

AN UNEXPECTED COMPLICATION IN THE TREATMENT OF BASEDOW'S DISEASE: ACUTE CANDIDA STOMATITIS

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Abstract: The endocrine ophthalmopathy (exophthalmia) is a quite frequent affection in Basedow's disease. In the absence of treatment, its evolution is most frequently self-limited, but there are patients who develop severe complications, a real threat for the view. The authors present the case of a patient with severe endocrine ophthalmopathy, who, upon the initiation of corticotherapy i.v., 1000 mg/day, developed angular cheilitis and acute candida stomatitis. Finally, the authors focus on the fact that, in all the cases in which a person is submitted to corticotherapy, extra - oral mycosis centres of contagion or the risk factors for the fungi infection of the oral cavity should be detected, through anamnesis and clinical examination.

Keywords: Basedow-Graves's disease, endocrine ophthalmopathy, corticotherapy, oral candidiasis

Rezumat: Oftalmopatia endocrină (exoftalmia) este o afecțiune relativ frecventă în boala Basedow. În lipsa tratamentului evoluția sa este de cele mai multe ori autolimitantă, dar există pacienți care ajung la complicații grave ce amenință vederea. Corticoterapia este tratamentul de elecție al exoftalmiei, prin ea urmărindu-se diminuarea discomfortului ocular, prevenirea desfigurării și evitarea complicațiilor ce amenință vederea. Autorii prezintă cazul unei paciente cu oftalmopatie endocrină severă, care la inițierea corticoterapiei i.v., 1000 mg/zi, a dezvoltat cheilită angulară și stomatiită acută candidozică. În final se insistă asupra faptului ca în toate cazurile în care unei persoane urmează să i se facă corticoterapie, trebuie prin anamneză și examen clinic să se detecteze eventualele focare extra-orale de micoză sau factorii de risc pentru infecția fungică a cavității orale

Cuvinte cheie: Basedow-Graves, oftalmopatie endocrină, corticoterapie, candidoză orală

INTRODUCTION

Basedow's disease has three major manifestations: hyperthyroidism (thyroid hyperfunction), diffuse goiter (volume augmentation of the thyroid gland) and exophthalmia (endocrine ophthalmopathy).

Basedow-Graves disease is self-immune and is characterized by anti-thyroid antibodies synthesis (IgG), detectable in 85% of the patients. The antibodies are fixed on the cell receptor for TSH and the result is a long term

stimulation of the thyroid function. Their acting mechanism is the same as for TSH, through adenylate - cyclase.(1)

The antibodies interaction with the cell antigen (receptor for TSH) does not produce the cell destruction, but its effect is the proliferation and the stimulation of its activity. A similar stimulating effect is held by the IgG anti-immune globulin of the lymphocyte B. The result is the blastic transformation of the lymphocyte.

The action of the anti - TSH antibodies is not submitted to feedback control through thyroid hormones whose synthesis is stimulated. The thyroid is activated, secreting thyroid hormones in excess (hyperthyroidism) and increasing its volume (goiter).

Ophthalmopathy is the result of a hypertrophy of the extra ocular muscles, the augmentation of the adipose tissue and of the intra - orbital conjunctive tissue, with inflammatory cell infiltration of the immune cells. The antibodies and the T lymphocytes recognize the antigen determinants on the extra ocular muscles or on the orbital fibroblasts, with cell-mediated, cytotoxicity, antibodies dependent or independent.(2,3)

Endocrine ophthalmopathy or Graves' ophthalmopathy sums up the ocular manifestations that accompany a thyroid dysfunction and are materialized in one or bi-lateral exophthalmia, congestion or edema of the eyelids, conjunctives, tear glands as well as ophthalmoplegia (affection of the external muscles of the ocular globes).

Graves' ophthalmopathy is very often accompanied by hyperthyroidism (77%), in 20% of the cases, the function of the thyroid is normal and 3 % of the patients with endocrine exophthalmia are hypothyroids. Exophthalmia appears usually after the installation of hyperthyroidism (in 41% of the cases); in 19% of the patients, it precedes the thyroid hyperfunction and in 20% of the cases, hyperthyroidism and ophthalmopathy occur simultaneously. Usually, the period of time between the debut of the two affections does not exceed one year or one year and a half.(4)

The alterations of the orbit components, less those of the ocular globe, are the inflammatory infiltrate (lymphocytes, mastocytes, plasmocytes), the hypertrophy of the extrinsic muscles of the eye and retroocular fat augmentation, through hydrophilic mucopolysaccharides,

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as well as through *de novo* adipogenesis.(2) The underlined transformations have self-immune mechanisms. Circulating T – cells, spread against the antigen at the level of the follicular thyroid cells, recognize the antigen epitopes, elements that are found inside the retrobulbar tissues of the orbit; among them, the fibroblasts are acting as aim-cell, as well as receptor-cell.

The treatment of oral candidiasis is done with local antimicrotics, administrated under the form of compressed tablets, dragees or solutions for oral irrigations, the first being preferred due to the long contact of the medication with the oral mucous, the patient being instructed to let the dragee melt slowly in the mouth for 3-5 minutes. The parenteral administration of fluconazole has the advantage of requiring only one dose a day, but it needs care because of its multiple undesired effects.(5,6)

Case presentation

The patient aged 38, known with Basedow for 1 year, under treatment with thiamazol 10 mg/day, is hospitalized in June 2008 for the accentuation of the ocular signs: photophobia, foreign body sensation, vague view, diplopia, lagophthalmia.

Case history

The disease started in March 2007 with loss of weight, tremor, transpirations, palpitations, diffuse goiter. The treatment with synthesis antityroids, adrenergic beta-blockers and sedatives was suggested and every three months after, euthyroidism was obtained. In September 2007, bilateral exophthalmia occurred, being more expressed in the right eye. She was a smoker (20 cigarettes a day) and in spite of her physician's insistence, she did not quit smoking.

Initial objective exam

Severe exophthalmia of the right eye (picture 1), diffuse goiter of average size, pulse 86/min. normoponderal, warm and wet teguments.

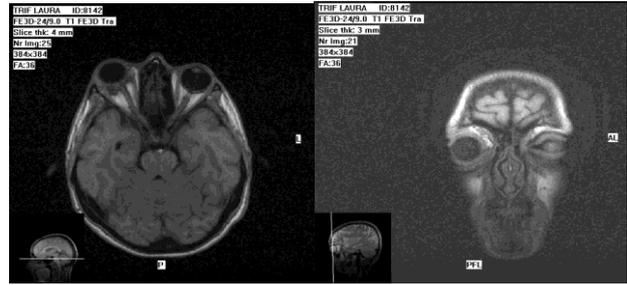
Picture no. 1. Severe exophthalmia



Picture no. 2. Acute candida stomatitis



Picture no. 3. MRI of the orbits (axial and coronal) MRI.



Para clinical examinations and hospitalization

- FT4 3,4 ng/dl < TSH 0,04U/ml, cholesterolemia-140 mg %.
- Exophthalmometry: right eye 28 mm, left eye 18 mm
- MRI of the orbits: severe exophthalmia of the right eye, through marked hypertrophy of the extra-ocular muscles, external, superior and internal right. Bilateral optic neuritis (picture 3)

The diagnosis of Basedow's disease was established, as well as hyperthyroidism and severe active endocrine ophthalmopathy.

Treatment

Taking into consideration the biological (hormonal) signs of the thyroid hyperfunction, the dose of thiamazol was increased at 20mg/day. For ophthalmopathy, the parenteral treatment with methyl – prednisolon 1000 mg i.v. / day (pulse – therapy) was started.

Subsequent evolution

The inflammatory ocular phenomena (palpebral and conjunctive edema) improved 3 days after. In the 4-th day of corticotherapy, the patient accused the sensation of burning and paresthesia at the level of the oral commisure, taste modifications and tongue pain. Objectively, rhagades occurred in the corners of the mouth, red, bright tongue, without papillae aspect tongue. The dentist examination established the diagnosis of angular cheilitis, acute erythematous stomatitis and partial edentate (picture 2).

The samples taken from the lesions, on native preparation, in the lab, emphasized hives and pseudo hives of *Candida albicans*.

The anti-thyroid and immune-suppressor treatment with corticosteroids was completed with local anti-fungi (oral use nistatine suspension 500 00ui/15ml). The solution was put in the oral cavity, 1 spoon (15ml) after meals, four times a day, for 14 days. 10 days after, the clinical signs and symptoms of acute candida stomatitis disappeared.

DISCUSSIONS

Synthesis glucose - corticoids play an important place among the therapeutic means of the Graves' ophthalmopathy. Although a larges series of immunosuppressors and immunomodulators have been introduced in the pharmacological use, cortisones have not been abandoned.(7) Strong anti-inflammatory, used in

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standard schedules of treatment, first intention medication in the treatment of the self immune affections, cortisones are still irreplaceable. They are quite well tolerated in short cures, but in long term treatments, they show significant side effects. In spite of these side reactions, the quality of life improved a lot in the patients with Graves' ophthalmopathy.(8)

One of the side effects that appear quite soon in corticotherapy, or even sooner if the patients present other associated affections, too, is candida. Its severity varies from soft forms that give the patient a certain discomfort, up to severe forms (candidemia), with lethal potential.(9)

Candida albicans is commensurable for the persons with a normal immune system, but it becomes pathogen (opportunistic germ) in the conditions in which the organism has a reduced defence capacity. Under the influence of some favouring factors, *Candida albicans* passes from the saprophyte phase in that of parasite.

Candida is a microscopic fungi belonging to yeasts. *Candida albicans* is exclusively a saprophyte of the digestive, respiratory, vaginal mucous, being always absent as pathogen from the healthy teguments. Other species can be normally met on the mucous and on the skin. 25% - 75% of the general population are healthy bearers of yeasts in the oral cavity, but only 10 – 15 % of the persons, those with reduced immunity, develop candida.

The most frequent oropharyngeal candidiasis are:

- *perlèche*: it is mostly found in edentate persons. It is localized on the labial commissures where a painful fissure can be seen, covered by a white deposit;
- angular cheilitis is manifested through erythema, edema and desquamation of the lips' commissures. It is accompanied by the sensation of tension, burning and local paresthesia;
- stomatitis (muguet): it interests the mucous of the oral cavity, as a whole or only some areas (cheeks, tongue, palate, gums). It starts by a diffuse erythema of the mucous. The interested oral mucous becomes smooth, bright and painful. Initially the tongue may be without papillae, then it is covered with small rough, white or creamy deposits, adherent at their bottom;
- chronic stomatitis (chronic muguet): acute stomatitis can become chronic, extending on the whole oral cavity; it evolves silently, but acute pains may appear because of the favouring factors such as corticotherapy;

Laboratory diagnosis for oral candidiasis is simple; using a sterile rod, a small quantity is taken from the white plaque, from an erythematous lingual plaque or from the fossa with angular candidiasis. It is sometimes necessary to proceed to a more severe curetting with the tongue pressure. From the tested material, a native preparation is done, with KOH 10% solution examined in the optic microscope with objective 10. The presence of the pseudo-filaments or of the filaments is an element of pathogenicity.

Yeasts increase rapidly in 24 hours, on specific mediums allowing the pathogen agent to be isolated and identified, as well as the appreciation of the number of colonies. Due to the fact that yeasts are considered saprophytes in the oral cavity, the mycological interpretation is done by taking into account their abundance.

The mycological exam is not a practice of routine based on the reason that the clinical diagnosis is often obvious. Although, in the difficult cases (atypical clinical aspect, necessary differential diagnosis, recurrence in spite of an adequate treatment), taking mycosis tests is necessary.

In the special case of our patient, we appreciate that the appearance of stomatitis and candida cheilitis was due to many factors (smoking, partial edentation, hypercatabolism of immunoglobulin by thyroidal hyperfunction) but the launching factor was the corticotherapy that depresses the cell-mediated immunity, as well as the serum level of immunoglobulins. Corticosteroids, in pharmacological doses, destroy the T and B circulating lymphocytes and diminish the peripheral monocytes, stating a drug immune depression. In fact, corticotherapy also diminishes the number of T and B circulating lymphocytes, without reducing the number of the B lymphocytes. Corticotherapy involves the diminishing of the mononuclear cells number, the alteration of the chemical-tactic and cytotoxic capacity of these cells, involving the lowering of their migration towards the infected areas and, as a consequence, the process of phagocytosis is also decreased, raising thus the level of toxicity for *Candida*.(10)

CONCLUSIONS

1. Oral candidiasis is a risk factor for persons with self immune affections and who are going to be submitted to an immunosuppressor treatment with corticosteroids.
2. Its incidence increases along with the glucocorticoids dose, systemically administered, with a significant risk for doses over 0,5 mg – body/day.
3. The length of the treatment with corticosteroids has an intensifying effect on the occurrence of candidiasis, even after short term administration.
4. Oral candidiasis appears precociously in the systemic corticoid therapy, in persons with affected immune status, situations in which the corticotherapy requires antimycotic co-medication.
5. In all the cases in which a person is about to attend corticotherapy, possible extra-oral mycosis centres of contagion should be detected through anamnesis and clinical examination.
6. Means of sanitary education (food hygiene, personal hygiene) and the primary and secondary prophylaxis of the opportunistic infections in patients with immune deficit, have a capital importance in preventing oral candidiasis.

REFERENCES

1. Prabhakar BS, Bahn RS, Smith TJ. Current perspective on the pathogenesis of Graves' disease and ophthalmopathy. *Endocr Rev* 2003;(24):802–835.
2. Bahn RS. Clinical review 157: pathophysiology of Graves' ophthalmopathy: the cycle of disease. *J Clin Endocrinol Metab* 2003;(88):1939–1946.
3. Gerding MN, van der Meer JW, Broenink M, Bakker O, Wiersinga WM, Prummel MF. Association of thyrotrophin receptor antibodies with the clinical features of Graves' ophthalmopathy. *Clin Endocrinol (Oxf)* 2000;(52):267–271.
4. Perros P, Crombie AL, Kendall-Taylor P. Natural history of thyroid associated ophthalmopathy. *Clin Endocrinol (Oxf)* 2000;(42):45–50.
5. Prummel MF, Bakker A, Wiersinga WM, Baldeschi L, Mourits MP, Kendall-Taylor P, Perros P, Neoh C, Dickinson AJ, Lazarus JH, Lane CM, Heufelder AE, Kahaly GJ, Pitz S, Orgiazzi J, Hullo A, Pinchera A, Marcocci C, Sartini MS, Rocchi R, Nardi M, Krassas GE. A Multi-centre study on the characteristics and treatment strategies of patients with Graves' orbitopathy: the first European Group on Graves' Orbitopathy Experience. *Eur J Endocrinol* 2003;(148):491–495.
6. Rose JG, Burkat CN, Boxrud CA. Diagnosis and management of thyroid orbitopathy. *Otolaryngol Clin North Am* 2005;(5):1043–74.
7. Bartalena L, Baldeschi A, Dickinson A, Eckstein P, Kendall-Taylor, Marcocci C, Mourits M, Perros P, Boboridis K, Boschi A. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO *Eur J Endocrinol* 2008;(3):273-285.
8. Yeatts RP. Quality of life in patients with Graves' ophthalmopathy. *Trans Am Ophthalmol Soc* 2005;(103):368-411.
9. Covaciu Claudia. Modificări ale reactivității imunocelulare la infecția cu *Candida albicans*, induse de corticoterapie. *DermatoVenerol. Bucuresti*, 2006;(2):93-95.
10. Mavor AL, Thewes S, Hube B. Systemic fungal infections caused by *Candida* species: epidemiology, infection process and virulence attributes. *Curr Drug Targets* 2005;(6):863-874