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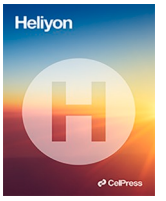

Case report

FH deficient uterine leiomyomas-a case series

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ABSTRACT

Introduction: Fumarate hydratase (FH) deficient uterine leiomyomas account for only 0.4 % of all uterine leiomyomas. They are characterized by some distinct histological features and may be associated with Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome.
Methods: Herein we present a series of five cases of FH deficient uterine leiomyomas in patients with a mean age of 30 years. All five patients underwent myomectomy. Three of these cases had an outside histopathologic diagnosis ranging from Smooth muscle tumor of uncertain malignant potential (STUMP) to Leiomyosarcoma while two cases were operated at our centre. All five cases were reported as suggestive of FH deficient leiomyomas and were advised germline testing along with genetic counselling.
Results: Immunohistochemically four of the cases showed moderate to strong positivity for 2-SC with a complete loss or reduced expression of FH while one case showed absence of 2-SC staining.
Discussion: Mutations in FH lead to reduced enzyme activity and accumulation of fumarate leading to a complete loss or aberrant reduced expression seen on immunohistochemistry, which confirms the diagnosis. It is important to differentiate it from a leiomyosarcoma or other malignant spindle cell tumors as these tumors follow a benign course. Their association with HLRCC also needs to be established for a suitable follow up since HLRCC-associated RCCs are often aggressive.
Conclusion: Management of such leiomyomas is myomectomy or hysterectomy with advice of genetic testing to rule out HLRCC. Histomorphology and immunohistochemistry are imperative for a correct and timely diagnosis.

1. Introduction

Leiomyomas are the most common uterine tumors in women occurring in the fifth decade [1]. They are benign smooth muscle tumors with many subtypes showing varied morphological patterns. Fumarate hydratase (FH) deficient leiomyomas account for 1 % of all uterine leiomyomas [2]. These occur at a relatively younger age and may be seen in both sporadic and syndromic settings. Syndromic association is seen with a rare autosomal dominant syndrome known as Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. The HLRCC tumor syndrome is also associated with cutaneous leiomyomata, aggressive renal cell carcinomas (RCCs) and early-onset, symptomatic uterine leiomyomata. Both syndromic and sporadic FH deficient leiomyomas exhibit certain typical morphological & immunohistochemical characteristics. Herein we report five cases of FH deficient leiomyomas, over a period

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of one and a half years, one of which was tested and found to have germline mutation in the FH gene.

2. Methods

All five cases were critically reviewed and subjected to immunohistochemical examination. One of the patients underwent Next generation sequencing (NGS) at an outside laboratory and the results for the same were obtained.

3. Results

3.1. Clinical details

The clinical details of all five cases are highlighted in Table 1. Case 1 was a 29 year old lady whose per abdomen examination revealed a soft to firm, large bosselated mass with restricted mobility arising from the pelvis and reaching up to the epigastrium. On per speculum examination, cervix was not seen and a large firm mass was felt extending into the pouch of Douglas, and the uterus was not felt separately from this mass. Magnetic resonance imaging (MRI) scan findings were suggestive of an ovarian primary so she was evaluated for the same. The serum tumor markers (CA 125, CA 19.9, CEA, AFP, Inhibin and LDH) were within normal limits. She underwent a surgical resection and was found to have a single large uterine mass intraoperatively which was extending from the right adnexa to the left and was therefore misconstrued as bilateral adnexal masses on imaging. The mass was reported as a benign spindle cell tumor on frozen section.

Second case was also a young woman, who underwent a myomectomy procedure which was reported at an outside lab as an atypical leiomyomatous lesion with diffuse severe cytological atypia. The paraffin embedded blocks were brought to our hospital for review.

Case 3 was a 36 year old lady. Her cervical Pap smear was reported as negative for intraepithelial lesion/malignancy while the endometrial biopsy was reported as secretory endometrium. She underwent myomectomy at an outside hospital where her histopathological diagnosis was of a Smooth muscle tumor of uncertain malignant potential (STUMP) The blocks were received at our hospital for review.

The fourth case also underwent myomectomy for uterine fibroids at an outside hospital and the specimen was reported as a well differentiated leiomyosarcoma and the blocks were brought to our hospital for review.

Case 5 was a 46 year old lady whose per abdomen examination revealed a mass in the hypogastrium. On per speculum examination there was bilateral forniceal thickening with a vault mass palpable in the anterior fornix. Her serum tumor markers were within normal limits. She underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy at our hospital.

3.2. Histopathological findings

Table 2 enumerates the histopathological findings and diagnoses of all the cases. Sections from the specimens of all five cases showed a spindle cell tumor composed of elongated cells arranged in long sweeping to poorly formed fascicles (Fig. 1a). Case 1 was given a provisional diagnosis of cellular leiomyoma at our hospital while Case 5 showed histomorphological features of a usual type leiomyoma. Case 2 was classified as Atypical/symplastic leiomyoma on morphology both from outside labs and on review at our

Table 1
Clinical presentation and imaging findings.

Cases:	Age: (years)	Presenting complaints:	Magnetic Resonance imaging (MRI) findings:
Case 1	29	Primary infertility x 6 months Menorrhagia x 6 months No h/o pain abdomen/bowel & bladder disturbances	Right and left pelvic masses: **26 × 4 × 0.7cm & 17 × 12 × 10cm respectively** **No intratumoral necrosis** -No significant lymphadenopathy -possibly ovarian origin
Case 2	25	Primary infertility Menorrhagia	Uterus diffusely enlarged with **multiple** intramural & submucosal leiomyomas involving posterior wall & fundus; largest measures **9 × 7 × 3cm** -Bilateral ovaries are polycystic
Case 3	36	Primary infertility x 4 years Menorrhagia x 2 years h/o lower abdominal fullness No h/o bowel/bladder disturbances No h/o loss of appetite/weight loss	Large 13 x 1 × 9 cm circumscribed focal lesion involving uterine body & fundus Endometrial thickness: 5.2mm -No significant lymphadenopathy
Case 4	30	Multiple abortions	Uterus anteverted & enlarged, with **numerous** well defined nodular myometrial lesions; submucosal & subserosal with ?necrosis largest measures 5 × 3cm
Case 5	46	Dysmenorrhea	Bulky uterus with a large fibroid arising from the uterine fundus & anterior body with interspersed cystic/necrotic areas measuring 8 × 8cm in size -Multiple cysts in bilateral ovaries largest 2.2 × 1cm suggestive of endometriotic cyst -bilateral fallopian tubes tortuous & dilated -No significant lymphadenopathy

Table 2
Histopathological findings, immunohistochemistry and diagnosis.

Cases:	Histopathological diagnosis (outside):	Histopathological findings & diagnosis (our lab):	Immunohistoche-mistry (IHC):	Final diagnosis:
Case 1	NA	- Cellular spindle cell tumor in fascicles - thick walled dilated vessels - focal "alveolar" edema - eosinophilic cytoplasmic inclusions - prominent eosinophilic nucleoli with perinucleolar halo - mitosis: 1//mm^2 **Cellular leiomyoma**	SMA + FH: global loss MIB 1 labelling index: 1–2%	**Fumarate hydratase (FH) deficient leiomyoma** -Advised germline testing and genetic counselling
Case 2	Atypical leiomyomatous lesion with diffuse severe cytological atypia	- spindle cell tumor -multinucleate tumor giant cells & bizarre cells - dilated thin walled vessels - stromal edema - eosinophilic cytoplasmic inclusions - prominent eosinophilic nucleoli with perinucleolar halo -mitosis: 1/mm^2 **Leiomyoma with bizarre nuclei**	SMA + FH global loss 2SC: moderate nuclear cytoplasmic positive MIB 1 labelling index: 1 %	
Case 3	Smooth muscle tumor of uncertain malignant potential (STUMP)	- spindle cell tumor - infarct like necrosis - thin walled dilated vessels - stromal edema - eosinophilic cytoplasmic inclusions - prominent eosinophilic nucleoli with perinucleolar halo - no significant atypia - mitosis: 1/mm^2 **Usual type leiomyoma**	SMA + FH global loss 2SC: diffuse strong positive MIB 1 labelling index: 2 %	
Case 4	Well differentiated Leiomyosarcoma	- spindle cell tumor - focal infarct like necrosis - hemangiopericytomatous vessels - Prominent eosinophilic nucleoli with perinucleolar halo - no significant atypia - mitosis: 5/mm^2 **Mitotically active leiomyoma**	SMA + FH: weak heterogenous expression 2SC: variable strong positive MIB 1 labelling index: 5 %	
Case 5	NA	- spindle cell tumor - thin walled dilated vessels - patchy stromal edema - no evidence of atypia - mitosis: 1/mm^2 **Usual type leiomyoma**	SMA + FH global loss 2SC: diffuse positive MIB 1 labelling index: 2 %	

hospital. Case 3 which was diagnosed as STUMP externally, was reported as a Usual type leiomyoma with presence of infarct like necrosis on review while Case 4 which had been given a diagnosis of malignancy from outside, was reported as a mitotically active leiomyoma with presence of focal infarct necrosis (Fig. 1h) at our hospital.

Morphologically all the cases showed a diffuse hemangiopericytomatous pattern of vasculature. Focal "alveolar" edema and presence of eosinophilic cytoplasmic inclusions rendering a "rhabdoid" appearance to cells was noted in Cases 2 and 3 (Fig. 1b–g). Prominent eosinophilic nucleoli with perinucleolar halo was seen in four of the cases (Case 1–4) (Fig. 2a). Case 2 showed presence of bizarre cells and multinucleate tumor giant cells while Case 4 showed increased mitosis (Fig. 2b and c).

3.3. Immunohistochemical findings

On immunohistochemistry (IHC) Smooth muscle actin (SMA) was diffusely positive in all the cases. MIB 1 labelling index ranged from 1 to 5%. All the cases except Case 4 showed a global loss of FH on IHC (FH monoclonal antibody, Abbkine, 1:300 dilution) while Case 4 showed a weak heterogenous expression (Fig. 3a–e). Every case had internal controls (blood vessels) which showed strong expression. Immunostain for 2-Succinocysteine (2-SC) (Anti 2SC antibody, Discovery, 1:1500 dilution) was positive (moderate to strong expression) in all cases except Case 1 which showed absence of any staining (Fig. 3f–j). A final diagnosis of FH deficient leiomyoma was rendered and germline testing with genetic counselling was advised for all the patients. Case 1 underwent Next generation sequencing (NGS) at an outside laboratory and a pathogenic variant was detected in the FH gene (FHc.999C > A p. Cys333Ter). None of the other cases underwent genetic testing. Three of the patients (Case 2,3 and 4) have conceived and all patients are presently symptom free, after one year of follow up.

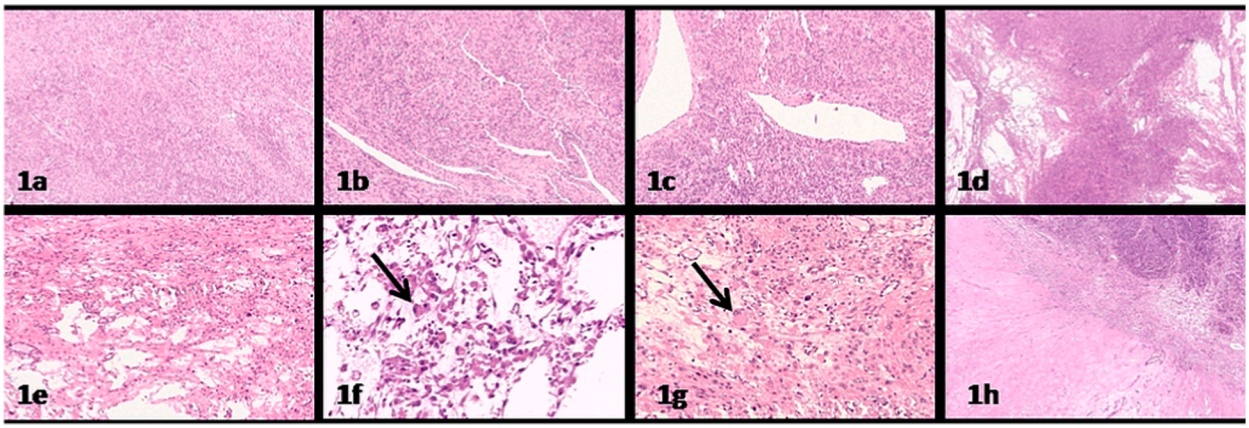

Fig. 1. Histopathological findings (H and E stain)
1a: Poorly formed fascicles of spindle shaped tumor cells (magnification 500μ)
1b,c: Hemangiopericytomatous pattern of vasculature(magnification 500μ)
1d,e: "Alveolar" edema of the stroma (magnification 500μ)
1f,g: Eosinophilic (rhabdoid) cytoplasmic inclusions in the tumor cells(magnification 250μ)
1h: Infarct necrosis (magnification 500μ).

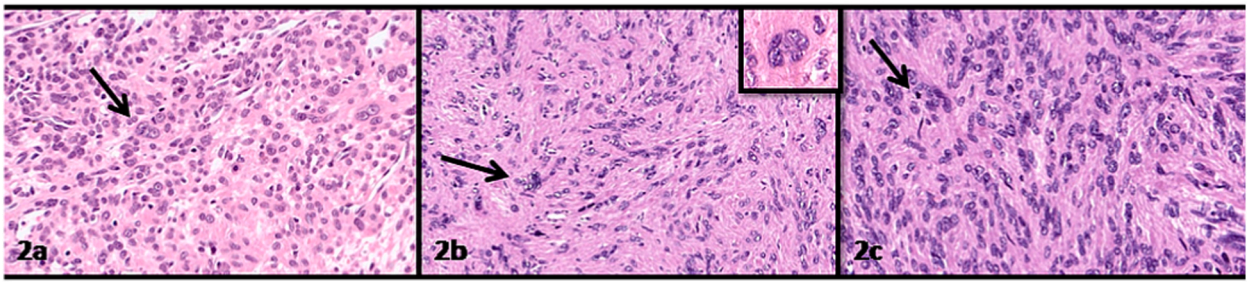

Fig. 2. Histopathological findings (H and E stain) at magnification 250μ
2a: Prominent eosinophilic nucleoli with perinucleolar halo (marked by arrow)
2b: Interspersed bizarre cells seen in Case 2 (Inset shows a multinucleate tumor giant cell)
2c: Increased mitosis seen in Case 4 (arrow marked).

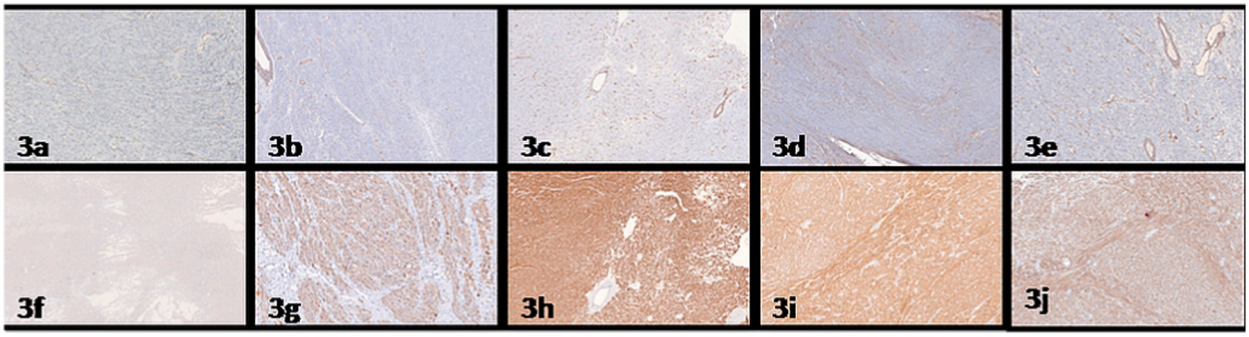

Fig. 3. Immunohistochemical findings for FH and 2SC of all five cases at magnification 1mm
3a–e: FH immunostain for cases 1–5 respectively
3f–j: 2SC immunostain for cases 1–5 respectively.

4. Discussion

FH gene, located on chromosome 1 (1q42.3-q43) encodes for the protein fumarate hydratase which catalyses the conversion of fumarate to L-malate in the tricarboxylic acid/TCA cycle [3]. Mutations in *FH* gene lead to reduced enzyme activity and accumulation

of fumarate. Increased fumarate levels lead to protein succination and generation of antioxidant response elements (AREs) aiding in tumorigenesis. Expression of 2- succinocysteine (2- SC) on IHC is a marker of protein succination [4]. FH deficiency also creates "pseudohypoxia" due to stabilization of Hypoxia inducible factor (HIF) 1α further enhancing tumor progression due to angiogenesis and epithelial mesenchymal transition [5]. FH deficiency is associated with several neoplasms such as FH deficient RCCs, leiomyomas, cutaneous leiomyomata and rarely, some malignant paragangliomas and pheochromocytomas [6]. FH deficient RCCs occur almost exclusively in patients of HLRCC and are characterized with early onset and aggressive nature. These RCCs commonly have a papillary morphology with presence of prominent eosinophilic nucleoli [7]. FH deficient leiomyomas are commonly associated with sporadic mutations and account for 1 % of all unselected uterine leiomyomata and up to 25 % of atypical/symplastic leiomyomata [8]. A recent study by Li H et al. identified 52 out of a total of 161 uterine smooth muscle tumors that were FH deficient, out of which the majority were either symplastic leiomyomas or STUMPs [9]. They present in younger women with multiple, large sized tumors requiring early surgical intervention. Four of the five cases presented here were young females with a mean age of 30 years while one was a 47 year old female. All the patients presented with complaints of primary infertility, menorrhagia/dysmenorrhea or multiple abortions possibly caused by the mass effect of the fibroids. They were found to have multiple uterine leiomyomata and required early myomectomies. This finding is similar to that detected by other researchers previously [2].

On follow up, after nearly one year, Case 2 was detected with a unilocular cystic lesion involving the right kidney measuring approximately 5 × 4 cm in size. The patient however, did not undergo any management for the same as she was otherwise symptom free and pregnant. FH deficient leiomyomas can act as a red flag in the timely detection and management of FH deficient RCCs associated with the HLRCC syndrome in the patients as well as their families [10] This makes it imperative for the patients to undergo germline testing once detected with FH deficient leiomyomas. Case 1 had bilateral breast nodules which were suggestive of fibroadenomas on imaging. No other lesion was detected.

Case 3 had a family history of breast cancer in the paternal aunt and pancreatic cancer in the paternal grandfather. Although many studies have previously documented the presence of family history of FH associated tumors such as uterine leiomyomata or cutaneous leiomyomas [10], no association with pancreatic and breast cancers has been found in literature so far.

FH deficient uterine leiomyomas are known to have certain characteristic morphological features such as the presence of hemangiopericytomatous/staghorn vasculature, stromal edema imparting lung alveolar parenchymal appearance or "alveolar" edema, prominent nucleoli with perinucleolar clearing, hypercellularity, nuclear atypia and cytoplasmic hyaline globules as described in literature [1]. Four of our cases showed most of these features while one case (Case 5) displayed only a subtle hemangiopericytomatous pattern with presence of focal & patchy stromal edema. This case lacked evidence of any hypercellularity, atypia, cytoplasmic inclusions or prominent nucleoli. This shows that though histomorphological findings may provide clues to the pathologist, they are inconstant and lack objectivity. Immunohistochemistry can act as an important ancillary tool in the diagnosis. Immunostain for FH has been used by many researchers while 2SC has been used only in recent times due to its previous commercial unavailability [11]. Mostly there occurs a loss of staining for FH [9] as was seen in four of our cases, however, there can also be a weak expression as was seen in one of our cases. This may be caused due to a pathogenic missence mutation [12]. Expression of 2SC is considered more sensitive in detecting FH mutated tumors. Joseph et al. found that all cases of FH deficient tumors in their study were positive for 2SC [13]. This is in discordance with our findings as one of our cases (Case 1) was found to be negative for 2SC on IHC, yet, there was a germline FH mutation detected later in the patient. A combination of both markers on IHC can overcome such limitations.

It is imperative to differentiate FH deficient leiomyomas from leiomyosarcoma or other malignant spindle cell tumors on histopathology, as they have an entirely different therapeutic approach and prognostic implication. Such erroneous diagnoses may occur due to misinterpretation of the cytological atypia and hypercellularity seen in FH deficient leiomyomas. STUMPs show morphological features exceeding the criteria of leiomyoma yet falling short of a leiomyosarcoma. These are rare tumors which have only one of the criteria of leiomyosarcoma which may be increased mitosis or atypia or coagulative tumor cell necrosis. Case 3 was misdiagnosed as STUMP possibly due to the infarct like necrosis which was wrongly interpreted as tumor cell necrosis. A diagnosis of conventional (spindle cell) uterine leiomyosarcoma is rendered based on the presence of two or more of the criteria namely marked cytological atypia, tumor cell necrosis or mitosis $\geq 4/mm^2$ [1]. One of our cases was erroneously reported as a leiomyosarcoma before being reviewed at our centre. The possible reason might be due to the presence of increased mitosis along with infarct like necrosis wrongly deciphered as tumor necrosis. This shows that a careful examination of the type of necrosis is mandatory taken in conjunction with other histopathological findings and the clinical history of the patient in order to prevent overcalling the diagnosis. Surgical management of FH deficient leiomyomata comprises myomectomy which is sufficient as these tumors follow an essentially benign course.

The clinical importance of recognizing these tumors lies in the fact that in the appropriate context, they may help in a timely diagnosis of HLRCC allowing early intervention for patients and their families. One of our cases (Case 1) who underwent genetic testing was detected to have a germline mutation in the FH gene and is being kept under close surveillance. HLRCC patients are born with one defective allele and develop a second hit by loss of heterozygosity. Almost all women with HLRCC develop uterine leiomyomas, however, only 15–25 % develop RCC [14] These RCCs are more aggressive presenting at higher stages imparting significant morbidity & mortality. It is difficult to identify patients only by personal and family history due to the absence or unavailability of significant history at the time of pathological examination as was seen in our study. A checklist for all cases is provided in Table 3 showing which criteria were met according to the WHO classification of tumors of the female genital tract. Case 1 which has been found to have a pathogenic variant in the FH gene did not have any other associated tumors or any family history of cancers.

5. Conclusion

The key to recognizing FH deficient tumors, lies in the knowledge of their existence with the salient histomorphological features

Table 3
Checklist of cases with diagnostic criteria for HLRCC.

	Diagnostic criteria for clinically suspected HLRCC (Major criteria or ≥2 minor criteria)						
Cases	Major criteria:	Minor criteria			Confirmation of diagnosis **(A or B + C)**		
	Multiple, histologically confirmed cutaneous piloleiomyomas	Severely symptomatic uterine leiomyoma before the age of 40 years (surgical therapy needed)	Renal cell carcinoma before the age of 40 years	A first-degree family member fulfilling one of the minor criteria	A. pathogenic variant of FH is detected	**B.** ≥2 cutaneous leiomyomas (with ≥1 histologically confirmed) without a family history of HLRCC or ≥ 1 cutaneous leiomyoma with a family history of HLRCC	**C.** ≥1 renal cell carcinoma with compatible morphology and IHC (with or without a family history of HLRCC
Case 1	–	+	–	–	+	–	–
Case 2	–	+	? Renal cystic lesion,not investigated	–	not tested	–	Renal lesion not investigated
Case 3	–	+	–	–		–	–
Case 4	–	+	–	–		–	–
Case 5	–	-(age >40 at presentation)	–	–		–	–

+: present; -: absent; HLRCC: Hereditary leiomyomatosis and renal cell carcinoma.

and the practice of applying a combination of FH and 2SC on immunohistochemistry. With a high clinical index of suspicion, detection of FH deficient leiomyomas can aid in the diagnosis of HLRCC allowing early intervention.

Ethics declaration

Ethics approval for this study was not sought because it was a retrospective case series with no additional tests performed. Only tests during routine diagnostic workup were performed for which the general informed consent was taken at the time of admission.

Data availability statement

The data associated with the study has been obtained from the hospital records and can be made available on request.

CRediT authorship contribution statement

Meenakshi Kamboj: Conceptualization, Data curation. **Prerna Chadha:** Conceptualization, Writing – original draft, Writing – review & editing. **Anila Sharma:** Conceptualization. **Divya Bansal:** Conceptualization, Data curation. **Gurudutt Gupta:** Conceptualization, Writing – review & editing. **Anurag Mehta:** Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24449.

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