

## CASE REPORT

# Metastatic primary pulmonary melanoma successfully treated with checkpoint inhibitors

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## SUMMARY

Our patient is a 69-year-old man who presented to the emergency department with left-sided hemiparesis that started 4 hours prior to presentation. Brain CT showed right basal ganglia and internal capsule haemorrhagic strokes. MRI revealed multiple brain lesions suspicious for metastases. Further workup revealed a 5 cm lung mass and a 1 cm pancreatic nodule. Biopsy of both pulmonary and pancreatic lesions was consistent with melanoma and was similar histologically. The patient underwent cyberknife stereotactic radiosurgery to the brain metastases followed by immunotherapy with pembrolizumab, and then by nivolumab and ipilimumab. The patient remains free of disease progression 2 years after treatment.

## BACKGROUND

Melanoma is a malignancy of the pigment producing melanocytes. It usually affects the skin, but has been described in other organs. Only one previous report exists of a thoracic melanoma metastasising to the pancreas and presented as acute pancreatitis.<sup>1</sup> Patients with metastatic disease are not surgical candidates and, until recently, had very poor prognosis. Newer treatment options have improved survival and these include anti-programmed cell death-1 (PD-1) inhibitors, anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitors and tyrosine kinase inhibitors. In this report, we are presenting a case of primary pulmonary melanoma (PPM) with metastasis to the brain and pancreas successfully treated with immune checkpoint inhibitors.

## CASE PRESENTATION

A 69-year-old man presented to the emergency department with acute left-sided hemiparesis of 4 hours duration. This started acutely and was noticed when the patient had difficulty getting out of bed in the morning. He had no other neurological symptoms, and review of symptoms was otherwise negative. His medical history was significant for well-controlled hypertension and prostate adenocarcinoma treated with radical prostatectomy 4 years prior to admission and with no recurrence. He did not smoke, drink or use any illicit drugs. Family history was negative for stroke or malignancy. Physical exam was significant for elevated blood pressure (170/90 mm Hg) and grade II/V muscle weakness in both left limbs.

## INVESTIGATIONS

An emergent CT of the brain showed right basal ganglia and internal capsule haemorrhagic strokes

(figure 1). Brain MRI demonstrated haemorrhages in the posterior aspect of the right putamen measuring approximately 3.7×3.2 cm and in the posterior limb of the right internal capsule measuring 1.1 cm×0.5 cm. Several round masses were also evident within the medial aspect of the right thalamus, the posterior medial cortex of the left frontal lobe, and the posterior and superior cortices of the left temporal lobe. These findings were suspicious for metastasis and a CT of the chest, abdomen and pelvis was subsequently performed. This showed a 5 cm lung mass (figure 2) and a 1.5 cm pancreatic mass in the uncinate process of encasing the blood vessels. CT-guided biopsy of the thoracic mass and an endoscopic ultrasound-guided fine needle aspirate of the pancreatic mass were done. Pathology from the lung biopsy showed nests of malignant cells with eccentric nuclei, prominent nucleoli and scant dense cytoplasm with increased mitotic figures (figure 3A,B). Immunohistochemistry was strongly positive for S100, MART-1 (figure 3C,D) as well as HMB-45. These findings were consistent with metastatic melanoma. BRAF V600 mutation was not present. The pancreatic biopsy showed similar findings (figure 4).

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis for this patient was broad. Even though tumours of pancreatic origins can metastasise to the lung, they rarely metastasise to the brain. Non-small cell lung cancer is a common tumour that metastasises to the brain and pancreas, and was included in our differential. Other malignancies that could involve the brain, lung and pancreas included colon cancer, gastric cancer or malignant melanomas. Metastatic melanoma of skin, ocular or pulmonary origin is a possibility.

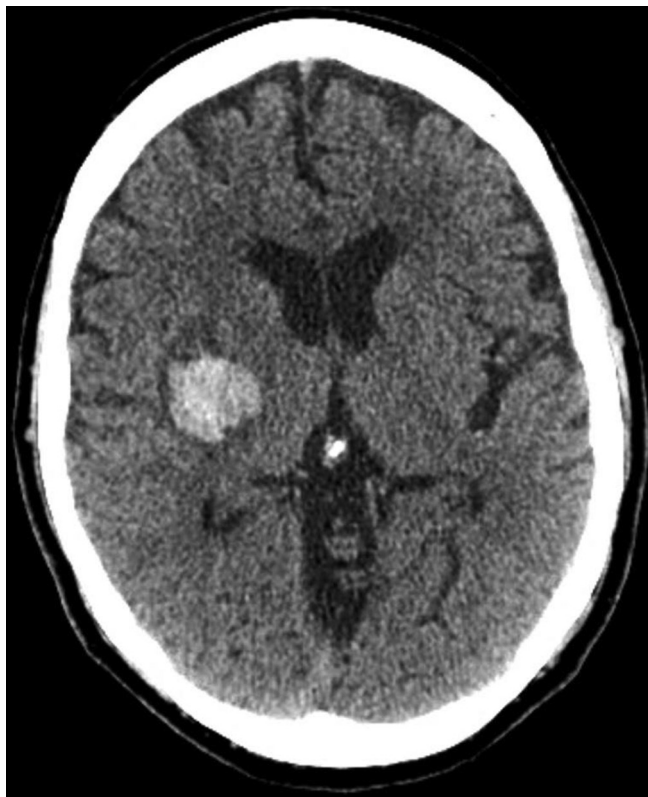
Our patient had no history of skin lesions or any resected nevi or lesions. A thorough search for primary cutaneous or mucosal source was negative. Skin, nail and ophthalmologic exams showed no suspicious lesions. Exhaustive CT imaging was performed to look for other primaries in the chest, abdomen and pelvis; none were identified. Oesophagogastroduodenoscopy and colonoscopy were also performed and were negative.

## TREATMENT

The patient underwent cyberknife radiosurgery to the right thalamic, right basal ganglia, left frontal lobe and left temporal metastases. He was then started on immunotherapy with pembrolizumab.

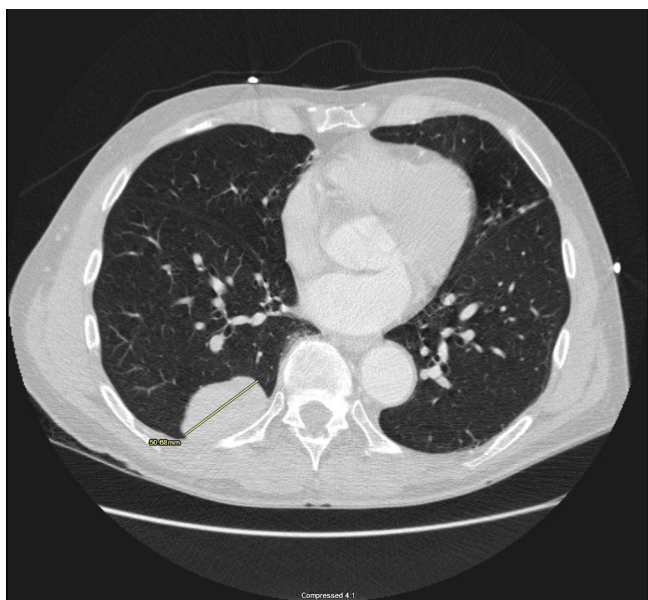


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**Figure 1** CT of the brain showing a 2.3×2.7 cm acute intraparenchymal haemorrhage in the posterior aspect of the right putamen.

He did well initially with no adverse events noted. Repeat testing initially showed stable lung and pancreatic lesions with no new metastasis identified. However, 9 months later, a CT of the chest showed an increase in the size of the tumour; subsequently pembrolizumab was discontinued and the patient was started on nivolumab and ipilimumab.



**Figure 2** Thoracic CT showing a 5 cm right lower lobe pleural-based mass.

## OUTCOME AND FOLLOW-UP

The patient is currently still on immunotherapy with nivolumab and ipilimumab. Most recent surveillance imaging showed no increase in size of the lung or pancreatic masses.

## DISCUSSION

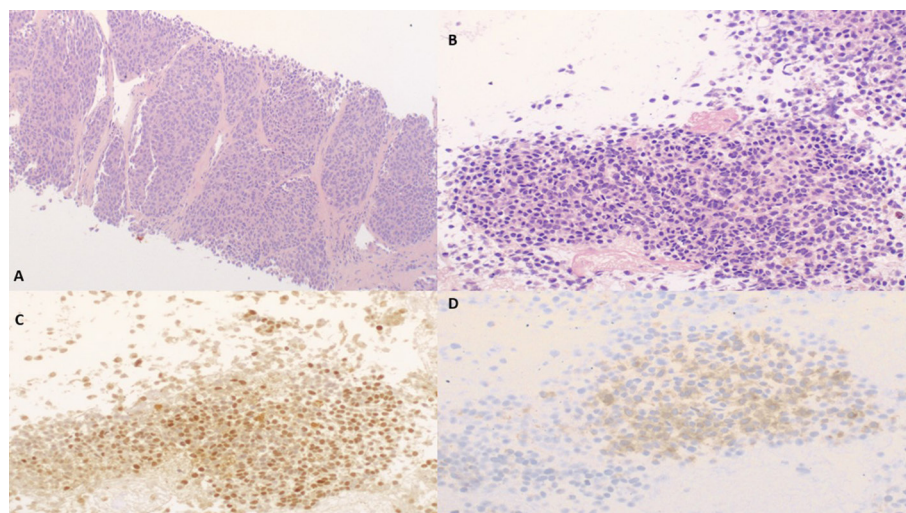
Malignant melanoma is a malignancy of pigment-producing melanocytes. It is the fifth leading cancer in men and the seventh in women in the USA<sup>2</sup> with an incidence of 26.3 cases per 100 000 people.<sup>3</sup> Melanomas in the lung are usually a metastatic disease while PPM is a very rare occurrence. Metastatic melanoma to the lung usually presents as multiple nodules, rarely presenting as a single solid lesion. Conversely, PPM usually presents as a single mass-like lesion and often in an advanced stage on diagnosis.<sup>4,5</sup> Almost a third of patients diagnosed with PPM are asymptomatic at the time of diagnosis.<sup>5</sup> Airways as well as parenchyma and pleura can be involved. Melanoma is among the tumours that most commonly metastasise to the brain.<sup>6</sup> The metastases are often multiple and have a tendency to bleed, typically presenting acutely with headache, focal neurological deficits and seizures. Solid melanomas found in the pancreas are always metastatic,<sup>1</sup> with the skin being the most common primary. Only one previous case of PPM metastatic to the pancreas has been reported.<sup>1</sup>

Diagnosis of PPM has relied on the following criteria<sup>5,7</sup>: (1) single lung tumour; (2) the presence of one of the three typical histopathologic appearances<sup>5</sup>; (3) no previously excised melanoma; and (4) no other primary on presentation. Our patient had no previous melanomas excised and none found on exam; no other primary found after extensive search in the gastrointestinal tract, eyes and nails. He also had a single tumour in the lung. Histology showed nesting of the melanoma cells just beneath the bronchial epithelium. As such, our patient fulfilled all criteria for the diagnosis of PPM. All throughout the clinical course, the patient did not have any signs or symptoms of pancreatic or pulmonary disease.

Until recently, the prognosis of metastatic melanoma was very poor, with a median survival less than 1 year.<sup>8</sup> Similarly, survival for patients presenting with PPM is poor, and treatment relied on surgical resection.<sup>6,8</sup> Lobectomy and/or pneumonectomy are preferred over wedge resection as it decreases the rate of recurrence. Surgical resection is not recommended in patients with advanced PPM.<sup>9</sup> Surgical resection was also the mainstay treatment for single metastatic lesions to the brain until recently, with whole brain radiation used for palliation when multiple metastases are present. Unfortunately, the latter had poor outcomes as melanoma is considered radiation resistant.<sup>10</sup> More recently, stereotactic radio surgery has gained favour as it was shown to improve disease control with fewer side effects.<sup>11,12</sup>

After the discovery of BRAF V600 mutation in patients with melanoma, tyrosine kinase inhibitors were developed to target this mutation and have been shown to improve survival.<sup>13</sup> The BRAF V600 mutation activates the mitogen-activated protein kinase pathway, thus leading to increased proliferation and survival of neoplastic cells.<sup>13</sup> Several tyrosine kinase inhibitors have been approved by the US Food and Drug Administration for treatment of BRAF mutation positive melanoma. These include vemurafenib, dabrafenib, trametinib and dabrafenib. Combination therapy with different tyrosine kinase inhibitors is an area of active investigation.<sup>14</sup> Unfortunately, our patient did not have the BRAF V600 mutation and would not have benefitted from these medications.





**Figure 3** Pathology from the CT-guided lung biopsy. (A) Low-powered light microscopy showing nests of malignant cells in H&E staining. (B) High-powered microscopy showing cells with eccentric nuclei, prominent nucleoli and scant dense cytoplasm with increased mitotic figures. Occasional pigmented macrophages are also noted. (C) Immunohistochemistry showing strong positivity for S100. (D) Immunohistochemical staining positive for MART-1.

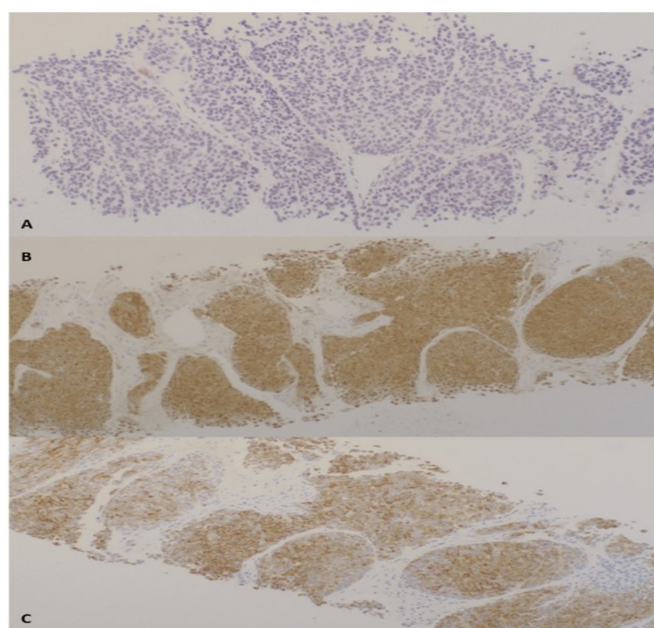
Other newer treatments used in melanomas are immune checkpoint inhibitors. Immune checkpoint blockade has been shown to induce tumour regressions in several cancer types including melanoma.<sup>15</sup> The interaction of PD-1 with programmed cell death ligands PD-L1 and PD-L2 inhibits T-cell activation and proliferation.<sup>16</sup> They also target CTLA-4.<sup>15</sup> CTLA-4, PD-1 and PD-L1 inhibition improves tumour recognition and disrupts the immune system inhibition. The most widely used PD-1 inhibitors in melanoma are pembrolizumab and nivolumab along with the CTLA-4 inhibitor, ipilimumab.

Combination therapy is currently being tested with promising preliminary results. In a randomised phase III clinical trial, it

was shown that nivolumab in combination with ipilimumab had a significant advantage over nivolumab or ipilimumab alone with median progression-free survival of 11.5, 6.9 and 2.9 months, respectively, regardless of the presence or absence of PDL-1 receptor activity.<sup>17</sup> In patients with negative PD-L1 activity, the combination therapy seemed to be more effective than nivolumab alone with a median progression-free survival of 11.2 and 5.3 months, respectively; however, the study was not designed for formal statistical comparison between the latter two groups.

The percentage of patients with a complete response was higher in the combination therapy group (11.5%) than in either the nivolumab group (8.9%) or the ipilimumab group (2.2%). Treatment-related adverse events of any grade that led to discontinuation of the study drug occurred more in the combination therapy arm (36.4%).<sup>17</sup>

Our patient did not have the BRAF V600 mutation and was initially treated with pembrolizumab alone. He did well at first, but 9 months later his lung mass increased in size and pembrolizumab was discontinued. He was subsequently started



**Figure 4** Endoscopic ultrasound-guided fine needle aspiration of the pancreatic mass. (A) Low-powered H&E stain showing nests of malignant cells similar in appearance to the pulmonary biopsy. (B) S100 staining showing strong positivity. (C) MART-1 staining showing strong positivity.

### Learning points

- ▶ Primary pulmonary melanoma is a rare cancer that carries a poor prognosis.
- ▶ Until recently, the only effective treatment was surgical resection.
- ▶ Stereotactic radiosurgery has improved survival for brain metastasis with less cognitive impairment as compared with whole brain irradiation.
- ▶ Newer treatment modalities have improved survival in metastatic melanoma with the use of tyrosine kinase inhibitors for BRAF V600 mutation positive tumours, or programmed cell death-1 and cytotoxic T lymphocyte-associated antigen-4 combination therapy in mutation negative patients.
- ▶ Combination therapy may increase the chances of survival without disease progression in patients with melanoma with metastatic disease on initial presentation.

on a combination of nivolumab and ipilimumab. He underwent stereotactic radiosurgery for his brain metastases with no residual neurological signs. He was seen in clinic regularly and is still doing well without disease progression more than 2 years after the initial diagnosis.

In conclusion, here we are presenting a case of PPM with metastasis to the brain and pancreas treated with immune checkpoint inhibitors. To our knowledge, this is the first case of metastatic malignant melanoma with pulmonary origin involving the pancreas and the brain on presentation. Such patients, who are not surgical candidates, have improved survival with PD-1 inhibitors, and a combination of PD-1 and CTLA-4 inhibitors may increase the chances of survival without disease progression.

**Contributors** JA was involved in the manuscript planning, literature review, drafting of manuscript and case review. NT was involved in case review, data collection and manuscript drafting. JG was involved in literature review and drafting of manuscript. GAH is the corresponding author and was involved in literature review, and drafting and editing the manuscript.

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## REFERENCES

- 1 Sobesky R, Duclos-Vallée JC, Prat F, *et al.* Acute pancreatitis revealing diffuse infiltration of the pancreas by melanoma. *Pancreas* 1997;15:213–5.
- 2 Nikolaou V, Stratigos AJ. Emerging trends in the epidemiology of melanoma. *Br J Dermatol* 2014;170:11–19.
- 3 Azoury SC, Lange JR. Epidemiology, risk factors, prevention, and early detection of melanoma. *Surg Clin North Am* 2014;94:945–62.
- 4 Allen MS, Drash EC. Primary melanoma of the lung. *Cancer* 1968;21:154–9.
- 5 Wilson RW, Moran CA. Primary melanoma of the lung: a clinicopathologic and immunohistochemical study of eight cases. *Am J Surg Pathol* 1997;21:1196–202.
- 6 Johnson JD, Young B. Demographics of brain metastasis. *Neurosurg Clin N Am* 1996;7:337–44.
- 7 Jensen OA, Egedorf J. Primary malignant melanoma of the lung. *Scand J Respir Dis* 1967;48:127–35.
- 8 Hodi FS, O'Day SJ, McDermott DF, *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–23.
- 9 Farrell DJ, Kashyap AP, Ashcroft T, *et al.* Primary malignant melanoma of the bronchus. *Thorax* 1996;51:223–4.
- 10 Ellerhorst J, Strom E, Nardone E, *et al.* Whole brain irradiation for patients with metastatic melanoma: a review of 87 cases. *Int J Radiat Oncol Biol Phys* 2001;49:93–7.
- 11 Lippitz B, Lindquist C, Paddick I, *et al.* Stereotactic radiosurgery in the treatment of brain metastases: the current evidence. *Cancer Treat Rev* 2014;40:48–59.
- 12 Siu TL, Huang S. Cerebral metastases from malignant melanoma: current treatment strategies, advances in novel therapeutics and future directions. *Cancers* 2010;2:364–75.
- 13 Chakraborty R, Wieland CN, Comfere NI. Molecular targeted therapies in metastatic melanoma. *Pharmacogenomics Pers Med* 2013;6:49.
- 14 Long GV, Weber JS, Infante JR, *et al.* Overall survival and durable responses in patients with braf v600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. *J Clin Oncol* 2016;34:871–8.
- 15 Wolchok JD, Kluger H, Callahan MK, *et al.* Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 2013;369:122–33.
- 16 Robert C, Long GV, Brady B, *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372:320–30.
- 17 Larkin J, Chiarion-Sileni V, Gonzalez R, *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med Overseas Ed* 2015;373:23–34.

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