Role of Cytology in Early Diagnosis of Cerebrotendinous Xanthomas

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Abstract
Cerebrotendinous xanthomatosis is a rare autosomal recessive lipid storage disease characterized by widespread tissue deposition of two neutral sterols, cholestenol and cholesterol, resulting in tendinous xanthomas, juvenile cataracts, progressive neurological defects, and premature death from arteriosclerosis. Because it is a treatable cause of cerebellar ataxia and dementia, its early diagnosis is desirable. Here, we have reported the case of an 11-year-old boy with this disorder who was diagnosed based on the cytological findings of fine needle aspiration and clinical features.

Keywords: Cerebellar ataxia, cerebrotendinous xanthomatosis, cholestenol

Introduction
Cerebrotendinous xanthomatosis is a rare inborn disorder of bile acid synthesis in which hepatic conversion of cholesterol to cholic and chenodeoxycholic acids is impaired.[1] The diverse symptoms include bilateral juvenile cataracts and chronic diarrhea, followed by progressive cerebellar ataxia and pyramidal tract signs, mental retardation, dementia, seizures, intellectual decline, premature atherosclerosis, and the development of tendon xanthomas (particularly of the Achilles tendons) in late adolescence and early adulthood.[2] Early diagnosis is important because patients benefit from therapy and the progress of the disease can be prevented.[3] Most cases have been reported to be diagnosed by neurological and radiological findings. Here, we report a case of cerebrotendinous xanthomatosis in a 11-year-old boy wherein cytomorphology has played an important role in the early diagnosis of the syndrome.

Case Report
A 11-year-old boy was referred to our department for fine needle aspiration cytology of multiple bilateral swellings of the legs by the orthopaedic outpatient department. The patient had bilateral presenile cataracts, subaverage intelligence, ataxia, and psychiatric symptoms (behavioral changes, agitation, aggression, depression) from an early age. There was history of frequent attacks of diarrhea during childhood. He was the youngest of three siblings. There was no history of consanguinity or similar illness in the family.

The swellings were insidious in onset and noted for the last 5 years. On examination, they were found to be firm, painless, not adherent to the underlying bone, and had a smooth surface. They were present bilaterally along the Achilles tendon, both ankles, and upper end of tibia [Figure 1a].

Roentgenogram of the swellings showed soft tissue shadows without any bony involvement. Fine needle aspiration was done from three sites of both the legs. The stained smears showed foamy histiocytes admixed with Touton giant cells having multiple nuclei arranged in a garland-like fashion surrounded by foamy cytoplasm. Some foreign body type of giant cells, few polymorphs, and large number of extracellular cholesterol crystals were present in the background [Figure 1b and c].

Biochemical tests revealed hemoglobin, total count, blood sugar and thyroid profiles within normal limits. Lipid profile revealed...
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This disease is exceptionally rare in the Indian population. More than 300 patients with CTX have been reported to date worldwide, and approximately 50 different mutations have been identified in the CYP27A1 gene, which is localized on the long arm of chromosome 2.[7] However, the prevalence of this syndrome is estimated to be several-fold higher (3 to 5 per 100,000). These underdiagnoses could be attributed to the absence of noticeable clinical manifestations in most cases, such as the apparent absence of xanthomas, especially when presenting only with neuropsychiatric symptoms.[2]

Tendon xanthomas, especially over the Achilles tendon, are characteristic of the disorder, however, they can also present elsewhere such as around elbow, patella, neck muscle tendons as well as affecting CNS, lungs, and bones.[6] In our case, the xanthomas were present in unusual sites such as around both ankles and upper end of tibia. Very few articles are available on the cytological features of tendinous xanthomas.[9-11] They have clinical and cytological resemblance to those seen in familial hypercholesterolemia or hyperlipoproteinemia, however, biochemical analysis reveals that they contain high amounts of cholestenol and normal cholesterol.

Although our patient had many classic features of cerebrotendinous xanthomatosis (including cataracts, tendon xanthomas, diarrhea, and a complex neurodegenerative disorder), the relative timing and combination of these features was distinctive and expands the cerebrotendinous xanthomatosis clinical spectrum. While the patients typically develop cataracts in their second or third decade and neurological symptoms usually occur after the third or fourth decade, our patient was unusual in presenting with both in the first decade of life.

Conventional magnetic resonance imaging studies are sensitive for diagnosis, and have shown focal/diffuse white matter abnormalities and different degrees of cerebral and cerebellar atrophy in these patients. The bilateral nonhomogeneous, hyperintense magnetic resonance signal in dentate nuclei, and surrounding cerebellar white matter can be considered as a neuroradiological feature suggestive of cerebrotendinous xanthomas and could become an important diagnostic marker.[6]

The presentation and course widely vary, and treatment can dramatically alter the natural history, especially with early initiation before the widespread deposition of cholestenol in neural tissues has occurred. The management includes replacement therapy, surgery, and other symptomatic therapy. A combination of chenodeoxycholic acid with HMG-CoA reductase inhibitors is the mainstay of therapy.[12]

Discussion

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Conclusion

Unfortunately, as in our case, the disease is not usually diagnosed before cholestenol has already been extensively deposited in many tissues. In Indian population, as also in our case, the socioeconomic condition of the patient who could not afford the diagnostic brain magnetic resonance imaging or confirmatory genetic analysis posed a hindrance for early therapy. Here lies the utility of aspiration cytology along with classical clinical features and normal serum cholesterol levels to diagnose cerebrotendinous xanthomatosis.

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Conflicts of interest

There are no conflicts of interest.

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