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Characteristics of Epidemic Keratoconjunctivitis due to Novel Adenovirus Types

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Abstract

Specific types of human mastadenovirus (HAdV) D and E often cause epidemic keratoconjunctivitis (EKC). Types of HAdV-8, -37 and -64 (formerly -19a) lead most severe clinical symptoms among them. Novel types of HAdV-D characterized as recombinant products were recently identified as the cause of EKC. They are designated as HAdV-53, -54, -56 and -64. We here review the characteristics of EKC caused by new types, which are spread in Japan.

Introduction

Epidemic Keratoconjunctivitis (EKC) is caused by types in D and E species of *Human mastadenovirus* and is transmitted by direct contact of the hand and the conjunctiva. In the past, many EKC patients were identified by oculists and healthcare workers involved in the medical treatment of EKC, but now, ophthalmologic clinics, hospitals, etc., are frequently found as places source of EKC in nosocomial outbreaks. Because adenovirus is highly resistant to various dis-infectious compounds, its infectivity is strong [1]. Type 8 was first isolated by Jawetz in tissue culture from an EKC patient who returned from Asian travel in 1954 [1]. EKC was defined as a disease showing acute follicular conjunctivitis, pre-auricular lymphadenopathy, and corneal involvement Mitsui et al. [2] in 1959 during a Japan Ophthalmologic Conference. On 1969 adenoviral EKC case reports temporarily decreased due to the AHC (acute hemorrhagic conjuncitivitis epidemic of RNA virus such as EV70 [3] That is, enterovirus 70 and adenovirus adhere to the conjunctiva at the same receptor, sialic acid [4]. On 1984, type 37 was isolated from a Sexually Transmitted Disease (STD) in genital organs other than the conjunctiva. However, other reports of type 37 presented it also as cause of adenoviral EKC, and it continues as one of the main agents of EKC in Japan until now [5-7]. Type 22, which originally was isolated from trachoma patients in infant, recombined with types 37 and 8, in a novel recombinant type isolated in 2008 and designated as the novel type 53 [8-11]. Similarly, the chimeric type 54 was also detected in EKC patients in Japan [12]. On other hand, another recombinant type of types 9 and 15 was reported in foreign countries and seemed to have invaded Japan after 2009 as the novel type 56 [13].

Transmission and Epidemiology

The transmission of EKC has been speculated for long time to be due to direct contact with infected patients. Due to the viral stability outside of infected cells, the virus can survive for extended periods of time in different surfaces. It has been suggested infected the virus can be transmitted by the hand of hospital doctors and nurses by touching towels contaminated with viruses in hospitals, clinics, workplaces and homes. Although there is no difference in frequency due to age, it spreads mainly in active adults. In recent serological investigations, the antibody prevalence rate for workers in eye clinics by type 8 is less than 30%, for type 19 and 37 type it is 10%, the new type is 5% in Japan [14]. According to the survey of occurrence trend after the nationwide surveillance program against Infectious Disease including EKC reports from approximately 600 ophthalmic fixed points nationwide showed 31,399 EKC reports (49.53 reported per fixed point) in January to December 2006, 23,537 (35.82) in January to December 2007, 24,266 (36.06) in January to December 2008. Peaks of EKC prevalence through year are seen at the 34th week mainly around August as the season, but in some areas hospital infections occur from emergency patients etc. even in winter. Adenovirus were typed under 51 serotypes, which were identified in the neutralization test of the neutralizing mainly the determinant in hexon. However type 52 to 72 has been reported as a genotype since 2000 and

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the fiber and the penton base also participated in the classification of novel human adenovirus in less degree [15,16]. Recently the number of cases due to type 8 has decreased in Japan, while the number of cases due to type 37, 53, 54 and 56 has been steadily increasing [17]. Furthermore, type 4 of E species is also epidemic by year and is etiology of EKC [18].

Clinical Feature

EKC by type 8, 37, 54 is more severe than 53, 56, 64 type [19]. In new-type EKC, cultured from the conjunctival scraping of patient with EKC and it often requires a blind passage for many generations. Adenovirus adhered to the lower eyelid conjunctiva has latent conjunctiva on the fornix consisting of columnar epithelial conjunctiva and grows in its region like a moist chamber, so the incubation period is 8 to 14 days in patients. It occurs when the amount of virus reaches a certain amount, and it accompanies swelling of the eyelid. Both sides on conjunctiva are easily infected because of its strong infectivity, but symptoms of the first eye are generally more intense though there are not many cases of simultaneous binocular onset. It involves swelling of the pre-auricular lymph nodes. When the inflammation reaches the cornea, superficial keratitis, corneal erosion, ulceration occurs and spotted cloudiness multiple times under the corneal epithelium can last several years. In EKC, a small bleeding point occurs in the palpebral conjunctiva, and it can be distinguished from the small bleeding point of the bulbar conjunctiva of AHC by enterovirus type 70 and coxsackie virus group 24 type mutant strain [20]. In addition, pseudomembranous conjunctivitis with neonates and infants with eye diseases caused by herpes virus, as well. Chlamydia and EKC cause pseudomembranous conjunctivitis because they show still the monolayer of conjunctiva epithelial cell. Therefore, infected conjunctiva infected type 8 causes pseudomembranous conjunctivitis and it mechanically produces damages and mixed streptococci infection causes corneal perforation, so antibiotics need to be supplied carefully.

Etiologic Diagnosis

After virus isolation by tissue culture of adenovirus by A549 cells (human alveolar basal epithelial adenocarcinoma cells) using sample materials such as tear, ocular discharge and conjunctival scraping. The isolated products are used to identify the type by neutralization reaction. However, more experience and time are required to apply this process, because tissue cultures due to slow growing require longer time to CPE expression in the case of novel adenoviruses related to EKC. And its standard antiserum is deficient in the new type because of slow growing, and additionally, it requires the skill and long time for the cell culture and the neutralization test and it is difficult to return to the clinical site. On other hand, the study analysis of the genome of adenovirus has progressed since 2005, it has been revealed that neutralizing antibody are determined not only by hexon, but also by the fiber of adhesion and the penton base of internalization. Both proteins have been also suggested to be involved in the onset of EKC.

For this reason, identification by genetic sequencing of penton, hexon, and fiber domains has been made with PCR and genotypes could now be used for the identification of adenoviruses, but the identification by this method is limited due to the involved cost. Since the report of type 52, more than 20 novel types have been reported as consequence of recombination events. Among species A to F adenoviruses, D species account for more than half of all identified types. Moreover, besides types that cause epidemic keratoconjunctivitis, many other novel types have been found in immune deficient patients such as AIDS patients and infants with diarrhea. Furthermore, despite types in species B and E also cause mild EKC, the types in species D caused most severe cases. However, novel types such as 53 and 56 are less frequently associated with severe infections than types 8, 37 and 54. As clinicians needed to return the result of virologic studies to the bed side, rapid commercial kit were developed to properly identify the cause of the EKC case [21]. As a quick diagnostic method, a PCR + sequence method [22], it becomes possible to identify the molecular type, epidemiological investigation called molecular epidemiology becomes possible, and it is expected to be linked to public health and for identification of index case in nosocomial outbreak. It is conducted at a specific facility, but surveillance projects can also be identified at specific local health laboratories or National Institute of Infectious Diseases in Japan. Research on genome is progressing from elucidation of type to the function of more than 40 proteins coded in genomes of adenoviruses by molecular biology at amino acid level. On the other hand, a commercial kit using a monoclonal antibody targeting the hexon of Adenovirus type 2 gives the information by dead virus that may be misleading information in clinical level. Then, the relation between negative cases of culture-positive live virus and commercial growing viruses and slow growing adenovirus causing EKC remains as a task to be solved.

Treatment and Prevention

There are no effective drugs for adenoviruses in general. If the inflammation and infiltration to the cornea is detected, it is recommended the use of eye drops of anti-inflammatory agent symptomatically and treats it with a steroid agent. Newborns and infants have the possibility of mixed infection of bacteria, so eye drops of antibacterial agents are applied. It is also highly recommended the eye disease careful handling and disposal of the secretions of patients, hand washing and disinfection of patients properly. As the eyedropper bottles are contaminated with virus, it is advised to be careful not to use eye drops of patients, sterilize contaminated hospital instruments with autoclave, or disinfect with alcohol, iodine and new effective compound. The basis of prevention is thorough prevention of direct contact with infection. Especially medical personal and patients should pay attention to things that come into contact with eyes such as towels, eye drops and medical equipment. We need treatment for treatment of adenovirus caused ocular infections in particular the new medicine against sialic acid-binding type to relieve acute symptoms and preventing occurrence of corneal opacities affecting vision [23].

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