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Mooren's corneal ulcer – pathogenesis, clinical characteristics and treatment

Mooren's ulcer is a rare disease with progressive and recurrent character (3, 9, 10, 12, 19, 23, 24, 26). Pain of the affected eye is the main symptom and in a slit lamp one can observe peripheral ulceration of the cornea that spreads around and towards the centre of the cornea, which usually causes a great impairment of vision. In pathogenesis a great role play probably auto-antibodies against antigen of corneal stroma (CO-Ag). The treatment depends on the clinical state and consists of topical and systemic steroid therapy or immunosuppression and surgical interventions such as conjunctival excision, lammelar keratoplasty or amniotransplantation.

EPIDEMIOLOGY

Wood and Kaufmann (24) divided patients into two groups considering age of manifestation, clinical state and the course of the disease. Type I appears usually only unilaterally, in older people, with benign course and better response to the treatment. Type II is connected with people under the age of 35 years and more severe pain. It is resistant against therapy and more often is found bilaterally. However not all scientists agreed with these characteristics. Watson (23) took into account the clinical state and results of fluorescein angiography of the anterior segment of an eye and proposed three different types of Mooren's ulceration. The first one appears in older white patients, more often in women. The closure of superficial limbal plexus, severe pain, poor response to the treatment, and high tendency of recurrence are very characteristic of it. Bilateral aggressive ulcers are very common in young men in India. They are not so painful and have a good response to the treatment with neovascularization and leakage of new vessels. The third type of ulcer "bilateral benign" one can observe in starving middle-aged people from India. It responds well to the diet supplementation. Pain and distortion of limbal plexus are very infrequent.

In Schanzlin's et al.'s studies (19) a benign type of Mooren's ulcer was observed in 25% of patients over 35 years, with no predilection to sex. On the other hand, type II with worse prognosis appeared in both eyes in 75% of black people under the age of 35. What's more, Lewallen and Courtright (12) made analysis of 287 case histories of Mooren's ulcers and discovered this type of ulcer to be 1.6 times more common in men than in women. Bilateral type was diagnosed in 43% older people against 30% in patients under the age of 35, which did not support Wood and Kaufman's hypothesis. The most numerous group of people was studied in China (3). Scientists reviewed 550 cases of Mooren's ulcer. 79.5% of patients were under 35, in 30% of cases disease occurred bilaterally. Recurrences were observed in 25.6%, among them 70% were diagnosed during the first 6 months after treatment.

RISK FACTORS

Because of not fully discovered pathomechanism of this disease it is difficult to evaluate its risk factors. According to clinical observations as risk factors authors mention undergoing surgical intervention such as keratoplasty, cataract extraction or trabeculectomy, corneal chemical burns, viral keratitis, helminth infestations of gastrointestinal tract or infections of hepatitis C virus (1, 3, 9, 13–15, 17, 19, 22–24, 26, 27). Recently there has been more attention given to genetic factors. In 2000 Taylor (22) et al. and in 2003 Liang (13) et al. observed correlation between Mooren's ulcer and HLA-DR17 (3) and HLA-DQ2 antigenes. Further investigations have to be done to confirm these observations.

PATHOMECHANISM

Mooren's ulcer is thought to have an autoimmune aethiology. Support for this came from works of Gottsch et al. (6, 7) who identified antigen CO-Ag (cornea-associated antigen) in the stromal layer of the cornea. This antigen has appeared to be similar to calgranulin C found in circulating leucocytes. Under certain conditions antibodies with specificity to this antigen are produced by the patient and immunological response is started. Keratoplasty or corneal injury during cataract extraction may be one of the initial mechanisms. Probably configuration of the corneal layers is redistributed and hidden stromal antigens are uncovered. In helminth infestations which are common in West Africa (14) the main role plays protein binding Ca^{2+} fixed on the surface of the helminth. It is similar to the part of calgranulin C and may interfere or begin autoantibodies production. Similar mechanism can be observed in patients with hepatitis C viral infections (15, 17). HLA-DR17(3) and HLA-DQ2 may exceed antigen presentation and in this way start hyperactivity of the immunological system (13, 22). On the other hand Berkowitz and Brown (1) underline local ischemia, lymphocyte infiltrations and immunological complexes in adjacent conjunctiva as the cause of stromal antigens uncovering due to the proteolytic mechanism.

PATHOMORPHOLOGY

In the lesions excised from the ulcerative cornea one can usually observe thickening of the stroma. There can be also found immunological complexes and inflammatory cells. Epithelium and endothelium in the beginning of the process remain normal. Frequently there are new blood vessels growing in the ulcer direction from the conjunctiva. Adjacent conjunctiva is oedematous. Further investigations have to be performed to evaluate the presence of CD4 lymphocytes, molecules with strong expression of VCAM-1, ICAM-1, LFA-1 and progenitor cells with CD34, c-kit and STRO-1 markers observed by scientists (27).

CLINICAL CHARACTERISTICS

Patients with Mooren's corneal ulcer usually complain about severe pain that is compared with small lesions at the beginning of the process (3, 9, 10, 12, 19, 23, 24, 26). Impairment of visual acuity can be also observed. In slit-lamp examination vessel dilatation and stromal infiltrations, semicircular shape of ulceration close to the limbus and unchanged epithelium and endothelium are very characteristic. In the course of the disease ulceration spreads circumferentially approximately 2–3 mm from the limbus and causes abnormal epithelialization (Fig. 1). Sometimes lesions cover the entire cornea, also the central part. Cornea becomes very thick and perforations can appear. Infiltrates and dilated blood vessels of adjacent conjunctiva are observed (Fig. 2). Besides perforation rare

complications are endophthalmitis with hypopion, cataract, glaucoma and neovascularization of the cornea. Atrophy of eye and blindness are not very rare.

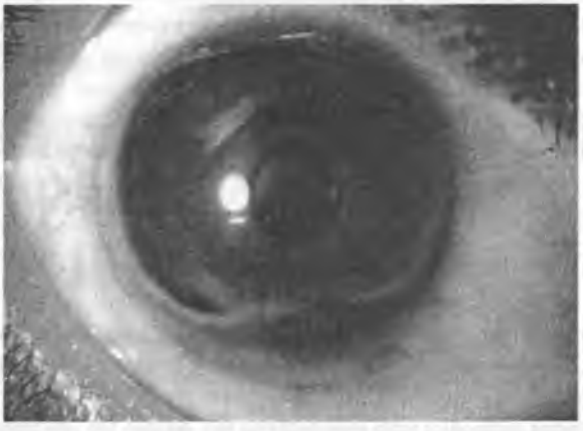

Fig. 1. Circumferential spreading of lesions with primary ulcer at 6 o'clock

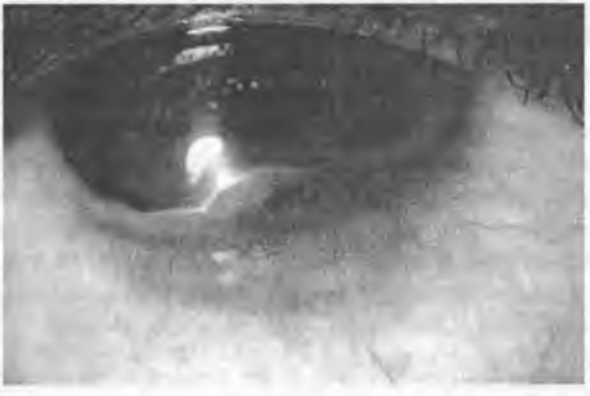

Fig. 2. Adjacent conjunctiva with dilated blood vessels

DIFFERENTIAL DIAGNOSIS AND TREATMENT

Similarly to Mooren's ulcer there be can manifested systemic diseases such as chronic rheumatoid arthritis, systemic lupus erythematosus, periarteritis nodosa and Wegener's granulomatosis (10, 23, 26). Up to now effective treatment has not yet been worked out because of recurrent and progressive character of the disease. Therapy is adapted to individual response and course of ulceration. There are few options to be considered.

Steroid therapy. Most of scientists begin with topical steroids (prednisolone or dexamethasone) given in high doses hourly. Usually if this therapy is effective along the time it is reduced. After 8 days without significant improvement iv steroids 1mg/kg should be administered (5, 8, 26, 28).

Immunosuppression. This treatment is chosen as the alternative if steroid therapy fails (5, 8, 28). Topical application of cyclosporin A gives a possibility to avoid many side-effects of its systemic administration. However, if needed, oral drugs such as cyclosporin A, methotrexate,

azathioprine, cyclophosphamide, mycophenolate mofetil may be the second choice therapy. Recently there have been reports of topical use of Fk506 (Tacrolismus) which acts similarly to cyclosporin A but has a stronger immunosuppressive effect (18). The administration of interferon alfa 2b is reserved for cases with coinfection of hepatitis C virus (15, 17).

Monoclonal antibodies. In the past few years there have been trials to use immunomodulatory monoclonal-antibodies therapy in severe non-responding to conventional treatment cases of Mooren's ulcer. One of them is Campath-1, humanized mAb which recognizes activated lymphocytes, but its direct mechanism remains unclear (4, 25).

Surgical treatment. Among the methods of surgical treatment authors suggest conjunctival excision, conjunctival peritomy, lamellar keratoplasty, sclero-corneal transplantations, single or multilayer amniotic membrane application, usually at the same time with medical treatment (2, 10, 16, 20, 21, 26). The effectiveness of simultaneous therapy with topical cyclosporin A and lamellar keratoplasty according to Chen et al. (3) report was assessed at 73% in Mooren's cases. Some scientists propose amniotic membrane transplantation over the peripheral cornea and limbus with a hole in the centre to maintain clear vision (11).

CONCLUSIONS

Mooren's corneal ulcer is an infrequent ophthalmic disease which is caused probably by autoimmunological response to antigen CO-Ag present in corneal stroma. Further investigations need to be performed to define precise pathomechanism. Preserving good visual acuity is uncertain due to progressive and recurrent character. The effects of treatment in many cases are not satisfactory.

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SUMMARY

The aim of this study was to present current knowledge about non-infectious corneal ulceration of Mooren type. Articles and books published between 1980 and 2006 served as the sources. In the study we focused on epidemiology, clinical and histological manifestation of this rare disease, risk factors (including HLA investigations), pathomechanism, course of the disease and new methods of treatment. Mooren's ulcer is a rare disease, especially in white people. Untreated or with poor response to the treatment can cause blindness. In clinical characteristics predominantly there is peripheral corneal thickening, mostly affecting the stroma. The disease spreads circumferentially. Perforation of the cornea can appear. Histologically one can observe lymphocyte infiltration, new blood vessels, decreased stromal layer, and in adjacent conjunctiva blood vessels dilatation and oedema. Mooren's

ulcer is progressive, usually recurrent and can affect both eyes. Currently there is a question of the primary pathomechanism of this illness, and the answer is probably connected with antigens of the corneal stroma and disorders of the immunological system. Frequently the disease begins after corneal trauma, surgical interventions, helminth infestations or infections of hepatitis C virus. Treatment of Mooren's ulcer is not satisfactory due to the remitting and progressive course. Usually therapy consists of topical and systemic cyclosporin A and corticosteroids. Cyclophosphamide, azathioprine, FK-506 or mycophenolate mofetil or Campath-1H containing monoclonal antibody can be also administered. Besides medical therapy, conjunctival excision, amniotic membrane transplantation or keratoplasty may be needed.

Wrzód Morena – patogeneza, obraz kliniczny i leczenie

Celem pracy było przedstawienie najnowszych poglądów na temat nieinfekcyjnego owrzodzenia rogówki typu Moorena. Korzystano z publikacji i książek z okresu 1980–2006. W pracy uwzględniono epidemiologię, obraz kliniczny i histologiczny tego rzadkiego schorzenia, czynniki ryzyka (w tym badania genetyczne HLA), patomechanizm, przebieg choroby oraz nowoczesne metody leczenia. Wrzód Moorena jest chorobą rzadką, szczególnie u osób rasy białej. Nieleczona lub w formie opornej na leczenie może doprowadzić do ślepoty. W obrazie klinicznym dominuje obwodowe ścieńczenie rogówki, dotyczące głównie istoty właściwej. W dalszym przebiegu schorzenie może obejmować cały obwód. W rzadkich przypadkach może wystąpić perforacja rogówki. W obrazie histopatologicznym obserwuje się w rogówce nacieki limfocytarne, tworzenie nowych naczyń krwionośnych, ścieńczenie istoty właściwej rogówki, a w przylegającej spojówce obrzęk istoty właściwej i poszerzenie naczyń krwionośnych. Wrzód Moorena ma charakter postępujący, z tendencją do nawrotów, może występować w obu oczach. Obecnie poszukuje się odpowiedzi na pytanie o właściwy patomechanizm tej choroby, wskazując na antygeny istoty właściwej rogówki oraz związane z nimi zaburzenia układu immunologicznego. Zazwyczaj w wyzwoleniu kaskady immunologicznej istotną rolę odgrywają urazy rogówki, zabiegi chirurgiczne, infestacje pasożytnicze przewodu pokarmowego czy zakażenia wirusem zapalenia wątroby typu C. Leczenie owrzodzenia rogówki typu Moorena jest trudne ze względu na nawrotowy i postępujący charakter. Miejscowo i ogólnie zazwyczaj stosuje się cyklosporynę A oraz kortykosterydy. W wybranych przypadkach podaje się również leki immunosupresyjne, takie jak cyklofosfamid, azatioprynę, interferon, FK-506 i mykofenolat mofetylu, a także preparat złożony z przeciwciał monoklonalnych Campath-1H. Stosuje się także leczenie operacyjne, takie jak wycięcie spojówki, naszycie błony owodniowej, przeszczep rogówki.