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CASE REPORT

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Collision tumor, a metastatic melanoma within a meningioma: a case report

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Abstract

Background Collision tumors, involving two distinct neoplasms in a single anatomical site, are rare. Among these, the metastasis of melanoma into an intracranial meningioma is particularly uncommon, with only four previously reported cases. Melanoma, known for its aggressive metastatic potential, contrasts sharply with the small number of collision tumor reports. The coexistence of these tumors poses diagnostic and therapeutic challenges, particularly in patients with a stable meningiomas.

Results We present the fifth documented case of melanoma metastasizing to a meningioma, the first to include genetic analysis revealing an *NRAS* mutation in the melanoma. The patient, a 58-year-old man, developed a hemorrhagic transformation of a stable left frontal meningioma. Surgical resection confirmed a biphasic tumor with melanoma cells infiltrating the meningioma. Despite initial treatment with immune checkpoint inhibitors, the patient's condition progressed with widespread metastatic melanoma, ultimately leading to death.

Conclusions The rarity of reported melanoma-to-meningioma metastasis highlights the need for further research into the genetic and pathophysiological mechanisms underlying tumor-to-tumor metastasis. Advances in genomic technologies could help identify biomarkers associated with such rare phenomena. This case also emphasizes the importance of monitoring patients with stable meningiomas and a history of melanoma for potential metastasis. Future research should explore whether prophylactic management of benign meningiomas could mitigate this risk and assess the long-term outcomes of collision tumors compared to typical metastatic brain tumors.

Keywords Melanoma, Meningioma, Collision tumor, Tumor-to-tumor metastasis (TTM)

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Introduction

Collision tumors, which arise when two histologically distinct neoplasms coexist within the same anatomical site, are rare occurrences in clinical practice. Among these, the metastasis of melanoma into an intracranial meningioma is an uncommon phenomenon.

Melanoma often is an aggressive tumor with a propensity for metastasis to various organs including the brain. Conversely, meningiomas are typically benign, slow-growing tumors arising from the meninges. The coexistence of these two distinct tumor types within the intracranial space presents unique diagnostic and therapeutic challenges.

We encountered a rare case of melanoma metastasizing into an intracranial meningioma. A review of the literature aimed at assessing the risks of leaving a benign, stable meningioma untreated in melanoma patients identified only four previously reported cases of collision tumors involving meningioma and melanoma. This suggests that such occurrences may often go unreported. However, further analysis of these collision tumor cases is crucial to inform and refine the future management of benign meningiomas coexisting with melanoma.

Case presentation

A 58-year-old man presented for medical care with worsening right-sided epistaxis. He was referred to an otolaryngologist, who discovered a melanoma in his nasal passage. He underwent multiple surgeries and treatments, including 66 Gy radiation and six cycles of adjuvant chemotherapy with cisplatin and temozolomide. Molecular testing detected an *NRAS* mutation, p.Gly183Ala (c.548G > C).

Nine months after completing adjuvant therapy, he presented with progressive headaches and subsequently word-finding difficulties. Magnetic resonance imaging (MRI) scan demonstrated hemorrhagic expansion and transformation of the left frontal lesion. The previously seen enhancing dural-based mass overlying the left middle frontal gyrus (Fig. 1A and B), which has been stable for more than 6 months had increased in size from 25 × 16 × 14 mm (Fig. 1B) to 26 × 24 × 25 mm (Fig. 1C), with new internal hemorrhage that had ruptured into the adjacent subdural space, resulting in a large left holohemispheric subdural hematoma. Mass effect was seen including a rightward midline shift of 1.2 cm and left uncal herniation. On examination, he was alert but drowsy and complaining of a headache. He was taken to the operating room for diagnostic and therapeutic purposes and underwent resection with a wide dural cuff around the dural-based lesion (Simpson grade 1). This lesion had a central whitish, fibrous, tan component consistent with a benign meningioma as well as surrounding darker melanotic portions concerning for melanoma metastases. While the tumor masses were mostly distinct, there were foci of melanoma cells within the meningioma. Frozen pathology was consistent with this biphasic histologic morphology with fibrous tumor-containing whorls consistent with pre-existing meningioma that had become secondarily seeded with metastatic melanoma. The subdural hematoma was evacuated, and a subdural drain was placed. Histopathology showed two lesions: discohesive malignant cells with pleomorphic nuclei and granular cytoplasmic pigment accumulation in some cells, diagnostic for melanoma under microscope. The meningioma otherwise revealed cohesive sheets of cells with whorl formation and meningothelial syncytial clusters, diagnostic for meningioma WHO grade 1 (no brain invasion, no histologic features of a grade 2 lesion). Immunohistochemical staining for SSTR2-alpha as a marker of meningothelial cells and Mart-1 as a marker for melanoma demonstrated that close to the gross boundary between the two tumors, there were islands of melanoma within the meningioma. No foci of meningioma were identified within the more solid areas of melanoma (Fig. 2).

Following surgery, the patient was administered ipilimumab at 3 mg/kg and nivolumab at 1 mg/kg intravenously every three weeks for four induction doses. This was then followed by maintenance therapy with nivolumab at 3 mg/kg every two weeks. He was hospitalized for progressive neurological symptoms a month after the first surgery. MRI revealed post-surgical changes related to the resection of a left frontal meningioma and associated metastatic lesion. There was an 11 mm thick subdural fluid collection subjacent to the craniotomy site (Fig. 1D) with areas of restricted diffusion seen on diffusion weighted imaging (not shown). He again underwent surgery, which revealed inflammatory tissue associated with melanoma. Most of the specimen consisted of granulation tissue that appeared to be primarily oriented around foreign material, presumably from the prior surgery. Some fragments featured extensive collagen deposition. Small foci of melanoma were present. He showed gradual improvement before discharge. Unfortunately, the patient's course over the subsequent six months was highlighted by progressing disease outside the CNS, with new and growing hepatic and bony metastases that were not responsive to immunotherapy and that led to his death.

Autopsy At the postmortem evaluation, the cause of death was identified as widely metastatic melanoma, involving the heart, lungs, liver, spleen, pancreas, thoracic lymph nodes, abdominal mesentery, stomach, small and large bowel, left spermatic cord, left ureter, bilateral peri adrenal fat, and vertebral bodies. The resected and treated lesion in the middle frontal gyrus showed predominantly

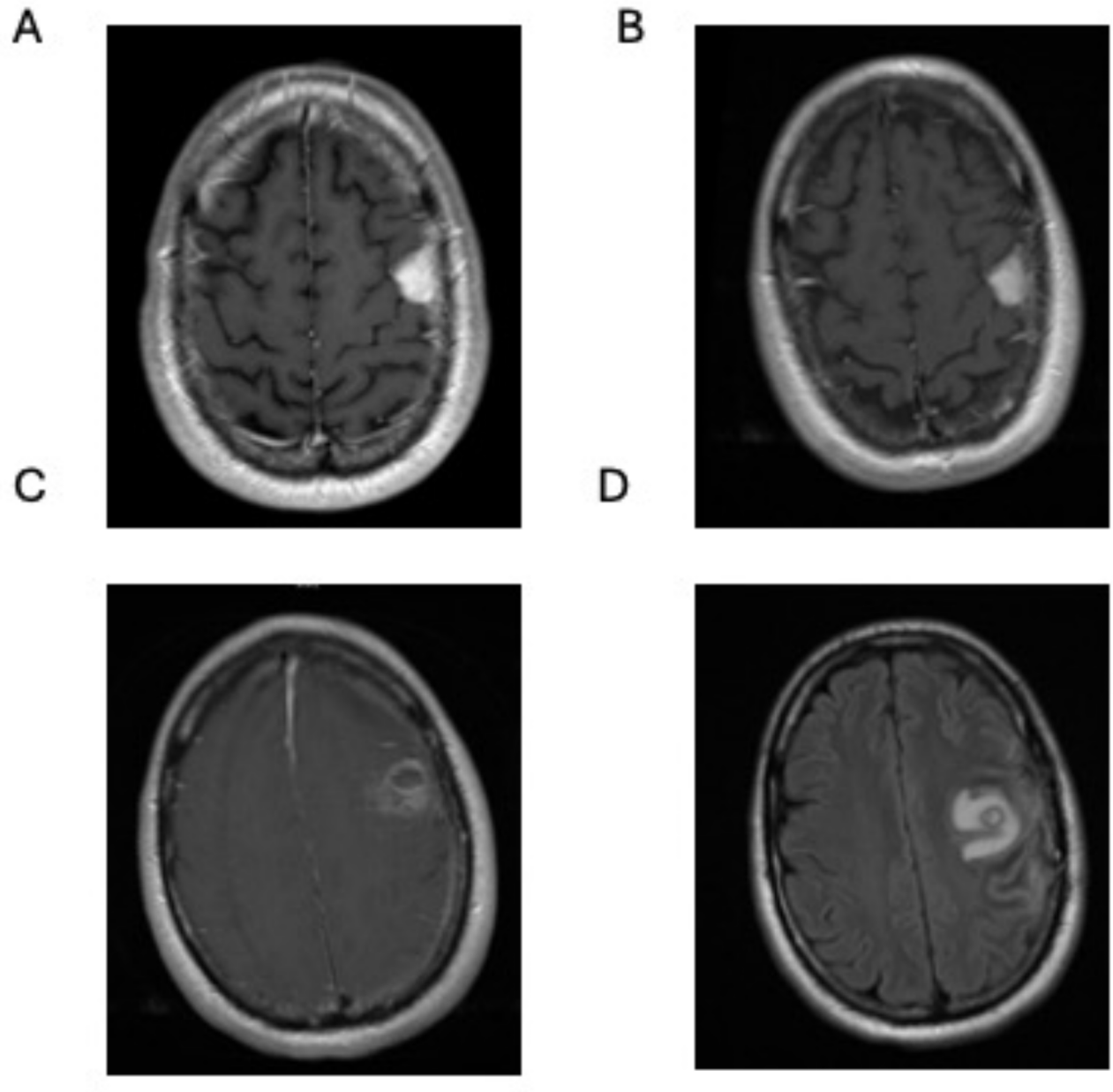

Fig. 1 MRI images depicting the progression of melanoma metastasis to a convexity meningioma over time. **A**: MRI image from one year before the first operation, showing a previously stable meningioma (T1 enhancement). The image reveals a uniform, dural-based enhancing lesion measuring 23.8 × 19.7 × 13.2 mm located at the posterior left frontal convexity. **B**: MRI image from six months before the first operation, showing a stable meningioma (T1 enhancement). The lesion remains uniform, dural-based, and unchanged in size at the left frontal convexity. **C**: MRI image obtained nine months after the completion of adjuvant therapy, when the patient presented with progressive headaches followed by word-finding difficulties (T1 enhancement). The image reveals hemorrhage within a left frontal convexity meningioma, which has significantly increased in size since the previous scan. The hemorrhage extends into the adjacent subdural space, resulting in a large left holohemispheric subdural hematoma with a maximal thickness of up to 10 mm. Additionally, thin subdural hematomas are observed along the left anterior falx. **D**: MRI image obtained one month after the first surgery, when the patient exhibited progressive neurological symptoms (FLAIR). The image shows an extra-axial fluid collection within the left frontal resection cavity

reactive changes with only scant cells suspicious for remaining tumor. The other grossly identified parenchymal lesion was predominantly a hemorrhagic lesion, likely to have had an underlying tumor that was moderately obliterated by the destructive hemorrhage. There was no evidence of diffuse leptomeningeal tumor involvement.

While cases of melanoma metastasizing to other tumors, including meningiomas, is a recognized phenomenon, only four cases of this combination of tumors have been previously reported. Below, we review the previous four cases reported.

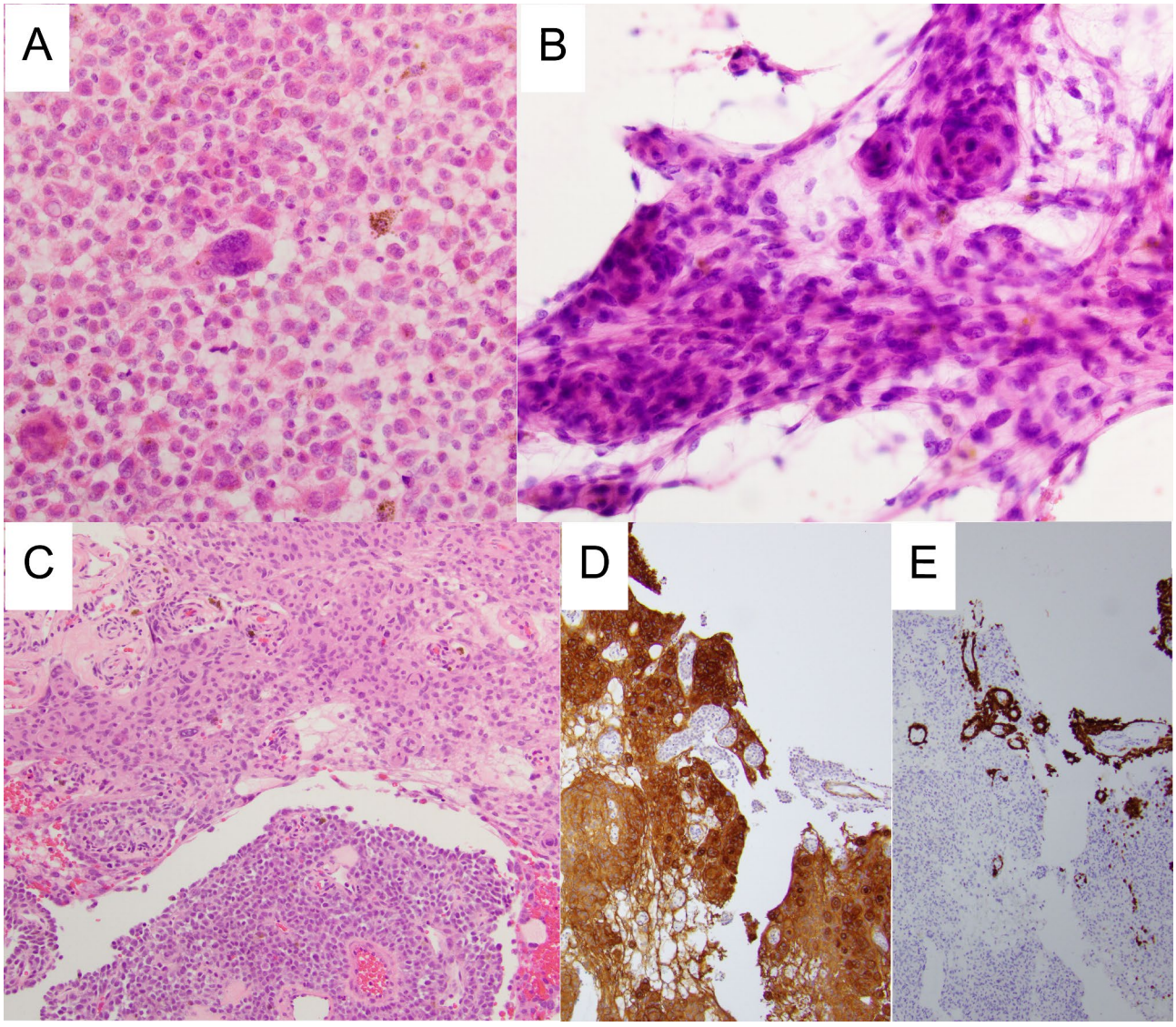

Fig. 2 Pathology findings. **A** and **B**: H&E-stained intra-operative smears prepared from grossly distinct regions of the resected mass demonstrated distinct diagnostic findings, with discohesive malignant cells with pleomorphic nuclei and granular cytoplasmic pigment accumulation in some cells, diagnostic for melanoma (**A**) as well as cohesive sheets of cells with whorl formation and meningothelial syncytial clusters, diagnostic for meningioma (**B**). **C**: H&E-stained section of paraffin-embedded tissue at the boundary between the two grossly distinct portions of the lesion with diagnostic features of meningioma in the upper portion of the field and melanoma in the lower portion. **D** and **E**: Immunohistochemical staining for SSTR2-alpha as a marker of meningothelial cells (**D**) and Mart-1 as a marker from melanoma (**E**) demonstrates that close to the gross boundary between the two tumors, there are islands of melanoma within the meningioma. There were no foci of meningioma identified within the more solid areas of melanoma

First case A 63-year-old man was reported to have a right conjunctival melanoma. Seven years later, he developed metastatic disease in a submandibular lymph node. Subsequently, a 3 cm right frontal convex meningioma was discovered and resected. The meningioma was surrounded by a thin subdural hematoma, and pathological examination confirmed melanoma infiltration [14].

Second case A 75-year-old woman was found to have a melanoma-meningioma collision tumor during an autopsy. The case involved vulvar melanoma metastasizing to a falx meningioma. Histologically, the meningioma was a fibroblastic meningioma (WHO grade 1) [11].

Third case A 53-year-old woman had a stable left sphenoid wing meningioma for four years. Ten months after having a melanoma resected from her left forearm, she reported increased headaches and dysphasia. Three days later, her condition deteriorated, and the tumor was extracted, revealing an infarcted center. Tumor rim with fibroblastic meningioma was infiltrated by melanoma [7].

Fourth case A 51-year-old woman had a right arm melanoma excised. Fifteen months later, she experienced right-sided weakness and difficulty speaking. Her previously stable left sphenoid wing meningioma, which had been stable for three years, was found to have increased in size. By the time of surgery it had caused a hemorrhage. Histology showed the presence of metastatic melanoma within the meningioma [10].

Discussion and conclusions

In this report, we present a case of melanoma metastasizing into an intracranial meningioma.

The phenomenon of tumor-to-tumor metastasis (TTM) presents a unique and complex challenge in oncology, particularly when examining the rare instances of melanoma metastasizing to meningiomas. This case adheres to the rigorous criteria established by Campbell et al. [1, 11], which stipulate that for a "true" tumor-to-tumor metastasis to be recognized, several conditions must be met: the existence of at least two primary tumors, the classification of the recipient tumor as a true neoplasm, established growth of the metastatic neoplasm within the recipient tumor (not attributable to contiguous growth or tumor emboli), and exclusion of cases where lymph node metastasis occurs in the context of existing lymphoreticular malignancies.

Meningiomas are the most reported recipient tumors in TTM. The primary sources of these metastases are breast carcinoma (33.6%), lung carcinoma (28.2%), and, less frequently, melanoma (2%) [9, 12]. Meningiomas account for 36.4% of central nervous system tumors, with an incidence of 4 per 100,000 individuals and a female-to-male ratio of 2.5:1, predominantly affecting individuals in their 50s and 60s [6, 8]. Several pathophysiological mechanisms have been associated with tumor-to-tumor metastasis (TTM). For TTM to establish in the recipient tumor, three conditions are considered essential [9]:

1) The tumor must be hypervascular, making it susceptible to hematogenous metastasis.
2) It must be well-nourished to support the growth of donor tumor cells.
3) It should exhibit slow growth.

Also, *ICAM* expression is common in meningiomas and may also facilitate the adhesion of metastases to meningioma blood vessels [3]. However, the mechanism of tumor-to-tumor metastasis is still unknown. It is not known why this frequency is lower in melanoma than that of lung and breast cancers. The majority of brain metastases originate from primary cancers in the lung (40–50%) or breast (15–25%), or from melanoma (5–20%) [2]. There might be an actual numerical difference, but the possibility of publication bias cannot be ruled out. Collision tumors are rare, and their features are not well understood. This case is only the fifth documented instance of melanoma metastasizing to a meningioma. Notably, it is the first case to include genetic analysis of the melanoma, which revealed an NRAS mutation, although the genetic details of the meningioma were not examined.

The most recent similar case, reported in 2010, lacked molecular data, emphasizing the importance of future cases including such analyses. Understanding the genetic factors that might make melanoma more likely to metastasize to meningiomas is essential. Advances in genetic analysis may help identify markers that explain this phenomenon. Additionally, certain histologic and molecular features of a meningioma may create a more favorable environment for melanoma metastasis. Further molecular analysis of these tumors could lead to improved diagnostic and management strategies for these rare cases. A molecular model to predict response to radiotherapy for meningioma was recently developed. Using a similar approach, it may be possible to develop a predictive model for TTM in the future [13].

Cases have been reported where malignant tumors metastasize to meningiomas, leading to rapid growth of the affected meningioma [12]. Clinicians should consider the possibility of TTM in patients with a history of cancer who present with a previously stable meningioma that has recently begun to enlarge. In cases where melanoma metastasizes to a meningioma, hemorrhage, a common feature of melanoma metastases may contribute to this accelerated growth. Our case involved hemorrhage, consistent with two previously reported instances of melanoma-meningioma collision tumors. Given the frequent association of hemorrhage with CNS melanoma metastases [4], its presence in melanoma collision tumors involving meningiomas is unsurprising.

In cases of tumor-to-meningioma metastasis, most recipient meningiomas are found in the convexity (39.8%), parasagittal region (26.6%), anterior skull base (18.58%), posterior fossa or tentorium (9.73%), and spine (5.26%) [12]. The epidemiology of primary meningioma locations differs somewhat: convexity (lateral hemisphere) (20–37%), parasagittal (medial area of hemispheres) (13–22%), including falcine meningiomas (5%), spine (7–12%), and skull base (43–51%) [5].

Over the past 15 years, melanoma treatment strategies have undergone significant transformation, beginning with the approval of ipilimumab. These advancements have greatly extended the life expectancy of melanoma patients. The risk of collision tumors involving stable benign meningiomas may emerge as an important consideration in patient management. Evaluating prophylactic interventions, such as resecting benign meningiomas, or more likely to be adopted, more frequent CNS imaging

in patients with melanoma and known meningioma, could help mitigate the potential risk of metastatic seeding by melanoma and/or allow for earlier intervention. However, careful assessment of the risks and benefits of such approaches is necessary.

Key questions remain, including whether the prognosis of collision tumors differs from typical metastatic brain tumors, whether non-surgical treatment options might be effective, and whether alternative methods for detecting metastasis beyond monitoring for rapid tumor growth can be developed. Addressing these questions will be critical to optimizing the management of melanoma patients with stable benign meningiomas.

Abbreviations

BBB Blood-brain barrier
CNS Central nervous system
TTM Tumor-to-tumor metastasis

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This research was approved by the Massachusetts General Hospital Institutional Review Board and all human participants involved in this work provided written consent prior to study commencement.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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