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Case Report

A young female of Cowden syndrome presenting with Lhermitte-Duclos disease: An illustrative case

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ABSTRACT

Background: Lhermitte-Duclos Disease (LDD), or dysplastic gangliocytoma, which is a benign hamartomatous condition involving the cerebellum, has a possible association with Cowden syndrome (CS), a rare autosomal dominant disorder due to germline mutations in the phosphatase and tensin homolog (PTEN) tumor-suppressor gene in chromosome 10. Combined CS and LDD cases are rarely reported in the literature.

Case Description: We present here a case of a young female patient presented at the emergency department with a severe headache associated with vertigo, vomiting, and cerebellar ataxia. A magnetic resonance imaging scan revealed mixed intensity posterior fossa lesion with almost preserved cerebellar cortical striations. Her facial skin had extensive trichilemmoma. Her symptoms improved after the excision of the posterior fossa lesion through suboccipital craniotomy and histopathology revealed LDD.

Conclusion: In a low-resource country where genetic testing for neurosurgical condition is still inadequate, we used the validated Cleveland Clinic Adult Clinical Scoring for PTEN Testing and the patient had an 82–98% chance for a PTEN gene mutation. Finally, she along with her family was adequately counseled and was advised for regular screening and monitoring since it is a premalignant condition where early detection is imperative if any cancer arises in the near future and is now under our follow-up.

Keywords: Cerebellar ataxia, Cowden syndrome, Lhermitte-Duclos disease, Malignancy, Phosphatase and tensin homolog, PTEN

INTRODUCTION

Multiple hamartoma syndrome eponym as Cowden syndrome (CS) is a rare autosomal dominant disorder.[5] This cancer predisposition syndrome is characterized by multiple hamartomas in a variety of tissues from all three embryonic layers due to the germline mutations of the phosphatase and tensin homolog (PTEN) tumor-suppressor gene.[2,5,8] CS belongs to PTEN hamartoma tumor syndrome (PHTS) which also includes Lhermitte-Duclos Disease (LDD), Bannayan-Riley-Ruvalcaba Syndrome, Proteus syndrome, Proteus like Syndrome, Segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus (SOLAMEN) syndrome, macrocephaly/autism syndrome, and juvenile polyposis syndrome.[1,8]

In addition, LDD is a rare disorder characterized by slowly progressive unilateral dysplastic gangliocytoma of the cerebellar cortex first recognized in 1920 by Lhermitte and Duclos.[7,8,11,13]

Besides, LDD is a rare condition, it is a very rare type of posterior cranial fossa tumor that can either arise as an isolated condition or with association with CS.[9,12] A literature search in November 2022 resulted in <230 articles on LDD in PubMed.

Adult LDD is considered as one of the pathognomonic criteria for diagnosing CS, along with mucocutaneous lesions, facial trichilemmomas, acral keratoses, and papillomatous papules.[6,10] However, adult-onset LDD and CS are considered as single phacomatosis that belongs to PHTS.[6,17]

Clinical symptoms generally arise from/are related to mass effect changes in the posterior fossa and can include headache, nausea, and visual disturbances and sometimes, might cause blindness too. These early symptoms can be controlled by sometimes through shunt placement (e.g., Ventriculoperitoneal shunting) which can help with the release of cerebrospinal fluid blocking. The severity of symptoms can vary depending on the size of the lesion, and patients with isolated LDD may be asymptomatic for years. If the lesion grows large enough, patients may also exhibit signs of cerebellar dysfunction and obstructive hydrocephalus.[9] Surgery is considered at that time to resect that abnormal growth. Table 1 gives a brief summary of LDD.[1,3,9]

CASE DESCRIPTION

Patient presentation

A young female patient (27 years old) presented at the Emergency Department of Dhaka Medical College Hospital on November 2020 with a severe headache associated with vertigo and vomiting. The neurological assessment revealed average intelligence and marked cerebellar ataxia. Papilledema was noted on fundoscopy. She had 2 years of history of headache with nausea. After primary resuscitation,

Table 1: Summary table of LDD.[8,12,13]

Etiology	PTEN mutation that leads to dysplastic gangliocytoma of the cerebellum.
Incidence	Highly rare – only <230 known cases of LDD have been published in PubMed-indexed literature as of November 2022.
Gender ratio	No gender predilection
Age predilection	Most frequently diagnosed in 2nd or 3rd decade
Risk factors	Genetic correlation between LDD and Cowden syndrome, an autosomal dominant syndrome characterized by multi-organ hamartomatous tumors
Treatment	Observation, unless mass effect symptoms warrant surgical intervention. Complete surgical resection is curative.
Prognosis	This is a slow-growing, benign tumor, so the prognosis is generally favorable.
Radiology	MRI is usually sufficient for diagnosis Gross: focal, well-circumscribed lesion restricted to one of the cerebellar hemispheres with folia hypertrophy. Widened cerebellar folia with apparently preserved striations; called corduroy/laminated appearance. T1: Hypointense signal T2: "Tiger stripes" appearance of alternating low and high signal or hyperintense with apparently preserved cortical striations.

LDD: Lhermitte-Duclos disease, PTEN: Phosphatase and tensin homolog, MRI: Magnetic resonance imaging

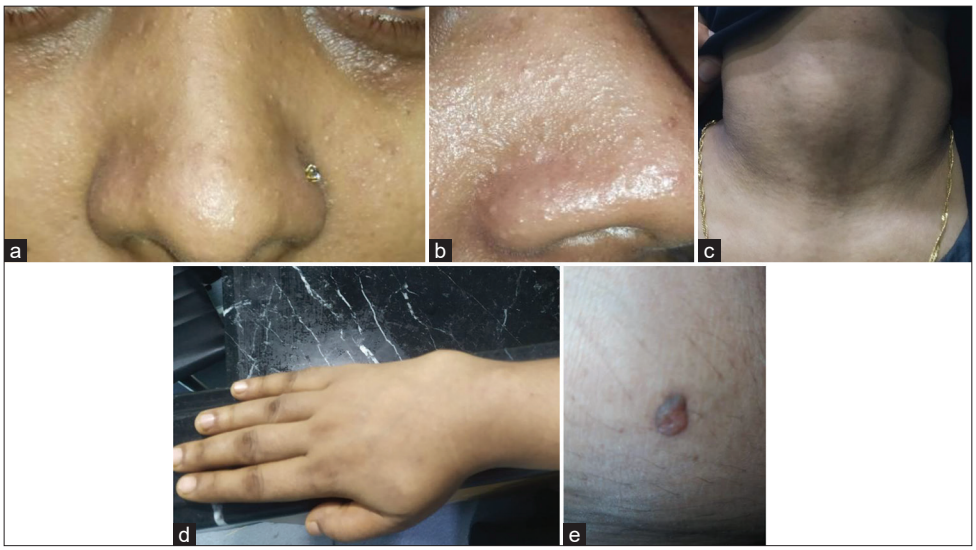


Figure 1: (a) Photo of face showing trichilemmoma (anterior view). (b) Photo of face showing trichilemmoma (anterolateral view). (c) Patient had neck swelling. Later confirmed by ultrasonogram as multinodular goiter with thyroiditis. (d) Soft swelling in lateral aspect of wrist joint. (e) Trichilemmoma of the thigh.

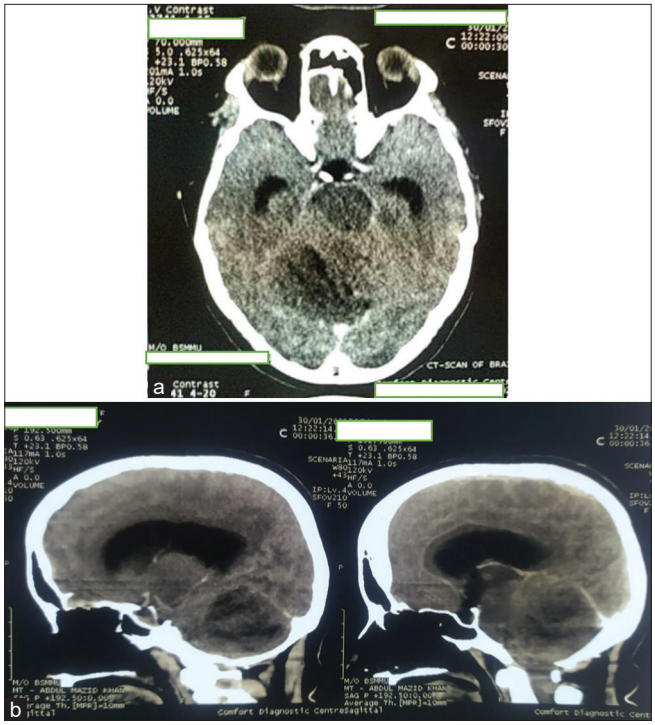


Figure 2: Initial contrast-enhanced computed tomography (CT) scan of brain (a) axial image and (b) sagittal section showing ill-defined hypodense area with mild heterogeneous enhancement in right cerebellum involving middle cerebellar peduncle having perilesional edema and mass effect compressing pons, effacement of 4th ventricle resulting mild dilatation of both lateral and 3rd ventricles.

detailed history and examination was carried out and previous records were checked. Clinical examination revealed mild anemia and firm flat-topped brownish papules over the face and hyperkeratosis over several areas in the body. Multiple lipomas were palpated in the limbs and torso. She also had neck swelling. Physical examination findings are shown in Figure 1. Computed tomography (CT) scan revealed a mildly heterogeneously enhancing mass lesion in the right cerebellar hemisphere with significant compression over pons and causing tri-ventriculomegaly [Figures 2 and 3]. Magnetic resonance imaging (MRI) scan T1-weighted image film revealed mixed intensity posterior fossa lesion and T2-weighted image film revealed an inhomogeneous hyperintense lesion with almost preserved cerebellar cortical striations [Figure 4]. Initially, we thought it to be a glioma or medulloblastoma from radiological imaging. However, we also kept LDD as a differential diagnosis due to the lesions classical appearance as seen in MRI.

The patient also gave us a recent history of cholecystectomy due to cholelithiasis. Before making the diagnosis of cholelithiasis, an ultrasonogram (USG) was done due to her complain of frequent abdominal pain [Figure 5a]. The resected gallbladder specimen revealed multiple adenomatous polyps [Figure 5b] and was also confirmed in histopathology. On breast examination, lumps palpated on both sides which were later investigated with USG revealed normal breast. Thyroid function was normal [Figure 5]. Figure 6 shows the USG of neck illustrating multinodular goiter with thyroiditis.

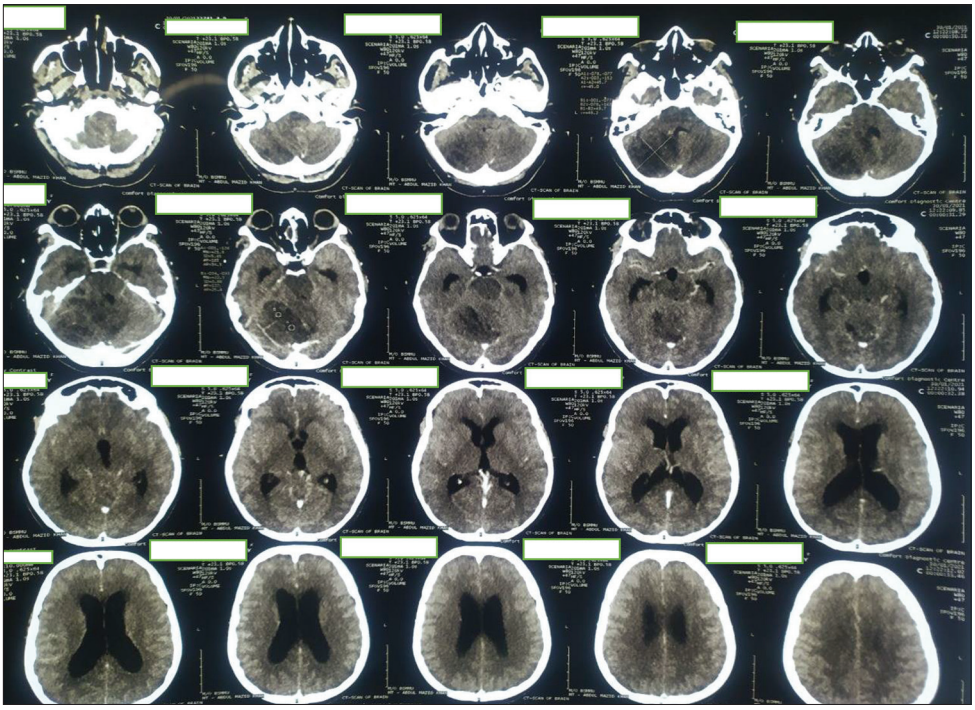


Figure 3: Pre-operative computed tomography (CT) scan of the head of the patient. CT feature consistent with mild heterogeneously enhancing mass lesion in right cerebellum and mass effect resulting involving middle cerebellar peduncle having perilesional edema triventriculomegaly.

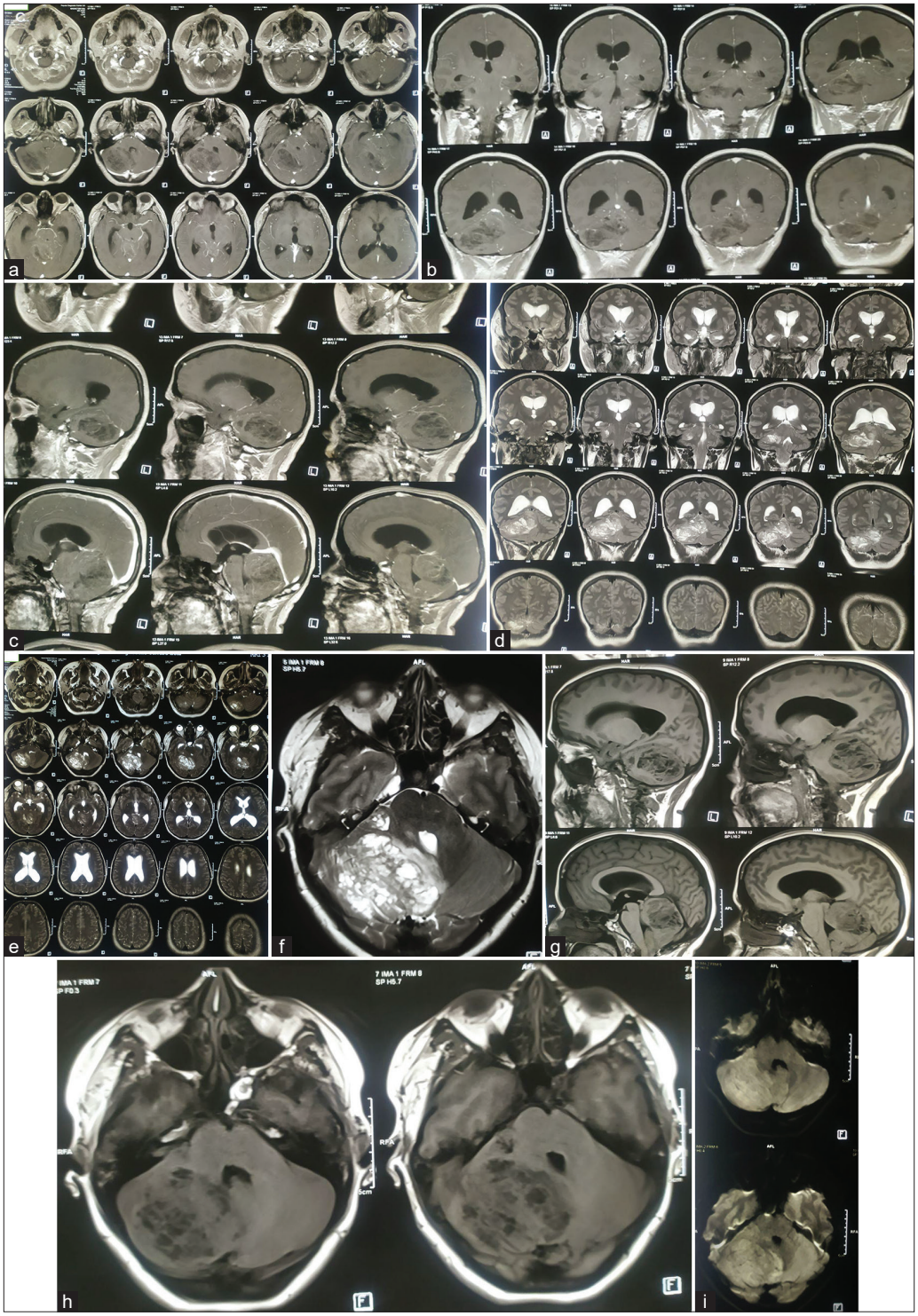


Figure 4: (a) Preoperative magnetic resonance imaging (MRI) of the brain of the patient. (a) T1 contrast axial sequences, (b) T1 contrast: coronal sequence, (c) T1 contrast: sagittal sequence, (d) T2-weighted image (T2WI) coronal Sequence, (e) T2WI axial sequence, (f) T2WI axial image focusing on cerebellar lesion, (g) T1-weighted image (T1WI) sagittal sequence, (h) T1 WI axial, and (i) diffusion-weighted imaging sequence. Contrast-enhanced MRI scan of brain showing mild heterogeneously enhancing, tigroid, or striated mass lesion on right cerebellum involving middle cerebellar peduncle having perilesional edema and mass effect compressing pons, effacement of 4th ventricle resulting tri-ventriculomegaly; suggestive of low-grade glioma. Differential – medulloblastoma, Lhermitte-Duclos Disease (LDD) (which was later confirmed in histopathology to be LDD).

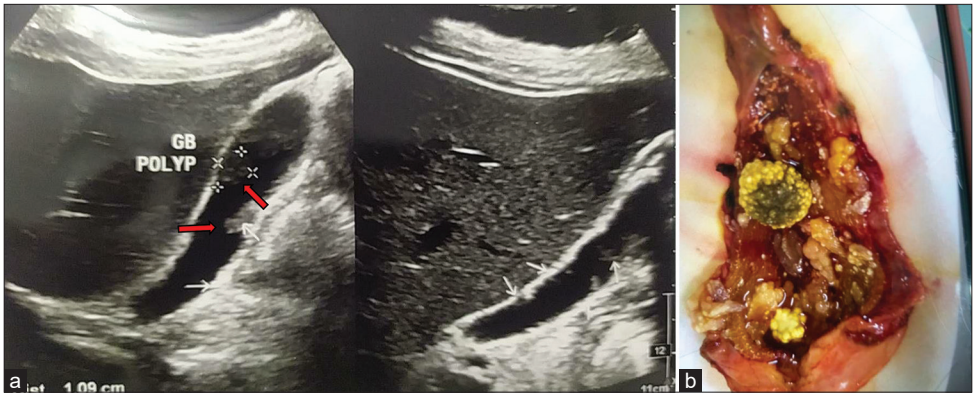


Figure 5: (a) Multiple gallbladder (GB) polyps with cholelithiasis; two mobile bright echogenic structures (marked in red arrows) in the lumen of gallbladder casting distal acoustic shadows (Larger one 1.5 × 0.6 cm). Numerous soft-tissue echogenic structures without acoustic shadows are seen adherent with both anterior and posterior wall. (b) Multiple GB polyps (5 or more) with pigmented stones after cholecystectomy.

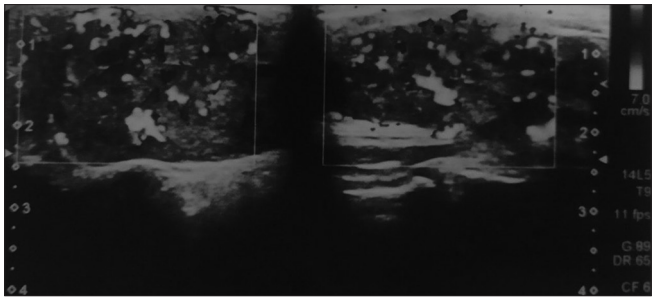


Figure 6: Ultrasonogram of neck suggestive of multinodular goiter with thyroiditis.

Management

The patient was monitored closely to figure out the treatment plan. With decisions from a multidisciplinary medical board, our patient underwent surgical excision of the posterior fossa lesion through suboccipital craniotomy which resulted in improvement of cerebellar symptoms. The patient underwent total resection of the cerebellar lesion. Figure 7 shows a postoperative CT scan. The subsequent histopathology of the resection lesion confirmed it to be a case of LDD [Figure 8]. It revealed derangement of the normal laminar cellular organization of the cerebellum. There was thickening of the outer molecular cell layer, loss of the middle Purkinje cell layer, and infiltration of the inner granular cell layer with dysplastic ganglion cells of various sizes and abundance of fibrillary astrocytes. These appearances went in favor of dysplastic gangliocytoma or LDD (differential diagnosis: fibrillary astrocytoma). As genetic testing is readily not that available and also very expensive in Bangladesh, the striated appearance of the affected side of the cerebellum, seen through MRI, is subjected to appear as one of the strongest indicators of LDD here. LDD has a very strong correlation with CS as described in the earlier section and our patient physical examination findings with clinical history suggest CS. All the findings of our patient going in favor of our diagnosis of CS are illustrated in Figure 9. Finally, all these clinical findings lead to a diagnosis of CS. The patient is on our follow-up and taking treatments accordingly. She took her last follow-up with us in June 2023.

DISCUSSION

Our previous provisional diagnosis was low-grade glioma or medulloblastoma from the initial radiological imaging at presentation. However, due to all these physical examination findings, clinical history, imaging, and histopathology, we concluded this case to be an LDD with CS. The diagnostic criteria for CS are as follows in Table 2.[6] Among the criteria discussed in Table 2, our patient had a cerebellar tumor, facial trichilemmomas, keratoses, gallbladder adenomatous polyps, and also a number of minor criteria (e.g., nodular goiter with thyroiditis, bulky uterus suggestive of fibroids, and lipomas). CS is an often "difficult-to-recognize" hereditary cancer predisposition syndrome caused by mutations in phosphatase and tensin-homolog deleted on chromosome 10 (PTEN).[6]

While significant functional research has been conducted, the full function of PTEN, the phosphatase enzyme is yet unknown.[17] It removes phosphate groups from tyrosine, serine, and threonine, and is crucial for downregulating the PI3K/AKT pathway. PTEN localizes to specific nuclear and cytoplasmic components. The wild-type protein acts as a lipid phosphatase, causing G1 cell cycle arrest and apoptosis, inhibiting cell migration, spreading, and downregulating cell cyclins. Germline pathogenic variants in PTEN, including missense, nonsense, splice site, and large deletions, contribute to the disease. Exon 5, which encodes the phosphate core motif, is a common location for pathogenic

Table 2: International Cowden consortium operational criteria for the diagnosis of CS.

Diagnostic criteria	Description
Pathognomonic criteria	
Mucocutaneous lesions*	Trichilemmomas*, Acral keratosis, Papillomatous papules*, Mucosal lesions
Major criteria	
LDD*	
Breast carcinoma	
Thyroid carcinoma (non-medullary)	Especially follicular thyroid carcinoma
Macrocephaly (megalencephaly)	≥95th centile
Endometrial carcinoma	
Minor criteria	
Other Thyroid Lesions*	For example, adenoma or multinodular goiter*
Mental retardation	Intelligence quotient ≤75
Gastrointestinal Hamartomas*	
Fibrocystic disease of the breast	
Lipomas*	
Fibromas	
Genitourinary tumours or malformation*	For example, renal cell carcinoma, uterine fibroids*
Operational diagnosis	
• Mucocutaneous lesions alone	
– Six or more facial papules, of which three or more must be trichilemmoma	
– Cutaneous facial papules and oral mucosal papillomatosis	
– Oral mucosal papillomatosis and acral keratoses	
– Palmoplantar keratoses, six or more	
• Two major criteria (one must include LDD or macrocephaly)	
• One major and three minor criteria	
• Four minor criteria	
Operational diagnosis in family where one person is diagnostic for CS	
• The pathognomonic criterion	
• Any one major criterion with or without minor criteria	
• Two minor criteria	

LDD: Lhermitte-Duclos Disease, CS: Cowden syndrome. *Marked ones are present in our patient.[6,15,16]

Table 3: Cleveland clinic adult scoring system to identify candidates for PTEN testing.

Manifestations	Score
Neurological	
Macrocephaly	6
Lhermitte-Duclos disease	10
Autism or developmental delay	1
Breast and Gynaecological	
Invasive breast cancer at age <40 years	4
Invasive breast cancer at age between 40 and 49 years	2
Fibrocystic breast disease	1
Endometrial cancer at age <30 years	10
Endometrial cancer at age 30–49 years	6
Endometrial cancer at age ≥50 years	1
Fibroids	1
Gastrointestinal	
Polyposis syndrome (≥5, any type)	6
Intestinal hamartoma or ganglioneuroma, any number	10
Glycogenic acanthosis	10
Skin	
Trichilemmomas, biopsy proven	10
Oral papillomas	6
Penile freckling	6
Acral keratosis	1
Arteriovenous malformations	6
Skin lipomas	1
Endocrine	
Thyroid cancer at age <20 years	10
Thyroid cancer at age <50 years	4
Thyroid cancer at age ≥50 years	1
Thyroid goiter, nodules, adenomas, or Hashimoto's thyroiditis (one or more features)	4
Genitourinary	
Renal cell carcinoma	1

According to the Cleveland Clinic Adult Scoring System, PTEN mutation testing is recommended for individuals with a total score of 10 or higher. An online CC score calculator can be accessed at http://www.lerner.ccf.org/gmi/ccscore/for convenient scoring.[4,16] PTEN: Phosphatase and tensin homolog

variants. Truncated, absent, or dysfunctional PTEN protein, resulting from pathogenic variants, leads to uninhibited AKT1 phosphorylation, impairing cell cycle arrest and apoptosis. Dysregulation of the mitogen-associated protein kinase pathway also occurs due to the lack of protein phosphatase activity. Consequently, derangements of both of these pathways contribute to the pathogenesis of abnormal cell survival and evasion of apoptosis.[17,18]

Genetic testing is confirmatory for CS diagnosis that typically involves identifying mutations or variants in the PTEN gene. In developed nations, there are certain standardized genetic assessments to diagnose CS such as multiplex ligation-dependent probe amplification, traditional Sanger sequencing, and next-generation sequencing (NGS). multiplex ligation-dependent probe amplification (MLPA®), a technique used to identify large deletions or duplications in the PTEN gene, involves hybridizing specific probes to the deoxyribonucleic acid (DNA) and subsequently amplifying them to detect copy number changes.[14] Sanger sequencing, also referred to as the "chain-termination method," is a technique that provides information about the sequence and arrangement of the four nucleotide bases in a DNA segment. Developed by Frederick Sanger and colleagues in 1977, it continues to be regarded as the gold standard in sequencing technology due to its high accuracy in detecting different diseases that include CS.[15] NGS is a deep sequencing technology that

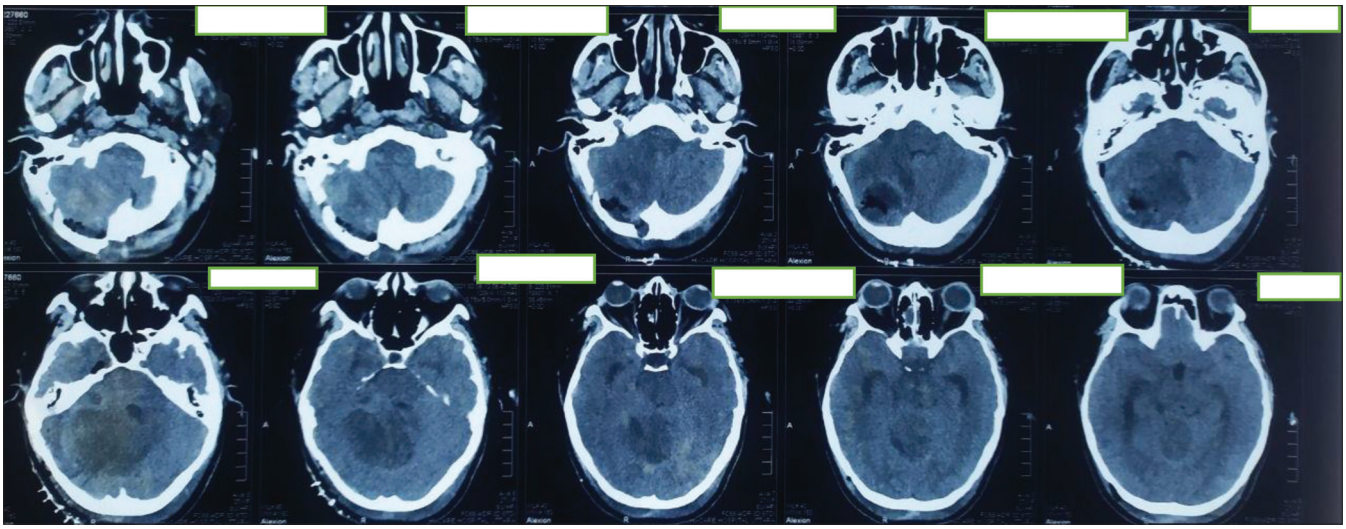
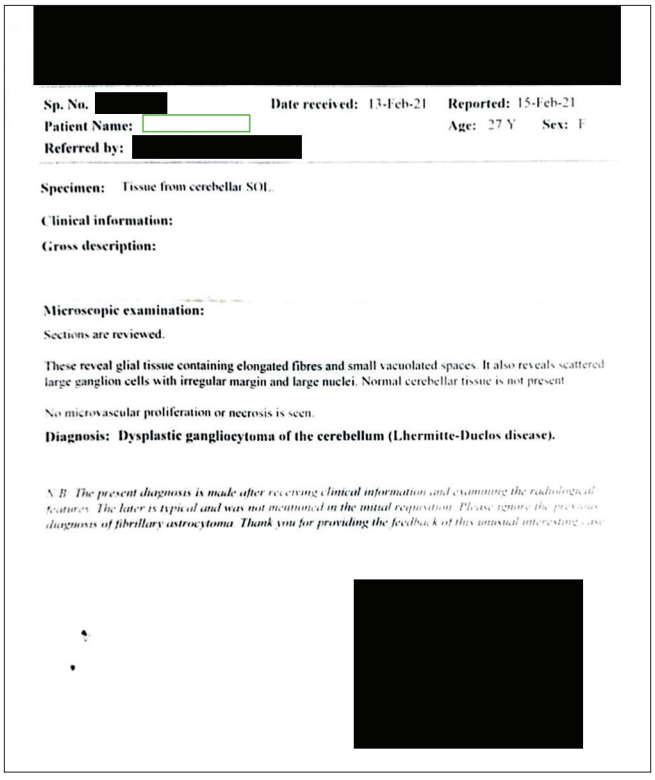


Figure 7: First postoperative day computed tomography scan. Large irregular mixed density area seen in the right cerebellum and extends in the right cerebellopontine angle region. Mass effect is evident by effacement of 4th ventricle and shifting of mid line towards left right side. Postoperative pneumocephalus and edema seen in right cerebellum and temporal lobe.



Sp. No. [redacted] Date received: 13-Feb-21 Reported: 15-Feb-21
Patient Name: [redacted] Age: 27 Y Sex: F
Referred by: [redacted]

Specimen: Tissue from cerebellar SOL.

Clinical information:

Gross description:

Microscopic examination:

Sections are reviewed.

These reveal glial tissue containing elongated fibres and small vacuolated spaces. It also reveals scattered large ganglion cells with irregular margin and large nuclei. Normal cerebellar tissue is not present.

No microvascular proliferation or necrosis is seen.

Diagnosis: Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease).

N.B. The present diagnosis is made after receiving clinical information and examining the radiological features. The later is typical and was not mentioned in the initial requisition. Please ignore the previous diagnosis of fibrillary astrocytoma. Thank you for providing the feedback of this unusual interesting case.

[redacted]

Figure 8: Histopathology report of the cerebellar SOL suggestive of Lhermitte-Duclos Disease. These reveal glial tissue containing elongated fibers and small vacuolated spaces. It also reveals scattered large ganglion cells with irregular margin and large nuclei. Normal cerebellar tissue is not present in the specimen.

simultaneously analyzes a panel of genes associated with PTEN.[14] Unfortunately, none of these standard genetic testing are available in Bangladesh for clinical use and public access to genomic testing is almost rare. Therefore, the patient was not able to receive any genetic assessment.

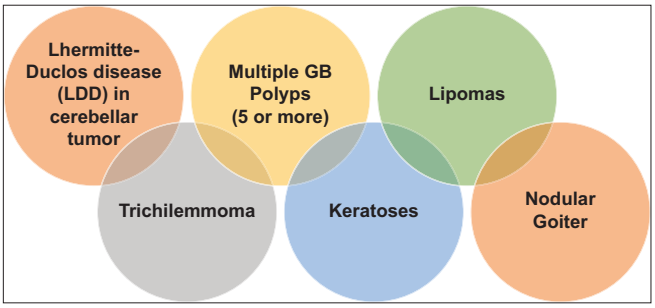


Figure 9: Suggestive features of the presented patient to Cowden syndrome.

That is why we used Cleveland Clinic Adult Clinical Scoring for PTEN Testing (can be accessed here: http://www.lerner.ccf.org/gmi/ccscore/).[4,16] Table 3 describes the scoring system. The online scoring tool showed that the patient had an 82–98% chance of a PTEN gene mutation. In a low-resource country where genetic testing is not yet widely available, the scoring system might aid to do genetic counseling for a predisposition for cancer. Our case may also guide physicians from low-resource country to do genetic counseling in such diseases based on other clinical findings even without genetic testing due to financial constraints or patient's nonadherence. Since this is a genetic disorder and can be associated with other malignancy, our patient along with her family was adequately counseled and was advised for regular screening and monitoring.

CONCLUSION

It is captivating how a single genetic mutation can lead to a broad variety of abnormalities, as seen in our case, necessitating surgery, family counseling, and monitoring the patient carefully. While genetic testing for such disorders is not possible in low-resource country, thorough clinical examination and proper laboratory investigations and imaging should be done as early as possible to lessen the complications and detect or exclude associated malignancies that might appear someday in the future. Proper counseling for early identification of precancerous symptoms and regular follow-up is instrumental in treating this rare genetic condition.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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