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Mikulicz's Disease with hypophysitis — a new IgG4-mediated disorder

Choroba Mikulicza-Radeckiego z zapaleniem przysadki — nowe zaburzenie związane z IgG4

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Abstract

Introduction: We present a case of Mikulicz's Disease with hypophysitis. This is a rare clinical association as part of the group of IgG4-related diseases, a group of disorders which can have multiorgan involvement.

Methods: A 55-year-old male patient was diagnosed with Mikulicz's disease. He was treated with oral steroids for six months with complete resolution. After two years the patient presented with fatigue, generalised weakness, and weight loss of 11 kg over six months. On evaluation he was found to have panhypopituitarism. MRI pituitary revealed homogeneously enlarged, well enhancing pituitary with thickening of the stalk. Serum IgG4 levels were significantly elevated. The patient was treated with methyl prednisolone pulse therapy followed by oral steroids for three months. He developed diabetes insipidus after starting steroid therapy. There was a significant resolution in the enlargement of the pituitary and stalk thickening at three months.

Results: The clinical, biochemical, and radiological findings of hypophysitis associated with Mikulicz's disease are presented with a brief review of literature.

Conclusions: IgG4-related diseases are rare and have recently been recognised as a cause of hypophysitis. They can have multiorgan involvement. A high index of suspicion is required for clinching this rare diagnosis, which can be confirmed by measurement of serum levels of IgG4. Steroid therapy can reverse the inflammatory changes in IgG4 hypophysitis. **(Endokrynol Pol 2016; 67 (6): 622–626)**

Key words: *IgG4; hypophysitis; Mikulicz's disease*

Streszczenie

Wstęp: W pracy przedstawiono przypadek choroby Mikulicza-Radeckiego z zapaleniem przysadki. Jest to rzadko występujące połączenie zaburzeń należących do grupy chorób związanych z IgG4, które mogą obejmować wiele narządów.

Metody: U mężczyzny w wieku 55 lat rozpoznano chorobę Mikulicza-Radeckiego. Stosowano doustne steroidy przez 6 miesięcy, uzyskując całkowite ustąpienie choroby. Po 2 latach chory zaczął odczuwać zmęczenie i ogólne osłabienie, a ponadto w ciągu 6 miesięcy schudł 11 kg. Badanie wykazało wielohormonalną niedoczynność przysadki. Badanie rezonansu magnetycznego przysadki uwidoczniło równomiernie powiększoną, ulegającą wzmocnieniu po podaniu kontrastu, z pogrubioną szypułą. Stężenie IgG4 w surowicy było istotnie podwyższone. U pacjenta zastosowano najpierw terapię pulsacyjną metylprednizolonem, a następnie 3-miesięczne leczenie steroidami podawanymi doustnie. Po rozpoczęciu leczenia steroidami u chorego rozwinęła się moczówka prosta. Po 3 miesiącach nastąpiło istotne zmniejszenie powiększonej przysadki i pogrubionej szypuły.

Wyniki: Przedstawiono kliniczne, biochemiczne i radiologiczne objawy niedoczynności przysadki związanej z chorobą Mikulicza-Radeckiego oraz krótki przegląd literatury.

Wnioski: Choroby związane z IgG4 występują rzadko. W ostatnim czasie wykazano, że mogą powodują one niedoczynność przysadki. Mogą one obejmować wiele narządów. Rozpoznanie tej rzadkiej choroby można potwierdzić, oznaczając stężenie IgG4 w surowicy. Można potwierdzić diagnozę, mierząc stężenie IgG4 w surowicy. Leczenie steroidami może spowodować ustąpienie zmian zapalnych z niedoczynności przysadki związanej z IgG4. **(Endokrynol Pol 2016; 67 (6): 622–626)**

Słowa kluczowe: *IgG4; niedoczynność przysadki; choroba Mikulicza-Radeckiego*

Introduction

Immunoglobulin G4 (IgG4)-related diseases or IgG4-positive multiorgan lymphoproliferative syndrome is characterised by dense infiltration of IgG4-positive plasma cells (> 50% of infiltrated IgG-positive cells) into multiple organs or tissues in association with increased serum levels of IgG4 (> 135 mg/dL) [1–2].

The clinical spectrum extends from Mikulicz's disease (MD) to autoimmune pancreatitis and hypophysitis.

Mikulicz's disease is an autoimmune condition characterised by symmetrical and persistently enlarged lacrimal, salivary, and submandibular glands. It was considered as a subtype of Sjögren syndrome for a long time, but negative anti-Ro and La antibodies,

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Table I. *Hormonal profile*
Tabela I. *Profil hormonalny*

Investigation	Before Treatment	After Treatment at 3 Months
Free T4 (0.8–1.8 ng/dL)	0.39	0.928
Thyroid Stimulating Hormone (0.35–5.5 ulU/mL)	0.083	3.28
Prolactin (5–25 ng/mL)	49.04	14.97
Cortisol (5–25 ugm/dL)	0.77	1.2
ACTH (5–20 pg/mL)	12.3	–*
Follicle Stimulation Hormone (2.5 –10 mIU/mL)	0.8	–*
Luteinizing Hormone (2.5–10 mIU/mL)	0.51	–*
Testosterone (4–11 ng/mL)	0.03	3.35
IGF 1(81–238 ng/mL)	32	–*
Serum IgG4 (3–200 mg/dL)	800	402
Fasting Plasma Glucose (60–100 mg/dL)	93	86
Serum Osmolality (275–295 mOsm/Kg)	304	294
Urine Osmolality (300–900 mOsm/Kg)	98	562

*Not Repeated
Hormonal evaluation was done 3 months after therapy. He was on thyroxine 100 ugms/day, prednisolone 5 mg/day, T. desmopressin 0.1 mg TDS, and injection testosterone enanthate 250 mg intramuscular (3 weeks after the dose). Prednisolone was omitted 24 hours before evaluation.

high serum levels of IgG4, and an infiltration of IgG4-positive cells within the salivary gland distinguish it from Sjögren syndrome.

Herein we report a case of a 55-year-old man with MD, presenting with hypophysitis two years later.

Case report

A 55-year-old man without any previous medical disorders developed dry mouth, dry eyes, and bilateral submandibular and parotid gland swelling in 2012. He was evaluated for Sjögren's syndrome. His serum anti-Ro and -La antibodies were negative. The diagnosis of Mikulicz's disease was considered by exclusion and he was started on oral prednisolone 60 mg/day, which was gradually tapered over a period of six months. The patient had complete resolution of the parotid, and the submandibular swellings and dryness of the eyes improved.

He was asymptomatic for the next two years, after which he presented again with generalised weakness, malaise, fatigue, and weight loss of approximately 11 kg over six months. His vitals were stable and the systemic examination was unremarkable.

His routine investigations (haemogram, renal function tests, electrolytes, liver function tests, calcium profile) were normal. On hormonal evaluation, he was found to have secondary hypothyroidism, hypocortisolism, and hypogonadism suggestive of panhypopituitarism. (Table I).

Magnetic Resonance Imaging (MRI) of the pituitary showed a diffuse mass lesion of size 14 × 13 × 13 mm involving the whole of the pituitary. The pituitary stalk was markedly thickened (8 × 9 mm). There was intense enhancement with gadolinium (Fig. 1). The posterior pituitary bright spot was absent. These findings were consistent with lymphocytic hypophysitis.

He was evaluated to rule out other causes of hypophysitis (Table II). His serum angiotensin-converting enzyme, alpha-fetoprotein, carcinoembryonic antigen, and anti-neutrophilic cytoplasmic antibodies were negative ruling out most of the other aetiologies. CT scan of the chest and abdomen did not show any evidence of tuberculosis or other chronic granulomatous lesions. His serum IgG4 levels were 800 mg/dL (3––200 mg/dL), suggesting IgG4-related disease involving the pituitary gland.

Injection methyl prednisolone 1 g IV OD was given for three days followed by oral prednisolone 60 mg/day, which was gradually tapered over the next three months. (3) His clinical symptoms, plasma glucose, and serum electrolytes were closely monitored. He developed polyuria and polydipsia after initiation of steroid therapy. Plasma and urine osmolality were suggestive of central diabetes insipidus (Table I). His serum Anti-Diuretic Hormone (ADH) was not estimated. He was started on L-Thyroxin 100 ugms/day, injection of testosterone 250 mg intramuscular every month, and tablet desmopressin 0.1 mg every eight hours.

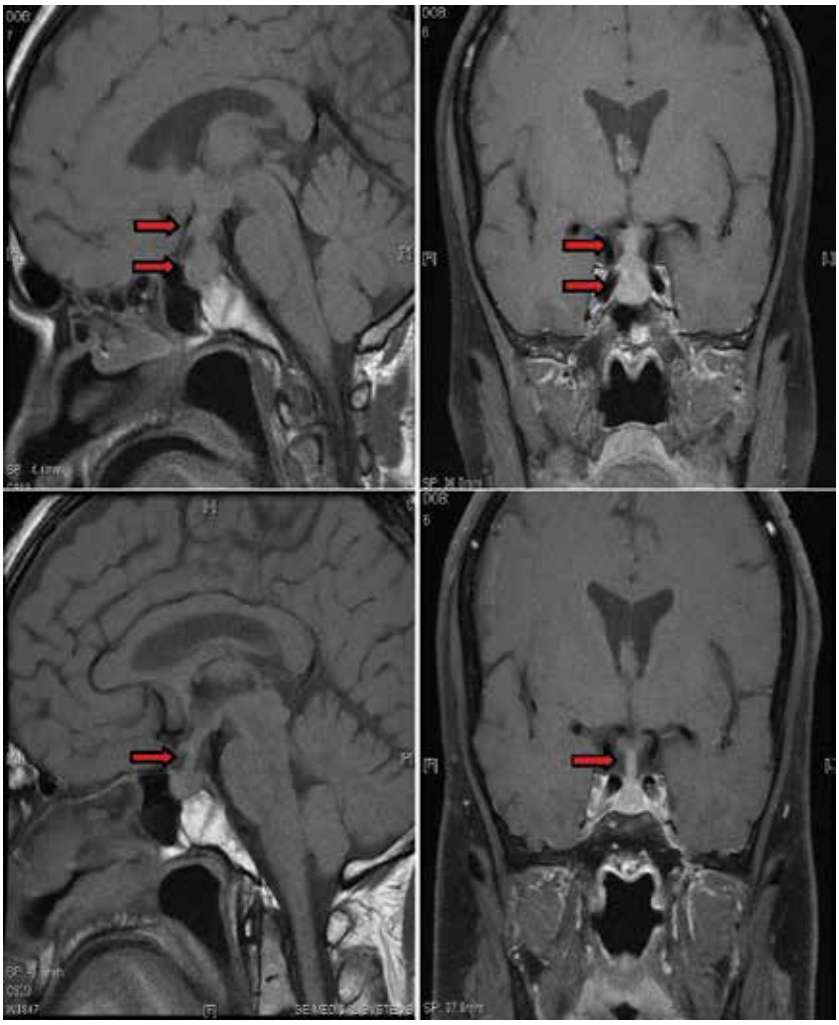

Figure 1. *Upper panel MRI pituitary shows a diffuse mass lesion of size 14 × 13 × 13 mm involving whole of the pituitary. Upper arrow shows the pituitary stalk which was markedly thickened (8 × 9 mm). Lower arrow shows the pituitary. Lower panel — Resolution of the changes after steroid therapy*

Rycina 1. *Górny panel rezonansu magnetycznego przysadki mózgowej przedstawia rozległe zmiany o rozmiarach 14 × 13 × 13 mm zajmujące całą jej powierzchnię. Górna strzałka pokazuje znacząco pogrubiony lejek (8 × 9 mm), zaś dolna przysadkę mózgową. Dolny panel przedstawia rozwój zmian po terapii steroidowej*

At three months, the pituitary imaging showed a dramatic reduction in the pituitary swelling. The gland measured 10 × 8.6 × 12.7 mm with a stalk of 5.6 × 3.9 mm. The posterior pituitary bright spot was absent (Fig. 1)

A reduction of the serum levels of IgG4 was noted (Table I). On hormonal evaluation, his pituitary functions showed no recovery, and currently he is adequately supplemented with thyroxin, prednisolone, testosterone, and desmopressin.

Table II. ***Differential diagnosis***
Tabela II. ***Rozpoznanie różnicowe***

Lymphocytic Hypophysitis
Sarcoidosis
Tuberculosis
Wegener's Granulomatosis
Germinoma
Pituitary Adenoma
Langerhans Cell Histiocytosis

Discussion

We report an extremely rare case of a recently recognised entity, IgG4-related immune hypophysitis with panhypopituitarism complicating Mikulicz's disease. To our knowledge, there have been only 29 such cases reported so far [4]. The first case of IgG4-related hypophysitis was reported in Japan in the year 2000 [5].

Table III. *Criteria to diagnose IgG4-related hypophysitis [9]*
Tabela III. *Kryteria diagnostyczne niedoczynności przysadki związanej z IgG4 [9]*

Criteria	
1	Pituitary histopathology mononuclear infiltration of the pituitary gland, rich in lymphocytes and plasma cells, with more than 10 IgG4-positive cells per high-power field
2	Pituitary MRI: Sellar mass and/or thickened pituitary stalk
3	Biopsy-proven involvement in other organs: Association with IgG4-positive lesions in other organs
4	Serology: Increased serum IgG4 (> 140 mg/dL)
5	Response to glucocorticoids: Shrinkage of the pituitary mass and symptom improvement with steroids
Diagnosis of IgG4-related hypophysitis is established when any of the following is fulfilled: **Criterion 1 OR Criteria 2 and 3 OR Criteria 2, 4, and 5**	

The disease usually affects middle-aged or elderly males. The male-to-female ratio is 2.9:1 [6]. Serum IgG4 measured before giving steroids is much higher than that following steroids, as shown by Caputo et al. [7].

The spectrum of IgG4-related disorders is wide. It can manifest as Mikulicz's disease, autoimmune pancreatitis, interstitial pneumonitis, retroperitoneal fibrosis, interstitial nephritis, pachymeningitis, and as inflammatory pseudotumours involving the orbits and lungs [1, 2]. These manifestations can occur before hypophysitis. Multiorgan involvement is a feature noted throughout the clinical course of IgG4-related diseases.

A dense infiltration of IgG4-positive plasma cells in various affected organs is a characteristic finding. The exact trigger for IgG4 elevation has not been established. Conflicting reports have implicated Th1 cells and Th2 cells in disease pathophysiology [8]. Within the organs, increased CD4-positive T cells lead to activation of innate immune cells, which secrete cytokines and interleukins. This perpetuates the inflammatory response and leads to fibrosis.

In the review by Bando et al. [4] only 14% of the patients solely exhibited hypophysitis, which was diagnosed by histopathology. In 2011 Leporati et al. [9] suggested five criteria to diagnose IgG4-related hypophysitis (Table III).

Based on criteria 2, 4, and 5 we established the diagnosis of IgG4-related hypophysitis in our patient. The MRI findings in most of the patients with IgG4-related hypophysitis are similar to those observed with other causes of hypophysitis. According to previous case reports, imaging in IgG4-related hypophysitis may present as a thickening and mass of pituitary stalk or pituitary gland [10–12].

Hypopituitarism is a well-known result of hypophysitis; however, Hattori et al. have reported a case with all hormonal axes preserved [13].

Almost all cases of IgG4-related hypophysitis responded well to glucocorticoid therapy. Although methylprednisolone pulse therapy was used initially, oral prednisolone therapy is also effective. The initial dose of prednisolone is 0.6 mg/kg for 2–4 weeks, which is then tapered by 5 mg every 1–2 weeks for 2–3 months to determine a maintenance dose (2.5–5 mg/d).

We gave our patient pulse therapy with a hope of recovering anterior and posterior pituitary functions as seen in other studies [14, 15]. However, in our patient at three months the endocrine axes did not recover.

Caputo et al. reported relapse in a case of IgG4-related hypophysitis, after treatment with a high dose of prednisolone, who was then successfully treated with azathioprine [16].

Conclusions

IgG4-related diseases are rare and were recently recognised as a cause of hypophysitis. A high index of suspicion is required for clinching this rare diagnosis. Multiorgan involvement should lead to the consideration of IgG4 diseases, which can be confirmed with serum IgG4 levels. Regular follow-up is important to pick up any new findings as early as possible.

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