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Mycobacterial spindle cell pseudotumour of the brain in an immunocompetent adult

Sir,

Mycobacterial spindle cell pseudotumour is a rare tumour-like lesion that predominantly occurs in immunocompromised individuals, especially those with HIV infection. Most

commonly described in the lymph nodes, this neoplastic mimic has also been reported in various other anatomical locations like skin, soft tissue, bone marrow, spleen, retroperitoneum and lungs. Brain is a rare site for mycobacterial spindle cell pseudotumour with only five documented cases.^{1–5} Here, we describe the second case of mycobacterial spindle cell pseudotumour involving the brain in an adult lacking any evidence of immunosuppression.

A 53-year-old male presented with evening rise in temperature, night sweats and weight loss (about 10 kg in 2 months) since September 2019. One month later, he developed slurred speech, deviation of angle of mouth to left and right upper limb weakness. For these symptoms he was evaluated elsewhere with magnetic resonance imaging (MRI) which showed multiple intra-axial space occupying lesions, the largest measuring 5.5×2.2 cm in the right occipital lobe. The lesions were hypointense to isointense on T2-weighted and FLAIR images and hyperintense on diffusion weighted images. The lesions showed thick ring and nodular post-contrast enhancement (Fig. 1A–D). He was referred to our institute and treatment with anti-tubercular drugs along with corticosteroid was started. Following this, there was symptomatic improvement. However, after 4 months, he had an episode of seizure. A repeat MRI at this point showed no change in the size of the lesions.

Fig. 1 Imaging and histopathology findings: (A) MRI showing multiple intra-axial lesions that are hypointense to isointense on T2-weighted image and (B) FLAIR sequence. (C) The lesions are hyperintense in diffusion weighted image with (D) thick ring and nodular post-contrast enhancement. (E) Histopathology shows a lesion with fascicles of spindle cells admixed with lymphocytes, plasma cells and (F) few ill-formed granulomata (H&E). (G) The spindle cells are diffusely positive for CD68 (immunoperoxidase). (H and inset) Acid-fast bacilli were detected on Ziehl–Neelsen stain.

Table 1 Review of literature of mycobacterial spindle cell pseudotumour in the brain

Study	Age/sex	Clinical presentation	Site	Species	Immune status	Treatment and follow-up
Morrison <i>et al.</i> ¹ 1999	38y/M	Headache, slurred speech, nystagmus, ataxia for 2 months	—	<i>Mycobacterium avium intracellulare</i>	Sarcoidosis on corticosteroids (intermittent) Low CD4 count HIV-negative	ATT Multiple surgical debridement Good outcome FU: not available
Phowthongkum <i>et al.</i> ² 2008	40y/M	Right hemiparesis, progressive truncal ataxia, and vertigo for 1 month	Multiple lesions in the left cerebral peduncle and medulla	<i>Mycobacterium haemophilum</i> , <i>Mycobacterium simiae</i>	HIV-positive Low CD4 count	Partial resection of lesion in left medulla ATT ART FU: 3 months post-surgery with residual neurological deficits
Sadek <i>et al.</i> ³ 2008	63y/M	Headache and word finding difficulties for 4 months	Left frontal lobe	<i>Mycobacterium avium intracellulare</i>	Pulmonary sarcoidosis (not on treatment) HIV-negative No evidence of immunocompromised state	Resection ATT FU: 1 year with clinical and radiological resolution
de Oliveira <i>et al.</i> ⁴ 2015	41y/M	Productive cough, fever, night sweats, and weight loss for 1 month	Two occipital and one temporal lobe lesions	<i>Mycobacterium tuberculosis</i>	HIV-positive Low CD4 count Pulmonary and cervical lymph nodal tuberculosis	ATT ART Resection of temporal lesion FU: not available
Lim <i>et al.</i> ⁵ 2016	66y/M	Neck pain and ataxia for a few weeks	Right cerebellar hemisphere	<i>Mycobacterium avium intracellulare</i>	Sarcoidosis Low CD4 count HIV-negative	Resection ATT FU: 1 year and doing well
Present case	53y/M	Constitutional symptoms, slurring of speech, upper limb weakness for 2 months	Multiple supratentorial and infratentorial lesions	Mycobacterial culture negative	HIV-negative No evidence of immunocompromised state	ATT Resection of right occipital lesion FU: 5 months post-operative and doing well

ART, anti-retroviral therapy; ATT, anti-tubercular treatment; FU, follow-up; M, male.

He was a diabetic and hypertensive, on medications for the past 1 and 4 years, respectively, and HbA1c level in September 2019 was 9.0%. Complete haemogram showed a total leukocyte count of 8200 cells/mm³ (normal range 4000–11000 cells/mm³) with 39% lymphocytes (normal range 20–40%) and enzyme-linked fluorescent assay for HIV was negative. Surgery was planned to confirm tubercular pathology and to rule out any other possibilities like metastasis. Right occipital craniotomy and excision of the right occipital lesion was performed 6 months after the onset of symptoms. Intraoperatively, the lesion was seen surfacing in the right occipital lobe near the junction of torcula and transverse sinus. It was hard in consistency, grey-white, lobulated and mildly vascular with good planes with the arachnoid membrane and brain parenchyma. On sectioning, a small cystic cavity with whitish content was found within the lesion. The cyst content did not yield any growth on mycobacterial culture even after 8 weeks of incubation.

Microscopic examination of the lesion showed a well-circumscribed lesion composed of compact fascicles of spindle cells admixed with lymphocytes and plasma cells. The spindle cells were CD68-positive and GFAP-negative. Occasional ill-formed granulomas and small cysts bordered by foamy macrophages and foci of necrosis were also present. Acid-fast bacilli were detected in both the spindled histiocytes and in the foamy macrophages in Ziehl–Neelsen stain (Fig. 1E–H). Based on these features, the lesion was diagnosed as mycobacterial spindle cell pseudotumour.

Mycobacterial spindle cell pseudotumour is characterised by a tumour-like proliferation of spindle shaped histiocytes containing acid-fast bacilli. It is generally associated with an immunocompromised state and can be caused by both tuberculous and non-tuberculous mycobacteria. In a study by Sfeir *et al.*,⁶ out of the 51 cases of mycobacterial spindle cell pseudotumour, 51% were associated with HIV infection and 45.1% of cases involved the lymph nodes. Most commonly, *Mycobacterium avium* complex was isolated (47.1%) followed by *Mycobacterium tuberculosis* complex (16%).

The five documented cases of mycobacterial spindle cell pseudotumour affecting the brain are described in Table 1.^{1–5} All of them occurred in adult males (age range 38–66 years, mean 49.6 years). Of these, two cases were associated with HIV infection and presented as multiple intracerebral lesions.^{2,4} The rest of the three cases^{1,3,5} had underlying sarcoidosis and two among them were treated with corticosteroids and had low CD4 count.^{1,5} Only a single case of mycobacterial spindle cell pseudotumour has been described in an apparently immunocompetent 63-year-old male.³ In addition, dural based mycobacterial spindle cell pseudotumour in the right temporal region has also been described in association with sarcoidosis and pulmonary *Mycobacterium avium* complex infection.⁷

The present case is the second case of intracerebral mycobacterial spindle cell pseudotumour to occur in an individual without any evidence of immunosuppression.

Due to its rarity and uncommon histomorphological pattern, it is important not to mistake mycobacterial pseudotumour for a spindle cell neoplasm. The presence of inflammatory infiltrate of small lymphocytes and plasma cells and presence of ill-formed granuloma indicate an infective process. Immunohistochemical markers like CD163 and CD68 will establish the histiocytic nature of the spindle cells, with CD163 being a more specific marker than CD68.⁸ Presence of acid-fast bacilli on Ziehl–Neelsen stain will confirm the tubercular aetiology. Antitubercular therapy is the mainstay of treatment with the majority of patients positively responding to the therapy.⁶

In conclusion, mycobacterial infections can present with the unusual morphology of a spindle cell pseudotumour even in immunocompetent individuals and should be included in the differential diagnosis of spindle cell lesions in the brain.

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***FNBP1-BRAF* fusion in a primary melanoma of the lung**

Sir,

Primary melanomas of the lung (PML) are extremely rare lung cancers with less than 80 cases published in the English literature.^{1–3} Indeed, metastases of cutaneous primary tumours account for most melanomas diagnosed in the lung, while few pulmonary primary cases are expected to derive from the melanocytes of the tracheo-bronchial apparatus.⁴ Limited genetic studies have been performed in this setting. We report a case of PML with a previously undescribed *FNBP1-BRAF* fusion.

The study was conducted according to the Declaration of Helsinki and was approved by the research ethics committee of the Center Leon Berard, Lyon, France (Ref: L20-72).

A 55-year-old woman, actively smoking (15 pack year) with a previous medical history of multiple sclerosis and arterial hypertension was referred to the pneumology department for the investigation of a para-mediastinal mass of the left lung. This 7 cm diameter tumour was discovered during medical investigation for recurrent bronchitis (Fig. 1A). A drill biopsy of the pulmonary mass was performed.

Microscopic examination revealed infiltration of the bronchial mucosa by an undifferentiated tumoural proliferation made of small to medium sized cells harbouring high nucleocytoplasmic ratio and numerous mitotic figures frequently associated with necrosis. No infiltration of the surrounding epithelium was evidenced (Fig. 1B,C).

Immunohistochemistry demonstrated focal expression of the S100 protein and SOX10. No expression of MelanA, HMB45, cytokeratins (AE1/AE3), EMA, chromogranin A, synaptophysin, CD45, CD34, CD99 or TTF1 was observed. Proliferation index (Ki-67) was estimated around 20%. Extension work-up including a body scan positron emission tomography (PET) imaging and dermatological examination did not detect any other tumour location. The patient received chemotherapy (HoloXan and doxorubicine) before surgical resection.

Three years later, a superficial centimetric nodule arose on the right arm of the patient. Microscopic examination revealed dermal infiltration by tumour cells with medium size, amphophilic cytoplasm and large nucleus. No junctional component was detected. Immunohistochemistry confirmed expression of S100 (Fig. 1D) and SOX10, while no positivity was observed with the melanocytic markers HMB45, anti-MelanA and anti-MITF. Whole exome RNA-sequencing performed in the skin tumour identified a *FNBP1-ENST00000446176 (e13)–BRAFF-ENST00000288602 (e9)* fusion. Mutations in *BRAF*, *NRAS*, *C-KIT*, *TP53* genes or *CRTC-TRIM11* fusion were not evidenced. Furthermore, the *BRAF* rearrangement was confirmed using a *BRAF* fluorescence *in situ* hybridisation (FISH) break-apart probe in both

the lung primary tumour and the skin metastasis that showed an identical unbalanced pattern with gain of the 3' *BRAF* red signal in both samples (Fig. 1E).

Additional pulmonary and skin recurrences were detected with the PET scanner 6 years after the initial diagnosis. Biopsy of the skin tumour revealed a similar morphology to that previously described (Fig. 2A,B). Immunohistochemistry revealed expression of PS100, SOX10, MelanA and HMB45 in tumour cells (Fig. 2C–F). Presence of a *BRAF* fusion in the skin tumour was further confirmed by FISH again with a similar pattern.

The patient was treated with immune checkpoint inhibitors; however, bone and mediastinal lymph node metastases were detected 5 months after the final diagnosis.

Herein, we report a case of PML with a *FNBP1-BRAF* fusion. PML is an extremely rare tumour which accounts for 0.01% of primary lung cancers⁴ and metastatic melanoma appears as the main differential diagnosis in this setting.^{1,2} In 1968 Allen and Drash and in 1969 Jensen and Egedorf proposed that recognition of an intraepidermal component within the lung tumour might allow the distinction between primary tumours and metastasis.^{1,2} However, such findings were counteracted by the identification of intraepidermal involvement in pulmonary metastasis of cutaneous melanoma.⁵ Therefore, Wilson and Moran later defined PML as: (1) a solitary tumour, (2) malignant melanoma confirmed by immunohistochemistry, (3) no past history of excision for cutaneous, mucosal or ocular melanoma, (4) central pulmonary lesion, and (5) no demonstrable tumour elsewhere at the time of diagnosis.⁴ Accordingly, our case met these criteria at the time of diagnosis and, although a skin tumour was detected 3 years after the identification of the lung tumour, such large delay suggests it is unlikely that this cutaneous tumour was in fact a primary that had given rise to the lung location.

Although PML might initially arise from the bronchial apparatus, it could alternatively be regarded as a metastatic location of a so called malignant melanoma of unknown primary (MUP).⁶ While the origin of MUP is matter of debate, frequent detections of *BRAF*, *NRAS* and *NF1* mutations, high mutation burden and prominent UV signature (C>T transition) strongly argue in favour of a cutaneous origin for most of the MUP cases.⁷ In the PML setting, although no evaluation of the tumour burden and no research for mutational signatures have been conducted, the initial investigations in 10 PML cases (mainly isolated case reports) have not identified mutations in *BRAF*, *C-KIT* and *NF1* genes.³ Therefore, the absence of common oncogenic drivers of cutaneous melanoma in PML suggests an extracutaneous origin for these cases, as similarly observed for mucosal melanomas.^{8,9} By contrast, recent investigations by Yang *et al.* of 10 additional PML cases revealed high tumour mutation burden, frequent *RAF*, *NRAS*, *NF1*, *KIT*, or *KRAS* mutations, and dominant UV-signature mutation profile, strongly arguing for a cutaneous primary origin in these 'PML' cases.¹⁰

In this context, we detected a previously unreported fusion of the *BRAF* gene in a PML case. Indeed, although much less frequent than *BRAF* and *NRAS* mutations, *BRAF* fusions, with a conserved functional serine-threonine kinase domain, are an alternative mechanism leading to the activation of the MAP kinases pathway. *BRAF* fusions have been detected in about 0.3% of solid cancers including pancreatic, lung, thyroid, colorectal, carcinomas and pilocytic glioma. In