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Case Report

Lactotroph PitNET/adenoma associated to granulomatous hypophysitis in a patient with Crohn's disease: A case report

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Granulomatous hypophysitis is a rare and poorly understood condition. Although certain cases are treated as primary pituitary autoimmune disorders, rare cases may be associated with pituitary neuroendocrine tumours (PitNETs) and systemic inflammatory diseases. Here, we report a case of a 47-year-old man that underwent endoscopic trans-sphenoidal excision of a pituitary mass diagnosed as PitNET. On histologic evaluation, the neoplasm showed an admixture of granulomas with extensive inflammatory infiltrate and lactotroph PitNET/adenoma. Careful anamnestic examination revealed a diagnosis of Crohn's disease 20 years prior. Although rarely done, both PitNET and Crohn's disease may be associated with granulomatous hypophysitis, and our patient had both conditions. During the 6-year follow-up, PitNETs and hypophysitis did not recur, while Crohn's disease was only partially controlled by medical therapy. To our knowledge, this is the first description of association of granulomatous hypophysitis, PitNET and Crohn's disease.

Key words: Crohn's disease, granulomatous disorders, hypophysitis, lactotroph PitNET/adenoma, pituitary neuroendocrine tumours.

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INTRODUCTION

Hypophysitis is a rare disease of the pituitary gland, with an annual incidence of one case for every nine million people.[1] It can be asymptomatic or manifest with headache, visual dysfunction and hormonal disorders, including diabetes insipidus and hypopituitarism. On a morphological basis, hypophysitis can be classified as lymphocytic (68% of all cases), granulomatous (19%), plasmacytic (8%, usually related to the spectrum of IgG4-related diseases), xanthomatous (4%) and necrotizing (<1%).[2] Mixed forms of hypophysitis are also described (e.g. xanthogranulomatous hypophysitis). Based on etiopathogenesis, hypophysitis may be primary or secondary, the latter when an external cause of pituitary inflammation is identified. In this regard, a large variety of possible causes of secondary hypophysitis have been described, including infections (mycosis and tuberculosis), drugs (mostly immune checkpoint inhibitor toxicity), Rathke's cyst rupture and many systemic inflammatory and autoimmune diseases, such as granulomatosis with polyangiitis, sarcoidosis and Langerhans cell histiocytosis.[1–3] Specifically, other than the most common inflammatory or infectious diseases, granulomatous hypophysitis may be related to various other etiological causes, including pituitary neuroendocrine tumours (PitNETs) and Crohn's disease (CD). PitNETs are primary neoplasms of the adenohypophysis, accounting for 15% of all primitive intracranial tumours. The association of PitNETs with granulomatous inflammation of the pituitary gland remains an exceptionally rare occurrence.[4–7] CD is an inflammatory bowel disease (IBD) that commonly affects different segments of the gastrointestinal tract, although extra-intestinal involvement has been described.[8–10] Extra-intestinal manifestations of CD may be

due to a multifactorial aetiology, including genetic predisposition, immune dysregulation and intestinal microbiota dysbiosis. The etiopathogenesis may include an abnormal immune response to shared epitopes in the gastrointestinal mucosa and extra-intestinal tissues.[8–10] CD-associated granulomatous hypophysitis has also been reported, but it is exceptionally rare.[11–13] Here we present a patient who had granulomatous hypophysitis, PitNET and CD simultaneously. To the best of our knowledge, it is the first reported case of this specific clinical picture.

CLINICAL SUMMARY

A 47-year-old man presented at the emergency room with headaches and a gradual reduction of left eyesight without any other focal neurological deficits. A suspicion of retrobulbar optic neuritis was formulated on clinical grounds, and the patient was admitted to the neurology ward. Magnetic resonance imaging (MRI) with gadolinium contrast medium was conducted, revealing an endosellar and suprasellar space-occupying lesion, with a greatest axis of 28 mm, isointense in T1 sequences (Fig. 1, panels A, B) and hyperintense in T2 sequences (not shown). The optic chiasm and left optic nerve were compressed, and the left cavernous sinus was invaded with the encasement of the left carotid artery. The lesion showed homogenous contrast enhancement (Fig. 1, panels C and D). The pituitary stalk and the neuropituitary bright spot were not visible. Therefore, pituitary macroadenoma became the most likely diagnosis. A hormonal panel was performed, and prolactinemia was 328 ng/mL (normal male range value: 4–15 ng/mL), though the patient did not experience evident clinical manifestations of hyperprolactinemia. Surgery was recommended to relieve mass effects and allow for histological diagnosis. The patient underwent endoscopic neurosurgery with a transsphenoidal approach, which resulted in a macroscopically complete excision of the mass.

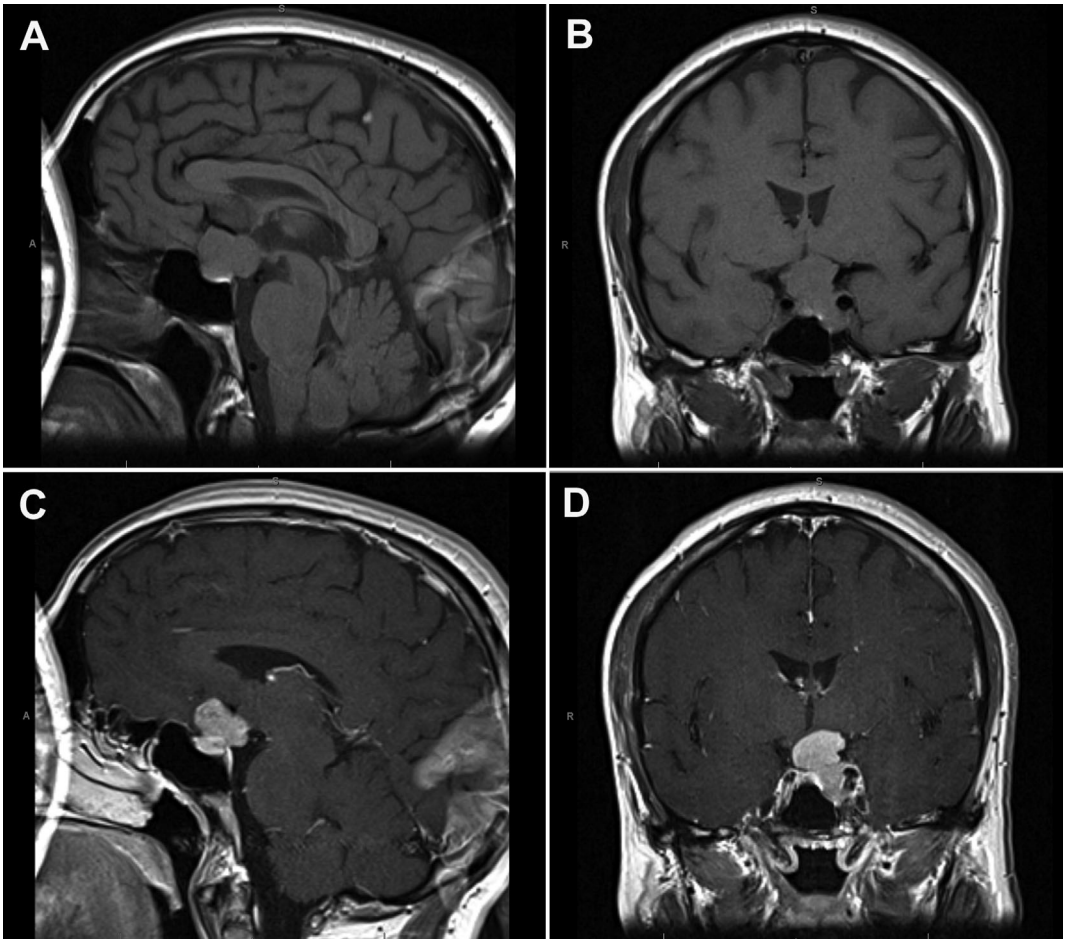

Fig 1 Neuroradiological exams. Brain magnetic resonance imaging highlighted an endosellar and suprasellar space-occupying lesion, with greatest axis of 28 mm, isointense in T1 sequences with a homogenous contrast enhancement. (A, B: sagittal and coronal T1-w before contrast enhancement; C, D: sagittal and coronal T1-w after contrast enhancement).

PATHOLOGICAL FINDINGS

On gross examination, the samples were pink-greyish, comprising a total volume of 1 cm^3. Histological examination revealed a PitNET with a predominantly solid architecture, composed of medium-sized cells showing round nuclei, fine chromatin and occasional nucleoli (Fig. 2, panels A and B). The mitotic rate was low (1–2 mitosis per 10 high power fields, corresponding to 2 mm^2). Notably, we found a second cellular component consisting of a dense inflammatory infiltrate mainly composed of lymphocytes and macrophages, some of which appeared to form granulomas composed of medium-sized epithelioid cells and multinucleated giant cells (Fig. 2, panel C). The neoplastic proliferation was diffusely positive for cytokeratin 7/8 (CAM-5.2), synaptophysin and prolactin (Fig. 2, panels D–F), but negative for the remaining pituitary hormones (growth hormone, adrenocorticotropic hormone, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone) (not shown). The diffuse cytoplasmic pattern of expression of prolactin was considered diagnostic of densely granulated lactotroph PitNET/adenoma. Indeed, for a 28-mm densely granulated lactotroph PitNET/adenoma, prolactinemia would be expected to be higher than 328 ng/mL, perhaps justified by the histopathological evidence that part of the lesion was occupied by granulomatous hypophysitis. This diagnosis was further confirmed by the positivity of PIT-1 nuclear transcription factor (Fig. 2, panel G), which is expressed by the pituitary cell lineage that includes lactotroph cells. P53 expression showed weak positivity in only 2–3% of the neoplastic cells (not shown). The proliferation index, as assayed by Ki67 expression, was <2% (not shown). To properly define the nature of the aforementioned granulomas, additional immunohistochemical stains and histochemistry were requested. Periodic acid–Schiff (PAS) and PAS-diastase (PAS-D) stains were used to rule out fungal infections, and Ziehl-Nielsen stain was performed to seek acid-fast bacilli and rule out tuberculosis. PAS, PAS-D and Ziehl-Nielsen were all negative (Fig. 2, panels H–J). As expected, immunohistochemical stains showed both CD68-positive histiocytes and CD3-positive T lymphocytes within the granulomas (Fig. 2, panels K and L). Plasmacells, B lymphocytes and CD4- and CD8-positive T lymphocytes were barely detected (not shown).

CLINICAL FEATURES AND FOLLOW-UP

A careful anamnesis revealed that the patient had received a diagnosis of CD 20 years prior, with colic, ileal, duodenal and gastric involvement. Revision of his first colonic and gastric biopsies showed extensive inflammatory infiltrate throughout the gastrointestinal tract, Paneth cell metaplasia of the left colon (suggesting a long-standing colitis) and the presence of granulomas in the colonic and gastric walls (Fig. 3, panels A–C). The patient presented no post-operative complications, and his prolactin level normalised. In the subsequent 6 years of follow-up, he had no

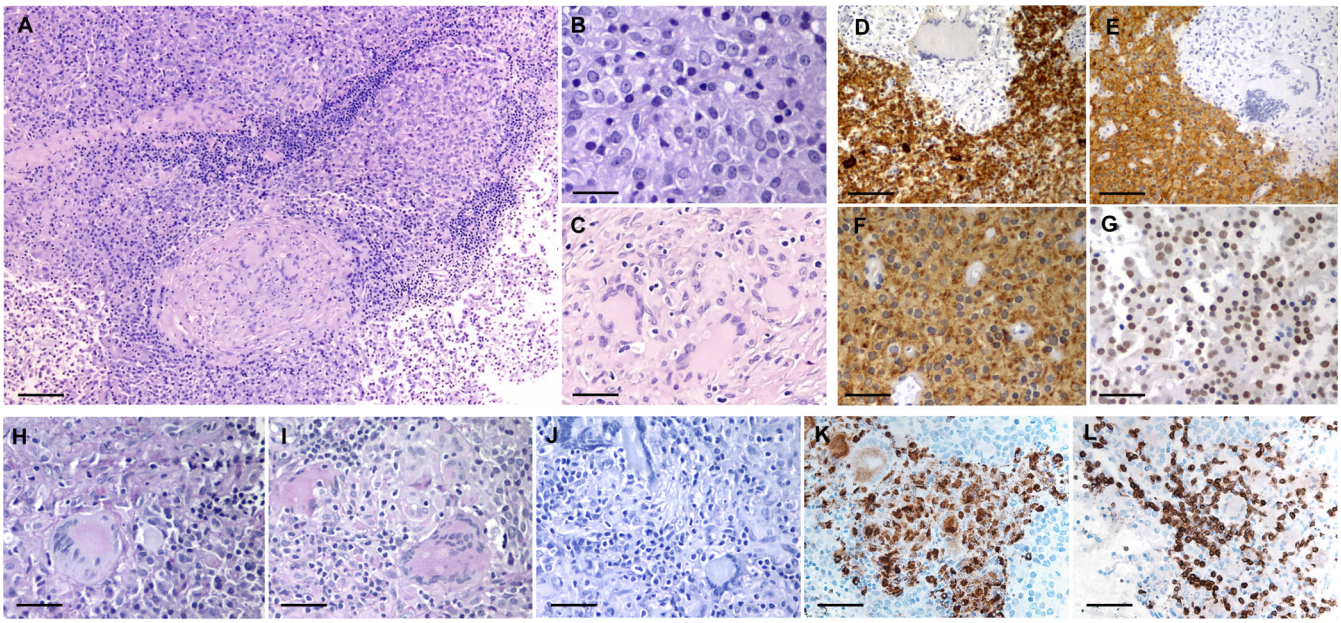

Fig 2 Pituitary neuroendocrine tumour with granulomatous hypophysitis. Haematoxylin and eosin staining highlights a predominantly solid growth of the PitNET with an extensive inflammatory component (A, B, as a detail). Inflammation shows granulomas and giant multinucleated cells (C, as details from A). Neoplastic cells displayed diffuse positivity for cytokeratin 7/8 (D), synaptophysin (E) and prolactin (F). Neoplastic cells also expressed the PIT-1 nuclear transcription factor (G). Granulomas tested negative for PAS, PAS-D and Ziehl-Nielsen stains (H, I, and J respectively). Immunohistochemistry for CD68 and CD3 was also performed, highlighting histiocytes and T-cells (K and L respectively). Scale bars: ×4 μm (A), ×20 μm (D, E, F, G), ×40 μm (B, C, H, I, J, K, L).

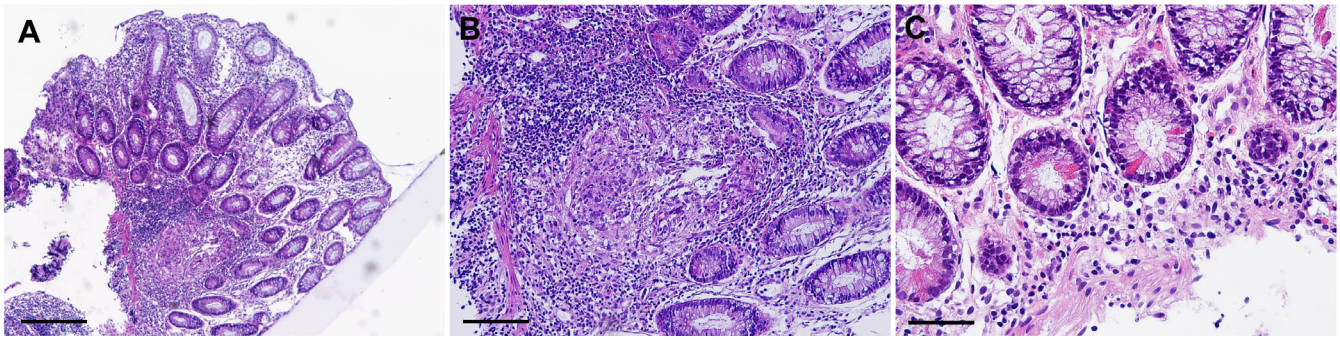

Fig 3 Crohn's disease. The patient's original colonic biopsies, stained with haematoxylin and eosin (H&E), showed inflammation and granulomas (A, B, the latter as a detail from A). Paneth cell metaplasia, suggesting a long-standing colitis, is shown in the colon biopsy (C). Scale bars: ×4 μm (A), ×10 μm (B), ×20 μm (C).

recurrence of pituitary disease, and brain MRIs were negative (not shown). His CD, however, intermittently relapsed on clinical and histological grounds, although in the last 2 years of follow-up colon biopsies were negative.

DISCUSSION

We report a case of a 47-year-old man who simultaneously presented with lactotroph PitNET/adenoma, granulomatous hypophysitis and CD. We first considered the association of PitNETs with granulomatous hypophysitis and found in the scientific literature only four reported cases,[4–7] including a patient with lactotroph PitNET/adenoma.[4] The authors suggest that PitNET-associated granulomatous hypophysitis may be the consequence of a hypothetical, unknown antigen produced by adenomatous cells, triggering a granulomatous inflammatory response by surrounding pituitary parenchyma cells in susceptible patients. However, there is no clear evidence of this putative pathological mechanism. Interestingly, we found few reported cases describing the association of granulomatous hypophysitis with both PitNETs and CD (Table 1). However, no reported cases were found describing an association between all three conditions—granulomatous hypophysitis, PitNETs and CD—simultaneously. The association of granulomatous hypophysitis and CD was reported in three cases.[11–13] Notably, in one of these cases, hypophysitis was responsive to CD therapy,[13] suggesting a common pathological mechanism. Our patient was under long-term CD treatment with corticosteroids and salazopirine and periodically monitored by clinicians. Notably, during the period preceding the diagnosis of PitNET, the patient experienced a worsening of his CD, also highlighted by both endoscopic examination and colon biopsies (not shown), suggesting a relationship between CD and the granulomatous hypophysitis that populated the PitNET. Remarkably, following neurosurgery, the overall clinical picture improved, although the CD intermittently relapsed and, due to the inefficacy of the corticosteroid treatment, treatment with an anti-TNFα therapy (Adalimumab) was scheduled. As reported in the

Table 1 Case reports with association between granulomatous hypophysitis, pituitary neuroendocrine tumours and Crohn's disease

Year and reference	Patient	Association	Clinical features	Size
1983; ref. 4	54 y/o, M	Granulomatous hypophysitis and lactotroph PitNET/adenoma	Left-sided headache; hyperprolactinemia	n.s.
2017; ref. 5	59 y/o, F	Granulomatous hypophysitis and PitNET (non-functioning; recurrence)	Headache, visual deficits; normal hormonal panel	26 mm
2019; ref. 6	35 y/o, M	Granulomatous hypophysitis and gonadotroph PitNET/adenoma	Incidental finding; normal hormonal panel	n.s.
2007; ref. 7	44 y/o, M	Granulomatous hypophysitis and corticotroph PitNET/adenoma)	Hypogonadism, focal neurological symptoms; reduced levels of FSH, LH and IGF-1	20 mm
2009; ref. 11	32 y/o, M	Granulomatous hypophysitis and Crohn's disease	Headache, diplopia; normal hormonal panel; rectal bleeding, diarrhoea	n.s.
1991; ref. 12	age n.s., F	Granulomatous hypophysitis and Crohn's disease	Hemianopia; hypopituitarism; chronic active proctocolitis; patient was pregnant	n.s.
2020; ref. 13	43 y/o, F	Granulomatous hypophysitis and Crohn's disease	Headache, visual deficits; hyperprolactinemia, secondary hypothyroidism, adrenal insufficiency	19 mm

Abbreviations: F, female M, male; n.s., not specified; y/o, years old.

literature,[11–13] patients with CD may be prone to not only intestinal but also extra-intestinal granulomatous inflammation and, therefore, susceptible to developing granulomatous inflammation in different topographical sites, including the pituitary gland. Interestingly, extra-intestinal manifestations of CD were more often observed in Crohn's patients with histological evidence of granulomas.[14]

In line with these observations, CD patients have an increased risk of extra-intestinal autoimmune and inflammatory disorders compared to the general population.[8–10] Of course, other possible causes of granulomatous hypophysitis (e.g. infections, drug toxicity, Rathke's cyst rupture, other systemic inflammatory and autoimmune disorders) need to be ruled out on clinical and pathological grounds. In particular, sarcoidosis and Crohn's disease are granulomatous disorders with overlapping histological features, and distinguishing these two entities may be problematic in the absence of clinical correlations, especially regarding extra-intestinal manifestations.[15] Histologically, granulomas in sarcoidosis are typically much more well formed and with some peculiar histological features, such as Schaumann and asteroid bodies. In our case, the diagnosis of sarcoidosis has been ruled out based on both histological and clinical data that made it possible to exclude a concurrent sarcoidosis. Although the molecular mechanisms underlying this association remain unknown, it may be hypothesised that in our patient, CD may have acted as a background risk factor for the development of granulomatous lesions, whereas his PitNET played the role of a cofactor triggering inflammation.

Our report underlines the importance of careful anamnestic evaluation in the face of hypophysitis since morphology alone is usually not sufficient for an etiological diagnosis. The patient's history of CD was fundamental in establishing the secondary nature of his granulomatous hypophysitis and explaining the rare and curious combination of these seemingly independent diseases. Infections must always be ruled out with specific stains (and, again, with a detailed clinical picture), and occult or misdiagnosed systemic inflammatory conditions must be searched for. In conclusion, a careful and accurate clinical assessment is of paramount importance for properly defining the aetiology of granulomatous hypophysitis, which remains a rare and poorly understood disease.

DISCLOSURE

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be interpreted as a potential conflict of interest.

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AUTHOR CONTRIBUTIONS

AP and PLP are the primary authors of the manuscript. SS, RS and GL were the clinicians providing surgical material and clinical information. PLP, AP and VV provided substantial contributions to the conception, design and revision of the manuscript. MC provided the technical support.

ETHICAL STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with local legislation and institutional requirements. The patient provided his written informed consent to participate in this study and for the publication of any potentially identifiable images or data included in this article.

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