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Multifocal extracardiac rhabdomyomas: extending the phenotype of Birt–Hogg–Dubé syndrome

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Potential therapies used in MIS-A include intravenous immunoglobulin (IVIg), aspirin, anticoagulation, corticosteroids and tocilizumab.[1] With our evolving understanding of K-MIS-A, treatment protocols are yet to be standardized. Although we gave only anticoagulants to our patient, he recovered completely without any cardiac sequelae, as seen at follow-up. The CDC's detailed data on 27 cases of MIS-A included two cases with deranged inflammatory markers, ECG and TTE changes, which recovered on only anticoagulants without IVIg or steroids.[1] Hence, there might be a subset of patients with K-MIS-A who may recover spontaneously without conventional therapies. The focus of our case is to reiterate the possibility of COVID-19-associated K-MIS-A and timely diagnosis through early identification of dermatological manifestations and antibody testing, even when COVID-19 RT-PCR is negative. Further information on the investigations is available on direct request.

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Multifocal extracardiac rhabdomyomas: extending the phenotype of Birt–Hogg–Dubé syndrome

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Dear Editor, Birt–Hogg–Dubé (BHD) syndrome is characterized by a triad of benign skin tumours, pulmonary cysts with an attendant risk of pneumothorax and renal cancer. BHD is caused by heterozygous pathogenic variants in *folliculin* (*FLCN*), a tumour suppressor gene. Single cardiac and extracardiac rhabdomyomas have been infrequently reported[1] in patients with BHD, but not conclusively linked as part of the phenotype as these may have been coincidental events. Here we report a case of a patient with BHD with multifocal extracardiac rhabdomyomas, adding evidence to support rhabdomyomas as part of the BHD phenotype.

A 63-year-old man presented complaining of fullness in the submandibular region. He had multiple facial fibrofolliculomas and trichodiscomas (Figure 1a), for which he previously received ablative laser therapy. He was known to carry a familial heterozygous germline pathogenic variant in *FLCN* [NM_144997.5: c.469_471delTTC (p.Phe157del)] and had two brothers who were also carriers of the pathogenic variant. This variant segregated with the BHD phenotype in this family and has been reported in several prior BHD syndrome pedigrees.[1] One affected brother had a history of unilateral human papillomavirus-positive tonsillar squamous cell carcinoma, which had metastasized to the lymph nodes. Ultrasound and computed tomography studies of the head and neck in the proband demonstrated three homogeneous soft-tissue masses within the left submandibular and bilateral sublingual spaces (Figure 1b). A percutaneous ultrasound-guided core biopsy was obtained from the left submandibular tumour. Histological examination revealed large eosinophilic cells with occasional cross-striations, interspersed with pale areas. Immunohistochemistry demonstrated strong positivity for desmin in keeping with rhabdomyoma (Figure 1c). Rhabdomyoma DNA analysis demonstrated loss of heterozygosity (LOH) at the site of the patient's *FLCN* pathogenic variant, compared with control tissue (Figure 1d). Subsequent imaging has shown these tumours to have remained static over a 4-year period.

Extracardiac rhabdomyomas are categorized as adult, fetal and genital types.[2] Adult-type extracardiac rhabdomyomas have a predominance in men (average age of presentation 65 years) with the head and neck being the main site.[3] Patients may present with dysphagia and hoarseness, and other symptoms may include pain and new-onset snoring. Multifocal extracardiac rhabdomyomas are rare, with 33 cases ever reported, predominantly in male patients over the age of 50 years.[3] Such cases are suggestive of a genetic predisposition; however, unlike cardiac rhabdomyomas

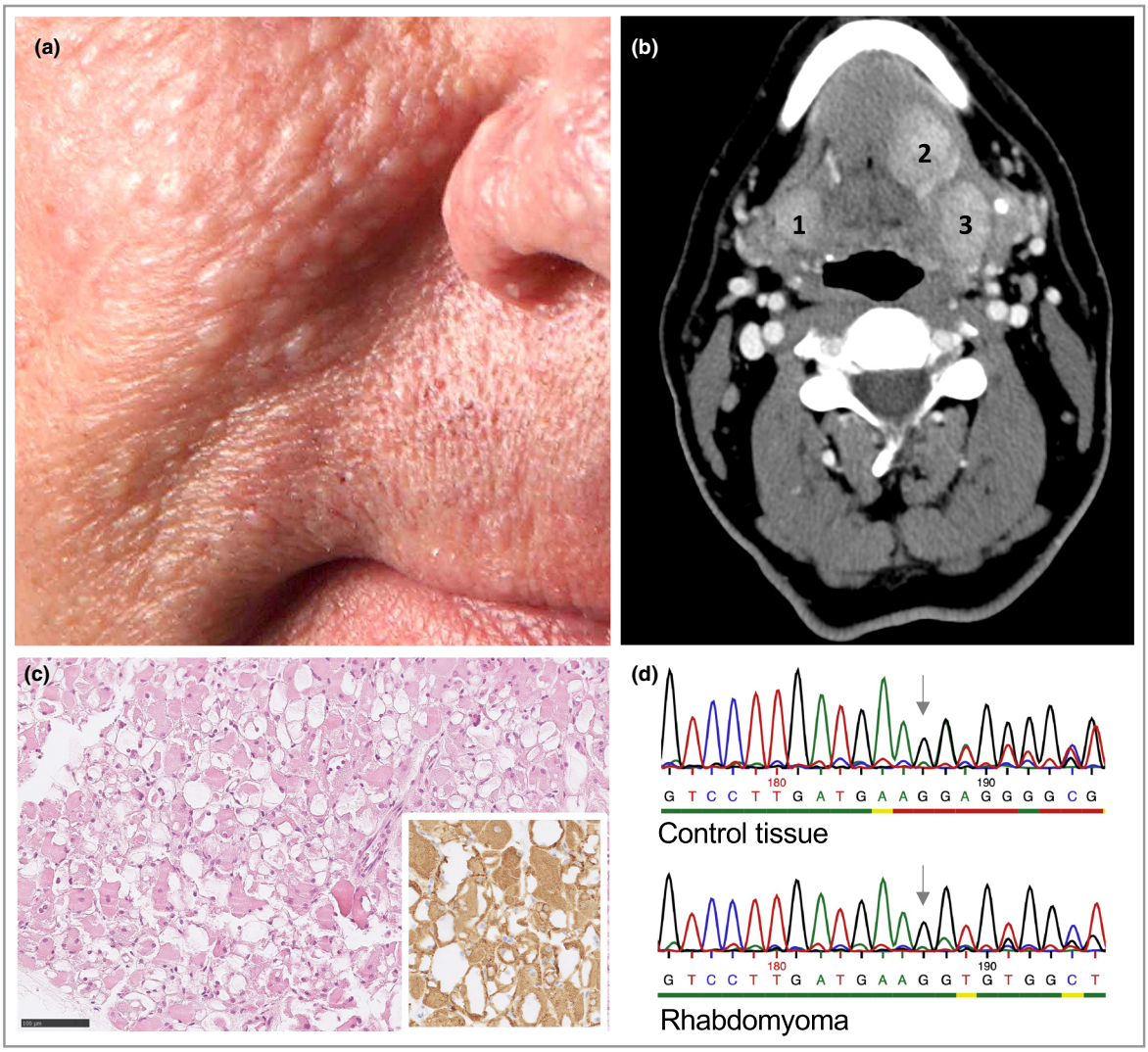

Fig 1 (a) Facial trichodiscomas and fibrofolliculomas. (b) Axial contrast-enhanced computed tomography showing right sublingual (1), left sublingual (2) and submandibular (3) rhabdomyomas demonstrating moderate enhancement and smooth margins. An incidental adjacent calculusis seen within the submandibular salivary gland. (c) Immunohistochemistry of rhabdomyoma, showing strong positivity for desmin (inset). (d) Sanger sequencing demonstrating the germline heterozygous *FLCN* pathogenic variant, with loss of heterozygosity evident in the rhabdomyoma.

which have been reported in tuberous sclerosis and Möbius syndrome,[4] a genetic basis has not been elucidated.[3,5] It is of interest that in one case of multifocal extracardiac rhabdomyomas,[3] multiple perinasal papules were noted; however, BHD was not considered and a skin biopsy was not performed.

There have been prior reports of BHD and single extracardiac rhabdomyomas reported in the larynx[2] and parathyroid glands.[6] In addition, a case of two cardiac rhabdomyomas has been reported in a 5-month-old boy, presenting with an out-of-hospital cardiac arrest. Notably, that child carried the same pathogenic variant in *FLCN* as our patient, and had no pathogenic variants in the tuberous sclerosis genes *TSC1* or *TSC2*.[1] Finally, in the Nihon rat model of BHD (which carries a germline *FLCN* pathogenic variant), cardiac rhabdomyomas are reported in 12% of heterozygote rats.[1]

FLCN is located on chromosome 17 and plays a role in regulating diverse metabolic and cellular pathways, including the mammalian target of rapamycin (mTOR) signalling pathway.[7] As the TSC1/TSC2 complex also regulates mTOR signalling, it has been suggested that deregulated mTOR signalling may account for rhabdomyoma formation in both tuberous sclerosis and BHD syndrome.[2] LOH, a frequent genetic event in tumour predisposition syndromes, is seen to involve *FLCN* in BHD-related renal cancer, but has not been demonstrated in the keratinocytes of fibrofolliculomas.[8] Our case reporting the multifocal presentation of extracardiac rhabdomyomas, and the demonstration of LOH of *FLCN* in rhabdomyoma tissue, adds support to rhabdomyoma being an infrequent but linked phenotypic feature in BHD. Patients with multifocal rhabdomyomas may benefit from phenotypic assessment to determine whether they satisfy clinical diagnostic criteria for BHD syndrome. If confirmed to carry a pathogenic variant in *FLCN* following genetic testing, they may benefit from genetic counselling, advice regarding the risk of pneumothorax and renal cancer surveillance.

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Adalimumab dose intensification in hidradenitis suppurativa: effectiveness and safety results of a multicentre study

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Dear Editor, Adalimumab is the only approved biologic therapy for the debilitating skin condition hidradenitis suppurativa (HS). Although several clinical trials, as well as real-world studies, support its efficacy at dosages of 40 mg per week or 80 mg every other week,[1–3] a subgroup of patients may show insufficient disease control or a progressive loss of response with time. Dosage intensification is an effective strategy in other chronic inflammatory diseases, such as Crohn disease (CD), rheumatoid arthritis and psoriasis, but evidence regarding HS is scant.[4] This study analyses the effectiveness and safety of adalimumab intensification in patients with moderate-to-severe HS in a multicentre cohort.

Data were collected from a prospective, descriptive study of patients with HS treated with subcutaneous adalimumab 80 mg every 7–12 days at the dermatology department of University Hospital Doctor Peset, Valencia, between January 2015 and December 2020. These data were combined with retrospective studies of adalimumab dose intensification in HS from the department of dermatology of Tallaght University Hospital, Dublin, and the study of Zouboulis *et al.*[4] Study variables measured in the entire cohort included patient demographics, comorbidities and HS classification. As intensification doses of adalimumab were variable, the results of each study were calculated in monthly cumulative doses.

The primary endpoint was clinical response to adalimumab dose intensification, which was assessed by the Hidradenitis Suppurativa Clinical Response (HiSCR) and International Hidradenitis Suppurativa Severity Score System (IHS4). Achievement or not of HiSCR was assessed and IHS4 was calculated at weeks 4–12 in the entire cohort and at week 24 in the prospective study. The Dermatology Life Quality Index (DLQI) and incidence and severity of side-effects according to the Common Terminology Criteria for Adverse Events classification were evaluated as secondary endpoints. Quantitative variables were described as the median value and interquartile range (IQR), and qualitative variables as frequencies. Statistical significance was calculated with a one-tailed Wilcoxon signed-rank test or exact Wilcoxon–Mann–Whitney test. Variable correlation was assessed by Spearman's rho.

Thirteen patients were included in the prospective study (five female, eight male), with a cumulative adalimumab dose of 200 mg per month in five of 13 patients (80 mg per 12 days) and 240 mg per month in eight of 13 patients (80 mg per 10 days). The retrospective studies included 22 patients (13 female, nine male), with a monthly cumulative dose of 320 mg per month (80 mg per 7 days) (Table 1). The median duration of standard-dose adalimumab treatment prior to intensification was 32 months (IQR 13·5–48).

HiSCR response was similar in both groups; overall at week 12 it was achieved by 23 of 35 patients (66%). The median IHS4 of the entire cohort at baseline (before adalimumab dose intensification) was 11 (IQR 8–28) (severe HS), with moderate severity in the prospective study and severe HS in the retrospective ones. At week 12, the median IHS4 of the entire cohort decreased to 6 (IQR 1–9) (moderate HS; $P < 0{\cdot}001$). The improvement of IHS4 classification was also significant ($P < 0{\cdot}001$). At week 24, the median IHS4 of the prospective study patients decreased to 4 (IQR 0–6) (moderate HS; $P = 0{\cdot}018$). In the retrospective studies DLQI improved significantly (Table 1). Neither the