AMALIY VA TIBBIYOT FANLARI
ILMIY JURNALI
ISSN: 2181-3469
Jild: 03 Nashr:04 2024 yil

SCIENCE BOX

PRETIBIAL MYXEDEMA: PATHOGENETIC FEATURES AND CLINICAL ASPECTS

Akhmedov Nodir Ilkhomovich
Assistant of the department of endocrinology, Bukhara State Medical Institute named after Abu Ali ibn Sino

Annotation. *Pretibial myxedema (PM), or thyroid dermopathy, is a rare extrathyroidal manifestation of Graves' disease (GD). The condition is accompanied by mucinous skin changes, mainly in the area of the anterior surface of the leg. Severe forms can lead to lymphatic congestion and disability. It is assumed that long-term and intense autoimmune aggression is necessary for the manifestation of PM. However, data on the role of antibodies to the TSH receptor in the genesis of PM are very controversial. Recently, indications have emerged that IGF-1 receptors are involved in the pathogenesis of this manifestation of HD. In typical cases, PM is localized on the anterior and lateral surfaces of both legs and has a diffuse, tumor, plaque-like or elephantine form. Early diagnosis comes down to regular preventive examination of the pretibial area. A diagnostic biopsy is indicated only in doubtful cases. Maintaining euthyroidism, quitting smoking, avoiding injury, and wearing tight shoes that impair lymphatic drainage can reduce the risk of developing PM in patients with GD. Currently, there are no generally accepted clinical guidelines for the diagnosis and treatment of thyroid dermopathy. This review provides the latest information on the etiopathogenesis of PM and the management of patients with this pathology.*

Key words: *pretibial myxedema, thyroid dermopathy, Graves' disease.*

Introduction. Pretibial myxedema (PM), or thyroid dermopathy, is one of the extrathyroid manifestations of Graves' disease (along with endocrine ophthalmopathy and thyroid acropathy). The prevalence of PM among patients with Graves' disease (GD) ranges from 0.5 to 4.3%. Thyroid dermopathy is often combined with endocrine ophthalmopathy and rarely with acropathy. It is currently believed that cellular immunological, molecular, and environmental factors are involved in the pathogenesis of PM. It is assumed that antibodies to thyroid-stimulating hormone receptors (AT-rTSH) and insulin-like growth factor-1 (AT-rIGF-1) are involved in the process.

The specific location of thyroid dermopathy in the lower leg area (PM developed in the lower leg area even on the surface of skin transplanted from another area) also raises a number of questions. One theory explains this localization by the heterogeneity of fibroblasts, while the other connects the location of the pathological process with mechanical factors.

The course and outcome of PM depend not only on the treatment, but also on the initial severity of the process. More than 1/2 of patients with a mild form of PM develop complete or partial remission, while the severe form is difficult to treat. Early recognition of signs of PM is essential to prevent severe lymphatic obstruction. All patients with endocrine ophthalmopathy should be carefully assessed for PM.

Pathogenetic mechanisms of development of pretibial myxedema. The role of TSH and IGF-1 receptors

The role of activating AT-rTSH in the development of thyrotoxicosis in HD has been well studied. However, the pathogenesis of extrathyroidal manifestations of the disease appears to be more complex.

Recent studies have demonstrated a complex cascade of reactions involved in the activation of the autoimmune process in the skin tissue of the pretibial region.

It is assumed that the pathogenetic processes in tissues with PM and endocrine ophthalmopathy are similar. In both cases, the differentiation and proliferation of fibroblasts and the synthesis of glycosaminoglycans (hyaluronic acid and chondroitin sulfate) play a key role.

The thyroid-stimulating hormone receptor (sTSH), the main autoantigen in HD, is a G-protein coupled molecule with a large extracellular domain. It is he who plays a key role in the pathogenesis of PM. This theory is supported by the high titer of AT-rTSH in the blood of almost all patients with PM, including those with euthyroidism. In patients with thyroid dermopathy (but not in healthy individuals), extracellular sites of the TSH receptor are present on fibroblasts of the skin of the pretibial area. However, there is evidence of the presence of rTSH in the skin of the shoulder, buttocks and foreskin in healthy people.

Recently, the attention of scientists has shifted from rTSH to the IGF-1 receptor as the main autoantigen in the development of extrathyroidal manifestations of HD. Retrobulbar fibroblasts contain an increased number of rIGF-1 receptors, which correlates with the activity of endocrine ophthalmopathy. It has been shown in cell cultures that stimulation of fibroblasts with IGF-1 significantly increases their secretion of hyaluronic acid. Abs to the IGF-1 receptor have not been detected at the moment.

Since neither TSH nor M22 monoclonal antibodies activate phosphorylation of the IGF-1 receptor, it is assumed that interaction of the two receptors is responsible. In particular, when stimulating fibroblasts obtained from patients with endocrine ophthalmopathy with low doses of M22, rTSH modulates the activity of rIGF-1, which enhances the secretion of hyaluronic acid (Fig. 1).

Further study of etiopathogenesis, identification of predictors and risk factors for PM, as well as the development of early diagnostic methods will help reduce the risk of PM and the development of its severe forms.

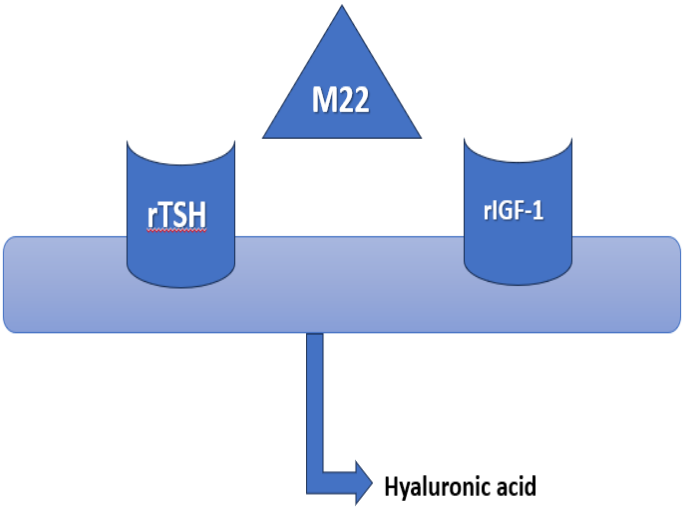

Fig. 1. Interaction between TSH and IGF-1 receptors.

AMALIY VA TIBBIYOT FANLARI
ILMIY JURNALI
ISSN: 2181-3469
Jild: 03 Nashr:04 2024 yil

The specific location of thyroid dermopathy is most likely due to mechanical factors such as trauma and slow lymphatic drainage. Poor lymphatic drainage is hypothesized to increase the half-life of cytokines. Trauma can provoke the activation of fibroblasts and their active production of glycosaminoglycans. Cases of thyroid dermopathy of the forearm, shoulder, palm, upper back and neck after injuries to the corresponding areas of the body have been described.

When skin was transplanted from the pretibial area, myxedema developed both at the graft sites and in the lower leg area, which also supports the mechanical theory.

The theory of fibroblast heterogeneity in different areas of the skin is currently considered less substantiated.

Smoking is considered a high risk factor for both endocrine ophthalmopathy and PM. It is assumed that smoking aggravates autoimmune processes in tissues.

Prevalence, clinical picture and course features

The prevalence of PM ranges from 0.5–4.3% among patients with Graves' disease and mild to moderate endocrine ophthalmopathy (EO); among persons with EO requiring orbital decompression and/or accompanied by optic neuropathy, it reaches 13%.

In typical cases, patches of purple, yellow, and brown color appear on the skin of both legs (Fig. 2). When hyperkeratosis joins, the color may change. The most common plaque form is characterized by extensive foci of infiltrated edematous tissue. The diffuse form is characterized by pastosity of the legs without the formation of a pit when pressed. In rare cases of elephantiasis, severe lymphostasis and nodular tissue degeneration occur. Cases of thyroid dermopathy of the forearm, shoulder, palm, upper back and neck have been described after previous trauma, as well as in places of scars and burns. Ulcerations are not typical for PM. In rare cases, the condition is accompanied by burning and itching. PM often occurs after the manifestation of endocrine ophthalmopathy, during the first 2 years after the diagnosis of hyperthyroidism, but cases of PM appearing many years after the onset of HD have been described.

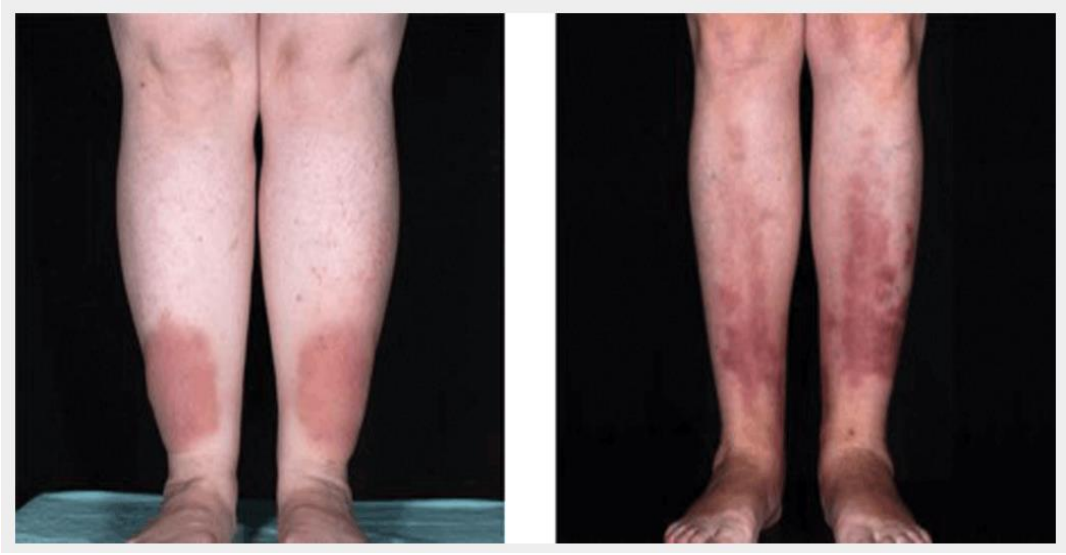

Fig 2. Plaque-like and diffuse forms of pretibial myxedema.

Diagnosis of pretibial myxedema

Diagnosis of PM is usually not difficult. When PM is combined with EO, AT-rTSH titers are significantly higher than in the absence of these manifestations of HD. The absence of AT-rTSH in the

blood serum makes the diagnosis of PM unlikely. This may indicate a more severe course of the autoimmune process in individuals with dermatological extrathyroidal manifestations of GD, which is why PM can serve as a signal for more active detection and treatment of EO. In doubtful cases, a skin biopsy is performed to confirm the diagnosis.

When stained with hematoxylin and eosin, fragmentation of collagen fibers is visible (Fig. 3, on the color insert and in the "Additional information" section), between the bundles of which, when stained with Alcian blue and Schiff-iodic acid, accumulations of mucin can be detected. It is noteworthy that the collagen fibers of the papillary dermis retain their normal structure.

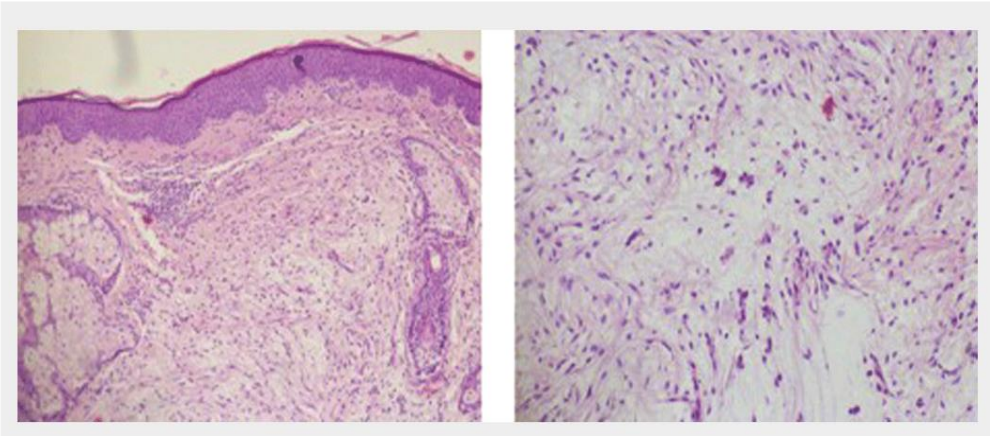

Fig 3. Histological picture of pretibial myxedema. a — hematoxylin and eosin staining, ×100; b — staining with hematoxylin and eosin, ×200.

Since severe PM is difficult to treat, identifying symptoms at an early stage is extremely important. All patients with HD, especially those with EO, should be carefully assessed for PM.

More than 1/2 of patients with a mild form of PM develop complete or partial remission. Thus, early recognition of signs of PM is fundamental to prevent severe lymphatic obstruction.

The existence of a subclinical stage of PM is assumed, the identification of which is of utmost importance for the early initiation of therapy. J. Wortsman found dense deposits of mucin in the papillary dermis in patients with GD and EO without clinical signs of thyroid dermopathy. The author concluded that mucopolysaccharide deposition is a common phenomenon in HD, and PM is a clinical manifestation of the late stages of the pathological process.

S. Shih et al. Using a digital infrared thermal imager, we detected a focal decrease in temperature in the affected area in patients with PM and in 65% of cases among patients with GD without obvious signs of thyroid dermopathy. The authors explain such changes by the accumulation of glycosaminoglycans, which disrupt heat transfer from large arteries to the skin surface. Ultrasound signs of PM were also identified - hypoechogenicity, thickening of the epidermis and dermis, and an unclear boundary between the dermis and subcutaneous tissue. There were no significant differences in ultrasound parameters between individuals with HD without PM and healthy people, which the authors attribute to the small sample of healthy individuals.

Treatment

Due to the relative rarity of PM, large randomized trials evaluating different treatments for this condition are lacking. Treatment of PM should primarily be aimed at achieving euthyroidism. It is assumed that both hyper- and hypothyroidism, resulting from conservative or radical treatment of GD, provoke the occurrence or aggravate the course of PM.

Total ablation of the thyroid gland (as a method of eliminating AT-rTSH) can serve as a preventive measure, but data on this matter are very contradictory.

Local use of glucocorticoid drugs, such as clobetasol propionate, triamcinalone acetonide, is quite effective if treatment was started within the first few months of the onset of PM. In nodular and plaque-like forms of PM, injections of corticosteroids into the affected area give a pronounced positive effect up to complete remission.

C. Lan et al. conducted a randomized trial examining different treatment regimens for pretibial myxedema with triamcinalone acetonide injections. The most effective was local administration of a solution of triamcinalone acetonide once every 7 days. There are no data on the benefit of systemic use of corticosteroids in severe forms of PM. For severe lymphostasis, decompression physiotherapy can be recommended.

Recently, there have been isolated reports of the positive effects of surgical removal of affected lesions. Since cases of PM recurrence in the area of postoperative scars and mechanical trauma have been repeatedly described previously, the use of a surgical treatment method cannot be recommended. Successful use of plasmapheresis and somatostatin analogues in PM has been reported.

A deeper understanding of the pathogenesis of extrathyroidal manifestations of GD should provide the possibility of more targeted and advanced therapy for PM. Drug candidates include rituximab, tyrosine kinase inhibitors, TSH receptor blockers and IGF-1.

Conclusion.

Data on the pathogenesis of PM are very controversial, and clinical recommendations for the management of patients with this condition are lacking. It is assumed that long-term and intense autoimmune aggression is necessary for the manifestation of PM. The role of AT-rTSH and AT-rIGF-1 in the pathogenesis of PM has not been sufficiently studied.

Most likely, the main triggers for PM are trauma and impaired lymphatic drainage in the lower extremities. In a typical course, PM is localized on the lateral surface of both legs and can be represented by diffuse, tumor, plaque-like or elephantine forms. Cases of the development of thyroid dermopathy of the forearm, shoulder, palm, upper back and neck after injury, as well as in places of scars and burns, have also been described. PM often occurs after the manifestation of endocrine ophthalmopathy, during the first 2 years from the moment of detection of hyperthyroidism. Early diagnosis of PM currently comes down to regular preventive examination of the pretibial area. Diagnostic biopsy is indicated only in doubtful cases. The presence of a subclinical stage of PM requires confirmation. Maintaining euthyroidism, quitting smoking, avoiding injury, and wearing tight shoes that interfere with normal lymphatic drainage may reduce the risk of PM in patients with GD. Due to the relative rarity of PM, large randomized trials evaluating different treatments for this condition are lacking.

The mild form in some cases can regress without any therapy, but can become more severe. Given the more favorable outcome with early initiation of therapy, it is recommended to begin treatment when the first signs of PM are detected.

A number of publications have noted the positive effect of using glucocorticosteroids (GCS) under an occlusive dressing for mild and moderate PM; in more severe forms, injections of GCS and somatostatin analogues into the lesion are effective. Surgical removal of affected lesions is currently not recommended due to the frequent recurrence of PM in the area of postoperative scars.

Further study of etiopathogenesis, identification of predictors and risk factors for PM, as well as the development of early diagnostic methods will help reduce the risk of PM and the development of its severe forms.

References

1. Fatourechi V. Thyroid dermopathy and acropachy. Best Pract Res Clin Endocrinol Metab. 2012;26(4):553-565. https://doi.org/10.1016/j.beem.2011.10.001
2. Schwartz KM, Ahmed DDF, Ahmed I, Fatourechi V. Development of localized myxedema in a skin graft. Int J Dermatol. 2002; 41(7):401-403. https://doi.org/10.1046/j.1365-4362.2002.01535_3.x
3. Morris JC, Hay ID, Nelson RE, Jiang N-S. Clinical utility of thyrotropin-receptor antibody assays: comparison of radioreceptor and bioassay methods. Mayo Clin Proc. 1988;63(7):707-717. https://doi.org/10.1016/s0025-6196(12)65533-5
4. Chang T-C, Wu S-L, Hsiao Y-L, et al. TSH and TSH-receptor antibody-binding sites in fibroblasts of pretibial myxedema are related to he extracellular domain of entire TSH-receptor. Clin Immunol Immunopathol. 1994;71(1):113-120. https://doi.org/10.1006/clin.1994.1059
5. Stadlmayr W, Spitzweg C, Bichlmair AM, Heufelder AE. TSH-receptor transcripts and TSH-receptor-like immunoreactivity in orbital and pretibial fibroblasts of patients with graves' ophthalmopathy and pretibial myxedema. Thyroid. 1997;7(1):3-12. https://doi.org/10.1089/thy.1997.7.3
6. Cianfarani F, Baldini E, Cavalli A, et al. TSH-receptor and thyroid-specific gene expression in human skin. J Invest Dermatol. 2010;130(1):93-101. https://doi.org/10.1038/jid.2009.180
7. Smith TJ. Is IGF-I-receptor a target for autoantibody generation in graves' disease? J Clin Endocrinol Metab. 2013;98(2):515-518. https://doi.org/10.1210/jc.2013-1004
8. Matos K, Manso PG, Marback E, et al. Protein expression of VEGF, IGF-1 and FGF in retroocular connective tissues and clinical correlation in graves' ophthalmopathy. Arq Bras Oftalmol. 2008;71(4):486-492. https://doi.org/10.1590/s0004-27492008000400004
9. Krieger CC, Neumann S, Place RF, et al. Bidirectional TH and IGF-1-receptor cross talk mediates stimulation of hyaluronan secretion by graves' disease immunoglobins. J Clin Endocrinol Metab. 2015;100(3):1071-1077. https://doi.org/10.1210/jc.2014-3566
10. Krieger CC, Place RF, Bevilacqua C, et al. TSH/IGF-1 receptor cross talk in graves' ophthalmopathy pathogenesis. J Clin Endocrinol Metab. 2016;101(6):2340-2347. https://doi.org/10.1210/jc.2016-1315
11. Davies TF. Trauma and pressure explain the clinical presentation of the graves' disease triad. Thyroid. 2000;10(8):629-630. https://doi.org/10.1089/10507250050137680
12. Missner SC, Ramsay EW, Houck HE, Kauffman CL. Graves' disease presenting as localized myxedema in a thigh donor graft site. J Am Acad Dermatol. 1998;39(5):846-849. https://doi.org/10.1016/s0190-9622(98)70363-9
13. Fatourechi V, Bartley GB, Eghbali-Fatourechi GZ, et al. Graves' dermopathy and acropachy are markers of severe graves' ophthalmopathy. Thyroid. 2003;13(12):1141-1144. https://doi.org/10.089/0507250360731541

14. Hofbauer LC, Muhlberg T, Konig A, et al. Soluble interleukin-1 receptor antagonist serum levels in smokers and nonsmokers with graves' ophthalmopathy undergoing orbital radiotherapy. J Clin Endocrinol Metab. 1997;82(7):2244-2247. https://doi.org/10.1210/jcem.82.7.4068