Research and Review Insights

Mini Review

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Endocrine involvement in granulomatosis with polyangiitis

Salem Bouomrani*, Mayada Ben Hamad, Nesrine Regaieg, Nesrine Belgacem and Safa Trabelsi

Departments of Internal Medicine, Military Hospital of Gabes, Tunisia

Abstract

Endocrine involvement during the course of GPA is exceptional, and only a few sporadic observations were reported. Thus the exact meaning of endocrinopathies associated with this vasculitis is not yet well known. Fortuitous association or specific localization of vasculitis in the endocrine glands? The purpose of this mini-review is to study the endocrine involvement in granulomatosis with polyangeiitis and to discuss its possible pathogenic mechanisms.

Introduction

Granulomatosis with PolyAngiitis (GPA), formerly known as Wegener's granulomatosis, is a necrotizing vasculitis of small- and medium-sized vessels associating diffuse inflammation of the vascular wall and peri- and extra-vascular granulomatosis. In its generalised/systemic form, the GPA associates an ear, nose and throat (ENT), pulmonary and renal involvement with typically a rapidly progressive necrotizing glomerulonephritis with extracapillary crescents, while the absence of renal damage at the time of diagnosis defines the limited forms of GPA whose prognosis is better [1,2].

Antineutrophil cytoplasmic antibodies (ANCA) type cytoplasmic (c-ANCA) with specificity for proteinase 3 (PR3) are of great contribution to the diagnosis of this affection. They are found in more than 90% of generalised forms and about 50% of limited forms [1,2].

In the absence of treatment, GPA is a serious disease whose evolution is constantly towards death. Corticosteroids and immunosuppressors have completely changed this prognosis. Endocrine involvement associated with GPA is exceptional, and only a few sporadic observations were reported. Thus the exact meaning of endocrinopathies occurring during the course of this vasculitis is not yet well known. Fortuitous association or specific localization of vasculitis in the endocrine glands?

Endocrine disorders during GPA

Endocrine disorders during GPA are far dominated by central diabetes insipidus, of which about 10 cases are reported in the literature [3,4-6]. This is secondary to granulomatous infiltration of the posthypophysis and/or the pituitary stalk. The observation of Khalifa M *et al.* [4] confirmed this by showing an increase in the size of the pituitary gland and the infundibulum and a disappearance of the spontaneous hypersignal of the posthypophysis.

This central diabetes insipidus may be the first clinical manifestation of GPA as illustrated by the two observations of Al-Fakhraoui A *et al.* [7], and some authors estimate the frequency of pituitary involvement during the course of GPA at 1% (in the series of 819 cases of GPA of the French Vasculitis Study Group) [8] to 1.3% (in the series of 637 patients with GPA of Mayo-Clinic) [9].

In addition, some sporadic cases of other endocrine disorders were reported during GPA, namely: Pan-hypopituitarism related to a diffuse infiltration of the anterior pituitary gland by granulomas, objectified by imagery and responsible for irretrievable destruction of the gland even after adequate corticosteroid and immunosuppressive treatment [3,5,6,10].

This granulomatous hypophysitis specific for GPA may be responsible for a complete or dissociated hypophyseal insufficiency depending on the localization of the granulomas in the gland [11,12]. This specific granulomatous hypophysitis was confirmed by histological exam in rare cases, and sectoral involvement would be associated with a better prognosis because of the possibility of total functional recovery after systemic corticosteroid treatment [11,13].

Adrenal gland involvement with adrenal granulomatous vasculitis during systemic GPA (associated with pulmonary and renal involvement) which has evolved favorably after systemic corticosteroids and cyclophosphamide [14]. Similarly, a fatal adrenal localization of GPA was reported by Thomas GO *et al.* [15].

Testicular involvement both in adult and pediatric forms of GPA [16-18].

Primary hyperparathyroidism or more classically hyperparathyroidism-like presentation related to hypercalcemia by ectopic activation of vitamin D due to the activated macrophages of GPA granulomas [19,20].

Type 1 diabetes mellitus [21,22]. The Swedish study of Hemminki K. et al, based on Sweden's "multi-generation" registry, concluded that type 1 diabetes mellitus in progeny was significantly associated with 13 parental diseases including GPA with a Standardized Incidence Ratio (SIR) of 2.12 [23].

Correspondence to: Salem Bouomrani, Department of Internal Medicine, Military Hospital of Gabes, Gabes 6000, Tunisia, Tel: +00216 98977555; E-mail: salembouomrani@yahoo.fr

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A hyper-prolactinemia most often moderate and associated with pituitary involvement related to the compression of the pituitary stalk by GPA granulomas [3,6].

Thyroid disease: unusual and reported only as sporadic cases. Hypothyroidism is extremely rare during GPA: 1 case in the series of 77 patients with GPA of Cordier JF *et al.* [4,24-26]. Similarly, the frequency of hyperthyroidism during GPA is estimated at ≈1% [27].

Mechanisms of endocrine involvement during GPA

Endocrine involvement during GPA can result from two main mechanisms [4]

A direct damage of the glandular parenchyma by the granulomatous vasculitis this specific endocrine involvement of GPA was reported for the first time by Thomas GO and Lewis RJ in 1979 on the autopsy findings of a man who died after an adrenal haemorrhagic infarction complicating an active GPA. Granulomatous angiitis was objectified in adrenal and thyroid glands [15]. Since then, only a few sporadic cases confirmed histologically were reported.

Khalifa M et al [4], reported an interesting case of a 56-year-old woman with GPA in its limited form (sinusitis and pulmonary nodules) who was diagnosed with a thyroid cold nodule of 3 cm discovered on physical examination and confirmed by ultrasound and scintigraphy. The thyroid function tests were normal (TSH at 1.31 mui/l and FT4 at 12.3 pg/ml) and the anti-thyroid antibodies were negative. Puncture was inconclusive and histological examination of the subtotal thyroidectomy specimen demonstrated necrotizing vasculitis with perivascular giant cell granulomas consistent with a thyroid localization of GPA. Van Durme C et al, reported the original finding of multiple endocrine diseases with central diabetes insipidus, hypogonadotropic hypogonadism, hyperprolactinemia, and hyperthyroidism in a 48-year-old woman with GPA. The PET-scan demonstrated a simultaneous increased uptake in the pituitary gland, nostrils, left lung and the left lobe of the thyroid gland. Thyroid cytopuncture confirmed vascular inflammation and the presence of GPA-specific giant cell granulomas. Thyroid dysfunction had normalized after corticosteroid and immunosuppressive treatment of GPA [3].

An association between two autoimmune diseases

These associations are in favour of the autoimmune origin of GPA, the dys-immune character common to GPA and autoimmune endocrine diseases (Hashimoto thyroiditis, Grave's disease, type 1 diabetes mellitus,..), and a similar predisposing genetic background [21,22,28-31].

Finally, it's important to note the specific cases of antithyroid drugs (propylthiouracil (PTU) and methimazole (MMI) -induced GPA during the treatment of hyperthyroidism and in particular Grave's disease [32]. It is estimated that ≈25% of patients with PTU-treated Grave's disease will develop ANCA antibodies and some of these patients will develop true ANCA-associated systemic vasculitis including GPA [33,34].

Conclusion

Despite their apparent rarity, the endocrine involvement during granulomatosis with polyangiitis is important to know and sometimes even to look for systematically because it sign the generalized character of this vasculitis. The endocrine disorders associated with GPA are by far dominated by central diabetes insipidus, and are most often related to a specific localization of granulomatous vasculitis in the endocrine glands. More rarely it may be an association with autoimmune endocrinopathies because of the autoimmune nature of this vasculitis (ANCA-associated angeiitis).

Conflicts of interest

No conflicts.

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