial features. On systemic examination, normal higher mental functions and no focal neurological deficits on central nervous system examination;S1 and S2 were heard, with no murmurs

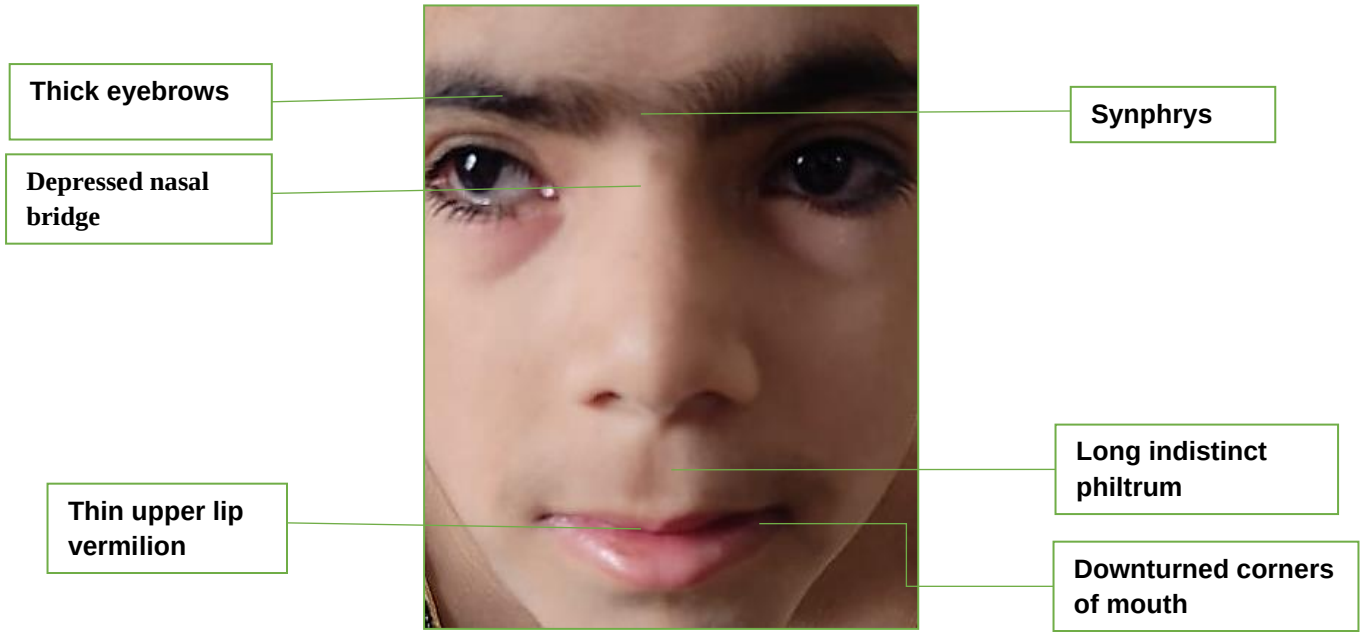

Figure 2. Facial features of child suggestive of Cornelia de Lange syndrome (CdLS)

on cardiovascular examination; bilaterally equal air entry and normal vesicular breath sounds on respiratory system examination; per abdomen soft and non-tender.

On local examination, the swelling was found to be on the right side of the neck in the submandibular region, with a lemon-sized swelling measuring 4cm X 3 cm, normal skin over the swelling, and no erythema or discharging sinus. The swelling was firm, mobile, and non-tender, with no localized temperature increase, and no axillary or inguinal lymphadenopathy.

On laboratory evaluation, complete blood picture with peripheral smear revealed the presence of normocytic normochromic predominantly admixed with few microcytes along with neutropenia (Absolute neutrophil count 1344 per µL). All liver function and renal function test parameters were shown within normal ranges except LDH (325 IU/L) with elevated levels and all viral markers were shown non-reactive. X-ray chest was shown mediastinal lymph nodes at the right para tracheal and the right hilar region as shown in the figure 3. USG neck showed multiple enlarged, homogenous, hypoechoic LNs in submental, submandibular, and jugulodigastric region with the largest measuring 3.8 cm X 1.9 cm in right mandibular region suggestive of cervical lymphadenopathy's abdomen and pelvis were normal.

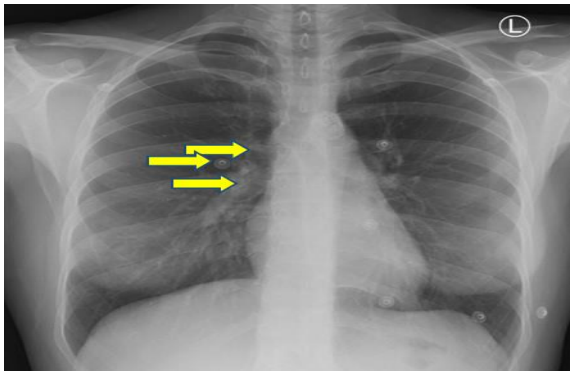

Figure 3. Chest X ray PA view showing mediastinal lymph nodes.

The child underwent an excision cervical lymph node biopsy under general anesthesia, and the biopsy sample was sent for evaluation using various methods including histopathological examination, ZN stain, CBNAAT, and MGIT for TB diagnosis.

Assay Information

Assay	Assay Version	Assay Type
Xpert MTB-RIF Ultra	4	In Vitro Diagnostic

Test Result: MTB DETECTED VERY LOW; RIF Resistance DETECTED

Analyte Result

Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
SPC	25.6	143	NA	PASS
IS1081-IS6110	22.1	535	NA	PASS
rpoB1	32.2	218	POS	PASS
rpoB2	32.0	144	POS	PASS
rpoB3	35.6	65	POS	PASS
rpoB4	30.5	218	POS	PASS

User:	mycobac		
Status:	Done	Start Time:	07/21/23 09:46:49
Expiration Date*:	06/30/24	End Time:	07/21/23 11:04:52
S/W Version:	5.1	Instrument S/N:	834613
Cartridge S/N*:	693966054	Module S/N:	661048
Reagent Lot ID*:	38409	Module Name:	B3
Notes:	TISSUE		
Error Status:	OK		

Errors
<None>

Figure 4. Xpert MTB-RIF Report showing MTB DETECTED, Rif resistance DETECTED

On Xpert MTB-RIF Ultra, MTB with Rifampicin resistance (rpoB1, rpoB2, rpoB3, and rpoB4) was detected and the child was initiated treatment as per treatment guidelines of NTEP. Finally, the child was diagnosed and labelled as Extra pulmonary tuberculosis (EPTB) (Rifampicin resistant) with Cornelia de Lange syndrome.

DISCUSSION:

This case report presents a unique scenario involving the coexistence of two distinct yet clinically significant conditions: Extra-pulmonary Tuberculosis (EPTB) and Cornelia de Lange Syndrome (CdLS). EPTB, particularly Tuberculous Lymphadenitis (TBL), is a manifestation of Mycobacterium tuberculosis infection affecting lymph nodes outside the lungs. Conversely, CdLS is a multisystem disorder characterized by physical, cognitive, and behavioral abnormalities.(9)

The presentation of EPTB with rifampicin resistance in this case, primarily manifesting as cervical lymphadenopathy, underscores the importance of considering tuberculosis in the differential diagnosis of neck masses, especially in endemic regions.(10,11) Despite the absence of classic respiratory symptoms, diagnostic evaluation including clinical, radiological, and microbiological investigations led to the identification of *Mycobacterium tuberculosis* along with rifampicin resistance through molecular testing (Xpert MTB/Rif Ultra), led to prompt initiation of anti-tubercular therapy (ATT).(12,13)Furthermore, the coexistence of CdLS adds complexity to the clinical picture. CdLS is a genetically heterogeneous disorder often characterized by distinct craniofacial features, limb abnormalities, and developmental delay (14). In this case, the child exhibited cardinal facial features suggestive of CdLS, aiding in the clinical diagnosis. Notably, the presence of CdLS might complicate the clinical management of EPTB with Rifampicin resistance due to potential challenges in medication adherence, monitoring, and addressing associated comorbidities.(15)

The diagnostic journey highlighted the significance of a multidisciplinary approach involving pediatricians, clinical geneticists, and infectious disease specialists to ensure accurate diagnosis and comprehensive management. Additionally, the socio-economic context, familial factors, and healthcare accessibility play pivotal roles in shaping the clinical outcomes and adherence to therapy. Early recognition, timely intervention, and holistic care delivery are crucial for the successful diagnosis and management of Drug-resistant EPTB and CdLS. Long-term follow-up and supportive care are essential to optimize the patient's overall well-being and mitigate complications.

Like many other case reports of TBL, this case presented with painless neck swelling and constitutional symptoms such as failure to thrive and lymphadenopathy.(16)The coexistence of CdLS adds a unique dimension to this case, distinguishing it from typical presentations of TBL alone. The diagnostic approach in this case involved a combination of clinical examination, imaging (X-ray, ultrasound), and molecular testing (Xpert MTB/Rif Ultra), which aligns with standard protocols for diagnosing TBL. The additional consideration of CdLS required a comprehensive phenotypic assessment and genetic evaluation, which may not be necessary in cases without syndromic features.(17)TBL and CdLS require multidisciplinary care from pediatricians, geneticists, and infectious disease specialists. TBL, like other similar cases, is treated with anti-tubercular therapy (ATT). The presence of CdLS may necessitate targeted interventions to address associated developmental delays, cognitive impairments, and limb abnormalities, influencing the overall management strategy. Long-term follow-up is required in both TBL and CdLS cases to

monitor treatment response, address complications, and improve outcomes. The prognosis and long-term outcomes may vary depending on the severity of CdLS features and the response to ATT for TBL.(16,17)

By comparing this case report with similar studies, clinicians can gain a broader perspective on the clinical spectrum, diagnostic challenges, and management considerations for complex medical conditions like TBL and CdLS. Additionally, identifying patterns and trends across cases can inform evidence-based practices and improve patient care outcomes.

CdLS is associated with a wide range of cognitive impairments, including intellectual disability, learning difficulties, and behavioral challenges. In order to address cognitive impairments and support learning and social integration, structured support can be offered through behavioral interventions and tailored educational programs.(18) For Limb abnormalities Orthopedic interventions can help improve mobility, function, and overall musculoskeletal health.(19).Collaborative care involving pediatricians, developmental specialists, therapists, educators, and support services is key to providing comprehensive and coordinated interventions.(20) Regular monitoring and reassessment of needs are necessary to tailor interventions to the individual's evolving needs and optimize outcomes over time.

CONCLUSION:

The case illustrates the complexity of encountering multiple medical conditions in a single patient, with TBL presenting as cervical lymphadenopathy and CdLS manifesting with distinctive craniofacial features, limb abnormalities, and developmental delays. The absence of typical respiratory symptoms in the context of TBL underscores the importance of considering tuberculosis in the differential diagnosis of neck masses. Molecular testing (Xpert MTB/Rif Ultra) played a crucial role in confirming the diagnosis of TBL with drug resistance, while clinical genetic evaluation confirmed CdLS. The case emphasizes how comprehensive evaluation and management of complex medical conditions such as TBL and CdLS require a multidisciplinary approach involving pediatricians, clinical geneticists, and infectious disease specialists. Each discipline contributed unique expertise to tailor interventions to the individual's needs. Tailored interventions were essential to address associated developmental delays, cognitive impairments, and limb abnormalities in CdLS. Anti-tubercular therapy (ATT) was initiated based on the molecular diagnosis of TBL, considering the patient's unique clinical and genetic profile. Long-term follow-up is crucial to monitor treatment response, address complications, and optimize patient outcomes in complex medical conditions. Regular monitoring by a multidisciplinary team allows for ongoing assessment and modification of treatment plans as needed.

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