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ORIGINAL ARTICLE

Disease heterogeneity in IgG4-related hypophysitis: report of two histopathologically proven cases and review of the literature

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Abstract

IgG4-related hypophysitis (IgG4-RH) is a rare disease, which can occur singularly or as manifestation of a systemic IgG4-related disease (IgG4-RD). Less than one hundred cases have been reported in the literature, very few of which were histopathologically documented. We analyzed the clinical, radiological, and histopathological features of two cases of IgG4-RH, the former observed in a 66-year-old man in the context of an IgG4-RD, and the latter affecting a 21-year-old woman, as an isolated lesion. In addition, we performed a comprehensive review of the previously published histopathologically documented cases of IgG4-RH. Pituitary samples from both patients showed dense lymphoplasmacytic infiltration, interstitial and storiform fibrosis, and high numbers of IgG4-positive plasma cells, consistent with IgG4-RH. From the literature review, we retrieved 18 papers reporting a total of 22 cases of histopathologically documented IgG4-RH. The revision of these cases, also including the two reported herein, showed an equal distribution of IgG4-RH in the two sexes, albeit significant clinico-pathological variation was found between cases arisen in female and male patients, respectively. In detail, IgG4-RH females were affected in their second-third decade of life, with a solitary pituitary lesion, low IgG4 serum level, and frequent association with autoimmune disorders. By contrast, IgG4-RH in men was a disease of the elderly, often in the context of a systemic IgG4-RD, with high IgG4 serum levels. Our study shows that IgG4-RH, as currently defined, is a clinically heterogenous disease, with different features in the two sexes. Indeed, cases diagnosed in young women, as our case 2, mostly do not present other evidence of IgG4-RD and might be better classified as lymphocytic hypophysitis with abundant IgG4+ plasma cells. For this reason, the histopathological examination of the pituitary lesion, particularly in female patients, may still be useful for a correct differential diagnosis with other variants of primary hypophysitis.

Keywords Hypophysitis · IgG4-related disease · IgG4-related hypophysitis · Pituitary gland

Introduction

Primary hypophysitis (PH) is a rare disorder, accounting for about 0.4% of all diagnoses on surgical samples of pituitary gland [1]. Histological examination is the gold standard diagnostic tool. The most common histological type of PH is lymphocytic hypophysitis, which seems to have an autoimmune etiology and is mostly diagnosed in young women in the peripartum period. The second most common histological variant is granulomatous hypophysitis, which, in its primary form, has an unknown etiology. Extremely rare forms are xanthomatous, necrotizing, and IgG4-related hypophysitis.

IgG-4 related disease (IgG4-RD) is a new entity featuring mass lesions in multiple organs, peculiar inflammatory infiltrate at histopathological examination, and frequently, but not always, elevated IgG4 serum levels [2]. Among all the

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possible involved organs, the pituitary gland is a very rare, but well recognized, target site and IgG4-related pituitary disease (formerly known as inflammatory pseudotumor or as lymphoplasmacytic hypophysitis) has been included as a histologic type of PH. In the preoperatory setting, IgG4-related hypophysitis (IgG4-RH) may mimic proliferative lesions such as pituitary neuroendocrine tumors or craniopharyngiomas. On the other hand, at histological examination, it can be misdiagnosed as other primary or secondary inflammatory lesions or lymphoproliferative diseases, with important therapeutic and prognostic implications. Although the histological examination of pituitary tissue is the gold standard, the integration of radiological, serological, and clinical data has been proposed as an alternative to establish diagnosis by Leporati and coworkers [3].

Herein, we report two cases of IgG4-RH, arisen respectively in an old man and in a young woman. An accurate review of the histologically documented cases of IgG4-RH reported in the English literature has been performed, aiming to a better definition of the clinico-pathologic features of this recently recognized and rare entity.

Case histories

Case 1 A 66-year-old male presented at the neurosurgery department of ASST dei Sette Laghi-University of Insubria, Varese, Italy, with bilateral deficit in grip and bitemporal hemianopia. In the suspect of a sellar disease, hormonal status assessment and cerebral magnetic resonance imaging (MRI) were performed. Blood analysis showed mild hyperprolactinemia (PRL 57.8 ng/ml n.v 4.8–23.3), low serum levels of follicle-stimulating hormone (FSH < 0.3 mU/ml) and luteinizing hormone (LH < 0.3 mU/ml). A 22-mm craniocaudal sellar and suprasellar expansive lesion, with mild depression of the sellar floor and compression of the optic chiasm, was observed at the cerebral MRI (Fig. 1). A non-functioning (NF) pituitary neuroendocrine tumor was hypothesized and the patient underwent endonasal endoscopic transsphenoidal surgery (TSS). The surgical sample was sent to the pathology department and a diagnosis of a possible IgG4-RH was formulated. Post-operatively, the patient developed panhypopituitarism with persistent hypogonadotropic hypogonadism with undetectable testosterone, central hypothyroidism (TSH 0.2 mU/L, FT4 0.7 ng/dl), GH deficiency (IGF-1 50 ng/ml), central hypocortisolism (cortisol < 0.3 ng/ml after a single day of HC suspension), hypoprolactinemia (PRL 0.5 ng/ml), and diabetes insipidus. The post-operative MRI after gadolinium injection showed neither residual mass, nor chiasmatic compression. Three months after diagnosis, 18FDG-PET showed a metabolically active lesion in the right upper pulmonary lobe with hypermetabolism. Lung biopsy documented IgG4-RD. The patient is alive after 18 months from the diagnosis, with no further lesion.

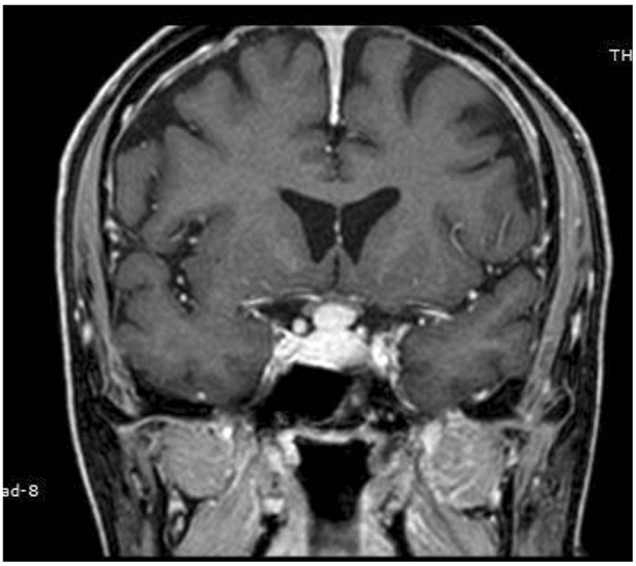

Fig. 1 Pre-operative brain MRI, T1 coronal view, after gadolinium injection shows sellar and suprasellar lesion with optic chiasma compression

Case 2 A 21-year-old female presented at the neurosurgery department of the University Hospital of Lausanne, Switzerland, for blurred vision and headaches, associated with galactorrhea, and oligomenorrhea. An isolated mild hyperprolactinemia (35 μg/l, norm 4.2–21 μg /l) was observed. Cerebral MRI showed a 16 × 24 × 11 mm intrasellar mass with suprasellar extension and compression of the optic chiasm (Fig. 2a). A pituitary neuroendocrine tumor was suspected. Because of the visual symptoms, confirmed by the ophthalmological evaluation, the patient underwent an endonasal endoscopic TSS. A gross total resection was performed (Fig. 2b). The surgical sample was sent to the Pathology Institute, where an IgG4-RH was diagnosed. After the diagnosis, a systemic work-up was performed including the dosage of serum level of TSH, FT4, prolactin, IGF-1, and IgG4, all within reference ranges. The gonadotropic axis was not interpretable because of oral contraception. At 1-year follow-up, the patient had no hormonal substitution and no diabetes insipidus. A biopsy of a minor salivary gland and a thoraco-abdominal CT scan were also performed and were negative for other localizations of the disease.

Materials and methods

Histopathological review

Formalin-fixed and paraffin-embedded histological samples of the two cases of IgG4-RH were collegially

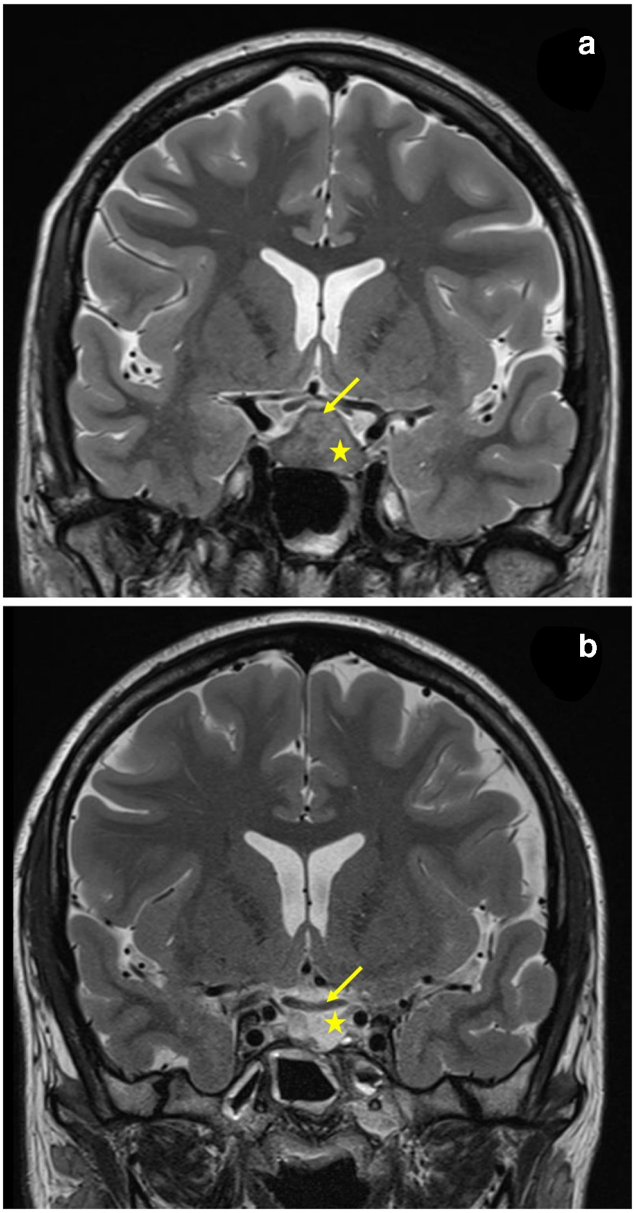

Fig. 2 **a** Pre-operative brain MRI, T2 coronal view, after gadolinium injection shows sellar and suprasellar lesion (star) with optic chiasma compression (arrow). **b** Post-operative MRI T2 coronal view after gadolinium injection shows gross total resection without residual mass (star) and without chiasmatic compression (arrow)

reviewed by two expert endocrine pathologists (SU and SLR) and a neuropathologist (J-PB). The following parameters were defined: presence/absence of lymphoplasmacytic infiltration; presence/absence of eosinophil granulocytes; presence/absence of storiform fibrosis; presence/absence of obliterative phlebitis; presence/absence of phlebitis, not otherwise specified; absolute number of IgG4-positive plasma cells per high power field (HPF, × 400); IgG4-positive/IgG-positive (IgG4+/IgG+) plasma cell ratio (percentage).

Review of the literature

The PubMed database of the National Center for Biotechnology Information (NCBI) of the US National Library of Medicine was searched using the following string: hypophysitis [AND] IgG4. All articles written in English and including the histopathological evaluation of the pituitary lesion were selected. For each article, the reported cases were singularly identified and, for each case, the following parameters were considered: sex, age, presenting symptoms, MRI, pituitary hormonal levels, extrapituitary localization, IgG4 serum levels, therapy, and histological features as detailed in the previous section.

Statistical analysis

Associations in 2-way tables were tested for statistical significance using the Fisher exact test (2-tail). The analyses were performed using GraphPad Prism V5.0 software. A p value $\leq$ 0.05 was considered as statistically significant.

Results

Histopathological review

The two cases showed very similar histopathological features. We observed pituitary tissue largely obliterated by an abundant lymphoplasmacellular infiltrate, with interspersed eosinophilic granulocytes (Fig. 3a). Lymphoid follicular structures were focally observed (Fig. 3b) and a thickening of reticulin fibers, with focal formation of storiform collagen fibrosis, was seen (Fig. 3c, d). High numbers of well differentiated, polytypic (with a normal kappa/lambda ratio) plasma cells were present in both cases (Fig. 4a, b). The vast majority of plasma cells were immunoreactive for the gamma chain of immunoglobulins (IgG), and a significant proportion of them expressed IgG4. More specifically, the absolute number of IgG4+ plasma cell was higher than 10 per HPF, and the percentage over the total amount of IgG+ plasma cells was higher than 40% (Fig. 5a, b). At the end of the collegial histopathological review, a unanimous diagnosis of IgG4-RH was reached for both cases.

Review of the literature

From the PubMed data base, we retrieved 18 papers, reporting a total of 22 histopathologically documented cases of IgG4-RH, published from 2007 to 2018 [3–20]. Details regarding clinico-pathological features of cases, including our two, are given in Tables 1 and 2.

In summary, an equal sex distribution of the disease was observed (12 males and 12 females). Female patients were

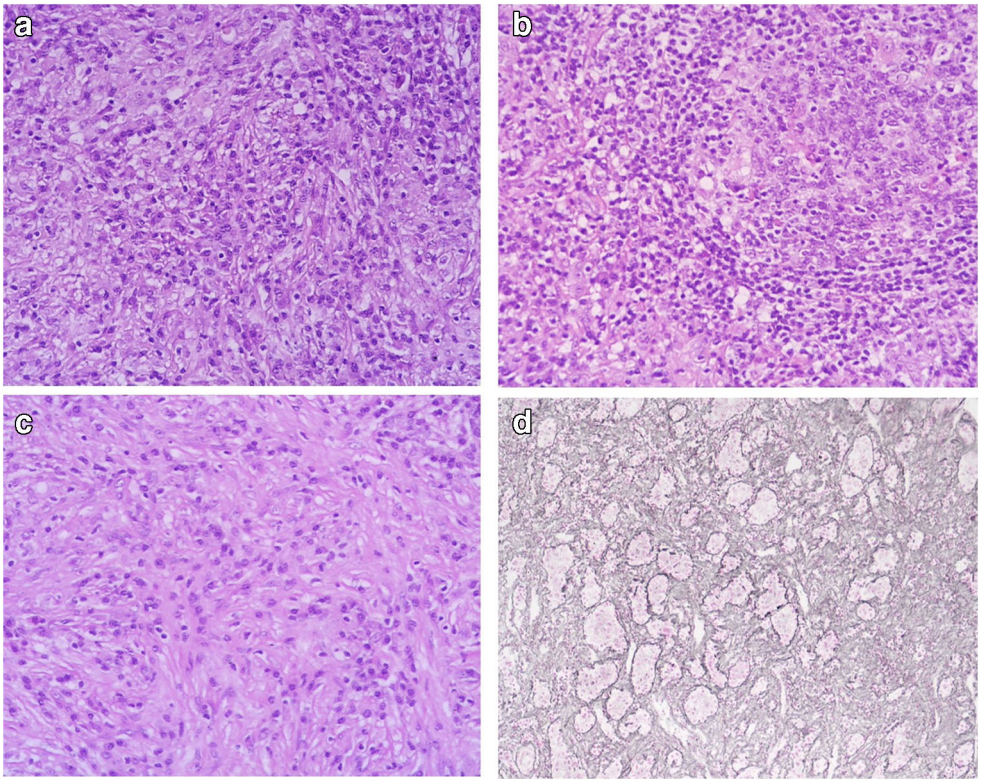

Fig. 3 Histological aspects of our case 1 (case 23 in Table 1). Pituitary parenchyma is completely replaced by dense inflammatory infiltrate with abundant lymphoplasmacytic component (**a**), lymphoid follicles (**b**) and focal dense fibrosis (**c** and **d**). (H&E, × 100 and × 200; Gomori stain, × 200)

significantly younger than males, with a mean age of 28.5 (range 14–58) vs 62.4 years (range 40–77) ($p < 0.0001$). From a clinical point of view, patients presented with mass symptoms (visual defects, headache, nausea, and vomiting), general symptoms (malaise, fatigue, anorexia, fever), or signs of endocrine dysfunction. At MRI, a discrete mass lesion of

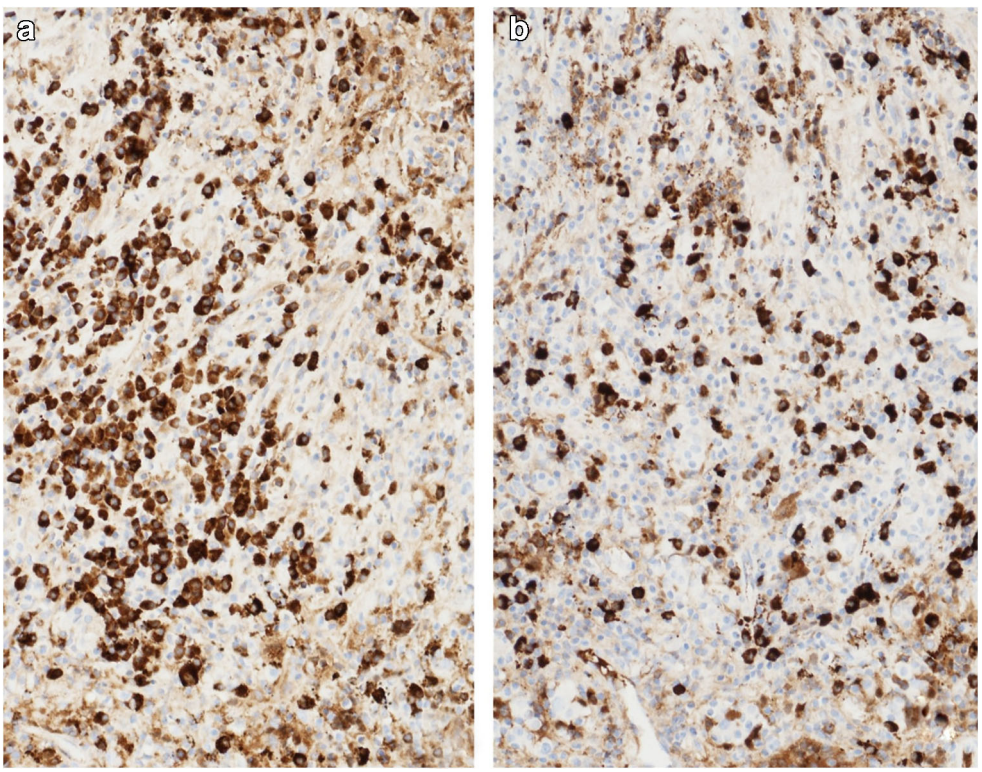

Fig. 4 Immunostains for kappa (**a**) and lambda (**b**) chains of immunoglobulins show absence of monotypic restriction in plasma cells (immunoperoxidase with hematoxilin contrast, × 200)

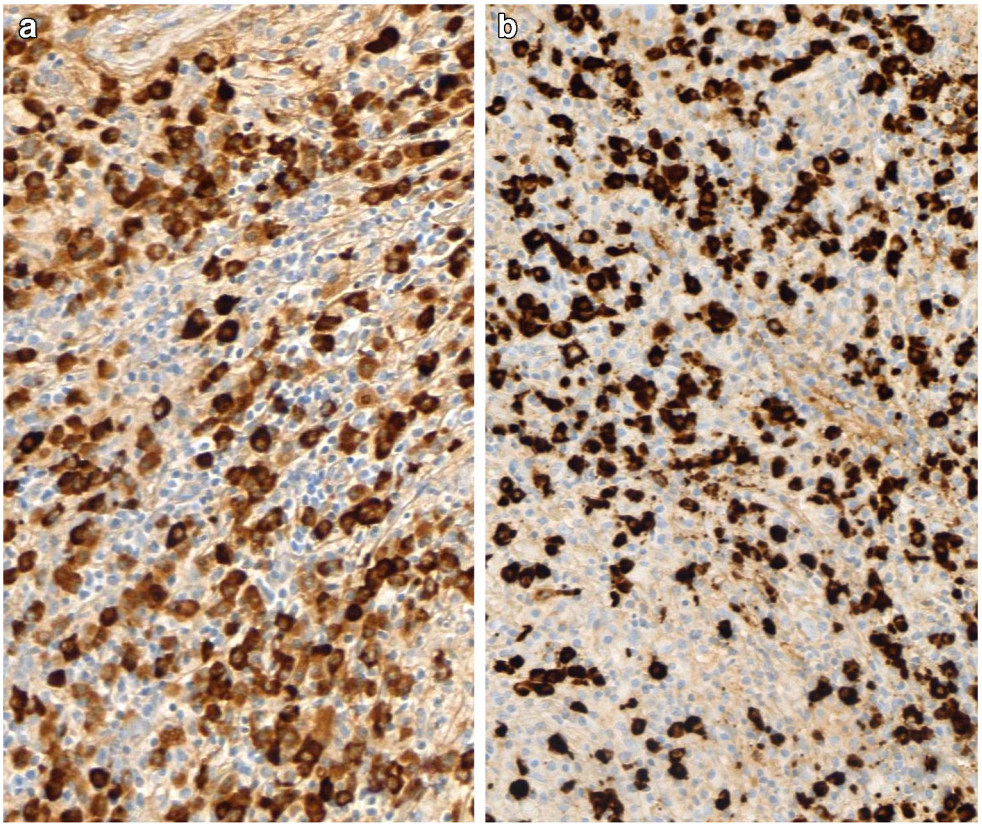

Fig. 5 Immunostains for IgG (**a**) and IgG4 (**b**) show an IgG4/IgG ratio > 40%, with > 50 IgG4+ plasma cells xHPF (immunoperoxidase with hematoxilin contrast, × 200)

the pituitary gland or of the sellar region was described in 17 patients, raising the suspect of a tumor. In the remaining 7 cases, a swelling of the pituitary gland, of the stalk, or of the infundibulum was present, leading to a radiological diagnosis of an inflammatory process. At blood examination, pituitary hormones levels were decreased in virtually all cases, with deafferentation hyperprolactinemia in three patients. No sex distinction was found either in the clinical presentation, or in the imaging of the disease.

The histopathologic findings always included dense lymphoplasmacytic infiltrate and a IgG4+/IgG+ plasma cell ratio > 10% with an absolute number of IgG4+ x HPF > 10. In a consistent number of cases, the other morphologic criteria for IgG-RD [2] were either not met or not looked for. In detail, storiform fibrosis was reported in 9 cases, increased eosinophilic count in 8 cases, and lymphoid follicles in 2 cases, whereas phlebitis, obliterative or not, was never reported. Available data about the histopathological features and plasma cell count were insufficient to compare female versus male patients.

IgG4 serum levels were normal in 13 out of the 19 patients in which they were assessed. It is worth to note that, of the six patients with increased serum IgG4 levels, only one was female.

The follow-up of the patients demonstrated that IgG-RH was not part of a systemic IgG4-RD in more than a half of the cases. Interestingly, only one of the female patients showed an extrapituitary localization of IgG4-RD, whereas five out of the twelve men presented IgG4-RD in extrapituitary organs. Postoperatory therapy always included corticosteroids, with only one non-treated case. Two patients were administered with rituximab and an additional one received azacitidin. There were no deaths of disease.

Discussion

IgG4-RH is a recently identified type of primary hypophysitis and is traditionally considered as a pituitary localization of systemic IgG4-RD, an immune-mediated disease firstly described in the pancreas and then observed in a variety of body sites [2]. Considering both English and Japanese literature, less than 90 cases of IgG4-RH have been reported since 2004, when the first case was published [21]. Based on the need of a pre-operative diagnosis, in order to avoid complication of transsphenoidal surgery, Leporati and coworkers proposed new diagnostic criteria, in which histopathological examination is not mandatory, provided that radiological, serological, and/or clinical specific criteria are met [3]. Consequently, histologically proven cases are extremely rare and specific morphological criteria for pituitary involvement in the course of IgG4-RD are not definitively clarified, yet.

In the present paper, we have described two cases of IgG4-RH and reviewed the English literature regarding IgG4-RH

Table 1 Clinical features of 24 cases of IgG4-RH

	Author	Sex	Age	Signs and symptoms	Imaging (MRI)	Endocrine signs and symptoms	Further localizations	Therapy	IgG4 serum
1	Wong [4]	M	77	Visual defects	Pituitary mass	Hypogonadism	Pancreas, gall-bladder	ND	Increased
2	Osawa [5]	M	74	Visual defects, thirst, fatigability	Swelling of pituitary infundibulum	Diabetes insipidus, (hypernatremia)	ND	Corticosteroids	Normal
3	Leporati [3]	M	75	Headache	Pituitary enlargement, stalk thickened and a dense mass within sphenoidal sinus with erosion of the sellar floor	Hypopituitarism	Sphenoidal sinus	Corticosteroids	Increased
4	Hsing [6]	M	66	General symptoms	Sellar mass	Hypopituitarism	Lung, pleura, mediastinum	Corticosteroids	ND
5	Hattori [7]	M	55	Visual defects	Swelling of pituitary gland and stalk	None	ND	Corticosteroids	Increased
6	Khong [8]	F	33	Secondary amennorhea	Sellar mass	Hypopituitarism	ND	ND	Normal
7	Caputo [9]	M	40	Lethargy, polyuria, polydypsia	Sellar mass	Hypopituitarism, diabetes insipidus	Lacrimal glands	Corticosteroids, azathioprine	Increased
8	Sosa [10]	F	25	Secondary amennorhea	Sellar/suprasellar mass	Hypergonadism, hyperprolactinemia	ND	Corticosteroids	ND
9		F	37	Cephalea, amenorrhea, polydipsia, polyuria	Sellar/suprasellar mass	Hypogonadism, hyperprolactinemia	None	Corticosteroids	Normal
10	Ngaosuwan [11]	M	43	Seizures, hypopituitarism, libido loss, aphasia, history of (since 2 years) headache, decreased appetite, cold intolerance, 10 kg weight loss, malaise	Sellar/suprasellar mass	Hypopituitarism	None	Corticosteroids	Normal
11	Decker [12]	F	16	Polyuria, Polydipsia	Solido-cystic sellar/ suprasellar mass	Diabetes insipidus	None	Corticosteroids	Normal
12	Anno [13]	M	76	General symptoms	Swelling of stalk and anterior pituitary gland	Hypopituitarism, hyperprolactinemia	None	Corticosteroids	Normal
13	Gu [14]	M	57	Eye swelling and redness, visual defects, malaise, poor appetite, cold intolerance, weight loss	sellar mass and cysts in stalk	Hypopituitarism	Multiple focality (intracranic, salivary glands, sinunasalis, chest, gall-bladder, colon-rectum)	Corticosteroids, rituximab	Increased
14	Hadjigeorgeu [15]	F	29	Visual defects	Solido-cystic sellar mass	ND	None	Corticosteroids, mycophenolate-mofetil	Increased
15	Murphy [16]	F	58	Fatigue, sleep problem, headache	Pituitary gland and stalk enlargement	Hypogonadism, diabetes insipidus	None	Corticosteroids	Normal
16	Rotondo [17]	M	49	Fever, headache, adynamia	Pituitary gland and stalk enlargement	Hypopituitarism, diabetes insipidus	None	Corticosteroids	ND
17		F	36	Headache, nausea, vomiting, neurologic symptoms	Sellar-suprasellar mass with a cysitic craniocaudal component	Hypopituitarism	Salivary glands	None	Normal

Table 1 (continued)

	Author	Sex	Age	Signs and symptoms	Imaging (MRI)	Endocrine signs and symptoms	Further localizations	Therapy	IgG4 serum
18	Koide [18]	F	25	Headache, visual defects; post-childbirth	Swelling of pituitary gland	Hypopituitarism	ND	Corticosteroids	Normal
19	Yuen [19]	M	71	Intracranial hypertension	Sellar mass	Hypopituitarism	None	Corticosteroids	Normal
10		F	24	Multiple sclerosis, recurrent migraine, diplopia, visual blurring (OC symptoms)	Cystic sellar mass	ND	None	None	Normal
21		F	24	Cephalea, OC symptoms, Hashimoto thyroiditis	Cystic soprasellar mass	Hypopituitarism, diabetes insipidus	None	Corticosteroids	Normal
22	Bullock [20]	F	14	Headache	Cystic sellar mass	Hyperprolactinemia	None	Corticosteroids, Rituximab	Normal
23	Uccella (present study)	M	66	Visual defects, deficit in grip	Sellar /extrasellar mass	Hyperprolactinemia, hypogonadism	Lung	Corticosteroids	ND
24		F	22	Headache	Intrasellar mass	Galactorrhea, mild hypocortisolism	None	Corticosteroids	ND

Table 2 Summary of the clinico-pathological features of 24 IgG4-RH

	N = 24
Sex	Males 12 Females 12
Age	Mean 45 years (M, 62.4; F, 28.5) Range 14–77 years (M, 40–77; F, 14–58)
Symptoms	Mass symptoms 14 Polyuria and polydipsia 4 Endocrine symptoms 5 General symptoms 7
MRI	Sellar/suprasellar mass 14 Pituitary/infundibular/stalk swelling 10
Pituitary function	Hypopitutarism 16 Hyperprolactinemia 4 Diabetes insipidus 5 Normal 1 Not determined 2
Histopathology of the pituitary lesion	Lymphoplasmacytic infiltrate 24 Lymphoid folllicles 2 Storiform fibrosis 9 Obliterative phlebitis none Phlebitis, NOS none Eosinophils 8 Incremented IgG4 plasma cells 21
Extrapituitary localization	None 13 Salivary/lacrimal glands 3 Biliary tract 2 Chest 2 Retroperitoneum 2 Pancreas 1 Eyes 1 Colon 1 Not determined 4
IgG4 serum levels	Normal 14 Elevated 7 Not determined 3
Therapy	Steroid alone 17 Steroid plus rituximab 2 Steroid plus azacitidine 1 Steroi plus Mycophenolate-mofetil 1 None 2 Not determined 2

with histopathological documentation. We retrieved a total of 24 cases, including our two, and we attempted a meta-analysis of their clinico-pathological and histological features.

We observed an equal distribution of the disease in the two sexes. This result is contrasting with the diffuse opinion that IgG4-RH is a disease of older males. However, if we look more carefully at the previously reported data on this topic, we find that the male-to-female ratio ranges from 9.3:1 [22], to slightly more than 2:1 [3] in different series. Interestingly, the lowest figures are reported in studies including only, or mainly, histologically proven cases. Intriguingly, the age of diagnosis was significantly lower in females, presenting the

disease in their third and fourth decade, than in males, with mean age around 60 years. These data, in association with the fact that at least one female patient developed IgG4-RH soon after delivery [18] and another one had multiple sclerosis [19], suggest the possibility that a number of hypophysitis affecting young female patients may have been misdiagnosed in the past as autoimmune lymphocytic hypophysitis, when either IgG4-RH was not recognized as an entity or diagnostic criteria were not well defined. Indeed, Bernreuther and coworkers retrospectively revised a series of 29 cases of primary hypophysitis, originally diagnosed as lymphocytic hypophysitis, granulomatous hypophysitis, and hypophysitis, not otherwise specified, and showed that more than 40% of cases could be re-classified as IgG4-RH, based on the standard morphological and immunohistochemical criteria [23]. On the other hand, a Japanese study has recently suggested that IgG4-RH may recognize at least in part, an autoimmune pathogenetic mechanism [24].

Another important difference between male and female patient was that the involvement of multiple sites by IgG4-RD was almost exclusively present in men, whereas only one female patient showed the concomitant presence of IgG4-RD in the pituitary and in the salivary glands. In addition, only one female patient presented elevated IgG4 serum levels post-operatively, whereas half of the males had high IgG4 serum levels, although corticosteroid therapy was administered to all patients, with no sex distinction. As far as other clinico-pathological features are concerned, we confirm, as previously reported by others, that, in most cases, signs and symptoms of IgG4-RH are consequent to mass effects, rather than to alterations of the pituitary-dependent hormonal axis. No differences were noted in the two sexes.

The revision of the histopathological features of histologically proven IgG4-RH highlighted that the lymphoplasmacellular infiltrate with high numbers of IgG4-positive plasma cells was the corner stone of the morphological diagnosis. The quantification of the plasma cells infiltrate was not always precise, and it was frequently indicated as > 10 IgG4+ plasma cells per HPF. In many cases, absolute values higher than 40 were reported, but data are too poor to effectively compare groups of cases. Other histopathological criteria used in the diagnosis of IgG4-RD [2], such as storiform fibrosis, eosinophilic infiltrate, and phlebitis, were mostly not specified. In our two cases, indeed, we observed both eosinophilic infiltrate and storiform fibrosis, with no distinction between the old man and the young woman. Phlebitis was not observed.

Our meta-analysis of the 24 histologically proven IgG4-RH reported in the English literature suggests that this entity, as currently defined, may encompass at least two different diseases: one arising in men in their sixties, mostly as part of a systemic IgG4-RD, with high IgG4 serum levels and involvement of other organs, and the other occurring in young women, possibly in an autoimmune context. Interestingly, a recent study by Shikuma and coworkers, including a revision of published cases diagnosed using Leporati's criteria [3], highlighted some clinico-pathological differences between IgG4-RH arising in males and females, partially anticipating our results [25]. As a whole, these data elicit a reconsideration of the boundaries of IgG4-RH. In particular, the role of the absolute number of IgG4+ plasma cells and/or of the IgG4+/IgG+ ratio as the sole histopathological criterion to establish the diagnosis should possibly be revised. In fact, one could speculate that abundant IgG4-containing plasma cells in the pituitary gland are a feature of conventional lymphocytic hypophysitis that occurs in young women who have other autoimmune disorders and no features of IgG4-RD. In this view, our analysis suggests that the diagnosis of IgG4-RD should be cautious in the pituitary gland and recommends that it should only be made conclusively when other manifestations are present, such as involvement of other organs and/or elevated serum IgG4.

We think that these preliminary and retrospective considerations may shed new light on this rare disease. A prospective, multicenter, study on new cases of IgG4-RH including the thorough clinical, serological, histopathological, and immunohistochemical analysis of male and female patients is advisable to get a deeper insight into this topic.

Author's contribution Silvia Uccella conceived and designed the study, and wrote, edited, and reviewed the manuscript.

Cristina Amaglio researched and analyzed data, and wrote, edited, and reviewed the manuscript.

Jean-Philippe Brouland, Eleonora Bianconi, Silvia Ippolito, Mahmoud Messerer, and Nathalie Rouiller researched and analyzed data, edited, and reviewed the manuscript.

Maria Laura Tanda and Fausto Sessa edited and reviewed the manuscript.

Stefano La Rosa conceived, edited, and reviewed the manuscript.

All authors gave final approval for publication.

Silvia Uccella takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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