Case Report

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Pulmonary benign metastasizing uterine leiomyoma (PBML): a case report and review of the literature

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Introduction and importance: Benign metastasizing leiomyoma (BML) is a rare disorder characterized by the presence of benign smooth muscle tumours in extrauterine sites, typically the lungs. It classically involves perimenopausal women with a history of uterine surgery. The condition follows an indolent course but may cause clinical symptoms with large or widespread lesions.

Case presentation: The authors report the case of a 47-year-old female who presented with a 6-month history of irregular vaginal bleeding and severe hot flushes. The patient had no previous history of gynaecological surgery. Ultrasonography and subsequent MRI identified a suspicious 105 × 65 mm mass involving the right uterine cornu and broad ligament. Computed tomography identified bilateral lung nodules, suspicious for metastases. Histological assessment of the final uterine surgical specimen identified a benign dissecting leiomyoma involving the broad ligament and cervix. BML was diagnosed after thoracoscopic resection of a lung lesion which revealed a histologically identical tumour with entrapped normal lung alveoli.

Clinical discussion: This case shows that there is a minority of patients without previous uterine surgery who still go on to develop pulmonary BML. In our case, a combined treatment approach was adopted, involving substitution of hormone replacement therapy to a non-hormonal alternative, thoracoscopic resection of lung lesions and interval surveillance imaging of the chest.

Conclusions: BML is a rare condition but should be considered as a differential in women with pulmonary nodules and a history of uterine leiomyomata. Its diagnosis and subsequent counselling can be challenging; therefore cases should be treated by multidisciplinary teams in tertiary specialized centres.

Keywords: benign metastasizing leiomyoma, diagnosis, surgical intervention, hormonal manipulation, case report

Introduction

Benign metastasizing leiomyoma (BML) is a rare disorder involving distant metastases from a primary myometrial smooth muscle tumour. It was first described by Dr. Paul E. Steiner, a pathologist at the University of Chicago in 1939[1]. He reported the case of a patient who died from extensive pulmonary metastases originating from benign leiomyomas, histologically identical to uterine leiomyomas. The lungs are in fact the most common site of metastasis, in which case the condition is referred to as pulmonary BML (PBML). It can, however, affect other atypical sites such as lymph nodes, the myocardium, breasts, liver, oesophagus, trachea, as well as the central nervous system[2,3].

Approximately 150 cases of BML have been reported in the literature[4]. Due to its rarity, the diagnosis of BML is challenging, as radiological evidence of lung lesions may point to primary lung pathology or an advanced malignant process. As a result of limited evidence in the literature, the management of BML cases is based on case reports or series, and expert multidisciplinary opinion.

Reported cases and series show that the vast majority of PBML cases are associated with a history of previous uterine surgery,

HIGHLIGHTS

- Benign metastasizing leiomyoma (BML) is a rare condition involving leiomyomatous deposits in extrauterine sites, typically the lung.
- BML diagnosis typically necessitates thoracoscopic evaluation of chest lesions to exclude primary lung pathology or metastasis from other primaries.
- Extrauterine lesions are characteristically positive for smooth muscle markers (α-SMA, caldesmon and desmin) as well as oestrogen and progesterone receptors.
- BML prognosis is favourable as lesions follow an indolent course but larger deposits may cause symptoms.
- Management is multidisciplinary and often multimodal, involving surveillance imaging, hormonal manipulation and/or surgical intervention.

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implying a possible role in surgical tumoral dissemination and metastasis[5]. Several authors have hypothesised a time relation between patients' primary gynaecological surgery and BML onset. The vast proportion of these cases are diagnosed several years after gynaecological surgery such as myomectomy, with new diagnoses reported even up to 23 years after initial surgery[6].

In this report we describe the diagnostic work-up, investigations and management of a PBML case, in a patient with no prior history of gynaecological surgery. We highlight the diagnostic, counselling and treatment challenges that can be encountered in such a rare clinical context. This case has been reported in line with SCARE Criteria[7]. This patient was managed by a multidisciplinary team in a tertiary cancer centre.

Patient information

A 47-year-old South Asian female presented with a 6-month history of irregular heavy vaginal bleeding associated with severe hot flushes. The patient had a long history of heavy menstrual bleeding with regular cycles. She complained of generalized weakness and a foul-smelling discharge but was otherwise not experiencing any other red flag symptoms.

The patient had a history of three uncomplicated spontaneous vaginal deliveries and two first trimester miscarriages. She was not on any regular contraception and had no recent unprotected sexual intercourse. She had a normal cervical screening history and was a non-smoker. The patient was keen to start hormone replacement therapy as menopausal symptoms were significantly impacting her quality of life. She did not have any family history of gynaecological cancers and was known to live with type 2 diabetes mellitus and hypertension which were well controlled on Metformin, Gliclazide and Ramipril.

Clinical findings

On examination the abdomen was soft with an enlarged 12-week sized uterus on bimanual examination. On speculum examination the vulva, vaginal walls and cervix were macroscopically healthy. A high vaginal swab was taken for culture and sensitivity testing. BMI was raised at 38 kg/m^2.

Diagnostic assessment and interpretation

A transvaginal ultrasound identified an anteverted uterus measuring $120 \times 60 \times 120$ mm, with a 38×33 mm irregular heterogenous hypoechoic area within the uterine cavity, representing a possible polyp or fibroid (Fig. 1). An intramural leiomyoma was visible involving the lower uterus and posterior cervix measuring 48×33 mm. There were no abnormal adnexal findings and no free abdominal fluid. A pipelle endometrial sample was taken to exclude endometrial hyperplasia or malignancy.

An MRI of the pelvis was performed 3 weeks later to further characterize the focal uterine cavity lesion. A fibroid measuring 105×65 mm was seen in relation to the right cornu of the uterus and appeared to be communicating with the endometrial cavity. This showed restricted diffusion and a necrotic/haemorrhagic area with no contrast enhancement (Fig. 2). It also confirmed the presence of a smaller posterior lower uterine fibroid involving the cervix. In retrospect, the distended uterine cavity seen on ultrasound was actually the aforementioned haemorrhagic central area within the broad ligament mass. Imaging was reviewed at the Gynae-oncology multidisciplinary meeting and there was consensus that the right cornual fibroid showed features suspicious for sarcomatous transformation. The patient's subsequent diagnostics and treatment were led by a surgical gynae-oncology team in a tertiary cancer centre.

A staging computed tomography (CT) scan of the chest abdomen and pelvis identified three new lung parenchymal nodules suggestive of metastases and measuring up to 12 mm (Fig. 3). There were incidental adrenal adenomas and lytic iliac bone lesions that had been present on previous scans with no interval changes. There were no signs of disease spread within the abdomen and pelvis and no lymphadenopathy.

The patient was counselled about the scan and biopsy findings. The endometrial biopsy was normal and showed shedding endometrium with oestrogen withdrawal effects. The vaginal swab was negative. We conveyed our suspicion of metastatic (radiologically stage 4) uterine leiomyosarcoma and explained that sampling of the superficial endometrium does not exclude an underlying uterine stromal neoplasm.

Therapeutic intervention

A recommendation was made for a total hysterectomy and bilateral salpingo-oophorectomy. In the context of lung metastases this was expected to be a palliative-intent procedure to resolve ongoing heavy bleeding. The surgical team explained that one would not expect this surgical intervention to improve overall survival but would improve quality of life and provide a definite histological diagnosis to guide adjuvant oncological treatment. Based on the final histological results, the potential consideration of interval thoracoscopic resection of the oligometastatic lung disease was also discussed. This would be considered if complete resection was deemed achievable and if it would not cause any significant delays to oncological treatment.

Surgery was performed by a consultant-led surgical gynae-oncology team within 6 weeks from presentation. Surgery was performed via midline laparotomy and included total hysterectomy, bilateral ureterolysis, bilateral salpingo-oophorectomy and resection of three enlarged right external iliac lymph nodes. Intraoperatively we identified an enlarged multifibroid uterus with a 6 cm posterior cervical fibroid and a 12 cm right broad ligament mass. This mass was adherent to the right pelvic side wall and ureter. The tubes, ovaries and other peritoneal surfaces were normal.

The patient was discharged on the fifth postoperative day. The patient experienced severe hot flushes postoperatively and transdermal low-dose oestrogen hormone replacement therapy (HRT) was started with good effect. Extended low molecular weight heparin thromboembolism prophylaxis was prescribed for 28 days.

Follow-up and outcomes

Histological assessment of the specimen showed a lobular white nodular mass with a central cystic area of haemorrhage, involving the broad ligament and extending into the cervix and right parametrium. This was a cotyledonoid dissecting leiomyoma comprising intersecting fascicles of smooth muscle cells which dissected between myometrial fibres. Hydropic

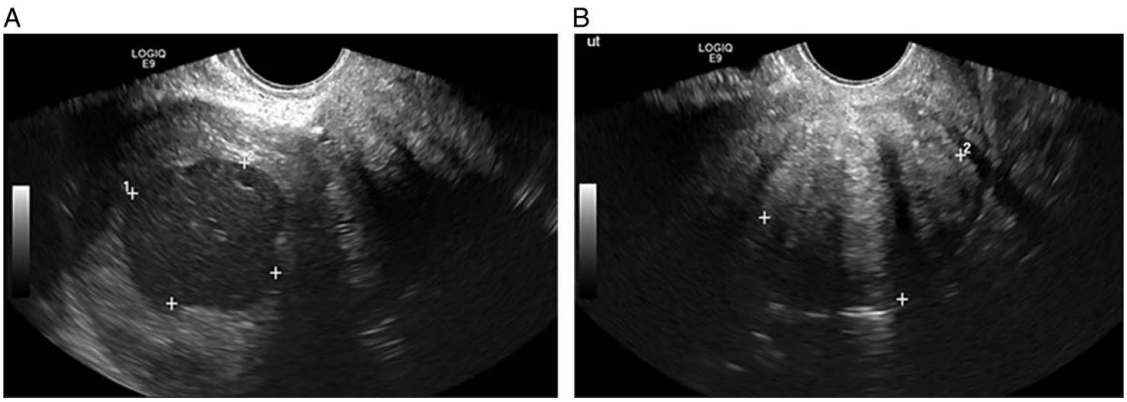

Figure 1. Transvaginal pelvic ultrasonography images showing a heterogenous hypoechoic area within the uterine cavity (A) and a posterior lower uterine fibroid involving the cervix (B).

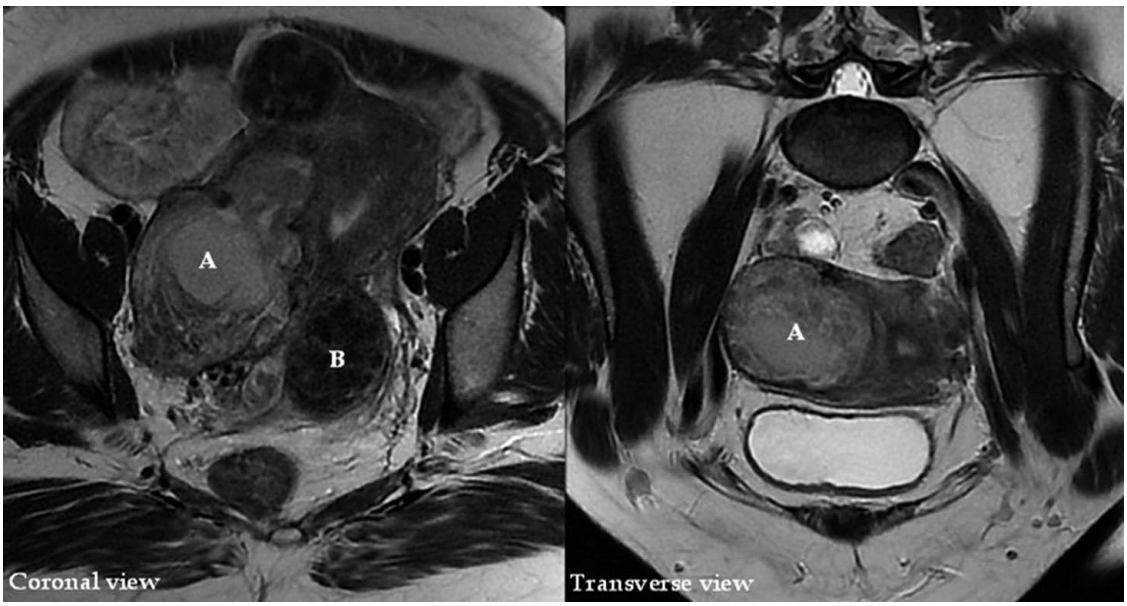

Figure 2. T2-weighted Pelvic MR images showing a right cornual mass extending to the broad ligament with restricted diffusion (A) and a posterior lower uterine fibroid involving the cervix (B).

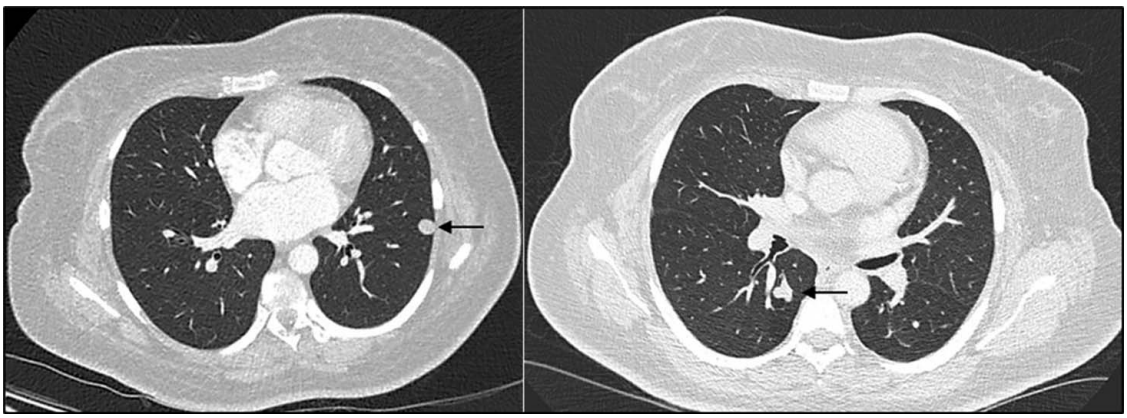

Figure 3. CT Thorax images showing a 12 mm peripheral nodule in the left lower lung (left image) and a bilobed 9 mm nodule in the right middle lung lobe (right image). CT, computed tomography.

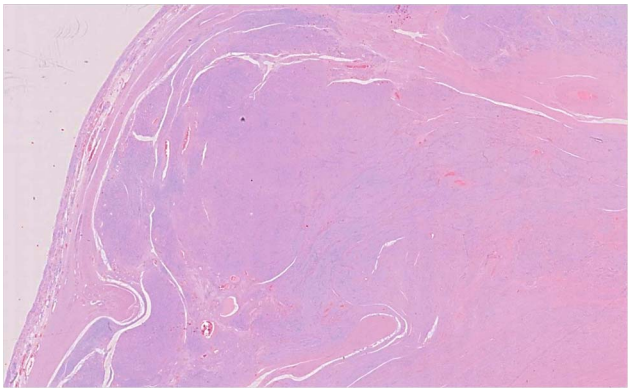

Figure 4. H&E slide showing uterine leiomyoma comprising intersecting fascicles of smooth muscle cells without significant cytological atypia or necrosis. H&E, hematoxylin and eosin.

changes and cystic degeneration were noted. There was no significant cytological atypia, necrosis, or increased mitoses to suggest malignancy (Fig. 4). Immunohistochemistry (IHC) revealed that tumour cells were diffusely positive for smooth muscle markers (α-SMA, caldesmon and desmin) and oestrogen and progesterone receptors, whereas CD34, HMB45, ALK1 and MelanA were all negative. The three resected right external iliac lymph nodes showed reactive changes.

In view of this unexpected benign finding, the patient was counselled by the Cardiothoracic team regarding the possible aetiology of the lung lesions. At that stage, the possible differential diagnoses included metastasis from another primary, hamartoma or carcinoid. A video-assisted thoracoscopy and diagnostic wedge resection of the more accessible peripheral left lung nodule was performed. The patient made an excellent recovery and was discharged on the first postoperative day.

Histologically the lung parenchyma showed an 11 mm circumscribed nodule with features in keeping with a benign smooth muscle tumour (identical to the uterine tumour), and entrapped normal bronchioalveolar epithelium. There was no cytological atypia and the mitotic count was less than 1/10 high power fields (Figs. 5 – 6). IHC was identical to the uterine smooth muscle tumour.

Postoperative repeat CT of the thorax showed mild enlargement of the right lung lesion from 9 to 12 mm. Following further counselling and gynae-oncological multidisciplinary team discussion, transdermal oestrogen HRT was stopped and a selective serotonin reuptake inhibitor alternative was prescribed. Due to the previously experienced severe vasomotor symptoms the patient was understandably not keen on stopping HRT. Interval imaging was scheduled (CT thorax after a further 3–6 months) and a further cardiothoracic consultation was sought for consideration of thoracoscopic resection of the right lung lesion. The patient was also counselled on the potential role for Letrozole, especially if she was not keen on pursuing further surgery or if interval imaging showed further lesional growth. She underwent successful complete thoracoscopic resection of the right lung bilobed nodule and remains well and asymptomatic.

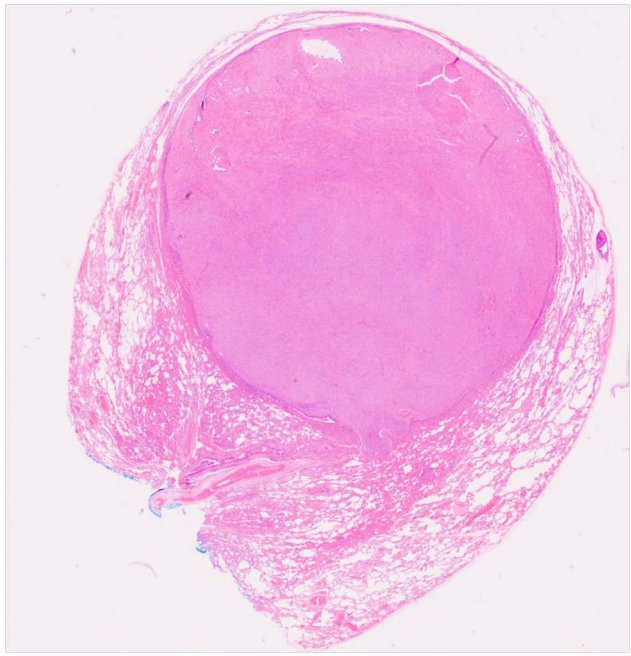

Figure 5. Low magnification image showing the thoracoscopically resected left lung nodule, with histological features of a benign smooth muscle tumour composed of intersecting fascicles of bland spindle cells with blunt-ended nuclei and pale cytoplasm within a hyalinised stroma.

Discussion

Uterine leiomyomas are common gynaecologic tumours, more than half of which occur in women over the age of 30[8]. PBML normally refers to lung metastases originating from uterine leiomyomas, in a similar pattern to distant endometriosis affecting the lung[9]. The average age of BML patients at diagnosis is 48 years with a 3-month to 23-year diagnostic interval between hysterectomy and lung findings[10,11]. Eighty-seven percent of PBML cases present with multiple lung nodules (70% bilateral nodules and 17% unilateral nodules) while 13% of patients have

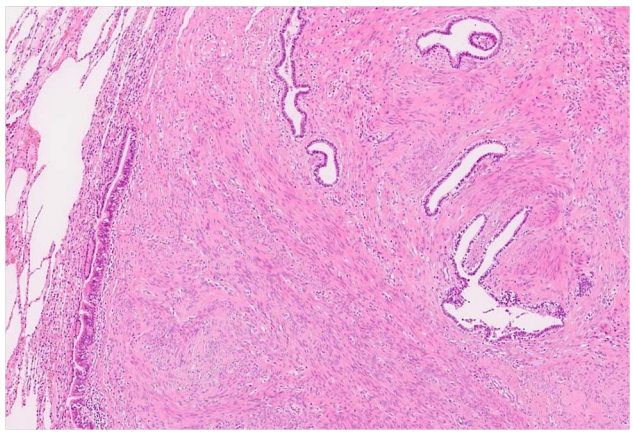

Figure 6. High magnification view of the resected left lung nodule showing the smooth muscle tumour with entrapped normal bronchioalveolar epithelium.

a solitary lung nodule[12]. Thoracoscopic or open lung biopsy is the gold-standard diagnostic modality.

There has been controversy on the origin, aetiology and classification of this condition. Several hypotheses have been proposed to explain the origin of PBML. These include (1) haematogenous spread of benign uterine leiomyoma cells, (2) metastasis from a low-grade leiomyosarcoma to the lung or (3) multiorgan focal proliferation of smooth muscle cells in response to hormonal exposure. PBML lesions are often positive for bcl-2, an apoptosis protein regulator that is typically abundantly expressed in uterine leiomyomas. This favours a metastatic process over multiorgan smooth muscle proliferation[13]. Furthermore, more recent cytogenetic studies are consistent with a monoclonal origin of both uterine and lung lesions[14,15]. The exclusive occurrence in females, hormone receptor positivity in extrauterine lesions, and response to hormone manipulation also support this hypothesis[16]. The Ki67 index has limitations when differentiating between PBML and a low-grade leiomyosarcoma, in fact slow-growing low-grade malignancies in other organs such as the prostate and thyroid may have Ki67 indexes that are equivalent to or even lower than those noted in PBML[17].

Lymphangiomeimyomatosis is in the differential diagnosis of PBML. Radiologically the former often presents as cystic and the diagnosis relies upon histological assessment and IHC as the lesional cells in lymphangiomeimyomatosis are positive for HMB45 and Melan-A[18]. Prognosis of PBML is overall favourable as lesions follow an indolent course. Larger tumour lesions may, however, lead to embolization, pulmonary infarction or symptomatic disease such as respiratory failure or compression symptoms.

Another clinical differential diagnosis is thoracic endometriosis, a rare manifestation of extragenital endometriosis. Lesions on the visceral pleura and diaphragm are the most commonly described sites (29.6% and 38.8%, respectively)[19]. Lung nodules are less commonly encountered and often reside in peripheral lung parenchyma[20,21]. It is hypothesised that these extragenital lesions arise from retrograde menstruation with subsequent passage of endometrial cells into the pleural space through lymphatic channels, diaphragmatic fenestrations or via haematogenous spread. Hormonal changes affect ectopic extragenital sites in thoracic endometriosis but unlike PBML, symptomatology may be cyclical in nature and may include catamenial haemoptysis or haemothorax. As with PBML, hormonal treatment and combined approaches including video-assisted thoracoscopy have been used with considerable success for this condition[22].

Due to the absence of trials assessing the management of PBML, there is no consensus on its management. Three major approaches can be taken when managing these patients. Once lung lesion biopsies have excluded malignant metastasis to the lung or primary lung malignancy, a conservative approach with imaging surveillance can be employed for asymptomatic patients. The role of repeat imaging is to look for significant interval changes that would prompt a more interventional approach. Interval timing should be individualized according to the radiological features at presentation.

Secondly, hormonal manipulation can be utilized to stabilize PBML and cause lesional regression. These lesions are hormone sensitive and thus may regress after menopause[11] or equally can recur on oestrogen replacement therapy[23]. Anti-oestrogen therapy, including bilateral oophorectomy (for premenopausal women), gonadotropin-releasing hormone agonists, selective oestrogen receptor modulators and aromatase inhibitors such as Letrozole should be considered as treatment options, particularly for younger patients with mild clinical manifestations[24,25].

Thirdly, surgical resection may be considered. This is especially the case for patients with symptomatic PBML (e.g. respiratory or compressive symptoms), patients who do not respond to hormone manipulation therapy or in cases where diagnostic uncertainty persists.

Conclusion

Although BML is a very rare condition, it should be considered as a differential in women with a history of uterine leiomyomata with solitary or multiple pulmonary nodules, particularly if presentation is in the perimenopause and if there has been previous uterine surgery. Accurate histopathological analysis along with IHC is essential to exclude other mesenchymal neoplasms, with a potential role for cytogenetic analysis. Patient counselling can be challenging particularly when recommending bilateral oophorectomy or menopause-inducing medications in premenopausal women. Counselling should be multidisciplinary and needs to convey the indolent course of the condition and the safety of conservative or hormonal management options.

Ethical approval

Nil required.

Consent

Written informed consent was obtained from the patient 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.

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Author contribution

M.B.—first author, drafted manuscript, guarantor. S.L.S.L.—case management, manuscript review. A.F.—case management, manuscript review. M.S.—manuscript editing. K.K.W.L.—case management,. manuscript review. A.L.—consultant responsible for case management, supervisor, manuscript review. All authors have approved the final version of the manuscript.

Conflicts of interest disclosure

Nothing to declare.

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