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Uterine preservation in low-grade endometrial stromal sarcoma

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ABSTRACT

Data on uterine preservation in the management of low grade endometrial stromal sarcoma (LGESS) is scarce due to rarity of this tumor type. Standard management of LGESS involves extrafascial hysterectomy with bilateral salpingo-oophorectomy with debulking of any extrauterine metastatic disease. High estrogen and progesterone receptor expression facilitates adjuvant hormone therapy post-surgery. LGESS frequently affects young women, thus fertility preservation is an important issue in management. Here we describe uterine preservation in two young women diagnosed with LGESS followed by GnRH analogue therapy with favorable outcome. The first case was diagnosed with recurrent endometrial polyp invading myometrium requiring wedge resection of uterus with free margins. Second case presented with a vaginal mass arising from cervix and excision was done through vaginal route. Both patients were prescribed GnRH analogue therapy for six months post-surgery and are currently on follow-up. These case reports add to literature on feasibility of uterine preservation in the management of LGESS.

1. Introduction

Low-grade endometrial stromal sarcoma (LGESS) is a rare sarcoma subtype that arises in the endometrial stroma. Tumor is slow-growing and resembles normal stromal cells found in the uterus. Endometrial stromal sarcomas represent less than 1 % of all uterine malignancies and account for only a small percentage of all uterine sarcomas (6–20 %) (Davidson et al., 2020). It typically occurs in women of reproductive age, but can occur in women of any age (16–83 years) and presents with abnormal uterine bleeding, nonspecific pelvic pain, or pelvic mass (Chan et al., 2008). Diagnosis involves a combination of imaging studies and histopathological analysis of tumor tissue (Sousa et al., 2021; Lee et al., 2020). Standard treatment of LGESS involves extrafascial hysterectomy and bilateral salpingo-oophorectomy with lymph node evaluation depending on radiologic and clinical findings (Amant et al., 2014; Gadducci et al., 2023). Hormone receptor expression (70–90 %) is high in these tumors and adjuvant antiestrogen hormone therapy utilizing aromatase inhibitors, progesterone, or gonadotropin releasing hormone (GnRH) analogues is recommended in stage II-IV disease (Deshmukh et al., 2019). Prognosis is favorable compared to other types of uterine sarcomas, with high survival rates (>90 %) for early-stage (stage I-II) but it drops to 50 % for advanced stage (stage III-IV) disease (Abeler et al., 2009; Thiel and Halmen, 2018). However, the risk of recurrence remains a concern, even several years after initial treatment (Moore and McCluggage, 2020; Bai et al., 2014). Due to the rarity of LGESS, there is a paucity in literature regarding role of uterine preservation in its management. Here we present two cases of LGESS in young women managed with uterine conserving surgery.

2. Case presentation

2.1. Case 1

A 22-year-old patient presented with chief complaints of heavy menstrual bleeding since two years. Bleeding was heavy in amount and duration, lasting for 9–10 days with associated dysmenorrhea. She was diagnosed with an endometrial polyp and prescribed combined hormonal therapy for three months without improvement in symptoms. Patient presented to our centre and on examination a polypoidal growth of 4x2 cm protruding through the cervix was noted. Transvaginal sonography showed the polyp arising from the uterine cavity. Polypectomy was done and histopathology suggested a mesenchymal

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neoplasm. Immunohistochemistry showed diffuse vimentin, SMA and H-caldesmon positivity, desmin/CD10 scattered positivity with Ki67 labelling index of 1–2 %. Patient was asymptomatic for around six months after the procedure, following which heavy menstrual bleeding recurred. Ultrasound and MRI of pelvis suggested an endometrial polyp and patient underwent hysteroscopic polypectomy. Histopathology was suggestive of endometrial stromal nodule with absent mitoses and CD10, CD34, WT-1, SMA positivity, focal desmin positivity, hormone receptor (estrogen and progesterone) positivity and Ki67 labelling index of 10 % on immunohistochemistry. Follow-up after three months with MRI showed recurrence of polyp 2X2 cm size near right cornu with 50 % myometrial invasion. Patient was counselled for surgical management but declined. Hormonal treatment in the form of aromatase inhibitor (letrozole tablet 2.5 mg OD) was given for six weeks but symptoms recurred, and pelvic MRI showed an increase in size of lesion (Fig. 1A). Patient was planned for uterine preserving surgery after multidisciplinary tumor board discussion. Intraoperative hysteroscopy and ultrasonography showed a deep-seated myometrial tumor. Patient underwent laparotomy with wedge resection of right cornu of uterus along with right salpingectomy. On gross pathologic assessment, tumor was grey brown in color of size 4x3.5x1 cm invading adjacent myometrium. Microscopic examination showed oval to spindle shaped cells arranged in islands and nests with invasion into myometrium in tongue shaped manner with no areas of necrosis or high-grade features (Fig. 2, A-B). Immunohistochemistry showed hormone receptor positivity (estrogen- focal and progesterone- diffuse), BCOR negativity and Ki67 labelling index of 10–12 % with final diagnosis of low-grade endometrial stromal sarcoma (Fig. 2, C-F). Patient was started on adjuvant hormonal treatment with GnRH analogue (Injection Leuprolide 3.75 mg IM) within three weeks of surgery and continued for six months on a monthly regime. Patient is currently doing well with no evidence of disease on follow-up at six months.

2.2. Case 2

The second case is that of a 19-year-old patient referred to the emergency department with continuous vaginal bleeding for five days with hypovolemic shock. Patient had four episodes of heavy vaginal bleeding within last one month with history of multiple blood transfusions and symptomatic treatment. On clinical examination, large polypoidal mass (10x10 cm) was seen in the vagina. Ultrasound and MRI of the pelvis showed a vaginal mass of size around 9x9x7 cm in upper two-thirds of vagina with morphological features consistent with sarcomatous changes (Fig. 1B). Uterus, cervix, adnexa, and other distant organs were normal on imaging. Biopsy from vaginal mass suggested cervical leiomyoma/benign endocervical polyp. On immunohistochemistry, vimentin positivity, SMA focal positivity, and negativity for desmin, myogenin, PanCK, CD10, cyclin D1, LCA, CD34, TLE1, and synaptophysin was noted. After multidisciplinary team discussion patient was planned for surgical management. During vaginal surgery, after adhesiolysis to release flimsy adhesions of mass to the vaginal walls, mass was found to be arising from anterior lip of cervix with broad base. Mass was excised with adequate margins (Fig. 1C). On gross pathologic examination, tan brown to grey white soft tissue mass of size 8x7x4 cm with internal cystic areas with mucinous fluid was noted. On histopathology, tumor cells were round to oval with minimal nuclear atypia in background of collagenous stroma with negative margins (Fig. 3, A-C). Immunohistochemistry showed positivity for ER, PR, CD10 and focal positivity for desmin, BCOR, and cyclin D1 suggesting a diagnosis of hormone receptor positive low-grade endometrial stromal sarcoma (Fig. 3, D-H). This patient was also prescribed GnRH analogue (Injection Leuprolide 3.75 mg IM) for six months duration post-surgery. Patient is currently disease-free on follow-up after six months.

3. Discussion

Low grade endometrial stromal sarcomas pose diagnostic and management conundrums as exemplified by the above cases. Appropriate work-up and uterine preserving surgical management could accomplish complete resection of tumor with adequate margins thus preserving reproductive function.

There have been isolated case reports of successful management of low-grade endometrial stromal sarcoma utilizing fertility sparing approaches. Jin Y et al studied the feasibility of fertility sparing treatment in five women with LGESS using a combination of local resection of mass with uterine reconstruction followed by hormonal therapy using progesterone or gonadotropin treatment for five to six months. During follow-up period of 21–55 months, all women survived, three conceived, one patient had disease recurrence on progesterone and underwent hysterectomy. They concluded fertility sparing treatment to be suitable in young women with LGESS with clear margins (Jin et al., 2015). In another study by Zheng Y et al, five women with LGESS were subjected to fertility sparing surgery followed by endocrine therapy for one year. Four out of five women in study recurred locally and they further underwent uterine preserving surgery. Two of these conceived spontaneously and all patients were alive on follow-up. The same authors

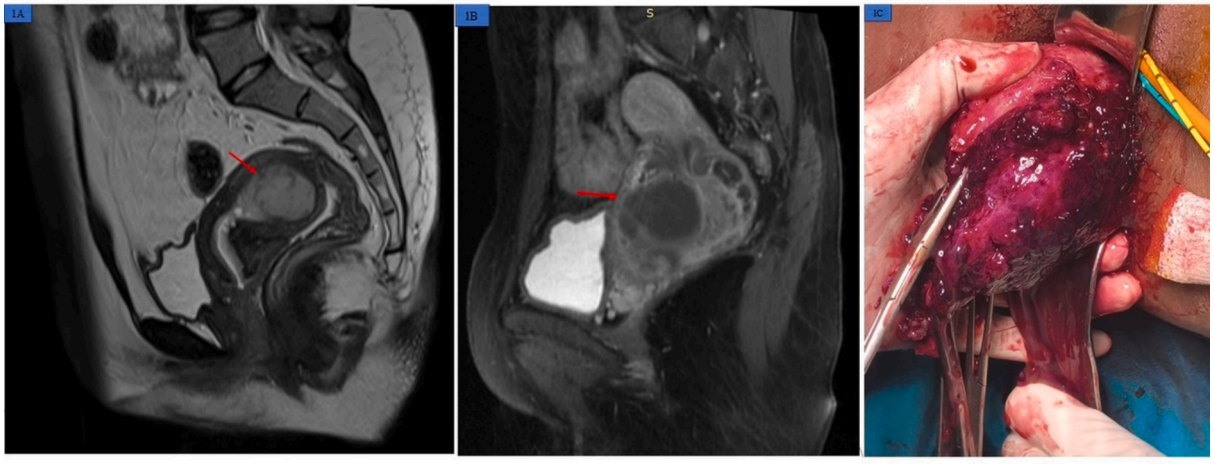

Fig. 1. 1A: Plain T2 weighted MRI image in sagittal section showing well defined T2 hyperintense homogenously enhancing lesion in subendometrial region of fundus of uterus. 1B: Contrast enhanced T1 weighted MRI image in sagittal section showing heterogeneously enhancing solid lesion with multiple T1 hypointense internal cystic spaces, with T1 hyperintense hemorrhagic components within, arising from upper 2/3rd of vagina with no extension to adjacent organs 1C: 8 x 8 cm fleshy vaginal mass arising from the anterior lip of cervix.

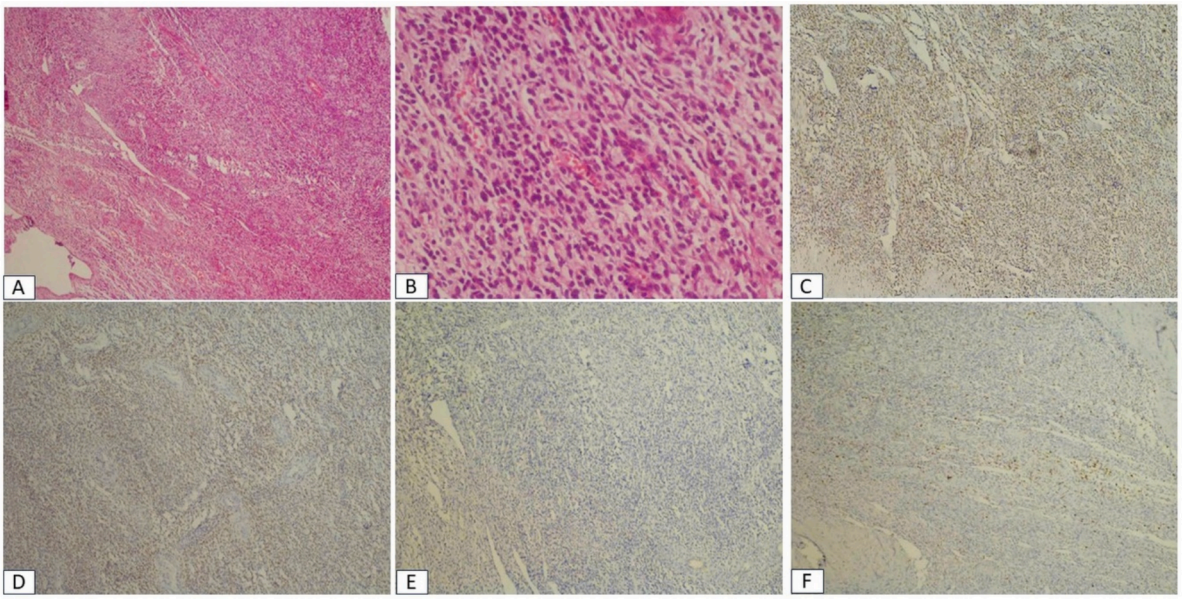

Fig. 2. Hematoxylin and eosin (H&E) stained section shows oval to spindle shaped cells arranged in islands and sheets(x200) **(A)**, Higher magnification shows oval to spindle shaped cells along with intervening blood-filled capillaries with no features of high-grade atypia (x400) **(B)**. Immunohistochemistry for Estrogen receptor (ER) shows focal positivity **(C)**, Progesterone receptor (PR) shows diffuse positivity **(D)**, BCL6 transcriptional corepressor (BCOR) shows negativity **(E)**, and shows ki67 labelling index of 10–12% **(F).**

reviewed data on 1070 women with LGESS from the SEER database and found no statistically significant survival difference between uterine sparing versus radical surgery groups (Zheng et al., 2020). Laurelli G et al (2015) also studied conservative surgical management of LGESS in six women over four years. They underwent one-step hysteroscopic tumor resection and were prescribed megestrol acetate for two years post-surgery. One woman became pregnant post-surgery and did not require hormonal treatment while the remaining five patients tolerated hormonal therapy well. All remained disease-free during follow-up (Laurelli et al., 2015).

Bai H et al conducted a retrospective analysis of 153 patients with low-grade endometrial stromal sarcoma spanning 34 years from 1979 to 2013 at their centre. They found that myomectomy was performed in 12.4 % of cases, with the remaining 87.6 % undergoing hysterectomy. Ovarian function was preserved in 28.8 % of cases, while the rest underwent bilateral salpingo-oophorectomies. Additionally, pelvic lymphadenectomy was performed in 30.1 % of cases. Some patients received adjuvant therapy, including hormonal therapy (35.9 %), chemotherapy (17.6 %), and radiotherapy (21.6 %). Over mean follow-up of 74.2 months (range: 1–396), the 5-year relapse-free survival (RFS), overall survival (OS), and survival after relapse (SAR) rates were 66.1 %, 95.8 %, and 82.9 %, respectively with mean relapse free interval of 4.1 years. Ovary-sparing procedures, positive resection margins, and myomectomy were identified as independent adverse factors for relapse. Although recurrence rates were higher after uterine and ovarian preserving treatment in LGESS, there was no adverse impact on overall survival in this group compared to those who underwent standard treatment in the form of hysterectomy with bilateral salpingo-oophorectomy. They also concluded that uterine and ovarian sparing surgery in adjunct with adjuvant hormonal therapy with close follow-up can be considered in young women desiring fertility preservation (Bai et al., 2014). Thus, wedge resection with adequate margins of the involved part of the myometrium may be a better surgical option than myomectomy.

Although LGESS constitutes less than 1 % of uterine malignancies it ranks as the second most common uterine malignant mesenchymal tumor after leiomyosarcoma (Davidson et al., 2020). Imaging plays a crucial role in evaluating early-stage LGESS and aiding in fertility-sparing management options. MRI pelvis and CT scan of the chest, abdomen and pelvis are important for precise staging, with MRI being the preferred modality for evaluating myometrial involvement, adjacent organ spread, and lymph node status (Sousa et al., 2021). MRI pelvis was employed for local surgical planning and CT scan of chest and abdomen was done to look for distant spread of disease before commencing treatment in both the cases.

Histologically, LGESS exhibits cells resembling proliferative phase endometrial stroma and displays infiltrative growth, with or without lymphovascular space invasion. Immunohistochemistry, particularly ER/PR, desmin, CD10, and cyclin D1 staining aids in diagnosis, focusing on the degree of positivity rather than just positivity itself (Lee et al., 2020). Immunohistochemistry also assists in selecting appropriate adjuvant therapy, particularly in fertility-sparing management. LGESS or endometrial stromal nodule (ESN) can sometimes be difficult to distinguish from cellular leiomyoma on biopsy specimens due to similar histomorphology with difficulty to comment upon boundaries and overlapping immunohistochemical features. This was also the case with our cases with initial biopsy specimen pathologic report suggesting leiomyoma/ESN, thus requiring assessment of final excision specimen for adequate pathologic assessment. On molecular profiling, CXorf67-MBTD1 fusions have been identified in low-grade endometrial stromal sarcoma. Additionally, a novel MEAF6-SUZ12 fusion has recently been reported in cases of LGESS.

In cases where women desire to preserve fertility and have not completed childbearing, uterine sparing surgery may be considered in investigational settings due to favorable oncologic outcomes associated with early-stage LGESS (Amant et al., 2014; Gadducci et al., 2023). However, the feasibility and safety of fertility-sparing management has only recently been explored, and due to the rarity of LGESS, data is scarce and primarily based on case reports. Current guidelines advocate for hormone therapy as a crucial component in managing low-grade endometrial stromal sarcoma (LGESS) (Amant et al., 2014). LGESS often highly expresses estrogen receptors (ER) and progesterone receptors (PR). Patients with ER/PR-positive LGESS typically respond well to hormonal therapy, making evaluation of hormone receptor status essential. Progestins, particularly megestrol acetate (MA) or medroxyprogesterone acetate (MPA), are commonly used in LGESS treatment,

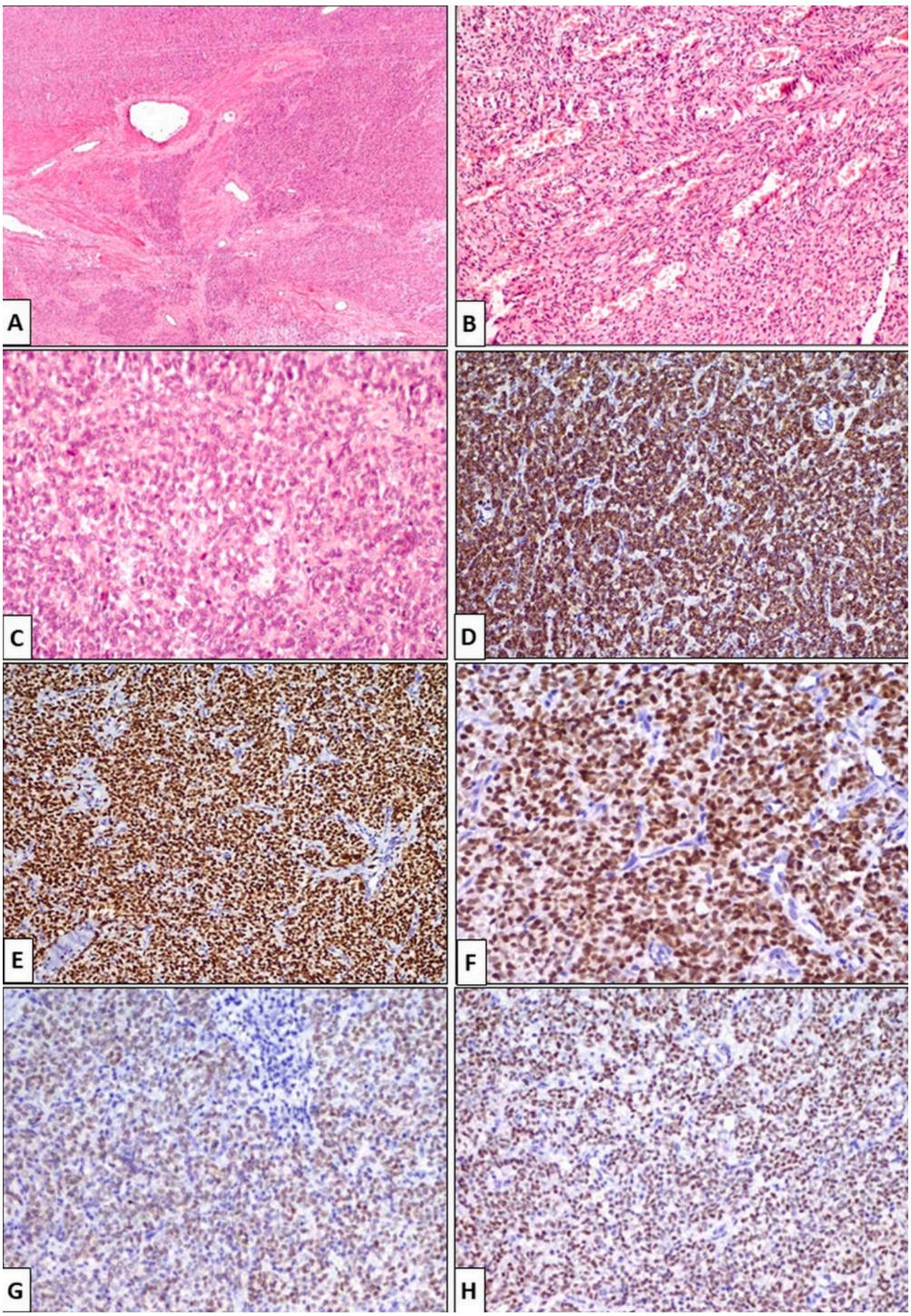

Fig. 3. Haematoxylin and eosin (H&E) stained section shows irregular, densely cellular islands of tumor cells invading the myometrium (x40) **(A)**. Hypocellular areas displaying focal whirling of tumor cells around arteriolar-type vessels, similar to proliferative-phase endometrial stroma (x100) **(B)**. Higher magnification shows tumor comprising of monotonous spindle to oval cells with minimal nuclear atypia in a background of collagenous stroma (x200) **(C)**. These tumor cells are diffusely immunopositive for CD10 (**D**), Estrogen receptor (ER) (**E**) and Progesterone receptor (PR) (**F**). The tumor cells are focally immunopositive for Cyclin D1 (**G**) and BCL6 transcriptional corepressor (BCOR) (**H**).

but there is no consensus regarding the optimal hormone therapy regimen in terms of drug, dosage, or duration (Amant et al., 2014).

Adjuvant hormonal therapy incorporating GnRH analogue for six months was utilized in both the cases. This is because ovarian function suppression (OFS) utilizing GnRH analogues is the most potent medical means of temporary ovarian suppression. Studies reporting on adjuvant hormonal therapy in LGESS management after fertility sparing surgery have used it for various time durations ranging from six months to two years (Jin et al., 2015; Zheng et al., 2020; Laurelli et al., 2015). Moreover, high-dose progesterone therapy over long periods may cause side effects such as headache, fatigue, weight gain, breast pain or tenderness, dizziness, etc. leading to high rate of discontinuation over long term use in these young women (Deshmukh et al., 2019).

Although the risk of recurrence is not necessarily increased by

uterine preservation, it remains high at around 30 %, even in cases of durable complete response (Bai et al., 2014; Agarwal et al., 2017). We administered GnRh analogues in the initial six months reserving progesterone for subsequent therapy.

4. Conclusion

These case reports suggest that low-grade endometrial stromal sarcomas, although rare, pose a challenge in terms of diagnosis and management in young women. The fertility preserving approach described, which involves uterine-preserving surgical techniques along with adjuvant hormonal suppression using gonadotropin analogues, has shown good outcomes in these women. These cases add to literature on uterine preserving surgical management of this uncommon entity. However, a multicentric prospective study incorporating a larger sample size will provide high quality evidence on management.

5. Consent statement

Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Shalini Rajaram: Writing – review & editing, Supervision, Conceptualization. **Lakhwinder Singh:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Ayush Heda:** Writing – review & editing. **Latika Chawla:** Writing – review & editing. **Ravi Hari Phulware:** Data curation. **Ashok Singh:** Data curation. **Simardeep Kaur:** Data curation.

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.

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