Case Report

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Surgery Section

Arteriovenous Malformation of Lower Lip in Familial Cerebral Cavernous Malformation Syndrome: A Case Report

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ABSTRACT

Familial Cerebral Cavernous Malformations (FCCM) is a genetic condition marked by the presence of numerous vascular abnormalities within the brain and spinal cord. These lesions are composed of closely packed, thin-walled vascular spaces lined by endothelium, varying in size from a few millimetres to several centimetres. Despite the potential manifestations, approximately half of those with FCCM may never experience any related symptoms throughout their lives. We present a rare case of a middle-aged female with FCCM syndrome who was diagnosed with an Arteriovenous Malformation (AVM) of the lower lip. It is characterised by the presence of a bluish, compressible and pulsatile swelling. Symptoms often appear between the second and fifth decades of life and may include seizures, neurological deficits, headaches, or haemorrhages, though many individuals remain asymptomatic. Diagnosis is based on imaging findings and genetic testing while treatment focuses on managing symptoms and surgically addressing problematic lesions when necessary. This report highlights the coexistence of these vascular anomalies, emphasising the congenital, clinical and therapeutic considerations involved in managing such patients.

Keywords: Autosomal dominant, Capillary, Familial, Haemagioma

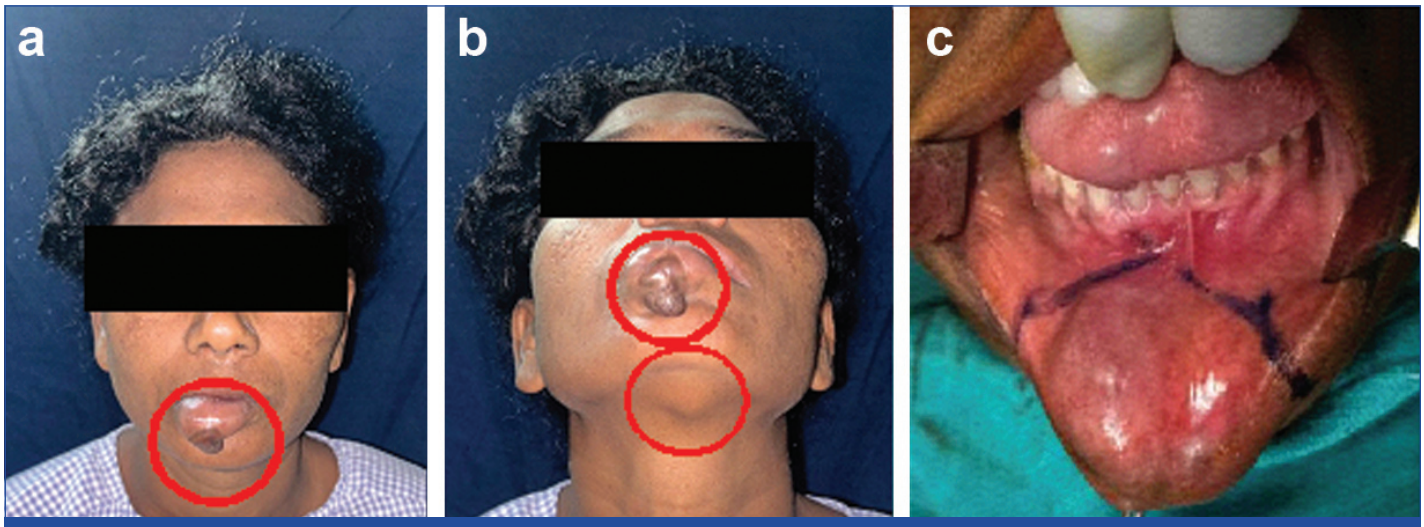
CASE REPORT

A 38-year-old female with a chief complaint of swelling over the lower lip for 20 years visited the oral and maxillofacial surgery department at our institute. She was a lean built individual with no previous significant medical or dental history. She presented with multiple swellings all over her body with aesthetic concern regarding the swelling over the lower lip. The swelling over the lip was small sized initially and had gradually increased to the size of 3×2 cm approx. developing gradually over the last 20 years extending below the lower vermillion border. There was history of occasional bleeding from the lesion. On examination it was a localised, irregular in shape- rounder on the superior and more lobulated on the inferior side, darker than normal skin in colour, with diffused borders, soft on palpation, non-tender, pulsatile and non-indurated swelling, causing discomfort and intermittent bleeding [Table/Fig-1a-c]. Main concern for the patient was the unpleasantness of the swelling. On general physical examination, it was found that she had multiple such swellings all over her body [Table/Fig-2a-f]. On taking familial history, her father and brother gave evidence of similar presentation of swellings which signifies the familial decent and hereditary relevance [Table/Fig-3a-e].

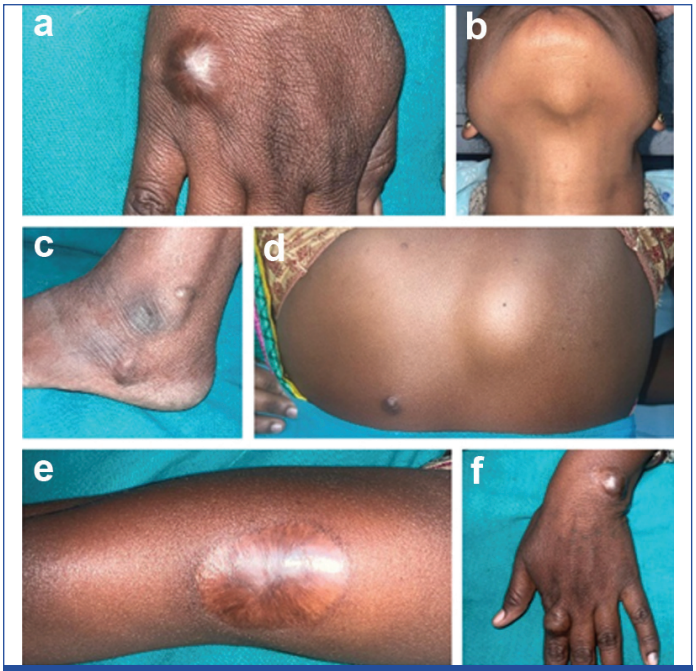
She also gave history of seizure episodes once per year in frequency for the past three years approx. which lasted for a maximum duration of 10 minutes. Patient had visited several centres for last 20 years where cytopathological investigations, ultrasonography imaging were carried out, details of which were incomplete leading to indefinite conclusions. There was no previous evaluation done for the FCCM syndrome before the patient visited our centre.

MRI brain and neck [Table/Fig-4a-i] demonstrated “hyperintense lesions in bilateral infratemporal fossa, bilateral buccal space, tongue, sublingual space, floor of the mouth, left tonsillar fossa, left retro and para-pharyngeal space extending to submandibular region, vallecular, bilateral strap muscles, supra-clavicular region, which were suggestive of multiple cavernous malformations/slow flow venous malformations”.

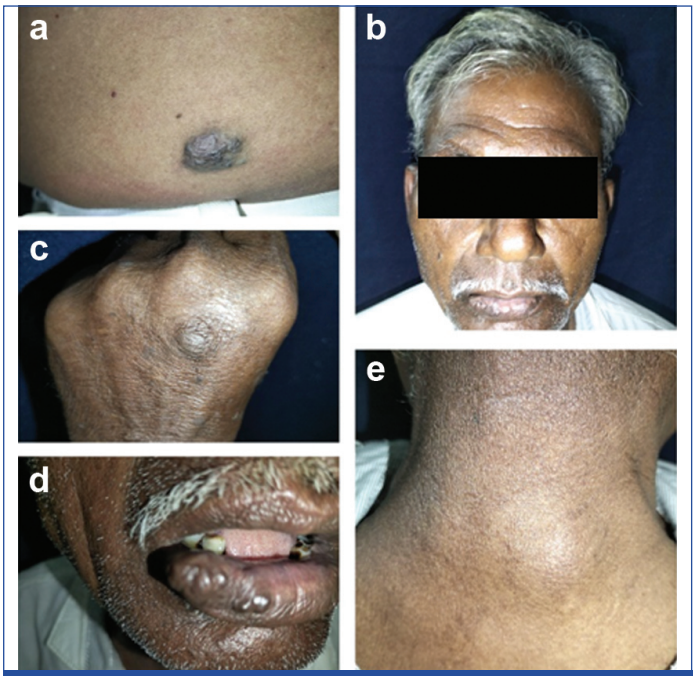
Doppler ultrasound of the lip report was suggestive of as a slow-flow vascular lesion consistent with AVM. Whole body STIR cor screening suggested “lesions in bilateral scapular region, bilateral shoulder,



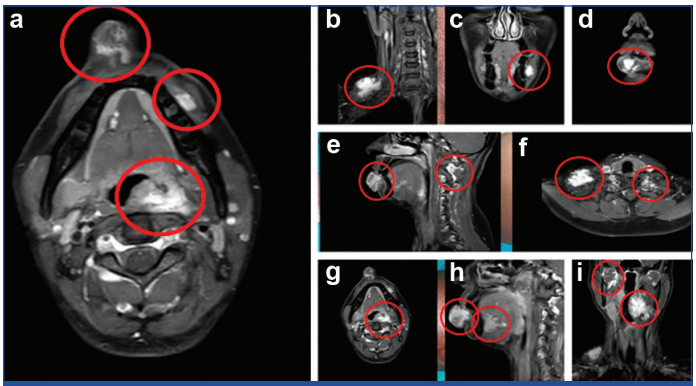
[Table/Fig-1]: (a) Frontal (b) Worm’s view clinical photograph of the patient (c) Intraoral pre-operative photograph.



[Table/Fig-2]: a-f) Multiple AV malformations over the various body parts of the patient as seen in FCCM syndromic patients.



[Table/Fig-3]: a-e) Multiple AV malformations over the various body parts of the patient's father signifying the hereditary relationship of the syndrome.

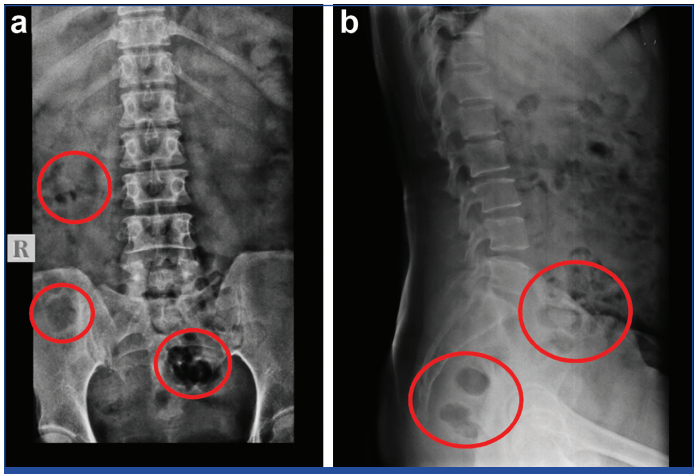


[Table/Fig-4]: a-i) MRI brain and neck -showing multiple cavernous malformations/slow flow cavernous malformations in various cuts representations, circle marked shows scattered vascular malformations as seen in the scan.

upper back, arms, forearms, thighs, gluteal region, in spleen, anterior to left kidney, bilateral adnexa, etc. The findings were suggestive of multiple cavernous malformations/slow flow venous malformations".

Patient's routine blood investigations were all within normal limits with increased D-Dimer levels of 3006 ng/mL {Normal value is below 500 ng/mL [1]}.

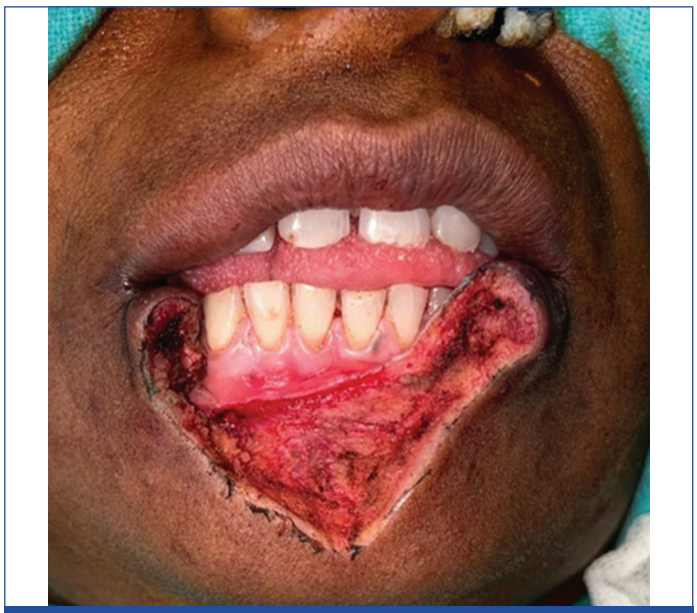
She was advised a full body MRI scan for assessment of various other located lesions and swelling. The radiographs [Table/Fig-5] and MRI report were suggestive of lesions in the abdomen, spleen, anterior to the lower pole of left kidney, bilateral adnexa, etc., Patient was also advised molecular genetic testing for the molecular diagnosis of the condition but due to economical constraints, was not willing for the same.



[Table/Fig-5]: a,b) shows the X-ray imaging of the abdomen and pelvis.

Owing to all the clinical findings noted and familial history with radiological findings, a final diagnosis was confirmed of FCCM syndrome.

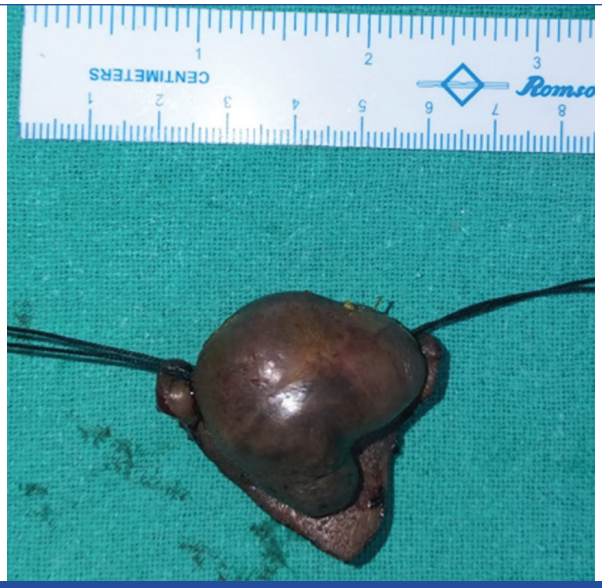
She was planned for excision of the AVM [Table/Fig-6] over lower lip under general anaesthesia. Local excision of the cavernous lesion which was more than 4×3 cm [Table/Fig-7] and primary closure [Table/Fig-8,9] was done as it was a slow-flow malformation.



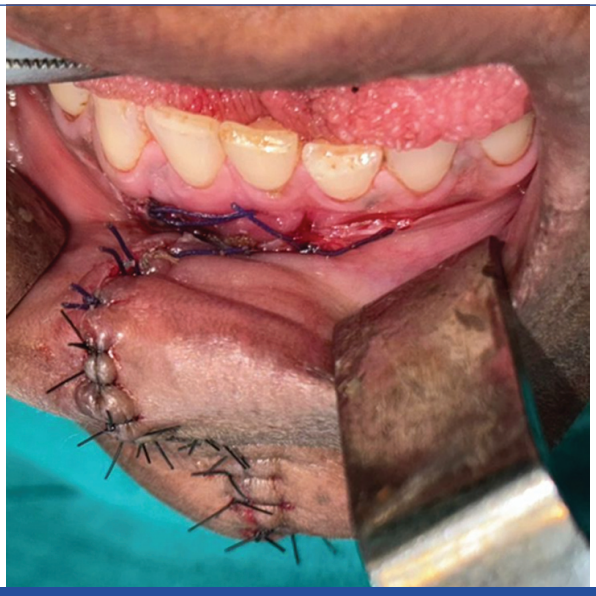
[Table/Fig-6]: Surgical defect created due to excision of the malformation.

Careful ligation of feeding vessels during resection was done by blunt dissection and tying the vessels with 3-0 vicryl sutures. Smaller vascular branches were cauterised with a bipolar electrocautery. Complete lesion excision were performed to minimise recurrence.

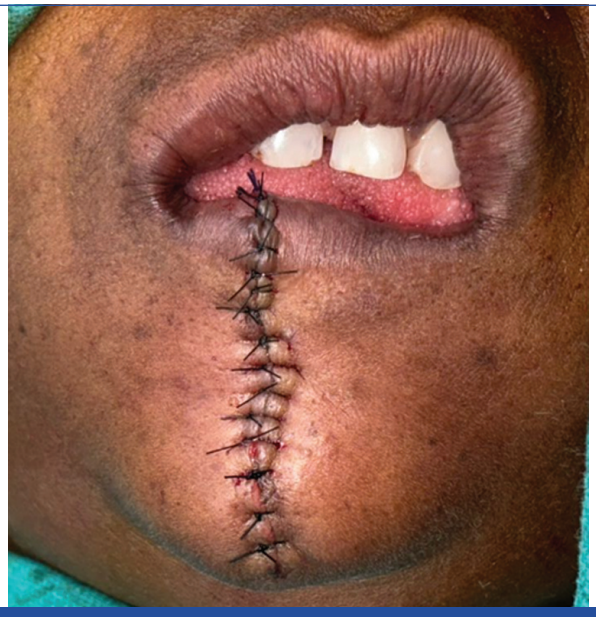
Postoperative healing and recovery was uneventful [Table/Fig-10]. Patient was discharged and was maintained on regular follow-up. Post-operative histopathology report was suggestive of "Arteriovenous malformation". Microscopic image revealed stratified squamous epithelium overlying fibrous connective tissue, which was infiltrated by neutrophils, lymphocytes, and mast cells. In the



[Table/Fig-7]: Excised specimen.



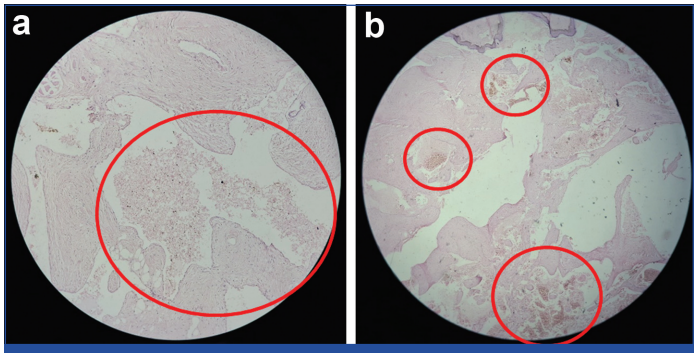
[Table/Fig-8]: Immediately post-op intraoral closure.



[Table/Fig-9]: Immediately post-op extraoral primary closure.

deeper layers, the connective tissue exhibited numerous vascular channels of different calibres with both thick and thin walls. Some of these channels appeared empty, while others were surrounded by regions of haemorrhage [Table/Fig-11a,b].

[Table/Fig-10]: Follow-up clinical photograph of patient at 6 months postoperative period showing healing of the primary closure site over the chin region with minimal scar tissue formation with satisfactory results.



[Table/Fig-11]:a) Histopathological picture of the AVM stained with H & E stain (5x magnification); b) 3x magnification, marked circles are the various irregular vascular malformaltions with varied uptake of dye with differing characteristics and sizes.

Neurological follow-ups included MRI scans every six months to monitor CCM. No new neurological symptoms or extracranial lesions at the 1-year follow-up were noted.

DISCUSSION

The lesions with direct communications between endothelial-lined artery/arteries and vein/veins bypassing the capillary bed collectively comprise of the arterio-venous malformations [2]. Head and neck AVMs are found in 0.1% of the population, with extracranial AVMs comprising only 8.1% of these cases. Vascular abnormalities may affect any section of the vascular tree; arteries, capillaries, veins, or lymphatics, or a combination of these [3]. AVMs are vascular lesions characterised by direct arterial-to-venous connections without an intervening capillary bed [4]. While isolated AVMs are often sporadic, they can occur in the context of syndromic conditions such as Hereditary Haemorrhagic Telangiectasia (HHT) or Parkes Weber Syndrome [5]. FCCM syndrome represents rare yet significant vascular pathology with presence of multiple cavernous malformations often in the Central Nervous System (CNS) which predisposes to haemmorhages, seizure activity and neurological deficits [6]. The presence of an AVM in an FCCM patient is usual and may indicate an overlap or shared mechanisms in vascular anomaly syndromes encompassing genetic testing in addition to refined clinical and radiological assessment via a multidisciplinary approach [7].

Symptomatic lesions presenting with haemorrhage, mass effect, intractable seizures, or focal neurologic deficits are managed by

surgical resection, when feasible; radiosurgery (e.g., SRS) may be considered for deep or surgically inaccessible lesions. Seizures and headaches are treated symptomatically with standard antiepileptic drugs and pain management, along with rehabilitation for neurologic deficits. Surveillance includes regular brain MRI with susceptibility-weighted imaging for new neurologic symptoms, and genetic testing for at-risk family members when the pathogenic variant is known [8].

The total number of CCMs in a person can range from just a few to several hundred, commonly between 6 and 20, depending on the individual's age and the sensitivity of the imaging technique used. While CCMs can be observed in infancy or childhood, most cases are diagnosed between the ages of 20 and 50 years, either accidentally or due to clinical symptoms such as seizures, localised neurological impairments, headaches, or intracerebral bleeding. Additionally, about 9% of individuals may present with vascular lesions on the skin, and nearly 5% may have retinal involvement [8].

FCCM follow an autosomal dominant inheritance pattern. In most cases, affected individuals have a parent who also shows symptoms of the condition. However, the exact percentage of cases resulting from a new (de novo) mutation is currently unclear. Each offspring of a person with FCCM has a 50% likelihood of inheriting the disease-causing genetic variant. When a specific pathogenic variant is known within a family, options such as prenatal diagnosis and preimplantation genetic testing can be considered for pregnancies at risk [6].

FCCM is caused by mutations in one of the three genes: KRIT1 (CCM1), CCM2, or PDCD10 (CCM3) [9], being a crucial component, these genes encode proteins that regulate endothelial cell signalling pathway, vascular permeability, and angiogenesis. Mutations in these genes disrupt endothelial barrier integrity which in turn forms structurally weak and leaky blood vessels, which predispose patients to cavernous malformations. Most commonly occurring mutation is seen in KRIT1 gene whereas the most severe mutation is seen in PDCD10/CCM3 gene [9]. The variability in size, shape, location depicts the phenotypic heterogenecity of this syndrome with its familial decent and genetic pre-disposition. Endothelial dysfunction in FCCM could extend beyond the CNS, potentially explaining the occurrence of extracranial vascular anomalies. The diagnostic flow is challenged as there is a variable clinical presentation of the syndrome such as multiple AVM's, delineating neurological symptoms like seizures, cranial malformations, deficits, etc., Magnetic resonance imaging play a pivotal role in interpreting the disease. A modality, Gradiant Echo is also implied to differentiate the vascularities from other vascular malformations as slow flow formations [6]. The genetic basis of the condition may be missed in certain individuals who carry the mutation but appear to have a sporadic case, presenting with only a single lesion [10].

The presence of epilepsy during assessment serves as a strong indicator for future seizure activity, highlighting the need for tailored treatment approaches. Further investigations involving larger patient groups are crucial to enhance the knowledge and clinical handling of fCCMs [11]. Relatives of any age who are at risk but show no symptoms can undergo genetic testing if the pathogenic variant specific to the family has been identified, enabling early detection and ongoing surveillance for potential development of CCMs [12]. A study comparing FCCM syndrome and Cerebral Amyloid Angiopathy (CAA), identify key clinical and MRI-based distinctions. FCCM typically presents earlier, has genetic links, and specific lesion patterns, enabling differentiation from CAA using proposed diagnostic criteria and avoiding unnecessary invasive testing [13]. In paediatric FCCM group, the 5-year annual and cumulative risk of symptomatic bleeding aligns for both children and adults with various forms of CCM. Initial brain MRI findings may offer predictive value for symptomatic haemorrhage [14].

In a study by Han HH et al., a 13-year-old boy with a posttraumatic lower lip AVM underwent successful preoperative embolisation followed by surgical excision witnessed by the efficient collaboration between surgical and interventional radiology teams led to a well-defined resection and no recurrence over six months [15].

This case can be summarised as a young woman who presented with a family history of vascular anomalies, was advised genetic testing due to suspected FCCM, highlighting complex genotype- phenotype variability and management challenges. Early detection of lesions- especially in cosmetically or functionally critical areas- can prevent haemorrhage or infection. Treatment ranges from observation to surgery based on symptoms like haemorrhage or seizures. The help of Interventional radiology in the form of sclerosants, Liquid embolic agents, endovenous laser or mechanical occlusion devices can be employed for symptomatic malformations that are not suitable for surgical excision [16]. Complete excision is preferred to minimise recurrence which can cause seizures if occurring in brain [9]. During treatment, surveillance imaging of both CNS and extracranial lesions is essential through MRI and doppler to check up on the treated lesions, their recurrence/growth and to assess if there are any newly formed malformations. Given the hereditary nature of FCCM, family members should undergo genetic screening.

CONCLUSION(S)

This case highlights a rare association between FCCM and a lower-lip AVM, broadening the spectrum of vascular anomalies linked to FCCM. It enlightens the importance of differential diagnosis and emphasises as for better understanding the pathogenesis and refine management strategies to optimise both functional and cosmetic outcomes. Further research is needed to establish the prevalence of extracranial vascular anomalies in FCCM patients, elucidate shared genetic or molecular pathways between FCCM and AVMs, develops targeted therapies that address vascular dysregulation in FCCM and its associated anomalies.

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