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Primary papillary epithelial tumour of the sella: expanding the spectrum of TTF-1-positive sellar lesions

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Primary papillary epithelial tumour of the sella: expanding the spectrum of TTF-1-positive sellar lesions

Aim: To describe four novel primary epithelial tumours of the sella with papillary architecture and Thyroid Transcription Factor 1 (TTF-1) expression. **Methods**: Paraffin-embedded tissue from the four cases and recurrence of patient 1 was investigated with haematoxylin–eosin, special histochemical stains, immunohistochemistry with a broad panel of antibodies and next-generation sequencing. The ultrastructure of one tumour was studied in tissue retrieved from paraffin. **Results**: The lesions occurred in three females aged 20, 26 and 42 years and a male aged 49 years. They presented with signs and symptoms secondary to pituitary stalk compression. Preoperative neuroimaging documented mixed solid and cystic, enhancing sellar masses with suprasellar extension. Histologically, the tumours showed thin papillae lined by a single layer of cytokeratin and TTF-1-positive cuboidal and cylindrical cells with mildly atypical nucleus. Next-generation sequencing performed in three cases did not identify any mutations. The main differential diagnosis included metastasis from lung or thyroid carcinoma, extraventricular choroid plexus papilloma and sellar ependymoma. **Conclusion**: We suggest the descriptive term of primary papillary epithelial tumour of the sella (PPETS) for this entity and propose that it could represent the intracranial equivalent of thyroid-like low-grade nasopharyngeal papillary adenocarcinoma. The cell of origin of PPETS remains undetermined although the intense and ubiquitous expression of TTF-1 may suggest a derivation from the infundibulum or ventricular recess. Our study expands the spectrum of sellar TTF-1-positive tumour and challenges the view that they all derive from pituicytes.

Keywords: papillary tumour, pituitary gland, sella, TTF-1

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Introduction

Primary non-neuroendocrine tumours of the pituitary gland account for about 10% of sellar region neoplasms. Of these, about 1% comprises lesions including the group of Thyroid Transcription Factor-1 (TTF-1)-expressing tumours of the posterior lobe, neural and para-neuronal tumours, salivary gland-like tumours, ectopic choroid plexus papilloma (eCPP), primary sellar melanocytic neoplasms and primary sellar atypical teratoid rhabdoid tumours [1-3]. Due to their rarity, the last four entities have not been included in the WHO Classification of Pituitary Tumours [4].

Thyroid Transcription Factor-1 is a 38kDa nuclear DNA-binding protein that belongs to the NKX2 homeodomain transcription factor family with a critical role in controlling embryonic development and differentiation. It activates the expression of a set of genes in the thyroid gland and lung, and is also expressed in basal ganglia neurons, cortical interneurons, hypothalamic neurons, ependymal cells of the third ventricle, tanycytes and pituicytes. Deletion of T/EBP (TTF-1) in mice results in defects in the ventral region of the forebrain. The oncogenic role of TTF-1 remains enigmatic. Current evidence indicates that gene networks regulated by NKX2-1/TTF-1 might be different in normal and neoplastic tissues and even among different tumour types [5-8].

We document four primary epithelial tumours of the sella with striking papillary architecture and intense TTF-1 nuclear expression. We propose the descriptive name of primary papillary epithelial tumour of the sella (PPETS) to define the entity and suggest PPETS could represent the sellar equivalent of thyroid-like low-grade nasopharyngeal papillary adenocarcinoma (TLLGNPPA) [9-11]. Given their similarities, PPETS and tumours previously documented as sellar eCCP may represent the same entity. PPETS expands the spectrum of TTF-1 expressing tumours of the sellar region and its existence challenges the view that TTF-1-positive tumours of the infundibulum invariably derive from pituicytes [12-14].

Patient histories

Patient 1 A 20-year-old female presented with a 3-month history of headache and secondary amenorrhoea for the last 5 months. On examination, she had bitemporal haemianopia. Her visual field defect gradually progressed and she also developed diplopia. She was otherwise well, and her neurological examination was normal. Pituitary hormones were as follows: Prolactin 50.2 ng/ml (women 4.79–23.3 ng/ml); GH 0.7 (basal < 1 ng/ml); ACTH 18 (5–60 pg/ml); TSH 2.74 (0.27–4.2 micro IU/ml); FSH 8.51 (women 3.5–12.5 mIU/ml); LH 3.65 (women 2.4–12.6 mIU/ml). Clinical and biochemical features were consistent with normo-gonadotropic hypogonadism.

A Magnetic Resonance Imaging (MRI) scan showed a solid and cystic, heterogeneously enhancing intrasellar tumour measuring 45 x 35 x 25 mm, encroaching on the optic chiasm and extending to the third ventricle. The sellar floor was intact. No extension into the cavernous sinuses was noted, corresponding to Knosp grade 2 [15]. A preoperative diagnosis of pituitary macroadenoma was considered. A month after onset, the patient underwent a trans-nasal, trans-sphenoidal approach with gross total excision of the tumour. Subsequently, she was put on hormone replacement and remained well for the following 10 months when she returned to clinic complaining of visual disturbances and headache. An MRI documented tumour regrowth. The recurrence measured 37 x 30 x 25 mm and similar to the primary tumour, it did not invade the adjacent bone or extend to the cavernous sinus. The recurrence was again removed trans-sphenoidally. Extensive investigations including total body MRI, thyroid ultrasound and PET scan returned negative results. She has been kept on hormone replacement because investigations did not reveal any other lesions. The patient has been on close follow-up and she is well and free of disease at the last visit 51 months after surgery.

Patient 2 This 26-year-old female presented with a short history of amenorrhoea. She had her first menstrual cycle at the age of 13 years, but her cycles had always been irregular. For this reason, she had been on combined systemic oestrogen and progesterone replacement therapy for five years, which was suspended 4 years before her current presentation. Her family history included diabetes, dyslipidaemia, glioma and breast cancer in distant relatives. More recently, she also developed galactorrhoea. Prolactin level was 52.45 ng/dL (0min) and 50.05 ng/dl (120 min) (normal range: 2–27 ng/ml).

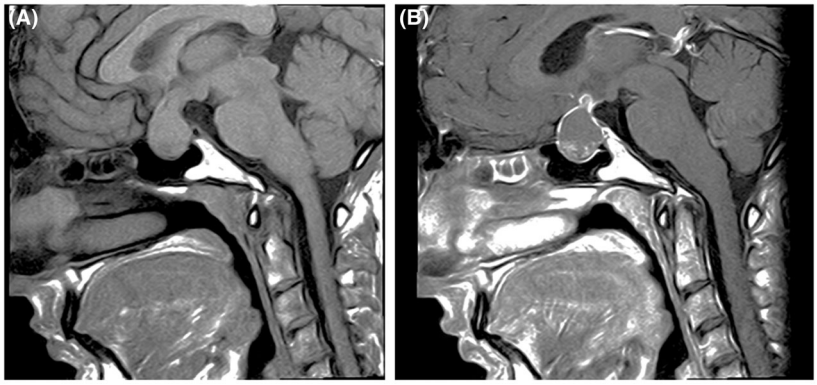

Figure 1. (Patient 2): Pre (**A**) and postcontrast (**B**) T1-weighted sagittal sequences document a solid and cystic lesion expanding the sella and extending to the third ventricle.

An MRI study of the sella documented a solid and cystic lesion measuring 18x26x18mm that returned a hyperintense signal on T2-weighted sequences apart from a hypointense component towards the sellar floor. The lesion enhanced after gadolinium administration and impinged on the optic chiasm and third ventricle (**Figures 1A,B**). No extension to the cavernous sinuses was present (Knosp grade 2). The possibility of craniopharyngioma was suggested preoperatively. A CT-scan demonstrated thinning of the sellar floor and possible breach of the bone with possible small extension to the sphenoid sinus. No other lesions with the nasal cavities or sphenoid sinus were observed. On confrontation, visual field exam was normal on both sides. Her hormonal status included central hypoadrenalism (peak cortisol 9.8 μg/dl, ACTH 7.8 pg/ml) and central hypothyroidism (fT4 5.1 pmol/l, TSH 2.7 mU/l). Prior to surgery, she was therefore commenced on thyroxine, hydrocortisone and vitamin D supplement. She underwent transsphenoidal surgery with gross total removal of the lesion. She developed diabetes insipidus postoperatively, treated with desmopressin acetate 60 μg 1cp/day. Following surgery, ACTH secretion returned to normality and her adrenal and thyroid function recovered. Hormone replacement therapy was therefore suspended 2 months after surgery. Given the histological diagnosis, she was extensively investigated with total body CT-scan and FdG PET and no other lesions were discovered. At the last follow-up visit a year after surgery, she had normal thyroid, adrenal and GH functions. Conversely, normo-gonadotropic hypogonadism persisted, requiring adequate supplementation therapy. Diabetes insipidus resolved. MRI showed no evidence of recurrent disease.

Patient 3 This 49-year-old male patient was identified by reviewing retrospectively the cases referred to the Department of Pathology and Laboratory Medicine at Mayo Clinic, Rochester, MN. The clinical history and tissue available for review are therefore limited. The patient presented to medical observation with visual symptoms. Neuroimaging documented a solid and cystic pituitary mass that was diagnosed as nonfunctioning pituitary adenoma, for which he underwent transsphenoidal surgery.

Given the papillary architecture, the lesion was diagnosed as possible metastasis from a thyroid primary. The patient underwent a total thyroidectomy that revealed two foci of papillary microcarcinoma (PMC) measuring 3 mm and 1.5 mm respectively. No evidence of disease elsewhere was found including loco-regional lymph nodes with total body CT-scan and ^{131}I-scan. A conservative treatment plan was pursued and the patient was under regular followed up. Eight years after transsphenoidal surgery, he underwent a nephrectomy for a chromophobe renal cell carcinoma and three years later, he developed chronic renal failure. He also developed seizures, which are controlled medically. At the last available follow-up, 11 years from the original presentation, he had no evidence of a pituitary recurrence or of any metastatic deposits from his PMC.

Patient 4 A 42-year-old female presented with paraesthesia in the upper limbs, more evident at the left site with numbness in the territory of the third branch of trigeminal nerve. No other neurological defects were found. She did not have a visual field

defect on confrontation. Pituitary hormones levels were normal. She underwent brain MRI, which showed a sellar and suprasellar solid and cystic lesion measuring 20 x 16 x 28 mm with calcification (Figure S1a and Figure S1b). The optic chiasm was compressed. No compression of the third, fourth and sixth cranial nerves or invasion of the cavernous sinus was present. She underwent trans-sphenoidal surgery leading to a gross total removal of the lesion. Postoperatively, she developed transient diabetes insipidus and adrenal cortical insufficiency, initially treated with desmopressin and steroids but it then resolved. No other tumour was found outside the sella.

Methods

Tissue from the four tumours and recurrence of patient 1 were fixed in formalin and processed to paraffin embedding. Five-micron-thick sections were cut from each block and stained with haematoxylin–eosin (H&E), Periodic Acid Schiff (PAS), PAS following diastase treatment and Masson-Fontana and Gordon–Sweet's silver impregnation for reticulin fibres. The lesions from patients 1, 2 and 4 were investigated with immunohistochemistry on a BenchMark ULTRA Slide Staining System (Roche Diagnostics, Indianapolis, IN, USA), using the following primary antibodies directed against: pancytokeratin (Novocastra Newcastle UK; cocktail monoclonal AE1 and AE3; dilution 1:50), cytokeratin 7 (Dako Agilent Stockport UK, monoclonal OV-TL 12/3, dilution 1:50), cytokeratin 8 (Becton Dickinson San Jose CA, monoclonal CAM5.2; dilution 1:50), cytokeratin 20 (Dako Agilent, Ks20.8; dilution 1:50), EMA (Novocastra, monoclonal GP1.4; dilution 1:500), TTF-1 (Novostastra, monoclonal clone SPT24; dilution 1:50; Dako Agilent, 8G7G3/1; dilution 1:100), CDX2 (Cell Marque, Rocklin, California, USA, monoclonal AMT28, dilution 1:50), β-catenin (Ventana/Roche, monoclonal clone 14; dilution 1:1), chromogranin A (Dako Agilent, monoclonal Dak-A3; dilution 1:200), synaptophysin (Novocastra, monoclonal 27G12; dilution 1:500), vimentin (Dako Agilent, monoclonal SRL-33; dilution 1:200), GFAP (Dako Agilent, monoclonal 6F2; dilution 1:1000), S-100 protein (Dako Agilent; polyclonal; 1:1000); Napsin A (Novocastra, monoclonal IP64; dilution 1:500), thyroglobulin (Dako Agilent, DAK-Tg6; dilution 1:100), HMB45 (Dako Agilent, monoclonal M0634; dilution 1:50), PAX8 (Proteintech, polyclonal; dilution 1:250), Transthyretin (Novocastra, polyclonal; dilution 1:100), LIN28A (Abcam, Cambridge UK, rabbit polyclonal, dilution 1:100), OLIG-2 (Abcam, rabbit polyclonal, dilution 1:200), cKIT (CD117) (Leica Biosystem, Breckland, Linford Wood, Milton Keynes, UK, monoclonal NCL-L-CD117, dilution 1:300), alpha-fetoprotein (Dako Agilent, rabbit polyclonal, dilution 1:500), OCT3/4 (Leica Buffalo Grove, USA, mouse monoclonal NCL-L-OCT3/4, dilution 1:100), Ki-67 (Dako Agilent; monoclonal MIB-1, dilution 1:100), INI-1 (Cell Marque, monoclonal MRQ27; dilution 1:500), FSH (Cell Marque Darmstadt Germany, monoclonal 83/122A8; 1:2000), LH (Cell Marque, monoclonal 3LH5B6Y; dilution 1:100), TSH (Cell Marque, monoclonal 5404; dilution 1:50), PRL (Biogenex, monoclonal BGX031A; dilution 1:50), ACTH (Dako Agilent, monoclonal, clone 02A3; dilution 1:1000), GH (Cell Marque, monoclonal 54/92A2; dilution 1:50), Steroidogenic Factor 1 (Abcam Cambridge UK, monoclonal EPR19744; 1:150), PIT1 (Novus Biologicals Abingdon Oxon UK, polyclonal; dilution 1:100), TPIT (Atlas Antibodies, Stockholm Sweden; monoclonal CL6251; 1:300), EGFR (Dako Agilent, clone H11, code M3563; dilution 1:50), BRAFV600E (Ventana, VE1 clone; prediluted) and CD68 (Dako Agilent, clone KP1; dilution 1:200).

A limited immunopanel including AE1 and AE3, cytokeratin 7, cytokeratin 8, EMA, TTF-1 (clone SPT24), GFAP, S-100, thyroglobulin and pituitary hormones was available for the tumour from patient 3. The paraffin block of this patient was disposed of 10 years after surgery. No further immunostains or molecular analysis was possible.

The Ki-67 labelling index was calculated as the number of positive cells out the overall number of neoplastic cells in three different fields at the magnification of x40 as previously recommended [16].

Electron microscopy

A fragment from the primary tumour of patient 1 was retrieved and reprocessed for electron microscopy from the paraffin block. After dewaxing in xylene and rehydration to distilled water, the fragments were fixed in 3% glutaraldehyde, post-fixed in 1% osmium tetroxide and embedded in Taab-812 epoxy resin (Merck, Darmstadt Germany). The quality of specimen was checked on Toluidine-blue stained semithin sections.

Ultrastructure was examined with a JEM1400 plus transmission electron microscope (Joel, Peabody MA 01960, USA).

Next-generation sequencing

For patients 1 (recurrence) and 2, genomic DNA was isolated from the formalin-fixed and paraffin-embedded tumour samples using the cobas® DNA Sample Preparation Kit (Roche Diagnostics Ltd Burgess HillUK), a generic manual specimen preparation based on nucleic acid binding to glass fibres. Sequence analysis was carried out following PCR enrichment using a QIAseq Targeted DNA custom panel (Qiagen, Germantown, MD, USA) and Illumina Next Generation Sequencing (Illumina, San Diego CA, USA).

The panel targeted 37 commonly mutated oncogenes (*AKT1, ALK, AR, ATRX, B2M, BRAF, CDKN2A, CTNNB1, DDR2, EGFR, ERBB2, FGFR3, GNA11, GNAQ, GNAS, H3F3A, H3F3B, HIST1H3B, HIST1H3C, HIST2H3C, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MET, NRAS, PDGFRA, PIK3CA, PTEN, RET, STK11, TERT, TP53, VHL*), however, the whole coding sequence of all 37 genes was not targeted. Mutation and variant calling by custom bioinformatics analysis pipeline validated to detect SNVs and small insertion/deletion mutations (<40bp) to 5% mutant allele frequency. Alterations were categorized following American College of Medical Genetics guidelines and Association for Molecular Pathology tiering.

For the tumour of patient 4, the NGS panel in use at the University Hospital of Lausanne was tested at the time of initial diagnosis and not repeated for this study in tumours 1 and 2. DNA was isolated from the formalin-fixed and paraffin-embedded tumour sample and an amplicon-based DNA library was prepared using a customized primer panel targeting hotspot regions of 52 genes relevant to cancer (custom Ion AmpliSeq panel, Ion Torrent, Thermo Fisher Scientific, Waltham, MA, USA), and subsequently sequenced on an Ion S5 System (Ion Torrent, ThermoFisher Scientific, Waltham, MA, USA).This NGS panel included 27 of the 37 genes tested in patients 1 and 2 and also the following 25 gene:*ABL1, APC, ATM, CDH1, CSF1R, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FLT3, HNF1A, JAK2, JAK3, KDR, MLH1, MPL, NOTCH1, NPM1, PTPN11, RB1, SMAD4, SMARCB1, SMO* and *SRC*.

AR, ATRX, B2M, GNA11, H3F3A, H3F3B, HIST1H3B, HIST1H3C, HIST2H3C, hTERT were not investigated in patient 4.

Results

The four primary tumours and the recurrence of patient 1 showed similar papillary architecture, although some variation between cases was observed. The papillae consisted of a single layer of tightly packed cylindrical or cuboidal cells lining a fibro-vascular core; pseudostratification of tumour cells was seen, particularly in cases 2, 3 and 4 (**Figures 2, 4, 5A, 7B**). The neoplastic cells had eosinophilic cytoplasm and round to ovoid, slightly hyperchromatic nucleus with dense chromatin and inconspicuous nucleolus. No nuclear inclusions or groves were identified (**Figures 5A** and **7B**). The connective tissue of the fibro-vascular cores was oedematous in some papillae and compact and hyalinized in others. In cases 1 and 4, the core of several papillae contained lymphocytic infiltrates admixed with plasma cells (**Figure 2A**) and foamy histiocytes (**Figure 7B**). A few multinucleated giant cells were present in cases 1 and 2 (**Figures 5B**). Focal squamous metaplasia was found in case 1 (**Figure 2B**). No glands or evidence of intra or extracellular mucin production, ciliated or pigmented cells were observed. There was focal microcalcification in cases 2, 3 and 4. Specimens from patient 1 and 2 contained fragments of anterior hypophysis without pathological features of note. No neurohypophysis was present. No mitoses were identified. There were haemosiderin-laden macrophages and extravasation of red blood cells in cases 1 and 2. Necrosis was present in cases 1 and 4 (**Figure 7A**). There was no evidence of bone invasion.

The neoplastic cells expressed CK7 (**Figure 3A**) and showed focal expression of cytokeratin AE1/AE3, cytokeratin CAM5.2 and cytoplasmic and apical expression of EMA (Figure S2). Tumours 3 and 4 showed focal CK7 and diffuse AE1/AE3 expression. Vimentin was expressed focally in cases 2 (**Figure 6A**) and 4, whereas it was negative in case 1 and it was not tested in patient 3. TTF-1 expression was intense and ubiquitous in all lesions (**Figures 3B**), apart from cells showing squamous metaplasia in case 1. Expression of INI-1 was retained. Multinucleated giant cells (cases 1 and 2) and foamy macrophages were CD68 positive. Immunoreactions for pituitary hormones and transcription factors, synaptophysin, chromogranin, CK20, GFAP, S-100 protein,

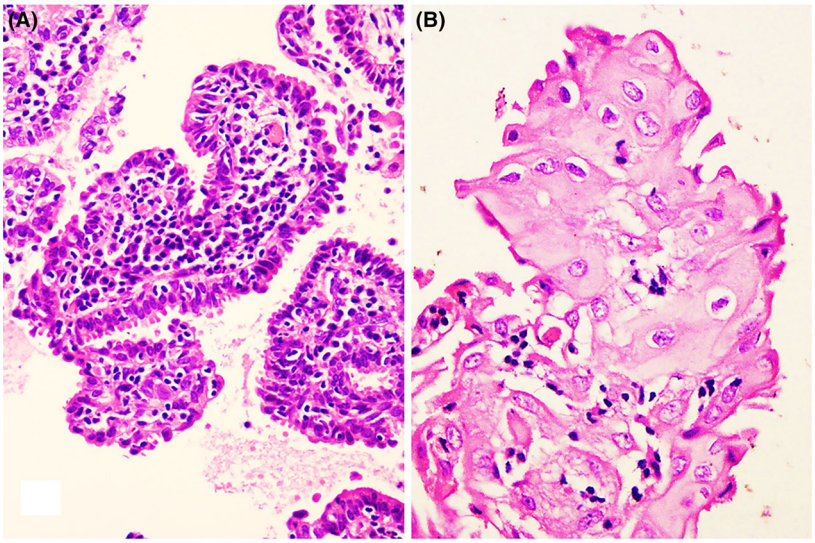

Figure 2. (Patient 1 – primary): Cells lying papillae often show with apical snouting (**A**, haematoxylin–eosin – x10); focal squamous metaplasia is present (**B**, zhaematoxylin–eosin – x20).

transthyretin, Napsin A, thyroglobulin, PAX8, p53, EGFR, BRAFV600E, CDX2, LIN28A, OLIG-2, cKIT, alpha-fetoprotein and OCT3/4 were negative. Both primary and the recurrent lesions showed Ki-67 labelling indices lower than 1% (**Figure 6B**).

Ultrastructural examination was attempted in primary tumour of patient 1. Preservation of tissue for EM was suboptimal following retrieval from paraffin. Nevertheless, it showed microvilli, intercellular tight junctions (Figure S3) and intermediate filaments further confirming the epithelial origin of the lesion. There were no excess mitochondria or lysosomes, and there was no evidence of cilia, intracytoplasmic vacuoles or membrane-bound neurosecretory granules.

Next-generation sequencing

The recurrent tumour of patient 1 and the primary lesion of patients 2 and 4 did not show any relevant variants in the genes examined. No tissue was available from patient 3 for next-generation sequencing.

Incidence of PPETs

In order to understand the frequency of PPETS, we reviewed the diagnostic database of the Department of Cellular Pathology at Salford Royal Foundation Trust, the Department of Pathology at PIGMER in Chandigarh and the Cellular Pathology Department at Humanities in Milan. A total of 3139 cases were found between January 2008 and December 2018. The original slides of 21 pituitary metastases operated on in the three institutions including a lung micro papillary adenocarcinoma were reviewed. No diagnoses of sellar ependymoma or sellar choroid plexus papilloma and no PPETS other than the lesions reported here were found indicating that PPETS accounts for less than 0.1% of sellar tumours operated on in our institutions in an 11-year period.

Discussion

We have documented four primary intra and suprasellar epithelial tumours with papillary architecture and TTF-1 expression, for which we propose the descriptive term of PPETS. The lesions occurred in three females and one male, all presenting with signs and symptoms of mass effect. Neuroimaging features of the four lesions were similar and included cystic and solid, enhancing component, extension to the third ventricle with chiasmatic compression but no involvement of the cavernous sinuses. Invasion of the sellar floor was suggested in the preoperative MRI in case 2. Primary Papillary Epithelial Tumour of the Sella is extremely rare. We only found two examples in over 3000 tumours operated trans-sphenoidally in our institutions and no

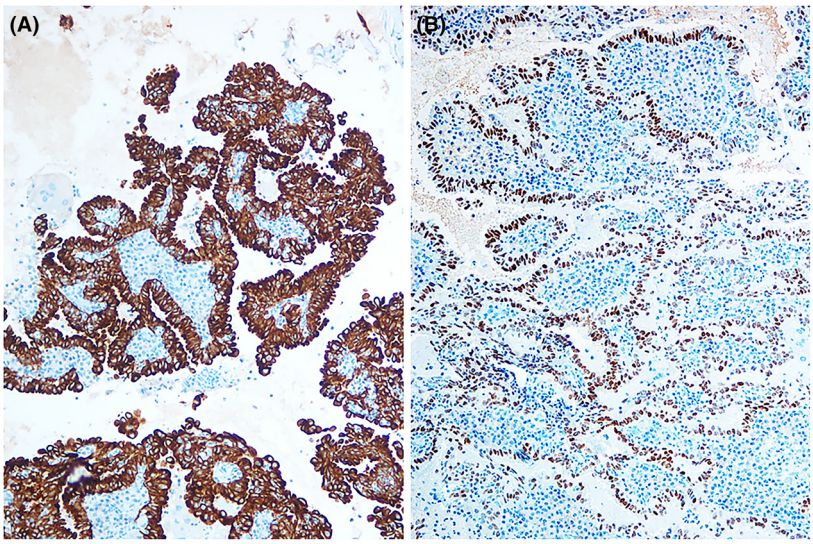

Figure 3. (Patient 1 – recurrence): Neoplastic cells express cytokeratin 7 (**A**, immunoperoxidase – x10) and show nuclear TTF-1 expression (**B**, immunoperoxidase – x4).

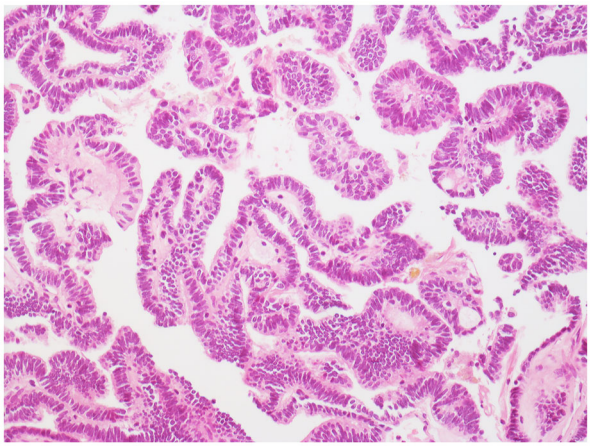

Figure 4. (Patient 2): Papillae in this tumour are less cohesive than case 1; fibro-vascular cores contain foamy macrophages; no lymphocytes or plasma cells are present in this area (Haematoxylin–eosin – x4).

mention of a similar lesion is reported in large review of over 7000 sellar and suprasellar lesions recently published by Abushamat and colleagues [17], further emphasising the rarity of PPETS.

The absence of pituitary hormone and pituitary lineage restricted transcription factors ruled out the possibility of a primary tumour of adenohypophyseal cells. Given the papillary architecture, and the expression of cytokeratins and TTF-1, PPETS was distinguished from a metastatic papillary thyroid carcinoma (PTC) or lung micropapillary carcinoma [18]. The patients were carefully investigated over the years. No primary tumours outside the sella were found in patients 1, 2 and 4. The immunoprofile of their lesions including the absence of thyroglobulin or napsin expression, and the bland light microscopic features were not in keeping with a metastatic deposit. Next-generation sequencing did not show any mutations in *BRAF, HRAS* and *KRAS* genes that are commonly mutated in PTC [19]. Finally, the absence of CDX2 expression excluded the diagnosis of columnar variant of PTC [20,21]. Patient 3 underwent thyroidectomy and was found to have two microscopic foci of PTC, respectively, measuring 1.5 mm and 3 mm. The original slides from his thyroid primary lesions were reviewed. The features were typical of PTC, including thyroglobulin expression and were therefore different from his sellar lesion. Papillary thyroid carcinomas smaller than 1.0 cm are defined as PMC. They are a common disease [22-24]. In several countries, the availability of more accurate diagnostic techniques along with increased medical surveillance has led to a considerable increase in the detection of incidental PMC without a corresponding increase in mortality [25]. Low-risk PMC is an indolent disease that does not grow or grows very slowly and only very rarely spreads to neck lymph nodes [26-28]. For this reason, the absence of any metastatic deposits in

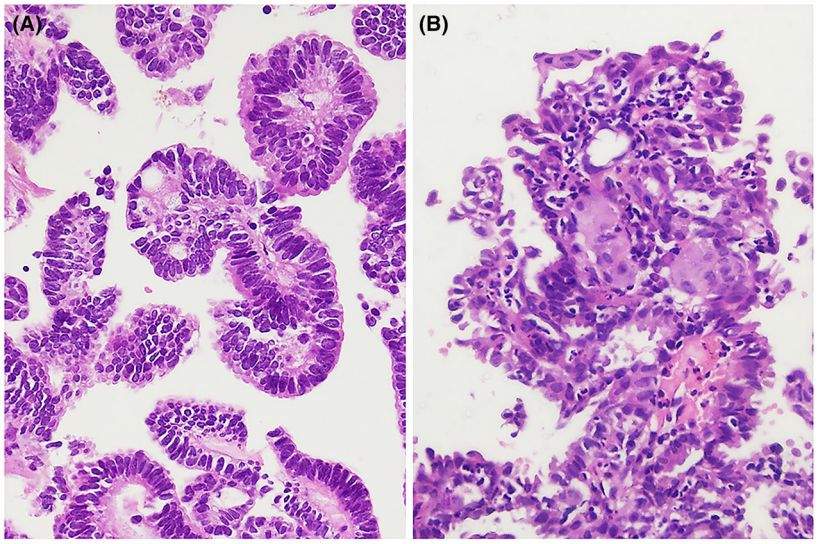

Figure 5. (Patient 2): Tumour cells can at times be tightly packed and show pseudostratification (**A**, haematoxylin–eosin – x10). Multinucleated giant cells are seen in the stalk of papillae (**B**, haematoxylin–eosin – x20).

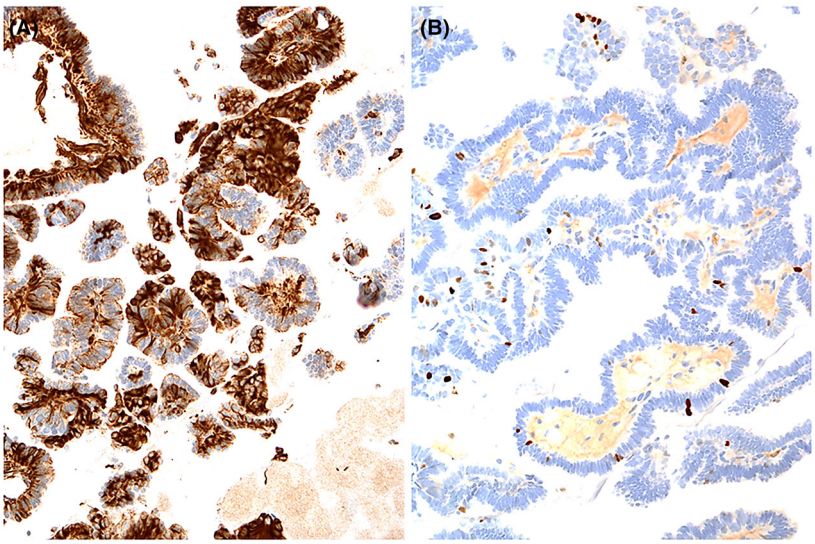

Figure 6. (Patient 2): Several tumour cells express vimentin (**A**, immunoperoxidase – x10); less than 1% of neoplastic cells are positive for Ki-67 (**B**, immunoperoxidase – x4).

lymph nodes in patient 3 during the 11-year follow-up would be unusual for PTC. Also, pituitary deposits from PTC are exceedingly rare accounting for 2–3% of all pituitary metastases [29-32]. Metastases to the sella occur more often in patients who have an established diagnosis of PTC. Notably, immunostains to confirm the diagnosis of metastatic PTC to the pituitary were only performed in a few cases [reviewed in ref 33]. The question of whether a few of the documented metastatic PTC to the pituitary could have been examples of PPETS and the primary thyroid lesion an incidental finding remains open.

Rare primary tumours with papillary architecture have previously been described in the sella and regarded as examples of extraventricular eCPP [34-37]. Sellar eCPP and PPETS are very similar, and although none of the published examples of sellar eCPP were tested for TTF-1, they could represent the same entity.

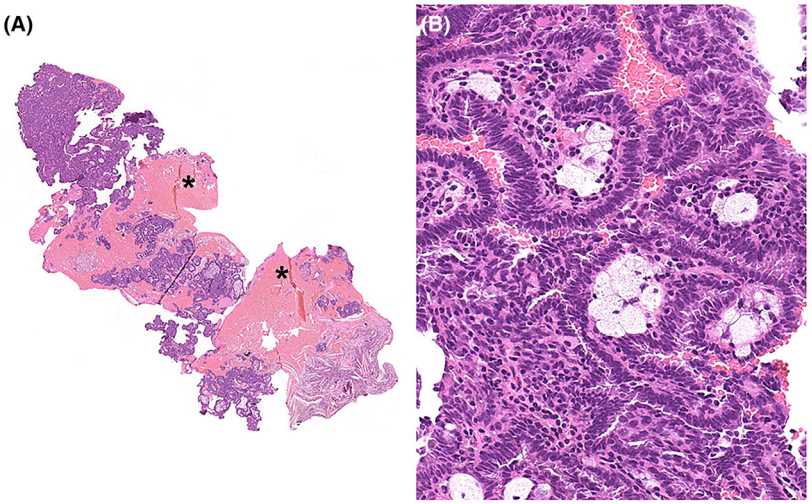

Figure 7. (Patient 4): the whole mount (**A**) of this tumour demonstrates areas of haemorrhagic necrosis (asterisk) accounting for the cystic component seen in the preoperative neuroimaging. The core of papillae contains lymphocytes, plasma cells and foamy histiocytes (**B**, haematoxylin–eosin, x20).

Reported sellar eCPPs present as solid or solid/cystic, sellar and suprasellar lesions without cavernous sinus extension or breach of the sellar floor. Unlike conventional CPPs [38,39] and similar to PPETS, sellar eCPPs show diffuse expression of cytokeratin 7 and focal expression of EMA and lack of cytokeratin 20 and S-100 protein. Vimentin was positive in two examples [36,37]. Transthyretin was only tested in one sellar eCPPs and it was reportedly positive [37]. In addition, the suggested origin of sellar eCPPs from ectopic choroid plexus rests in the sella has never been substantiated. The exceedingly rare pigmented papillary epithelial neoplasm of the pituitary fossa was excluded based on the immunoprofile as they contain melanin and express transthyretin, S100, Vimentin and HMB45 and are negative for EMA and pancytokeratin. TTF-1 was neither tested in the original description nor in a more recently reported case [40,41]. One case of primary sellar papillary adenocarcinoma was documented by Hampton and colleagues as part of the spectrum of primary sellar tumours that arise from ectopic salivary gland remnants in the pars intermedia [42]. Unlike our four cases, the lesion exhibited overtly aggressive features including nuclear atypia and pleomorphism, prominent nucleoli, frequent atypical mitosis and necrosis.

Sellar ependymoma enters the differential diagnosis with PPETS. Sellar ependymoma belongs to the group of TTF-1-positive posterior pituitary tumours. Its reported features vary from those of a classic ependymoma with ependymal and perivascular rosettes to lesions that consist of sheets and fascicles, but it is best regarded as a variant of pituicytoma [1,43,44]. In addition to TTF-1 expression, the immunoprofile of sellar ependymoma includes S-100 protein and dot-like rather than cytoplasmic, apical EMA. Ultrastructural evidence of intra and intercellular lumina containing microvilli and cilia and cell-to-cell junctions that are reminiscent of pituicytes with ependymal differentiation help confirm the diagnosis [14]. Unlike PPETS, cytokeratin is only focally expressed in sellar ependymoma.

Given the unusual features of PPETS, the vicinity of sella and sphenoid sinus and the possible breach of sellar floor in patient 2, we considered nonsalivary and nonintestinal type low-grade adenocarcinoma of the sinonasal tract (SNAC) in the differential diagnosis. Histologically, low-grade SNACs can show papillary features, but they are more often composed of back-to-back glands and tubules with little or no intervening stroma. Cribriform and trabecular growth are also described [45-47]. As seen in PPETS, papillae and tubules are lined by a single layer of uniform columnar or cuboidal cells showing minimal atypia, but they typically lack TTF-1 expression. Also, the distinctive expression of vimentin in the basal part of the neoplastic cells in ETV6 SNAC [46] was not a feature of PPETS. In contrast, the light microscopic features and immunoprofile of PPETS are remarkably similar to TL-

LGNPPA [9-11,48]. Review of neuroimaging and intraoperative inspection confirmed the sellar floor was intact in our patients, and no nasal or pharyngeal lesion was present. This supported the view that the lesions documented here originated from the sella despite similarity with TL-LGNPPA. TL-LGNPPA is extremely rare. First documented by Wenig *et al.* in 1988 [9] as a distinct entity, TL-LGNPPA has been included into the WHO classification of head and neck tumours in 2005 as a malignant neoplasm of nasopharynx. Striking papillary architecture and aberrant TTF-1 expression that mimic papillary thyroid carcinoma are its distinguishing features. Examples of TL-LGNPPA reported so far always present as polypoid intranasal masses, originating from the roof of the nasopharynx and posterior edge of the nasal septum, and with sizes up to 4 cm. No examples occurring in the sphenoid sinus have been documented. Adenocarcinoma is a misnomer as surgery is curative and prognosis is excellent [10-11,48]. No local recurrence or metastatic spread has been reported.

The cell of origin of PPETS remains unclear. Ubiquitous, intense nuclear expression of TTF-1 suggests the derivation from the pituitary infundibulum, median eminence or the organum vasculosum of the lamina terminalis rather than the anterior gland. TTF-1 is not expressed in the anterior hypophysis [49], whereas none of the above TTF-1-positive structures have been reported to contain cytokeratin-positive cells. The neurohypophysis, organum vasculosum of the lamina terminalis and median eminence belong to the circumventricular organs (CVO), a complex of highly vascularized, midline structures lacking the normal blood–brain barrier [50,51]. Recent evidence suggests that the entire roof of the third ventricle is a common CVO progenitor domain and stem cell properties of CVO have been demonstrated in an animal model [52]. These findings might suggest the potential of stem cells to differentiate toward an epithelial phenotype giving rise to PPETS. On the other hand, TTF-1 is not restricted to tumours of the infundibulum. Using tissue microarrays, Kristensen and colleagues [53] compared the two anti-TTF-1 clones 8G7G3/1 and SPT24 in a wide spectrum of 155 primary CNS tumours. In addition to a minority of high-grade gliomas, they observed weak and focal expression in central neurocytoma, one ependymoma and one choroid plexus papilloma. Using the clone SPT24 of anti-TTF-1 antibody, Zamecnik *et al.* only observed TTF-1 in two ependymomas, whereas none of the other primary CNS lesion they investigated was positive [54]. More recently, Asa and colleagues observed weak TTF-1 expression in sellar neurocytoma [55].

In conclusion, we have documented a novel primary sellar tumour with striking papillary architecture, cytokeratins and TTF-1 expression. This entity expands the spectrum of TTF-1-expressing primary tumours of the third ventricle, infundibulum and sella. The lesion should be distinguished from sellar metastases from thyroid and lung, sinonasal low-grade adenocarcinomas and sellar ependymomas. We suggest that PPETS and sellar eCPPs may be the same tumour type and represent the intracranial equivalent of TL- LGNPPA.

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Author contribution

FR, DC and BF have identified the cases, contributed to the design of the study and wrote the manuscript; KG, CG, AL assessed the patient and contributed to writing of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

Ethical Approval

Patients 1, 2 and 4 have consented to the publication of this study; patient 3 was lost to follow-up.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. (Patient 4)**:** the tumour of patient 4 shows heterogenous enhancement of the solid areas (A, sagittal postcontrast T1-weighted sequence); no invasion of cavenous sinues is present (B, axial postcontrast T1-weighted sequence).

Figure S2. (Patient 4): neoplastic cells show cytoplasmic, apical expression of EMA (immunoperoxidase, x20).

Figure S3. Ultrastructural examination of tissue reprocessed from paraffin shows intercellular tight junction (arrow) (orignal magnification x 1 2,000; printed magnification x 59,000) (Patient 1, primary tumour).

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