PRETIBIAL MYXEDEMA: PATHOGENETIC FEATURES AND CLINICAL ASPECTS

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ABSTRACT

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.

Keywords: 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% [1]. 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 [2]) 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 detection of signs of PM is necessary to prevent TByellow 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 [3]. 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 [4, 5]. However, there is evidence of the presence of rTSH in the skin of the shoulder, buttocks and foreskin in healthy people [6].

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 individuals with EO requiring orbital decompression and/or accompanied by optic neuropathy, it reaches 13% [12, 15]. In typical cases, areas of purple, yellow, and brown appear on the skin of both legs. When hyperkeratosis is added, the color may change [1]. 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 [16]. Cases of thyroid dermopathy of the forearm, shoulder, palm, upper back and neck have been described after previous trauma, as well as in areas of scars and burns [11, 17–19]. Ulcerations are not typical for PM. In rare cases, the condition is accompanied by burning and itching [20]. 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 [21].

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 [22]. The absence of AT-rTSH in the blood serum makes the diagnosis of PM unlikely [16]. 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, between the bundles of which, when stained with Alcian blue and sciffiodic acid, accumulations of mucin can be detected. It is noteworthy that the collagen fibers of the papillary dermis retain their normal structure. 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.

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 [25, 26]. 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 [27, 28]. In nodular and plaque forms of PM, injections of corticosteroids into the affected area give a pronounced positive effect up to complete remission [29, 30].

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[46]. 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 HD. Due to the relative rarity of PM, large randomized trials evaluating different treatments for this condition are lacking[40,41,44,45].

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