diagnosis of IgG4-RD, in that there is no known or described serum elevation of IgG4. Further notable histopathological additions to the criteria include storiform fibrosis and obliterative phlebitis⁹ which were not readily observed within this case. However, even these features may be more likely to manifest in older lesions and so absence of these may be insufficient to rule out the diagnosis of IgG4-RD.²

Still, this current case displayed numerous histopathological findings that were most consistent with an IgG4-related cutaneous pseudo-lymphoma with crystal-storing histiocytosis.

The more commonly used treatment for the cutaneous manifestation of IgG4-RD is systemic steroids alongside surgical excision.² The relapse rate appeared high with systematic review of case studies within the literature reporting roughly only 11% of patients achieving complete resolution of disease without a relapse.² There is currently no clear consensus for treatment of cutaneous IgG4-RD. However, further studies have reported successful treatment with agents such as topical corticosteroids, rituximab, azathioprine and methotrexate.²

The crystal-storing histiocytosis has been described in a variety of inflammatory and neoplastic conditions of plasmacytic cells. This phenomenon within this case, clinically and histologically at this point in time has an inflammatory association, however close patient follow-up will be pertinent nonetheless. A suggestion has been made for consideration of serum IgG4 levels and the patient is for follow-up in the respective clinical outpatient department.

This report provides further insight into an extremely rare condition with an associated rare finding of CSH. Temporally, the isolated cutaneous finding is rarer still and adds important clinical (demographic) and histopathological findings to the current paucity of literature surrounding cutaneous IgG4-RD and CSH.

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Multicentric EBV-associated smooth muscle tumour with involvement of the pituitary gland

To the Editor,

We report the unusual presentation of a multicentric Epstein–Barr virus (EBV)-associated smooth muscle tumour (EBV-SMT) in a renal transplant patient, occurring in the pituitary gland, and with apparent progression in histological appearance. EBV-SMTs are rare neoplasms occurring almost exclusively in the setting of immunosuppression, including in primary immunodeficiency, post-transplant, and HIV-associated immunodeficiency. They may occur anywhere in the body, but are most frequently reported in the liver, lungs, and gastrointestinal tract in post-transplant patients.

A 27-year-old female presented in 2020 with secondary amenorrhoea, 6 months after the removal of her contraceptive progesterone implant. Her medical history was significant for congenital abnormalities, including a hypoplastic right kidney and left-sided vesicoureteric reflux resulting in recurrent urosepsis and end-stage renal failure. Renal transplant was performed in 2014 with no immediate complications or rejection. In 2015, she presented with lymphadenopathy and was diagnosed with stage IV EBV-positive diffuse large B-cell lymphoma. During chemotherapy, new liver lesions were detected on routine imaging, with multiple biopsies demonstrating a bland spindle cell neoplasm with no mitoses or necrosis. Smooth muscle actin (SMA), caldesmon and EBV-encoded RNA *in situ* hybridisation (EBER-ISH) were diffusely positive and Ki-67 was 5%. These findings were consistent with EBV-SMT. In 2016, EBV-SMT was again diagnosed in a biopsy from a left cervical node. Biopsies in 2017 and in 2019 of bladder lesions also showed EBV-SMT.

She was referred to endocrinology for investigation of her amenorrhoea. Clinical examination demonstrated an incomplete third nerve palsy with decreased pupillary light response and a mild superior temporal quadrantanopia in the left eye. A pituitary panel was performed to investigate her amenorrhoea, showing hyperprolactinaemia [1132 mIU/L (reference interval 71–566 mIU)]. FSH was 10.9 IU/L (1.7–21.5), LH was 1.7 IU/L (1.0–96.0), and oestradiol was 51 pmol/L (45–1461). Other hormone levels were not significantly abnormal in the context of transplant-related steroid immunosuppression. Imaging revealed a 35 mm pituitary fossa lesion with bilateral cavernous sinus invasion and left-sided optic chiasm compression. Radiological findings favoured a pituitary macroadenoma, but differentials also included lymphoma. A biopsy was performed, with histology showing EBV-SMT. She proceeded to a debulking procedure, with histology confirming a moderately cellular EBV-SMT associated with

Fig. 1 Histology of Epstein–Barr virus-associated smooth muscle tumour involving the pituitary gland. (A) Cellular spindle cell neoplasm (H&E), (B) Ki-67 10–15%, (C) EBER-ISH-positive, (D) SMA-positive.

partially infarcted anterior pituitary tissue. The Ki-67 index was 10–15% (Fig. 1).

Subsequently, she developed bilateral cervical lymphadenopathy. Magnetic resonance imaging of the neck demonstrated a C5 vertebral lesion with an associated pathological fracture. Bilateral neck dissection and C5 corpectomy both showed EBV-SMT. Notably, the latter showed high cellularity with poorly differentiated morphology, with high nuclear to cytoplasmic ratio and prominent nucleoli. Ki-67 was 20%. In comparing biopsies from 2015–2020, there was significant variability in histological appearance, cellularity, and proliferative index (Fig. 2), with overall progression over time.

EBV-SMTs are rare neoplasms occurring almost exclusively in immunosuppressed patients.^{1,2} A single-centre retrospective study of 5006 solid organ recipients over 31 years found only three cases of post-transplant EBV-SMT.³ The type of organ graft does not appear associated with the incidence of EBV-SMT.⁴ One single-centre study found an incidence of 1.67% of EBV-SMT in kidney transplant patients, occurring at a median of 9 years post-transplant.⁵ Risk factors include EBV seronegativity followed by primary EBV infection and persistently high EBV viral loads (>16,000 copies/mL).³ In our case, EBV viral load was not assessed until recently, with a level of 1994 copies/mL in February 2021.

The only reported pituitary EBV-SMTs are from a case series of 21 EBV-SMTs associated with HIV infection, where two were in the pituitary.² The clinical presentations of these cases were not characterised. Headache was the most common presenting complaint in a review of 53 EBV-SMTs involving the central nervous system, but exact tumour sites were not specified.¹ In solid organ transplants, the most

common sites of disease are the liver, lung and gastrointestinal tract,⁶ with fewer intracranial occurrences compared to HIV-associated cases.

The pathogenesis of EBV-SMT is not fully understood. EBV infects smooth muscle cells using an unclear mechanism, with hypotheses including cellular fusion with infected lymphocytes, or entry via surface receptor CD21.⁷ An analysis of renal transplant-associated EBV-SMTs demonstrated gene expression in keeping with a latency type III program, which is associated with production of a distinct set of viral proteins including latent membrane protein 2A (LMP2A).⁸ LMP2A activates the mTOR/Akt pathway, and is thought to be a driver of oncogenesis. This is supported by the frequent response of these tumours to mTOR inhibitors.⁸ Everolimus was trialled in this patient on initial diagnosis of EBV-SMT with no success.

EBV-SMT is frequently multifocal.^{1,5} Intracranial tumours are hypothesised to derive from the myogenous vascular wall.⁹ Viral episomal analysis of multifocal lesions demonstrated independent viral clones, suggesting that lesions result from multiple infection events rather than metastasis from a common primary.¹⁰ Histology characteristically demonstrates intersecting fascicles of spindled cells with blunt-ended nuclei. SMA, caldesmon and EBER-ISH are positive. In around half of cases, a second population of more primitive round cells is seen.⁶ Intratumoural T-lymphocytes are also a frequent observation. Cytologically malignant features including primitive areas, higher cellularity, necrosis, and mitotic activity can be observed; however, prognosis appears to be independent of histology, relating primarily to patient immunity status.⁶ Our case clearly illustrates the

Fig. 2 Histology of Epstein–Barr virus-associated smooth muscle tumour from selected sites, 2015–2020 (left column H&E, right column Ki-67 immunohistochemistry).

variation in histological appearance of this tumour, but temporal evolution of multicentric lesions within one patient has not been previously discussed in the literature.

In a systematic review of the literature, intracranial EBV-SMT arising in the setting of an organ transplant had

poorer outcomes versus those arising in HIV patients.¹ However, numbers are small due to the rarity of the disease, and additional research is warranted. A retrospective study of 16 patients with EBV-SMT post-kidney transplant found a survival rate of 75% over a mean follow up period of

5 years.⁵ Lower overall survival in transplant patients has been associated with multicentricity and intracranial involvement.^{4,6}

The optimal management of EBV-SMT remains unclear. Surgical resection is the most common therapy.^{1,5,9} Other strategies have included involved field radiation therapy, stereotactic radiosurgery, systemic chemotherapy, mTOR inhibitors, and modification of post-transplant immunosuppression therapy.^{1,4,5} However, there is no evidence supporting superiority of one modality over another.

In the appropriate clinical context, awareness of this rare entity is important to avoid delayed or missed diagnosis. EBV-SMT may occur in a range of unusual sites with variable histological appearance, as illustrated in the present case. Differential diagnoses may include other spindle cell neoplasms such as Kaposi sarcoma, leiomyoma, and leiomyosarcoma, as well as other poorly differentiated malignancies. This case highlights the variable appearances and range of presentations seen in EBV-SMT.

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Transformation of ganglioglioma to epithelioid glioblastoma, both with *BRAF* V600E mutation

To the Editor,

Ganglioglioma is a low-grade neuronal-glial tumour showing *BRAF* V600E mutation in 20–60% of cases. High-grade transformation of ganglioglioma is extremely rare, particularly in the absence of chemotherapy or radiation. The molecular basis of progressive disease is not well understood. Previous literature has documented transformation of *BRAF* mutant pleomorphic xanthoastrocytoma to *BRAF* mutant epithelioid glioblastoma, but such a link has not been well established in ganglioglioma.

The patient was a 19-year-old woman who presented in 2018 with a history of refractory epilepsy since the age of 11. Magnetic resonance imaging (MRI) showed a structural lesion within the left parahippocampal gyrus, considered most likely to be a developmental neoplasm such as a ganglioglioma. Surgical resection was performed. Histology showed a World Health Organization (WHO) grade I ganglioglioma, comprising a low-grade proliferation of astrocytes admixed with mildly dysmorphic neurons including rare binucleate forms (Fig. 1). Immunohistochemistry for GFAP highlighted astrocytic cells, while dysmorphic neurons were positive for chromogranin and NeuN. *BRAF* VE1 and CD34 showed patchy positivity in lesional cells. IDH1-R132H immunohistochemistry was negative and ATRX was retained. Ki-67 was 5%. Features were consistent with a ganglioglioma, WHO grade I. Molecular testing was not performed. Resection was favoured to be near complete on post-operative imaging.

The patient re-presented in 2020 with left-sided headache. MRI showed a 25 mm mass associated with the posterior margin of the resection cavity, compatible with recurrent tumour and highly suggestive of a high-grade glial neoplasm. Surgical resection was performed, with histology showing a markedly cellular lesion comprising sheets of malignant epithelioid cells with extensive necrosis and microvascular proliferation (Fig. 2). The cells showed hyperchromatic nuclei with coarse chromatin and eosinophilic cytoplasm. No low-grade component was identified. Tumour cells were positive for S100 and OLIG2, but negative for GFAP, SOX10 and AE1/3. *BRAF* VE1 stain was positive, with *BRAF* codon 600 mutation confirmed on polymerase chain reaction (PCR) analysis. Ki-67 was up to 40%. Features were consistent with an epithelioid glioblastoma, WHO grade IV. Next generation sequencing performed at Royal Prince Alfred Hospital Department of Neuropathology (Sydney) confirmed a *BRAF* V600E mutation, also detecting chromosome 7p gain and heterozygous CDKN2A/B deletion. No other pathogenic variants were detected (1p/19q co-deletion,