THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

EUTHYROID GRAVES'S OPTHALMOPATHY. CASE REPORT AND GENERAL CONSIDERATIONS

Rucsandra DANCIULESCU MIULESCU[1,2], Rodica DOROŞ[2] and Constantin DUMITRACHE[3]

[1] "Carol Davila" University of Medicine and Pharmacy, Bucharest
[2] "N.C.Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest
[3] Gral Medical Center, Bucharest

Corresponding author: Rucsandra Elena Dănciulescu Miulescu, 5-7 Ion Movila Street, Bucharest, District 2, Postal Code 11420, Tel: 0040748134500, Fax: 004021/2105575; rucsandra_m@yahoo.com

Accepted May 21, 2020

Graves' ophthalmopathy is an autoimmune chronic inflammatory disorder of the orbit and periorbital tissues that classically occurs in patients with Graves' hyperthyroidism, but in 5-10% occurs in patient with euthyroid status or hypothyroid chronic autoimmune thyroiditis. We describe the clinical case of 51-year-old Caucasian women presented with a 4-month history of eye pain, photophobia, proptosis, erythema of the conjunctivae. She had no symptoms of thyroid dysfunction and she was clinically euthyroid and had no palpable goitre. She denied any personal or family history of thyroid disease and she is a smoker. The thyroid antibodies: antibodies against the thyroid peroxidase and the thyrotropin receptor showed elevated levels with normal thyroid function. Computer tomographic scanning reveals hypertrophy of the body of the orbital muscles: upper right, medial right and lower right, bilaterally but no malignant orbital pathology. Glucocorticoid therapy with a favourable evolution was initiated and it was recommended to stop smoking. Periodic ophthalmological as well as endocrinological evaluation was required because any endocrine dysfunction can aggravate the evolution of Graves' ophthalmopathy.

Keywords: Graves's ophthalmopathy, euthyroid status, smoking.

INTRODUCTION

Graves's ophthalmopathy is an autoimmune chronic inflammatory disorder of the orbit and periorbital tissues probably due to the presence of autoantibodies in the orbital tissues. The disease classically occurs in patients with Graves' hyperthyroidism but in 5–10% occurs in patient with euthyroid status or hypothyroid chronic autoimmune thyroiditis[1].

The hallmark of affection is increase size of extraocular muscles and retro bulbar fat which have been associated with excessive glycosaminoglycan and inflammatory cytokines secretion. Orbital fibroblast plays a key role in the pathogenesis of Graves' ophthalmopathy. Hypoxia enhance glycosaminoglycan production and protein synthesis in extraocular muscle fibroblasts and extraocular muscle fibroblasts are capable of secreting inflammatory cytokines[2]. The common manifestation of the disease is proptosis, upper eyelid retraction, swelling, erythema of the periocular tissues, lids and conjunctivae[3].

The diagnosis of Graves' ophthalmopathy is supported by the presence of one or more thyroid-specific antibodies: antibodies against the thyroid peroxidase (TPOAbs) and the thyrotropin receptor (TRAbs). The occurrence of Graves' ophthalmopathy in the absence of thyroid antibodies has been rarely reported[1, 4]. In an article published in 2012 by San MN and co-workers in *Medical Clinics of North America,* entitled "The Evaluation and Treatment of Graves' Ophthalmopathy" the authors specify the immunopathogenesis of Graves' ophthalmopathy: "*Circulating autoantibodies directed against the thyrotropin receptor activate this receptor on orbital fibroblasts; this results in their increased secretion of hyaluronic acid, and the differentiation of a subset into mature adipocytes. In addition, activated T cells infiltrate the orbit, interact with autoreactive B cells, and secrete proinflammatory cytokines. These cellular changes lead to the extraocular muscle enlargement, orbital adipose tissue expansion, and orbital inflammation characteristic of the disease*"[3].

The management of Graves' ophthalmopathy therapy involves the administration of immunomodulators (steroidal and nonsteroidal therapy), orbital radiotherapy, surgery. The steroidal immunomodulators (glucocorticoids) treatment is recommended in moderate to severe forms. Several studies have shown that intravenous therapy is associated with better response than oral glucocorticoids[5, 6]. Nonsteroidal immunomodulators such as cyclosporine or azathioprine have been studied in an attempt to identify treatment that can supplant the need for high doses of glucocorticoids or in oral glucocorticoids resistant patients[7, 8, 9]. Agents that neutralize cytokine-induced inflammation or production of hyaluronic acid are attractive potential treatments for Graves' ophthalmopathy[10, 11, 12, 13, 14]. Orbital radiotherapy is recommended in selected active mild and moderate to severe Graves' ophthalmopathy and previous studies have shown a positive impact of radiotherapy on ocular motility[15]. The surgical treatment of Graves' ophthalmopathy includes orbital decompression, extraocular muscle surgery and eyelid procedures in order to improving the function and appearance[3,16].

CASE REPORT

A 51-year-old Caucasian women presented with a 4-month history of eye pain, photophobia, proptosis, erythema of the conjunctivae. She had no symptoms of thyroid dysfunction and she was clinically euthyroid and had no palpable goiter. She denied any personal or family history of thyroid disease and is smoker.

Investigation. Thyroid stimulating hormone (TSH): 2.319 ulU/mL (reference range: 0.55–4.78), free thyroxine (FT4): 1.30 ng/dL (reference range: 0.89–1.76). TRAbs and TPOAbs were positive: TRAbs–33.74 UI/L (measurement was performed by electro chemiluminescent, clinical decision limit: 1.75UI/L, 96% sensitivity, 99% specificity for detection of Graves' disease), TPOAbs: > 1300 UI/mL (reference range < 60). TSH, FT4 and TPOAbs were performed by direct chemiluminescence. Thyroid ultrasound scan showed no evidence of structural alterations. Computer tomographic scanning reveals hypertrophy of the orbital muscles: upper right, medial right and lower right, bilaterally but no malignant orbital pathology.

Symptoms appeared in March 2020 and following an ophthalmological examination it was recommended topical eye treatments. Signs and symptoms did not improve secondary to topical therapy and the patient was in May recommended secondary to an on-line consultation (due to restriction of eye examinations generated by the COVID-19 pandemic) initiating corticosteroid therapy-methylprednisolone 32 mg/day 2 weeks followed by progressive dose reduction. The patient was reassessed in June 2020. Exophthalmometry were performed to quantify proptosis in June (right eye 23 mm and left eye 21.5 mm) and July 2020 (right eye 22 mm and left eye 21mm) after 4 weeks and 6 weeks of treatment with glucocorticoid. Images of the patient's appearance prior to the initiation of corticotherapy later at 4 and 6 weeks are presented in Figures 1, 2, 3.

Figure 1. Patient with Graves' ophthalmopathy prior to initiation of glucocorticoid treatment.

Figure 2. Patient after 4 weeks of treatment with glucocorticoid.

Figure 3. Patient after 6 weeks of treatment with glucocorticoid.

DISCUSSIONS

Several risk factors have been identified from the development or progression of Graves' ophthalmopathy such as: genetics, ancestry, gender, thyroid dysfunction, mechanical factors, smoking[3].

Optimum management of euthyroid Graves' ophthalmopathy requires a partnership between the ophthalmologist and endocrinologist because patients can eventually develop thyroid dysfunction[1, 17]. Previous studies and case reports have highlighted that some patients develop thyroid dysfunction after the initial presentation with eye disease that influence the prognosis of the affection[1, 18, 19]. The results of a study published in 2000 by Koo DH *et al.* highlighted that 25% of patients with euthyroid Graves' ophthalmopathy develop hyperthyroidism within 15 to 45 months of follow-up underpinning the need for long-term follow-up[17]. In a retrospective study Suzuki N and co-workers evaluated 58 patients diagnosed with euthyroid Graves' ophthalmopathy of which 14 patients (24.1%) developed hyperthyroidism and 2 (3.4%) patients developed hypothyroidism[19].

Smoking is one of the strongest risk factors found to be associated with progression of Graves' ophthalmopathy. The association between smoking and Graves' ophthalmopathy was first described in 1987 by Hagg E. and Asplund K.[20]. Subsequently numerous studies have tried to explain the association between smoking and thyroid-associated ophthalmopathy. Several mechanisms have been proposed:

- smoking induces hypoxia which stimulates the orbital fibroblasts to synthesize glycosaminoglycans which exacerbates extra ocular muscle oedema[21];
- hypoxia affects adipocytokine production in orbital fibroblasts (leptin and monocyte chemotactic protein-1)[2];
- cigarette smoke extract increased adipogenesis in an *in vitro* model of Graves' ophthalmopathy[22].

The results of a prospectively study published in 1996 by Pfeishifter J and Zinger R in which they evaluated 253 patients with Graves' hyperthyroidism showed that smoking was associated with a 1.3-fold increased incidence of clinically relevant ophthalmopathy and with 2.6-fold and 3.1-fold increases in the incidence of proptosis and diplopia[23]. In a systematic review published in 2007 by Thornton J *et al.,* including 15 studies that followed the epidemiological evidence for a causal association between smoking and thyroid eye disease (TED), the authors concluded that "*Current-smokers were also more likely to experience disease progression or poorer outcome of treatment. Patients with Graves' disease and the general public should be educated about the risk of smoking and TED. These findings suggest that patients with Graves' disease or TED who are smokers should be given effective support to stop smoking*".[24] Cigarette smoking attenuates the treatment effect of Graves' ophthalmopathy (systemic glucocorticoids and orbital radiotherapy), which is why it is recommended smoking cessation of any patient with this affection[25].

CONCLUSION

Graves' ophthalmopathy is a disorder of the orbit and periorbital tissues that classically occurs in patients with Graves' hyperthyroidism but in 5–10% occurs in patient with euthyroid status or hypothyroid chronic autoimmune thyroiditis. We have surveyed the clinical features of 51-year-old Caucasian women with Graves' ophthalmopathy and euthyroid status. Due to the pandemic with COVID 19 access to ophthalmological consultations was timed but subsequently the evolution on the glucocorticoid stake was favourable. Since smoking can lead to aggravation of the evolution of the eye condition and reduced response to the characteristic therapy it was recommended to stop smoking. Periodic ophthalmological as well as endocrinological evaluation is required because any endocrine dysfunction can aggravate the evolution of Graves' ophthalmopathy.

REFERENCES

1. Tabasum A, Khan I, Taylor P, Das G, Okosieme OE. Thyroid antibody-negative euthyroid Graves' ophthalmopathy. *Endocrinol Diabetes Metab Case Rep*, doi: 10.1530/EDM-16-0008, 2016.
2. Ling Chng C, Lai OF, Chew CSM, Peh YP, Chong SMCF, Seah LL, Khoo DHC. Hypoxia increases adipogenesis and affects adipocytokine production in orbital fibroblasts–a possible explanation of the link between smoking and Graves' ophthalmopathy. *Int J Ophtalmol*, 7(3): 403-407, 2014.
3. Stan MN, Gamity JA, Bahn RS. The Evaluation and Treatment of Graves' Ophthalmopathy. *Med Clin North Am*, 96(2): 311-328, 2012.
4. Cakir M. Euthyroid Graves' ophthalmopathy with negative autoantibodies. *Journal of the National Medical Association,* 97: 1547–1549, 2005.
5. Kahaly GJ, Pitz S, Hommel G, Dittmar M. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. *J Clin Endocrinol Metab*, 90:5234–5240, 2005.
6. Macchia PE, Bagattini M, Lupoli G, Vitale M, Vitale G, Fenzi G. High-dose intravenous corticosteroid therapy for Graves' ophthalmopathy. *J Endocrinol Invest*, 24:152–158, 2001.
7. Kahaly G, Schrezenmeir J, Krause U, Schweikert B, Meur S, Muller W, Denneraum R, Beyer J. Cyclosporin and prednisone versus prednisone in treatment of Graves' ophthalmopathy: a controlled, randomized and prospective study. *Eur J Clin Invest*, 16:415–422, 1986.
8. Prummel MF, Mourits MP, Berghout A, Krenning EP, van der Gaag R, Koornneef L, Wiersinga WM. Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. *N Engl J Med*, 321:1353–1359, 1989.
9. Perros P, Weightman DR, Crombie AL, Kendall-Taylor P. Azathioprine in the treatment of thyroid-associated ophthalmopathy. *Acta Endocrinol*, 122:8–12, 1990.
10. Bahn RS. Graves' ophthalmopathy. *N Engl J Med*, 362(8): 726-738, 2010.
11. Dinarello CA. The role of the interleukin-1–receptor antagonist in blocking inflammation mediated by interleukin-1. *N Engl J Med*, 343:732–734, 2000.
12. Durrani OM, Reuser TQ, Murray PI. Infliximab: a novel treatment for sight-threatening thyroid associated ophthalmopathy. *Orbit*, 24:117–119, 2005.
13. Paridaens D, van den Bosch WA, van der Loos TL, Krenning EP, van Hagen PM. The effect of etanercept on Graves' ophthalmopathy: a pilot study. *Eye (Lond),* 19:1286–1289, 2005.
14. Tan GH, Dutton CM, Bahn RS. Interleukin-1 (IL-1) receptor antagonist and soluble IL-1 receptor inhibit IL-1-induced glycosaminoglycan production in cultured human orbital fibroblasts from patients with Graves' ophthalmopathy. *J Clin Endocrinol Metab*, 81:449–452, 1996.
15. Bradley EA, Gower EW, Bradley DJ,Meyer DR, Cahill KV, Custer PL, Holck DE, Woog JJ. Orbital radiation for Graves ophthalmopathy: a report by the American Academy of Ophthalmology. *Ophthalmology*, 115: 398–409, 2008.
16. Boulos PR, Hardy I. Thyroid-associated orbitopathy: a clinicopathologic and therapeutic review. *Curr Opin Ophthalmol*, 15: 389–400, 2004.
17. Khoo DH, Eng PH, Ho SC, Tai ES, Morgenthaler NG, Seah LL, Fong KS, Chee SP, Choo CT, Aw SE. Graves' ophthalmopathy in the absence of elevated free thyroxine and triiodothyronine levels: prevalence, natural history, and thyrotropin receptor antibody levels. *Thyroid*, 10: 1093–1100, 2000.
18. Wiersinga WM, Smit T, van der Gaag R, Koornneef L. Temporal relationship between onset of Graves' ophthalmopathy and onset of thyroidal Graves' disease. *J Endocrinol Invest*, 11(8): 615–619, 1988.
19. Suzuki N, Noh JY, Kameda T, Yoshihara A, Ohye H, Suzuki M, Matsumoto M, Kunii Y, Iwaku K, Watanabe N, Mukasa K, Kozaki A, Inoue T, Suigo K, Ito K. Clinical course of thyroid function and thyroid associated-ophthalmopathy in patients with euthyroid Graves' disease. *Clin Ophthalmol*, 12: 739-746, 2018.
20. Hagg E, Asplund K. Is endocrine ophthalmopathy related to smoking? *Br Med J*, 295: 634–635, 1987.
21. Metcalfe RA, Weetman AP. Stimulation of extraocular muscle fibroblasts by cytokines and hypoxia: Possible role in thyroid associated ophthalmopathy. *Clin Endocrinol (Oxf),* 40(1): 67–72, 1994.
22. Cawood TJ, Moriarty P, O'Farrelly C. O'Shea D. Smoking and thyroid-associated ophthalmopathy: A novel explanation of the biological link. *J Clin Endocrinol Metab*, 92(1): 59–64, 2007.
23. Pfeilschifter J, Ziegler R. Smoking and endocrine ophthalmopathy: Impact of smoking severity and current vs lifetime cigarette consumption. *Clin Endocrinol (Oxf)*, 45(4): 477–481, 1996.
24. Thornton J, Kelly SP, Harrison RA, Edwards R. Cigarette smoking and thyroid eye disease: a systematic review. *Eye*, 21(9):1135–1145, 2007.
25. Hegediüs L, Brix TH, Vestergaard P. Relationship between cigarette smoking and Graves' ophthalmopathy. *J Endocrinol Invest*, 27(3): 265–271, 2004.